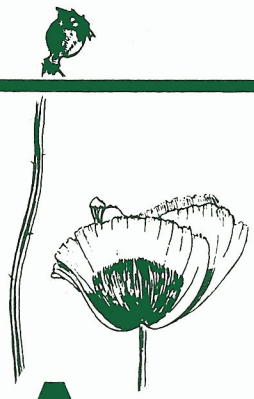
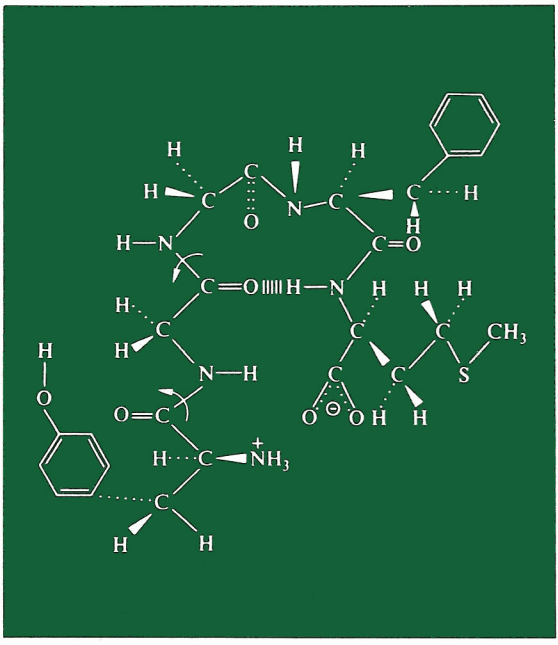


Opioid Analgesics

Chemistry and Receptors



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Opioid Analgesics

Chemistry and Receptors

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Foreword

The rapidly burgeoning research of the past two decades on agonist-antagonist analgesics and opioid receptors makes this exhaustive review of opioid analgesics particularly relevant and timely. After an introductory chapter the additional 12 chapters begin logically with morphine and congeners (4,5-epoxymorphinans) and end with opioid receptors. All principal chemical types of centrally acting analgesics (including endogenous opioid-like substances) and their antagonists as well as the mixed agonist-antagonists are treated thoroughly, although not always (and for good reason) in historical (chronological) order. A chapter on miscellaneous types (atypical structures for the most part) includes the benzimidazoles (etonitazene), aminotetralins (dezocine), tetrahydroisoquinolines (methopholine), and so on. Important aspects and correlations of chemistry, pharmacology, and biochemistry are discussed in depth. Literature citations are numerous. For educators, practicing laboratory scientists, and physicians, this scholarly review by two authors well versed in the chemistry, pharmacology, and biochemistry of opioid analgesics will be informative, stimulating, and thought-provoking.

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Preface

The history of opium predates the written word, although knowledge of its constituents dates back less than 200 years. Over the centuries its popularity for the relief of pain has waxed and waned, until today the opiates are widely recognized as excellent analgesics but with disadvantages that have impaired their use seriously. There is a clear need for a potent analgesic with minimal effects on the respiratory centers and gastrointestinal tract and preferably devoid of dependence liability. The discovery of endogenous peptides, although offering a means of understanding some of the actions of opioids at a molecular level, has not given us desired selective analgesics.

During the past several years ideas regarding the nature of opioid receptors have evolved rapidly. Multiple receptor hypotheses gained favor and a number of discrete receptor types have been characterized. This increasingly complex area has been covered in Chapters 10 and 13. So far we have no evidence for the chemical nature of opioid receptors or for whether differences between receptor types are gross or relatively small.

The aim of this book is to afford medicinal scientists an entry into the chemistry and biological activity of morphine and related compounds. Although our treatment is not exhaustive we have tried to be comprehensive, and new researchers in the field should soon discover those areas of opioid chemistry in need of exploration. In compiling information for the book it became clear how much more work must be done on the chemistry of compounds related to morphine.

To set the scene, the book commences with an introductory chapter that briefly covers definitions, testing methods, side effects, pharmacokinetics, and biochemical and bibliographical aspects. The 11 chapters that follow deal with specific classes of opioid ligand in which emphasis is placed upon chemistry (especially synthesis and molecular geometry), structure-activity analyses, and interrelationships within the group itself and in a wider context. It was felt important to devote a separate chapter to agents that behave as opioid antagonists or have dual agonist-antagonist effects and to kappa (κ) ligands. Among these chapters, a full account of opioid peptides is given, together with a description of how their study has provided evidence for the existence of

subspecies of opioid receptor. In the final chapter, a summary and critique of progress made toward the isolation and characterization of opioid receptors is presented and consideration is given to speculations upon receptor scenarios and ligand–receptor interactions.

Although this book has been written with the needs in mind of those actively engaged in research upon central analgesics, whether in academia or in pharmaceutical industry, it should also serve as a background and source book to postgraduate and senior undergraduate students of chemistry, medicinal chemistry, biochemistry, and pharmacology and their teachers.

Our colleagues in the field of central analgesics have been most helpful and forthcoming in the provision of valuable information and comment and are too numerous to list. We should, however, like to express our special appreciation to Bernard Belleau, George Dewar, Mark Froimowitz, Arthur Jacobson, Hans Kosterlitz, Everette May, Philip Portoghese, and Jan Tollenaere. We also thank Shirley Hancock, Eve Gonty, and Dawn Hodges for their careful and patient work on typing the manuscript.

Contents

Abbreviations

AD_{50}	antagonist dose effective in 50% of a population (usually expressed in mg/kg)
amino acids	IUPAC abbreviations are employed; those for less common residues such as 4-hydroxyproline (Hyp) are included in the text
Boc	*t*-butyloxycarbonyl
Bu	butyl
Bz	benzyl
cAMP	cyclic adenosine monophosphate
CD	circular dichroism
CNA	chlornaltrexamine
CNS	central nervous system
COA	*N*-methyl analog of CNA
CBM	cyclobutylmethyl
CPM	cyclopropylmethyl
CSF	cerebrospinal fluid
DADL	Tyr-D-Ala-Gly-Phe-D-Leu
DALAMID	amide of DADL
DAGO	Tyr-D-Ala-Gly-MePhe-Gly-ol
DCCI	dicyclohexylcarbodiimide
DMF	dimethylformamide
DMSO	dimethylsulfoxide
DSLT	Tyr-D-Ser-Gly-Phe-Leu-Thr
ED_{50}	agonist dose effective in 50% of a population (usually expressed in mg/kg)
EKC	ethylketazocine
Et	ethyl
FNA	funaltrexamine
FOA	*N*-methyl analog of FNA
gc	gas chromatography
gc/ms	combined gas chromatography/mass spectrometry
GIT	gastrointestinal tract

GPI	guinea pig ileum
GTP	guanosine triphosphate
hplc	high-performance liquid chromatography
IC_{50} (or ID_{50})	concentration of drug that displaces 50% of a radioactive ligand (binding assay) *or* causes 50% depression of the twitch induced by coaxial stimulation of smooth muscle (GPI, MVD assays)
im	intramuscular
ip	intraperitoneal
ir	infrared
iv	intravenous
ivent	intraventricular
^2J, ^3J	coupling constant (in Hz) over two or three bonds, respectively (in nmr)
K_e	equilibrium constant of antagonists obtained from the expression $K_e = a/\text{DR-1}$ where a is the molar concentration of antagonist and DR the ratio of the concentration of agonist required to depress the muscular twitch to the same extent in the presence and absence of a given concentration of antagonist
LAH	lithium aluminum hydride
β-LPT	β-lipotropin
Me	methyl
MHP	mouse hot-plate assay
MID	multiple ion detection (in ms)
ms	mass spectrometry
MST	mouse Straub tail
MVD	mouse vas deferens
MW (MWR)	mouse writhing assay (chemical writhing agent may be appended, e.g., MWQ (benzoquinone-induced))
NIH	National Institutes of Health (Bethesda, Md.)
NBA	*N*-bromoacetamide
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
nmr	nuclear magnetic resonance
NOE	nuclear Overhauser effect (in nmr)
ORD	optical rotatory dispersion
pA_2	negative logarithm of dose of antagonist that converts response to a double dose of agonist to that of a single dose
PDC	physical dependence capacity
po	per os (by mouth)
Ph	phenyl

PPA	polyphosphoric acid
Pr	propyl
Py	pyridine
QSAR	quantitative structure–activity relationships
R(*S*)	Rectus (Sinister) configurational symbols of the Cahn–Ingold–Prelog protocol
RTC	rat tail clip assay
RTF	rat tail-flick assay
RTA/A	rat tail-flick antagonist assay
RTP	rat tail pressure assay
SAR	structure–activity relationships
sc	subcutaneous
SSB	stereospecific binding
TFA	trifluoroacetic acid
Ts	tosyl(*p*-tolylsulfonyl)
THF	tetrahydrofuran
tlc	thin layer chromatography
uv	ultraviolet
WK	Wolff–Kishner reduction
Z	benzyloxycarbonyl

1

Introduction

This book deals with substances commonly described as analgesics or analgetics that alleviate or abolish pain without at the same time inducing loss of consciousness. Their site of action is essentially within the central nervous system whereby they are distinguished from pain-relieving drugs such as aspirin and other anti-inflammatory agents that act at peripheral locations. Their central actions are depressant but they may be differentiated from general agents of this description such as barbiturates and anesthetics in that they influence specific sites, those concerned with the appreciation of pain and the control of respiration being the most notably affected. Nowadays a distinction is made between the terms *opiate* and *opioid* as applied to central analgesics. The former term refers to agents derived from opium or one of its constituents, while the latter is the more general term for agents with morphinelike properties; hence, the title of this book, *Opioid Analgesics.*

Since substances exist that block the actions of analgesics in a competitive manner, the latter are customarily termed opioid *agonists* (in spite of the fact that they inhibit rather than promote a pharmacological response), and the former are termed opioid *antagonists*, both formally being presumed ligands of the same opiate receptor. Some ligands possess both agonist and antagonist properties, dependent upon the circumstances of their use, and these are termed *mixed agonists-antagonists*, or *dualists.* Differentiation of the three ligand classes forms an important part of present-day research upon opioid drugs, and evidence is accumulating that ligands that are specific in either extreme (and often referred to as "pure") are relatively rare, especially as far as antagonists are concerned.

The confident characterization of a pain-relieving drug as a central analgesic is a vital aspect of this research area and is crucial for structure-activity analyses. The effectiveness of a drug in modifying the response of animals to noxious stimuli (i.e., its antinociceptive potency), its behavioral effects (e.g., lead-pipe rigidity in rats, Straub tails in mice), and reversal of its actions by an opioid antagonist such as nalorphine or naloxone, all contribute to such a characterization. Procedures of an *in vitro* nature, notably inhibition of electrically induced contractions of smooth muscle preparations (especially guinea

pig ileum and mouse vas deferens) and binding affinity measurements to opioid receptors, provide further tools for pharmacological investigations of this kind.[1] The extensive development of ligand-binding procedures dating from the early 1970s provides direct evidence of the existence (inferred for many years chiefly from classical pharmacological methods and structure-activity relationship data, SAR) and location of opioid receptors, has now achieved a level of sophistication that permits association of ligands with subspecies of opioid receptors (referred to as μ, δ, κ, etc.).

A wide variety of animal test procedures for the assessment of analgesic activity is available, all of which depend on quantifying the animal's response to a noxious stimulus before and after administration of the test compound.[2-5] Whatever the significance of such behavioral changes to human pain, these responses usually give a fair guide to the potency of the drug in man. Methods based on a graded or quantal (all or none) response are used; dose-response curves are plotted and the effective dose-producing analgesia (as judged, for example, by a given increase in response time) in a particular percentage of the animals is found. This is commonly 50 when the potency is expressed by the ED_{50} value. Choice of route of administration is important, with oral (po), subcutaneous (sc), intramuscular (im), and intravenous (iv) applications being the most usual. Techniques for the central administration of analgesics are now available but are chiefly used for compounds vulnerable to enzyme attack such as peptides and for structure-activity analyses requiring bypass of the blood-brain barrier.[6] It is most desirable that a standard drug, such as morphine or pethidine, be included by any particular set of assay data in order that the results may be compared with those of other assays of the compounds or their analogs. Hot-plate assays of analgesics in mice have been carried out for many years at the National Institutes of Health (originally estabished by Dr. Nathan Eddy) under standardized conditions and provide a valuable source of reference potency data for comparative structure-activity studies.[7]

The rat tail-flick (RTF, radiant heat focused on tip of tail), mouse hot-plate (MHP, animal placed on a plate maintained at 55-70° by organic solvents at reflux temperatures), and rat tail withdrawal (RTW, tail immersed in warm water) procedures all employ heat as the noxious stimulus. Pressure methods include the tail clip (artery clip applied to root of a mouse tail) and variable pressure (plunger head of a syringe mounted above tip of a rat's tail) tests. In electric shock methods, a voltage is applied to electrodes implanted in the tooth pulp of guinea pigs or rabbits or to the tails of mice. Chemical irritants are also employed; materials such as phenylquinone, acetylcholine, acetic acid, and bradykinin given by intraperitoneal injection induce a characteristic writhing syndrome (intermittent contractions of the abdomen, turning of the trunk and extension of the limbs) that may be quantified.[8] The test, although more objectionable on humanitarian grounds than the heat or pressure methods, is useful in detecting mixed agonists-antagonists such as nalorphine

and pentazocine that do not usually respond as agonists in other tests. Responses of rats to injection of dilute formalin under the skin of a paw provide a test claimed to simulate chronic rather than acute pain.[9]

The now common use of *in vitro* assays of analgesics has the advantage of minimizing pharmacokinetic factors that is gained through drug application to isolated tissues. These tests, dating from the late 1960s, are based on the inhibition of electrically stimulated smooth muscle contractions, usually of guinea pig ileum (GPI) or mouse vas deferens (MVD), by morphine and its congeners.[10] The GPI test allows assessment of both agonists (ID_{50} values, concentration that causes 50% depression of the twitch induced by coaxial stimulation) and antagonists (from the equilibrium constant K_e); of special importance, agents with mixed properties behave as agonists. Although the GPI preparation may appear an unlikely model for central analgesic receptors, its use in this respect is supported by the ability of the procedure to rank both agonists and antagonists in the order anticipated from results of *in vivo* analgesic evaluations and to differentiate between stereoisomers in the same manner as do tests for analgesia. Extension of the GPI test to the vas deferens of the mouse and other species has been important in providing evidence for the existence of subpopulations of opioid receptors and in studies of peptides related to the enkephalins. Binding assays also form an important adjuvant to present-day studies of analgesics and provide affinity data measured in terms of an IC_{50} value, the concentration of drug necessary to displace 50% of the specific binding of a radiolabeled reference ligand such as [^{3}H]naloxone. These assays serve for the detection of opioid receptors, correlation of ligand affinities with pharmacological potency and (from the influence of sodium ions and other factors on affinity) the differentiation of agonists, antagonists, and agents of mixed action. The validity of the affinity data depends critically on the measurement of specific as opposed to nonspecific binding (best distinguished using the stereospecific binding principles of Goldstein)[11] and on the experimental conditions.

The ultimate criterion of usefulness of a novel analgesic is necessarily the result of its clinical trial, although tests for analgesia in man (healthy volunteers) involving experimentally induced pain have been devised [e.g., radiant heat focused on the forearm, forehead, or back; electrical stimulation of tooth pulp or fingers, contraction of muscle deprived of its blood supply (ischemic pain)].[3,12] Great care is necessary in the design of a meaningful clinical trial that employs pathological pain and must always be highly subjective in nature. Important aspects are allowance for comparisons with both a standard drug and a placebo, elimination of bias by randomization and double-blind protocols (neither administrator nor recipient of the drug have knowledge of its identity), and subjection of the data to accurate statistical analysis.[13]

The side effects of a novel analgesic are of major relevance from a clinical point of view. To date most synthetic agents and variants of natural products

share the well-known undesirable actions of morphine, now summarized.[14] With daily administration, tolerance to the analgesic actions of morphine usually develops within a few weeks and the dose needs to be gradually raised to produce the required relief from pain. Tolerance is closely associated with dependence (a term now preferred to the more emotive *addiction*), arguably the most serious drawback to the use of morphine.[15,50] Dependence involves both a physical and psychological need for the drug and is an international social problem of major dimensions, necessitating rigid control of the use and distribution of morphine and its surrogates, which are referred to as narcotics in this sense. Respiratory depression is another serious side effect of morphine, particularly in the clinical situation. In man, respiration is depressed by doses that are often below the analgesic threshold, and this effect is the prime cause of death with higher doses. Analgesic therapy must therefore be used with particular care in obstetrics, where fetal respiration may be affected; in respiratory ailments, such as bronchial asthma; and in cases where the patient is in a state of shock. The superpotent analgesics now used in veterinary practice carry a major hazard in this respect if accidentally absorbed by man. Morphine has a retarding action upon the digestive system, and small doses produce constipation (an effect utilized in smooth muscle *in vitro* assays). Its effect on the urinary bladder gives rise to urinary urgency but urination is made more difficult by increased tone of the vesical sphincter, and urine retention is observed even with therapeutic doses. Morphine has a direct stimulating action on the emetic trigger zone of the medulla, giving rise to nausea and vomiting. Other excitatory effects encountered are tremors and, more rarely, delirium. Carbohydrate metabolism may be deranged, resulting in hyperglycemia and the presence of reducing substances in the urine, but these effects are not often seen after therapeutic doses in humans. Myosis is a notable visible feature of the drug (mydriasis in cat and mouse), and the pinpoint pupil is characteristic of the addict. Finally, morphine is a powerful depressant of the cough center and opioids have long been employed as antitussives.

Although some authorities have challenged generally held views on the development of tolerance to and dependence on analgesics,[16] these topics remain of great concern to pharmaceutical industry and procedures for predicting and quantifying dependence (abuse) potential have been developed using both animal and human subjects.[5,7,17] Drug screening programs of this type have been carried out since the late 1930s at the National Institutes of Health Addiction Research Center, in Lexington, Kentucky, upon volunteers serving prison sentences for drug addiction offenses. In one procedure signs of physical dependence (abstinence phenomena) are evaluated by a point-scoring system after withdrawal of the drug from subjects previously stabilized on the test agent and the score is compared with that recorded after morphine. Relative physical dependence properties may also be determined by comparing doses equivalent to a given amount of morphine for maintenance of addiction as

seen by absence of the withdrawal syndrome. In the so-called allyl test, the abstinence syndrome is rapidly precipitated by administration of an analgesic antagonist such as nalorphine (*N*-allylnormorphine), avoiding the several days delay required for the syndrome to reach its peak after abrupt drug withdrawal. The same kinds of procedure may be used in rhesus monkeys, but observation of signs and symptoms of abstinence in rodents treated chronically with the test compounds for physical dependence liability may now be done with mice that display an abstinence syndrome characterized by a stereotyped jumping behavior, a single endpoint induced by naloxone treatment.[18] Tests of drug-seeking behavior in which self-administration of drugs by the animal is possible by a lever-intravenous catheter device are also employed, as are assessments of the subjective properties of a compound.[19]

Pharmacological procedures for predicting side effects aside from abuse potential are well developed and reliable and include tests for respiratory depression (measurements of respiration rate, expired CO_2, and blood pCO_2, pO_2, and pH),[20] constipation effects (measurement of intestinal transit by the charcoal meal method in mice),[21] and the detection of alterations in the levels of circulating hormones such as luteinizing hormone, testosterone, antidiuretic, and growth hormone.[22] Some analgesics, notably those of the mixed agonist-antagonist class, have dysphoric and psychotomimetic reactions in man (morphine is notable for its euphoric action), and animal techniques are available that identify subjective and biochemical alterations characteristic of compounds that induce hallucinations in man.[23]

While study of the pharmacological effects of an analgesic of potential clinical value is of patent importance, the reverse aspect—namely, the fate of the compound within the body—must be given due attention in present-day investigations of analgesics.[24] Such studies are now commonplace, especially in submissions of information on novel drugs to licensing authorities, but interest in and appreciation of the significance of this aspect of drug action dates only from the late 1950s. Since that time reports of the absorption, distribution, excretion (pharmacokinetics), and metabolism of analgesics have appeared at an ever-increasing rate, made possible primarily by radical advances in methods for the analysis of low levels of drugs in biofluids. Apart from the value of data of this kind to pharmaceutical formulation and the detection of toxic metabolites and pro-drugs, this work is vital to a proper evaluation of SAR data in terms of receptor events because it permits allowance for pharmacokinetic factors.

The biochemical pharmacology or subcellular mechanism by which opioid ligands exert their effects remains largely unknown in spite of extensive studies of the interactions of opiates with central and peripheral biogenic agents involved in nervous transmission. Thus, there is now a substantial body of evidence linking the pharmacological actions of opioid agonists, antagonists, and dual-acting agents with each of the neurotransmitters acetylcholine,

dopamine, norepinephrine, serotonin (5-HT), and histamine. The evidence is complex, and sometimes inconsistent and contradictory, and may often reflect side effects of the ligands that are unrelated to events at opioid receptors. Most details of this work are outside the scope of this book (several reviews are available),[4,25,26] but an account of the involvement of opioid receptors in the regulation of adenylate cyclase activity is included. This phenomenon, especially in regard to neuroblastoma cell lines, provides a useful model system for opioid receptors (notably of the δ-subclass) and dependence at the cellular level.[27-30]

An approach of future promise to the development of nonopioid analgesics is investigation of materials that interfere with Substance P(SP).[31] This undecapeptide (H-Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-NH_2) is highly concentrated in the superficial laminae of the dorsal horn of the spinal cord and also occurs in the gray matter around lamina V, that is, in regions associated with the transmission of pain signals.[16] There is evidence that SP is the neurotransmitter for nociceptive primary afferents; hence its depletion or blockade of its release or the receptor at which it acts would be expected to result in analgesia. Thus, administration of capsaicin, the pungent principle of red pepper, causes long-lasting depletion of SP together with analgesia.[32] So far little progress has been made in the design of antagonists of SP, although some SP analogs with D-amino acid replacements block scratching and biting behavior (taken as indications of pain).[33]

The literature of topics relating to pain and its alleviation is now very great and the selective bibliography presented here refers chiefly to the chemical and pharmacological aspects of analgesics and their antagonists. Martindale[34] remains the single most useful source book for information on analgesics and analgesic antagonists in clinical use (see also a recent textbook).[51] The 1965 monograph edited by deStevens[35] has served for many years as a general text on the chemisty and pharmacology of analgesics. It was supplemented in 1982 by the book *Central Analgetics*, edited by Lednicer,[36] which comprises reviews on pain pathways, pharmacology (especially valuable), peptides, and synthesis-SAR analyses. Attention is drawn to specialist texts describing the morphinan-benzomorphan, diphenylpropylamine, and peptide groups in relevant chapters of this book. Many accounts of analgesics and their antagonists have appeared in the review publications *Progress in Medicinal Chemistry*,[37] *Progress in Drug Research*,[38] and *Advances in Drug Research*,[39] while *Annual Reports in Medicinal Chemistry* (published since 1965)[40] provides a valuable means of keeping up to date with current developments. Relevant articles also appear periodically in the *Annual Review of Pharmacology*.[41] Useful surveys of chemical and SAR aspects are included in medicinal chemistry texts such as that of Burger,[42] while most pharmacology texts (e.g., that of Goodman and Gilman[14]) cover the animal and clinical pharmacology of analgesics. The Dekker monographs on medicinal research serve the same purposes.[43] A

collection of data on the properties of isomeric groups of opioids is included in a handbook of drug stereoisomers.[53] The Drug Synthesis series published by Wiley includes useful preparative information, often only accessible in patent form.[44] Clouet[26] has edited a book on the biochemical pharmacology of opioids. Raven Press specialises in reporting scientific meetings devoted to opioids, and recent volumes deal with narcotic antagonists[45] and factors affecting the action of narcotics.[46] Probably the most prestigious annual meeting on opioids is that of the International Narcotics Research Conference (formerly the Narcotics Research Club), whose 1982 and 1983 proceedings have been published in separate issues of *Life Sciences*.[47] *Nature*[48] and the *Pharmaceutical Journal*[49] also publish accounts of related meetings. Reference to many other publications, additional to original research reports, are made throughout this book.

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2

4,5-Epoxymorphinans

2.1. INTRODUCTION

The latex obtained by incision of the unripe seed capsule of the poppy, *Papaver somniferum*, and known as opium is the source of several pharmacologically important alkaloids. Dioskurides, in about A.D. 77, referred to both the latex (*opos*) and a total plant extract (*mekonion*) and to the use of oral and inhaled (pipe-smoked) opium to induce a state of euphoria and sedation. Since before the Christian era the therapeutic properties of opium were evident, with the first written reference to poppy juice being by Theophrastus in the third century B.C.

In 1803 the German pharmacist Seturner achieved the isolation of morphine as one of the active ingredients of opium. He named the compound after Morpheus, Ovid's god of dreams, the son of sleep. Among the other alkaloids of opium are codeine, isolated in 1832, thebaine, narceine, narcotine, and papaverine. From the isolation of pure morphine to the elucidation of its structure by first Gulland and Robinson[1,2] and later Schöpf[3] took another 120 years. A total synthesis by Gates and Tschudi[4,5] confirmed the structure in the early 1950s.

Morphine alkaloids are a subgroup of isoquinoline alkaloids and are derived biogenetically from laudanosine bases by oxidative phenolic coupling.[6,7] Alkaloids of the opposite enantiomorphic group occur in several Japanese *Sinomenium* and *Stephania* species, the most important compounds being sinomenine, hasubanonine, metaphenin, and protometaphenine.

The object of this chapter is to summarize the chemistry of morphine and those pharmacologically interesting related compounds with an intact 4,5-epoxide bridge. In addition, comment will be made on biological activities and structure-activity relationships (SARs) wherever appropriate.

For more extensive accounts of the earlier chemistry of the opium alkaloids see references 8–11, 472, and 473.

(−)-Morphine, the naturally occurring enantiomorph, may be described as a 4,5-epoxymorphinan with the full systematic name 7,8-didehydro-4,5-epoxy-17-methyl-(5α,6α)-morphinan-3,6-diol. Some of the structural

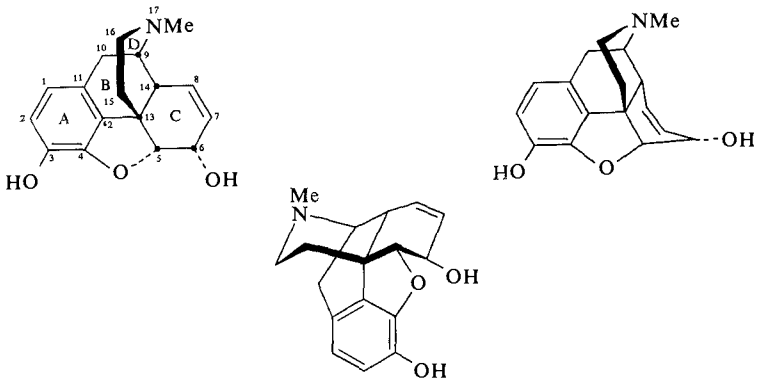


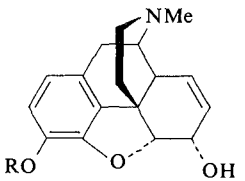
Fig. 2.1. Structural representations of morphine.

representations of morphine found in the more recent literature are illustrated in Fig. 2.1.

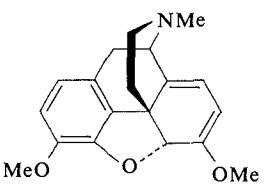
The morphine molecule possesses five asymmetric centers at carbons 5(*R*), 6(*S*), 9(*R*), 13(*S*), and 14(*R*), and it is this geometry that affords the familiar opioid pharmacological actions. The C-9 to C-13 ethanamino bridge restricts the number of possible optical isomers to 16 (i.e., eight racemic pairs).

(+)-Morphine, with the opposite geometry at each of the five chiral centers, does not elicit opioid pharmacological responses.

2.2. PHARMACOLOGICAL AND CLINICAL CONSIDERATIONS



1 R = H = Morphine
2 R = Me = Codeine



3 Thebaine

Morphine (**1**) and related compounds exert their major pharmacological actions on the central nervous system (CNS) and gastrointestinal tract (GIT). Their most important clinical property is the ability to induce analgesia, that is, to suppress pain, which they do without the patient necessarily losing consciousness. In addition, they induce drowsiness; depress respiration, which may be life-threatening; alter mood, often causing euphoria and physical

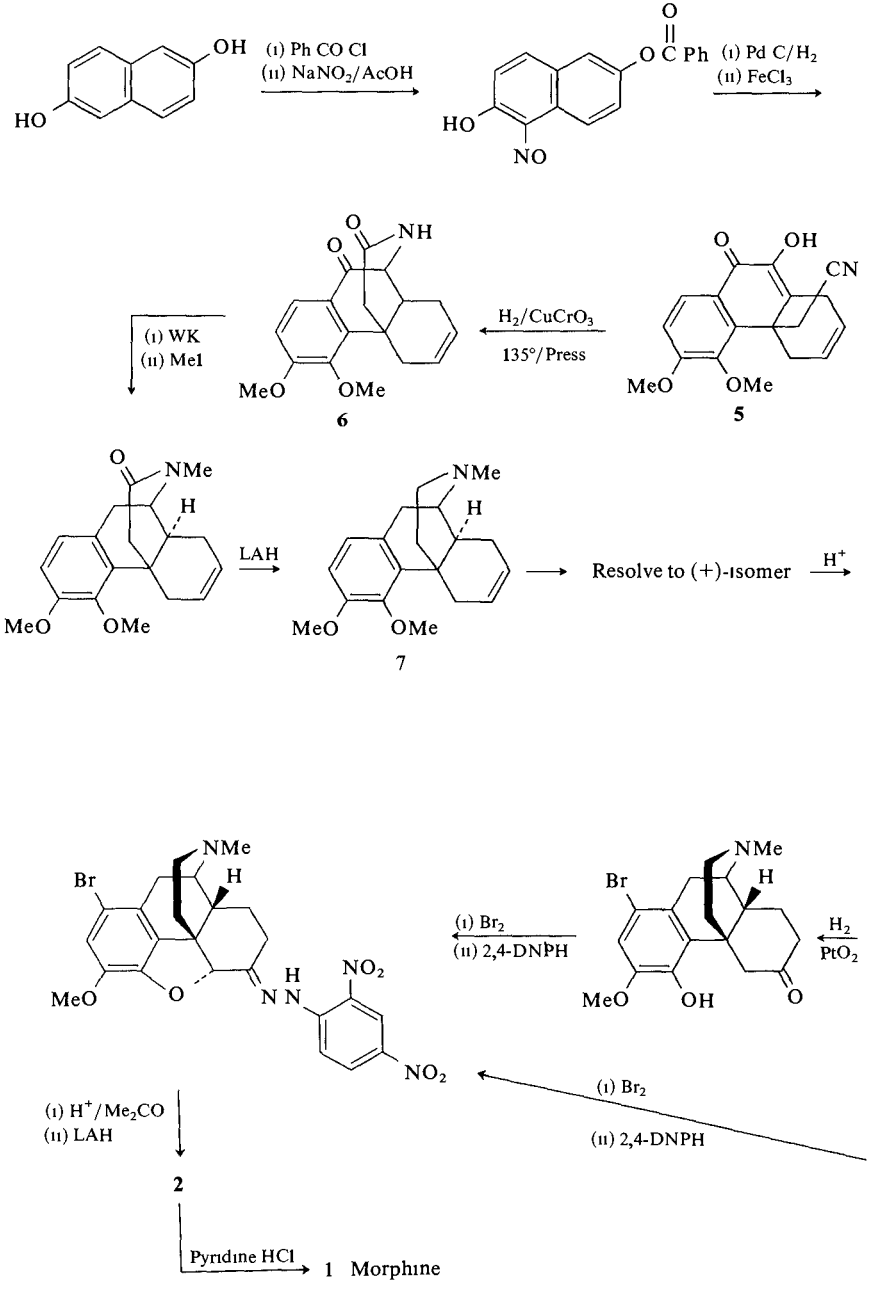
dependence; reduce GIT motility; and cause nausea and vomiting. These properties have been fully reviewed.[12-18]

The great clinical value of morphine is its ability to relieve severe pain. Although pain is highly subjective, the efficacy of morphine not only is apparent in clinical situations but may be demonstrated in subjects under experimental conditions. Morphine exerts a direct action on respiratory centers by reducing their responsiveness to carbon dioxide tension, and the degree of respiratory depression is dose related. Deaths from morphine overdose are almost always the result of respiratory collapse. The other major disadvantage of morphine is its abuse liability, leading to physical dependence; associated with this is the phenomenon of tolerance, where increasing amounts of the drug are required to maintain the desired pharmacological response. Dependence and tolerance are complex pharmacological and clinical subjects, well beyond the scope of this book but reviewed elsewhere.[15,18]

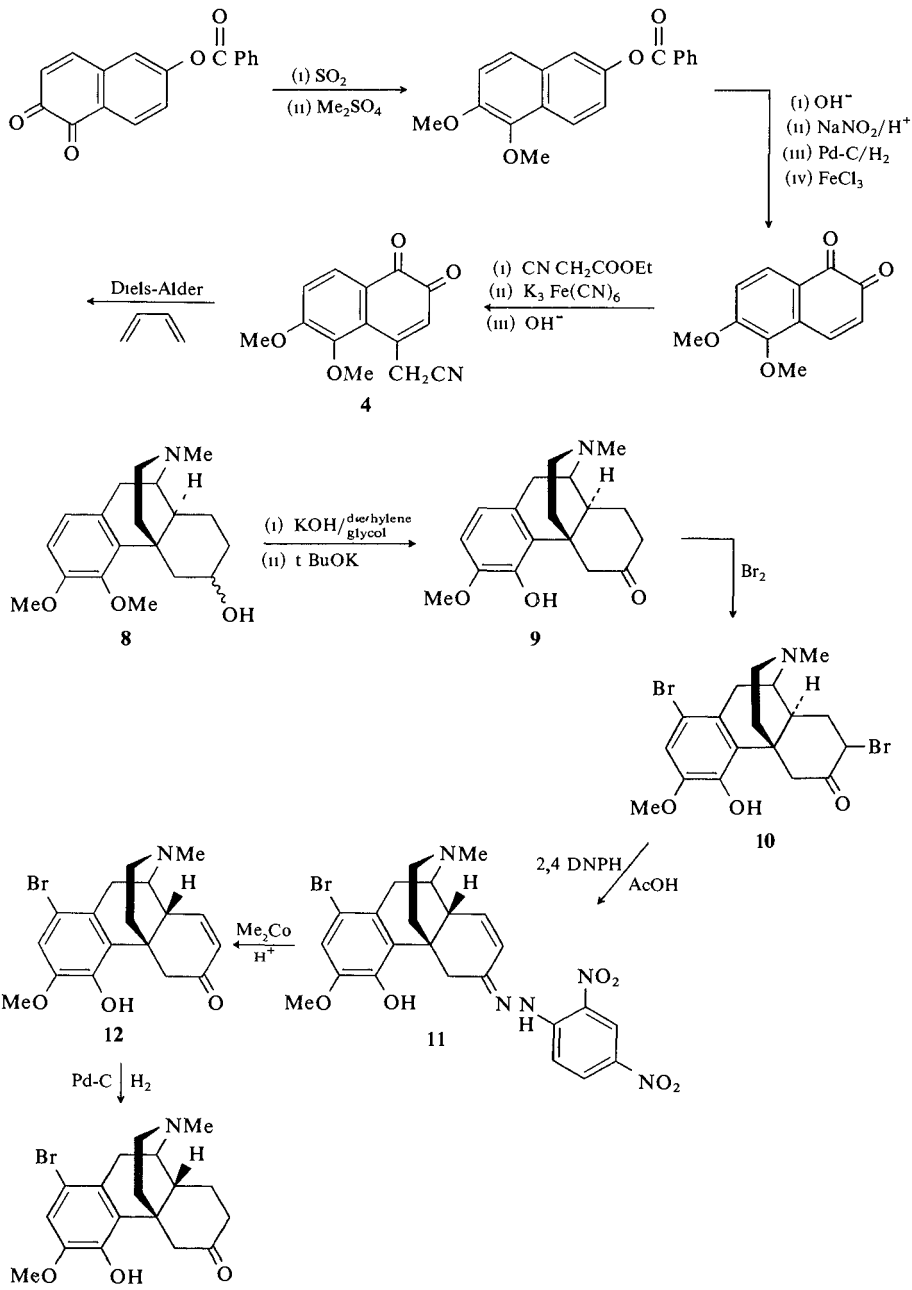
Masking of the phenolic 3-OH of morphine by methyl ether formation gives the naturally occurring analgesic and antitussive agent, codeine (**2**). In the MHP test, codeine has about one seventh the activity of morphine as an antinociceptive agent, and this is reflected in the human parenteral dose, where 60–120 mg of codeine is equivalent to 10 mg of morphine. Codeine is used clinically in the treatment of mild to moderate pain, but it also has extensive application as an antitussive agent. A significant difference between the activities of morphine and codeine is that the latter retains much of its activity after oral administration relative to its parenteral effect. Morphine, in contrast, loses much of its effect due to a considerable first-pass liver metabolism. Codeine, in addition, enjoys the benefit of low physical dependence capacity.

Acetylation of morphine was one of the earliest attempts of chemical modification aimed at suppressing its undesirable actions. Diacetylmorphine, or diamorphine or heroin, although initially hailed as a "nonaddictive" morphine substitute, soon disappointed its protagonists. Heroin has about twice the analgesic efficacy of morphine in both rodents (MHP) and humans. *In vivo*, heroin is metabolized rapidly in humans,[19-21] to 6-monoacetylmorphine, which has about four times the analgesic potency of morphine and which is itself hydrolyzed to morphine. The analgesic actions of heroin appear to be a combination of the effects of 6-monoacetylmorphine and morphine. Heroin is administered parenterally and has a very high physical dependence capacity. Although available for clinical use in the United Kingdom, it may not be manufactured in or imported into the United States.

Much of the chemical modification work described in this book has been stimulated by the desire to produce analgesics that have a pain-killing capacity greater than that of morphine while reducing considerably or preferably eliminating its major adverse effects.


OH
HO
(i) Ph CO Cl
(ii) NaNO2/AcOH
O
O C Ph
HO
NO
(i) Pd C/H2
(ii) FeCl3
O
NH
O
MeO
OMe
6
H2/CuCrO3
135°/Press
O
OH
CN
MeO
OMe
5
(i) WK
(ii) MeI
O
NMe
H
MeO
OMe
LAH
NMe
H
MeO
OMe
7
Resolve to (+)-isomer
H+
NMe
H
Br
MeO
O
H
N N
NO2
NO2
(i) Br2
(ii) 2,4-DNPH
NMe
H
Br
MeO
OH
O
H2
PtO2
(i) Br2
(ii) 2,4-DNPH
(i) H+/Me2CO
(ii) LAH
2
Pyridine HCl
1 Morphine

Scheme 2.1


O C Ph
(i) SO_2
(ii) Me_2SO_4
MeO
OMe
(i) OH^-
(ii) $NaNO_2/H^+$
(iii) Pd-C/H_2
(iv) $FeCl_3$
Diels-Alder
(i) $CN CH_2COOEt$
(ii) $K_3 Fe(CN)_6$
(iii) OH^-
CH_2CN
4
NMe
H
OH
8
(i) KOH/diethylene glycol
(ii) t BuOK
9
Br_2
Br
10
2,4 DNPH
AcOH
Me_2Co
H^+
11
12
NO_2
N
Pd-C
H_2

2.3. SYNTHESIS

Kametani[23] in 1977 reviewed the total synthesis of isoquinoline alkaloids, including alkaloids of the morphine series.

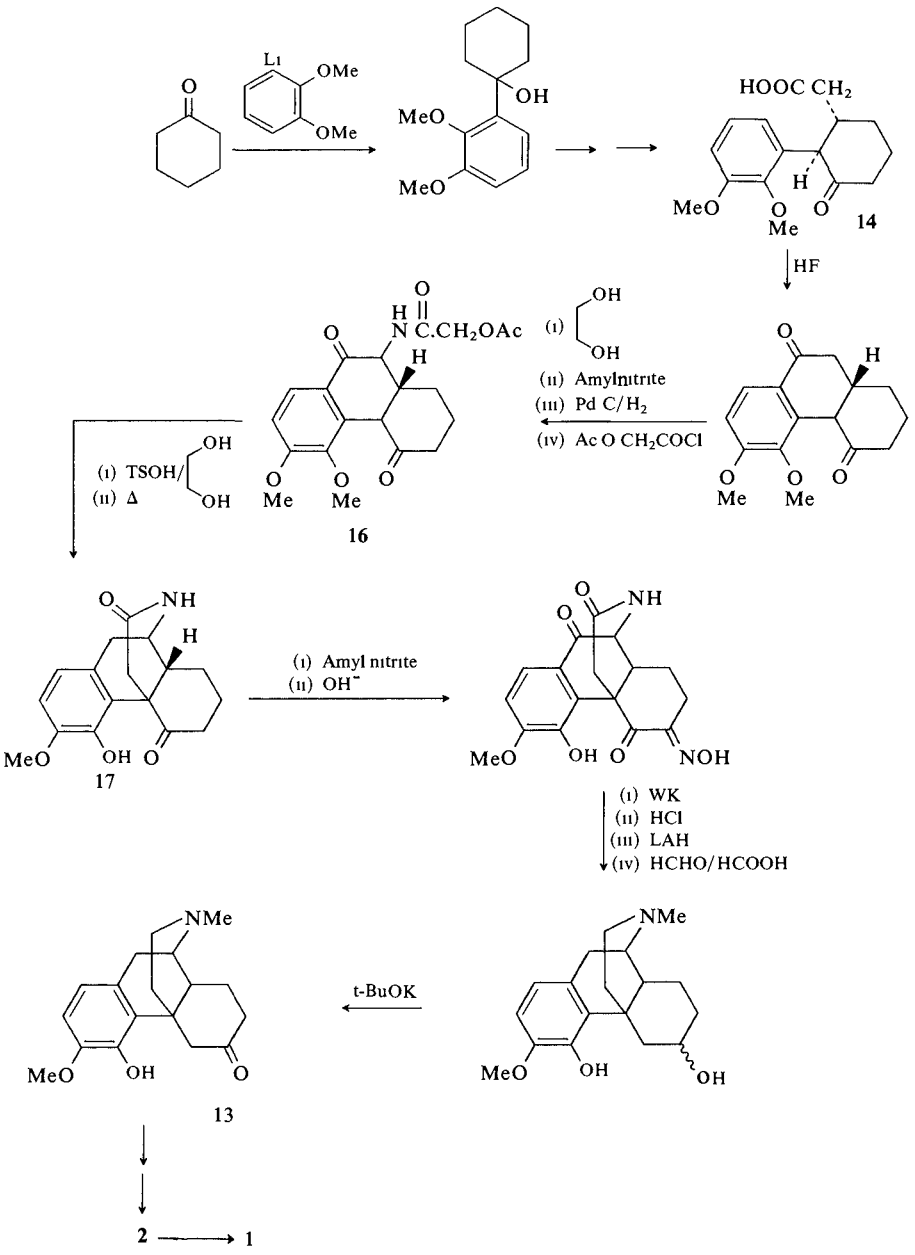
The first complete synthesis of (−)-morphine was achieved by Gates and his co-workers[4,5] in the early 1950s, although prior to that, morphinan and isomorphinan structures had been prepared.[24,25] Gates required the 4-cyanomethyl-1,2-naphthoquinone, **4** (Scheme 2.1), which is capable of undergoing Diels–Alder addition of butadiene to the partially saturated phenanthrene, **5**. On copper chromite catalyzed reduction, an unexpected cyclization occurred to the morphinan **6**, the nature of which was established from the series without methoxyl groups, with the aid of the then recently introduced ir spectroscopy.[26] The reaction sequence shown in Scheme 2.1 gave the isomorphinan, **7** which was resolved to afford the (+)-base, with the required stereochemistry at C-9 and C-13, and then hydrated with dilute sulfuric acid to the isomorphinan-6-ol, **8**, together with the 7-ol isomer. Oxidation to β-dihydrothebainone, **9** followed. Bromination of **9** gave the dibromo derivative, which on conversion to the corresponding 2,4-dinitrophenylhydrazone lost HBr with the rapid inversion of the C-14 center to give, after 2,4-DNP cleavage with acetone/HCl, 1-bromothebainone (**12**). By the reduction, bromination, and 2,4-DNP sequence illustrated, (−)-codeine (**2**) and (−)-morphine (**1**) resulted.

Elad and Ginsburg[27,28] approached the synthesis from the arylcyclohexanone, **14**, according to Scheme 2.2. The key cyclization, **16** → **17** occurred during ketalization, when in addition the 4-OMe group was demethylated. (±)-Dihydrothebainone (**13**) resulted from the pathway shown and this was resolved to the (−)-antipode with (+)-tartaric acid. This constitutes a synthesis of codeine and morphine following the final stages of Scheme 2.1.

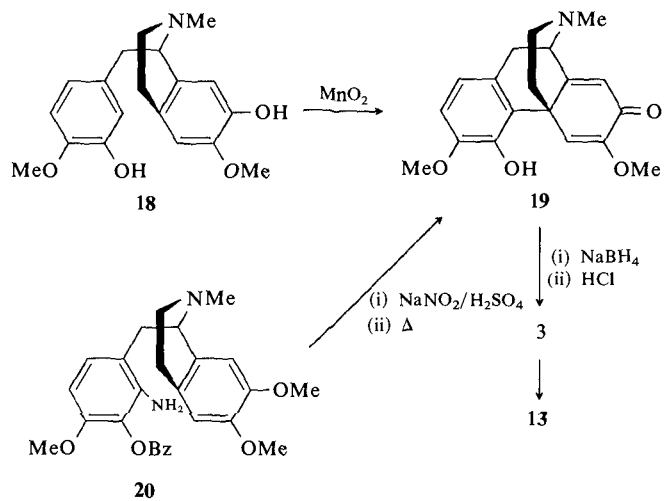
Barton[29] devised a biomimetic route to thebaine (**3**), dihydrothebainone (**13**), and thus morphine following observations of Battersby.[30,31] The alkaloid salutaridine (**19**) was derived from (+)-reticuline (**18**) by a low-yielding (0.03%) regioselective para-ortho phenolic coupling reaction according to Scheme 2.3. By the use of thallium tristrifluoracetate, Schwartz[32] improved yields to up to 23%.

The Pschorr reaction[33] has been useful in securing morphinandienones, many of which are difficult to obtain by phenolic oxidation. The *R*-(−)-2′-aminobenzylisoquinoline (**20**) was diazotized and the diazonium salt noncatalytically decomposed with heat to salutaridine (**19**) (Scheme 2.3).

A more recent attempt[34] to improve yields at the phenolic oxidation stage of the Barton synthesis rested on the argument that species such as hypervalent iodine[35] offered milder reaction conditions because the iodine (III ⇄ I) redox is closer to the potential required for the reticuline–salutaridine transformation. A range of aryliodosobistrifluoracetates was used, with the


Li
OMe
OMe
O
MeO
MeO
OH
HOOC CH2
H
MeO
O
Me
O
14
HF
O
H
O
N C.CH2OAc
H
O
O
Me
Me
O
16
(i) OH
OH
(ii) Amylnitrite
(iii) Pd C/H2
(iv) Ac O CH2COCl
O
H
O
O
Me
Me
(i) TSOH/ OH
(ii) Δ OH
O
NH
H
MeO
OH
O
17
(i) Amyl nitrite
(ii) OH⁻
O
NH
O
MeO
OH
O
NOH
(i) WK
(ii) HCl
(iii) LAH
(iv) HCHO/HCOOH
NMe
MeO
OH
O
13
t-BuOK
NMe
MeO
OH
OH
2
1

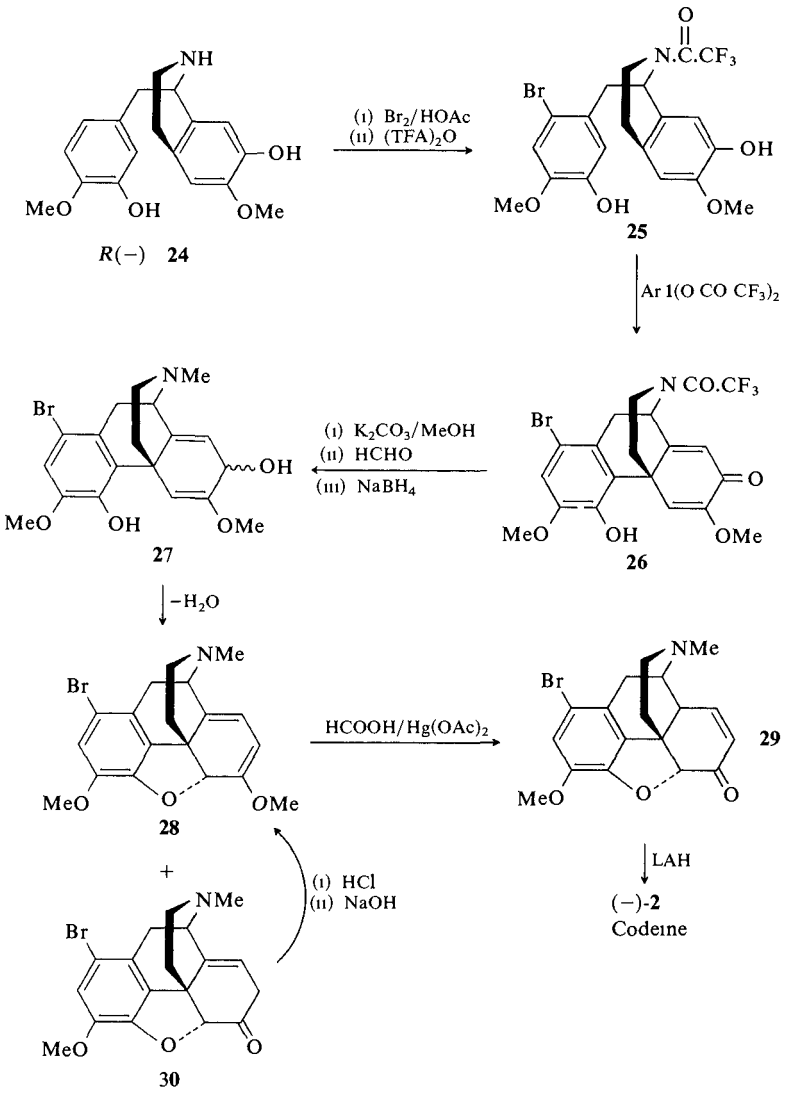
Scheme 2.2



Scheme 2.3

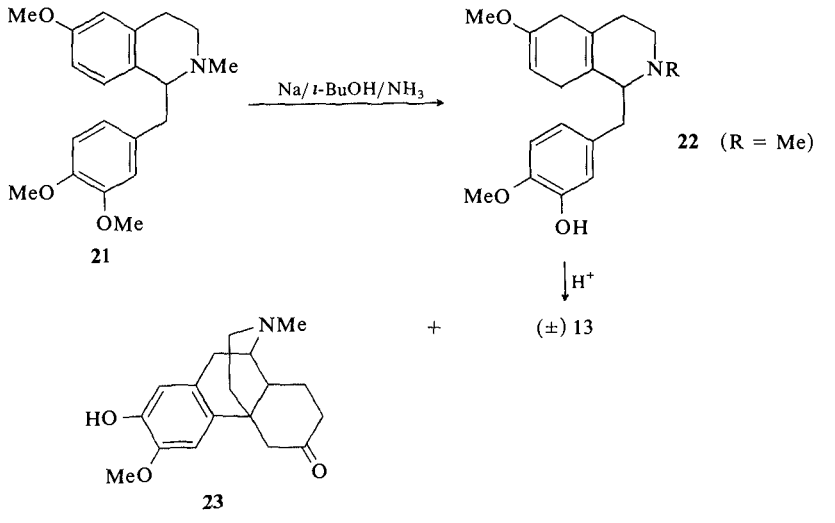
unsubstituted aryl affording the highest yield (21%). By this means a biomimetic synthesis of (−)-codeine from *R*-(−)-norrecticuline (**24**) was completed according to Scheme 2.4. Rice[36] and Maat[37] had previously demonstrated that blocking the 6-position of the benzyl group of compounds such as **24** directed cyclization to the required morphinan oxygen substitution pattern (see p. 32). Thus, bromination and *N*-protection with trifluoracetic anhydride gave **25**. *N*-Carbethoxy protection was also attempted, but it impaired subsequent reaction steps. Phenolic coupling in **25** occurred with various aryliodosobistrifluoracetates to **26**, and subsequent standard procedures gave **27**. The dineopentyl acetal of DMF caused dehydration[38] of **27** to **28**, and hydrolysis of the latter gave a mixture of enones (**29** and **30**). The former of these, 1-bromocodeinone, was reductively debrominated to (−)-codeine.

Although early attempts to synthesize morphine by way of the Grewe morphinan pathway (Scheme 3.1, p. 106) failed, (±)-dihydrothebainone (**13**) has been prepared[39] via the benzyltetrahydroisoquinoline (**21**). Birch reduction of **21** resulted in 3-OMe ether cleavage as well as aromatic ring reduction to **22**. A mixture of (±)-**13** as well as the isomeric **23** was given by cyclization and hydrolysis of the enol ether in boiling 10% HCl (Scheme 2.5). Efforts to attain a more expeditious and practical route to morphine and related alkaloids led Rice[36,40] to modify the Grewe electrophilic cyclization of 1-benzylhexahydroisoquinoline by introducing an easily removable substituent into the benzyl ring 6-position, thus directing ring closure to position 2 (Scheme 2.6).



Scheme 2 4

Previously,[37] the introduction of a 6-Me substituent had shown that the 3,4-dioxygenated morphinan was the exclusive product, rather than the yield being dominated by the 2,3-isomer as in the 6-unsubstituted benzyl derivatives. The ketal of **22** (R=CHO) was brominated with *N*-bromoacetamide (NBA)

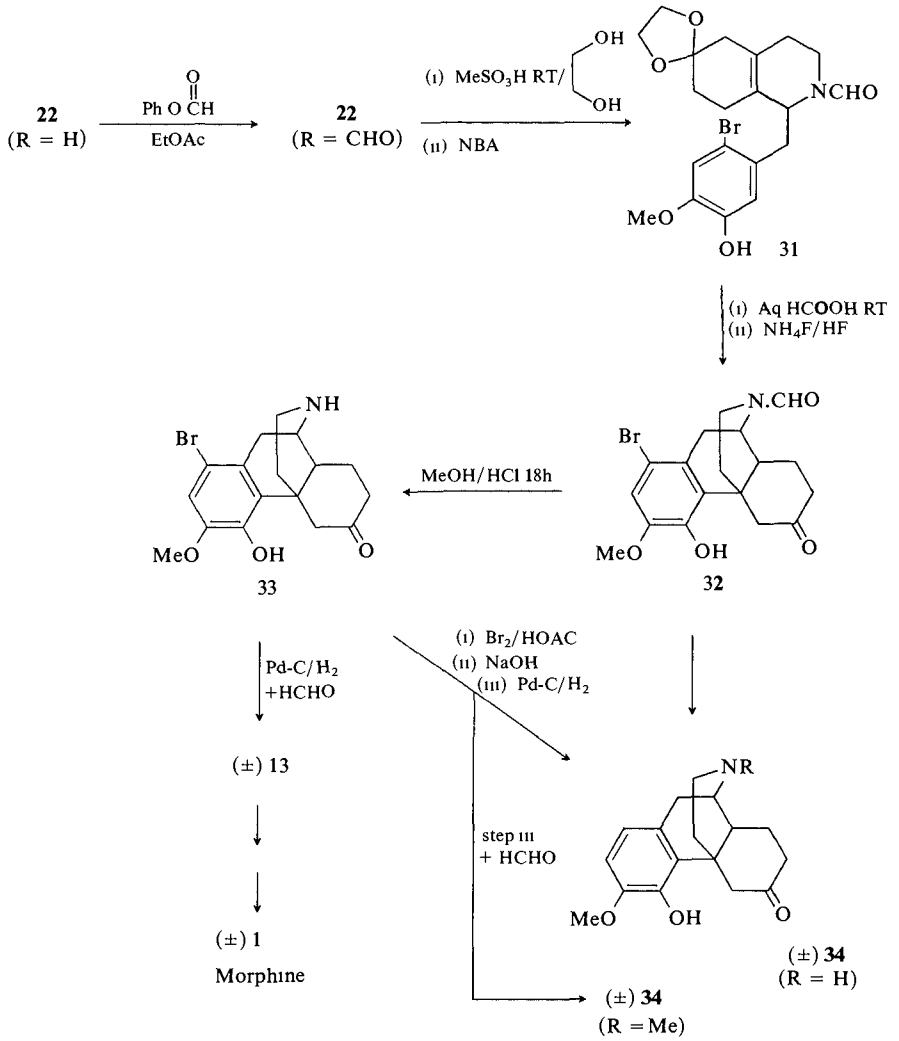


Scheme 2.5

to **31**, which cyclized (60%) under modified Grewe conditions to the racemic bromomorphinan-6-one, **32**. Hydrolysis of **32** gave the key intermediate (±)-1-bromonordihydrothebainone (**33**), which was converted to (±)-dihydrothebainone in 37% overall yield. Alternatively, bromination and base treatment effected cyclization of the 4,5-epoxide ring, and reductive removal of ring bromine, in the absence of formaldehyde gave (±)-nordihydrocodeinone (**34**, R = H) (30% overall) or with formaldehyde gave (±)-dihydrocodeinone in 29% overall yield. The former pathway constitutes the first direct oxygen bridge closure to a *N*-nor derivative and as such provides a direct route to antagonists and other *N*-substituted congeners. Resolution of the 1-benzyltetrahydroisoquinoline precursor of **22** to the R(+) species afforded (−)-enantiomers of **1** (R = H) and **34** (R = Me).

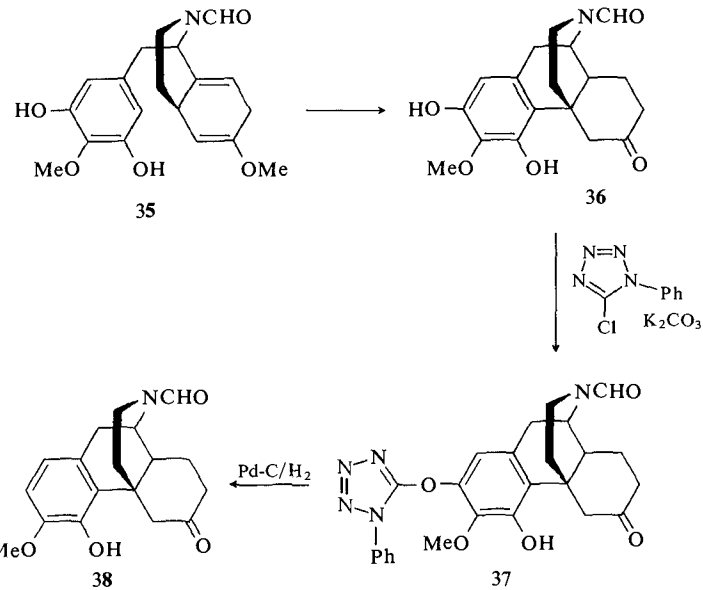
Another means[41-45] of avoiding loss of overall yield due to the formation of isomeric products at the Grewe cyclization stage employed a symmetrically substituted 1-benzyl moiety for the Birch reduction product, **35** at the precyclization step. Cyclization then gave a single product (**36**) but the 2-OH group had to be removed. This was effected selectively *via* hydrogenolysis of the 1-phenyltetrazol-5-yl ether (**37**)[46,47] to **38**, which in turn may be converted by methods described previously to (−)-codeine and (−)-morphine. Resolution is best performed at the 1-benzyltetrahydroisoquinoline stage (Scheme 2.7).

A novel route to arylmorphans and morphine-related alkaloids has been elaborated by Evans and Mitch.[48,49] They discovered that 1-methyl-4-phenyl-

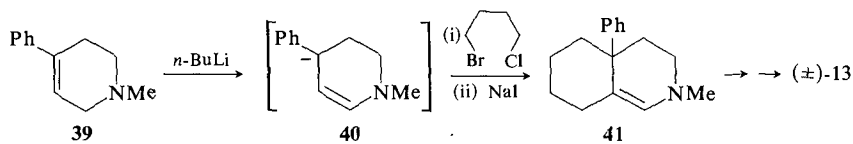


Scheme 2 6

1,2,3,6-tetrahydropyridine (**39**) when treated with *n*-butyl lithium formed the intermediate metalated enamine, **40**, which on treatment with, for example, 1-bromo-4-chlorbutane formed a 4,4-disubstituted tetrahydropyridine cyclizable to **41**. Scheme 3.6a (p. 113) illustrates the development of the synthesis to (±)-dihydrothebainone and thus to (±)-morphine (**1**).



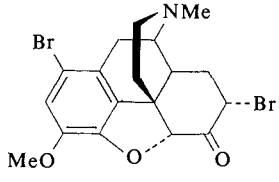
Scheme 2.7



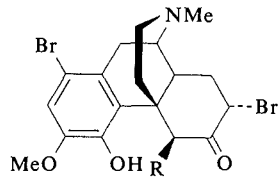
The closure of the 4,5-epoxide bridge during synthesis of compounds with structures related to morphine has been the subject of several investigations. Schöpf[50,51] was the first to achieve the closure of dihydrothebainone (**13**) in high yield, by dibromination followed by debromination effected with alkali. When the corresponding isomorphinan-6-one (i.e., B/C *trans*-dihydrothebainone) was treated in a similar manner, cyclization was less efficient.[52] This pathway was employed during early syntheses of both metopon[53] (**74**, Scheme 2.12) (p. 36) and morphine.[5]

For many years it was assumed that bromination occurred at C-5 as well as at C-1, and this assumption appeared to be endorsed by the ease of cyclization of B/C *cis* compounds relative to their B/C *trans* isomers. In the former the alicyclic bromine was ideally located for displacement by the phenoxide anion. However, Bentley[54] had suggested, without experimental evidence, that C-7 appeared to be the more likely site of C-ring bromination. Once isolation of B/C *cis* and B/C *trans*-dihydrothebainone and dihy-

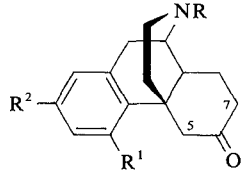
drocodeinone had been achieved[55] it became clear, from a consideration of their ir carbonyl absorptions (1725 cm^{-1}) that the C-ring bromine must occupy an equatorial position. As C-5 could not accommodate such an orientation on steric grounds, the bromine appeared to be more likely to have been inserted at C-7. Gates and Shepherd[55] offered additional evidence in support of this, in that tribromination of B/C *cis*-dihydrothebainone gave not the expected 1,5,7- or 1,7,7-tribromo derivative but 1,7-dibromocodeinone (**42**). During a study[56] of the conversion of dihydrothebainone to codeine, including mechanistic considerations of oxide bridge closure, a ^1H nmr examination of brominated dihydrothebainones failed to reveal the presence of a C-7 hydrogen (δ4-7) in 1,7β-dibromodihydrothebainone. Maat *et al.*[57] showed that bromination of (−)-dihydrothebainone (**13**) gave successively 1-bromo, 1,7α-dibromo- (**43**), and 1,5β,7α-tribromodihydrothebainone (44). Both ^1H- and ^{13}C-nmr studies confirmed their findings. Similarly,[58] monobromination of (−)-4-hydroxy-*N*-methylmorphinan-6-one (**45**) occurred in the aromatic C-1 position, and this also appeared to be the case for the corresponding 2,4-dihydroxy-*N*-formyl- derivative. However, the 4-acetoxy (**46**) and 2,4-diacetoxy compounds monobrominate alpha to the 6-ketone in either the 5- or 7-position with the ^1H-nmr of the product from **46**, suggesting a mixture of the two. Treatment of this mixture with K_2CO_3/MeOH at room temperature facilitated closure of the 4,5-epoxide bridge without the encumbrance of aromatic bromine. Reaction of thebainone-A enol methyl ether (47a) with



42

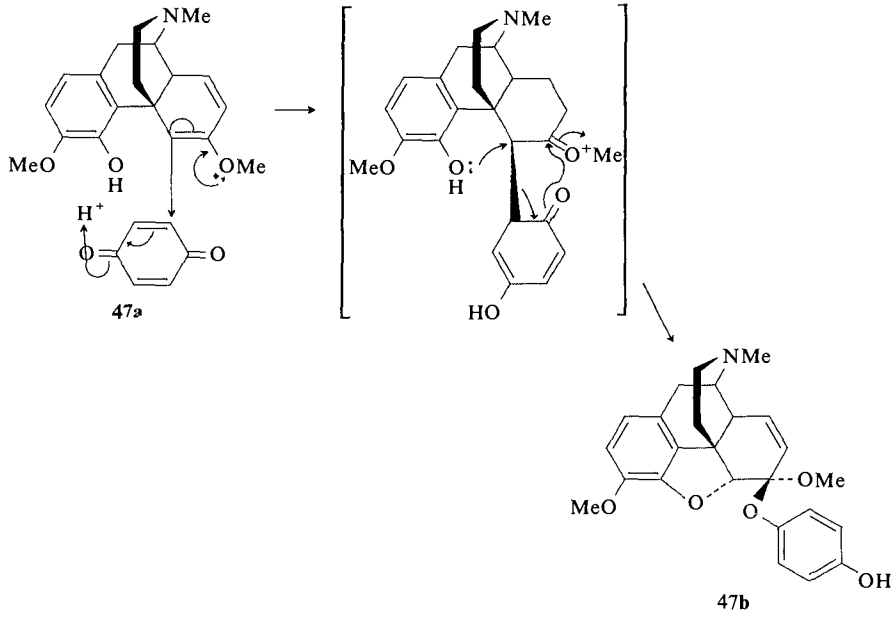


43 R = H
44 R = Br



	R	R^1	R^2
45	Me	OH	H
46	CHO	OAc	H
47	CHO	OAc	OAc

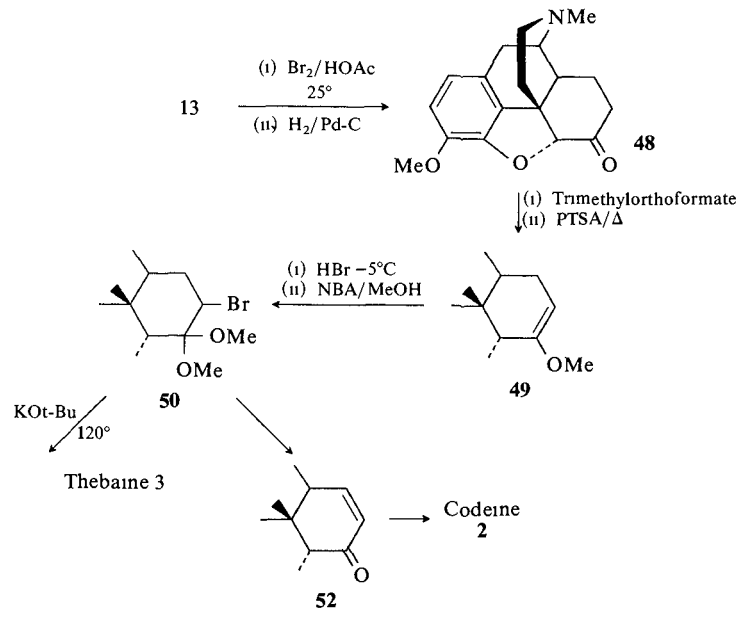
benzoquinone does not proceed as a Diels–Alder addition (cf. thebaine); instead an interesting oxygen bridge closure occurs to the 4,5-epoxymorphinan, 47b.[257]



As well as its availability as a byproduct of thebaine conversions, there are now several synthetic routes to dihydrothebainone (**13**). It is therefore a valuable intermediate for the preparation of codeine, and a high-yielding conversion has been developed.[56] The closure of the oxygen bridge was accomplished at step 1 and the 1-bromo group removed by hydrogenolysis to give dihydrocodeinone (**48**) (82%). Enol ether formation as illustrated in Scheme 2.8 was followed by the addition of methyl hypobromite, which brominates selectively at C-7 to give **50**. Elimination of HBr by strong base at 60° gave codeinone (**52**) convertible to codeine by the method of Gates.[59] Thebaine resulted from **50** with potassium *t*-butoxide at the higher temperature of 120°. Rapoport's group[60] had reported earlier the synthesis of thebaine and northebaine from codeinone dimethylketal and norcodeine dimethylketal, respectively.

2.4. INTERCONVERSIONS IN THE MORPHINE SERIES

The opium poppy *Papaver somniferum* contains two useful analgesic alkaloids, morphine and codeine, as well as thebaine, which not only may be



Scheme 2 8

elaborated to the "oripavine" range of analgesics and antagonists but is also capable of transformation into codeine and morphine. Clearly, the value of codeine and morphine as analgesics and the large demand for them requires a steady source of supply that, preferably, does not rely on supplies of opium. *Papaver bracteatum*[61-64] produces thebaine, but not morphine, as its major alkaloid in roots and dried latex and thus is a potential source of codeine. In addition, perhaps, the Rice[36] synthesis of morphine will offer a practical manufacturing process to therapeutic analgesics. One of the major objectives of avoiding opium production is the reduction of illicit sources[65] and ultimately the curtailment of the cultivation of *P. somniferum*. Thus interconversions between morphine, codeine, and thebaine are highly desirable for very practical reasons, not the least of which is the low yield of codeine from opium. Some approaches to these interconversions have been reviewed.[66,67]

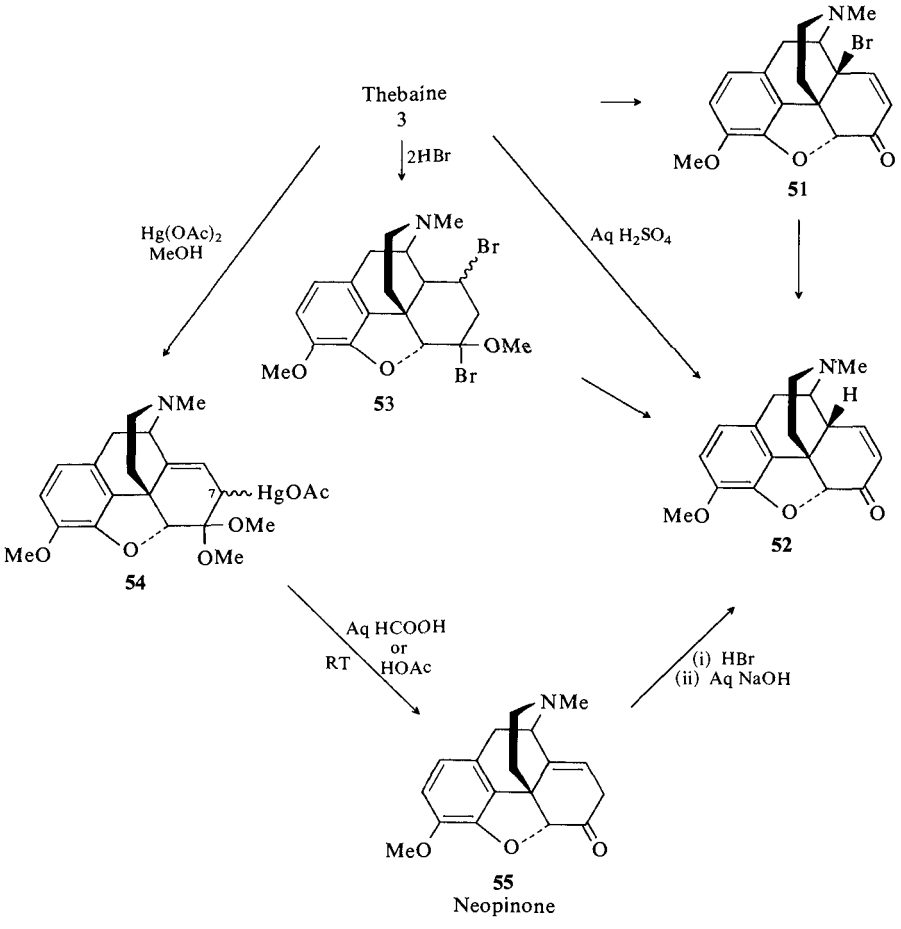
One of the earliest attempts[68,69] at developing a nondependence-inducing morphine derivative resulted in the preparation of *heroin* (3,6-diacetylmorphine or diamorphine) by acetylation of morphine. Reports of its reduced respiratory depression and dependence liability were soon shown to be misfounded, but its superior analgesic effects in animals and humans (twice morphine) are demonstrable. Pharmacological examination[70] of acyl derivatives of morphine showed that heroin and its higher and lower acyl homologs

have similar rodent analgesic potencies and have high primate physical dependence capacities.

The transformation of codeine to morphine requires cleavage of an aromatic 3-OMe group to give the phenol counterpart. Over the years this has proved troublesome because of the need for severe reaction conditions, for example, hot, strong acids or pyridine hydrochloride at 220°.[5,71,72] Problems of work-up and low yields (15–34%) were also encountered. An improvement in the yield (61%) was achieved with lithium diphenylphosphide in conversions of B/C *trans*-codeine and B/C *trans*-isocodeine to the corresponding morphines,[73,74] but this method is unlikely to have manufacturing potential. An efficient, high-yielding (90%) conversion of codeine to morphine by boron tribromide in chloroform has been developed by Rice[75] following a procedure previously applied to methyl ethers of simple phenols.[76] In another route,[77] of practical potential on a large scale, sodium propylmercaptide in DMF has given morphine yields of up to 80%.

Codeine occurs in opium in relatively small amounts (~0.3%) and yet it is in great demand as an analgesic. Much of the morphine derived from opium is therefore converted by methylation to codeine. Conventional methylation techniques have been employed, including dimethyl sulfate, diazomethane, and phenyltrimethylammonium chloride.

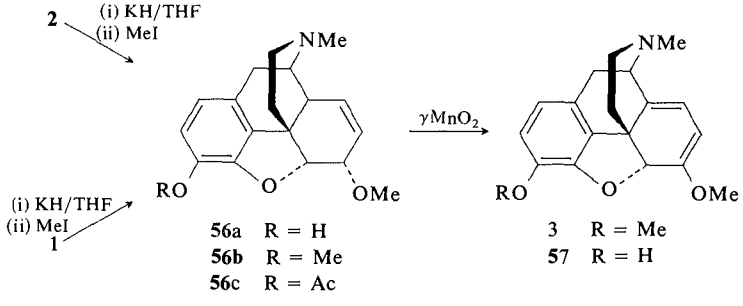
If the potential of *P. bracteatum*, in which thebaine is the major alkaloid, is to be realized, then efficient routes from thebaine to codeine are required. A French group[78] has effected such a conversion in 74% yield, but Barber and Rapoport[79] have achieved an 84% transformation in four steps. The first stage of the latter conversion is from thebaine (**3**) to codeinone (**52**). Clearly, the simplest way to achieve this would be by hydrolysis of the 6-OMe group. Unfortunately, yields from acid hydrolysis were poor (5%).[80,81] Conversion of thebaine to 14-bromocodeinone (**51**) was reported[82-84] to proceed in 85% yield and this intermediate may be reduced under a variety of conditions to **52**. The early French study[78] described the treatment of thebaine with 2 mol of anhydrous HBr (or HCl) to give 6,7-dibromotetrahydrothebaine (**53**), which was converted by base hydrolysis/dehydrobromination to **52**. Mercuric acetate, a weakly acidic electrophile known[85] to add readily to alkenes, was the Rapoport[79] approach. Treatment of thebaine with mercuric acetate in boiling methanol gave the 1,2-addition product (**54**) as a pair of 7-position epimers (2:1). The 7-C-Hg bond was readily susceptible to hydrolysis and in aqueous formic or acetic acid at ambient temperature quantitatively gave neopinone (**55**). Isomerization of the neopinone 8,14-double bond to give codeinone was effected by the addition of dry HBr or HCl followed by aqueous NaOH. Gates[59] had reported previously the near quantitative (90–95%) stereospecific $NaBH_4$ reduction of **52** to **2**, thus affording an overall thebaine to codeine conversion of 85%.



Scheme 2.9

Although thebaine from *P. bracteatum* is a potential source of codeine, it is also required as the starting material for narcotic antagonists bearing a 14-OH group (e.g., naloxone), as well as for Diels-Alder-derived agonists and antagonists (p. 69). For this reason, practical routes to thebaine from the more abundant alkaloids of *P. somniferum* have been sought. Although dihydrocodeinone has been converted[60] to thebaine (27%) in only four steps, the preparation of dihydrocodeinone (20%) from codeine is considerably more tedious.[86] Thus, this process hardly constitutes a practical synthesis. Direct methyl ether formation[87] from codeinone, which itself may be obtained in

75% yield from the silver carbonate oxidation of codeine,[88] to thebaine has also been employed giving 27% yield. Barber and Rapoport[89] converted codeine to its 6-methyl ether (**56b**) by treating the potassium salt (KH) of **2** with methyl iodide. No quaternization was reported. Oxidation of **56b** to thebaine (**3**) was best performed with active manganese dioxide (67% overall yield). Surprisingly, the dipotassium salt of morphine selectively methylates at the 6-position oxygen to give **56a**. The corresponding 3-acetate (**56c**), upon oxidation and hydrolysis, gave 73% of oripavine (**57**) a product that may be useful in obviating the difficult 3-OMe cleavage in the preparation of 6,14-*endo*-ethenotetrahydrooripavines.



2.4.1. 3-O and 6-O Morphine Derivatives

The phenolic 3-OH group of morphine may augment through hydrogen bonding the binding of the opiate aromatic pharmacophore to its receptor binding site. Masking of the 3-OH by conversion to the methylether (*codeine*) or ethylether (*ethylmorphine*) groups that are not easily hydrolyzed *in vivo* gives analgesics with about one tenth the activity of morphine. Although codeine probably exerts an analgesic action in its own right, the controversial view that it requires prior metabolic conversion to morphine has been expressed.[90-92] In the rat it has been demonstrated that *t*-butyl ethers are stable to metabolism,[93] and although the 3-*t*-butyl ethers of morphine and levorphanol had an *in vitro* receptor binding capacity similar to that of codeine, in animal tests the former was inactive (RTF) or weakly active (MW) and the latter was only marginally better.[95]

A series of C_1 to C_{12} straight-chain 3-O-alkyl analogs of morphine has been prepared[94] by conventional methods in an attempt to establish a relationship between lipophililicity and the rate of metabolism, particularly *N*-demethylation. No simple relationship was found.

3-Morpholinoethylmorphine is known as *pholcodine* and has found wide application as an antitussive agent. Other series with basic (e.g., **1**, R = $CH_2CH_2N\supset$) or urethane (e.g., **1**, R = CONHR′) 3-O- side chains have been reported.[96]

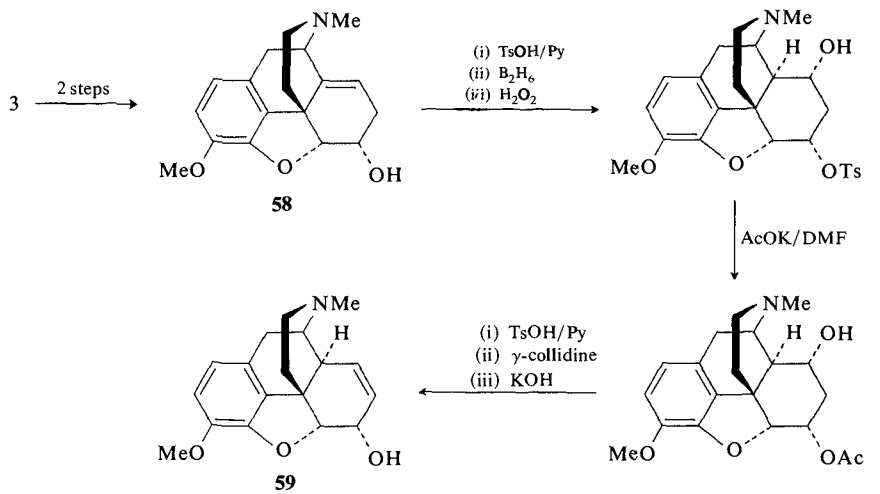
In contrast to the reduction in activity observed in the 3-ether series, the 6-sulfate ester and the 6-glucuronide each exhibit a greater analgesic potency than morphine.[97,98]

Heroin (3,6-diacetylmorphine) and its higher 3,6-diacyl homologs are similar in their analgesic activities in mice, but they also exhibit high levels of physical dependence in primates.[99] However, heroin has been found *not* to bind to opioid receptors[100]; all of its apparent binding was accounted for by 6-acetylmorphine. The corresponding 6-monoacyl derivatives behave little differently from their diester counterparts, all compounds tested being two to four times more potent than morphine. In contrast, 3-monoacetylmorphine was similar to morphine in its MHP responses ($ED_{50} \sim 1.2$ mg/kg).[101] These data support the view that rapid 3-deacetylation of heroin occurs in plasma and that 6-monoacetylmorphine is the opiate species that exerts the major analgesic contribution in the CNS.[102] A similar conclusion was drawn from the equipotencies of norheroin and 6-acetylnorheroin, although these potencies are considerably lower (ED_{50} 10.1 mg/kg) than that of heroin.[103] Other longer-chain esters in the 3- and 6-positions have been found to induce potent opiate effects in dogs.[104,105] 3-Glycyl- and 3-(O-acetyl-L-tyrosyl) esters of dihydromorphine (HCl salts) were reported[148] to be more soluble and more active than morphine, although full pharmacological data were not recorded.

2.4.2. Stereochemistry and Geometric Modifications

Many studies involving extensive chemical degradation have been performed in establishing the stereochemistry of morphine.[106-109] Unambiguous evidence came finally from an X-ray crystallographic analysis of the hydroiodide dihydrate salt,[110] and later of the hydrochloride trihydrate.[111] In the solid state, the piperidine ring exists in a chair conformation with the *N*-Me group oriented exclusively equatorially. Structural illustrations of morphine stereochemistry are given on p. 10, and as shown there, morphine has five asymmetric centers at carbons 5(*R*), 6(*S*), 9(*R*), 13(*S*), and 14(*R*). Recent ^{13}C nmr studies have suggested that the solution conformation may differ significantly from the solid-state form.[112] The simplest geometric change that may be envisaged in morphine and codeine is the formal inversion of the C-6 chiral center. The C-6 epimer of morphine is *α-isomorphine*, which has antinociceptive actions similar to morphine, but with a reduced toxicity; the codeine epimer, *isocodeine*, was somewhat less active than codeine.

Morphine has a B/C *cis* ring fusion, and formal inversion of the C-14 chiral center leads to a series of analgesically active B/C *trans*-4,5-epoxymorphinans. Japanese workers[113,114] have described a preparation of B/C *trans*-4,5-epoxymorphinans by the hydroboration of 8-dihydrodesoxycodeine, and the same group has synthesized B/C *trans*-morphine and B/C *trans*-codeine



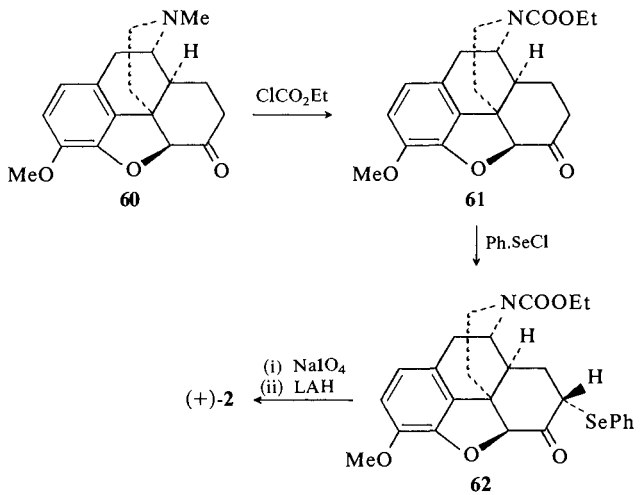
Scheme 2.10

(**59**) from isoneopine (**58**), which was readily available from thebaine.[117] The reaction sequence followed is outlined in Scheme 2.10. *O*-Demethylation of **59** to B/C *trans*-morphine was effected by the diphenylphosphide anion.[118]

Surprisingly, in view of the higher activity of B/C *trans*-morphinans over their B/C *cis*-counterparts (p. 136), B/C *trans*-morphine exhibited a lower level of antinociceptive activity than did natural morphine. The obvious difference between the two structures is the presence of the 4,5-epoxide bridge in B/C *trans*-morphine, which constrains the C-ring in a boat conformation (i.e., similar to the C-ring of morphine). In morphinans the C-ring is a chair structure.

(+)-Morphine, (+)-codeine, and (+)-heroin are all devoid of MHP (sc) antinociceptive activity,[119] although (+)-morphine did show some central actions in rats when administered intracerebrally.[120] Compounds of the (+)-morphine series are related configurationally to (−)-sinomenine (**53** of Chap. 3),[121] the absolute configuration of which has been demonstrated to be enantiomeric with that of natural (−)-morphine.

Goto[121-125] has prepared (+)-morphine and related structures from (−)-sinomenine. More recently, (+)-opioids have been required, not for their gross pharmacological actions, although these have been examined,[126] but as research tools for probing opioid receptors.[67] (+)-Codeine and (+)-morphine were synthesized[128] from (+)-dihydrocodeinone (**60**) derived in one step from sinomenine.[124] Conversion of **60** to the ethyl carbamate (**61**) facilitated the



Scheme 2.11

formation of the 7-phenylseleno- derivative (**62**) that oxidized introducing the 7,8-double bond. Subsequent reduction afforded (+)-codeine **2** (Scheme 2.11).

By exploiting the work of Weller and Rapoport[56] in the natural (−)-morphine series, the NIH group was able to improve overall yields from sinomenine to unnatural opioids considerably.[119] The availability of this unnatural series afforded a route to relatively large quantities of (+)-naloxone,[128] also valuable for receptor studies.

2.5. SUBSTITUTED 4,5-EPOXYMORPHINANS

2.5.1. Substitution on Nitrogen

One of the structural features of narcotic analgesics previously believed to be a prerequisite for analgesic actions was a tertiary N bearing a relatively small alkyl substituent.[129,130] However, normorphine[131] was shown to have a greater analgesic effect than an equivalent dose of morphine when administered to mice intracisternally, although by other routes its action was considerably weaker, and similar observations were made for *nor*-derivatives of codeine, desomorphine, and heterocodeine.[132-134]

Morphine and normorphine have similar *in vitro* potencies in GPI and MVD tests[474] and in binding assays versus naltrexone.[475] Normorphine is often the preferred standard in smooth muscle assays because it has a fast onset of action and is readily removed by washing.

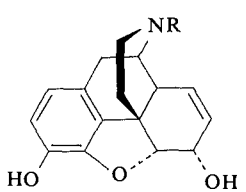
Systematic studies[133,135] of the effect of various *N*-substituents on morphine and related compounds on their pharmacological responses demonstrated that replacement of *N*-Me by *N*-Et resulted in only a slight fall in analgesic response. More hydrophobic groups such as propyl, pentyl, hexyl, and phenylethyl (phenethyl) gave an increase in activity. During this work antagonist actions were also evaluated. A *N*-phenethyl substituent was found to increase antinociceptive effects to about six times morphine and this was reflected in related series. On the other hand, analogs with substituents such as *N*-amyl and *N*-hexyl behaved in a morphinelike manner, and *N*-benzyl- and *N*-phenacyl- and *N*-cyclohexylmorphine exhibited only weak analgesic activities. Thus, many *N*-aralkyl derivatives of 4,5-epoxymorphinans have been synthesized and assayed for analgesia.[130,136]

In 1914 Pohl[137] prepared *N*-allylcodeine in an attempt to improve the analgesic properties of that drug, and he observed that instead it antagonized the sedative and respiratory depression effects of morphine. During the next ten years von Braun *et al.* made a large number of different *N*-substituted opioids.[138-140] Methods for *N*-demethylation of opioids such as morphine have been summarized and an efficient hydrazine demethylation process introduced.[141,142]

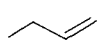
N-Allylnormorphine (*Nalorphine*) was prepared[143] in impure form[144] in 1941 for evaluation as an analgesic with low respiratory depression properties, but powerful morphine antagonist activity was observed, and subsequently this has been exploited extensively in the clinic.[144,145]

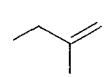
N-Propylnormorphine has also been shown to be a good antagonist, while *N*-isobutyl- and *N*-methylallyl- have not.[133,134]

The observation[146,147] that nalorphine exhibited morphinelike analgesic properties in humans, contrary to findings in rodent screens, had a profound impact on synthetic opioid research. It was believed to be the key to the design of potent analgesics that, while possessing antagonist properties, lack the undesirable actions of morphine—in particular, respiratory depression and abuse potential. Work in this area has been reviewed[145] and is described in detail in Chapter 12 of this book. Nalorphine (**63**a) is a mixed agonist-antagonist; there is evidence that it antagonizes μ-receptors and exerts its agonist effects at different species, possibly of the κ- or σ-types (Chapter 12, p. 405).



63

a R =  = Nalorphine

b R = 

c R = CPM

In its agonist actions in humans, 10–15 mg of nalorphine is roughly equivalent to 10 mg of morphine. It may prevent or reverse the actions of morphine on the GIT and CNS, including a rapid reversal of respiratory depression. Nalorphine itself, however, does give rise to some depression of respiration. In subjects physically dependent upon morphine, precipitation of the abstinence syndrome occurs. Many patients experience unpleasant excitation phenomena with nalorphine and other antagonists, including anxiety, hallucinations, nausea, difficulty in focusing, and insomnia. These are the reasons that nalorphine is not an acceptable analgesic in therapy.

N-(2-Methylallyl)normorphine (**63**b) is a rather more potent antagonist than nalorphine, and the *N*-CPM analog[149] not only is about three times as active as nalorphine as an antagonist but is three times more potent than morphine as an analgesic. It would seem that an *N*-substituent with a straight chain of three carbons affords optimum antagonist activity. Extending the chain by one carbon lowers activity, whereas a five-carbon chain or slightly more restores agonist activity.

Modifications elsewhere in the morphine molecule including the introduction of 14-OH will be considered later (p. 54 and Chapter 12).

The conformational freedom of the substituent on nitrogen has been proposed[150] as a possible factor in the control of the binding mode of an opioid to its receptor. Thus, different binding modes may dictate agonist or antagonist responses. To this end, a range of *N*-branch-chained (*N-sec*-alkyl- and *N-tert*-alkyl) analogs of morphine with a methyl group α to nitrogen have been synthesized. Computer-aided conformational analysis profiles assisted in compound selection. All *N-tert*-alkyl derivatives had very low RTF and MW analgesic potencies with correspondingly low receptor binding capacities.[151] In contrast, some *N-sec*-alkyl analogs exhibited analgesic activities and receptor binding affinities similar to that of morphine. Receptor binding, however, did not parallel activities *in vivo*. It is of interest to note that only a slight drop in *in vivo* activity occurs in **63** (R = $PhCH_2CHMe$) relative to the *N*-phenethyl counterpart, and the receptor binding affinities of the two compounds were similar. With nalorphine and *N-n*-propylnormorphine, the introduction of Me α to nitrogen caused a lowering of antagonist potency and receptor binding. The effects of α-carbon stereochemistry appeared not to be of great importance. Thus, a number of *N-sec*-alkyl analogs of morphine exhibited interesting agonist–antagonist properties, with **63** (R = *sec*-butyl(*S*)) having antinociceptive actions of the same order as morphine, an antagonist potency similar to nalorphine and a low PDC.

Kolb[152,153] has postulated that differences and anomalies seen in opioid activities for compounds with various *N*-substituents may be accounted for by long-range substituent effects on total molecular conformation. Such molecular distortion is likely to affect overall electron distribution, may influence lone-pair directionality and pK_a, and would modify opioid-receptor

fit. The proposal was based upon an assumption that the crystal and solution opioid structures are the same, a belief that has been questioned since on ^{13}C nmr evidence.[112] *N,N*-Diallyl- and *N*-methyl-*N*-allyl quaternary salts of morphine have been shown to be more antagonistic toward the peripheral effects of morphine than its CNS effects. It is possible that central actions may result from metabolic *N*-dealkylation. Similar observations have been made for quaternary salts of naloxone[154,155] and naltrexone.[155]

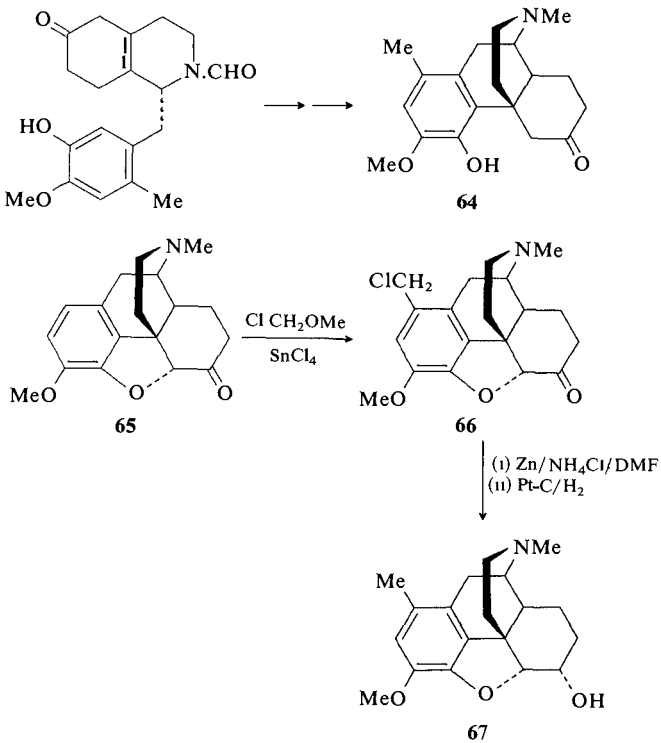
N-oxides of morphine and several morphine derivatives have been prepared by the action of isopropanol/H_2O_2 on the appropriate tertiary base.[156] At best, the *N*-oxides were weak analgesics, but dihydromorphinone *N*-oxide and codeine *N*-oxide did exhibit good antitussive properties.[157]

2.5.2. Aromatic Ring Substitution

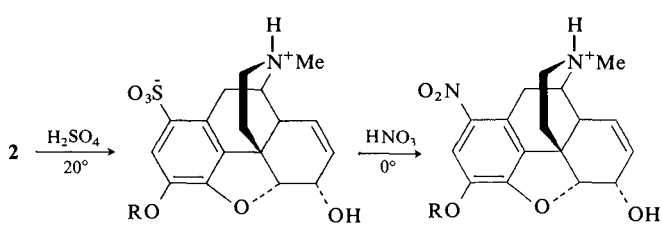
In an earlier section (p. 26) the effects of derivatizing the morphine 3-OH function were discussed. Ether formation, as in codeine, tends to reduce analgesic potency, whereas simple esters have a level of analgesic activity superior to that of morphine. As a general rule, substitution elsewhere in the aromatic ring of 4,5-epoxymorphinans results in a reduction of opioid actions. 1-Chloro- and 1-bromocodeine, for example, were weaker (0.5×) analgesics than codeine and the same applies to the 1-methylcarbonyl derivative.[158] In contrast, the more compact 1-fluorocodeine,[159] made from 1-aminocodeine via the diazonium fluoroborate, was equipotent with codeine, was bound comparably to rat brain receptor tissue, and had a similar pharmacokinetic profile. This suggested that the effects of the 1-position group were steric rather than electronic.

1-Bromo-4,5-epoxymorphinans are important intermediates in morphine syntheses (Schemes 2.1, 2.4, and 2.6), with the C-1 bromine either being required to direct cyclization in Grewe-style syntheses (Scheme 2.6) or occurring from an unwanted reaction during closure of the 4,5-epoxide bridge (Scheme 2.1). The position of electrophilic aromatic substitution of bromine in morphine has been a matter of some debate. Positions C-1 and C-2 were considered as equally likely substitution sites, but Small and Turnball[160] confirmed the identity of the product as 1-bromomorphine.

Blocking the 2-position of the benzyl moiety by Me in a Grewe synthesis, for the purposes of directing cyclization, gave rise to 1-methyldihydrothebainone (**64**),[161] a compound convertible to 1-methylmorphine. The same workers prepared (−)-1-methyldihydrocodeine (**67**) by tin(IV) chloride catalyzed Friedel-Craft substitution of (−)-dihydrocodeinone (**65**) with chloromethylmethylether in nitromethane. Reductive replacement of chlorine from **66** gave the corresponding codeinone that was hydrogenated to **67**. No biological data were reported. Earlier,[162] 1-ethylcodeine was obtained in low yield from reduction of Friedel-Craft-derived 1-acetylcodeine.

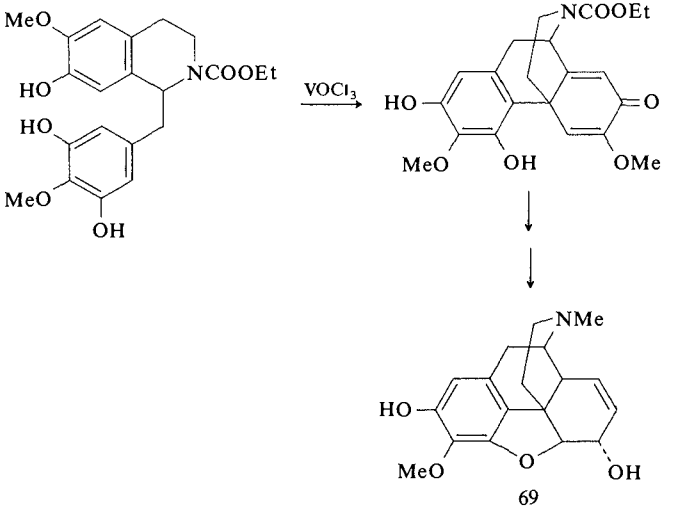


1-Nitromorphine is given by direct nitric acid nitration of morphine[163]; however, with nitric oxide, 2-nitromorphine results. These compounds may be elaborated further to amino derivatives and by diazomethane treatment to the corresponding codeines. Codeine with concentrated H_2SO_4 at ambient temperature afforded the zwitterion **68**, which in nitric acid gave 1-nitrocodeine. A similar conversion was achieved with ethylcodeine and hydrocodone.[164]



68

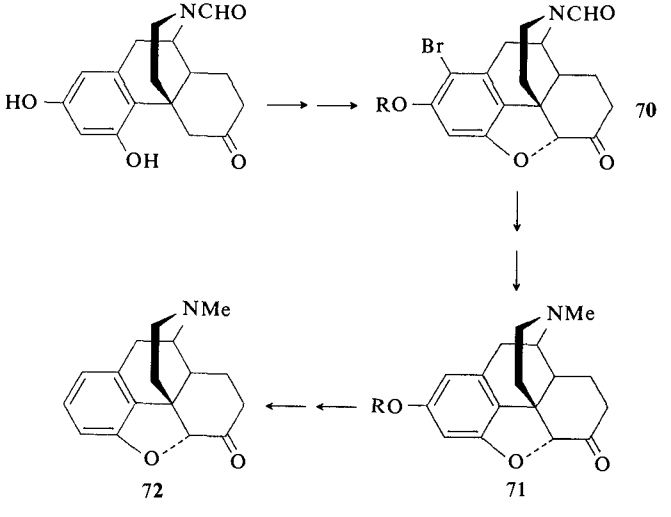
A biomimetic synthesis[165] of (±)-2-hydroxycodeine (**69**) has been reported, in 37% yield, by the vanadium oxychloride phenolic coupling of a 1-benzyltetrahydroisoquinoline with a symmetrical 3,5-dihydroxy-4-methoxy-substitution pattern in the benzyl ring.



69

During the total synthesis of (±)3-deoxy-7,8-dihydromorphinone (**72**), a morphine derivative lacking aromatic ring substitution,[166,167] two novel aromatic ring substituted analogs were isolated as intermediates, 4,5-epoxy-2-hydroxy-*N*-methylmorphinan-6-one (**71**, R = H) and a related 1-bromo derivative (**70**), together with their respective methyl ethers. No biological data on these were reported.

Morphine has been found to couple with the diazonium salt of 4-aminoacetophenone[168] to give a single product substituted at C-2. Codeine, on the other hand, gave a mixture of C-2 and C-8 substituted products.



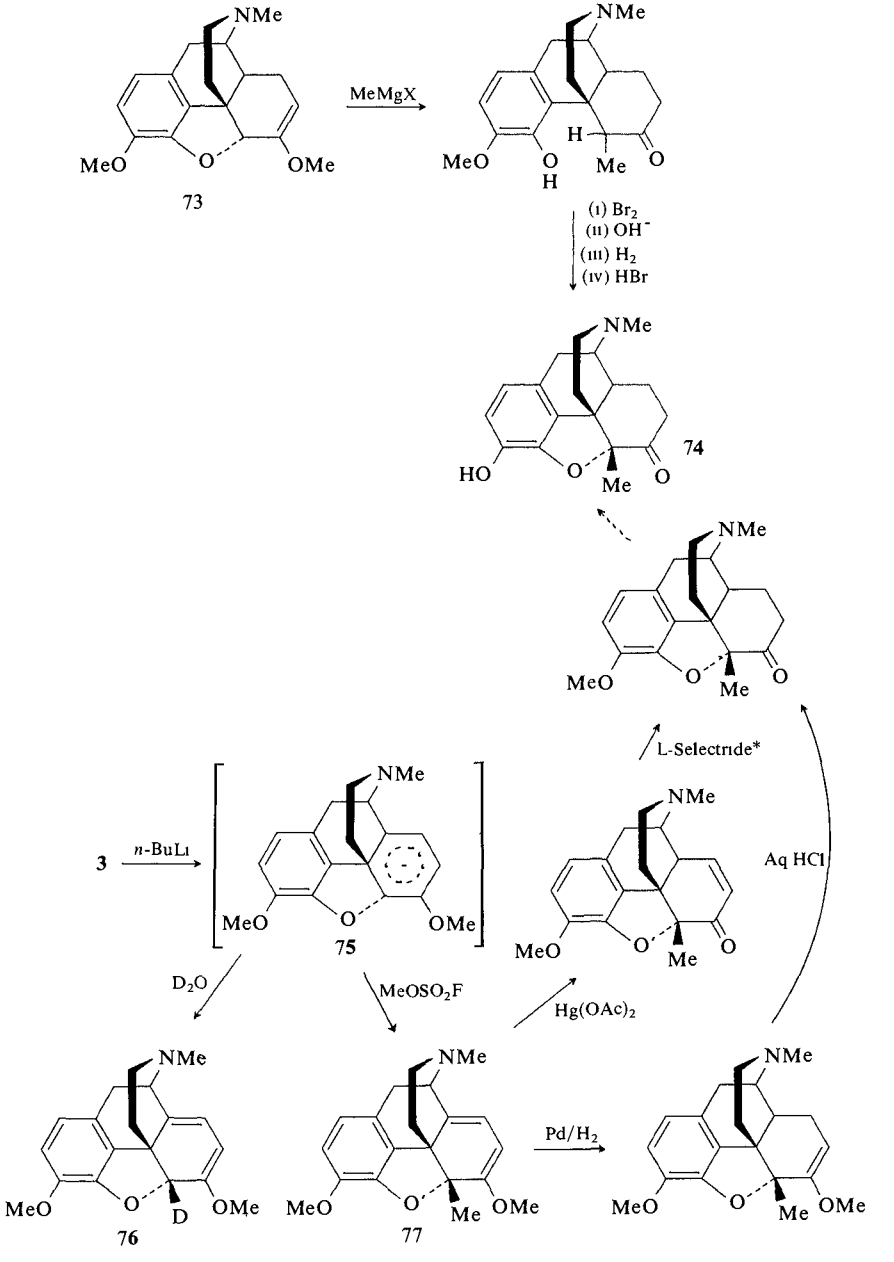
72 71

2.5.3. 5-Substituted 4,5-Epoxymorphinans

Dihydrothebaine (**73**) and other 4,5-epoxymorphinans with 6,7-unsaturation have been shown to react with Grignard reagents to afford predominantly 5-substituted derivatives with epoxide bridge-opening[169-171] (Scheme 2.12). Reclosure of the oxygen bridge was effected by bromination and treatment with base, and by means of standard chemistry gave 5-methyldihydromorphinone (**74**), known as *metopon*. Initially, it was believed that Grignard alkylation had occurred at C-7, but Stork and Bauer,[172] by an unequivocal synthesis of 7-methyldihydrocodeinone from dihydrocodeinone, demonstrated that this was, in fact, the minor reaction product. Dihydrocodeinone had been shown previously[173] to react with Grignard reagents in a similar manner, albeit rather slowly.

Metopon (MHP, sc, ED_{50}, 0.5 mg/kg) is a compound of significant pharmacological interest.[174] It is orally active and in humans is about three times as potent as morphine in the relief of chronic deep-seated pain, with a reduced respiratory depression, PDC, and GIT effects. Clearly, an analgesic of this sort would have received wide usage had manufacturing access been less difficult. Analogous compounds with 5-Et, 5-isoPr, and 5-*n*-amyl substituents have been evaluated pharmacologically.[175]

Thebaine (**3**) is an important precursor of many opioid analgesics, and recently, a route from it to metopon, giving 51% overall yield, has been described.[176] Treatment of thebaine with *n*-butyl lithium in THF at −78° was found to result in the deep burgundy red color of the thebaine anion, **75**. Addition of deuterium oxide to **75** gave 5-deuteriothebaine (**76**) the structure of which was suggested by the absence of a 5H signal in the ^1H nmr spectrum at δ5.34. Similarly, treatment of the anion with methylfluorosulfonate gave 5-methylthebaine (**77**); again the position of C-ring substitution was indicated by ^1H nmr. By the pathways illustrated in Scheme 2.12, 5-methylthebaine (**77**) may be converted to metopon. This thebaine to metopon transformation reaffirms the structure of metopon. Sargent and May[177] investigated the effect of variation of the *N*-substituent on pharmacological responses in 5-methyldihydromorphinones (**74**). *N*-Demethylation of 3,6-diacetylmetopon was performed either under standard von Braun, cyanogen bromide, conditions or with diethyl azodicarboxylate.[178] Normetopon proved to be a good antinociceptive agent in mice (ED_{50} 2.7 mg/kg, MHP, sc). *N*-Phenethyl often increases analgesic effects by a factor of 10, and very high activity was found for the *N*-phenethyl analog of metopon (ED_{50} 0.06 mg/kg, MHP, sc) but as anticipated, the compound was not an antagonist and had a high PDC in monkeys. On the other hand, the metopon *N*-allyl analog, which might have been predicted to have mixed agonist-antagonist properties, was only a modest analgesic (MHP, sc, ED_{50}, 2.0 mg/kg) with a remarkably high PDC in monkeys. Most surprising was its lack of activity in antagonist tests. No antagonists'



*Lithium tri-*sec*-butylborohydride

Scheme 2.12

actions were detected in compounds of this series, suggesting a possible impediment to antagonist receptor binding by a C-5 substituent.

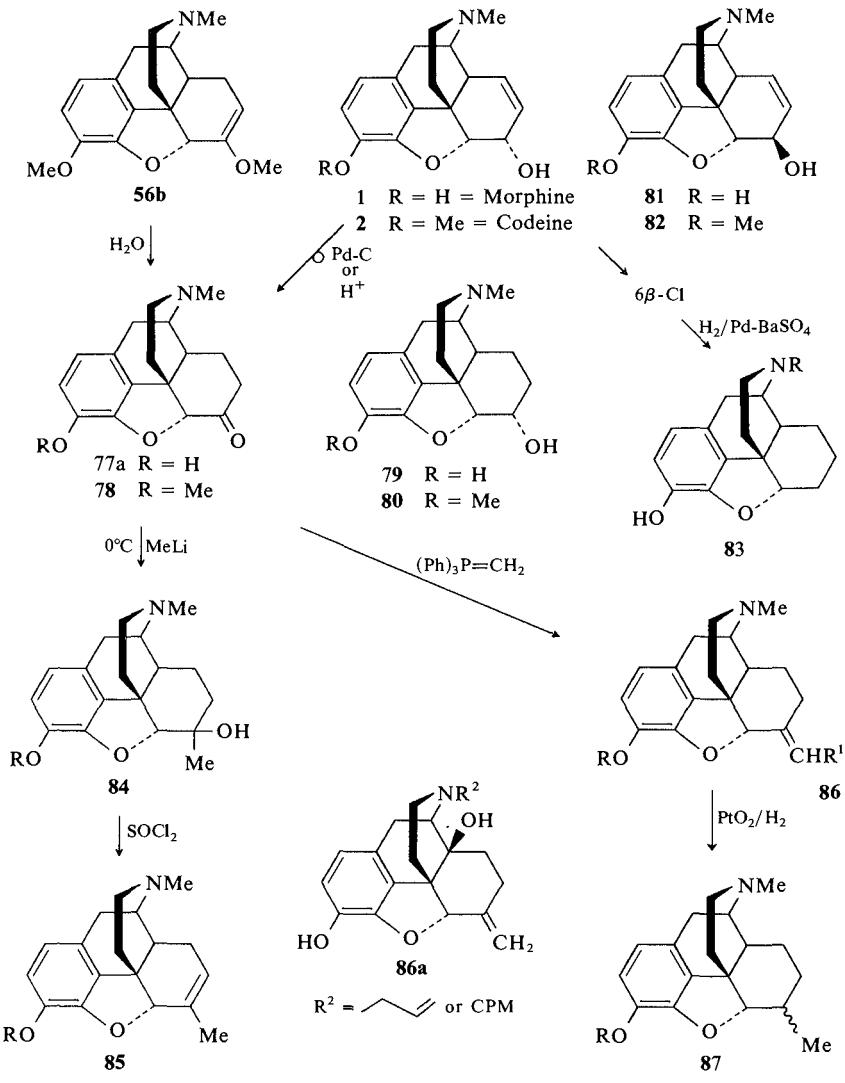
2.5.4. 6-Substituted 4,5-Epoxymorphinans

During early work on substitutes for morphine, the C-ring was extensively modified.[179] Many of these modifications are illustrated in Scheme 2.13.

Catalytic or strong acid rearrangement of the C-ring double bond in morphine or codeine results in the formation of the ketone, dihydromorphinone (hydromorphone or *dilaudid*), **77**a, or dihydrocodeinone (hydrocodone or *dicodid*), **78**. Both compounds have found clinical application and are several times more active as analgesics and in PDC in humans as their respective precursors (see ref. 478 for a reinvestigation of morphinone, the Δ^7 analog of **77**a). Dihydrocodeinone may also be prepared from the hydrolysis of dihydrothebaine (**56**b). Catalytic hydrogenation of morphine or codeine over palladium affords dihydromorphine (**79**) or dihydrocodeine (*paracodin*) (**80**), respectively. The latter possesses useful antitussive properties but is also an analgesic about equivalent to codeine (MHP).[180]

Formal inversion of the 6-OH group of **1** and **2** to *α-isomorphine* (**81**) and *isocodeine* (**82**) does not alter unduly MHP (sc) activities. Removal of the C-6 oxygen function altogether, by catalytic hydrogenation of *β*-chlorocodide followed by *O*-demethylation gave desomorphine[181] (**83**, R = Me) (dihydrodesoxymorphine-D), an analgesic 10 × morphine (MHP) with a rapid onset of action.[180] (−)-*N*-Phenethylnordesomorphine (**83**, R = CH_2CH_2Ph) prepared from the corresponding secondary amine was a very potent morphinelike agonist (85 × morphine, MHP, sc).[130] Both the *N*-CPM and *N*-dimethylallyl analogs of **83** were found to be modest analgesics, the former 0.25 × morphine and the latter equivalent to morphine (MHP, sc) with only a mild PDC and no antagonist action in monkeys. Nordesomorphine (**83**, R = H) was inferior to desomorphine as an analgesic.[177] The 6-oxo group of **77** and **78** is resistant to attack by Grignard reagents; however, alkyl lithium derivatives have given[182] with these ketones good yields of carbinols (**84**) that with thionyl chloride dehydrated to the 6-methyl-6,7-ene (**85**). Analgesic activity of both **84** and **85** (R = H) was good; the former had a longer duration of action and a lower PDC than morphine, whereas the latter had a short duration of action with an increased PDC.[183] Structures related to **85** with Et, *n*-Bu, and Ph as the C-6 substituent were also reported. The 6-phenyl derivative was a weak antinociceptive agent, whereas 6-ethyl and 6-*n*-butyl analogs were almost as potent as **85**. Acylation of the 3-OH increased general toxcity considerably.

A Wittig reaction with dihydrocodeinone (**78**) afforded the 6-methylene derivative (**86**, R = Me, R′ = H) that was hydrogenated to 6-methyldihydrodeoxycodeine (**87**, R = Me), another good analgesic (up to 25 × morphine).[184,235,236] Reaction of nalorphine with carbomethoxymethylene

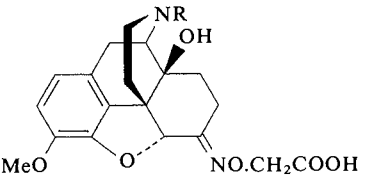


Scheme 2.13

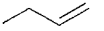
triphenylphosphorane[237] gave the Wittig product (**86**, R = H; R′ = COOMe and *N*-Me replaced by *N*-allyl) as a mixture of *cis-trans* isomers that were of little pharmacological interest. A series[238] of 6-methylene derivatives of naloxone and naltrexone (**86**a), however, gave good MHP and RTF activities po, with the analogs R^2 = allyl being equivalent to morphine (MHP.sc) and the naltrexone analog (R^2 = CPM) being 59 × morphine (MHP, sc, ED_{50},

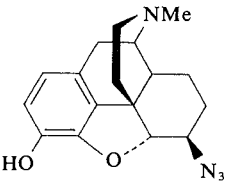
0.053 mg/kg). Clearly, the C-ring needs neither unsaturation nor an oxygen function for good opioid pharmacological properties. Indeed, formation of a 6-methyl ether as in heterocodeine results in an improvement of analgesic actions over morphine.

The 6-oxo group of 14-hydroxycodeinone may be converted directly to an oxime, which may be hydrogenated over Pd-C to **88** and then to corresponding morphine analogs. Compound **88** was claimed to have a selective antitussive activity and analgesia of long duration.[185]



88

R = Me or 



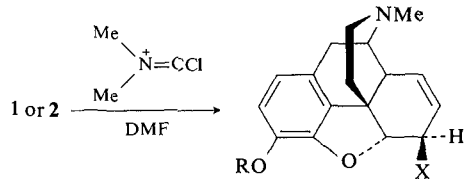
89
Azidomorphine

Dihydromorphine (**79**) has been converted via its 6-tosylate into 6-deoxy-6-azidodihydroisomorphine (**89**).[186] This derivative is a remarkably potent analgesic (300 times morphine in the rat and 50 times morphine in humans) and was reported to be less toxic than either morphine or fentanyl with a low PDC in monkeys. In humans, however, an abstinence syndrome[187-189] and ability to substitute for morphine[190] was reported.

Masking of the 3-OH function of **89** by methyl ether formation reduced analgesic activity to 13 × morphine.[191] Many other azidomorphines, several with 14-OH substituents, have been reported, and their pharmacological and clinical activities reviewed.[192] The importance of the nature of the azido substituent and its steric (β) orientation is difficult to establish because of a lack of comparable biological data on dihydroisomorphine. 6β-Substituents, however, do lead to higher antagonistic potencies than do corresponding 6α-compounds, where 6-NH_2[193] and 6-OH[194] groups are present in 14-hydroxymorphines.

Codeine upon treatment with thionyl chloride[195] gave a compound described as α-chlorocodide (**90**, R = Me); evidence for the structure of β-halocodides and a third isomer identified as 14-halocodides has been described. (α and β have positional, not steric, significance in these compounds.) The assignment of configuration at C-6 was proposed by Stork and Clarke.[197]

Substitution of chlorine for hydroxyl at C-6 of morphine was effected[198] with dimethylchloroformiminium chloride (Vilsmeier's reagent) in DMF. The resultant α-chloromorphide (**90**, R = H; X = Cl), together with the 6α-bromo- and 6α-iodo- derivatives, was described earlier.[175,199] The 6-halide configuration was determined as 6-axial by ^{1}H nmr.[198] The kinetics of S_N2'

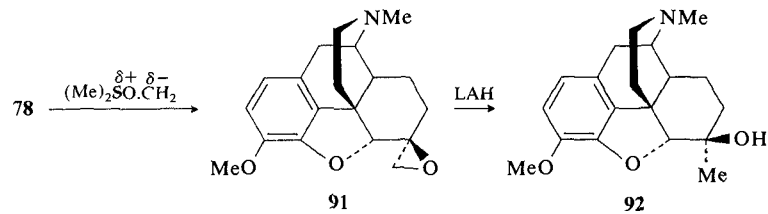


90

replacement of halogen in halocodides by piperidine[197] and their behavior upon catalytic hydrogenation[181] have been investigated.

Pharmacologically, α-chloromorphide is up to 15× more potent as an analgesic than is morphine (MHP sc, ED_{50}, 0.07) and 10× more potent than β-chloromorphide, which carries an 8β-Cl group (p. 53), but it is considerably more toxic in mice. Compound **90**, unlike β-halomorphides, did not bind to *in vitro* receptor preparations.

Alkyl thiol anions displace halogens from halocodides to give corresponding alkylthiocodides.[192] Dihydrocodeinone (**78**) has been reported[200] to react with sodium dimethyloxosulfonium methylide (dimsyl sodium), giving the 6-oxirane (**91**), which opened under reducing conditions to the methyl carbinol, **92**, an analgesic similar in potency to codeine.

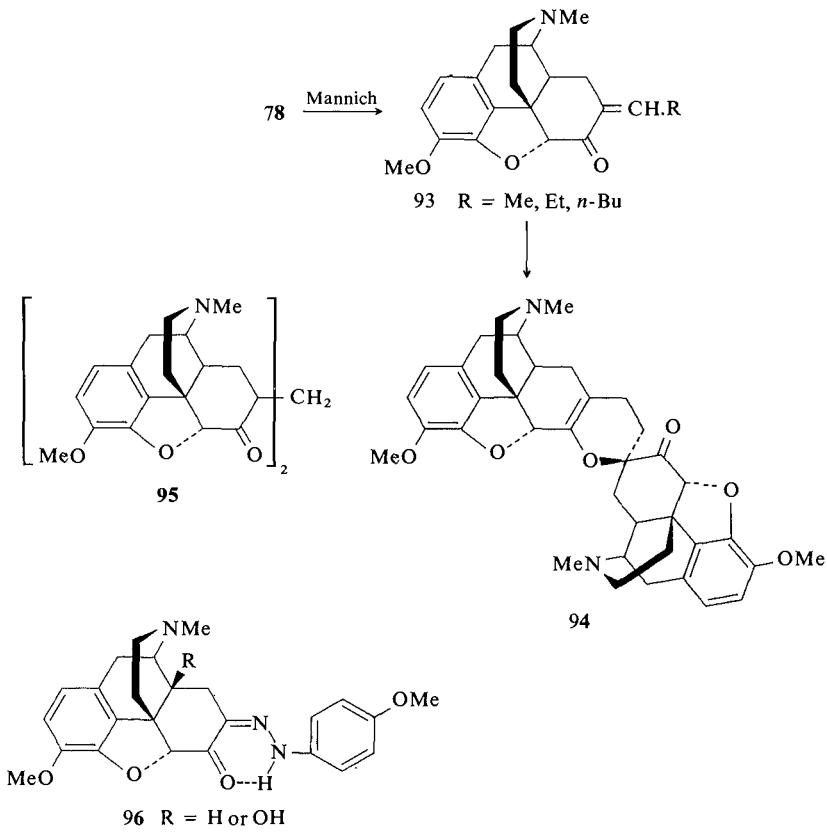


91 92

4,5-Epoxymorphinan oxiranes with and without a 14β-OH substituent and related structures have been described previously[201] but without biological data. Other 6-substituted 4,5-epoxymorphinans have been reported.[202] Those with a 14-OH group, including many receptor affinity binding agents, are discussed elsewhere in this book (p. 61).

2.5.5. 7-Substituted 4,5-Epoxymorphinans

The Mannich reaction with dihydrocodeinone[203] gave not the expected 7-dimethylaminomethyl Mannich base, nor the corresponding 7-methylene elimination product (**93**), but a dimer to which the symmetrical structure **95** was initially assigned. A reinvestigation[204] of the reaction with a milder Mannich reagent, *N,N,N′,N′*-tetramethylmethanediamine[205] confirmed that the only isolatable product was a dimer, but ^{1}H and ^{13}C nmr characteristics suggested a nonsymmetrical dimer of structure, **94**. The dimer arises from a



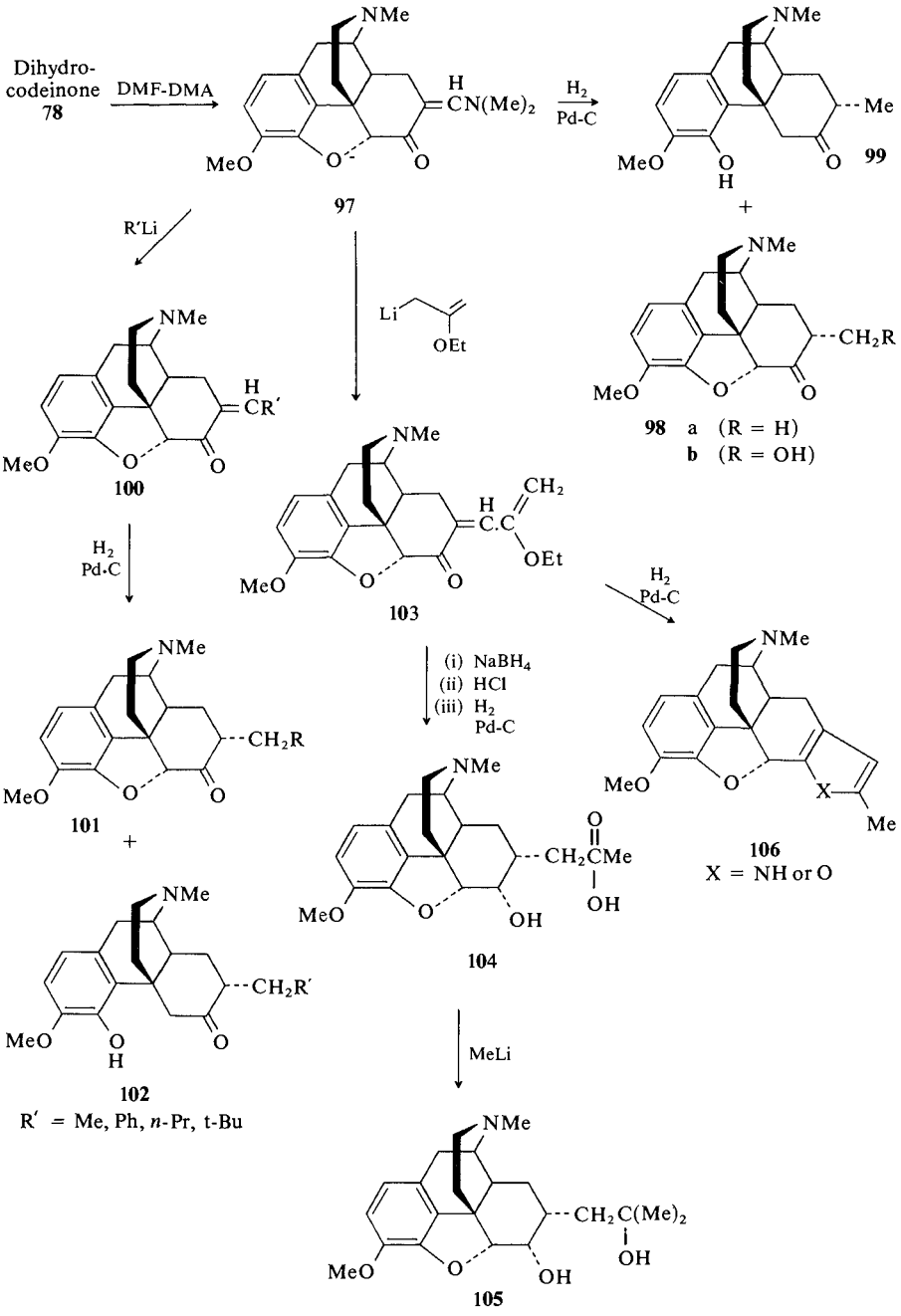
Diels–Alder, 1,4-cycloaddition between two molecules of the 7-substituted methylene elimination product, **93**.

Reaction of dihydrocodeinone (**78**) or 14-hydroxydihydrocodeinone with 4-aminoacetophenone diazonium salt gave the H-bond stabilized hydrazone (**96**), presumably via an intermediate azo derivative.[168]

A study[206] of the ketalization of 14-hydroxycodeinone resulted in the insertion of a hydroxyl function at C-7. Contrary to the 14-position halogenation seen with bromine and chlorine, iodination of thebaine occurred at C-7.[207]

The insertion of alkyl functions at C-7 has been achieved in a number of ways. During the synthesis of metopon (p. 35), 7-methyldihydrothebainone was isolated as a minor product and was cyclized to 7-methyldihydrocodeinone (**98**a). Later,[202] 14-hydroxydihydrocodeinone was reported to methylate at C-7 with MeI–NaH in liquid ammonia and THF. An attempt to repeat this reaction and extend it to **78** failed.[208]

Scheme 2.14 illustrates the synthesis of 7α-alkyldihydrocodeinones from dihydrocodeinone (**78**)[210] via the 7-[(dimethylamino)methylene] adduct, **97**,


Dihydro-
codeinone
78
DMF-DMA
97
H2
Pd-C
99
+
R'Li
Li
OEt
98 a (R = H)
b (R = OH)
100
103
H2
Pd-C
(i) NaBH4
(ii) HCl
(iii) H2
Pd-C
101
+
102
R' = Me, Ph, n-Pr, t-Bu
104
106
X = NH or O
MeLi
105

Scheme 2.14

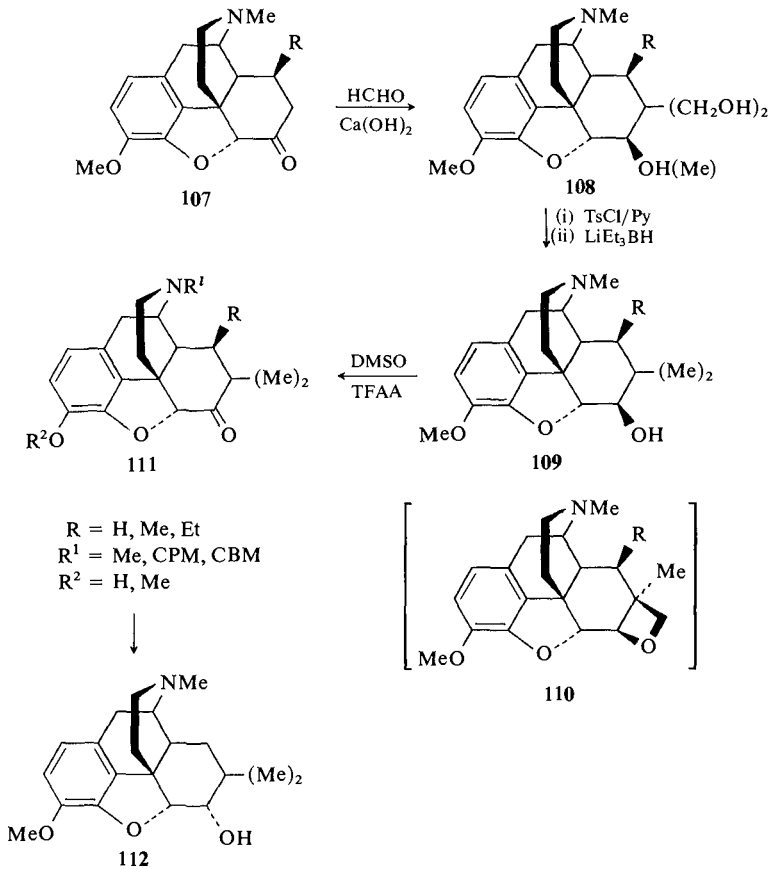
which was isolated (70%) from the reaction of **78** with dimethylformamidodimethylacetal (DMF-DMA).[209] Catalytic hydrogenation of **97** gave not only 7α-methyldihydrocodeinone (**98**a), but also the corresponding oxygen-bridge-opened morphinan, **99**. Hydrogenation of **97** in acetate buffer gave the hydroxymethyl derivative, **98**b. Lithium alkyls reacted with **97**, giving a range of unstable α,β-unsaturated ketones, **100**, which were hydrogenated to 7α-alkyldihydrocodeinones (**101**) and the corresponding morphinan-6-ones (**102**). CPM and CBM analogs of **98**a were made, rather laboriously, from 7β-methyldihydrothebaine-ϕ[210] (p. 126) because of the instability of 7α-methyldihydrocodeinone to acid. A similar sequence of reactions was performed on corresponding 14-hydroxycodeinones with *N*-Me, *M*-CPM, and *N*-CBM substituents.

The reason for the elaboration of C-7 alkyl substituted 4,5-epoxymorphinans was partly the exploration of a pathway to compounds with a tertiary alcohol group in the C-7 side chain, thus mimicking the 19-OH of *endo*-ethanotetrahydrooripavines. Kotick *et al.*[208] extended their study to include such compounds by treating **97** with α-ethoxyvinyllithium to yield **103**. Hydrogenation of this gave furano- and pyrrolo-4,5-epoxymorphinans (**106**), the latter incorporating ammonia during work-up. Sodium borohydride overcame this problem but resulted in dihydrocodeines (**104**, **105**) with appropriately substituted C-7 side chains that could not be oxidized to the corresponding dihydrocodeinones. Cleavage of the 3-OMe to give 3-OH derivatives was effected with BBr_3.

Pharmacologically, the presence of 7α-Me in 4,5-epoxymorphinans did not alter significantly MW and RTF analgesic responses. Larger 7α-alkyl groups resulted in diminished potency, and throughout no increases in agonist-antagonist activities were observed.

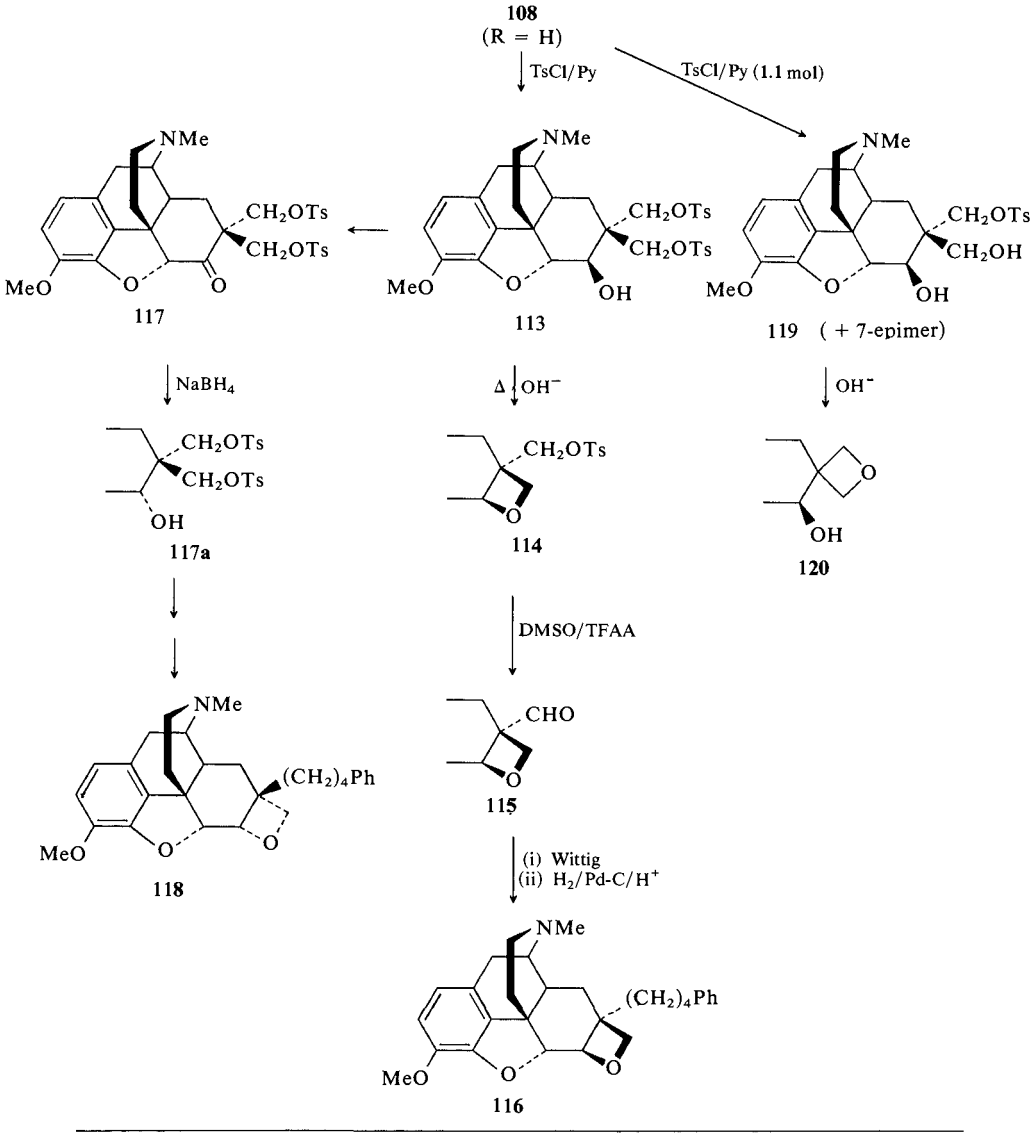
In 1938 Mannich and Schulte[211] reported that dihydrocodeinone (**78**) gave with formaldehyde and calcium hydroxide, 72% of 7,7-bis(hydroxymethyl)dihydroisocodeine (**108**, R = H) (Scheme 2.15). This observation was extended[212] to include the 8-Me and 8-Et analogs of dihydrocodeinone (**107**, R = Me or Et) and to the preparation of 7,7-dimethyl derivatives with Me, CPM, and CBM *N*-substituents. Leland and Kotick[212] discovered, from ^{1}H nmr and chemical shift data that the 6-OH group was not α- as originally assigned, but 6β-OH and that the presence of an 8-alkyl substituent, together with methanol in the reaction mixture, gave some 8-OMe derivative in addition to **108** (R = H). Tosylation, followed by lithium triethylborohydride reduction, gave **109**, oxidizable to **111**. C-Ring conformation again showed signs of modification by the presence of an 8-alkyl group, for during this reaction sequence, some 6β-,7β-oxetane (**110**) was formed. The dihydroisocodeine, **109** (R = H), was obtained as the dominant reduction product from the appropriate **111**.

The oxetanes (**110**, R = H and Me) are, rather surprisingly, equivalent to morphine in the MW analgesic test but are rather less active in the RTF assay.



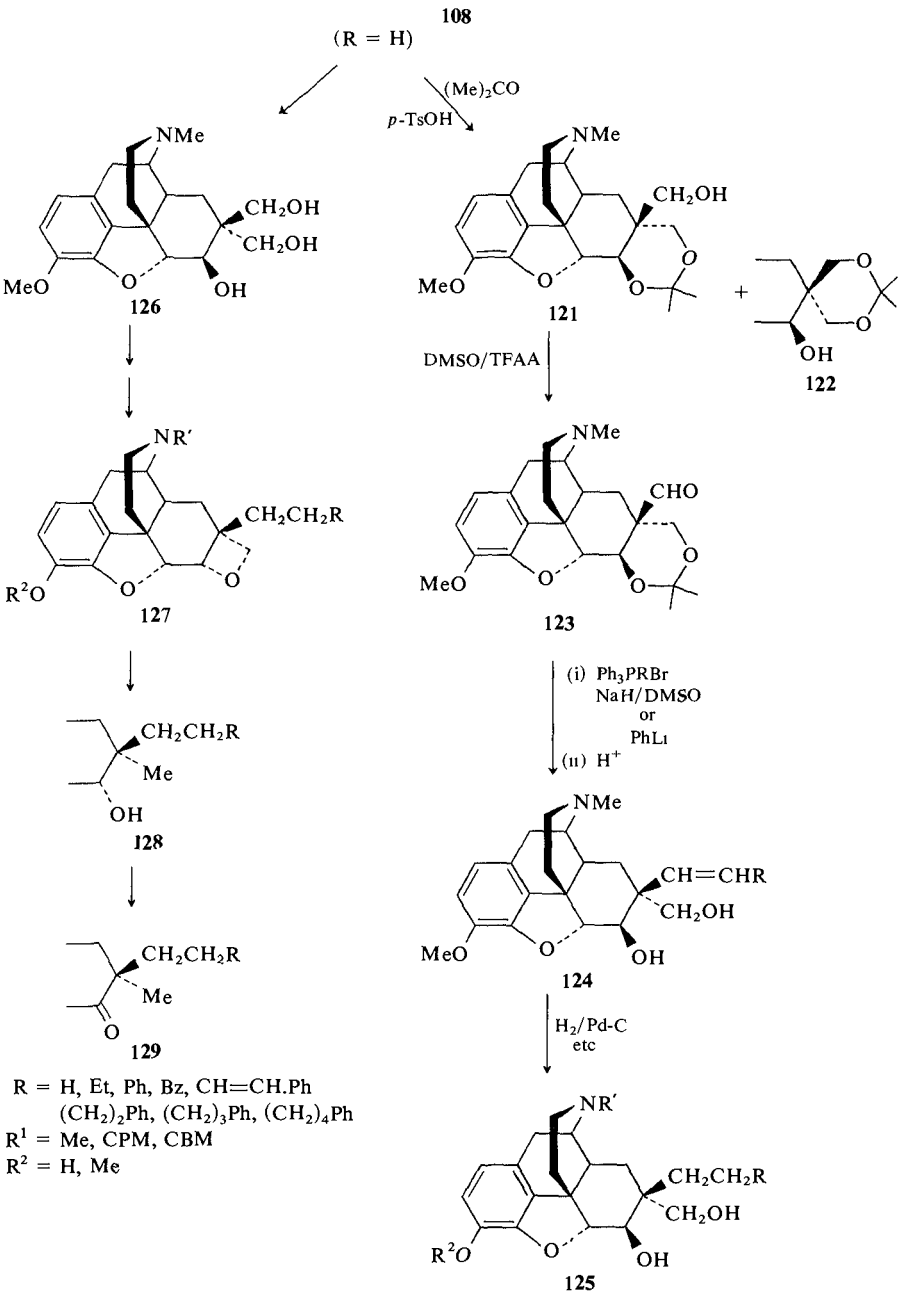
Scheme 2.15

Members of the 6α,7α-oxetane series bearing various substituents at C-7 have been prepared[213] according to Schemes 2.16 and 2.17. None of this series had a demonstrable opioid antagonist action; however, they were potent agonists (MW). For example, **127** (R = CH_2CH_2Ph; R′ and R^2 = Me) had an MW, sc, ED_{50} of 0.005 mol/kg (cf. morphine ED_{50}, 2.1), and the most potent compound, **127** (R = CH_2Ph, R′ = CPM, R^2 = H) had MW, sc, ED_{50} of 0.003 mol/kg. Generally, the 6-ketones tend to be more potent (two times) analgesics than the 6β-ols, whether in the dihydrocodeinone or dihydromorphinone series. The observation made by the same authors for corresponding morphinans[214-216] (p. 121) applies to the 4,5-epoxy ring-closed species. Introduction of alkyl groups into the C-ring modifies quantitatively the



Scheme 2.16

observed analgesic actions. There appears to be a delicate interplay of influences between C-ring, N, and 3-O substitution. Only one compound in this series, **111** (R = H, R′ = CPM, R^2 = Me), exhibited good agonist/antagonist potency (MW, sc, ED_{50}, 5.3 μmol/kg; RTF/A, 6.7 μmol/kg).


108
(R = H)
(Me)2CO
p-TsOH
NMe
CH2OH
CH2OH
MeO
O
OH
126
NMe
CH2OH
MeO
O
O
O
121
+
O
O
OH
122
DMSO/TFAA
NR'
CH2CH2R
R2O
O
O
127
NMe
CHO
MeO
O
O
O
123
(i) Ph3PRBr
NaH/DMSO
or
PhLi
(ii) H+
CH2CH2R
Me
OH
128
NMe
CH=CHR
CH2OH
MeO
O
OH
124
CH2CH2R
Me
O
129
H2/Pd-C
etc
NR'
CH2CH2R
CH2OH
R2O
O
OH
125
R = H, Et, Ph, Bz, CH=CH.Ph
(CH2)2Ph, (CH2)3Ph, (CH2)4Ph
R1 = Me, CPM, CBM
R2 = H, Me

Scheme 2.17

The level of pharmacological activity of the oxetanes **110** suggested a means of constructing nonepimerizable 7α- and 7β-substituted dihydromorphine.[217] Base treatment of the ditosylate, **113** derived from **108** (R = H), gave the oxetane (**114**) (Scheme 2.16). Oxidation of the α-tosylmethyl function to the corresponding aldehyde was followed by a Wittig reaction with cinnamyl triphenylphosphorane, and then catalytic hydrogenation in acid gave the 7α-phenylbutyloxetane, **116**, together with a little oxetane cleaved product. The former had no analgesic (MW) activity. Oxidation of **113**, followed by $NaBH_4$ reduction, gave predominantly the 6α-OH derivative **117**a, which was treated in a manner similar to that described earlier to give **118**, a 7β-butyl-α-oxetane isomeric with **116**. Compound **118** proved to be a very effective antinociceptive agent in the MW assay (ED_{50}, 0.003 mg/kg).

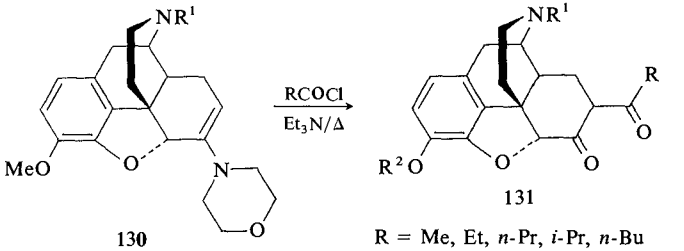
Reaction of **108** with a single mole of tosyl chloride in pyridine afforded, as well as **113**, an epimeric mixture of monotosylates (**119**). The 7α-tosylmethyl-epimer may be converted with base to the spirooxetane (**120**).

In extending these series of compounds with lipophilic groups of varying size held in a 7β- configuration, Kotick and co-workers[213] have reported a range of 7α-hydroxymethyl-7β-substituted isocodeines and isomorphines (**125**; R^2 = Me and H, respectively) prepared according to Scheme 2.17. All isocodeines tested (MW) were more potent than morphine with the best compound, **125** (R = CH_2Ph, R′ = CBM, R^2 = Me), having an ED_{50} of 0.04 μmol/kg. The corresponding isomorphines were much less active; for example, the best compound, **125** (R = CH_2Ph, R′ = CBM, R^2 = H), had an ED_{50} of 0.57 (about 4 × morphine). Introduction of a carbonyl group at C-7 (e.g., **129**) afforded good agonists, but once again no opioid antagonist actions could be demonstrated.

Thus, in series **127** and **125** with 7β-aralkyl substituents and alkyl chain lengths of two to four methylene units strong opioid agonists were obtained. It would appear that there is on the opioid receptor a lipophilic binding site of the sort proposed by Lewis, Bentley, and Cowan.[13] An additional aromatic ring terminal on the optimum chain appears to augment receptor binding. Although this binding site was proposed to account for the very high potencies of the 6,14-*endo*-ethanotetrahydrooripavines (p. 75), other 4,5-epoxymorphinans may be designed with similar properties by positioning an appropriate aromatic lipophilic moiety in a 7β-configuration.

Similar observations[218] have been made for a series of 7-alkanoyldihydrocodeinones and -dihydromorphinones. Acylation of the 6-morpholino enamine, **130**, gave the β-diketones, **131**. 7-Alkanoyldihydrocodeinones (**131**, R^2 = Me) were consistently weaker analgesics (MW) than their dihydromorphinone counterparts (**131**, R^2 = H).

The best level of antinociceptive potency (3 × morphine) was exhibited by **131** (R = C_5H_{11}, R′ = CPM, R^2 = H), which had an ED_{50} of 0.29 mg/kg. In *N*-CPM derivatives, SARs were similar to those of the

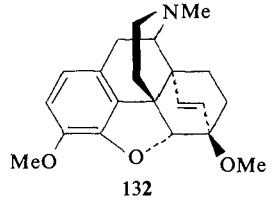


130 131

R = Me, Et, *n*-Pr, *i*-Pr, *n*-Bu
n-C_5H_{11}, C_6H_{13}, Ph, *p*-F-Ph
R^1 = Me or CPM
R^2 = H or Me

endo-ethanotetrahydrooripavines. Attempts to prepare side-chain carbinols by treatment of **131** with methyl lithium failed.

To test the proposal that conformational constraint of the 4,5-epoxymorphinan C-ring is, at least in part, responsible for the increased potency of 6,14-*endo*-ethanotetrahydrothebaine (**132**) over morphine, two cyclopropane-fused compounds, 7β,8β-methanodihydrocodeinone (**133**) and -dihydrocodeine (**134**), have been prepared.[219] Like **132**, these derivatives do not have the potency-enhancing influence of a lipophilic group extending outward and above the C-ring. Codeinone (**52**) did not react with most carbene sources, but diazomethane in the presence of lead acetate effected a conversion to **133** (R = Me), which reduced to **134** (R = Me). Analgesic agonist potencies (MW and RTF) in both *N*-Me derivatives were about seven times the activities of their unsubstituted counterparts. Antagonist actions (RTF/A) for *N*-CPM and *N*-CBM derivatives showed no significant change, although they were modest agonists. From these data it is clear that C-ring rigidity alone is not influential in enhancing 4,5-epoxymorphinan analgesic potency and that some other factor must account for the high level of activity (40 × morphine) exhibited by **132**.



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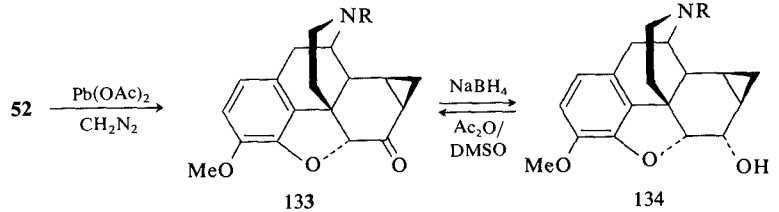
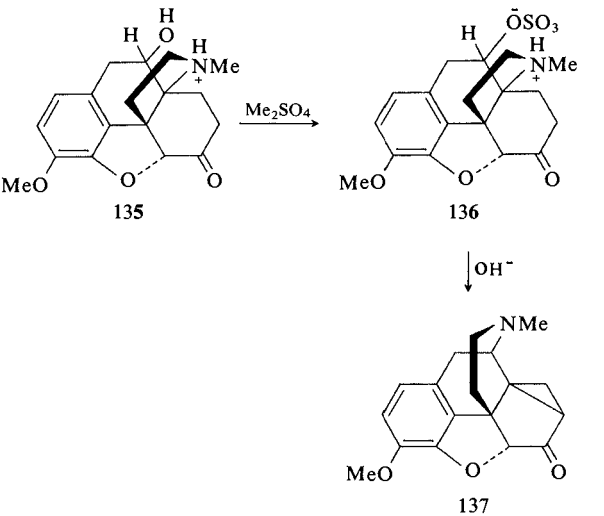


133 134

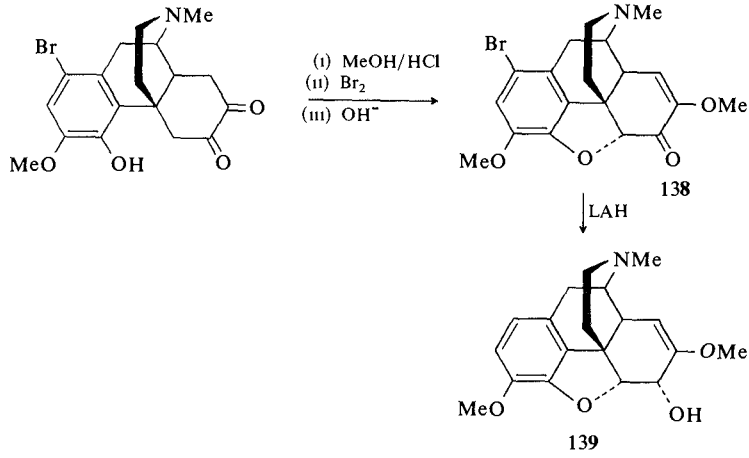
R = Me, CPM, CBM

Another 4,5-epoxymorphinan with a rigid C-ring has been prepared[220] and described as 7,14-cyclodihydrocodeinone (**137**), where the cyclopropane ring is within the C-ring. The hasubanan-6-one hydrochloride (**135**) was reacted with dimethyl sulfate to give **136**, which rearranged in base to 7,14-cyclodihydrocodeinone (**137**). The photolysis of these compounds has been described.[221] No biological data were reported.

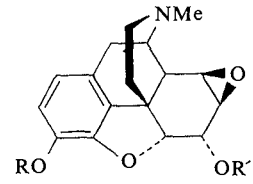


7-Methoxycodeine (**139**) has been prepared[222] from (−)-1-bromosinomeninone (**138**) in three stages (Scheme 2.18), and found to be about $\frac{1}{3}$ codeine (MHP, sc). In view of the acid instability of 7-methoxycodeine it was surprising to find that it was an equivalent analgesic to codeine when administered po. Perhaps the standard error limits of the biological test were wide enough to suggest that the compounds were equipotent.

Codeine-7β,8β-epoxide (codeine-7,8-oxide) (**140**) was suggested as being a metabolite of codeine by Yeh *et al.*,[223] but they failed to synthesize it. Subsequently, **140** was isolated[224] as a metabolite of codeine from a rat liver microsomal suspension and identified by GC/MS (MID) and HPLC. Identification was assisted by a prior stereospecific synthesis and X-ray characterization.[225] The same group[226] has described a synthesis for both morphine-7,8-oxide (**141**) and heroin-7,8-oxide (**142**), by the H_2O_2 oxidation of the 3-methoxymethylether of morphinone, followed by $NaBH_4$ reduction and HCl 3-ether cleavage to **141**. Treatment of morphine-7,8-oxide with acetic anhydride and pyridine gave heroin-7,8-oxide (**142**). These epoxides had twice the analgesic potency of the corresponding 7,8-enes, although the reverse had been reported for morphine-7,8-oxide.[227]



Scheme 2 18



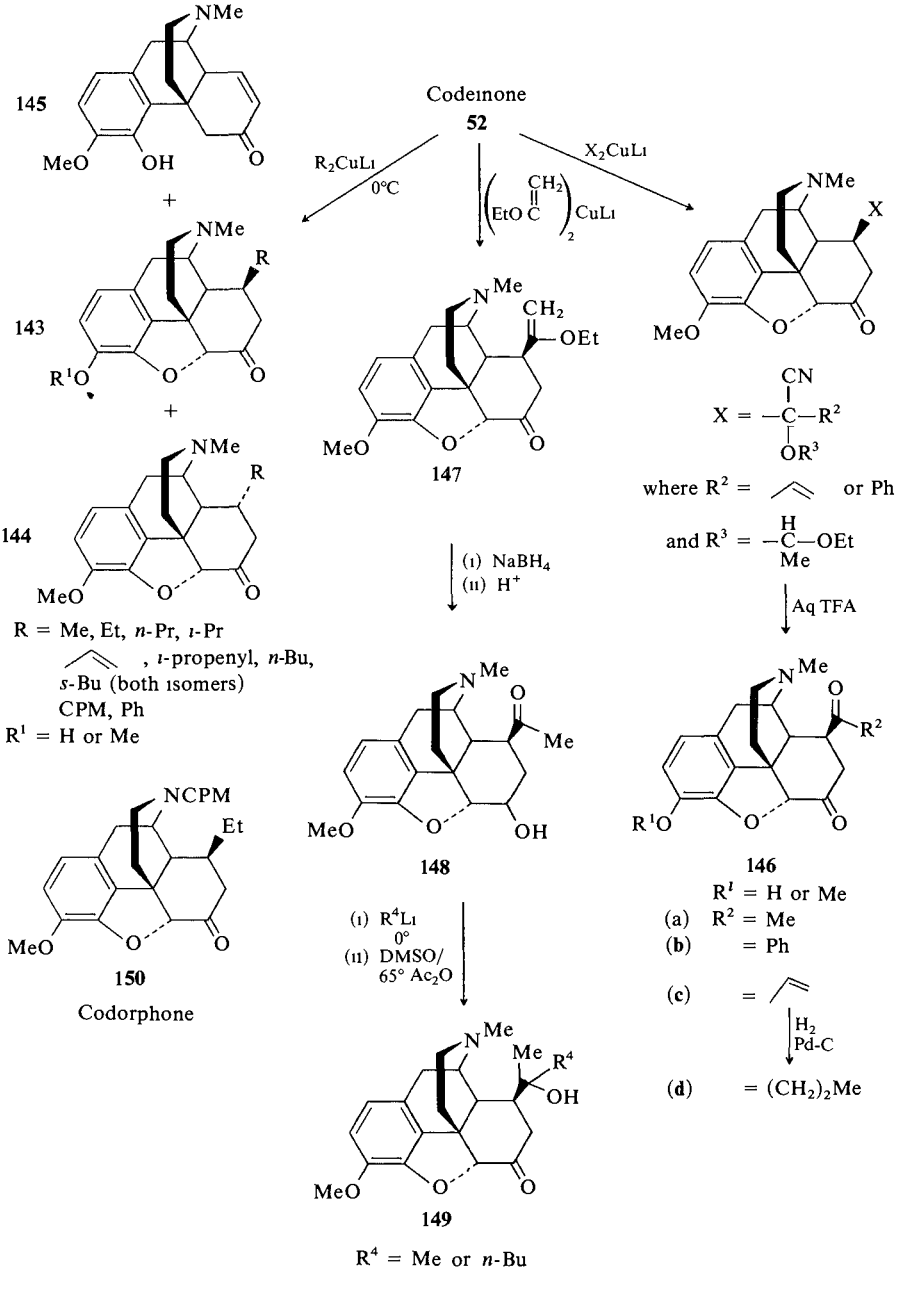
140 R = Me, R′ = H
141 R = H, R′ = H
142 R = Ac, R′ = Ac

Kotick[219] has also prepared 7β,8β-epoxides by a method similar to that described by the Japanese group and found them to be much weaker analgesics than codeinone.

2.5.6. 8-Substituted 4,5-Epoxymorphinans

The proposal[13] that there could be a lipophilic site on some opioid receptors that received the alkyl portion of the C-7 substituent of 6,14-*endo*-ethenotetrahydrooripavines and their ethano- analogs and that such a site is reflected in the solid-state conformation of leucine enkephalin,[228] has stimulated work on simpler 4,5-epoxymorphinans.

A group at Miles Laboratories has been particularly active in this regard, having synthesized many 7- and 8-alkyl derivatives of 4,5-epoxymorphinans. They generated[229] a series of 8β-alkyldihydrocodeinones (**143**) by the conjugate addition of lithium dialkylcuprates to codeinone (**52**) according to Scheme 2.19. Three products were isolated, the 8β-alkyldihydrocodeinone, **143** (54%);


145
NMe
MeO
OH
O
+
143
NMe
R
R¹O
O
O
+
144
NMe
R
MeO
O
O
R = Me, Et, n-Pr, i-Pr
, i-propenyl, n-Bu,
s-Bu (both isomers)
CPM, Ph
R¹ = H or Me
NCPM
Et
MeO
O
O
150
Codorphone
Codeinone
52
R2CuLi
0°C
X2CuLi
(EtO C CH2)2CuLi
N Me
CH2
OEt
MeO
O
O
147
(i) NaBH4
(ii) H+
N Me
O
Me
MeO
O
OH
148
(i) R4Li
0°
(ii) DMSO/
65° Ac2O
N Me
Me
R4
OH
MeO
O
O
149
R4 = Me or n-Bu
NMe
X
MeO
O
O
X = CN
C
R2
OR3
where R2 = or Ph
and R3 = H
C
OEt
Me
Aq TFA
N Me
O
R2
R¹O
O
O
146
R¹ = H or Me
(a) R2 = Me
(b) = Ph
(c) =
H2
Pd-C
(d) = (CH2)2Me

Scheme 2 19

the 8α-alkyl epimer, **144** (2%); and 6% of the morphinan, **145**. Establishment of the configuration at C-8 was from the upfield shift seen in the 8α-Me protons of **144** (R = Me), and due to aromatic anisotropy that could only be experienced by an axial Me. This stereochemical ratio is somewhat unusual in that lithium organocuprates normally introduce alkyl functions axially.[230] Another group,[231] however, has demonstrated that the conjugate addition may occur to give either the 8α- or 8β-alkyl derivative, depending upon the alkyl group and the reaction conditions. In this more recent study, configuration was established by ^{1}H nmr at 250 MHz.

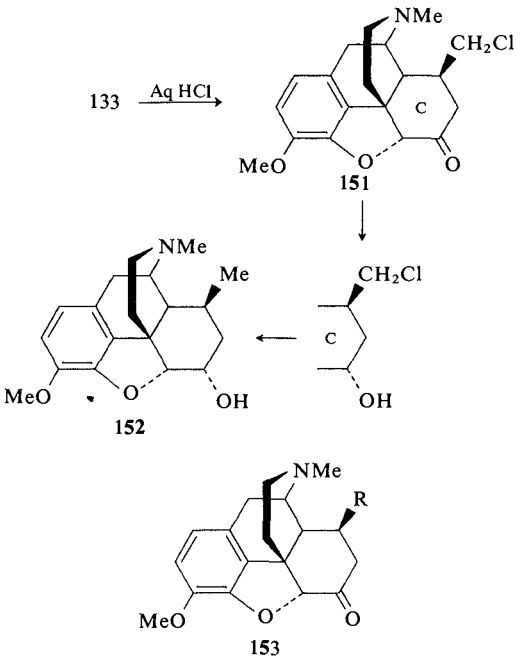
8β-Acyldihydrocodeinones (**146**) were made in a similar manner. The 8β-(*trans*-1-oxo-2-butenyl)- and 8β-benzoyl derivatives were prepared from protected acyl lithium cuprates, and the 8β-methylcarbonyl- (**146**) from the lithium bis(α-ethoxyvinyl) cuprate with codeinone, followed by mild hydrolysis of the intermediate, **147**. Preparation of 8β-t-alcohols may be achieved from **147** after reduction of the ring carbonyl, treatment with an appropriate alkyl lithium to **148**, and oxidation back to a ketone, **149**.

Only *N*-Me compounds of structure **143** gave reasonable analgesic (MW and RTF) responses, and none were an improvement over the corresponding 8-unsubstituted derivatives. Of the *N*-CPM and *N*-CBM derivatives in the **143** series, most failed to give compounds of interest, although some had mixed agonist-antagonist properties. The best compound (**150**) had a MW ED_{50} of 5.2 μmol/kg and an RTF/A ED_{50} of 1.93 μmol/kg and was a good enough agonist-antagonist to be submitted to phase I clinical trials under the name *codorphone*.[232]

Clearly, lipophilic substituents in the 8β-position on 4,5-epoxymorphinans do not interact with the opioid receptor putative lipophilic site. However, in binding studies Ghozland and others[231] were able to show that the somewhat lesser sterically hindered 8α-alkyl derivatives had a higher affinity for opioid receptor than did the corresponding 8β-isomers.

A similar selection of 8β-alkyl-14-hydroxydihydrocodeinones has been prepared.[233] 7β,8β-Methanodihydrocodeinone derivatives (**133** and **134**) were described on p. 48. Under the exceptionally mild conditions[234] of boiling 2*N* HCl, **133** was cleaved to the 8β-chloromethyl derivative, **151**, and this was reduced to 8β-chloromethyldihydrocodeine and converted to 8β-methyldihydrocodeinone (**152**), identical to the compound described earlier.[229]

Codeinone (**52**) has been shown to be an excellent Michael-type addition acceptor, and this was exploited during the previous study[234] to remove **52** during the purification of *N*-cyclopropylmethyl-7β,8β-methanodihydrocodeinone. Conjugate addition of mercaptoethanol to codeinone gave 8β-hydroxyethylthiodihydrocodeinone (**153**, R = —S—CH_2CH_2OH), which permitted chromatographic separation. A thorough Michael addition study[239] gave a range of structures (**153**) with hetero-atom-alkyl or unsaturated side



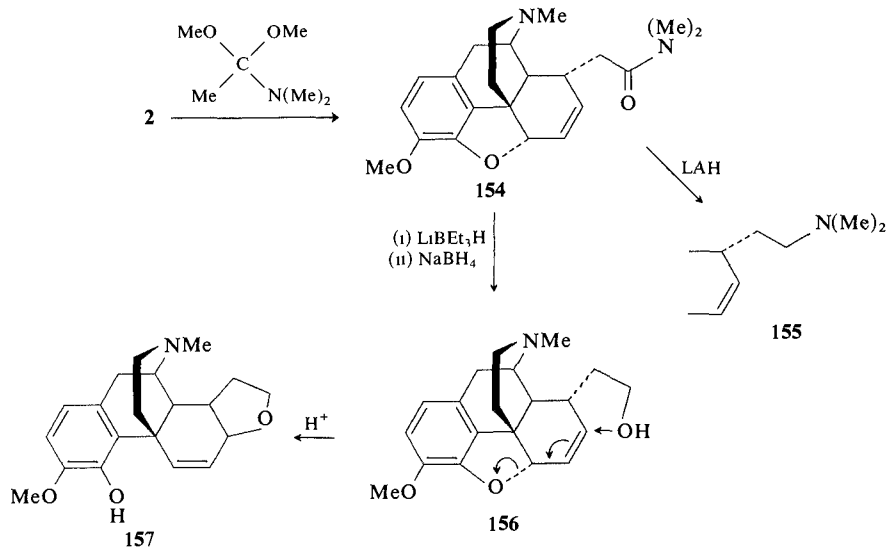
e.g., R = OMe, OEt, CH_2NO_2, $CH{=}CH_2$, CHO, CH_2CH_2F, etc.

chains, together with some dimethyl or diethyl ketals. No antinociceptive responses (MW) were observed.

Codeine has been shown[240] to undergo the Claison-Eschenmoser reaction to give amides such as **154**, which on LAH reduction gave the amine **155**, and with $LiBEt_3H$ followed by $NaBH_4$ gave **156**. In acid the latter rearranged to the tetrahydrofuranomorphinan (**157**). Catalytic hydrogenation of **154** gave, predominantly, morphinans (**157**). Isocodeine under similar conditions gave the 8β-epimer of **154**. No biological data were reported.

Halomorphides and halocodides were considered in the section on *6-substituted 4,5-epoxymorphinans* (p. 39). Much of that chemistry and the references relating to α-halomorphides (6-substituted) applies to the β-halomorphides (8-halogen substituted).

The discovery of β-chloromorphide in samples of illicit opiates[241] led an NIH group[198] to investigate their chemical and biological properties. β-Halomorphides, like their α-counterparts, were found by ^1H nmr to possess an axially positioned halide. Both series are more potent as analgesics than morphine (e.g., β-chloromorphide has a MHP, sc, ED_{50} of 0.8 mg/kg). They possess all the adverse properties of opiates and have also been shown to be more toxic than morphine.



Both α- and β-halomorphides bind reversibly to rat brain homogenates, but with the exception of β-chloromorphide, the degree of binding did not relate to analgesic potency.

Codeine, dihydrocodeinone, and 14-hydroxydihydrocodeinone couple with the diazonium salt of 4-aminoacetophenone at C-8, giving the corresponding azo adduct.[168]

In dilute acid, codeinone hydrates slowly to 8-hydroxydihydrocodeinone.[242] A similar but more facile hydration was seen[243] during the 3-O demethylation of 14-hydroxycodeinone with aqueous HBr, yielding as well as 14-hydroxymorphinone, 8,14-dihydroxydihydromorphinone.

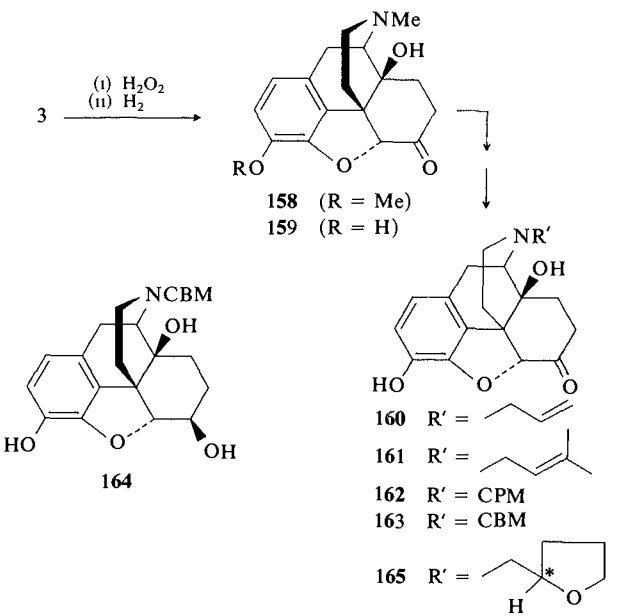
2.5.7. 14-Substituted 4,5-Epoxymorphinans

Introduction of a 14-OH substituent into a 4,5-epoxymorphinan nucleus may be accomplished from thebaine[244,245] by peroxide treatment followed by catalytic reduction to give 14-hydroxydihydrocodeinone, **158** (*Eucodal* or Oxycodone). This, in boiling HBr, was converted to 14-hydroxydihydromorphone, **159** (*Numorphan* or Oxymorphone).[246] Although both compounds are several times more potent as analgesics in humans than codeine and morphine respectively, both parenterally and po, they have been found to have no therapeutic advantages. 14-Hydroxydihydromorphinone had a considerably higher PDC than morphine.

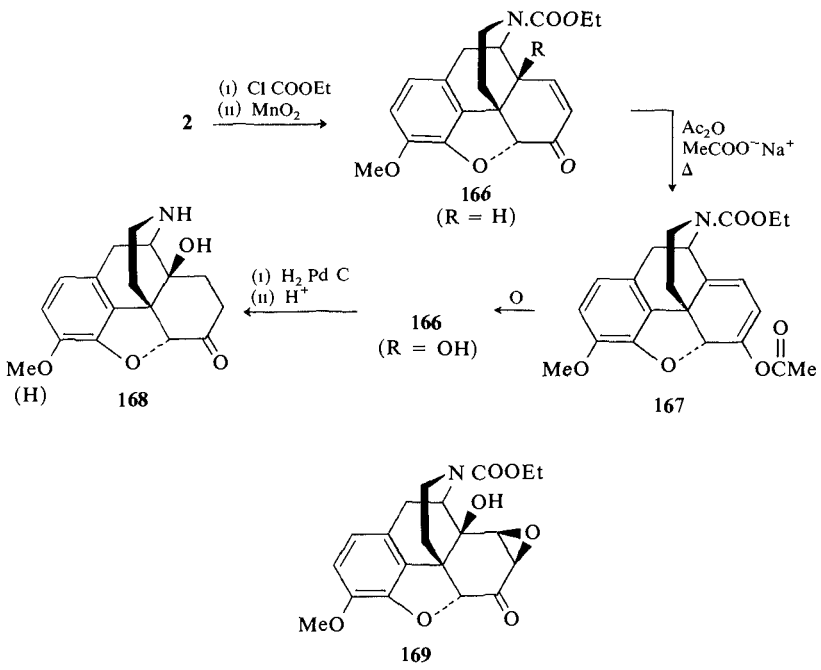
Antagonists were developed[247] from **159** by acetylation of the 3-OH and 14-OH groups, von Braun CNBr *N*-demethylation and treatment with, for

example, allyl bromide to yield, after hydrolytic removal of the acetyl protecting groups, *N*-allyl-7,8-dihydro-14-hydroxynormorphinone, *Naloxone* (**160**).

Naloxone is a powerful opiate antagonist (15-30 × nalorphine), but unlike nalorphine, it is without analgesic actions in rodents and humans.[248] It was reported to antagonize opiate respiratory depression without adverse effects of its own and produced no psychotomimetic actions.[249] By standard chemical procedures the *N*-dimethylallyl-, **161** (*Nalmexone*), *N*-cyclopropylmethyl-, **162** (*Naltrexone*), and *N*-cyclobutylmethyl- (**163**) analogs have been prepared,[250,251] and these mixed agonist-antagonists are described in Chapter 12. A related compound, *Nalbuphine*, (**164**) marketed as an analgesic with a low PDC, resulted from acylation on nitrogen with cyclobutylcarbonyl chloride followed by LAH reduction of both amide and ketone functions. Naloxone and Naltrexone have been reduced stereospecifically with formamidinesulfinic acid in aqueous alkaline to their respective 6β-OH metabolites.[252] Neither the 6α- nor 6β-derivatives displayed antagonist actions approaching the same order as the precursor ketones.



Attempts have been made to exploit the possibility of direct allylic oxidation of codeine with chromic acid,[253] MnO_2,[254] and SeO_2 plus *t*-butyl hydroperoxide[255] to the corresponding 14-OH derivative, but each approach gave a low yield. Schwartz and Wallace[255] achieved a six-step transformation of codeine to a noroxycodone (52%) and noroxymorphone (43%) according to Scheme 2.20. Oxidation of the carbamate of norcodeine gave **166** (R = H), which was converted to the dienol acetate, **167**. Subjection of this to



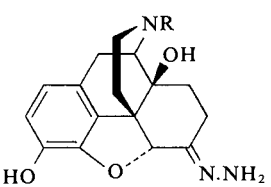
Scheme 2 20

photochemically generated singlet oxygen afforded the desired oxidation product, **166** (R = OH), for further transformation to noroxycodone, **168**, and on to noroxymorphone. The pyrrolidine enamine of **166** (R = H) gave mainly the 7β,8β-epoxide (**169**) on singlet oxygen oxidation.

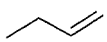
The 6-azido analog[251] of oxymorphone has an analgesic potency similar to that of the corresponding compound lacking the 14-OH group (p. 39), suggesting that the effect of the 6-azido and 14-OH substituents, which independently tend to enhance opioid actions, are not cumulative in their action. A similar observation was made for 14-hydroxyazidomorphine.[256]

Hydrazone derivatives[258] of oxymorphone, naloxone, and naltrexone have been made by reaction with anhydrous hydrazine and designated *oxymorphazone* (**170**), *naloxazone* (**171**), and *naltrexazone* (**172**). All three hydrazones exhibited a high binding affinity for *in vitro* rat brain receptor sites.

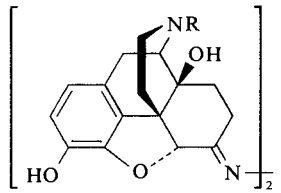
Compounds **171** and **172** were pure antagonists and, as expected, oxymorphazone was an agonist, giving long-acting effects in the RTF test relative to oxymorphone. A similar long action was found for naloxazone and naltrexazone in their inhibition of morphine analgesia in mice for more than 24 h. Naloxazone has become a valuable reagent in receptor studies because of its



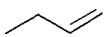
170 R = Me

171 R = 

172 R = CPM



173

R = Me,  or CPM

high affinity and long action (3 days) at μ binding sites. At high doses it appeared to block analgesia with little effect at other receptors.[259,260]

The reason for the irreversible opioid agonist and antagonist actions of 14-hydroxydihydromorphinone hydrazones (**170**, **171**, and **172**) has been attributed[261] to the formation of their respective azines (**173**). These azines, which may form if a large excess of hydrazine is not used during the synthesis of the hydrazones, have been found to be stable and to block opioid receptor binding *in vitro* irreversibly at 20–40 times the potency of their corresponding hydrazones.

Benzomorphans substituted on nitrogen with a 2-tetrahydrofurfuryl group[262] show discriminative activity according to the C-2 configuration of the tetrahydrofurfuryl group. High analgesic activity without antagonist effects resides in the *R* isomer, with one isomer having antinociceptive activity of 100 × morphine. The corresponding 4,5-epoxymorphinan-6-one (**165**) has been described[263] and the **R*-isomer was once again found to be a potent agonist (MW, sc, ED_{50}, 0.02 mg/kg; morphine, 0.5 mg/kg); however, MHP and RTF results were less encouraging. The **S*-isomer had no agonist actions, but both isomers exhibited antagonist properties, a surprising result in view of the findings in the benzomorphan series.

(+)-Naloxone has been synthesized[119-128] from (−)-sinomenine via (+)-7-bromodihydrocodeinone dimethyl ketal (p. 29). It possessed only 10^{-3}–10^{-4} the antagonist activity of (−)-naloxone in the rat brain receptor binding assay, GPI test, and neuroblastoma × glioma hybrid cell adenylate cyclase assay. This enantiomorph may be of value to test the stereospecificity of the actions of (−)-naloxone.

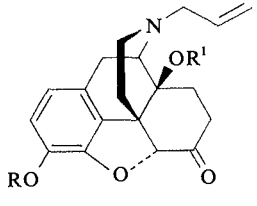
Antagonist actions in 4,5-epoxymorphinans are often substantially increased when oxygen is introduced into the molecule at C-14[264], and several explanations have been offered for this phenomenon.[265-268] In particular, the effect of a 14β-OH function upon the *N*-substituent and its directionality,[269,270] or upon molecular conformation,[271,153] has been given some consideration. The suggestion[272] that the 14-OH interacts both with the protonated tertiary nitrogen and with low-energy conformers of the *N*-substituent at a common anionic site on the opioid receptor has been tested[273] by the

preparation and biological evaluation of 14β-OMe and 14β-OEt derivatives of naloxone (**160**) and naltrexone (**162**) from the previously described 14β-alkoxycodeinones.[274,275]

All four compounds were found to be potent antagonists at μ and δ receptors in the MVD and were devoid of agonist actions. This was reflected in their *in vitro* receptor binding characteristics. Loew and Berkowitz[268] had postulated that strict steric requirements for the OH–N interaction with a common ionic site would be impaired by *O*-alkylation and that this should result in an enhancement of the agonist-antagonist ratio. The lack of agonist actions in the 14β-alkylated derivatives is evidence in contradiction of the common ionic site hypothesis.

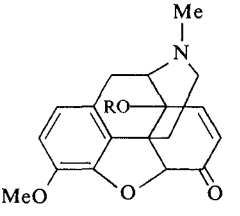
Acylation of the 14-OH group of compounds corresponding to codeine, 6-acetylcodeine, codeinone, and 6-deoxycodeine gave a wide range of 14-acyloxy- derivatives.[276] Earlier[277] the preparation of 14-acetoxycodeine-6-acetate had been described and 14-acetoxycodeinone was reported to be a rather better analgesic than 14-hydroxycodeinone but was more toxic.[278] An extensive pharmacological examination[279] of 14-acyl-4,5-epoxymorphinans revealed that 14-hydroxylation did not increase the potency of codeine, while *O*-acylation of that hydroxyl was advantageous in this respect. Although the 14-benzoate was similar in potency to the unacylated derivative, the phenylacetate caused a large increase in analgesic potency in rats. Likewise, extending the alkyl chain length in the ester function also increased analgesic potency, with the 14-*n*-pentanoate ester of Δ^7-6-deoxycodeine being about 75 × morphine in rats (5 × morphine in mice). Extension beyond that resulted in reduced potency. 14-Acylation of the Δ^7-analog of **158** also results in some potent agonists (Table 2.1). The cinnamate ester[280] is almost 200 × morphine, and perhaps here is further evidence of a receptor lipophilic site extending above and away from the plane of the opiate C-ring.

Mono- and disulfates and acetates of naloxone have been prepared[281] as antagonists that it was hoped would have a longer duration of action than the parent. The sulfates **174a, b, c** were inferior to naloxone, both po and iv in potency and duration of action. In contrast, the acetates **174d, e**, and **f** were equivalent to naloxone, iv, in antagonizing morphine-induced respiratory depression, and they were more potent and longer-acting as antagonists, po. *N*-Methylquaternary salts of naloxone and naltrexone exert predominantly peripheral antagonist actions as expected.[155]



174	R	R'
a	SO_3^-	H
b	H	SO_3^-
c	SO_3^-	SO_3^-
d	Ac	H
e	H	Ac
f	Ac	Ac

Table 2.1. Analgesic Activities of Some Esters of 14-Hydroxycodeinone in Mice (Tail-Clip Method)[a]



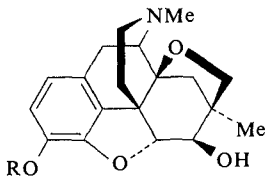
R	Relative activity (morphine = 1)
COMe	4
COEt	18.8
COPr	28.7
COBu	38.8
$CO.C_5H_{11}$	47.2
$CO.C_6H_{13}$	60.1
$CO.C_7H_{15}$	5.1
$CO.C_9H_{19}$	1.1
$CO.C_{11}H_{23}$	0.03
$CO.CH_2Ph$	52
$CO.CH_2CH_2Ph$	115
CO.CH = CHPh	177
CO.CH=CHMe	31

[a] From Refs. 279 and 280.

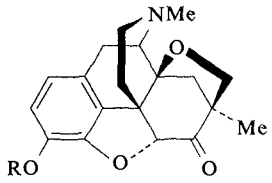
The synthesis and pharmacological activity of 7α-alkyl-[208] and 8-alkyl-[229] analogs of 4,5-epoxymorphinans have been discussed (pp. 40, 50). During this work the corresponding 14β-OH analogs were also prepared. Increase in the size of the 7α-alkyl substituent beyond Me causes a reduction in antinociceptive responses. In the 8-alkyl-14β-hydroxydihydrocodeinone series,[282] lithium dialkyl cuprates introduced an 8-alkyl group in both the 8α- and 8β-positions (up to 1:2), in contrast with findings in the 14-noroxy-series, where only traces of the 8α-epimer were detected. However, it is worth comparing this with a contrary report.[231]

7,7-Bis(hydroxymethyl)dihydroisocodeine (**108**) (Scheme 2.15, p. 44) provided an intermediate that could be converted to analgesic oxetanes (e.g., **110**) and to other, similar series (Schemes 2.16 and 2.17) all described earlier. Kotick[283] extended this work into series of 14-hydroxydihydrocodeines and 14-hydroxydihydromorphines. Here a facile cyclization between the 7β-tosyl-oxymethylene moiety and the 14β-OH occurred that denied access to

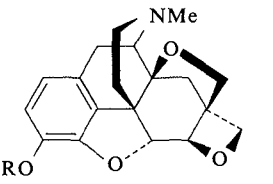
7β-aralkyl-14β-hydroxy-4,5-epoxymorphinans analogous to the potent opioid agonists found in the 14-noroxy- series. In addition to the oxetanes described earlier in this chapter, compounds **175–178** were isolated and characterized. Although, as for the very potent Diels–Alder adducts of thebaine, these compounds have a highly constrained C-ring, their agonist activity (MW) did not improve over that of morphine, thus adding additional evidence that molecular rigidity in itself is insufficient to endow a molecule with high opioid potency.



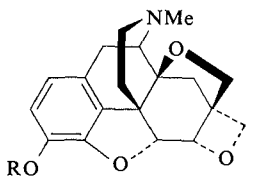
175



176



177



178

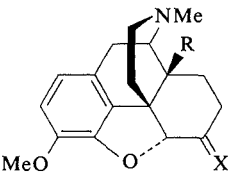
In view of the impressive levels of pharmacological activity seen with 14β-hydroxy-4,5-epoxymorphinans, it is not surprising that other electronegative groups have been inserted into the C-14 position. Thebaine (**3**)[284] was used as a precursor to the 14β-nitro-, 14β-acetamido, 14β-mercapto and 14β-halogenocodeines, codeinones, morphines, and morphinones, according to Scheme 2.21.

Addition of dinitrogen tetroxide to thebaine[285] gave both the 1,4- and 1,2-addition products, 8-nitrothebaine being isolated as well as **179** (R′ = NO_2).[286] Mild nitration of thebaine[287] with tetranitromethane in MeOH gave 14β-nitrocodeinone acetal (**182**, R′ = NO_2), convertible to **182** (R′ = NH_2) and **180** (R′ = NH_2). In benzene rather than methanol as solvent in the presence of air or oxygen, the epidioxide (**183**) resulted that was isomerized in NaOH/EtOH to 8- and 10-oxo-4,5-epoxymorphinans. Compounds **179** (R′ = NO_2; R′ = Cl; R′ = Br), **180** (R′ = SH), and **181** all had a substantially lower GPI activity than normorphine (see also Chapter 12, p. 405).

Thebaine was also the starting material for the preparation of 14-(arylhydroxyamino)codeinones[288] (**185**) by 1,4-addition of a nitrosobenzene and acid treatment of the adduct (**184**). Catalytic hydrogenation gave the 14β-arylaminodihydrocodeinones (**186**). Sodium methoxide treatment of **185** caused cyclization to the oxazoline derivative (**187**). None of these compounds, including **179** (R = NHOH), had interesting opioid activity.

14β-Methyl and 14β-ethyl-4,5-epoxymorphinan derivatives have been examined[289] in the GPI and MTF assays. 14β-Ethylmorphinone exhibited a very high level of agonist potency (117 × morphine). In another study 14-alkyl groups were introduced into 4,5-epoxymorphinans via a Claison–Eschenmoser reaction.[290] The 6-azido-14β-methyl derivative **188** was 5000 × morphine (sc) in the MTF test and **189** had 10^4 × the antinociceptive potency of morphine.

The same authors[291] have used similar means to insert dimethylamidomethyl, hydroxyethyl, and carboxymethyl groups at C-14.



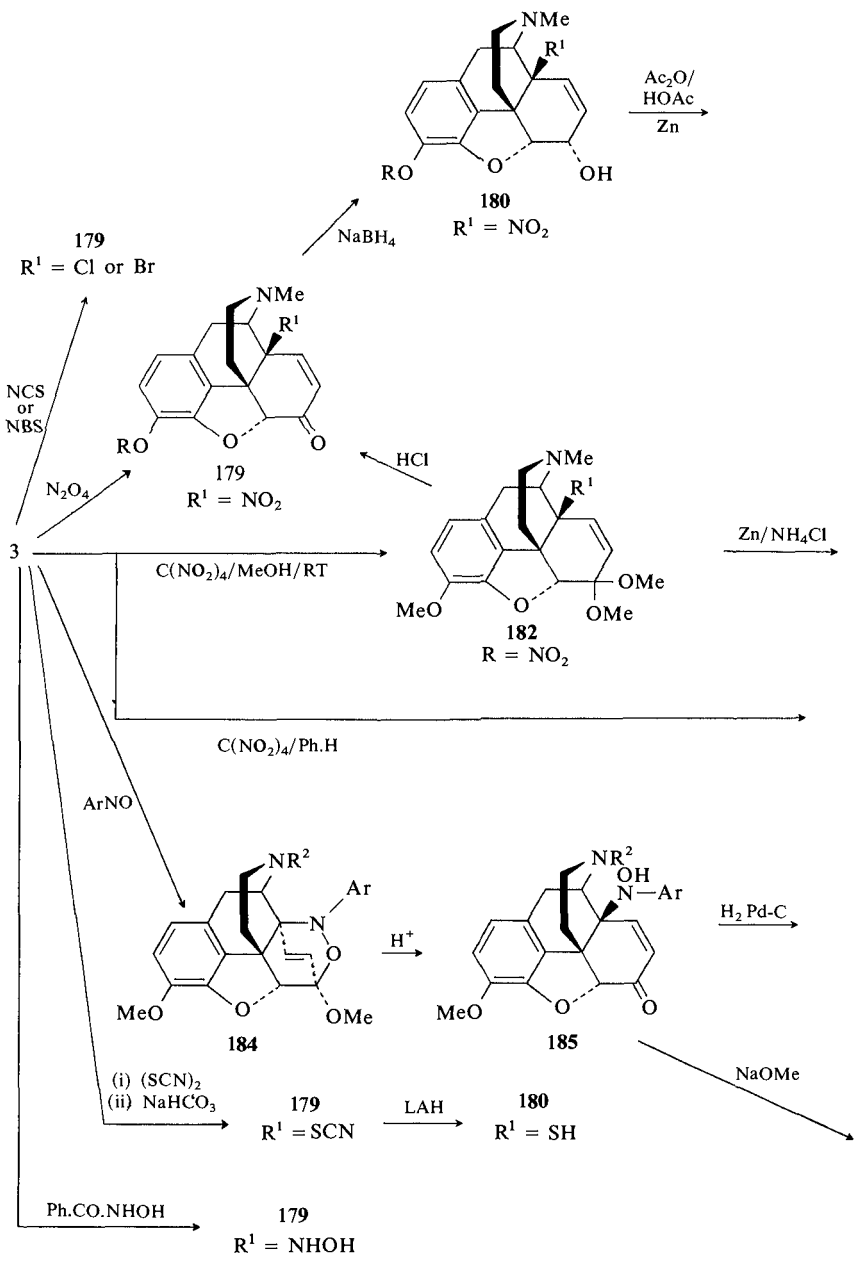
	R	X
188	Me	6β-N_3, 6α-H
189	Et	O

2.5.8. 6-Substituted-14-hydroxy-4,5-Epoxymorphinans as Receptor Probes

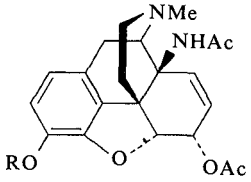
Opioid antagonists such as naloxone and naltrexone are of considerable importance as pharmacological probes in the investigation of opioid receptors.[292] By encouraging the covalent binding of antagonists to regions at or proximate to the receptor, Portoghese's group at the University of Minnesota has developed a range of 14-hydroxy-4,5-epoxymorphinans of great potential in opioid receptor studies.

Opioid receptor affinity labels have been reported for other narcotic analgesics, for example, piperidines,[293,294] benzomorphans,[295,296] and morphinans,[297,298] and the topic is further discussed in Chapter 13 (p. 445). Not only is the oxo-function in the 4,5-epoxymorphinan C-ring available for ready elaboration, but C-6 substituents, although they affect agonist potency, do not impair unduly receptor affinity.[299-301]

Chlornaltrexamine (β-CNA), **191** (R = CPM) was the first affinity labeling agent of this class to be described[302,303] with an alkylating function at C-6 able to bind covalently to narcotic antagonist receptors, which mediate antagonist activities both *in vivo* and *in vitro*. The synthesis of **191** started with naltrexone (**162**), an antagonist[304] with high receptor affinity.[299] Reductive amination of **162** with diethanolamine and sodium cyanoborohydride (Scheme 2.22) gave the desired 6β-[*N*,*N*-bis(2-hydroxyethyl)amino]-derivative, **190** together with the more abundant 6α-ol (40:60). Dehydroxychlorination of **190** HCl salt to chlornaltrexamine (**191**, R = CPM) was best effected with triphenylphosphine and CCl_4.[305] Reductive amination of **162** with ammonia gave a mixture of epimeric 6-amines (naltrexamines) with the 6α-amine predominating (2:1). An improved route[306] to the desired 6β-amino compound (**192**) was achieved via the iminium intermediate **194** from reaction

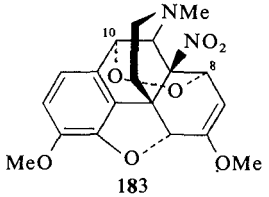

NMe
R1
RO
O
OH
180
R1 = NO2
Ac2O/
HOAc
Zn
NaBH4
179
R1 = Cl or Br
NCS
or
NBS
N2O4
179
R1 = NO2
HCl
3
C(NO2)4/MeOH/RT
MeO
OMe
182
R = NO2
Zn/NH4Cl
C(NO2)4/Ph.H
ArNO
NR2
Ar
N
O
MeO
OMe
184
H+
OH
N—Ar
185
H2 Pd-C
NaOMe
(i) (SCN)2
(ii) NaHCO3
179
R1 = SCN
LAH
180
R1 = SH
Ph.CO.NHOH
179
R1 = NHOH

Scheme 2.21

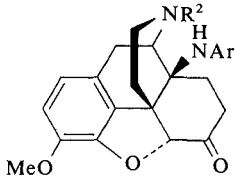


181

182 $R^1 = NH_2$ $\xrightarrow{HCl}$ **179** $R^1 = NH_2$ $\xrightarrow{NaBH_4}$ **180** $R^1 = NH_2$

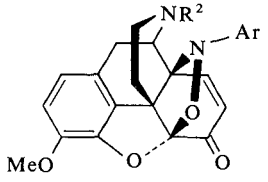


183

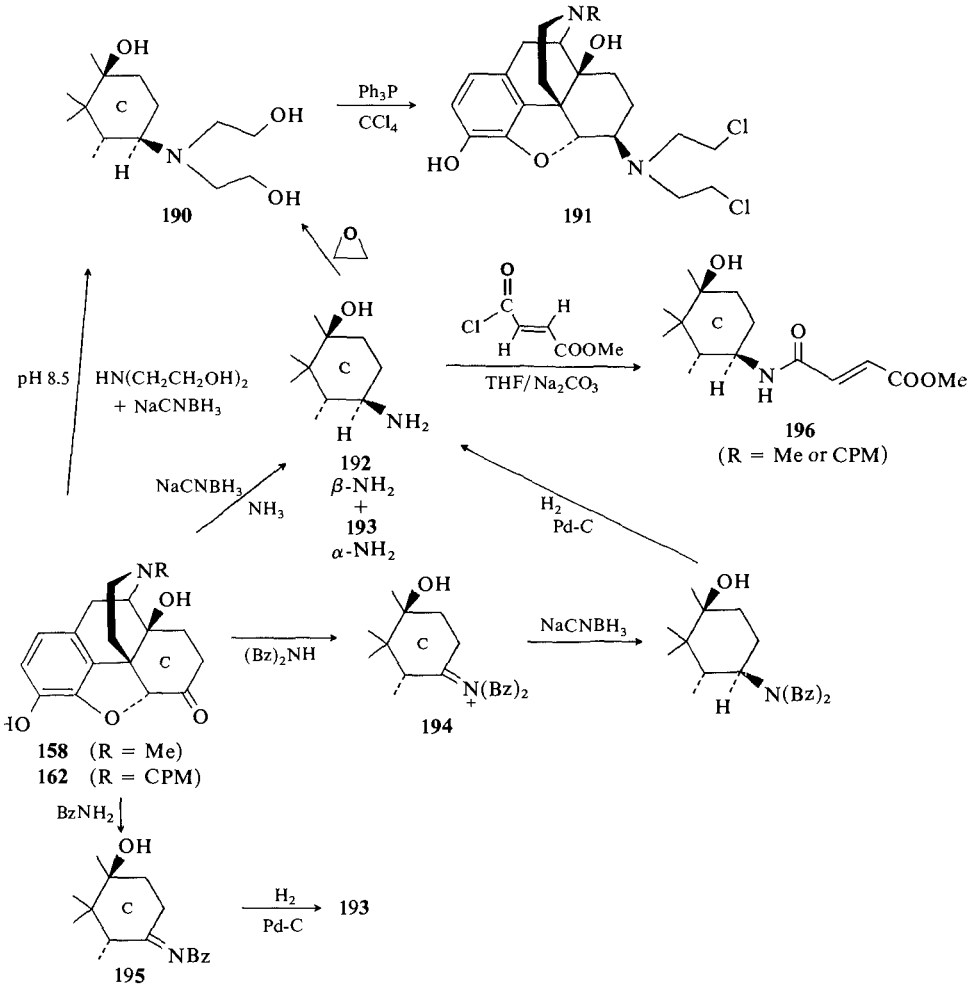


186

R = H or Me
R^2 = H or Me



187



Scheme 2.22

of **162** with dibenzylamine and azeotropic removal of water, followed by $NaCNBH_3$ reduction to the dibenzylamine and hydrogenolysis to **192**. The epimeric 6α-amino compound, **193**, was prepared from the monobenzylimine (**195**) by hydrogenation. Reduction of the 6β-amine in the presence of ethylene oxide under pressure gave 77% of **190**, thus confirming the stereochemistry about C-6. Stereochemical assignments were established by ^{1}H nmr.

Chlornaltrexamine was found to produce opioid antagonist actions in mice lasting from 3 to 6 days; in addition, a single icv dose prevented the development of physical dependence in mice for at least 3 days. Receptor

binding studies demonstrated a similar persistent action that could not be stopped, as it could with naltrexone, by washing the preparation. On the electrically stimulated GPI, chlornaltrexamine again produced specific irreversible opioid antagonist actions.[307] These properties strongly suggest that chlornaltrexamine binds covalently at antagonist receptors.

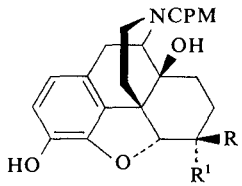
Chloroxymorphamine (β-COA), **191** (R = Me), on the other hand, produced irreversible agonist responses[307] also, presumably by an alkylating mechanism. Alkylation probably occurs from attack by a receptor nucleophilic group upon a mediating aziridinium ion. The mutagenic nature of compounds capable of generating aziridinium ions is likely to render compounds of this sort unacceptable for human therapy.

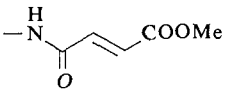
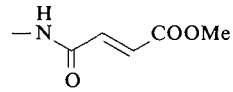
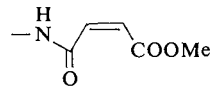
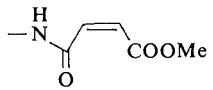
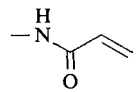
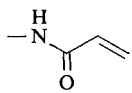
Once it was clear that the concept of making alkylating agents capable of binding at or near receptors was valid, the technique, therefore, was refined. Bis-functional nitrogen mustards are highly subject to random nucleophilic attack *in vivo* and *in vitro*, and a more selective binding to receptors could be encouraged with a less vigorous means of covalent bond formation. A more discriminate means, it was argued,[308] could be through Michael addition. Michael acceptors such as fumarate were positioned at C-6 to give antagonists and agonists corresponding to chlornaltrexamine and chloroxymorphamine, respectively. The amides **196** (R = Me and CPM), called *Fuoxymorphamine* (β-FOA) and *Funaltrexamine* (β-FNA), were made by treatment of the corresponding 6β-amines (**192**, Scheme 2.22) with the monomethyl ester of fumaroyl chloride.

In the GPI test β-FNA (**196**, R = CPM) produced a potent reversible agonist response, but upon incubation of the ileum preparation, β-FNA gave rise to an irreversible antagonist action. The prior addition of naltrexone, a reversible antagonist, blocked the take-up of β-FNA during incubation. In contrast, β-FOA (**196**, R = Me) under similar conditions produced a reversible agonist action in the GPI preparation, but upon incubation, no irreversible action was seen. Furthermore, the agonist actions of β-FOA were blocked by the postincubation irreversible actions of β-FNA. Thus, selectivity does appear to have been achieved by the Michael-acceptor approach to affinity labeling. The authors concluded, "This indicates either that β-FNA and β-FOA interact differently with a single receptor or that they associate with different receptors, as proposed in the original concept." [309] They go on to speculate that a similar difference may occur with chlornaltrexamine and chloroxymorphamine but that the higher and less discriminative reactivity of the *N*-mustards does not permit the observation of separate actions.

Thiol groups are known to react well with Michael acceptors and could be the nucleophiles responsible for the irreversible binding observed for **196**.[292]

Pharmacological studies[310,311] on β-funaltrexamine (**196**, R = CPM) have indicated that its MW and MTF antinociceptive actions were of short



	R(β)	R'(α)
196		H
197	H	
198	H	
199		H
200	H	
201		H
202	H	$NHCOCH_2I$
203	$NHCOCH_2I$	H
204	H	—N=C=S
205	—N=C=S	H

duration and appeared to be κ-receptor mediated. Its MVD responses[311,312] suggested a μ-opioid antagonist. In contrast, chlornaltrexamine was a non-specific μ-, κ-, and δ-antagonist.

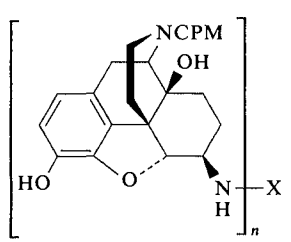
An examination[313] of the importance of C-6 chirality on the binding and pharmacological actions of naltrexone-derived receptor affinity labels was made possible by the accessibility of both 6α-naltrexamine (**193**) and 6β-naltrexamine (**192**).[306,299] These amines themselves possessed antagonist activity in mice with a prolonged duration of action.[299]

Epimeric pairs of naltrexone derivatives substituted either α- or β- at C-6 with groups carrying an electrophilic substituent (**196–205**) were examined. All compounds behaved as reversible agonists in the GPI asssay; however, only **196** (β-FNA) and **205** bound covalently after incubation, exhibiting a selective irreversible antagonist action against the morphine μ-effects, without affecting κ agonist actions. It would appear that both **197** (α-FNA) and **196** (β-FNA) bind at the same receptor in view of the observation that prior treatment of the GPI preparation with α-FNA (itself nonalkylating) inhibits alkylation of the receptor by β-FNA. No binding to κ-receptors was seen with

these compounds, and it was suggested that the κ-receptor region does not have sufficiently reactive nucleophiles in its vicinity. β-Funaltrexamine (**196**) was also found to bind irreversibly to MVD receptors, whereas its 6-epimer did not. Neither affected δ-receptors. Maleamates (**198** and **199**) and fumarates (**196** and **197**) are equally good Michael acceptors and the lack of irreversible binding capacity in the former is probably due to their obvious steric differences. The 6-isothiocyanate epimers **204** (α) and **205** (β) irreversibly blocked both α- and β-receptors. In the MVD assay, the 6β-iodoacetamide analog (**203**) was found to block irreversibly the actions of morphine. A review of these studies has been published.[314] From these and other considerations Portoghese and Takemori[315] have proposed that antagonists such as naloxone and naltrexone may exert their pharmacological actions by combining selectively with a receptor site, ρ, situated allosterically with respect to the μ-site. Agonists may bind to the ρ-sites, but only after the associated neighboring μ-site is occupied. Thus, the so-called purity of agonist or antagonist actions depends upon the relative affinities of ligands for the μ- and ρ-sites.

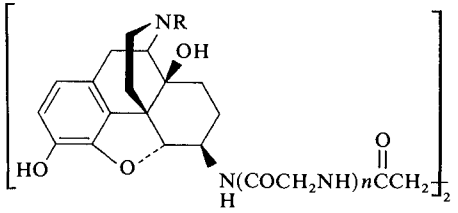
The connecting of two pharmacophoric moieties by an interlinking chain, the length of which may be varied, has been shown[316,317] to offer a means of investigating how close receptor sites are to each other in their occupied state. β-Naltrexamine was linked through its 6-amino function by chains of repeating oxyethylene (oxyethano) units that were chosen to minimize partition coefficient variation. These so-called spanner units were inserted by the gradual addition of tri- or hexaethylene glycol ditosylate[318,319] in diglyme-toluene to two equivalents of β-naltrexamine[316] to give **206**. Alternatively, symmetrical succinyl-bis-oligoglycine with from zero to four glycine units was used as "spanners" [317] for β-naltrexamine (**192**, R = CPM) and β-oxymorphamine (**192**, R = Me) bivalent ligands.

The bivalent ligand (**206a**) had an antagonist potency (GPI) against ethylketazocine (a κ agonist) 10 times that of the corresponding monovalent ligand (**206c**); but as an antagonist against morphine, no difference was seen.



		n	*X*
206	**a**	2	$-CH_2CH_2OCH_2CH_2OCH_2CH_2-$
	b	2	$(CH_2CH_2OCH_2CH_2OCH_2CH_2)_2O$
	c	1	$-CH_2CH_2OCH_2CH_2OCH_2CH_2OCH_3$
	d	1	$-CH_2CH_2OCH_2CH_2OCH_2CH_2OTs$

By doubling the "spanner" dimension from 3 to 6 oxyethylene units (**206b**) 15 times greater antagonist action than **206c** (MVD) against the agonist actions of [D-Ala, ^{2}D-Leu^5] enkephalin (DADL) resulted. In the **207**, succinyl-*bis*-oligoglycine "spanner" series, all compounds (R = CPM) antagonized the actions of morphine in the GPI. The highest potency occurred when $n = 0$ (i.e., the succinyl congener). In contrast with these data were those for the **207** (R = Me) agonist series. When $n = 2$, an agonist activity increase of 17 times was observed, whereas when $n = 0$, opioid agonism was no greater than that of oxymorphamine (**192**, R = Me).



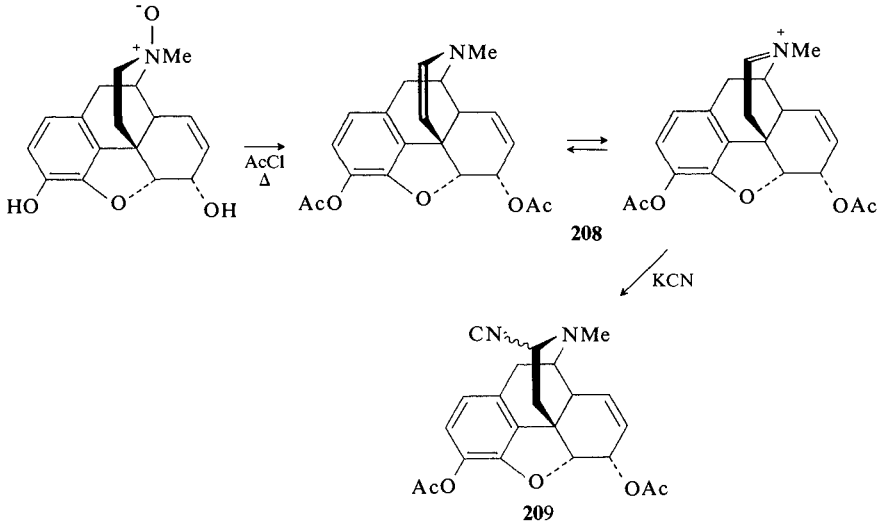
207 R = Me or CPM
n = O–4

Thus, μ, κ, and δ opioid receptors behaved differently toward bivalent ligands with differing interspatial distances. In each series enhanced potency over the monovalent ligand suggested dual occupancy of proximate receptors. Once one pharmacophoric unit finds its receptor, the second, being tethered but mobile, will itself find a binding site. Thus, distances between receptors of similar type are different, with, for example, **206a** having a "spanner" distance of ~9 Å, suggesting that κ receptors are closer together than are δ receptors [cf. **206b** (~20 Å)]. Whether the recognition site pairs are the same or different remains to be established. Furthermore, results from series **207** hinted that agonist and antagonist recognition sites may differ.

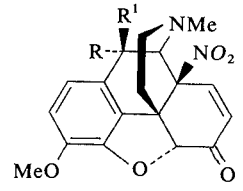
A similar independent investigation[320] of the pharmacological responses of dimers of oxymorphamine and enkephalins linked by a $(CH_2CH_2.S)_2$ chain also found that dimer potencies were greater than those of the monomer.

2.5.9. Miscellaneous 4,5-Epoxymorphinans

Impurities in illicit morphine or heroin samples are important in establishing the manufacturing source of the drug. $\Delta^{16,17}$-Dehydroheroinium chloride (**208**) has been found[321] in trace amounts in illicit heroin and may also be formed as a post-injection artefact during GC analysis of heroin samples. A synthesis from morphine-*N*-oxide by treatment with excess of hot acetyl chloride has been effected and **208** converted to 16-cyanoheroin (**209**) with aqueous KCN.



During a study of the nitration of thebaine with tetranitromethane,[287] the unusual epoxide **183** was isolated when the nitration was performed in the presence of air. In establishing the structure of **183**, two products (**210a** and **b**) oxygenated at C-10 were isolated.



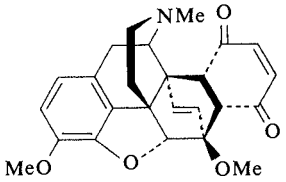
210 **a** R, R′ = O
b R = OH, R′ = H

2.6 DIELS–ALDER ADDUCTS OF THEBAINE

A dramatic stimulus was given to synthetic opioid research in the early 1960s with a report by Bentley and Hardy[322] that compounds derived from the addition of dienophiles to thebaine gave analgesic potencies of extraordinary levels, up to almost $10^3 \times$ morphine in the rat (RTF). The rationale for this approach was the view that if morphine and related compounds bound to receptors in order to initiate their responses, molecular flexibility would permit a molecule to adapt to a number of receptor types. It would elicit not simply the desired analgesic response, but in addition, the unwanted "side effects." Further, it was argued that greater molecular rigidity would restrict receptor fit and, it was hoped, afford a greater degree of selectivity

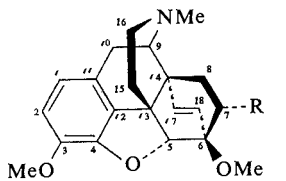
toward the analgesic receptor. Although present knowledge of opioid receptors would suggest that such a view is now an oversimplification of the situation, this novel approach more than 20 years ago proved to be highly successful and has influenced opioid design and receptor thinking since. A detailed review of the chemistry of thebaine Diels–Alder adducts up to 1970 has been published by Bentley.[473]

As early as 1956[323] it had been demonstrated that the benzoquinone Diels–Alder adduct, **211**, was about equivalent to pethidine (about one seventh times morphine) in rodent analgesic assays. However, at that time, appropriate pharmacological evaluation was not readily available to the investigators and the project remained fallow for several years.



211

Thebaine (**3**) gave a range of Diels–Alder addition products with dienophiles, initially α,β-unsaturated ketones, with aldehyde, ketone, nitrile, and ester centers, of general structure **212** (R = CN, CHO, CO.Me, COOMe, etc.), capable of further elaboration.[324,325] Addition of a dienophile to thebaine is restricted to the exposed face of the diene C-ring, thus affording 6,14-*endo*-ethenotetrahydrothebaine derivatives. Here *endo* implies that the 6,14-etheno bridge lies in a configuration opposite to the C-14 hydrogen and C-6 methoxyl, that is, α-to those groups (**212**). Clearly, the addition of the dienophile may occur in such a way as to give products epimeric at C-7, and according to atomic models, each could be formed with equal facility. Stereochemical control of Diels–Alder addition, however, gave adducts with 7α-substituents and only very small amounts of 7β- were detected. It is apparent that with unsymmetrical dienophiles (e.g., alkyl and aryl vinyl ketones, acrylic esters, and acrylonitrile), C-7 and C-8 substituted 6,14-*endo*-ethenotetrahydrothebaine derivatives could result. However, the addition appears to be under electronic control and gave only 7-substituted products with no C-8 substituted compounds detectable even during large-scale preparations.



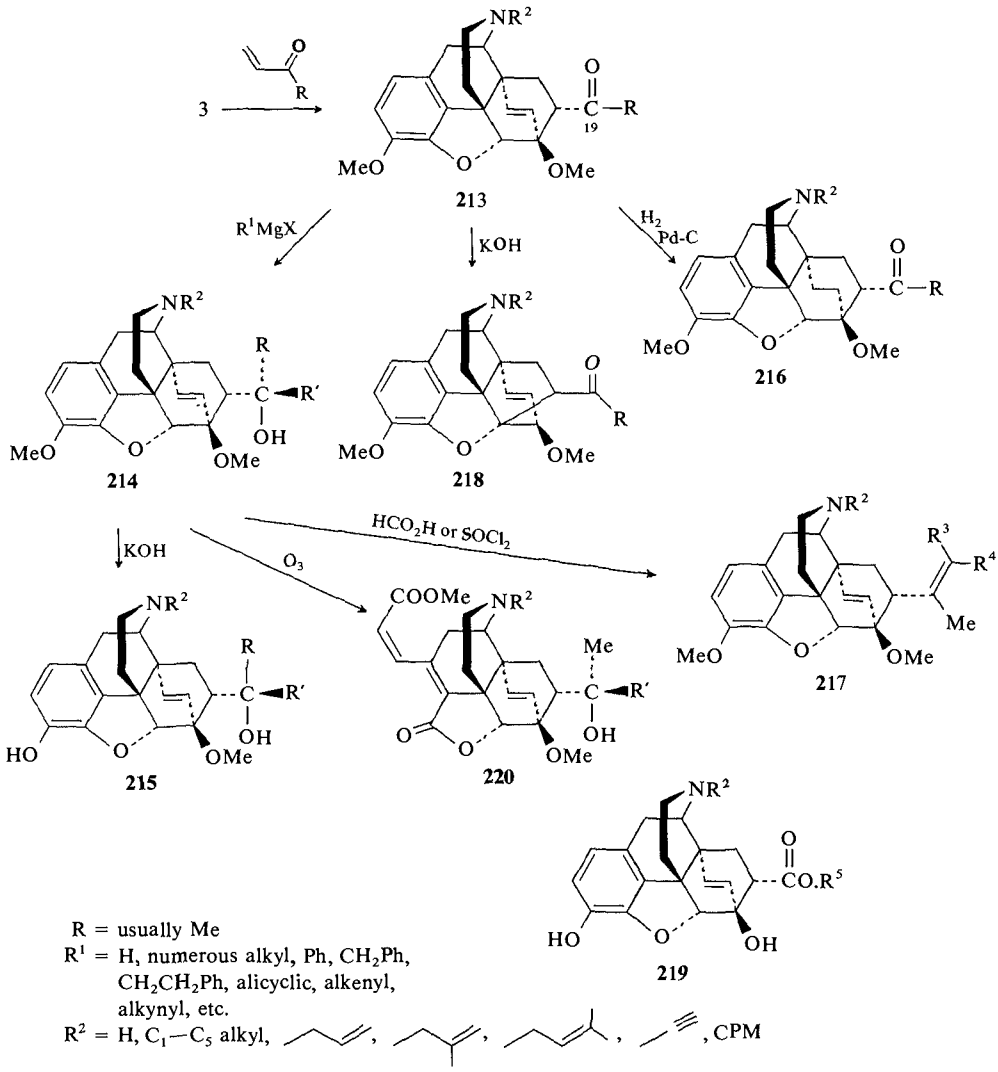
212

Reviews on the chemistry[473] and structure-biological activity relationships[13,326-329] are available.

Diels-Alder reactions of thebaine with alkylvinyl ketones[324] afforded 7α-alkylketones (**213**) that react readily with Grignard reagents[330] to give alcohols of general structure **214**. During Grignard attack a six-membered transition stage was proposed to account for the resultant stereospecific attack on the carbonyl from above the plane of the C-7 to C-19 bond, giving alcohols of fixed stereochemistry (**214**). Secondary alcohol from competing Grignard reduction constituted up to 30% of the product of some reactions. Ketones of structure **213** were reduced under Meerwein Pondoff conditions (aluminum isopropoxide) to the corresponding secondary alcohols (**214**, R′ = H). In this series, cleavage of the 3-OMe[331] must be performed under base conditions in view of the facile rearrangement in acid of opioids of this type. Potassium hydroxide in diethylene glycol at 200-220° proved to be the most effective conditions affording the oripavines, **215**. Hydrogenation of the 6,14-etheno double bond was effected over palladium on charcoal to give the corresponding 6,14-ethano series (**216**). To vary the *N*-substituent, *N*-demethylation was performed at various stages of the reaction sequence (Scheme 2.23) and under a variety of conditions.[331,332] Cyanogen bromide followed by KOH in diethylene glycol at 180° was employed to *N*-demethylate the alcohols **214** and **215**. 7-Ketones and 7-esters (**213**, R = alkyl or *O*-alkyl) were found to rearrange readily in strong base and these were *N*-dealkylated by diethylazodicarboxylate, followed by weak acid treatment, conditions that were effective also for **214**. The *N*-substituent was inserted under conditions described in Chapter 12, to give *N*-alkyl (up to C_5), allyl, dimethylallyl, 2-methylallyl, propargyl, and CPM derivatives.

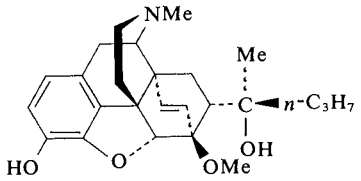
Etorphine (Immobilon) (**221**) has an exceptionally high agonist analgesic potency, in the order of 8600 × morphine in guinea pigs,[333] and although it has been demonstrated[334] to be a potent analgesic in humans, it had a low therapeutic index, causing considerable respiratory depression in primates. The major application of etorphine has been in veterinary practice[335-338] to subdue both large and small animals for surgical and manipulative procedures. An application that caught the imagination of both media and public is the use of etorphine for the immobilization of big game animals. The agonist actions of etorphine may be reversed by naloxone or *diprenorphine* (Revivon) (**222**), before CNS depression effects become harmful. In humans, reversal of agonist actions after accidental administration of very small amounts of etorphine is considerably more difficult. Extreme caution must be exercised in its use because of this and because of its percutaneous absorption potential.

Unfortunately, in a series such as this, antagonists have not yet been discovered with the potency to match agonists. *Diprenorphine* is about 100 × nalorphine as a morphine antagonist, and it exhibits no antinociceptive properties in the MW test.[339] However, in the GPI assay, some agonist actions were



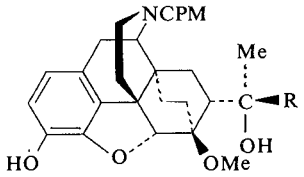
Scheme 2.23

observed,[341] and these were reversed by high doses of the "pure" antagonist naloxone.[13] Not only is diprenorphine able to reverse the actions of agonists such as morphine and etorphine, but it also antagonizes the agonist actions of mixed agonist-antagonists such as nalorphine, levallorphan, and pentazocine.[341]



221 Etorphine

Buprenorphine (Temgesic) (**223**), with a *t*-butyl group attached to C-19, rendering the molecule highly lipophilic, was found to be 75 × morphine as an agonist, with twice morphine's duration of action in rodents, and 4 × nalorphine as an antagonist.[327] It did not give rise to a PDC on chronic administration to primates or rodents.[342,343] Nalorphine and buprenorphine were equipotent as antagonists of phenazocine in rats.[344] Receptor binding assays suggested that buprenorphine behaved essentially as an opioid antagonist.[345] In humans, buprenorphine (0.6 mg, im) was equieffective with morphine (15 mg, im) as an analgesic with a longer duration of action in a double blind trial of patients recovering from Caesarian section,[346] and a similar effect was found in patients who had undergone major abdominal surgery.[347] No serious side effects were noted. Clinically, buprenorphine is used for the control of moderate to severe pain by either im injection or sublingual tablets.



222 R = Me, Diprenorphine
223 R = *t*-Bu, Buprenorphine

Many other chemical modifications have been made to this remarkable series of compounds in the exploration of structure-activity relationships.[473] Tertiary alcohols of general structure **214** (R = Me) have been dehydrated[348] by 98–100% formic acid to alkenes (**217**) via a C-19 carbocation intermediate. The anticipated carbocation rearrangement byproducts were also isolated. Dehydration was directed invariably to the side chain rather than to C-7, and the resultant alkenes were much reduced in analgesic potency. Carbocation rearrangements were catalyzed by concentrated HCl, and various bridged products have been investigated.[349,350]

Base (KOH) catalyzed rearrangements of 7α- and 7β-ketones of the 6,14-*endo*-etheno and *endo*-ethanotetrahydrothebaines (e.g., *nepenthone*, **213**, R = Ph) have also been shown to afford bridged systems [e.g., **218** (R = Ph)], the chemistry of which was investigated.[351] A product of photochemical rearrangement of thebaine Diels-Alder adduct with dimethyl acetylenedicarboxylate has been shown to be an unsaturated analog of **218** (R = OMe).[352]

A similar NaOH- or KOH-catalyzed rearrangement of the dihydrothebaine-quinone (**211**) occurred.[353]

7α-Amino-6,14-*endo*-ethenotetrahydrothebaine derivatives have been prepared[354] by the Curtius degradation of the 7α-carboxylic ester, **213** (R = OEt, R^2 = Me) via the corresponding hydrazide and azide. The 7α-amines were without analgesic activity. 7α-Aminomethyl derivatives were also made[355] from the same ester (**213**, R = OEt, R^2 = Me) by conversion to the corresponding amide and LAH reduction. Analgesic activities in these derivatives were lower than those in corresponding alcohols, although 3-O-demethylation caused the usual increase in both analgesic and antitussive potency. The 7α-amino derivatives have been converted to several useful affinity labels (p. 453).

3-*O*-Demethylation in these series is often difficult because 7-substituted 6,14-*endo*-ethenotetrahydrothebaines are subject to acid-catalyzed rearrangements, and 7-ketones and esters undergo base-catalyzed transformations. It was shown,[356] however, that ethyl 6,14-*endo*-ethenotetrahydrothebaine-7α-carboxylate, **213** (R = OEt, R^2 = Me), was sequentially 3-O-demethylated, 6-O-demethylated, and the 7-ester hydrolyzed by HBr/HOAc at room temperature. This permitted variation of both *N*-substituent and the ester function in 6,14-*endo*-etheno-7,8-dihydromorphine series (**219**). Interesting analgesic responses in this series were shown by **219** (R^2 = CPM, R^5 = Et), which was an antagonist (3 × nalorphine), and **219** (R^2 = CPM, R^5 = *n*-Bu), a potent opioid agonist (30 × morphine).

Different aromatic substituents have been introduced at C-1 and C-2 of 6,14-*endo*-ethenotetrahydrothebaine.[357] Phenols in this series [e.g., the 3-OH corresponding to **214** (R = R^1 = R^2 = Me)] undergo the Mannich reaction with formaldehyde and secondary amines readily. All compounds with a second amine function in the molecule had substantially reduced analgesic responses.

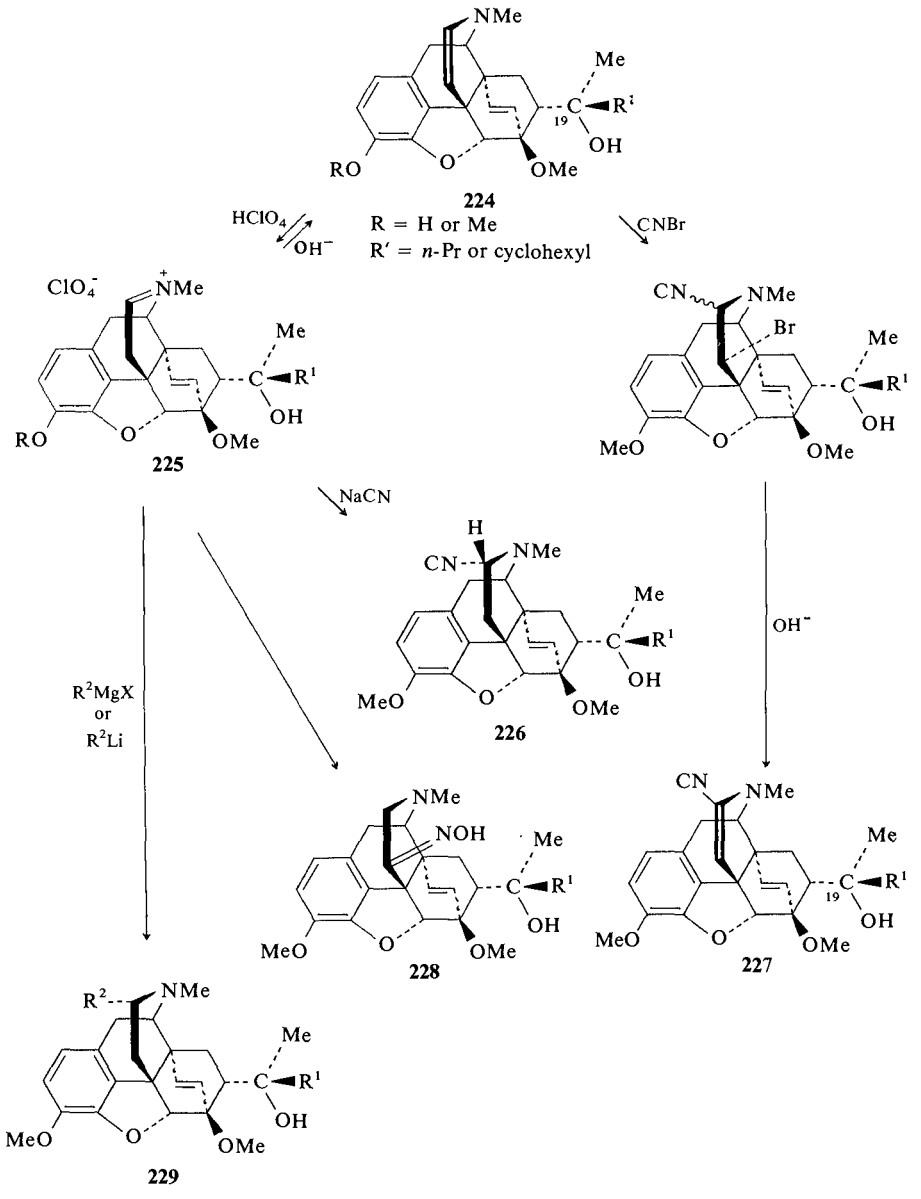
The ester **213** (R = OEt, R^2 = Me) was acetylated at C-1 with acetic acid/TFA, and the resultant 1-acetyl derivative was reduced by $NaBH_4$ to a mixture of diastereoisomeric secondary alcohols, which were then converted under Schmidt reaction conditions to the corresponding 1-acetamido analogs. Nitration of **213** (R = OEt; R^2 = Me) occurred at C-1, and the 1-nitro product was reduced and acetylated to the 1-acetamido compounds prepared via the Schmidt pathway described earlier. Chlorination of **214** (R = R^1 = R^2 = Me) occurred, as anticipated, at C-1. Only the 1-chloro derivatives exhibited any analgesic activity, and this activity was considerably lower than that of corresponding unsubstituted compounds. Removal of the 3-OH function of **214** (R = Me, R^1 = alkyl, R^2 = Me) has been effected by hydrogenolysis of the oripavine diethylphosphatyl esters, with a resultant drop in analgesic potency,[358] but this drop was less than that when the 3-OH was converted to 3-OMe.

Ozonolysis[359] of 6,14-*endo*-ethenotetrahydrothebaines has afforded aromatic ring cleaved products. Tertiary alcohols (**214**, R = Me, R^1 = alkyl; R^2 = Me, *n*-Pr or CBM), for example, gave the lactonic esters **220**, which had analgesic potencies similar to that of morphine. This somewhat surprising result suggested that the aromatic pharmacophore in opioids was not an essential feature for a compound to elicit opioid-like responses. The authors[359] indicated that this could be the case if pharmacophores elsewhere in the molecule compensated for the loss of aromatic binding.

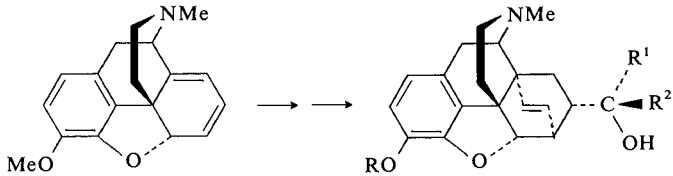
The piperidine bridge in rigid opioids has not been the subject of much attention; however, the Reckitt and Colman group[360] prepared a series of 15,16-didehydro-6,14-*endo*-etheno-6,7,8,14-tetrahydrothebaines and oripavines (**224**, R = Me and H, respectively) by mercury II acetate dehydrogenation of the corresponding saturated compounds (**213**). Tritiation at C-15 may be achieved by $NaBH_4$ reduction of **224** in the presence of tritiated water.[361] The didehydro compounds, **224**, had considerably reduced analgesic potency relative to the corresponding saturated carbinols. Reaction of the iminium perchlorate (**225**) with NaCN[362] gave predominantly 16α-nitrile (**226**) with a minor quantity (5%) of the 16β-epimer. Cyanogen bromide was added to **224** to yield a pair of 15-bromo-16-cyano compounds that lost HBr in alkali, giving the 15,16-didehydro-16-nitrile (**227**). The iminium perchlorate (**225**) gave with pentyl nitrite the 15-hydroximino-iminium salt, which, on reduction with $NaBH_4$, gave the 15-oxime, **228**. All compounds with 15- or 16-substituents had considerably lower analgesic potencies in rats than did the corresponding unsubstituted compounds.

A series of 16-alkyl and 16-aryl derivatives of *endo*-ethenotetrahydrothebaines has been prepared[363] by the reaction of Grignard reagents or lithium alkyls with **225**. Nucleophilic attack was from the least hindered (aromatic ring) side of the molecule to give 16α-alkyl- and aryl- products (**229**), all of which were, at best, weak analgesics. Some had reasonable antitussive actions.

Codeine may be isomerized to isocodeine with 2,4-dinitrobenzenesulfenyl chloride and then dehydrated to 6-demethoxythebaine (**230**). Diels-Alder addition of dienophiles to **230** has given a series of 6-deoxy-*endo*-ethenotetrahydrothebaines (**231**).[364] The *R*-enantiomer (C-19) of **231** (R = H, R^1 = Me, R^2 = *n*-Bu) had an analgesic potency and dose response curve equivalent to that of etorphine (RTF, sc). Both the *S*-enantiomer and the *R*-3-OMe derivative had antinociceptive activities 20–40 times that of morphine. Clearly, the 6-oxygen function is not necessary for high agonist potency. It would also appear, in view of the discrimintation in activities between *R* and *S* enantiomers (C-19), that there is a receptor binding site for the lipophilic function, extending from C-19.[13,365,366] A possible mode of binding to this site could be through H-bonding to the C-19 OH function. A similar approach to 6-deoxy-adducts has been reported.[367]



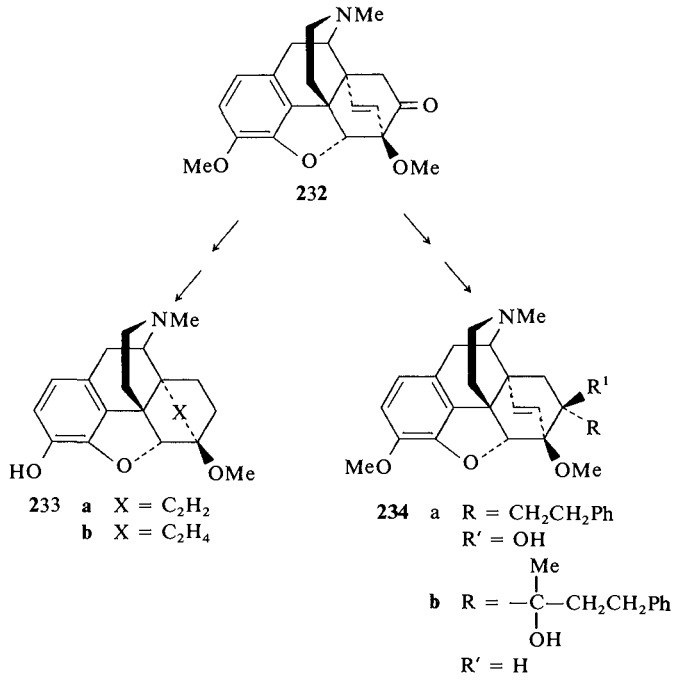
6,14-*endo*-Etheno-7-oxo-6,7,8,14-tetrahydrothebaine (**232**) has served as an intermediate for etorphine analogs lacking a C-7 substituent, the 7-oxo being removed under Huang-Minlon reductive conditions,[368] or possessing an alcohol function directly linked to the C-ring by reaction with organometallic reagents.[369] Derivatives **233a** and **233b** were 40 and 80 × more potent than

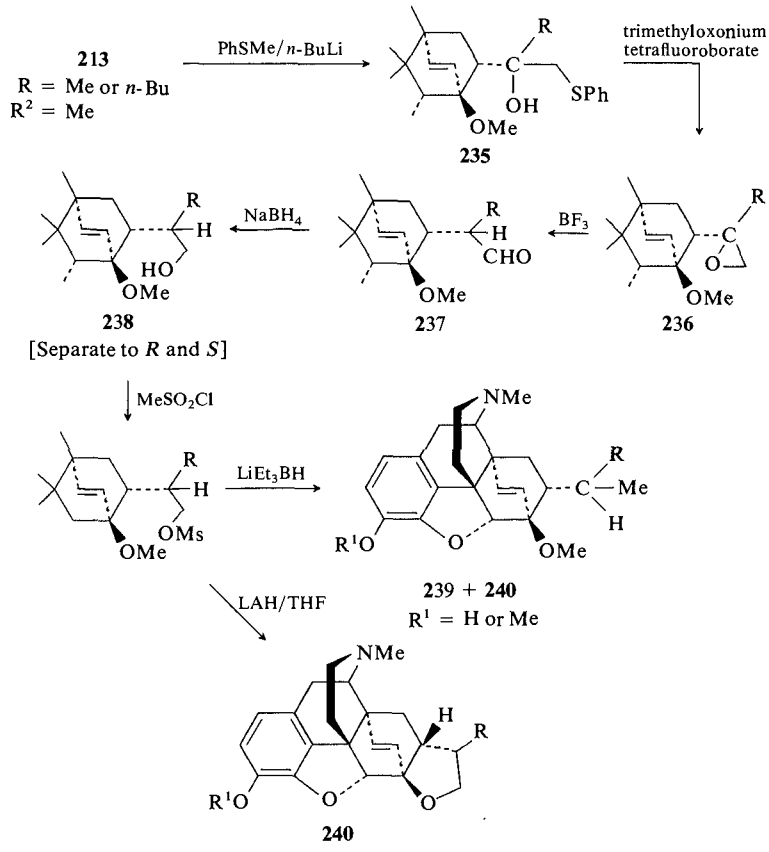


morphine in rats, which indicated the extent of the contribution of the 6,14-bridge to receptor binding. *N*-CPM analogs of **233** were opioid antagonists superior to nalorphine. Several tertiary alcohols derived from **232** were more effective analgesics than morphine in the RTF assay, but 7-ols such as **234a** (ED_{50}, 0.35 mg/kg, RTF, ip) were far less potent than corresponding 19-ols such as **234b** (ED_{50}, 0.0028 mg/kg, RTF, ip).[370]

Hutchins and Rapoport[371] prepared a series of 19-deoxy- and 6,20-epoxy derivatives of *endo*-ethenotetrahydrooripavines (*orvinols**). The synthesis followed the pathways shown in Scheme 2.24, with the appropriate ketone (**213**)

* The authors suggest that, rather than use cumbersome *Chemical Abstracts* nomenclature, the simpler "common" system be employed, i.e., the methyl vinyl ketone adduct of thebaine is a *thevinone*, its reduction product a *thevinol*, and compounds lacking a C-19 OH are *thevinans*. The 3-OH oripavines are, correspondingly, *orvinones*, *orvinols*, and *orvinans*.





Scheme 2.24

being converted to **235** by reaction with the thioanisole anion. Chromatographic purification of the diastereoisomeric product, followed by sequential treatment with trimethyloxonium tetrafluoroborate and aqueous NaOH, gave a diastereoisomeric mixture of epoxides (**236**) convertible via the aldehyde (**237**) to the diastereomeric alcohols (**238**). These were separated chromatographically to give *R*-**238** (R = *n*-Bu) (42%) and *S*-**238** (R = *n*-Bu) (36%). Conversion of these to their respective mesylates and reduction with lithium triethylborohydride gave mixtures of the 19-deoxy product (**239**) and the tetrahydrofuran (6,20-epoxy-) derivatives (**240**). The latter was isolated in improved yields with cold LAH.

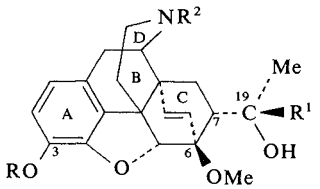
Table 2.2 gives the analgesic potencies (RTF) relative to morphine of enantiomorphs of both 19-deoxy- and 6,20-epoxy-*endo*-tetrahydrooripavines. There is clearly a high degree of receptor stereoselectivity in the series but no

Table 2.2 Comparative Agonist Activities of Some 19-Deoxy- and 6,20-Epoxy-*endo*-6,14-ethenotetrahydrooripavines (R′ = H)

	R	$ED_{50}\mu$mol/kg RTF	Relative analgesic response
Morphine	—	1.67	1
239	Me	0.18	9
19(*R*)-**239**	*n*-Bu	0.0089	187
19(*S*)-**239**	*n*-Bu	0.037	4
19(*R*)-**240**	*n*-Bu	0.090	19
19(*S*)-**240**	*n*-Bu	0.0081	206
19(*R*)-**238**	*n*-Bu	0.0021	773
19(*S*)-**238**	*n*-Bu	0.386	4

requirement for a C-19 hydroxyl H-bonded to the C-6 OMe, which has been proposed previously as being necessary to fix the spatial location of the C-7 lipophilic side chain.[366,372] Compound 19(*R*)-**238** would appear to have its hydroxyl function in a position for interaction, probably H-bonding, with a receptor hydrophilic site, while at the same time the side chain is held appropriately for binding with its corresponding receptor site.

2.6.1. Thebaine Diels–Alder Adducts—Structure–Activity Relationships



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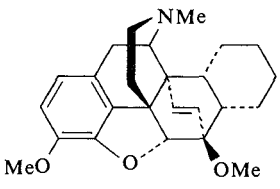


242

Several reviews of structure-activity relationships in this series have been published.[13,326-329]

A-ring modifications have not been extensive, but in general additional aromatic substituents tend to reduce potency below that of the parent orvinols or thevinols. As in other rigid opioid series, 3-phenols are usually 10–50 times more potent than corresponding methyl ethers. Compounds lacking an oxygen function at C-3 surprisingly lie between orvinols and thevinols in potency. The fact that the aromatic ring is not necessary for morphinelike actions and potency (e.g., **220**, Scheme 2.23) is by far the most interesting observation.

D-ring modifications most often entail variation of the *N*-substituent. In this series the pattern of activity is much the same as that in other rigid opioids. Groups such as *n*-propyl, allyl, dimethylallyl, and CPM afforded antagonists

in the thevinol series. However, with orvinols, the type of pharmacological response elicited depends heavily upon the nature of C-ring substitution. Irrespective of the nature of the *N*-substituent, antagonist properties may be lost when R = Me and R′ = alkyl > Et (**215**), but agonist properties may be exceptionally high. *N*-Cyclopropylmethyletorphine (19*R*), for example, is a pure agonist 1000 × morphine as an analgesic. The configuration about C-19 is critical and the corresponding 19*S* diastereoisomer is similar to nalorphine in antagonist potency. Thus, the C-7 substituent, if its stereochemistry and lipophilicity are such that it binds strongly to agonist sites, will reduce or abolish antagonist binding.[13] Any modifications made to C-15 and C-16 have substantially reduced opioid responses.

C-ring variations have by far the most significant influence on pharmacological responses in these series.

Although a lipophilic substituent at C-7, preferably with a C-19 OH of appropriate geometry, endows some orvinols and thevinols with high levels of opioid agontist activity, compounds lacking such a substituent (**233a** and **b**) have analgesic potencies up to 80 × morphine. This suggests that the 6,14-ethano- or etheno-bridge contributes substantially to receptor association. Potency is greatly influenced by the size of the C-7 tert-OH function. As the chain length of R′ of thevinols is increased, activity rises to a maximum at *n*-Pr (96 × morphine) and then declines. A terminal aryl group enhances activity, with the benzyl (150 × morphine) and phenethyl (500 × morphine) congeners being particularly good analgesics. In the orvinol series maximum activity is conferred by *n*-Bu (5200 × morphine) and iso-amyl (9200 × morphine) with phenethyl- and cyclohexyl-analogs exhibiting activities of 2200 × and 3400 × morphine, respectively.

Of paramount importance is the geometry of the C-19 (OH) center. Etorphine (19*R*) (**221**) has an agonist potency of 1000 × morphine, whereas its diastereoisomer, although still a good analgesic, is 20 × morphine. In each case the isomer with *R* configuration at C-19 is the more potent.

The suggestion[13] that the high potency of these tertiary alcohols was attributable, at least in part, to specific binding of the C-19 OH to a receptor site appeared to be contradicted by the very high potency of **242** (1000 × morphine). Another proposal envisaged intramolecular H-bonding between the 6-OMe and the C-19 OH, which, in *R* diastereoisomers would direct the lipophilic chain toward its receptor-receiving site.[13,365,366] The synthesis[364] of 6-deoxythevinols and orvinols (e.g., **231**; R = H, R′ = Me; R^2 = *n*-Bu) with activities equivalent to that of etorphine indicates that such H-bonding cannot play a significant role in directing the lipophilic moiety toward its receptor binding unit. A similar conclusion was drawn in the 4,5-epoxymorphinan series.[373] Extending their study of the role of the 6,7-region of the C-ring in receptor binding, Hutchins and Rapoport[371] examined 19-deoxy- and 6,20-epoxyorvinols and thevinols. Again, high levels of activity were

encountered in some C-19*R*-diastereoisomers of these series (Table 2.2), and to explain these a return to an intermolecular H-bonding site theory was proposed. Such bonding would still permit the holding of the lipophilic side chain in highly potent members of the series in a spatial orientation that would facilitate strong binding. The *S*-isomers would have their lipophilic chain held away from such a binding site. An examination of 6,20-epoxyorvinols demonstrates that the butyl group (**240**, R = *n*-Bu) is fixed with either α- or β-geometry. The furan with the α-*n*-Bu group was the more active diastereosiomer. In addition, 19-deoxy-compounds (e.g., 19*R*, **239**, R = *n*-Bu) are almost 200 times more potent than morphine as opioid agonists.

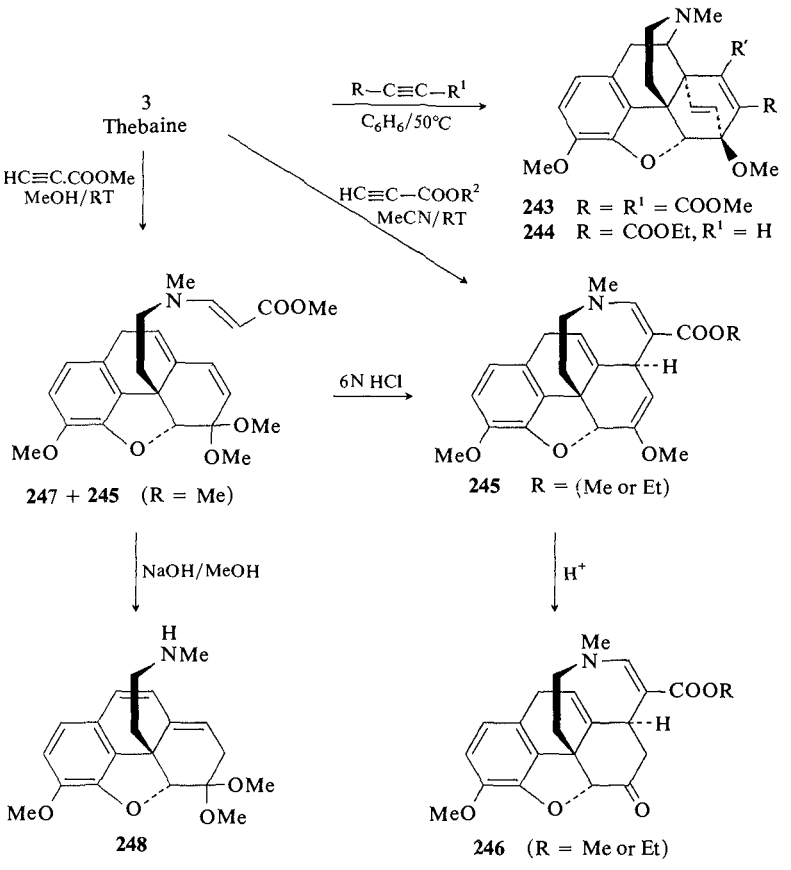
To account for these observations, Hutchins and Rapoport[371] proposed two binding sites for the C-ring, one for the C-7 lipophilic side chain (L), located below C-8 and approaching the 6,14-etheno bridge (such a site must differ from that accepting 7β-phenylbutyl- chains in **125** and **127**, the other a hydrophilic receptor site (H) to receive C-19 hydroxy above the C-ring. A compound such as 19*R*-**238** (773 × morphine) could be imagined as interacting with both sites, whereas the 19-deoxy analogs (19*R*-**239**, R = *n*-Bu) (187 × morphine) would only present a lipophilic interaction. Thus, the sites proposed would engage in synergistic and competitive binding of ligands, the response elicited being commensurate with the fit of both or one of the sites. Common features between this proposal and that for enkephalin-receptor interactions have been highlighted.[371]

Reduction of the 6,14-*endo*-etheno-bridge results in further enhancement of potency. For etorphine the potency becomes 11,000 × morphine, one of the most potent analgesics to have been reported.

2.6.2. Other Thebaine Addition Products

A Diels-Alder reaction between thebaine (**3**) and dimethyl acetylenedicarboxylate gave the anticipated product, **243**, in high yield. Ethyl propiolate, however, gave only 6% of the 1,4-addition product, **244**.[374] A reinvestigation[375] of the reaction between acetylenic dienophiles and thebaine has shown that the room temperature reaction in acetonitrile of propiolate esters gave the adduct **245**, which, on mild hydrolysis, gave corresponding ketones, **246**. Structure **246** (R = Me) was established by single-crystal X-ray analysis. When the reaction was performed in MeOH, the adduct **245** (R = Me) (32%) was given, together with 53% of the ketal **247**, which in 6N HCl was converted to **245** (R = Me). Prolonged heating of **247** in NaOH-EtOH gave the secondary amine **248**. Earlier Hayakawa *et al.*[376] reported the same transformation.

The reaction between nitrosobenzene and thebaine to give 14-arylamino-4,5-epoxymorphinans via 1,4-addition intermediates was discussed earlier (p. 60).[288,377,378]

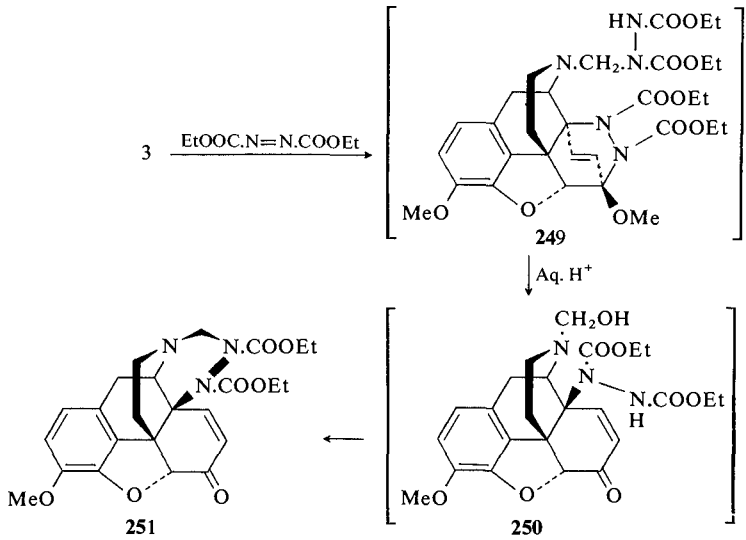


Scheme 2.25

Diethylazodicarboxylate may be employed as a reagent for the *N*-demethylation of thebaine to northebaine via an *N*-Me addition product. However, when thebaine was dissolved in diethylazodicarboxylate and allowed to stand, the hexacyclic product **251** was isolated,[9a] presumably from the Diels–Alder intermediate **249**, and after hydrolysis gave **250**. The putative intermediates **249** and **250** defied isolation.

2.6.3. Some Morphine Ring Variants

Derivatives of Diels–Alder adducts of thebaine constitute the most important variants of the 4,5-epoxymorphinan system. Several other compounds



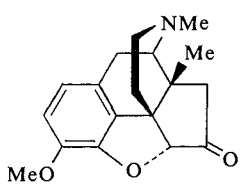
have been prepared or isolated from natural sources but are of little pharmacological interest.

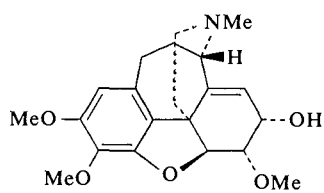
C-ring contracted 4,5-epoxymorphinans (**252**) have been reported[379] during studies on the photolysis of codeinone analogs.[220,221] A 7-membered C-ring lactam (**2a**, Chap. 4) was isolated as a product of the Schmidt rearrangement of dihydrocodeinone.[380] In neither report were biological data presented.

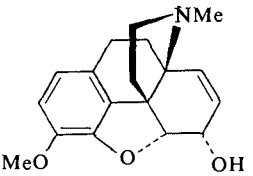
A B-ring homo-morphine alkaloid, (+)-kreysiginine (**253**) has been isolated from the Australian plant *Kreysigia multiflora*,[381] and its structure and stereochemistry have been determined. Although kreysiginine is of considerable biogenetic interest, it is of no known significance pharmacologically.

In an investigation of the point of attachment of the nitrogen in the alkaloid hasubanonine from *Stephania japonica*, the base **254** was prepared from 14-bromocodeinone.[384]

Sargent and Joshi[385] have transformed dihydrocodeinone, via a Hofmann degradation product, to the dihydromorphinone position isomer **225**. It had an MHP (sc) ED_{50} of 24.6 mg/kg, about one third codeine.







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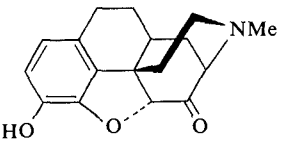

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2.7. SPECTROSCOPY AND OTHER PHYSICAL MEASUREMENTS

In this section a selection of studies relating to drug geometry, and having possible implications to pharmacological activity, has been included. Numerous studies characterizing products and establishing their stereochemistry may be found in publications relating to specific 4,5-epoxymorphinan series.

2.7.1. ^{1}H-nmr

Twenty-two 4,5-epoxymorphinans related to (−)-morphine were the subject of a 60 MHz ^{1}H-nmr study reported in 1964.[386] Assignments were made for most protons, but particular attention was paid to the conformation of the C-ring. Coupling values between the dihedral proton, C-5, Hα, and C-6 Hβ signals were determined and compared with those derived from the Karplus equation.[387] For 8,14-unsaturated analogs, agreement between the experimental and theoretical dihedral angles was reasonable for a C-ring half-chair conformation. In accord with X-ray data,[110] 7,8-unsaturated analogs of morphine had a C-ring boat conformation. Saturated C-ring analogs have C-5, C-6, proton coupling that indicated a chair conformation, in agreement with the chemical evidence of Elad and Ginsburg.[27,28] Similar conclusions were drawn from chemical shift data for C-6 -CO.CH$_3$ groups. Spectra were run in $CHCl_3$; thus, caution must be exercised in extrapolating these findings to the *in vivo* situation. A similar study has been published by Rüll.[389]

Jacobson and others[390] analyzed the ^{1}H-nmr spectra at 100 MHz of codeine and isocodeine derivatives, previously reported at 60 MHz,[391] in order to establish the conformation of the spiro-oxirane derived from codeinone.[200] Double irradiation and NOE experiments confirmed the structure illustrated (**91**).

A comparison has been made[392] between the solution, solid-state, and theoretical conformations of morphine in D_2O (+DCl) employing ^{1}H nmr at 100 MHz and 600 MHz and ^{13}C nmr at 25.2 MHz. Because of the increased chemical shift separation that occurred at very high field, the proton signals for C-15 and C-16 H could be assigned and examined. This, together with data from N-CH$_3$ and NH, and ^{13}C (C-15 and C-16), facilitated a close

examination of the piperidine ring. The data suggest that the morphine cation has a piperidine ring with a slightly distorted chair conformation, compatible with solid-state evidence. Although no piperidine ring inversion was possible in rigid opiates, a slow inversion of the *N*-substituent between equatorial and axial forms was apparent, with an axial-equatorial energy difference of about 1 Kcal/mole. These data conflict with theoretical estimates.[265] The nmr study does not make clear the degree of dissociation of the salts in D_2O solution, and as the cationic form of the drug inverts, in all probability through the base, the inversion rate will depend, in part, upon the dissociation equilibrium. It is often assumed in opioid receptor considerations that the *N*-substituent, on energetic grounds, is equatorial.[393] Glasel's findings shed doubt on this assertion.

Morphine alkaloids have been used as model compounds in a study of double bond and nitrogen and nonbonding electron anisotropic effects.[391,394] The ABC system of protons at 9, 10α, and 10β of several alkaloids of the morphine group has been the subject of theoretical analysis.[395]

An extensive account[396] of ^{1}H-nmr studies of 6,14-*endo*-ethenotetrahydrothebaines is available relating shift data to stereochemistry throughout and making comparisons with calculated spectra.

2.7.2. ^{13}C-nmr

Extensive assignments of ^{13}C bands for 4,5-epoxymorphinans have been published.[397,398] Carroll and co-workers[298] examined 25 derivatives of morphine, 14-hydroxymorphine, and 6,14-*endo*-etheno- and 6,14-*endo*-ethanotetrahydrothebaines. Assignments were aided by off-resonance decoupled spectra and by deuterium labeling. These reports have been reviewed.[399] Thebaine Diels–Alder adducts were found to have A-, B-, and D-rings with spatial orientations similar to morphine. The C-ring, however, differed in conformation in agreement with the distortion seen in X-ray structures.[400]

Natural abundance ^{13}C-nmr spectra of morphine sulfate in DMSO have been recorded and resonance bands assigned.[112] Additional low-intensity lines occurred in the D_2O solution spectrum, which were lost on raising the temperature to 70°. They have been attributed to the nitrogen invertomer in an equilibrium mixture.[112,392] Cross-polarization magic-angle-spinning (CP/MAS) ^{13}C-nmr spectra of crystalline morphine sulfate have been compared with solution spectra in D_2O.[476] Charge on N was found to affect carbon signals differently, with C-9, C-10, C-11, C-12, and C-4 being most affected, in agreement with Kolb *et al.*[401,402] It would appear that H-bonding from the morphine nitrogen or the 3-OH, together with crystal packing forces, causes significant differences between crystal and solution conformations. Moving from the latter to the former, significant shifts were seen for C-2,C-7,

C-11, C-15, and C-16, indicating a change in the piperidine bridge (C-15, C-16) to aromatic ring interspatial distance, a molecular parameter implicated in receptor responses.[403] Thus, similar to the conclusion drawn from ^{1}H nmr data, ^{13}C nmr suggests that the crystal conformation of morphine should not be taken as the form of the drug that interacts with its receptor(s).

A ^{13}C-nmr examination of opiate agonist-antagonist pairs morphine-nalorphine and oxymorphone-naloxone, has been carried out,[404] in $CDCl_3$ (bases) and D_2O (HCl salts) for the latter and DMSO-d_6 (bases) and D_2O-TFA (HCl salts) for the former. It was clear that these pairs have analogous conformations, thus casting doubt on suggestions that *N*-substituent orientation might be a major influence in the difference between agonist and antagonist responses.[271,273,405] Similar conclusions were reached from a 600 MHz ^{1}H-nmr study of agonist-antagonist pairs.[477]

2.7.3. ORD/CD

Several reports on ORD and CD spectra for (−)-morphine have been published.[406-410] When no carbonyl group is present in ring C, 4,5-epoxymorphinans exhibit a negative Cotton effect at about 280 nm, and a positive one around 254 nm associated with the aromatic chromophore.[407]

Related compounds with a B/C *trans* junction have ORD and CD spectra similar to their B/C *cis* isomers, reflecting the configuration at C-13 rather than at C-14.

A C-6 carbonyl function, as in dihydrocodeinone, introduced a negative Cotton effect into the spectrum at about 300 nm.[410]

2.7.4. Mass Spectra

Several studies of ms fragmentation patterns and their interpretation have appeared for opioids,[411-414] including a comparison of spectra for B/C *cis* and B/C *trans* derivatives. A summary of these data has been published.[473] The initial process under electron impact may be rationalized by the removal of an electron from the opioid nitrogen to give the molecular ion, followed by cleavage of a C—C bond β to nitrogen.

2.7.5. X-ray Studies

The structure of (−)-morphine was established conclusively[110] by X-ray crystallography from two projections of the hydroiodide dihydrate salt and confirmed for codeine and morphine by an X-ray study of their hydrochloride trihydrate salts.[111] The piperidine ring was shown to adopt a chair conformation with the *N*-Me equatorial. The absolute stereochemistry of morphine was also confirmed by X-ray studies.[415-417]

Diels–Alder adducts of thebaine may exhibit exceptionally high levels of opioid activity. The crystal structure of 7α-(1-(*R*)-hydroxy-1-methylbutyl)-6,14-*endo*-ethenotetrahydrothebaine hydrobromide (Etorphine **221**) was determined[400] and the C-ring cage structure was found to be severely distorted relative to the idealized Dreiding model.

2.8. METABOLISM OF 4,5-EPOXYMORPHINANS

Most opiates are subject to significant first-pass metabolism in the liver, and for this reason, parenteral administration is more effective than *per os*, although the latter is often of longer duration.[17,418] At therapeutic plasma levels, about one-third of the drug is bound to plasma protein. Codeine, which has the morphine 3-OH masked, behaves rather differently, and because of a lower first-pass loss, has a significantly greater po efficacy (about two thirds the parental effect).

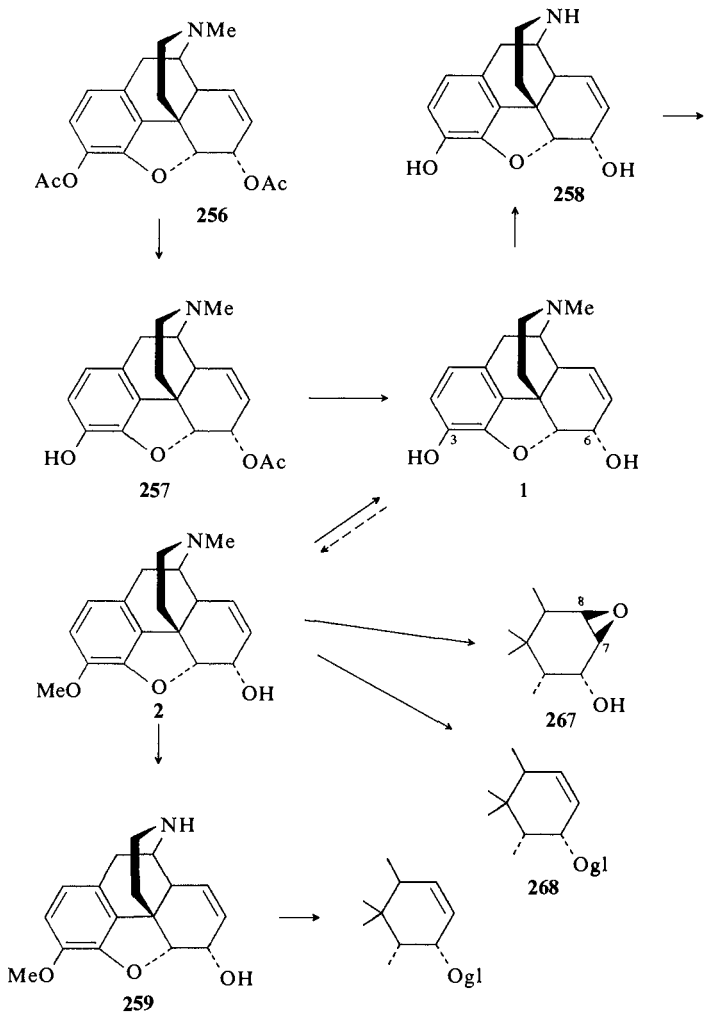
Opiates are drugs that exert their beneficial actions through the CNS, and although codeine and heroin have a reasonable level of passage across the blood–brain barrier, morphine's passage is much lower.[419]

Nalorphine and naloxone are also more effective parenterally than orally. Both are first-pass metabolized in the liver very rapidly, largely by glucuronide formation.[420,421] The effects of these antagonists are almost immediate upon intravenous administration and last between 1 and 4 h. Naltrexone, on the other hand, maintains a good level of oral activity and has a half-life of around 10 h.[422,423]

The metabolism of morphine and related opiates has been investigated extensively and reviewed.[424,426] It tends to be very rapid after parenteral administration but unpredictable after oral dosage. Scheme 2.26 illustrates the major metabolic pathways for morphine (**1**), codeine (**2**), and heroin (**256**).

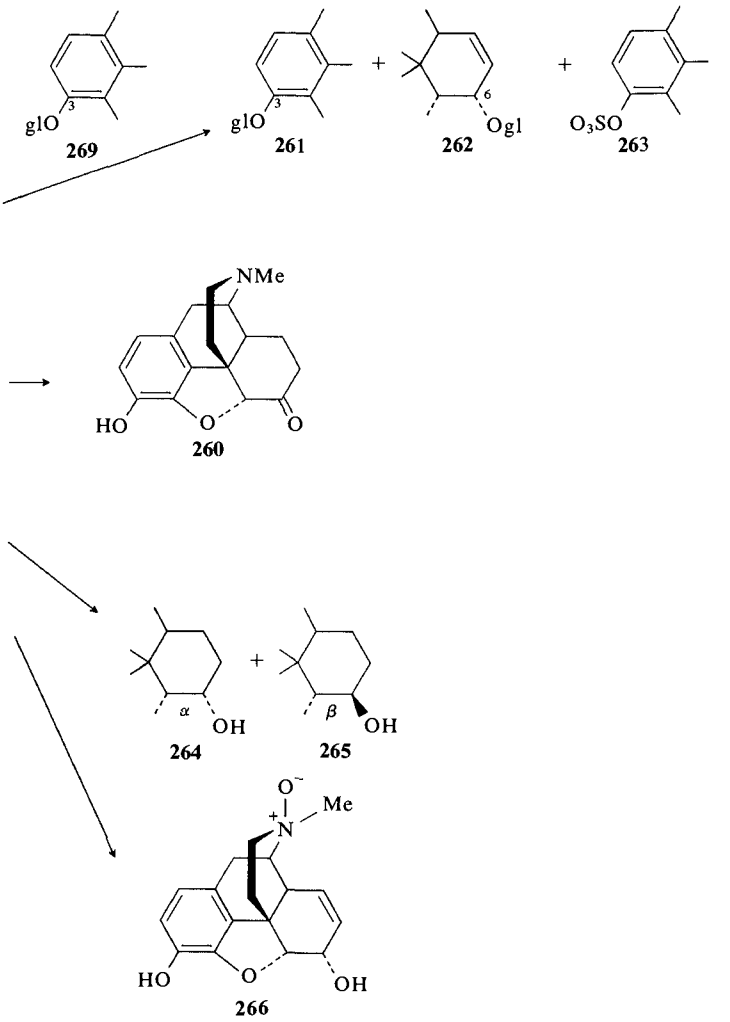
Conjugation with glucuronic acid is a major elimination route that occurs at the 3-OH and to a lesser extent at the 6-OH of morphine and the 6-OH of codeine. This route accounts for 65% of morphine in urine of humans.[430]

The synthesis of morphine 3- and 6-glucuronides (**261** and **262**) and codeine-6-glucuronide (**268**) has been reported[427] for the purposes of characterizing these metabolites unequivocally. Morphine-3,6-diglucuronide and morphine-3-sulfate (**263**) have also been isolated as minor human metabolites from morphine-dependent subjects.[428] Morphine-6-glucuronide (**262**) has been proposed as an active metabolite of morphine.[429] It is stable *in vivo* and has up to 4 × morphine's analgesic potency (MHP, sc), with about twice the duration of activity. More impressive is the 45 × morphine response elicited by **262** upon intracerebral (ic) injection. Stereospecific receptor binding affinity studies demonstrated this metabolite to have a higher receptor binding affinity than morphine. Similar results were reported for morphine-6-sulfate.



Scheme 2.26

Morphine-3-glucuronide (**261**) and the corresponding 3-sulfate had no MHP, sc, or ic activity, and morphine-3-phosphate and morphine-6-phosphate were similar to morphine in their responses. These activities were reflected in increased agonist potencies (MW, 3 × nalorphine) seen for nalorphine-6-glucuronide and -6-sulfate, with a maintenance of antagonist actions.



Heroin is rapidly hydrolyzed *in vivo* to 6-monoacetylmorphine (**257**) and thence to morphine (**1**) (see also p. 26). *N*-Demethylation and *O*-demethylation are significant metabolic routes in animals, with the former oxidative process leading to normorphine (**258**) from **1**, and norcodeine (**259**) from **2**, which may in turn be eliminated as their 3- and 6-glucuronides, respectively.

Oxidative removal of an *N*-methyl function appears to be only a minor metabolic process in humans and is unlikely to contribute to the analgesic effects of morphine to any extent.[431-433]

N-Trideuteriomethylnormorphine was synthesized[434] and used to investigate the *N*-demethylation of morphine by rat liver microsomal enzyme preparations. Nalorphine was found to inhibit, noncompetitively, morphine *N*-demethylation.

Type I binding of drugs has been associated with their metabolism.[435] This prompted a study[94] of *N*-demethylation of 4,5-epoxymorphinans with 3-O-alkyl functions from C_1 to C_{12}. There was no simple relationship between lipophilicity and the rate of metabolism and maximal Type I binding was the same for all analogs.

Normorphine has been found[436] to be excreted as normorphine-3-glucuronide (32%) in dogs. In addition, small amounts of dihydronormorphine (TMS derivative) and 15-dehydronormorphine (TFA derivative) were detected in extracts of dog urine by gc/ms. Dehydration of *N*-hydroxynormorphine, not detected during this study, was proposed, tentatively, as the source of the latter. The presence of dihydronormorphine was suspected from the isolation of dihydromorphine as a minor metabolite of morphine.[437]

Codeine is *O*-demethylated to morphine to about 13% of the parenteral dose.[438,439]

Some oxidation of morphine occurs to dihydromorphinone (**260**) in animals, but this was not detected in the urine of dependent humans.[428] *O*-Methylation of morphine to codeine has been reported,[442,443] but other studies[444,445] have failed to confirm this pathway.

Incubation of morphine and [^{14}C-methyl]-*S*-adenosylmethionine with rabbit liver homogenates resulted in the detection of 2-methoxymorphine as a minor metabolite.[446] Oxidation at C-2 may also have occurred in rat brain homogenates with the tentative identification of morphine-2,3-quinone as a minor morphine metabolite.[447] Morphine-*N*-oxide (**266**) and its 3-glucuronide have been isolated[448] from guinea pig urine after morphine adminstration, and α- and β-dihydromorphine (**264** and **265**) were also established as metabolites by gc/ms of extracts of the urine of several species.

Codeine-7β,8β-epoxide (codeine-7,8-oxide) (**140**) has been isolated (see Refs. 244, 448) as a codeine metabolite from a rat liver microsomal preparation and identified by gc/ms (MID) and hplc. It had two times the analgesic potency of codeine in the rat.[450]

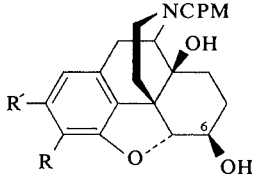
Heroin is rapidly metabolized in humans[22] and other species[451,452] to 6-acetylmorphine and morphine, the active metabolites.[100] Compounds lacking a free 3-OH function bind poorly to opioid receptor preparations, and heroin was no exception. Morphine and 6-acetylmorphine bound well to receptor preparations, and the binding of the latter accounted for all the apparent binding of heroin. In addition to 6-acetylmorphine and morphine, the 3-glucuronide of morphine (**261**) occurred as a major metabolite of heroin

and minor quantities of morphine-6-glucuronide (**262**), and normorphine (**258**) and its glucuronide (**269**) have also been detected in human urine after heroin administration.[453-455]

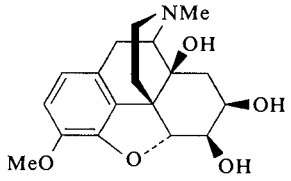
The presence of a 14-OH group in 4,5-epoxymorphinans resulted in some differences in metabolism, but major elimination routes remained via the 3-glucuronides in compounds with a free OH function.

Naloxone (**160**) was metabolized to the corresponding dihydromorphine in humans and rabbits[421,458] as well as to naloxone-3-glucuronide.[457,458] *N*-Deallylation[421,456] to nornaloxone also occurred in subjects receiving large oral doses of the drug.

Naltrexone (**162**), like naloxone, was more extensively metabolized after oral adminstration than following the parenteral route. Major metabolites in plasma, urine, and feces have been identified[459] by gc/ms as naltrexone-3-glucuronide and conjugated and unconjugated 6β-hydroxy reduction product (**270**). The geometry at C-6 had been established during an earlier study.[460] Minor quantities of the C-2 oxidation product, **270**, (R = OMe; R′ = OH) and **270** (R = OMe, R′ = H) were also found. Oxycodone (44) gave the unusual 6β,7β-dihydroxy metabolite (**271**) in rabbits.



270 R = OH
R¹ = H



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2.9. SUMMARY OF STRUCTURE–ACTIVITY RELATIONSHIPS

Throughout this chapter reference has been made to criteria necessary for activity in each substituted series. In this summary our aim will be to highlight those parameters that appear to be necessary for maximizing, or more realistically, optimizing, opioid actions.

Various aspects of structure activity relationships in 4,5-epoxymorphinans have been reviewed,[201,461-467] and specific consideration has been given to quantum chemical studies with particular reference to polar group variation,[468] stereoisomeric ligands as receptor probes,[469] partition and distribution coefficients,[470,471] and antagonists.[145]

Many of the comments in this section are reflected in structure-activity discussions on morphinans and benzomorphans. In the case of 4,5-epoxymorphinans, variation of the *N*-substituent and changes in the form (rigidity and conformation) of the ring system and the nature of substituents bring about dramatic qualitative and quantitative changes in biological responses.

(−)-Morphine, the natural alkaloid from which almost all opiate analgesics have been evolved, is stereospecific in the receptor interactions that are responsible for its opioid actions, namely, analgesia, depression of respiration, dependence liability, and GIT disturbances. Compounds with natural (−) and unnatural (+) geometry may exhibit antitussive actions.

Formal inversion of the C-14 chiral center of morphine to B/C *trans*-morphine did not result in the increase in antinociceptive activity seen with morphinans. The presence of the 4,5-oxygen bridge constrains the C-ring conformation to that of a boat, as opposed to the morphinan C-ring which is a chair.

Masking of the 3-OH of morphine, as in codeine (3-OMe), resulted in a several-fold reduction in analgesic potency, but the readily *in vivo* hydrolyzable 3-OAc, as in heroin, afforded a greater level of opioid potency. Here it may be that the presence of a free 3-OH, together with a masked 6-OH, as 6-OAc, glucuronide, or sulfate, is more conducive to agonist receptor binding. However, Reden *et al.*[479] offer the evidence of 3,6-dideoxydihydromorphine to suggest that oxygen in neither the aromatic ring nor the C-ring is necessary for receptor binding. In general, other changes in aromatic ring substitution reduce potency, increase toxicity, or both.

The conformation of the morphine C-ring has a substantial bearing, both qualitatively and quantitatively, on the nature of a compound's opioid actions. The presence of a 5-Me substituent, in metopon (**74**), for example, afforded a modest increase in antinociceptive actions, without a parallel increase in unwanted responses.

Substitution at C-6 was not necessary for good levels of analgesic activity, for desomorphine (**83**, R = Me) was 10 times more potent than morphine. However, some 6-azido-4,5-epoxymorphinans (e.g., **89**) were 50 × morphine as analgesics in humans, and although the same level of activity was seen in corresponding 14-OH derivatives, the fact that the presence of a 14-OH did not increase the level of potency indicates that in this case the 6- and 14-substituents affect receptor binding differently.

The C-7 and C-8 positions can exert an enormous influence on opioid actions according to the nature and geometry of the substituent. Compounds with 7β-phenbutyl or 7β-phenpropyl substituents, for example, **127** (R′ = CPM, R^2 = H), had MW activities of up to 700 × morphine, and corresponding 6-ketones tended further to increase activity twofold. There appears to be a delicate balance between the influences of the substituents on the C-ring, nitrogen, and 3-oxygen. Large lipophilic groups (e.g., 7β-aralkyl) with chain lengths of 2–4 appeared to bind to the type of receptor site envisaged by Lewis *et al.*[13] 8β-Lipophilic substituents in *N*-Me series offer no improvement over unsubstituted compounds, and therefore they do not conform spatially to a position compatible with optimum lipophilic site binding.

In general, a 14-OH group tended to enhance opioid potencies, par-

ticularly in antagonist series. Replacement of a 6-ketone in 14-OH series by hydrazones afforded a series of compounds with very high binding affinities for rat brain receptor sites and actions of long duration. Ether formation at the 14-oxygen abolished agonist actions, whereas if the 14-OH is antagonist directing, an increase in agonist/antagonist ratio might have been expected. Some 14-acyloxy-derivatives were up to 200 × morphine as analgesics affording further evidence for a lipophilic receptor moiety extending above and away from the plane of the morphine C-ring.

Although a 14-OH group did not enhance the activity of 6-azido-4,5-epoxymorphinans, the presence of a 14β-methyl group (**188**) afforded an RTF sc activity of 5000 × morphine. The corresponding 14β-ethyl 6-keto derivative (**189**) was 10^4 as potent as morphine!

Undoubtedly, some of the most dramatic potency increases arise with derivatives of Diels–Alder adducts of thebaine, with etorphine (**221**) being a remarkable 8600 × morphine in guinea pigs. SAR's in these series were discussed on p. 79. Although rigidity of the C-ring assists in enhancing opioid potency it is not the sole criterion for high potency. A lipophilic 7α-substituent is, clearly, important and although a 19-OH with appropriate stereochemistry is desirable for high levels of opioid activity, only when it is present with a C-19 lipophilic chain do optimum actions result. Thus, each group is capable of high activity by virtue of its own receptor binding capacity; both groups together, correctly oriented, afforded exceptionally high potency. A 6-oxygen function was not necessary for good levels of activity and was not required to H-bond to the 19-OH group. It would appear that the C-19 lipophilic group, which extends below the plane of the C-ring, must differ from the receptor moiety for 7β-aralkyl lipophilic groups of 4,5-epoxymorphinans. The etheno- or ethano-bridge of thevinols and orvinols also appears to bind to a receptor unit.

In all of the preceding series profound effects on pharmacological responses were exerted when the substituent on nitrogen varied (p. 29). Groups such as allyl, dimethylallyl, CPM, and CBM tend to endow the molecule with antagonist properties, whereas *N*-Me and *N*-phenethyl afford agonist properties.

The extensive investigations of SARs in the morphine series have highlighted the fact that although nitrogen is probably the primary pharmacophore for receptor binding, the subsequent "zipper" attachment of ligand to receptor and responses elicited depend heavily upon secondary perturbations. The aromatic ring, although not essential for opioid responses, as **220** has demonstrated, is necessary in most opiates and its binding is augmented by a free 3-OH group. But it is the influence of the conformation and substituent effects of the C-ring that are perhaps the most intriguing, and it is their exploration that may lead to a better understanding of the nature of multiple opioid receptors.

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3

Morphinans

3.1. INTRODUCTION

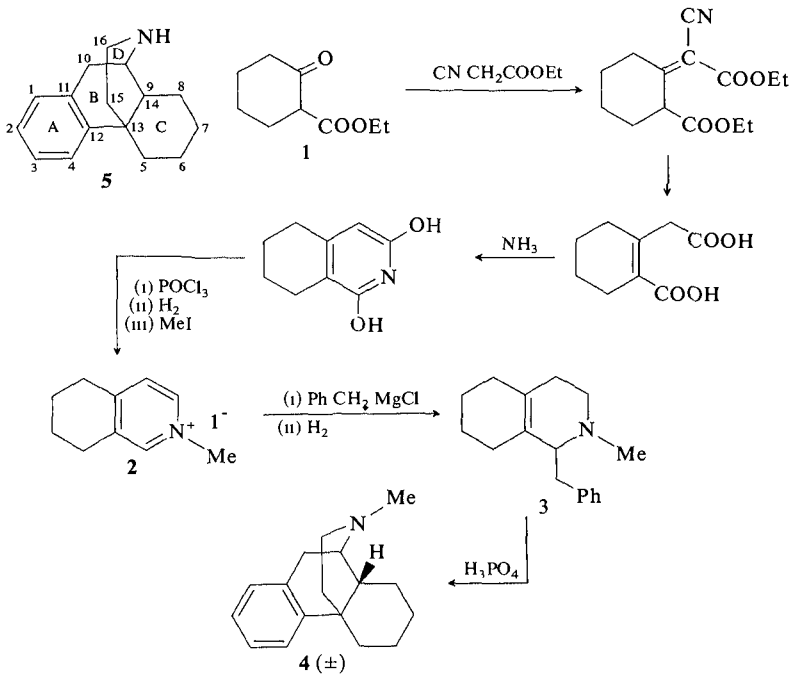
Once the structure of morphine had been established,[1,2] attempts at its synthesis were started. Although early efforts were frustrated, independent proposals by Robinson[3] and Schöpf[4] regarding the biosynthesis of the morphine skeleton from a 1-benzyltetrahydroisoquinoline prompted Grewe[5-7] to embark upon a synthesis which led to racemic *N*-methylmorphinan **4** (Scheme 3.1). Grewe demonstrated that 4, although possessing only the nitrogen functional group of morphine, retained similar analgesic properties (1/5 × morphine). This observation resulted in many studies that it was hoped would produce analgesics with a more clinically acceptable pharmacological profile than morphine, but possessing the morphinan structure (**5**). Inclusion of a 3-OH was found to enhance analgesia considerably without unduly affecting undesirable pharmacological properties.

The name *morphinan*, suggested by Robinson, is universally used for describing members of this series together with the nonsystematic numbering illustrated in **5**. Morphinans lack the furan bridge of morphine and its direct analogs and possess a B/C ring fusion that may be either *cis* (morphinans) or *trans* (isomorphinans, see p. 136).

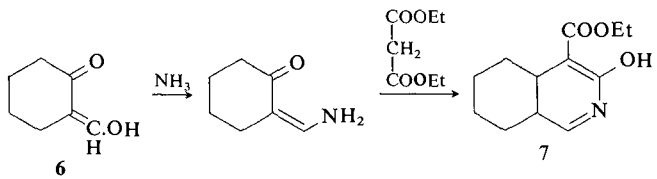
A full account of chemical and pharmacological studies on morphinans to the mid-1960s is available.[8]

3.2. SYNTHESIS

Several approaches to the synthesis of morphinans start with cyclohexanone intermediates leading to octahydroisoquinolines such as **3** by way of a route similar to that exploited by Grewe (Scheme 3.1). Amination of 2-hydroxymethylenecyclohexanone (**6**) followed by reaction with malonic ester afforded the hexahydroisoquinoline, **7**, that was decarboxylated and converted on a commercial scale to 5,6,7,8-tetrahydroisoquinoline[9] via the 3-chloro intermediate.

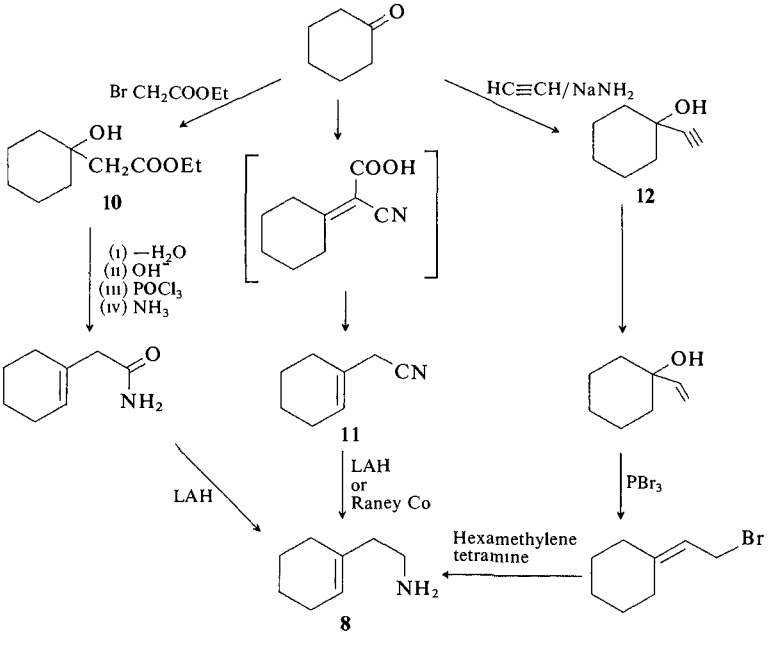


Scheme 3 1



1-Aminoethylcyclohexene (**8**) (cyclohexenylethylamine) is an intermediate in several syntheses of morphinans. Methods for its preparation are summarized in Scheme 3.2. Cyclohexenylethylamides behave like amides of phenylethylamines and will cyclize to isoquinoline derivatives under Bischler-Napieralski conditions (e.g., $POCl_3$).[10] Under the conditions described by Grewe,[5] cyclohexenylethylamides ring close, usually in good yield, to the corresponding morphinans (Scheme 3.3).

The promising analgesic activity of 3-hydroxy-17-methylmorphinan stimulated Schnider and Hellerbach[11,12] to seek a commercial synthesis of it via **8**. Bromoacetic ester reacted with cyclohexanone to give **10**, which was converted rather laboriously to **8** (Scheme 3.2). Cyanoacetic ester afforded a more fluent route by way of cyclohexenylacetonitrile (**11**). In the presence of



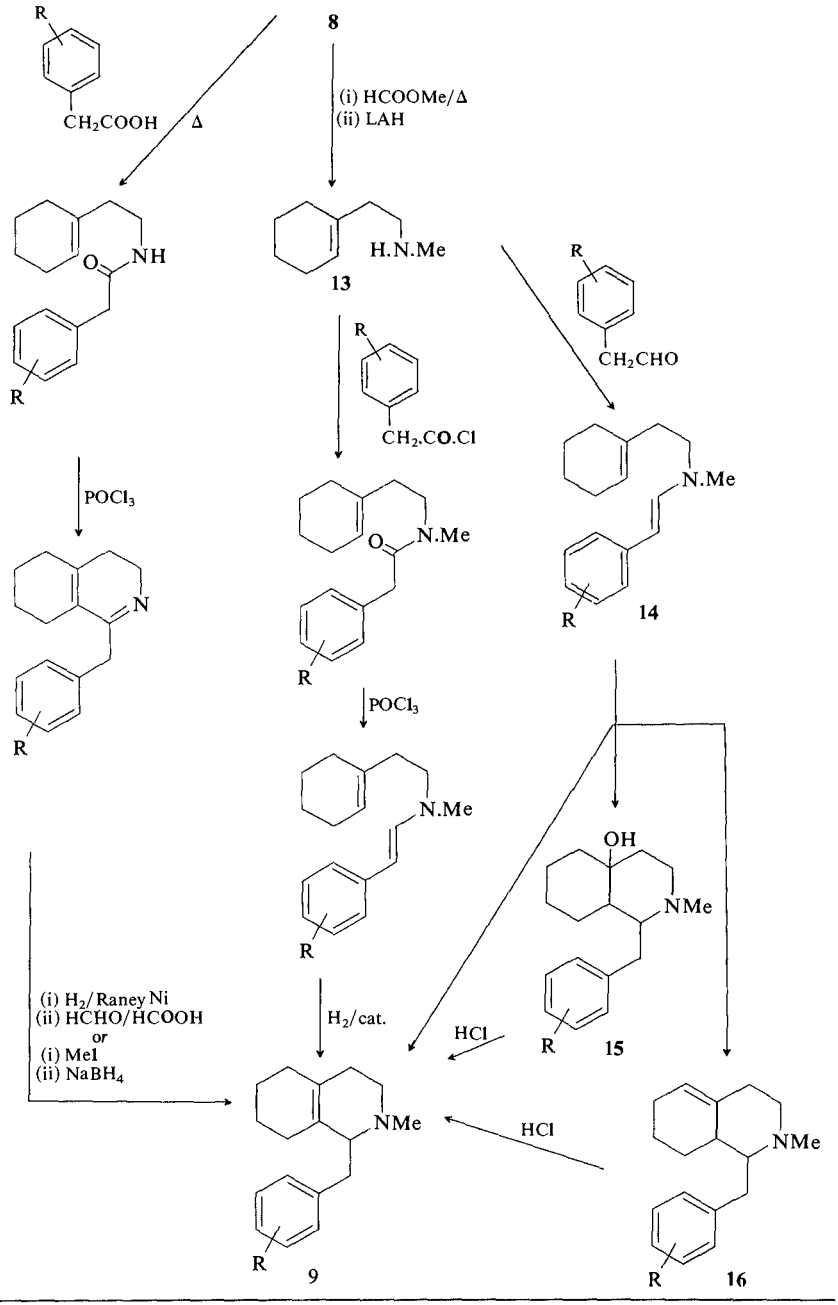
Scheme 3 2

sodamide, cyclohexanone reacts with ethyne, giving **12**, which may also be converted to **8**.[13] Reduction of phenylethylamines directly to **8** has been reported.[14-16] Amide formation with substituted phenylacetic acids or acid chlorides and subsequent cyclization and conversion to 2-benzyloctahydroisoquinolines (**9**)[11,12,17-20] is outlined in Scheme 3.3.

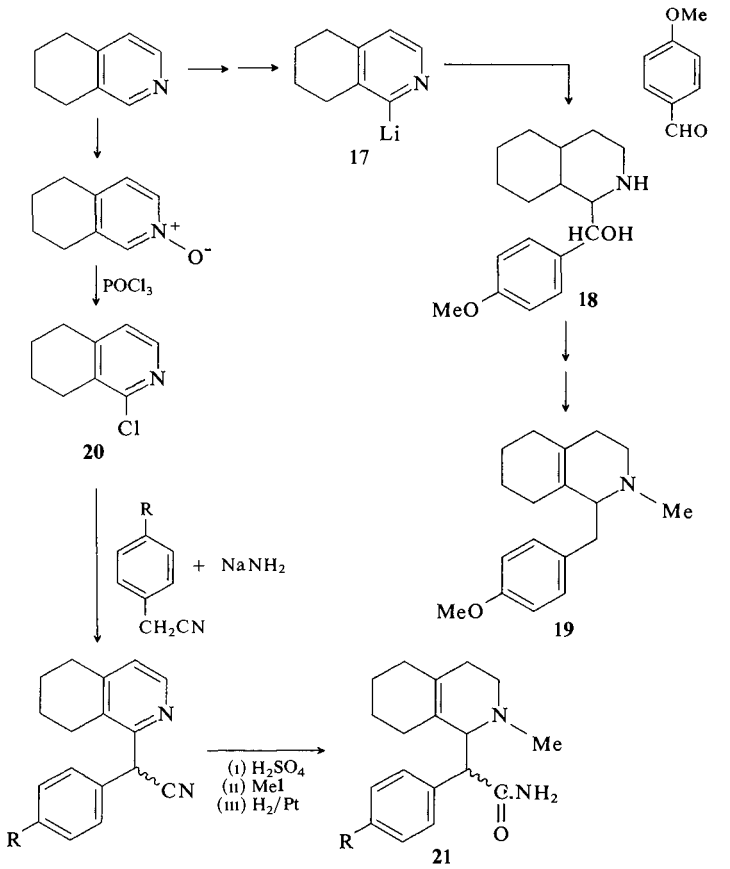
Cyclohexenylethylmethylamine (**13**) afforded enamines of general formula **14** with appropriate phenylacetaldehydes.[17] Such enamines may be cyclized under Pictet-Spengler conditions to **9** with variable amounts of the reduced isoquinoline byproducts **15** and **16** according to the reaction conditions. Both **15** and **16** gave **9** on treatment with aqueous HCl.

The pathways outlined in Scheme 3.3 overcome low yields encountered when 4-methoxybenzylmagnesium halides react with 5,6,7,8-tetrahydroisoquinolinium salts (e.g., **2**). Other routes were devised to achieve the same objective. Grewe *et al.*[21] exploited the 1-lithium derivative of the tetrahydroisoquinoline derived via the 1-amino intermediate, Scheme 3.4.

Reaction of **17** with an anisaldehyde gave **18**, which was readily converted to the morphinan precursor, **19**. In a similar manner, 1-chloro-5,6,7,8-tetrahydroisoquinoline (**20**) gave the 1-benzyloctahydroisoquinoline amide (**21**)[22,23] that cyclized with the loss of the amide function to the corresponding morphinan.

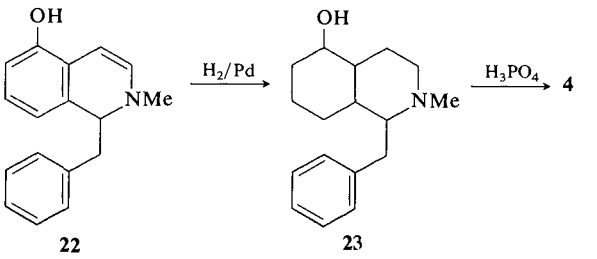

R
CH2COOH
Δ
8
(i) HCOOMe/Δ
(ii) LAH
H.N.Me
13
R
CH2CHO
R
CH2.CO.Cl
POCl3
N.Me
O
N
R
14
POCl3
N.Me
R
OH
NMe
R
15
(i) H2/Raney Ni
(ii) HCHO/HCOOH
or
(i) MeI
(ii) NaBH4
H2/cat.
HCl
NMe
R
9
HCl
NMe
R
16

Scheme 3.3



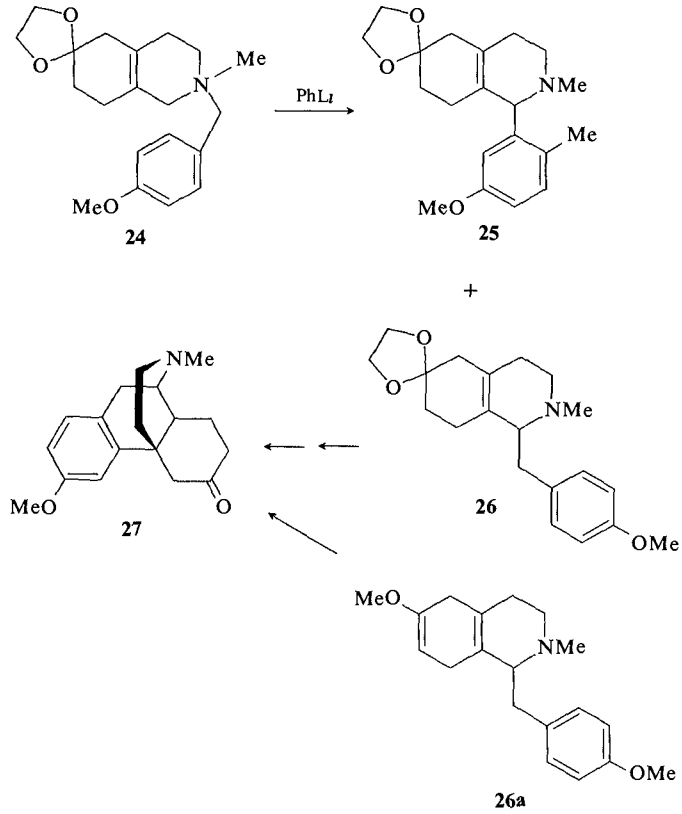
Scheme 34

1-Benzyl-5-hydroxydihydroisoquinoline (**22**) may be converted[24] to the latent octahydroisoquinoline (**23**) by catalytic hydrogenation over palladium. Cyclization to 4 occurred in phosphoric acid.



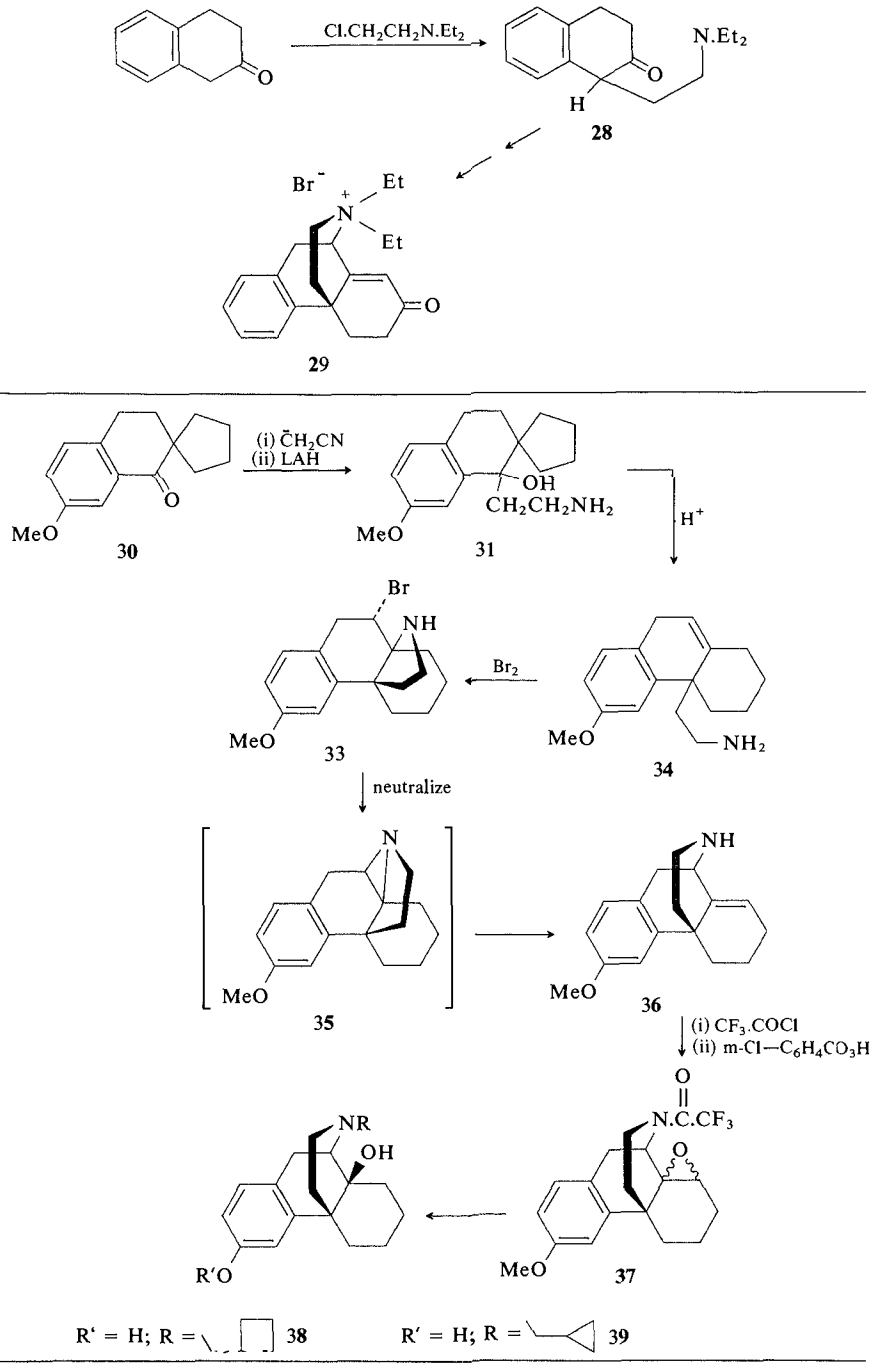
22 23

Maeda and Ohsugi[28] have described the synthesis of the octahydroisoquinolinium salt (**24**), which on Stevens rearrangement gave a mixture of **25** and **26**. The latter was transformed to the 6-oxomorphinan, **27**, which also resulted from direct phosphoric acid cyclization[156] of **26a**. The *N*-formyl analog of **26a** could not be made to ring close.



Both 1- and 2-tetralones have been exploited as intermediates to morphinans. An early report[25] described the isolation of the morphinan quaternary salt **29** in low yield from 2-tetralone. The monoalkylation product **28** has since proved elusive, with diakylation invariably occurring. Thus, the nature of the product claimed must be in doubt.

Alkylation of 7-methoxy-1-tetralone with 1,4-dibromobutane afforded a spiro intermediate (**30**) leading to 14-hydroxymorphinans[26,27] such as *butorphanol* (**38**) and *oxylorphan* (**39**), which are inaccessible from the Grewe route (Scheme 3.5). Alkylation of **30** with acetonitrile followed by reduction gave the primary amine (**31**), which, in strong acid, rearranged to **34**. Bromination of **34** gave the unsaturated morphinan, **36**, after neutralization, an aziridine (**35**) being invoked as an intermediate. Protection of the secondary amine


Cl.CH2CH2N.Et2
N.Et2
O
H
28
Br⁻
Et
N
Et
O
29
(i) ⁻CH2CN
(ii) LAH
OH
CH2CH2NH2
MeO
30
31
H+
Br
NH
Br2
MeO
33
34
NH2
neutralize
N
35
NH
36
(i) CF3.COCl
(ii) m-Cl—C6H4CO3H
O
N.C.CF3
NR
OH
R'O
37
R' = H; R = 38
R' = H; R = 39

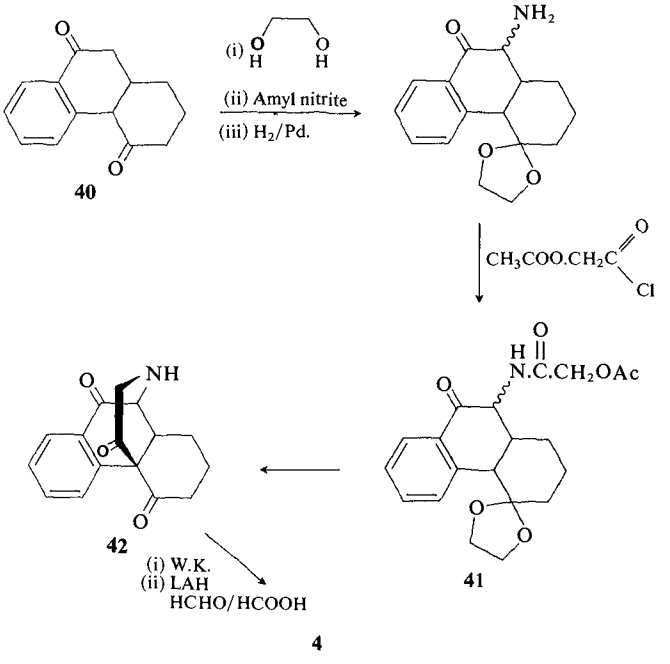
Scheme 3.5

followed by epoxidation and reduction resulted in a morphinan readily convertible to butorphanol (**38**) and oxylorphan (**39**) (see p. 132), both (−)-enantiomers resolved as tartaric acid salts.

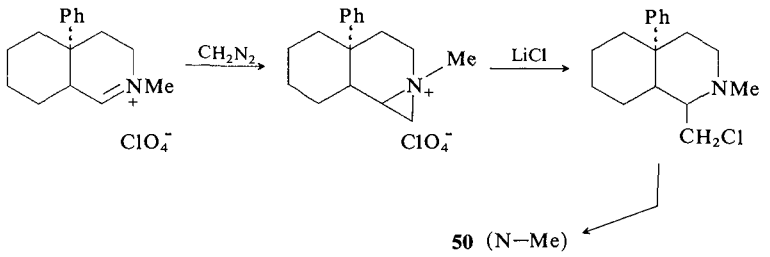
Ginsburg[29-31] took advantage of a preformed octahydrophenanthrene, **40** (Scheme 3.6). Conventional chemistry gave the ketal, **41**, but an attempt to ketalize the free ring carbonyl caused cyclization to the trioxomorphinan, **42**. Sequential reduction and *N*-methylation gave the previously described **4**.

A novel route to morphine-related compounds by way of an aryldecahydroisoquinoline synthon was published in 1980.[100] *N*-methylisomorphinan resulted from the aluminium chloride cyclization of a chloromethyldecahydroisoquinoline derived from an iminium perchlorate, according to Scheme 3.6a.

Evans and Mitch[101] elaborated this synthesis to afford a general approach to morphinans and to include a total synthesis of (±)-morphine (Scheme 3.7). The diastereomerically pure aziridinium salt, **43**, was prepared as illustrated and converted to the aldehyde (**44**) in 95% yield simply by dissolving in anhydrous DMSO at ambient temperature (Kornblum oxidation). Lewis acid catalyzed ring closure occurred in high yield (80%) to the isomorphinan-10-ol



Scheme 3.6



Scheme 3.6a

(**45**), which elaborated to the isomorphinan-6-one (**46**). Epimerization at C-14 to **47** constituted a new total synthesis of (±)-morphine (see Chapter 2).

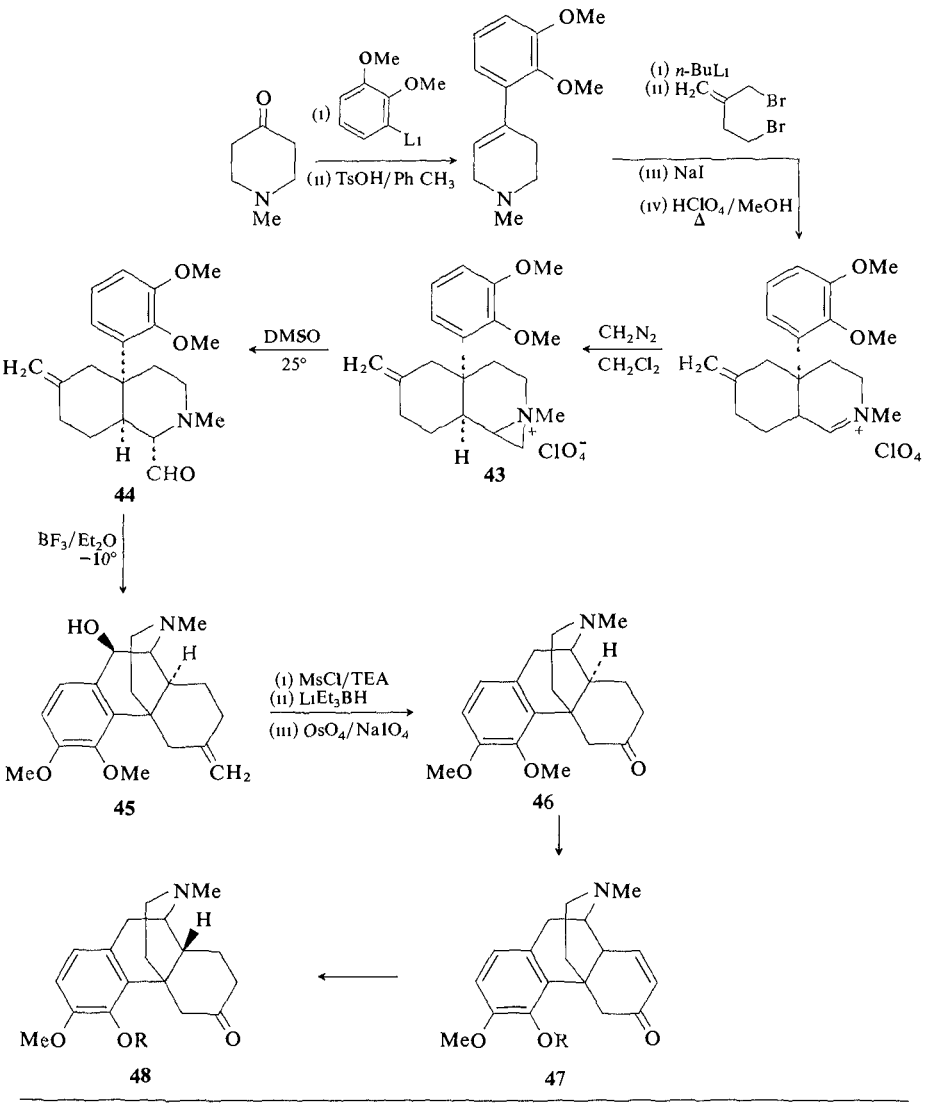
Gates and Helg[102] established earlier that β-thebainone (**47**, R = H) (B/C *trans*) could be readily inverted under both acid (HOAc) and base (NaOEt) conditions to give predominantly dihydrothebainone (**48**, R = H) (B/C *cis*), which was separated from the mixture in a pure yield of 60%. In addition, β-thebainone 2,4-dinitrophenylhydrazone is subject to quantitative conversion to the B/C *cis* isomer in warm acetic acid within 6 h.

3.3. STEREOCHEMISTRY

The morphinan nucleus possesses three chiral centers at C-9, C-14, and C-13. As two of these, C-9 and C-13, are bridged, and thus constrained, only two diastereoisomeric pairs occur. Morphinans (**49**) bear a *cis* B/C ring fusion and in this regard are related to morphine. Where the C-14 center is inverted (i.e., *trans* B/C fusion), compounds are known as isomorphinans (**50**), and these will be discussed later (p. 136). Note that in structures **49** and **50** the stereochemistry of ring C is shown in relationship to ring B.

Extensive structure-biological activity investigations followed the observation that **49** (R = H or OH; R′ = Me) possessed good antinociceptive properties. Resolution of racemic **49** (R = OH; R′ = Me) with L-(+)-tartaric acid indicated that the (−)-isomer was endowed with all the analgesic properties of the racemate (up to 8× morphine in humans). Subsequently, it was introduced into clinical use as *levorphanol* or "Dromoran." Unfortunately, its capacity for causing physical dependence was no less than that of morphine.

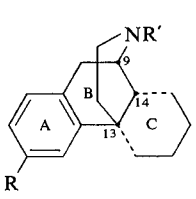
To secure the corresponding (+)-antipode resolution must be effected prior to cyclization at the penultimate stage. In Scheme 3.1, **51** (R = OH; R′ = Me) was resolved[34] with L-(+)-tartaric acid to yield (−) **49** (R = OH; R′ = Me). The corresponding (+)-morphinan was then isolated after cyclization of the remaining (+) **51**. Biological evaluation of (+) **49** (R = OH;



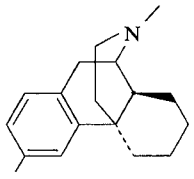
Scheme 3.7

R′ = Me) demonstrated that it lacked analgesic responses. The corresponding methyl ether, **49** (R = OMe; R′ = Me), however, proved to be a clinically useful antitussive agent known as *dextromethorphan* or "Romilar."

Resolution at the penultimate stage of the manufacturing process offered certain practical and commercial advantages and attempts were made to invert

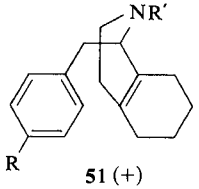


49



50

optically pure (+) **51** (R = OMe; R′ = Me) and related compounds. Successful racemization was achieved with Pd-Zn-Fe[32] and Co-Cu.[33]

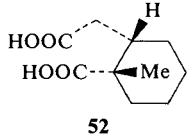


51 (+)

More recently,[157] dextromethorphan and levomethorphan have been resolved via their respective quaternary ammonium salts with *n*-alkyl iodides. The ratio of axial and equatorial isomers produced during quaternization with Me, *n*-Pr, and *n*-Bu iodides was assessed by ^{1}H- and ^{13}C-nmr.

As with morphine and the benzomorphans, variation of the *N*-substituent (Chapters 2 and 4) markedly affects opioid pharmacodynamic activity, and (−) **49** (R = OH; R′ = allyl) known as *levallorphan* or "Lorphan" is an antagonist several times more potent than nalorphine. Rather than prepare levallorphan by the *N*-demethylation **49**, (R = OH; R′ = Me) and allylation, on a commercial scale **51** (R and R′ = H) or **51** (R = H; R′ = $CH_2C_6H_5$) are obtained optically pure.[34] The former may be allylated and cyclized, whereas the latter was cyclized, debenzylated by hydrogenolysis, and finally converted to levallorphan with allyl bromide.

Circumstantial evidence suggested that levorphanol ((−) **49**, R = OH; R′ = Me), because its pharmacodynamic profile is similar to that of morphine, has the same absolute configuration. Proof of absolute configuration came from Hellerbach's group,[35] who subjected it to Hofmann degradation, followed by oxidative steps to the dicarboxylic acid, **52**, identical to that obtained from thebaine and abietic acid.

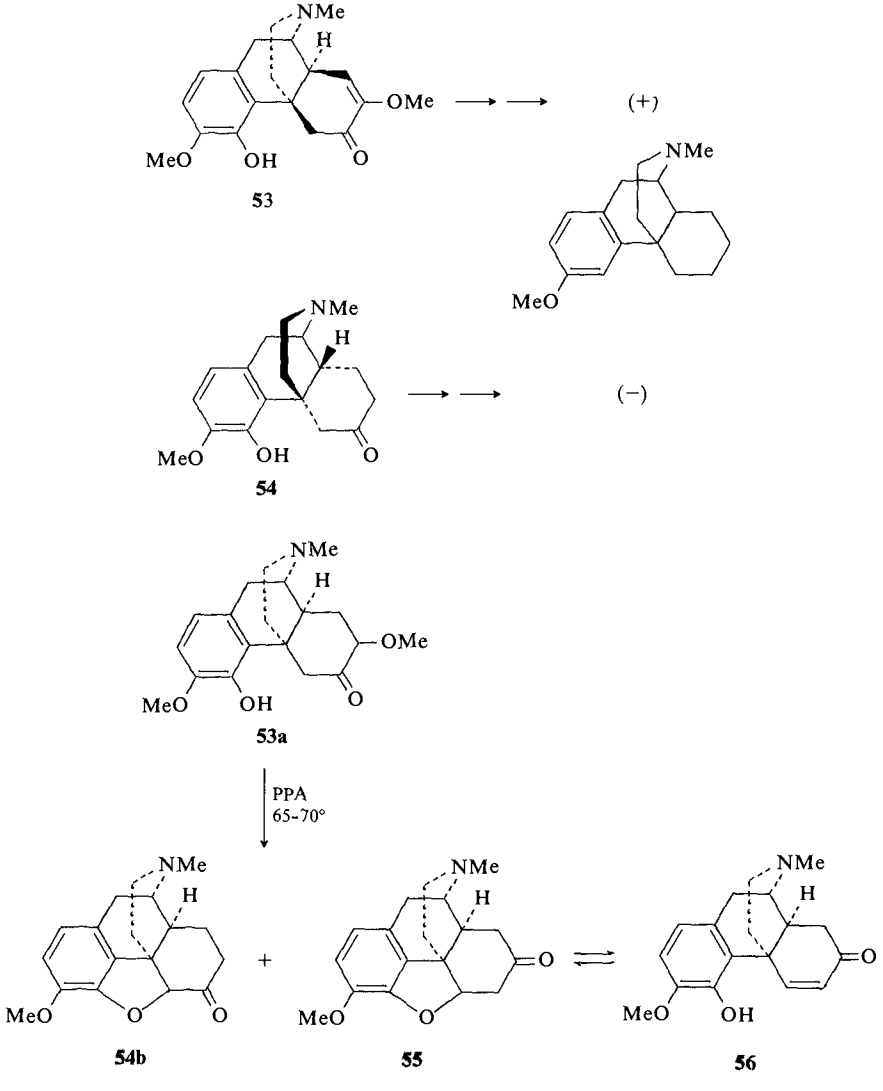


52

Sawa and co-workers[36] elegantly and unambiguously related the naturally occurring (+)-morphinan, sinomenine (**53**), and dihydrothebainone

(**54**) by degradation to (+)-3-methoxy-*N*-methylmorphinan and the (−)-antipode, respectively.

Optical rotatory dispersion[103,146] characteristics of (−)-levorphanol and (−)-morphine have been compared. The negative Cotton effects of each compound were attributed to the phenolic chromophores, and this afforded strong evidence for the configurations at C-9, C-13, and C-14 being identical in each. Circular dichroism[104] studies on other morphinan and codeine derivatives supported this conclusion.



During studies on the synthesis of opiates with unnatural stereochemistry, dihydrosinomenine (**53a**) is often cyclized initially to (+)-dihydrocodeinone (**54b**). In addition to the desired, **54**, the NIH group[159] isolated 10% of a ketone that proved upon recrystallization to be a mixture of 4,5-epoxide (**55**) and the 5-en-7-one (**56**). Structures were established by an extensive spectroscopic examination and were confirmed by X-ray crystallographic analysis. In the solid state (+)-4-hydroxy-7-oxo-3-methoxy-17-methyl-5,6-dehydromorphinan (**56**), the isomer that crystallizes most readily from ethyl acetate was found to consist of a stack of molecules in the form of an intertwined double helix with strong O(4)-N hydrogen bonds. The individual helices are not bonded together, except by van der Waals forces.

3.4. SUBSTITUTED MORPHINANS

3.4.1. Substitution on Nitrogen

The change from opiate agonist to antagonist or mixed agonist-antagonist on replacing methyl on nitrogen by allyl is apparent in (−)-morphinan series.[37,34] In this respect, morphinans resemble morphine and benzomorphans, and a more detailed account of opioid antagonists is given in Chapter 12. A listing with pharmacological data of all morphinans evaluated to 1965 has been published.[8] Unlike the benzomorphan series, most compounds tested for biological activity were optically pure [usually the (−)-enantiomer] and in addition were often oxygenated (phenolic) at C-3.

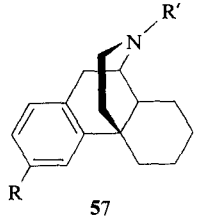
During early studies it was demonstrated that extending the *N*-alkyl chain (i.e., >Me) was of no biological advantage.[8,34,38] At first, with *N*-Et and *N*-*n*-Pr, activity fell, but beyond that to *N*-C_6H_{13} some restoration of activity was seen.

During the 1950s and 1960s the search for a nondependent, strong analgesic was a paramount objective. Gates and Montzka[39] argued that cycloprolylmethyl (CPM) bore some electronic similarity to allyl, and as nalorphine was a strong analgesic in humans with no detectable PDC,[40,41] they prepared CPM derivatives of morphine and (−)-morphinans by conventional chemistry. The results of their study were published simultaneously with the report of pentazocine and cyclazocine by Archer *et al.*[42]

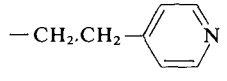
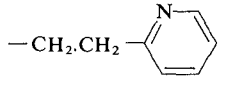
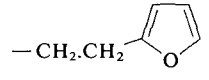
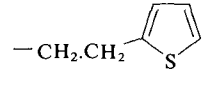
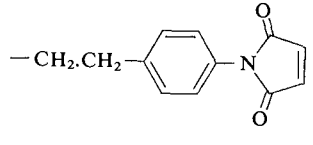
(−)-3-Hydroxy-*N*-cyclopropylmethylmorphinan proved to be not only a powerful morphine antagonist (AD_{50}, 0.03 mg/kg v. pethidine) that is about four times the potency of nalorphine, but was also a very effective analgesic in humans. As we now expect for compounds bearing *N*-"antagonist" substituents, very little antinociceptive activity was observed in most rodent assays, (e.g., RTF) under standard conditions.

Extension of the alkenyl or alkynyl chain afforded only weak agonist-antagonists,[34] although the propargyl analog behave pharmacologically very much like nalorphine.[43]

Numerous *N*-aralkyl-[44] and heteroaralkyl-[45] morphinan derivatives have been reported. *N*-Phenethyl-(Phenomorphan*) and *N*-phenacyl-(Levophenacylmorphan*) analogs of (−)-3-hydroxymorphinans (**57a** and **57b**) exhibited good MHP (sc) activities (ED_{50} 0.11 and 0.09 mg/kg, respectively). Substitution of the aromatic ring of the *N*-substituent caused some variation in the level of activity, but analgesia was maintained. Lengthening or shortening of the alkane chain or inclusion or substitution of oxygen or nitrogen into the chain resulted in diminution or loss of activity. The heteroarylethyl analogs **57c**, **d**, **e**, and **f** were all found to be good analgesics (MHP, sc ED_{50}, 0.063, 0.19, 0.01 and 0.019 mg/kg, respectively). Analogs bearing 3-methoxy substituents (**57**, R = OMe) showed a reduction in potency, as expected, whereas in the 3-acyloxy derivatives, activity was maintained.



57

	R	R′
a	—OH	$-CH_2.CH_2.C_6H_5$
b	—OH	$-CH_2.\overset{\overset{O}{\|}}{C}.C_6H_5$
c	—OH	
d	—OH	
e	—OH	
f	—OH	
g	—OH	

N-(β-Cyanoethyl)- and *N*-(γ-cyanopropyl)- derivatives of (±)-normetazocine were observed to have good antinociceptive activity in rodents.[46] The NIH[47] group confirmed this and made an extensive study of rigid opiates substituted accordingly. (−)-3-Hydroxy-*N*-(β-cyanoethyl) mor-

* These names are unfortunate and misleading, as they suggest that the compounds are related to arylmorphans (see Chapter 5).

phinan was about 50 × morphine (MHP) as an analgesic with a receptor binding affinity similar to that of levorphanol. Its effects were readily reversed. Curiously, the compound would not substitute for morphine and appeared to exacerbate withdrawal. The corresponding cyanomethyl analog had only half the antinociceptive activity of morphine (MHP) and the (+) enantiomorphs were inactive.

A phenethyl compound prepared as a potential ligand to the opioid receptor(s), by acting as a Michael acceptor, has been reported by the Portoghese group.[48] Compound **57g** was 5 × morphine as an analgesic but did not appear to be acting at the same receptor. A photoaffinity labeling reagent, *N*-β-(*p*-azidophenyl)ethylnorlevorphanol, has also been reported.[160,161]

In a study designed to establish whether or not an N cationic center was necessary for a stereospecific action at opioid receptors, Opheim and Cox[49] made a pair of enantiomeric quaternary salts, (−)-3-hydroxy-*N*,*N*-dimethylmorphinanium iodide and (+)-3-hydroxy-*N*,*N*-dimethylmorphinanium iodide related to levorphanol and dextrorphan, respectively. Only the *levo* enantiomer gave a dose-dependent inhibition of GPI longitudinal muscle that was naloxone reversible, and although this activity was lower than that seen with levorphanol, it did suggest the necessity for a cationic *N*-pharmacophore (p. 463).

3.4.2. Aromatic Ring Substitution

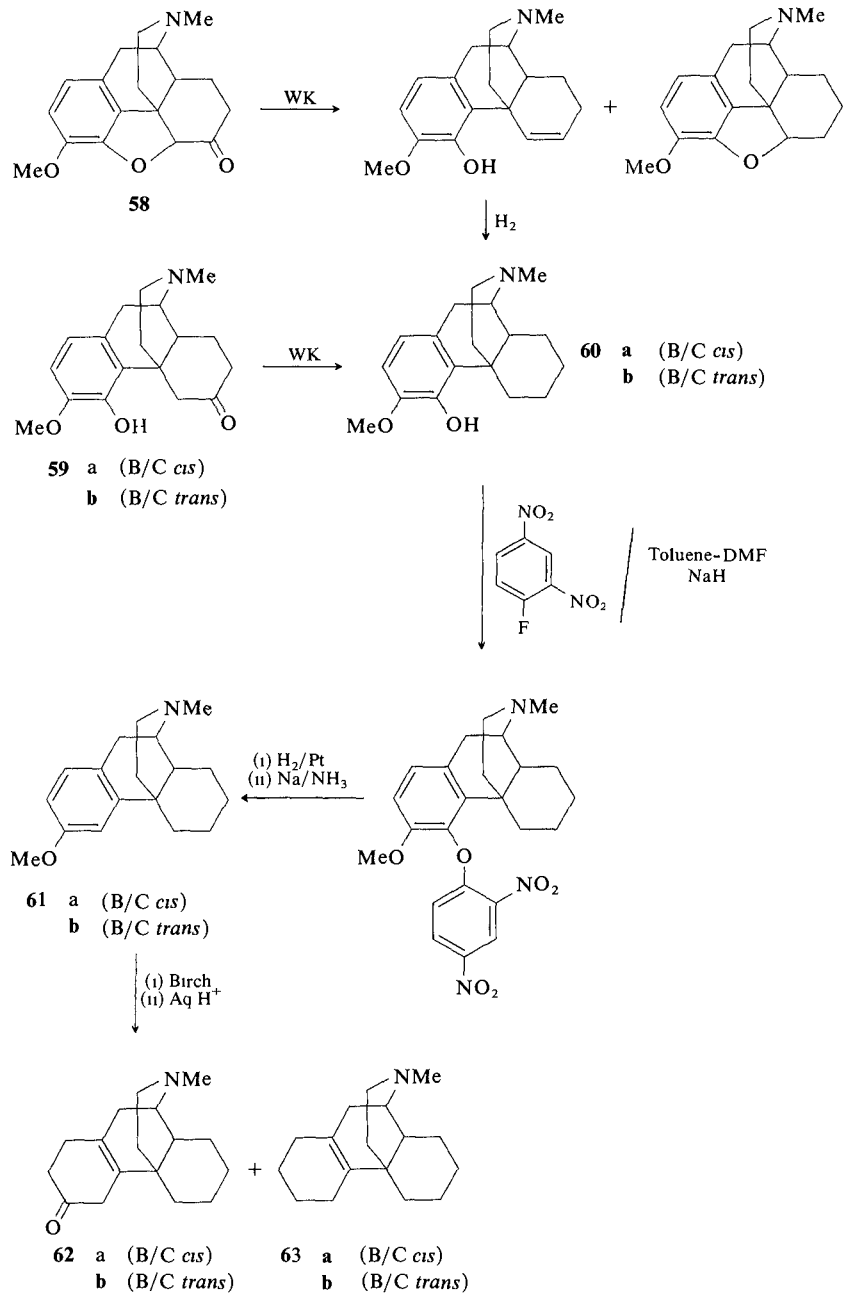
Like morphine, most analgesically active morphinans bear an oxygen function, usually as hydroxyl, in position C-3. The presence of 3-OH or 3-OAc invariably leads to a significant enhancement of opiate activity in these series, whereas 3-OMe affords, at best, a modest activity increase.[8] Other 3-position substituents significantly reduce or abolish activity.

Morphinan-6-ones with hydroxyl groups at positions C-1, C-2, and C-4 have been prepared and their chemistry and pharmacology have been reviewed.[50] These compounds will be discussed in a later section (p. 121).

Other 3-substituted morphinans were isolated during attempts to prepare 3-hydroxymorphinans by sequential nitration, hydrogenation to the amine, and diazotization of the unsubstituted precursor.[38] A mixture of 2- and 3-nitromorphinans was isolated, but no biological data were reported.

Alkylation of levorphanol with *N*,*N*-dimethylformamide di-*t*-butyl acetal gave the *t*-butyl ether,[50a] which was of reduced analgesic (MW, RTF) activity and receptor binding affinity and lacked antitussive actions.

Opioid receptor binding studies have been performed[51] on a series of *N*-Me, *N*-allyl, and *N*-CPM morphinans substituted with a phenolic OH group in the C-1, C-2, C-3, or C-4 positions. Interestingly, although the presence of a 3-OH afforded the strongest receptor binding, binding nevertheless occurred regardless of the position of the −OH or even its presence.


NMe
MeO
O
58
WK
OH
+
H_2
59 a (B/C *cis*)
b (B/C *trans*)
60 a (B/C *cis*)
b (B/C *trans*)
NO_2
F
Toluene-DMF
NaH
(i) H_2/Pt
(ii) Na/NH_3
61 a (B/C *cis*)
b (B/C *trans*)
(i) Birch
(ii) Aq H^+
62 a (B/C *cis*)
b (B/C *trans*)
63 a (B/C *cis*)
b (B/C *trans*)

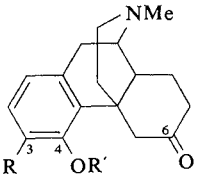
Scheme 3 8

Aromatic ring reduced morphinans and isomorphinans have been reported.[52] Birch reduction of 3-methoxy-*N*-methylmorphinan (**61a**) and the corresponding isomorphinan (**61b**) gave the respective 1,2,3,4-tetrahydro-3-oxo-derivatives (**62a** and **62b**) together with small amounts of the desoxo compounds **63a** and **63b**. The morphinan and isomorphinan precursors (**60a** and **60b**) were derived from (**58**)[53] or dihydrothebainone (**59**), according to Scheme 3.8. In the RTF test, no significant activity was observed for **62a** or **62b**.

In Japan, 3,17-dimethylmorphinan phosphate (*Dimemorfan*) has been marketed as a centrally acting antitussive agent,[54] and the related (+)-3-ethyl-17-methyl analog is reported in the patent literature to have analgesic and antitussive properties.[54a]

3.4.3. Morphinan-6-ones

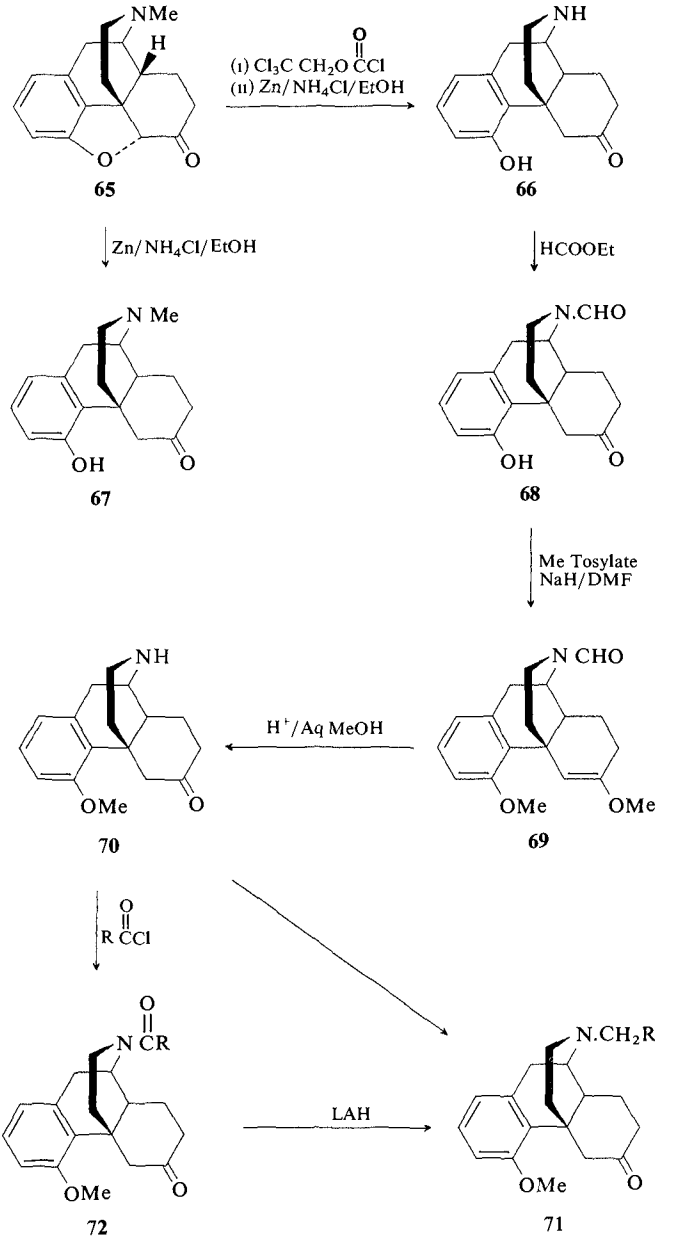
Morphinans bearing a 6-oxygen function have proved to be a valuable source of precursors for the synthesis of natural opiates.[53,55-58] Compounds such as dihydrothebainone (**64**, R = OMe; R′ = H) may be derived from thebaine, whereas others are totally synthetic.[8]



64

In 1964 a Japanese group[59] reported that the 4-methyl ether (**64**, R = OMe; R′ = Me), a total synthesis of which has now been described,[60,153] was several times more potent than morphine as an analgesic (MHP, sc ED_{50}, 0.35 mg/kg), whereas dihydrothebainone itself was only about $\frac{1}{2}\times$ morphine (MHP). Many years later, (−)-4-hydroxy-*N*-methylmorphinan-6-one (**64**, R = H; R′ = Me) prepared initially as a synthetic precursor for 3-deoxydihydromorphine[61] was found to be an excellent analgesic (MHP, sc ED_{50}, 1.6 mg/kg) in spite of the lack of a 3-OH function.[62,63] Earlier, it had been demonstrated that in the morphine series a 3-OH was not essential for analgesia.[64] Methylation of the C-4 oxygen caused a substantial increase in biological response (MHP, sc ED_{50}, 0.29 mg/kg). The 3-hydroxy-4-methoxy analog (**64**, R = OH, R′ = Me) was only $\frac{1}{2}\times$ morphine (MHP) and the corresponding catechol (**64**, R = OH, R′ = H) was reduced to about $\frac{1}{5}\times$ the activity of morphine (MHP). A 3,4-methylene bridged analog had a MHP (sc) ED_{50} of only about 6.3 mg/kg.

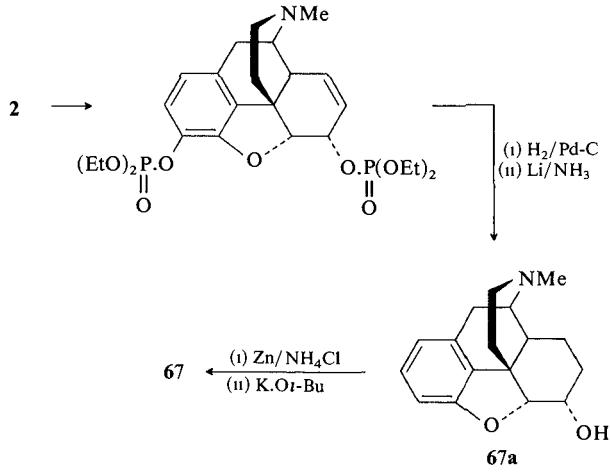
Stimulated by these observations, Brossi's group at NIH undertook an extensive investigation of morphinan-6-ones oxygenated in each available


NMe
H
O
O
65
(i) Cl3C CH2O CCl
(ii) Zn/NH4Cl/EtOH
NH
OH
O
66
Zn/NH4Cl/EtOH
HCOOEt
N Me
OH
O
67
N.CHO
OH
O
68
Me Tosylate
NaH/DMF
NH
OMe
O
70
H+/Aq MeOH
N CHO
OMe
OMe
69
R CCl
O
N CR
OMe
O
72
LAH
N.CH2R
OMe
O
71

Scheme 3.9

position of the aromatic ring and they have reviewed their results.[65] 4-Hydroxymorphinans have been synthesized via the Grewe route and resolved[66]; however, a superior approach was developed at NIH.[64] Optically pure 3-deoxydihydromorphinan-6-one (**65**) derived from morphine had been reported previously. Manipulation according to Scheme 3.9, *N*-demethylation and furan ring opening of **65** proceeded unexceptionally to **66**. The latter afforded the formyl intermediate **68** necessary for the elaboration of 4-methoxy analogs with a variety of agonist and antagonist *N*-substituents.[67]

Alternatively[62] removal of the morphine 3-OH may be effected via the 3,6-di(diethylphosphate) ester by sequential reduction to **67a**, followed by Zn/NH_4Cl epoxide ring cleavage and oxidation to **67**.

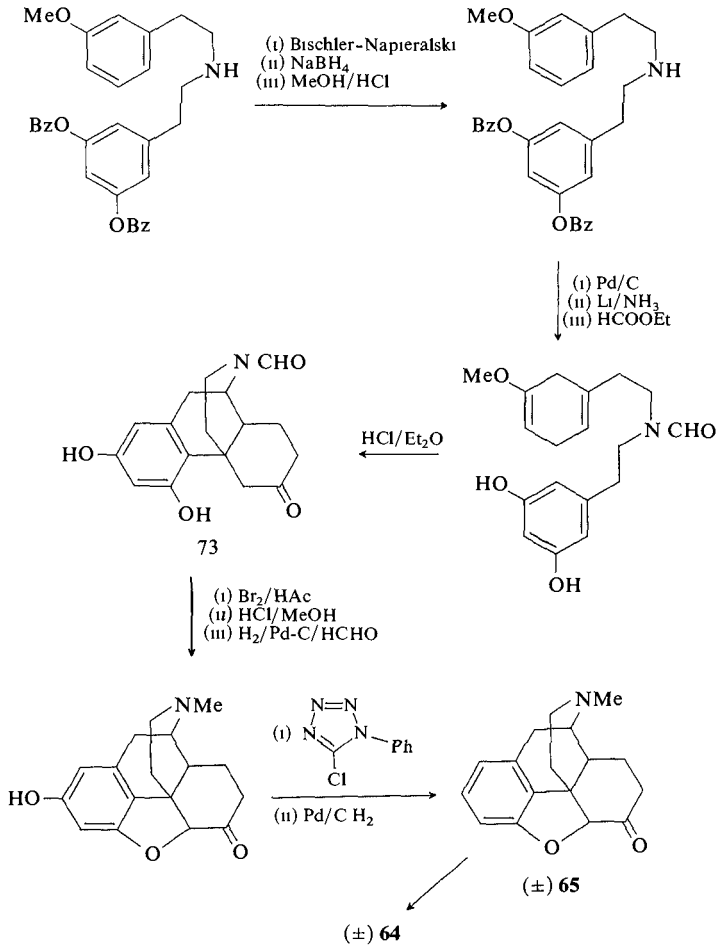


67a

A total synthesis of **64** (R = R′ = H; and R = H and R′ = Me) has been achieved[65,68,69] (Scheme 3.10) by a modified amine pathway (Scheme 3.3) and reminiscent of the synthesis of dihydrothebainone by Beyerman *et al.*[70,71] The 2,4-dihydroxymorphinan-6-one (**73**) was converted (39%) to the 3-desoxy-2-hydroxymorphinan-6-one, which was dehydroxylated by hydrogenation of the *N*-phenyltetrazolyl ether derivative to (±)-**65**.

Dihydromorphine has also been converted to **64** (R = R′ = H) and the 6-oxo group removed by Wolff-Kishner reduction.[72] Bromination (1 mol Br_2/HOAc) of (−)-4-hydroxy-*N*-methylmorphinan-6-one has been shown by ^{13}C nmr to occur predominantly in the 1 position.[79]

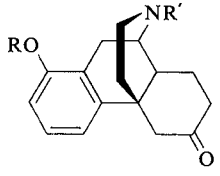
Compounds **64** (R = R′ = H; R = H; R′ = Me) are related configurationally to morphine and in analgesic tests had steep dose-response curves,[62,63] and **64** (R=H; R′=Me) was found to bind well to rat cerebellum membrane preparations. Analgesics similar to pentazocine resulted from antagonist *N*-substituents, with the best antagonist potency being between nalorphine and naloxone.



Scheme 3 10

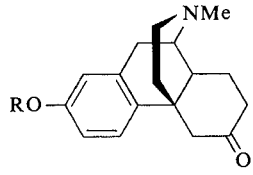
Morphinan-6-ones bearing oxygen functions elsewhere in the aromatic ring have been subject to relatively little study. An unsuccessful attempt was made to prepare (±)-1-hydroxymorphinan-6-ones from 1-(2-methoxybenzyl)octahydroisoquinoline (e.g., Scheme 3.1) under a range of forcing conditions.[65] The optically pure series was derived from (−) **64** (R = H, R′ = Me), which is in itself accessible from morphine.[73] Insertion of the 1-oxygen function was achieved finally by potassium nitrosodisulfonate (Fremy's salt) oxidation to the *p*-quinone,[74] reduction to the corresponding hydroquinone by zinc and methanol followed by sequential etherification with

benzyl bromide (reacting with the lesser hindered 1-OH) and 1-phenyl-5-chlorotetrazole. Reductive removal of the 4-position oxygen simultaneously released the 1-OH. The free phenol **74a** was without significant MHP (sc) activity, whereas the corresponding methyl ether was about $\frac{1}{3}$ × morphine (MHP, sc ED_{50}, 3.7).



74

a R = H; R^1 = Me
b R = Me; R^1 = Me



75

a R = H
b R = Me

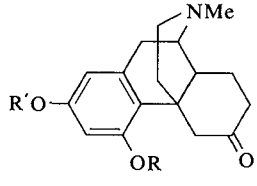
The related 1-hydroxymorphinans have been reported,[50,75] and although some members of the series demonstrated a strong receptor affinity, they were without antinociceptive activity.[51]

2-Hydroxy-*N*-methylmorphinan was also found to bind to opioid receptor(s), but its analgesic activity in the MW assay was of doubtful significance. Related morphinan-6-ones were synthesized via 3-methoxyphenylethylamide[76,77] (e.g., Scheme 3.10). Resolution at the 2-benzyltetrahydroisoquinoline stage afforded (−)-2-hydroxy-*N*-methylmorphinan-6-one (**75a**) and the corresponding methyl ether (**75b**). Neither compound exhibited significant MHP activity,[50] with the ether being only about $\frac{1}{6}$ × morphine. The (+)-enantiomorphs were prepared in a similar manner.[50]

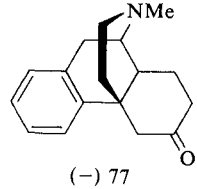
Several 14-hydroxymorphinan-6-one derivatives have been the subject of chemical and pharmacological studies (see p. 132).

During total synthesis studies on (±)-3-deoxy-7,8-dihydromorphine and (±)-4-methoxy-*N*-methylmorphinan-6-one, a series of racemic mixtures with both 2- and 4-oxygen substituents (**76**) was isolated and characterized.[69] 2,4-Dihydroxy-3-methoxymorphinan-6-ones were isolated in an investigation of the Grewe codeine synthesis.[78]

Brossi's group at NIH has also investigated morphinan-6-ones lacking aromatic substitution. The availability of (−) **64** (R = H, R' = OH) gave access to the desired product (−) **77** by catalytic reduction of the



76
R and R^1 = H or Me



(−) 77

4-*N*-phenyltetrazolyl ether.[80] Wolff–Kishner reduction of the ketone gave (−)-*N*-methylmorphinan, previously described[8] and resolved.[81]

Compound (−) **77** is a good antinociceptive agent (3 × morphine MHP sc and 2 × (−)-*N*-methylmorphinan), and it seems, therefore, that the 6-oxo function plays some part in events at opioid receptors.

High antinociceptive activity in morphinan-6-ones resides in the (−)-enantiomorphs, compounds configurationally related to morphine. The 6-oxo group enhances potency and could be involved in augmenting receptor binding. Clearly, a 3-OH group is not essential for analgesia and 4-OH or better 4-OMe endows morphinan-6-ones with high levels of activity. Even the loss of aromatic ring oxygen as in (−) **77** afforded a higher level of *in vivo* activity than did morphine. Brossi has attributed this to its more efficient passage of the blood–brain barrier.[50]

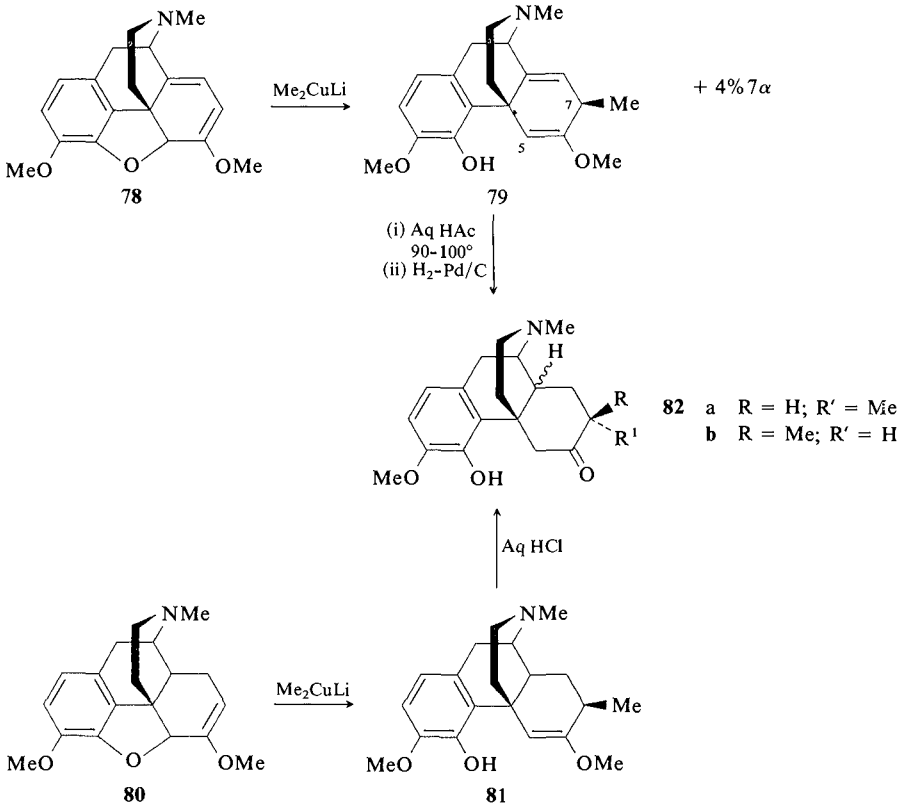
All of these series have pharmacological actions that parallel those of morphine, including dependence liability. They produce complete suppression of the abstinence syndrome in morphine-dependent monkeys, and their effects may be reversed by naltrexone.

3.4.4. 7-Substituted Morphinan-6-ones and Morphinans

The preparation of a 7-substituted morphinan in high yield was first accomplished in 1980.[82] Thebaine (**78**) was reacted with lithium dimethylcuprate to yield (90%) 7β-methyldihydrothebaine-φ (**79**) together with 4% of the 7α-epimer. Previously, dihydrothebaine[83] and the enol acetate of dihydrocodeinone[84] had been shown to react with methyl Grignard reagents affording predominantly 5-methyldihydrothebainone with only a trace of the 7-methyl isomer.[85] The production of **79** gave entry into a new series of morphinans.

In a manner similar to that outlined previously, dihydrothebaine (**80**) gave on reaction with Me_2CuLi the morphinan-6-one enol ether (**81**), which, on mild acid hydrolysis, yielded the 7α-methylmorphinan-6-one (**82a**) (B/C *cis*). The same product was obtained from **79** by first, acid hydrolysis of the enol-ether to a 3:1 mixture of B/C *cis* (morphinan) and B/C *trans* (isomorphinan) isomers, followed by catalytic hydrogenation of the appropriate isomer to a mixture of **82a** and **82b**.

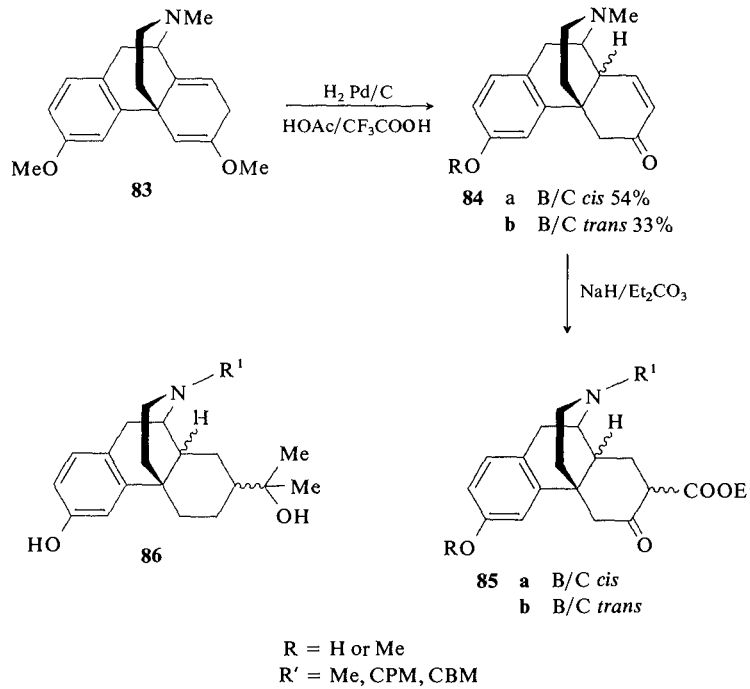
Deoxydihydrothebaine-φ (**83**) has been reduced[86] in high yield to the 3-methoxymorphinan-6-one (**84a**) and the corresponding isomorphinanone (**84b**) as illustrated. From these, diols of structure **86** were prepared. Both **85a** and **85b** (R = OH; R′ = Me) are equipotent with morphine (MW), although this activity is somewhat less than that of the related 7-unsubstituted analog. The *N*-CPM and CBM analogs in both 3-OH and 3-OMe series are mixed agonist–antagonists. Compounds of structure **86** had only weak opioid actions.



Scheme 3.11

Leland and Kotick[87] extended their work to include B/C *cis* and B/C *trans* series (**82**) with "antagonist" *N*-substituents (CPM and CBM) in place of methyl and with 8-alkyl substituents. The latter substituents were inserted by reaction of intermediates **87** and **88** with lithium methyl cuprate. Lithium ethyl cuprate gave little of the desired product, and it was found more convenient to proceed to 8-ethyl derivatives by hydrogenation of the more amenable 8-vinyl intermediate. Alkyl functions were assigned the diequatorial conformation by reference to studies on 8-alkylmorphinan-6-ones.[88]

All derivatives reported in these series were assayed for analgesia in the RTF and MW tests. Remarkably, members of most *N*-Me series of isomorphinans were substantially more active than morphine (RTF, ED_{50}, 0.68 for **89**, R = H; R′ and R^2 = Me, *cf* morphine 19.3 μmol/kg sc). 3-Methyl ethers bearing an *N*-Me group in the isomorphinan series were inactive in the RTF test, and the introduction of 7-Me or 7-Me, 8-short alkyl did not affect analgesic

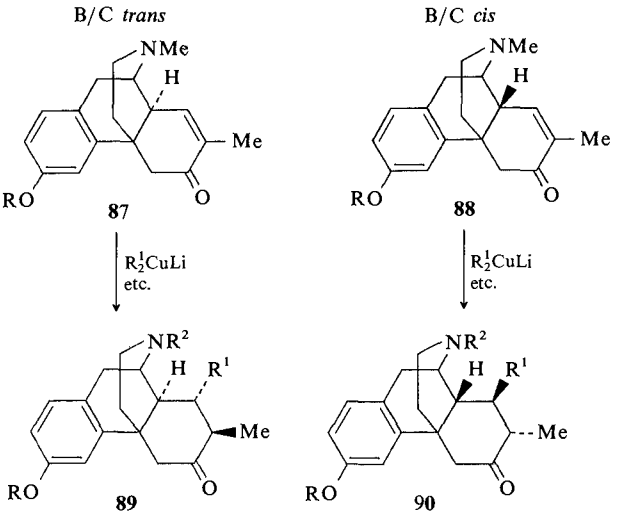


Scheme 3.12

potency unduly. Members of both B/C *cis* and B/C *trans* series with *N*-CPM and *N*-CBM substituents may exhibit agonist or mixed agonist/antagonist activities of a good order.

In 1982, it was noted[89] that 7-acylhydromorphones (**91**) possessed opioid agonist properties resembling those of the *endo*-ethanotetrahydrooripavines (p. 69). It was observed that a closer similarity to compounds such as etorphine and buprenorphine could be achieved by removing the furan oxygen bridge and examining morphinans and isomorphinans. The latter afford the same stereochemistry as the *endo*-ethanotetrahydrooripavines at C-**14**. Thus, pairs of epimeric alcohols of 7-(1-hydroxypentyl)isomorphinan (**95**) and the corresponding morphinans (**94**) have been synthesized[90] from the isomorphinan-6-one (**93**) and morphinan-6-one (**92**). The configuration of the side-chain chiral center was not determined.

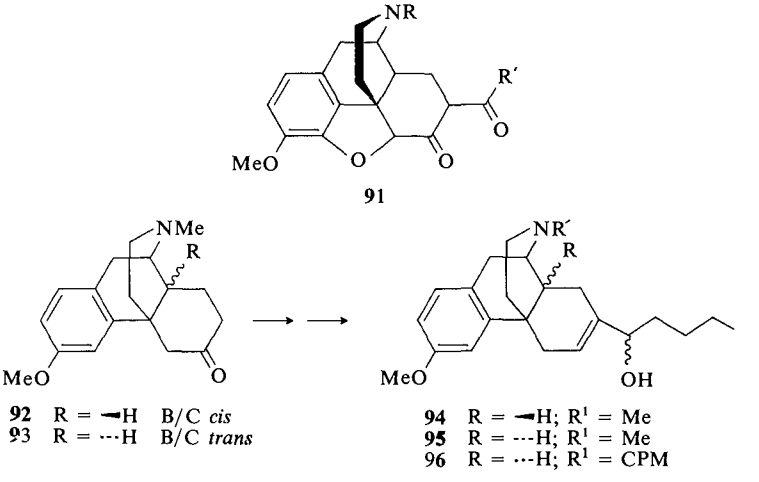
The pair of side-chain epimeric alcohols, **95**, gave very powerful agonist responses in the MW test (ED_{50}, 0.0058 and 0.0062 mg/kg; morphine ED_{50}, 0.79 mg/kg). Compound **94**, on the other hand, was inactive at 10 mg/kg, and the *N*-CPM derivative (**96**) was inactive in the antagonist RTF antagonist test at 10 mg/kg. The lack of discrimination in biological response between



R = H or Me
R^1 = Me, ⟋⟍, Et
R^2 = Me, CPM, CBM

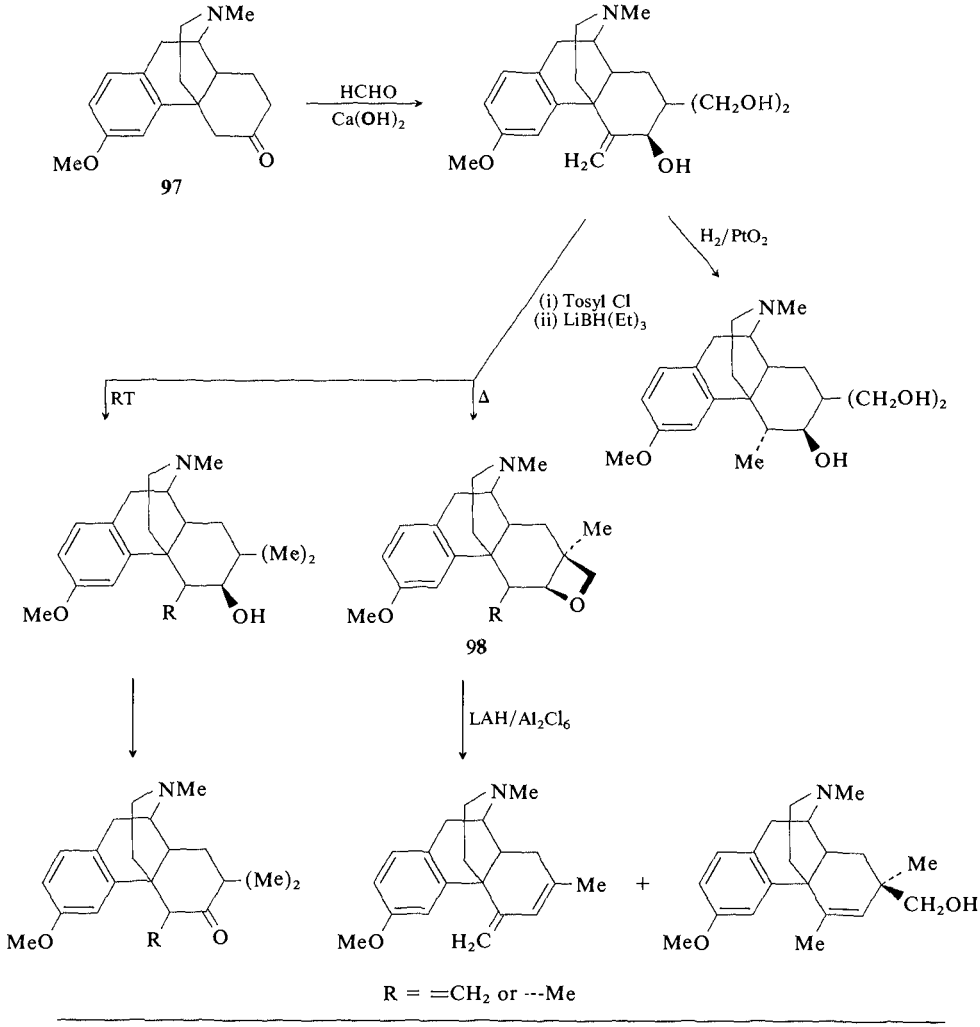
the epimeric secondary alcohols is similar to that seen in the secondary alcohols of the *endo*-ethanotetrahydrooripavine series[91] but contrasts with those for related epimeric tertiary alcohols.[92]

Morphinan-6-ones substituted in both the 5- and 7-positions resulted from the calcium hydroxide-induced reaction of formaldehyde with 3-methoxy-*N*-methylmorphinan-6-one (**97**).[93] Scheme 3.13 illustrates the reaction sequences followed, including the products given by the reductive cleavage of the oxetane moiety (**98**). No interesting antinociceptive activity was found.



92 R = ⟝H B/C *cis*
93 R = ···H B/C *trans*

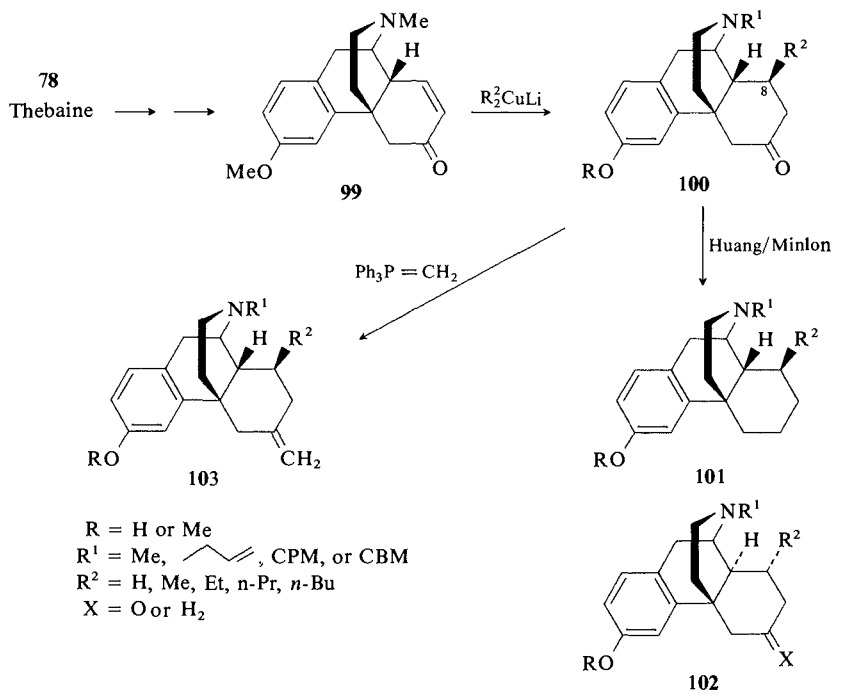
94 R = ⟝H; R^1 = Me
95 R = ···H; R^1 = Me
96 R = ···H; R^1 = CPM



Scheme 3.13

3.4.5. 8-Substituted Morphinan-6-ones and Morphinans

The morphinan-6-one (**99**), available from thebaine,[36,94,95] has been reacted with lithium dialkylcuprates to give 8β-alkylmorphinan-6-ones[96] (**100**) (Scheme 3.14). Variation of the *N*-substituent was effected by standard procedures, and reductive removal of the carbonyl under Huang-Minlon conditions to **101** also caused some 3-O-demethylation. Similar pathways were used for isomorphinan-6-ones and isomorphinans (**102**).



Scheme 3.14

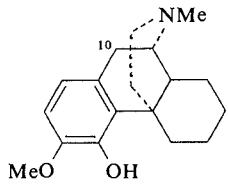
These series were assessed for antinociceptive responses in the RTF and MW (HOAc) tests and for opiate antagonism in the RTF antagonist assay. Although many of the compounds characterized were superior to morphine as agonists, **100** (R = Me or H; R′ = Me) exhibited a reduction in agonist potency as the 8-alkyl substituent was increased in size. The same applied to related isomorphinans, **102** (R = R′ = Me; X = O). However, the related phenolic isomorphinans (**102**, R = H) are very potent agonists (e.g., where R^2 = Me, the RTF sc ED_{50} was 0.93 μmol/kg). Loss of the sp^2 hybridized carbon at C-6 in the form of either morphinans or the corresponding 6-ols caused a dramatic diminution of both agonist and antagonist activity. In general, CPM and CBM *N*-substituents afforded good mixed agonist/antagonists, albeit with some confusing variations in responses that depended upon the nature of R, R′, and R^2. The *N*-cyclobutylmethylmorphinan-6-one (**102**, R = H; R′ = CBM; R^2 = Me) had an agonist-antagonist ratio of 0.1, and although it did not substitute for morphine in dependent rats, it completely substituted in monkeys!

Morphinan-6-one derivatives are usually more active as analgesics or antagonists than their morphinan counterparts, and replacement of oxygen at

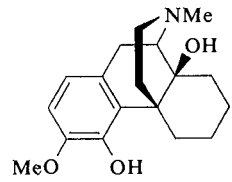
C-6 by methylene in naloxone and naltrexone has been shown to improve antagonist actions, particularly po.[97,98] Methylenetriphenylphosphorane in DMSO converted morphinan-6-ones, generally in good yield, to the corresponding methylene analogs (**103**).[99] This transformation had little effect on analgesic or antagonist potencies, but **103** (R = H; R′ = CBM; R^2 = Me) was shown to be an analgesic (MW ED_{50} 0.53 μmol/kg) and did not substitute for morphine in either rats or monkeys.

3.4.6. 10-Substituted Morphinans

No extensive work on this series has been reported. Oxidation[103] of the (+)-demethoxydesoxydihydrosinomenine (**104**), (−)-14-hydroxytetrahydrodesoxycodeine (**105**) and (+)-3-methoxy-*N*-methylmorphinan (dextromethorphan) with sodium dichromate or chromic oxide in sulfuric acid gave the expected attack at the benzylic position, thus affording 10-oxo derivatives.



104



105

A 10-hydroxy derivative of an isomorphinan was isolated during a total synthesis of (±)-morphine.[101]

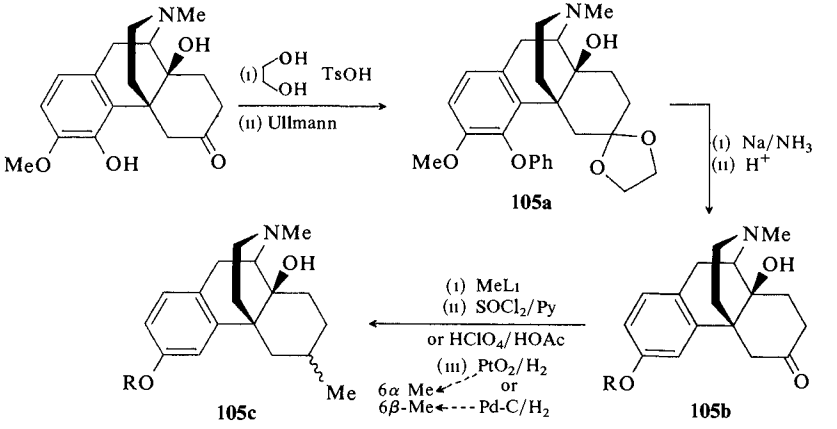
3.4.7. 14-Hydroxymorphinans

In antagonist series the insertion of a hydroxyl group into the **14**-position of morphinelike structures, usually via thebaine, gives compounds that are potent antagonists with, at best, weak analgesic actions (e.g., naloxone, nalmexone, and naltrexone) (see Chapter 2). This pharmacology contrasts with the 14-H analogs bearing antagonist *N*-substituents (e.g., nalorphine), which are often good analgesics but rather weaker antagonists (see Chapters 2 and 12).

In morphinan series, the Grewe synthesis will not afford 14-OH-substituted derivatives, and an alternative approach from a 1-tetralone has been discussed (Scheme 3.5). Butorphanol (**38**) and oxilorphan (**39**) resulted from these studies[26,27] and are the (−)-enantiomers resolved via their tartaric acid salts. These agents are analgesics with high antagonist potencies not only that are active both po and parenterally, but that have a prolonged activity relative to morphine. The former is about 30 × pentazocine as both an analgesic (MW) and an antagonist (RTF/A), and the latter is about 5 × pentazocine as an

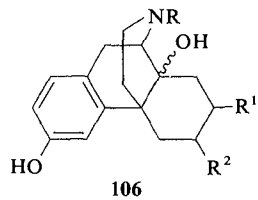
analgesic and 15 × as an antagonist. Butorphanol is a morphinelike analgesic of low abuse potential and is in clinical use. Both oxilorphan and butorphanol have been shown to bind strongly to opioid receptors from rat brain homogenates.[104]

(−)-14-Hydroxy-3-methoxy-*N*-methylmorphinan derivatives may also be derived[154] from 14-hydroxydihydrothebainone[154,155] first by the formation of the carbonyl-protected 4-phenylether (**105a**), then by reductive removal of the 4-OPh and hydrolysis of the ketal to **105b**. Insertion of a 6-Me group was performed with methyl lithium, dehydration, and stereocontrolled hydrogenation to either 6α-Me or 6β-Me 14-hydroxymorphinans (**105c**). Analgesic activities better than morphine were reported.



The introduction of diprenorphine (p. 73), a morphine analog lacking a 14-OH substituent but reportedly affording a predominantly antagonist action greater than that of naloxone, stimulated the Canadian Bristol Laboratories group to investigate morphinan C-ring substitution further.[105] At the epoxide stage in Scheme 3.5, the morphinan and isomorphinan isomers were separated and thus both 14-OH (isomorphinan) and 14-OH (morphinan) series became available with substituents or a ring junction at the 6,7-positions (**106**). Regardless of the orientation of the 14-OH group, compounds characterized were good antagonists, almost free of agonist actions, and often more potent than the unsubstituted C-ring precursor. Thus, it may be that the spatial area around ring C is important in controlling the agonist-antagonist ratio at the receptor. Affording some support for this suggestion is the weak antagonist activity shown by the *N*-Me derivative **107**, which has a lower agonist action than expected.

A synthesis of 14-hydroxymorphinans that defines the stereochemistry at C-14, and thus does not require a separation of isomers, has been published



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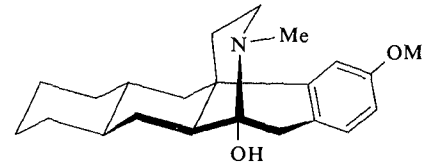
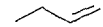
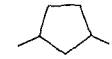
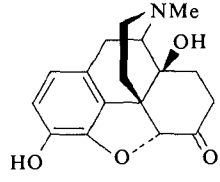


107

R = CPM, CBM,  , Me

$R^1 = R^2$ = H or Me (*cis* and *trans*),  (*trans*),

$-(CH_2)_4-$ (*cis* and *trans*).



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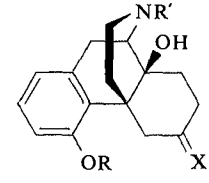
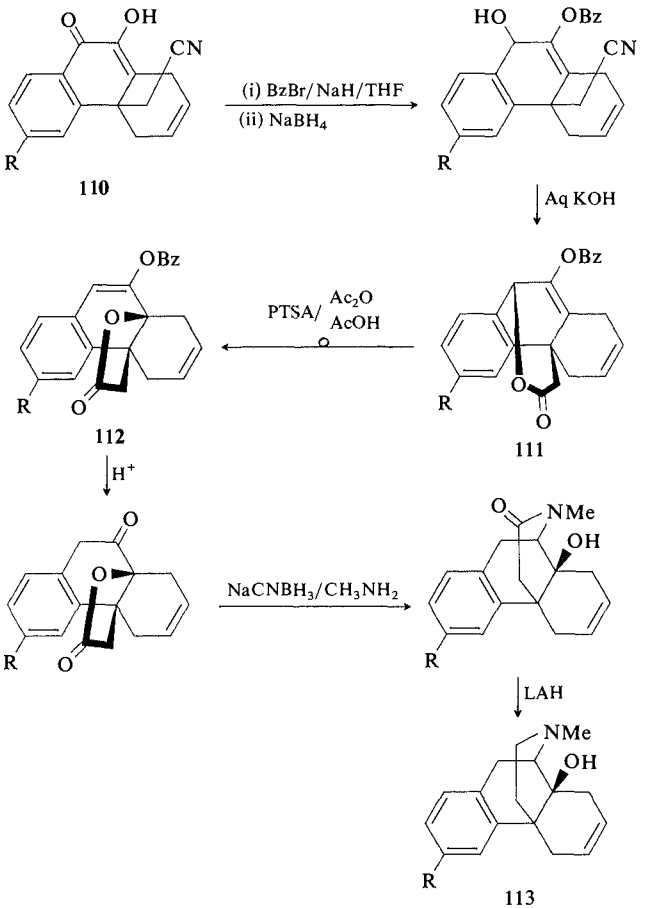


109

	R	R′	X	Mg/kg ED_{50}MHP/sc
a	H	Me	O	2.0
b	Me	Me	O	0.5
c	Me	Me	H_2	3.1
d	H	Me	H_2	3.0
e	Me	CPM	O	—
f	Me	CBM	O	—
Morphine sulfate				2.9
Levorphanol tartrate				0.5

by Zimmerman and Gates.[106] Starting from the reduced cyanomethylphenanthrene **110**, exploited extensively in the much earlier Rochester synthesis[107] of (±)-morphine, the lactone **111** was prepared and rearranged, under conditions similar to those used for allylic alcohol acetate rearrangements,[108] to lactone **112**. Here the stereochemical relationship between the final nitrogen bridge and the 14-OH substituent is fixed. Hydrolysis and reductive amination followed by LAH reduction afforded, in 30% overall yield, the required 14β-OH morphinan **113**.

Several 4-hydroxymorphinan-6-ones bearing a 14-OH function have been made from oxymorphone (**108**).[109] Here there is a marked contrast in the qualitative action observed relative to the actions seen in the 3,14-dihydroxymorphinans. Whereas, in the latter, high antagonist activities with little agonism occurred, 4-methoxy-14-hydroxy-*N*-methylmorphinan-6-one (**109b**), for example, was 6× as potent as morphine in the MHP antinociceptive assay. This activity is 4× that of the corresponding 3-OH analog.



Scheme 3.15

As the authors indicated, "the activity of these opioid aromatic ethers could not have been anticipated from any known structure-activity theory."

The *N*-CPM (**109e**) and *N*-CBM (**109f**) analogs were, as expected, opioid antagonists in the RTF/A assay, with the former being 3 × nalorphine and the latter roughly equivalent to nalorphine.[65]

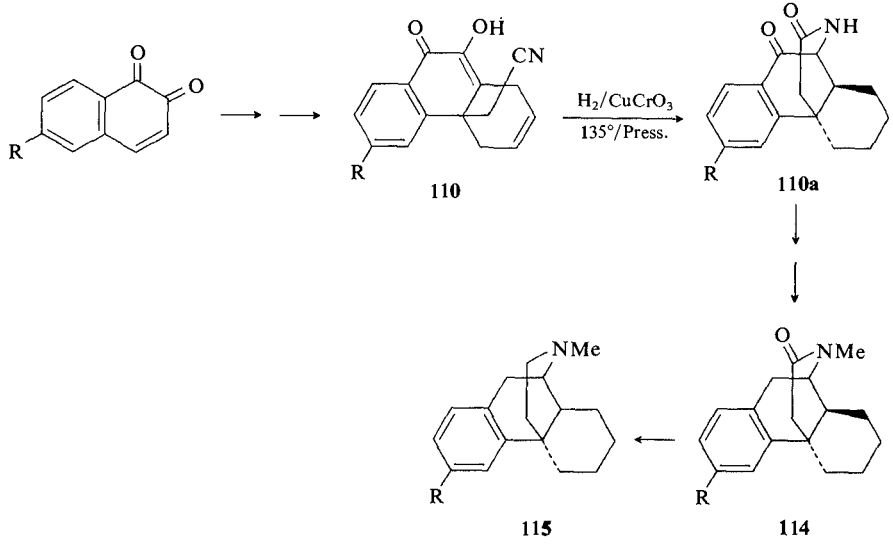
A series of 14-methoxymorphinan-6-ones prepared by methylation of the corresponding 14-hydroxy compound with methyl iodide and sodium hydride have been studied with the *N*-CPM, 3-OH derivative being a good mixed agonist-antagonist.[110] A similar activity was reported by the same authors for the related 14-ethoxy series.[111] Inclusion of a 7β-methyl group in the 14-methoxy series with *N*-CPM and 3-OH afforded a good antagonist[112] (RTF/A AD_{50}, 0.96 mg/kg).

3.4.8. Isomorphinans

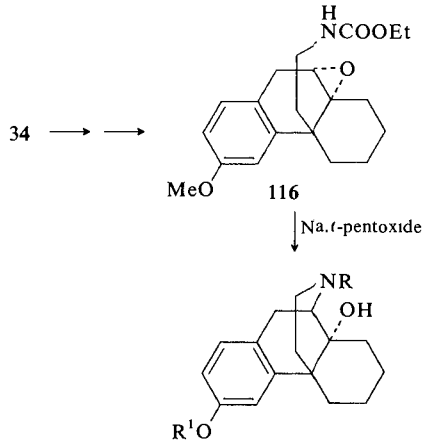
Morphinans are related directly to morphine in that they possess a B/C *cis* ring fusion. Isomorphinans, having a *trans* B/C fusion, may be considered as being related stereochemically to the *endo*-ethanotetrahydrooripavines.

During his work on the total synthesis of morphine (p. 14), Gates[113,114] prepared from 1,2-naphthoquinone as an intermediate 9,10-dioxo-13-cyanomethyl-5,8,9,10,13,14-hexahydrophenanthrene (**110**) which was converted to the *N*-methylisomorphinan (**114**, R = H). By exploiting the then recently introduced techniques of uv and ir spectroscopy, the high-pressure hydrogenation product from **110** was shown later[107] to be the cyclic amide **110a**. Gates and Webb[115] later described the synthesis of the enantiomers of 3-hydroxy-17-methylisomorphinan via **110** (R = OMe). The (−)-antipode was about 6 × morphine (RTF) as an analgesic, whereas the (+)-isomer was without such activity. Nitration[115] of **114** (R = H) with fuming nitric acid and acetic acid offered an alternative route to **115** (R = OH), reminiscent of the preparation of 3-hydroxy-*N*-methylmorphinan, described earlier.[38] As well as nitration occurring in the 3-position (50%), 2-nitro- (16%) and 1-nitro- (10%) isomers were isolated. All three were converted by way of the corresponding amines (Raney Ni/hydrazine hydrate) to their hydroxyisomorphinan counterparts. In the same study, some isomorphin-6-enes were described with (±)-3,6,17-trimethylisomorphin-6-ene being about 6 × morphine (RTF). The 1- and 2-hydroxyisomorphinans were without RTF activity; the latter showed a high degree or toxicity.

Reduced A-ring derivatives of isomorphinans have been described,[52] but they proved to be toxic, with analgesic levels of doubtful significance.



A total synthesis for 3,14-dihydroxyisomorphinans from 4a-(2-aminoethyl)-1,2,3,4,4a,9-hexahydro-6-methoxyphenanthrene (**34**, Scheme 3.5) has been published.[116] The urethane epoxide (**116**) was given upon treatment of **34** with ethyl chloroformate-triethylamine, followed by *m*-chloroperbenzoic acid oxidation. During base treatment, regioselective opening of the epoxide occurred with concomitant piperidine ring formation to **117**.



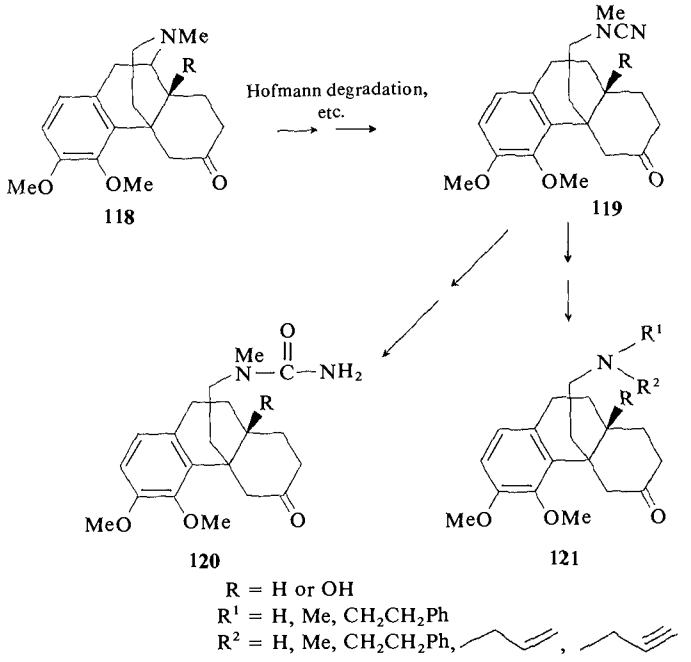
117 R = COOEt, Me or H

Synthetic approaches to morphinans from natural products possessing an 8,14- double bond also affords the corresponding isomorphinan series. Several of these have been described earlier under the appropriate morphinan subheading.[27,39,82,86-88,90,105]

3.4.9. Ring Variants Related to Morphinans

Early reports[117,118] suggested that cleavage of the morphinan piperidine ring at the 9,17-bond resulted in a significant drop in antinociceptive activity. However, the presence of a 14-OH function sometimes results in the maintenance of significant analgesic levels.[119] 3,4-Dimethoxy-14-hydroxy-17-methylmorphinan-6-one (**118**, R = OH) was subjected to Hofmann degradation (Scheme 3.16), followed by reduction and cyanogen bromide treatment, to give **119**. This intermediate afforded ureas (**120**) and bases (**121**). The analog **121** (R = OH; R′ = OMe; $R^2 = CH_2CH_2Ph$) was reported to have a good analgesic potency (about 3 × morphine; Haffner[120] ED_{50}, 2.6 mg/kg mice). Like morphine, it was a powerful depressor of respiration in cats. Compounds without basic nitrogen (e.g., **120**) were inactive.

Fusion of a cyclohexane or cyclopentane ring to the C-ring of morphinans was reported by the Bristol Laboratories Group[105] in 1976, and is discussed on pp. 133 and 462.



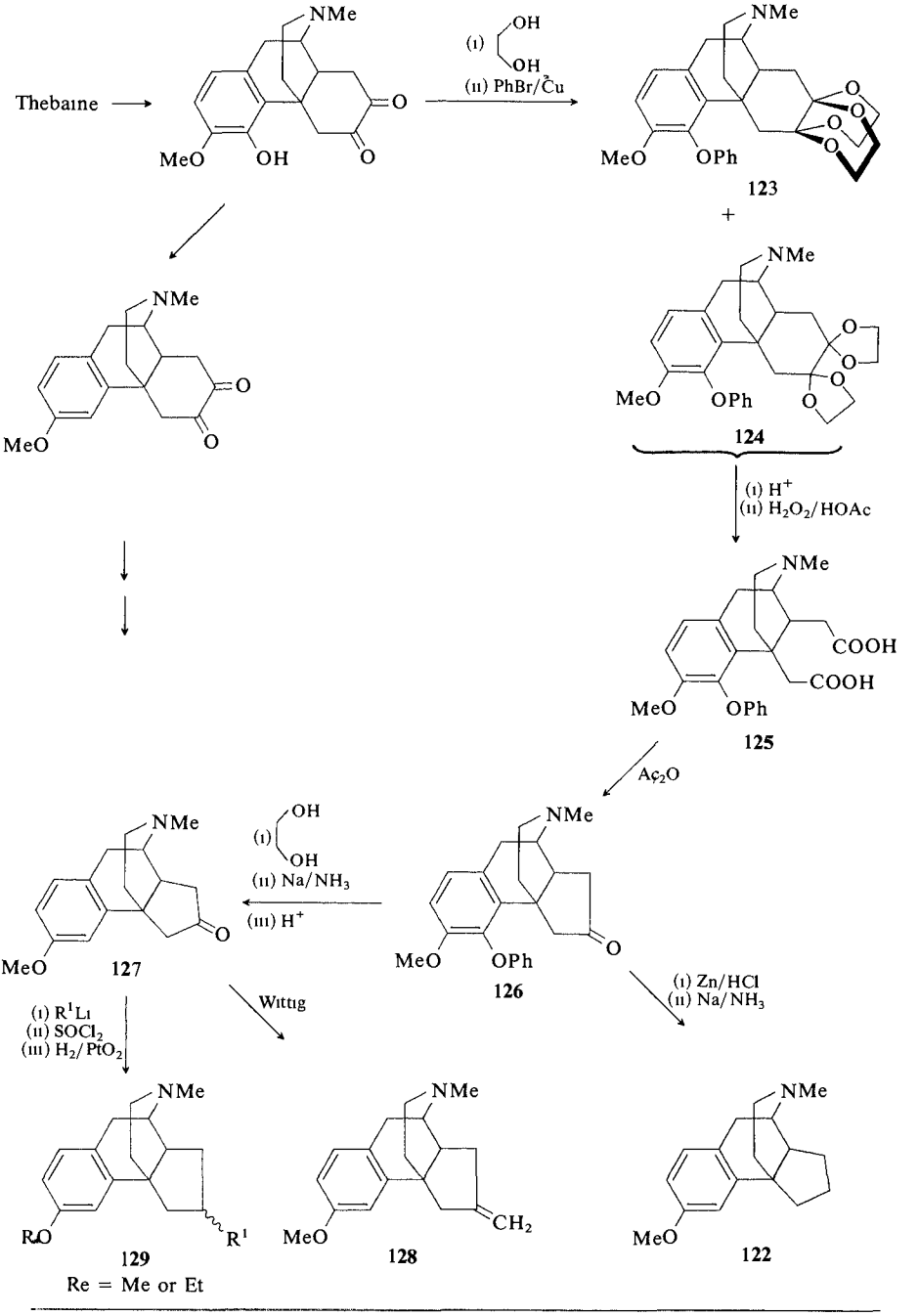
Scheme 3.16

A cyclopentane C-ring (±)-morphinan analog (**122**) was synthesized as early as 1955[121] and reported to be without significant activity. Sawa *et al.*[122] followed this earlier Japanese work, preparing 5-membered C-ring analogs from natural products related to morphine and sinomenine[148] according to Scheme 3.17.

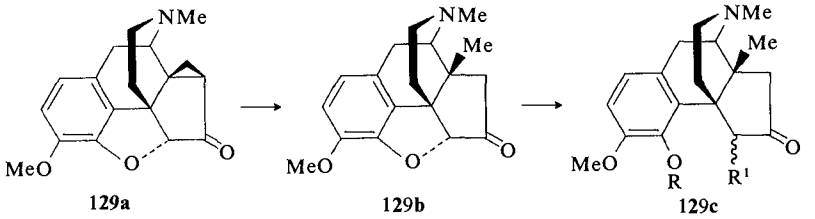
Removal of the 4-OH was mediated by the Ullmann formation of the phenyl ether, which could be removed reductively by Na/NH_3. To facilitate clean removal of the C-4 oxygen function, it was necessary to protect the ketone functions as ketals. A mixture of ketals (**123** and **124**) was isolated and both could be used in subsequent steps. Cleavage of the C-ring was effected by peroxide oxidation and recyclization of the benzomorphan 6,11-methylcarboxylates (**125**) to the C-cyclopentanone (**126**) occurred in acetic anhydride.

Removal of the 4-OPh gave **127**, which could be elaborated to alkyl derivatives, **129** (R′ = Me or Et), and the methylene compound (**128**). (−)-3-Hydroxy-6,16-dimethyl-C-normorphinan (**129**, R = H; R′ = Me) was found to be 19 × morphine in rodent tests.

Other five-membered C-ring morphinans (**129c**) have been isolated from the photolysis or catalytic hydrogenation (Pd-C), under various conditions, of 14-methyl-C-nordihydrocodeinone (**129b**) derived from cyclocodeinone (**129a**) (*p. 48*). *Biological data were not reported.*[147]


Thebaine
NMe
MeO
OH
O
(i) OH OH
(ii) PhBr/Cu
OPh
123
+
124
(i) H+
(ii) H2O2/HOAc
COOH
125
Ac2O
126
(i) Zn/HCl
(ii) Na/NH3
127
(i) OH OH
(ii) Na/NH3
(iii) H+
(i) R1Li
(ii) SOCl2
(iii) H2/PtO2
Wittig
R1
129
Re = Me or Et
CH2
128
122

Scheme 3.17

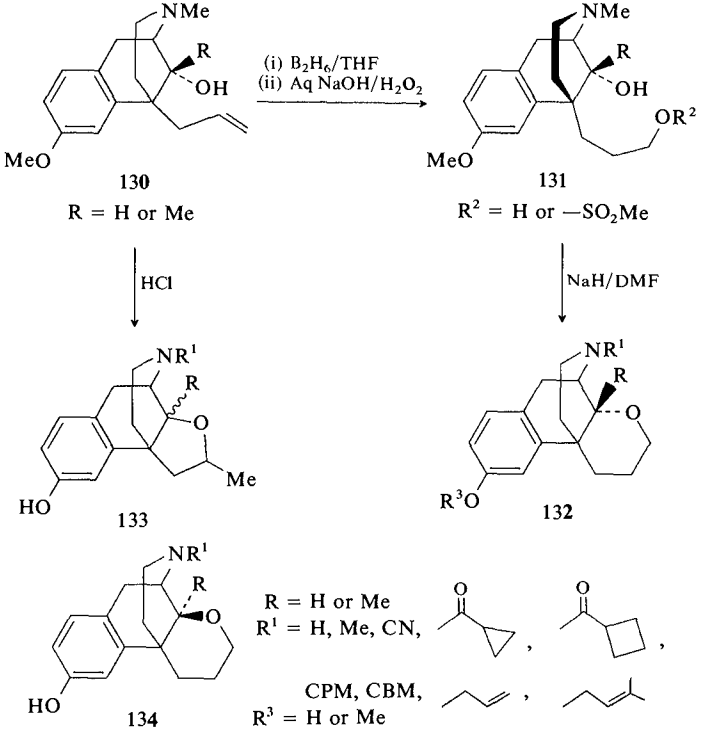


129a 129b 129c

R = H, Me, Ph, Ac
R' = OH, OMe, OEt, OAc, $N(Et)_2$

Three interesting series of C-ring variants, each with an oxygen heteroatom, have been described. In one series, the 8-oxamorphinans,[123] potent analgesics and agonist-antagonists were found. The other series are 8-oxaisomorphinans[124] and the so-called tetrahydrofuranobenzomorphans. All these were prepared from 6-allyl-8-methoxy-3-methylbenzomorphan-11-ones described in Chapter 4 (p. 184, and see also p. 420).

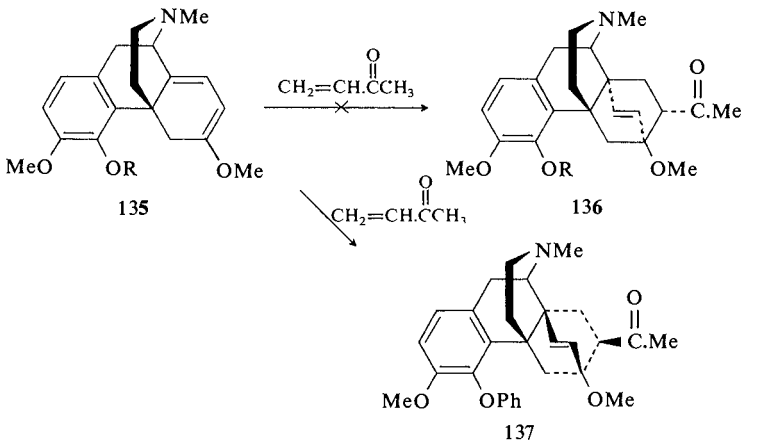
The 8-oxamorphinans are derived from the 9-ol (**131**), which, upon mesylation and strong base treatment, gave **132** (R = H or Me; R' = Me). Elaboration of the *N*-substituent was effected by standard methods, and the most active



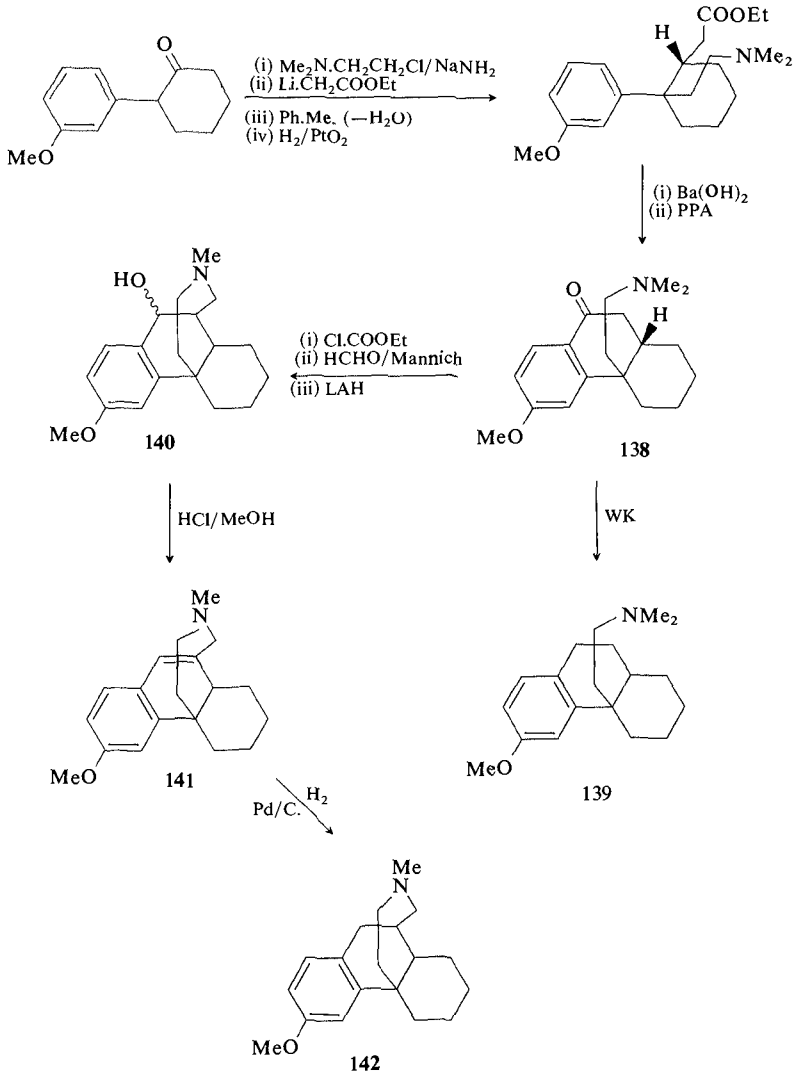
compounds were resolved. No significant activity was apparent in (+)enantiomorphs, but in the (−)series, both *N*-CPM and *N*-CBM (**132**, R = H or Me; R′ = CPM or CBM; R^3 = H) gave MW agonist activity at about the level of cyclorphan and butorphanol. This was many times higher than the corresponding 6-allylbenzomorphans (e.g., **130**, *N*-CPM), whereas the antagonist actions changed little. Changing the 14-substituent from H to Me caused enhancement of antagonist responses (Straub tail) and decreased analgesia.

In contrast, cyclization of **130** to the tetrahydrofuran C-ring analogs (**133**) caused a significant reduction in antagonist responses. Cyclization of 11β-hydroxybenzomorphans to 8-oxaisomorphinans (**134**) afforded only weak agonists or antagonists. This is curious, as the 11β-hydrobenzomorphans are more potent analgesics than their 11α counterparts, which are, in turn, precursors of the more potent 8-oxamorphinans.

Diels–Alder addition of methyl vinyl ketone to β-dihydrothebaine (**135**, R = H), derived from thebaine,[126] under standard reflux conditions, reacted slowly to give a poor yield of an adduct previously ascribed[127] the *endo* stereochemistry (**136**) analogous to the 6,14-*endo*-ethanotetrahydrooripavines. Reinvestigation[128] of this reaction demonstrated that yields could be improved to up to 80% by using the 4-OPh derivative of **135** (R = Ph) and adsorbent,[129] such as a silica gel or alumina column or an alumina slurry. X-Ray crystallographic analysis of **137** indicated that the product was an *exo*-ethenomorphinan, having the configuration at the 6,14-ring junction opposite from the adducts obtained from thebaine.[130] This may be a result of the release of strain on the "thebaine" molecule by furan ring opening, thus exposing both faces of the diene to attack by the dienophile.

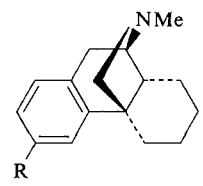


Expansion of the D-ring of a morphinan to **142** (Scheme 3.18) has been shown not to affect analgesic actions unduly (≡ morphine). Shiotani[131] prepared the key intermediate octahydrophenanthrene (**138**)

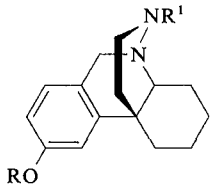


Scheme 3.18

from 2-(3-methoxyphenyl)cyclohexanone, according to Scheme 3.18, and this was Wolff-Kishner reduced to a compound (**139**) identical to the product derived from Hofmann elimination of (±)-3-methoxy-*N*-methylmorphinan.[132] Cyclization resulted from a Mannich reaction on the carbamate of **138**, and LAH reduction gave the alcohol **140**. Dehydration of **140** occurred under mild conditions to **141**, a reasonable infringement of Bredt's rule.

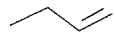


142a (R = H or OH)



142b

R = H or Me
R′ = Me, Bz, CPM,



, CH_2CH_2Ph

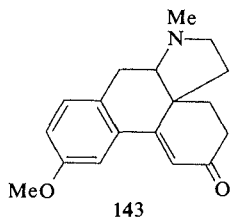
In connection with his investigations of the importance of nitrogen nonbonding electron orientation in morphinans to their stereospecific binding to opioid receptors, Belleau[149] reported a D-ring contracted morphinan (**142a**), but without synthetic details (see Chapter 13 p. 465).

Several *N*-substituted 9-azamorphinans (**142b**) have been described,[150-152] but only one compound, **142b** (R′ = CH_2CH_2Ph), had significant MHP (ip) analgesic activity ($\frac{1}{3}$ × morphine).

A series of compounds isomeric with morphinans, and described as *metamorphinans* (**144**), has been reported.[133] They were made from metathebainone (**143**),[149] which is readily accessible from thebaine,[134,135] and have the heterocyclic bridge between C-9 and C-14.

This structural modification fails to meet opioid receptor(s) requirements, and all opioid responses are lost. Other metamorphinans are reported in the literature (e.g., refs. 136, 137, and 138).

3-Methoxy-*N*-chloromorphinan may be prepared in 78% yield by treatment of 3-methoxymorphinan with sodium hypochlorate.[139] Upon silver ion catalyzed rearrangement, it gave 13% of **146**. The alkyl migration to the electron-deficient nitrogen was proposed as being mediated by a nitrenium ion transition state (**145**).



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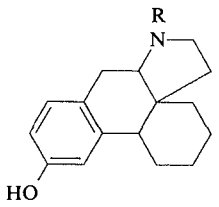
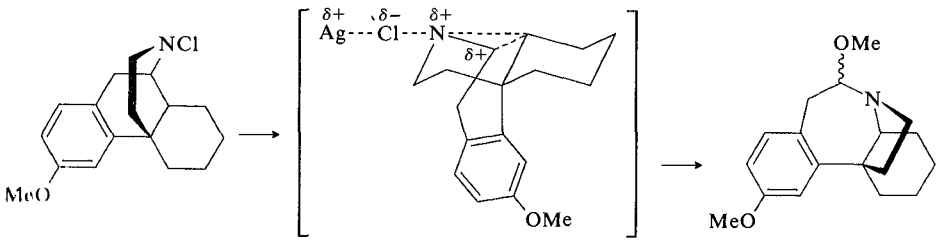


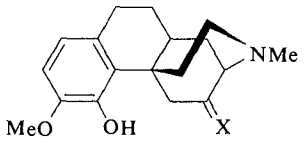
144 R = Me or CPM



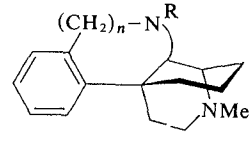
145 **146**

A further "morphinan" modification with the basic bridge between C-13 and C-7 was prepared[140] during an investigation of a new position isomer of dihydromorphinone. The transformation was achieved from dihydrocodeinone by Hofmann degradation and recyclization to a bromine inserted α to the 6-ketone at C-7. Opening of the furan ring gave **147** and **148**. Biological data on these compounds were not presented.

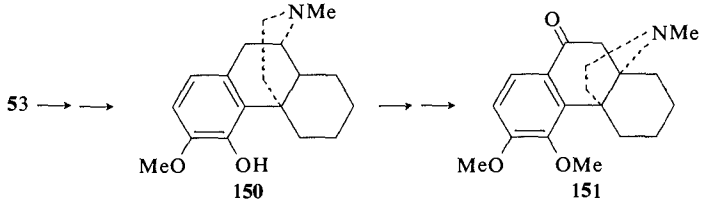
Rather more distant morphinan relatives are compounds of the general structure **149** (n = 1 or 2) prepared as bridged arylmorphans.[141,142] They were, at best, weak antinociceptive agents.



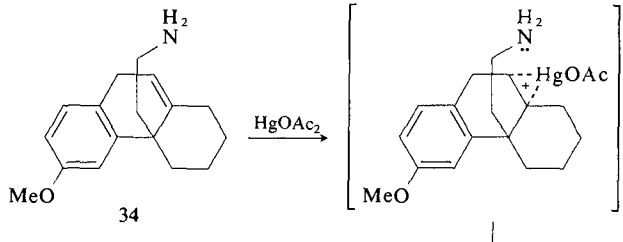
147 X = O
148 X = H, OH



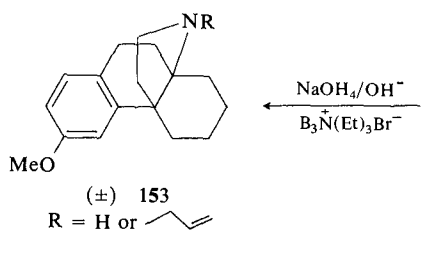
149
R = Me or CPM



150 **151**



34



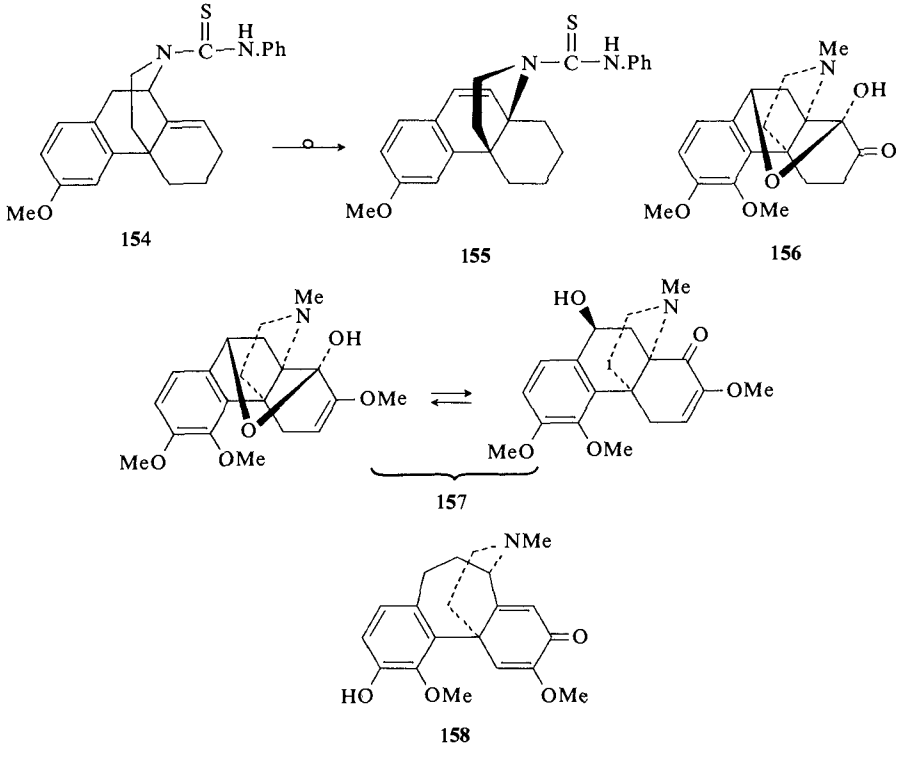
(±) **153**
R = H or

152

Sinomenine (**53**) is the principal alkaloid of *Sinomenium acutum* and is thus a naturally occurring (+)-morphinan. Other alkaloids[55] of the sinomenine subgroup have the reverse geometry to that associated with opioid pharmacological actions. Of these a hasubanan (**151**) related to hasubanonine from *Stephania japonica* Miers has been synthesized[143] from demethoxydeoxodihydrosinomenine (**150**). In addition, (±)-methoxyhasubanan (**153**) and the corresponding *N*-allyl analog have been synthesized[144] totally and found to have poor rat brain opioid receptor binding capacities relative to morphine and levorphanol, but **153** (R = H) was rather better than dextrorphan. The synthesis exploits an interesting intramolecular aminomercuration that directs cyclization of the basic center of **34** (see Scheme 3.5) to the C-14 position. None of the alternative morphinan product was isolated. Reductive demercuration of **152** was performed under phase transfer catalysis conditions.

Under acidic conditions 3-methoxy-17-(*N*-phenylthioamido)-$\Delta^{8,14}$-morphinan (**154**) rearranged to an isomeric hasubanan (**155**).[145] Two competing pathways were proposed to explain the transformation.

Related morphinan-like alkaloids of the sinomenine subgroup include metaphenine (**156**), prometaphenine (**157**) and androcymbine (**158**).



3.5. STRUCTURE–ACTIVITY RELATIONSHIPS

Work on the relationship between chemical structure and pharmacological activity of morphinans to 1966 has been reviewed by Hellerbach *et al.*,[8] and morphinans with antagonist properties were reviewed in 1973.[158] As is the case for 4,5-epoxymorphinans (Chapter 2) and benzomorphans (Chapter 4), molecular geometry is the major structure-biological activity influence, although the nature of the *N*-substituent imparts significant qualitative and quantitative variations in morphinan pharmacology.

The (−)-morphinans (i.e., those configurationally related to morphine) are responsible for all the antinociceptive properties of the racemate. In addition, such compounds tend to have parallel respiratory depression levels and PDCs. In (+)-series (e.g., dextromethorphan), clinically useful antitussive properties are encountered, again following the separation of biological activities noted in 4,5-epoxymorphinan optical antipodes.

Isomorphinans possess a B/C-*trans* ring fusion and in this they differ from B/C *cis* morphine geometry. Such geometry, however, may be related stereochemically to *endo*-ethanotetrahydrooripavines. Opioid activity tends to be increased in B/C *trans* series, and a compound such as 3-hydroxy-*N*-methylisomorphinan is several times more potent than morphine in rat analgesic tests.

Following the pattern of SARs in 4,5-epoxymorphinans and benzomorphans, the presence of a 3-OH group (8-OH in benzomorphans) usually endows morphinans with a much higher level of opioid potency. Masking the 3-OH group with an easily removable (*in vivo*) function, such as acetyl, changes antinociceptive activity little, whereas 3-methyl ether formation results in a significant drop in this property. However, this does not always apply, for the presence of a 3-OH is not necessary for good pharmacological properties in morphinan-6-ones.[50] (−)-4-Hydroxy-*N*-methylmorphinan-6-one is an excellent analgesic despite the lack of a 3-OH. Methylation of the 4-OH in 3-deoxy series causes a substantial increase in MHP activity, but the reintroduction of the 3-OH is counterproductive. Thus, in 4-OH or 4-OMe series, an additional oxygen at C-3 is detrimental to opioid activity.

Aromatic substitution elsewhere in the ring is of little or no benefit.

Morphinan-6-ones have proved to be a fruitful area of investigation, and some of this work has been reviewed.[50] As well as 4-methoxymorphinan-6-ones possessing strong analgesic activities, morphinan-6-ones lacking aromatic substitution may exhibit opioid actions greater than those of morphine. It is possible that the 6-ketone function plays some specific role at an opioid receptor; however, from a clinical standpoint it is disappointing that *all* the pharmacological actions of morphinan-6-ones parallel those of morphine.

Substituents elsewhere in the C-ring may also endow morphinans with interesting pharmacological properties. 7-Alkylisomorphinans tend to be more

potent analgesics than corresponding morphinans, particularly where a lipophilic side-chain at C-7 has a chiral center bearing an OH α to the ring carbon Under these circumstances, very high MW potencies result (e g , **95**) No discrimination is seen in pharmacological activity between epimeric secondary alcohols in this series, contrary to findings for *endo*-ethanotetrahydrooripavines Surprisingly, an *N*-CPM group (**96**) does not afford antagonist responses

Very potent agonists may also result from short-chain alkyl groups with an α-configuration at C-8 in isomorphinans In these, *N*-CPM and *N*-CBM exert their expected antagonist bias

Morphinan-6-ones are, as a rule, more active than corresponding morphinans, and it would appear that C-ring geometry and substitution patterns play a role in the drug-receptor union

The influence of a 14-OH substituent in 4,5-epoxymorphinans is reflected in the morphinan series Antagonist activities in *N*-CPM, *N*-CBM, and *N*-allyl series are increased relative to corresponding 14-H analogs, and they exert relatively weak analgesic actions This applies, regardless of the 14-OH configuration (i e , morphinan or isomorphinan) The introduction of a 6-oxo function into such structures enhances agonist responses

Profound effects on pharmacological activity are exerted when the *N*-substituent is varied (p 117) These changes in opioid responses parallel those seen in other rigid opiates Groups such as *N*-allyl, *N*-CPM, and *N*-CBM tend to endow the molecule with antagonist properties, whereas *N*-Me and *N*-phenethyl are endowed with agonist properties

Recent studies on both morphinans and 4,5-epoxymorphinans have posed several questions For example, clarification of the role of the C-3/C-4 oxygen and the C-6, C-7, C-8, C-14 region of the morphinan C-ring in the union of opiate with its receptor(s) is required

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4

Benzomorphans

4.1. INTRODUCTION

Simplification of the morphine structure to give series of morphinan congeners (Chapter 3) demonstrated not only that strong analgesics with activities greater than that of morphine could be developed, but that accentuation of other opiate properties (e.g., cough suppression) could be selected. Further simplification to a bridged naphthalene, by exclusion of the morphinan D-ring, rather than a phenanthrene structure, was, therefore, an obvious progression.

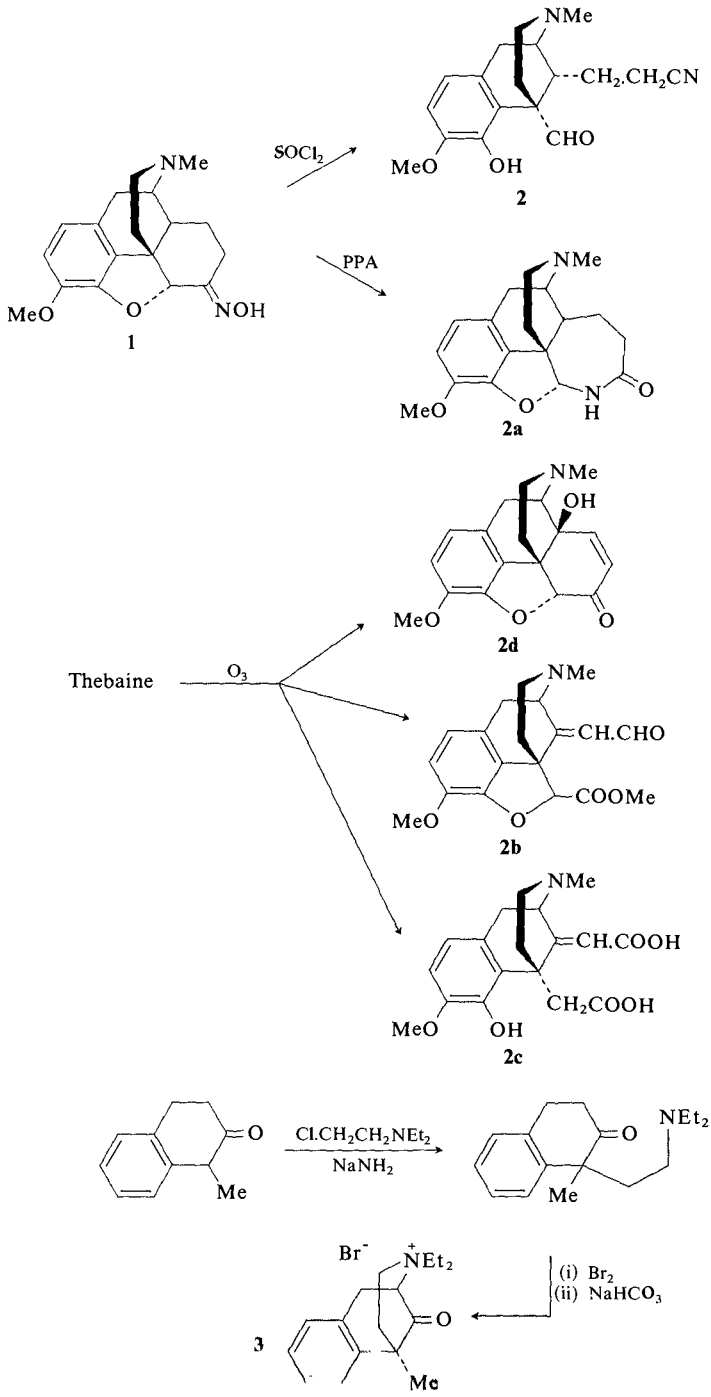
The chemistry of such bridged naphthalenes-benzomorphans and some related compounds has been reviewed previously.[1-3] The first synthesis of a benzomorphan was achieved by Barltrop[4]; however, prior to that synthesis, Schöpf,[5] in his investigations of the structure of morphine, had isolated the benzomorphan, **2**, from a thionyl chloride-induced, second-order Beckmann rearrangement of dihydrocodeinone oxime, **1**. Reinvestigation[5a,5b] of the Beckmann rearrangement and a study of the Schmidt reaction of 6-oxomorphinans confirmed Schöpf's work and led to the isolation of the anticipated lactam (**2a**).

Ozonolysis of thebaine[216] has been found to give three products. In two of these the unsaturated epoxymorphinan C-ring has been cleaved to give, as the major product (34%), the benzomorphan dicarboxylic acid (**2c**), and a furanobenzomorphan (14%) (**2b**). The minor component (3%) proved to be 14-hydroxycodeinone (**2d**) by comparison with an authentic sample. Compounds related to **2b** have also been derived by a codeine degradation.[220]

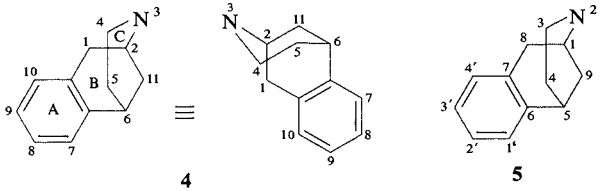
The Barltrop synthesis was from a 2-tetralone precursor and progressed only as far as the diethylammonium compound **3**.

During the 1950s May and his group[6] commenced an extensive study of the benzomorphans as a source of potential powerful analgesics with, it was hoped, reduced side effects. Several synthetic routes were established at that time.

Although throughout the chapter this series of compounds will be referred to by their popular trivial name, benzomorphans, the *Chemical Abstracts* name


NMe
CH2.CH2CN
CHO
MeO
OH
2
SOCl2
NMe
MeO
O
NOH
1
PPA
NMe
MeO
O
N
H
O
2a
NMe
OH
MeO
O
O
2d
Thebaine
O3
NMe
CH.CHO
COOMe
MeO
O
2b
NMe
CH.COOH
CH2COOH
MeO
OH
2c
O
Me
ClCH2CH2NEt2
NaNH2
O
NEt2
Me
Br-
+
NEt2
O
Me
3
(i) Br2
(ii) NaHCO3

for the ring system is *1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine.* Ring numbering associated with this systematic name is illustrated in 4, and that employed most often in the literature and associated with the name benzomorphan or 6,7-benzomorphan is shown in **5**.



4 **5**

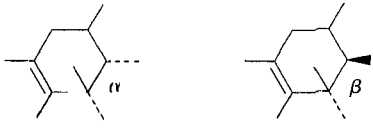
Chemical Abstracts numbering (4) will be used throughout.

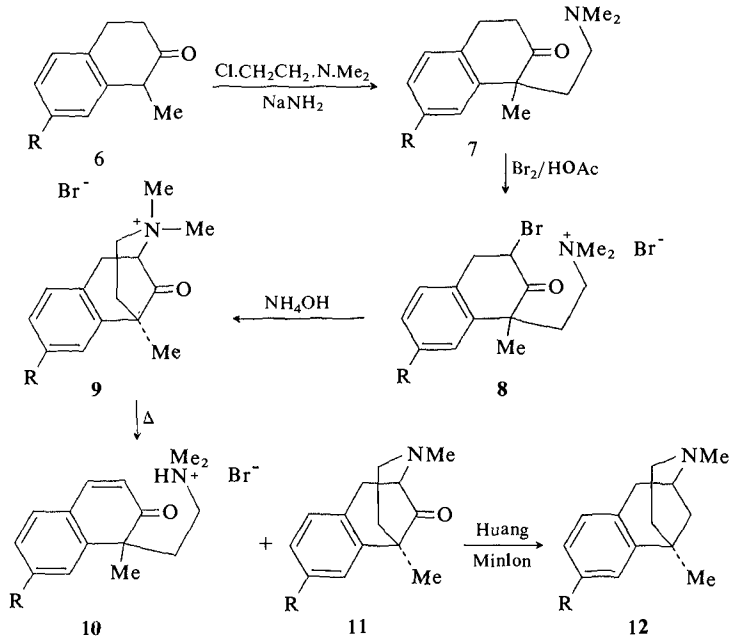
4.2. SYNTHESIS

The principal synthetic routes to benzomorphans require either tetralone or appropriately substituted pyridine precursors. Simple 6-alkyl or 6,11-dialkyl derivatives are prepared from either tetralones or pyridines. The 2-tetralone synthesis of Barltrop was extended by May *et al.*, particularly in the preparation of 3,6-dimethylbenzomorphan (**12**)[7] (Scheme 4.1). Initially, low yields in the conversion of **6** to **7** and of **9** to **11** led to the adoption of an alternative route via the 1-tetralone **22** (Scheme 4.3). Later, the 2-tetralone route modified to afford 8-hydroxy-3,6,11-trimethylbenzomorphan was effected in much improved overall yields. Care must be taken in the cyclization of **8** to the quaternary benzomorphan **9**, which requires only a single molar proportion of aqueous ammonia; excess leads to elimination of hydrogen bromide to give **10**. Dry distillation of **9** under high vacuum gives predominantly the β-unsaturated ketone **10** when an 8-methoxyl group is present (R = OMe). However, in boiling octan-1-ol up to 40% of the desired tertiary base **11** results with varying amounts of **10**.[8]

The presence of an 11-carbonyl function (Scheme 4.2) offers a means of inserting alkyl groups into a location mimicking a morphinan C-ring. Treatment of either the quaternary compound **9** or the corresponding tertiary base **11** with methylmagnesium chloride gave a methyl carbinol (**13a**) that was dehydrated directly with thionyl chloride[9] or by pyrolysis of the corresponding acetate (**13b**) perchlorate[10] to yield the 11-methylene derivative (**14**). Hydrogenation of **14** over platinum oxide afforded some degree of stereoselectivity, the free base or hydrochloride in ethanol giving 11α-methylbenzomorphan*

* The notation α-here is arbitrary and implies that the 11-position substituent on the B-ring is *cis* to the substituent in the 6-position, i.e.,





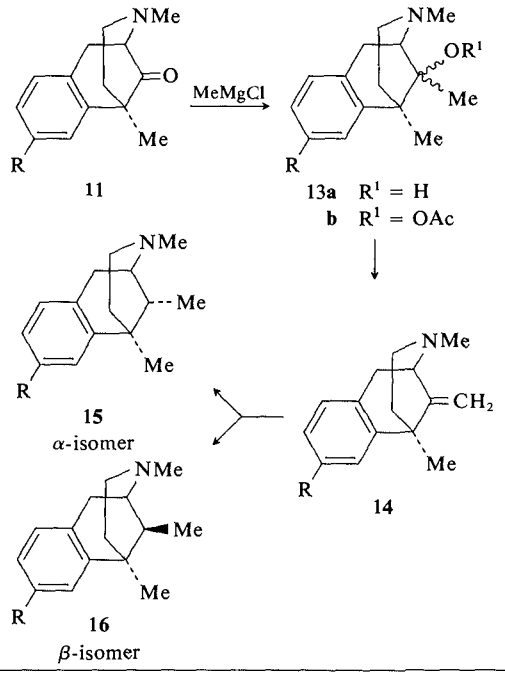
Scheme 4.1

(**15**), whereas in the presence of excess of acid, the β-isomer (**16**) was the predominant product.

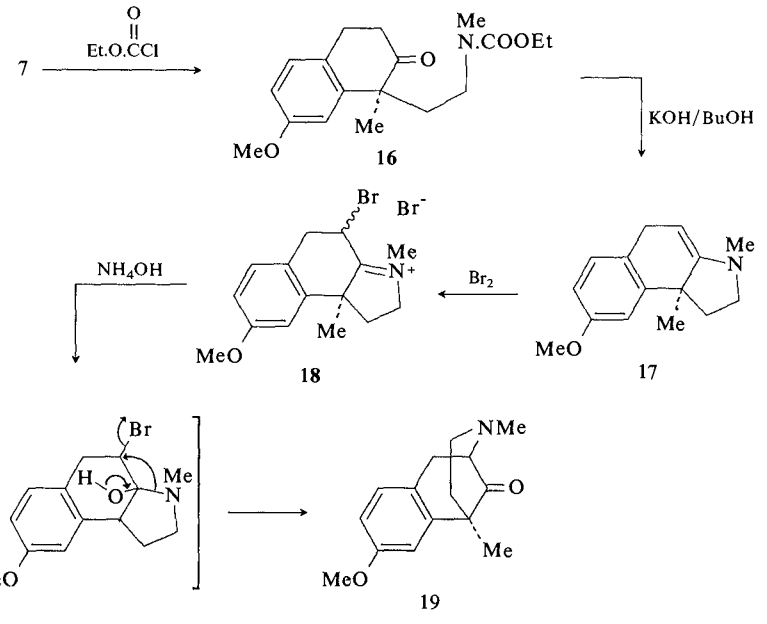
A modification of the standard 2-tetralone route has been reported by Takeda and others.[11,12] The 2-tetralone intermediate (**7**) is prepared in the usual manner and converted to the enamine (**17**). Good yields of 8-methoxy-3,6-dimethylbenzomorphan-11-one (**19**) resulted from bromination of the enamine followed by treatment with base. Belleau *et al.*,[12] who found that this approach was not widely applicable and often resulted in low yields, improved both the accessibility to and yields of a wide range of 11-oxobenzomorphans.

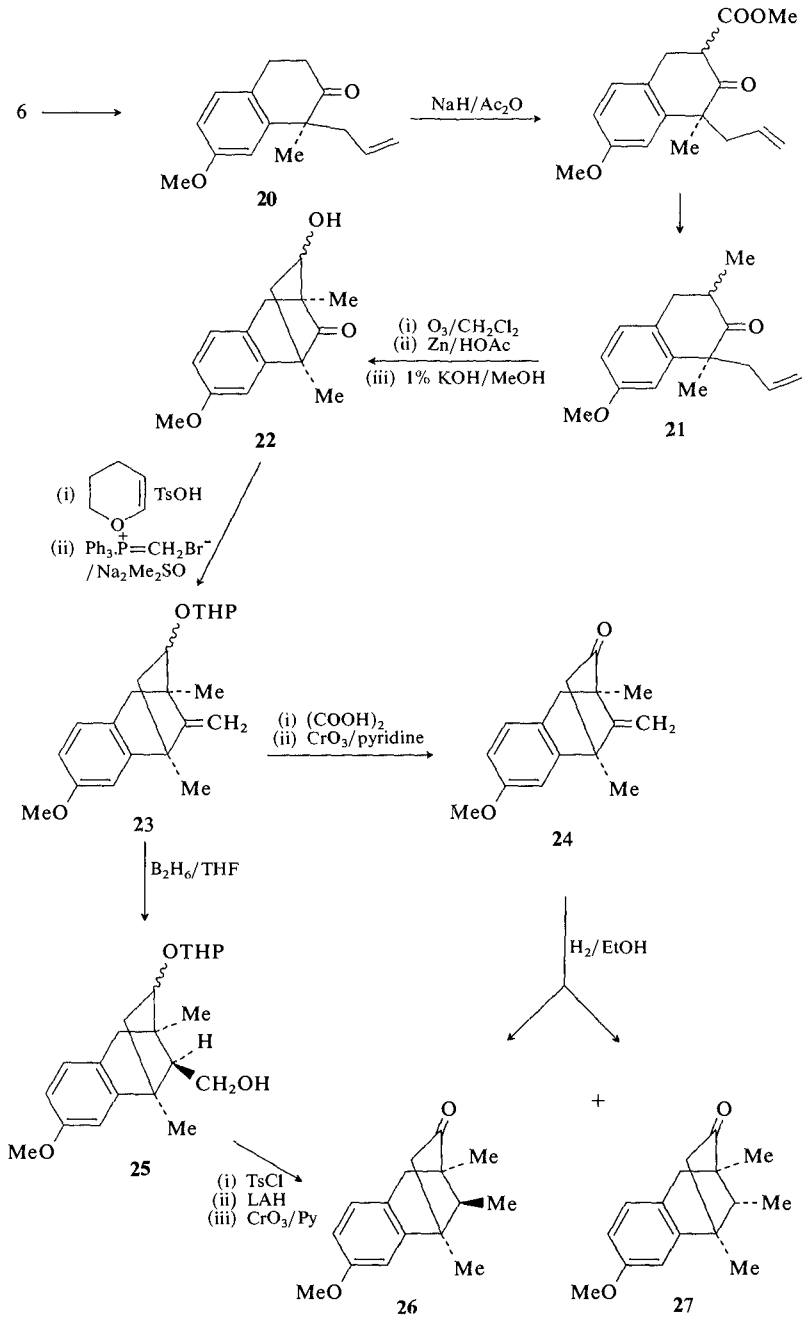
Beckmann rearrangement of C-ring ketones (**26** and **27**) prepared via a 2-tetralone (Scheme 4.3) afforded a route to 6,7-benzomorphans that were otherwise difficult to synthesize.[13-14a] The 11α- and 11β-methylnorbenzomorphans (**29**) were prepared in this way.

1-Tetralone intermediates also offer approaches to 6,7-benzomorphan synthesis. The 1-tetralone (**35**, Scheme 4.4) may be prepared in five stages from 1-cyano-1-phenylmethane (α-methylphenylacetonitrile) (hydratroponitrile) (**30**).[7] Significant yield losses may occur during the reverse-addition LAH reduction of (**31**). From the tetralone (**35**) the synthesis proceeds in a

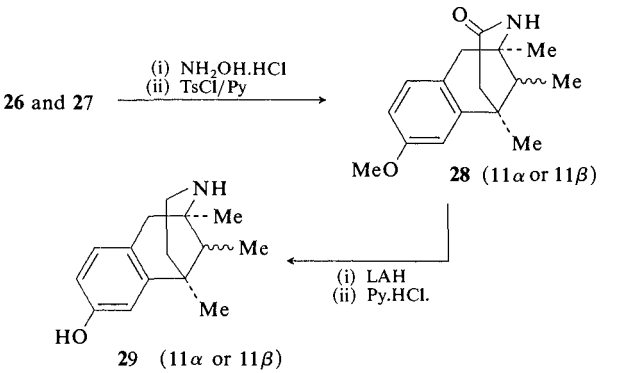

NMe
O
Me
R
MeMgCl
OR¹
11
13a R¹ = H
b R¹ = OAc
15
α-isomer
CH₂
14
16
β-isomer

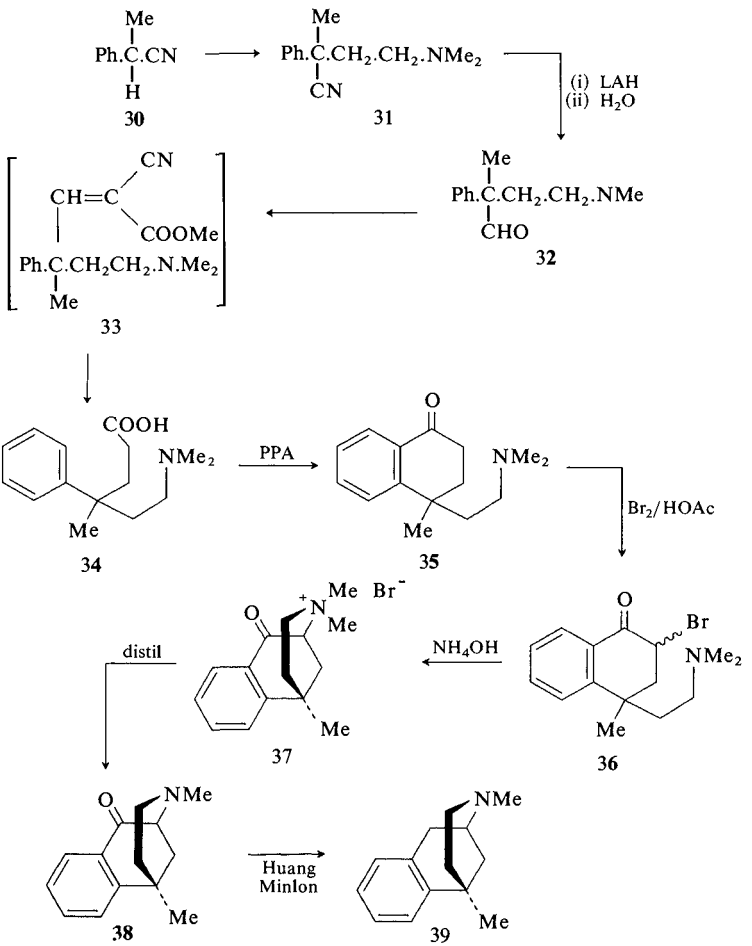
Scheme 4.2


7
Et.O.CCl
Me
N.COOEt
MeO
16
KOH/BuOH
Br
Br⁻
NH₄OH
Br₂
N⁺
18
17
H
O
McO
19


6
NaH/Ac2O
COOMe
MeO
Me
O
20
21
22
OH
(i) O3/CH2Cl2
(ii) Zn/HOAc
(iii) 1% KOH/MeOH
(i) TsOH
(ii) Ph3P=CH2Br-
/Na2Me2SO
OTHP
CH2
23
24
(i) (COOH)2
(ii) CrO3/pyridine
B2H6/THF
H2/EtOH
CH2OH
H
25
(i) TsCl
(ii) LAH
(iii) CrO3/Py
26
27

Scheme 4.3


26 and 27
(i) NH2OH.HCl
(ii) TsCl/Py
28 (11α or 11β)
(i) LAH
(ii) Py.HCl.
29 (11α or 11β)

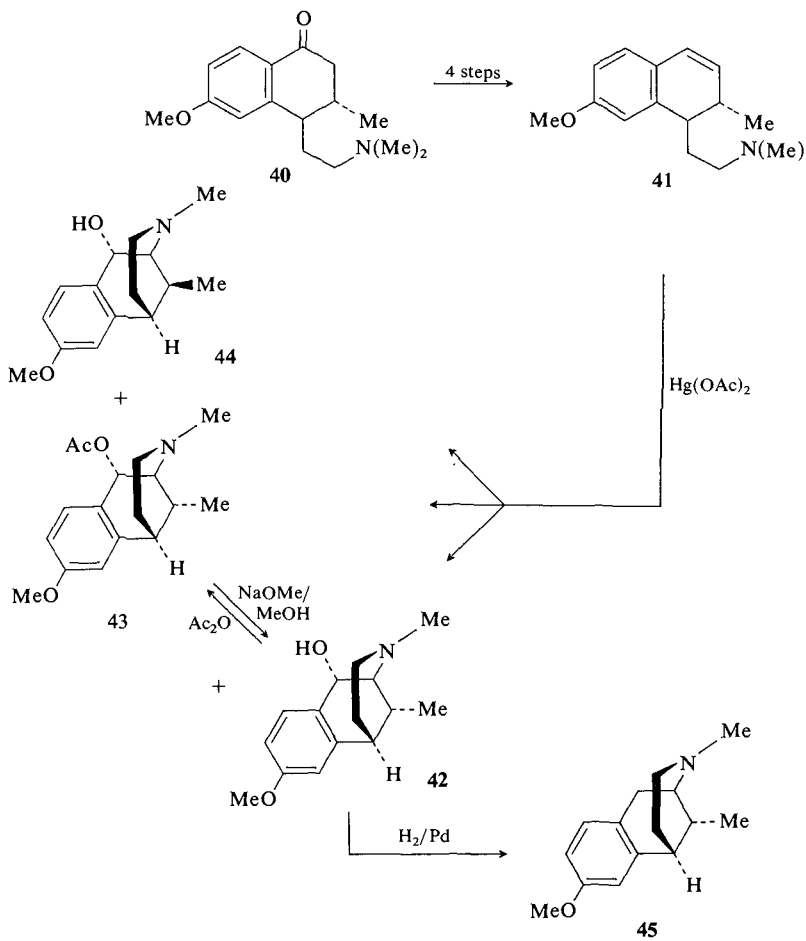

30
31
(i) LAH
(ii) H2O
32
33
34
PPA
35
Br2/HOAc
36
NH4OH
37
distil
38
Huang Minlon
39

Scheme 4.4

manner very similar to that described for 2-tetralones to give the 3,6-dimethylbenzomorphan (**39**).

An alternative cyclization via a 1-tetralone intermediate has been achieved by Inoue and May,[15] Scheme 4.5. The key intermediate (**41**) was prepared from *trans*-2,4-dihydro-4-(2-dimethylaminoethyl)-6-methoxy-3-methyl-1(2H)-naphthalenone (**40**). Treatment of **41** with mercuric acetate gave a mixture of the three benzomorphans (**42**, 49%; **43**, 13%; **44**, 5%). Hydrogenation of **42** afforded 3,11α-dimethyl-8-methoxybenzomorphan (**45**).

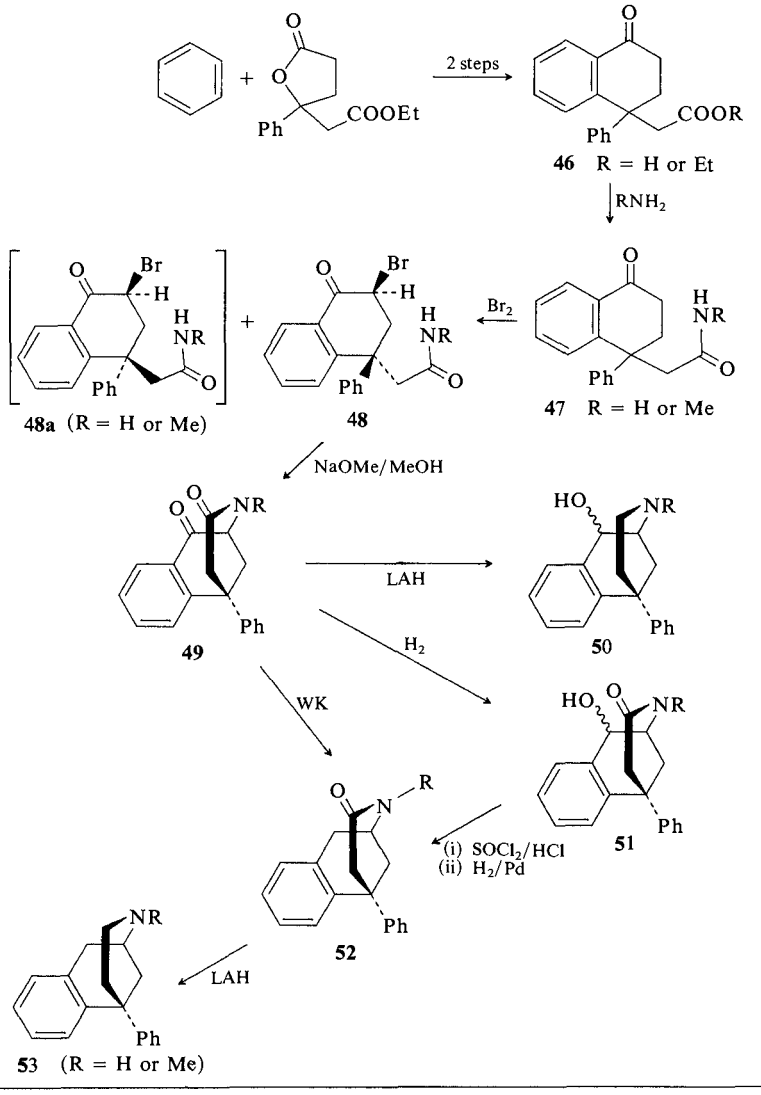
6-Arylbenzomorphans may be viewed as possessing pharmacophoric patterns relating to both 6,7-benzomorphans and methadone. Walker and



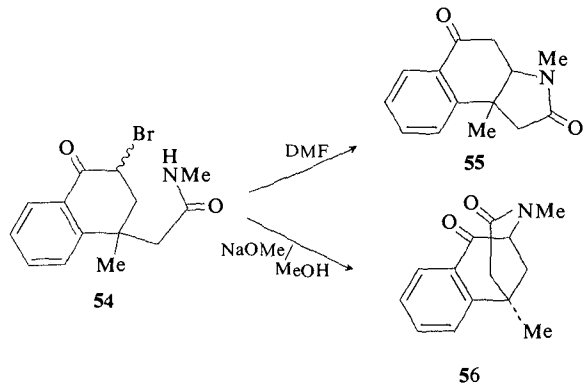
Scheme 4.5

Alkalay[16] recognized this "notable omission" in the analgesic literature and approached the synthesis by an imaginative 1-tetralone route (Scheme 4.6). Analgesic activity of **53** (R = Me) in the rat tail-flick test was low (25 mg/kg).

In an analogous series[17] the 2-bromo-4-methyltetralone (**54**) corresponding to **48** was ring closed (67%) under similar conditions to the 6-methylbenzomorphandione (**56**); however, in boiling dimethylformamide product **55**

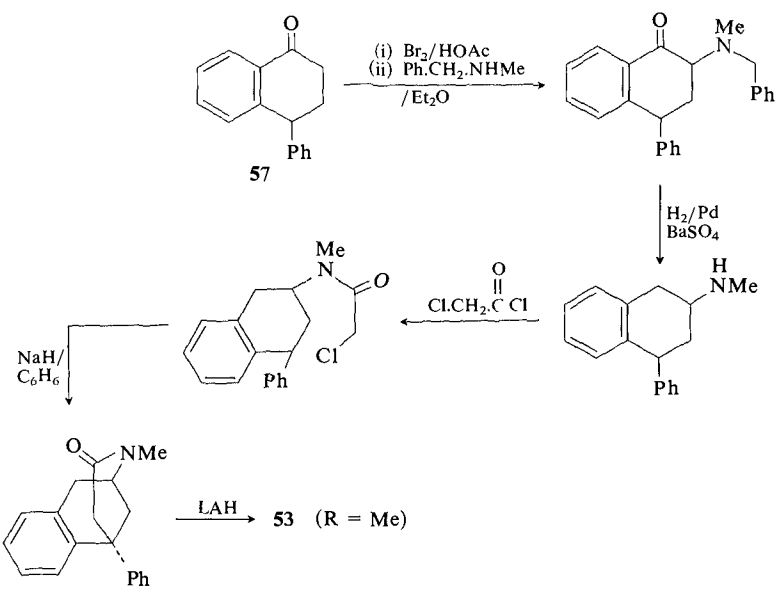


Scheme 4.6

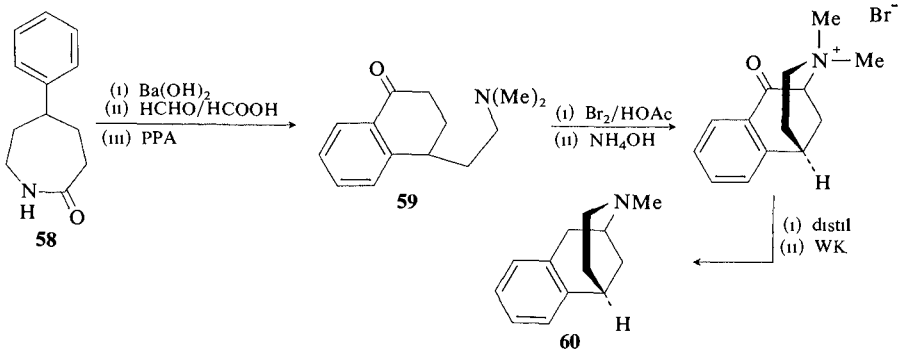


resulted. This was, presumably, by the elimination of HBr and subsequent conjugate addition of the amide nitrogen.

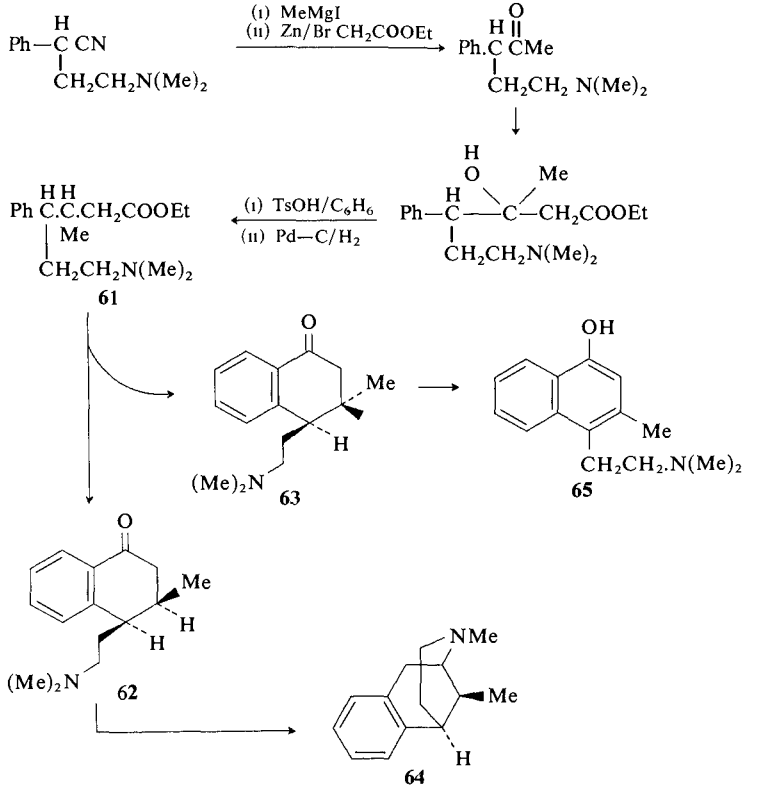
4-Phenyl-1-tetralone (**57**) has been used as a starting material for a synthesis to the 6-arylbenzomorphan (**53**) in a patent application.[18] Cyclization in this synthesis is to the activated 4-position of the tetralone.



4-Dimethylaminoethyl-1-tetralone (**59**) may be generated from 4-phenylcyclohexanone by Beckmann rearrangement to 5-phenylcaprolactam (**58**), followed by hydrolysis, *N*-methylation, and polyphosphoric acid cyclization.[219] Conventional transformations afforded the desired 3-methylbenzomorphan (**60**), first synthesized from 4-phenylpyridine in 1968.[20]



The presence of an 11-methyl group in 6,7-benzomorphans has been demonstrated to enhance analgesic responses. Synthetic approaches to benzomorphans lacking a 6-alkyl substituent from pyridines usually fail; as a consequence, a twelve-step 1-tetralone route was developed[19] (Scheme 4.7).

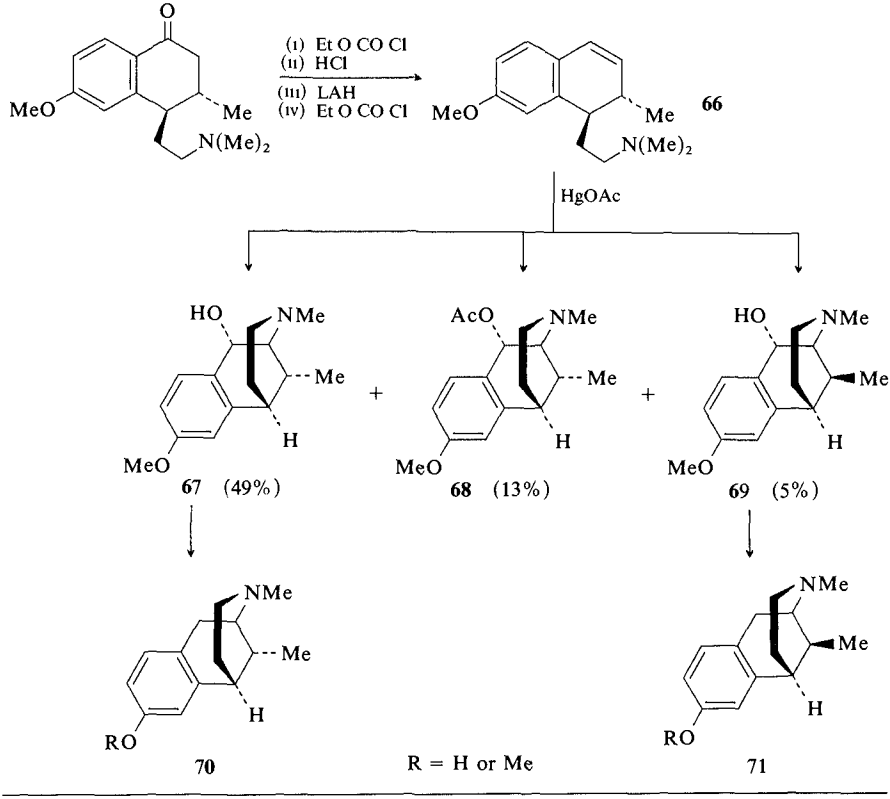


Scheme 4.7

Ring closure of the diastereoisomeric mixture (**61**) gave the isomeric tetralones (**62** and **63**) in the ratio 4:**1**. By conventional means the *cis* isomer **62** was converted to the required 3,11β-dimethylbenzomorphan (**64**), which exhibited codeine-like activity. Similar treatment of the *trans* substituted tetralone (**63**) gave only the naphthalene (**65**).

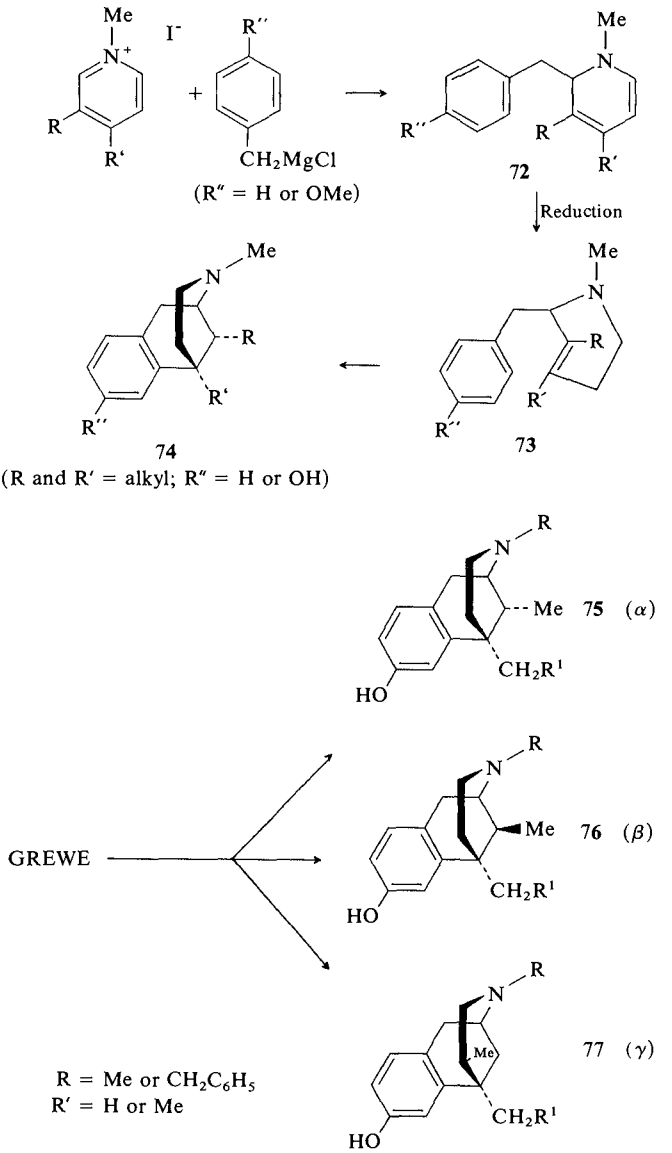
Inoue and May[21] later modified the preceding synthesis with the presence of an 8-methoxyl substituent (Scheme 4.8). The key intermediate dihydronaphthalene (**66**) gave on treatment with mercuric acetate 8-methoxy-2,11α-dimethyl-1α-hydroxybenzomorphan (**67**) in 49% yield, 5% of the 11β-methyl isomer (**69**) and 13% of the 1α-acetate (**68**) corresponding to **67**. Transformation to the desired 11-epimeric benzomorphans **70** and **71** was by standard methods.

Pharmacological conclusions reached during these studies are that 6-alkyl substituents enhance the analgesic activity of benzomorphans somewhat, whereas the inclusion of an 11β-alkyl substituent causes a substantial increase.



Scheme 4.8

In analogy to a synthesis of morphinans from 1,2,3,4,5,6,7,8-octahydroisoquinolines by Grewe,[22,23] May and Fry[24] prepared benzomorphans (Scheme 4.9). Treatment of 3,4-dialkyl or 4-alkylpyridinium methiodides with either benzyl or *p*-methoxybenzylmagnesium chloride in ether readily gives

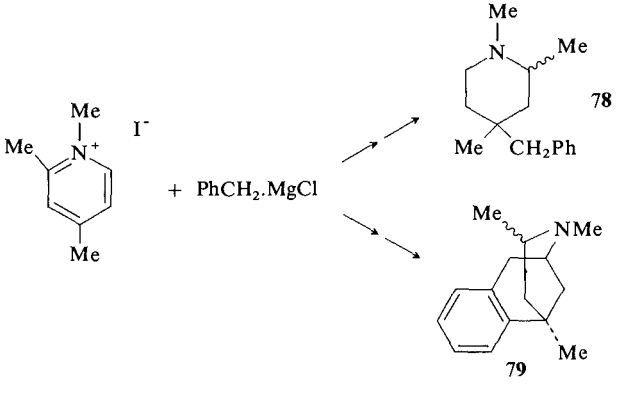


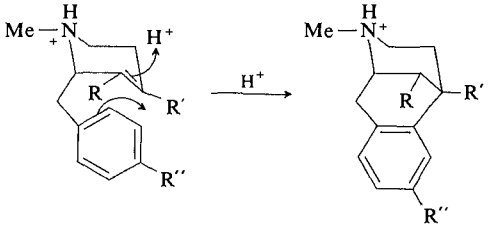
Scheme 4.9

dihydropyridines of structure **72** in a manner previously described by Freund and Bode[25] in 1909. Dihydropyridines of this type rapidly decompose, presumably by an auto-oxidative mechanism; however, they may, under some circumstances, be trapped as stable perchlorate salts.[26,27] Reduction to 2-benzyltetrahydropyridines (**73**) is accomplished either by sodium borohydride or less conveniently over palladium–barium sulfate. Ring closure to benzomorphans (**74**) may be effected either with polyphosphoric acid or hydrobromic acid. In the 4-methoxybenzyl series concurrent cleavage of the methyl ether occurs.

When 3,4-lutidine was the starting pyridine the predominant product was the α-isomer (**75**, R^1 = H, R = Me), that is, the *cis* 6,11-dimethylbenzomorphan. On a larger scale, about 1% of the *trans* or β-isomer (**76**, R^1 = H, R = Me) was isolated. Attack of the benzyl Grignard reagent at the 2-position of the 3,4,-lutidinium salt, with apparently little 6-position attack, appeared to be anomalous. Fry,[26] however, had isolated a small amount of 6-benzyl-3,4-dimethyldihydropyridine during his studies on the formation of 11α- and 11β-benzomorphans. In addition, Albertson *et al.*[28] isolated what they described as the γ-benzomorphan isomers (**77**) from Grewe syntheses employing either 3,4-lutidine or 3-methyl-4-ethylpyridine. Clearly, the presence of so-called γ-isomer resulted from 6-position Grignard attack. The possibility of attack at the 4-position of the pyridinium nucleus arises, and James and Parfitt[29] have isolated 2,4-dimethyl-4-benzylpiperidine from a Grewe synthesis starting with 2,4-lutidinium methiodide to the previously described[27] 3,4,6-trimethylbenzomorphan (**79**). Thus, contrary to earlier indications, Grignard attack during the Grewe synthesis occurs at all available pyridinium ring positions.

The mechanism of 4-alkyl- and 3,4-dialkyltetrahydropyridine cyclization proceeds under acid conditions in the anticipated manner; during *trans* addition to the tetrahydropyridine double bond, protonation occurs from the topside (Scheme 4.10). In the case of 2-benzyl-1,3-dimethyl-4-propyl-1,2,5,6-



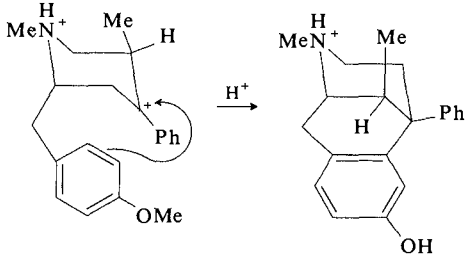


(±), *cis*, α, major product
(±), *trans*, β, minor product

Scheme 4.10

tetrahydropyridine, cyclization by polyphosphoric acid proceeds to give only the corresponding 11α-methylbenzomorphan.[30]

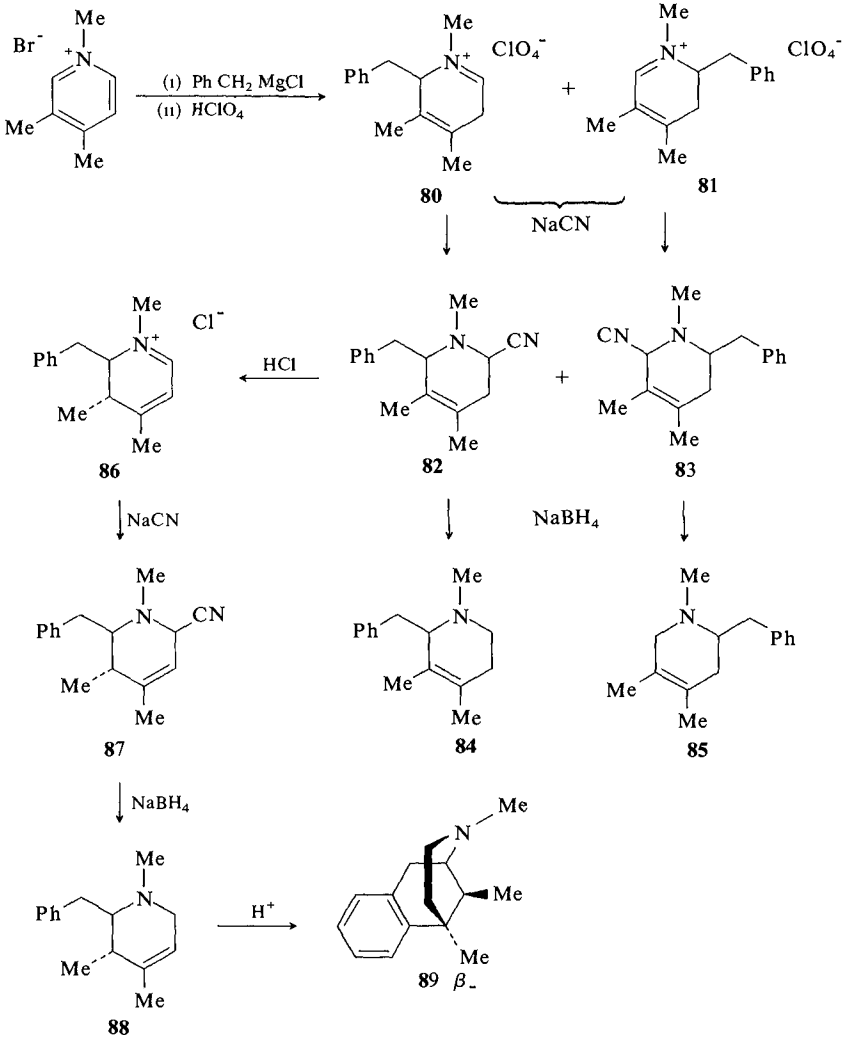
3-Alkyl-4-phenyltetrahydropyridines appear to cyclize via an alternative pathway to yield as the only product the 11β-alkyl-6-phenylbenzomorphan. Yokoyama *et al.*[31] suggest that in this case the 4-phenyl group stabilizes the largely *trans* benzyl carbonium ion intermediate, the *cis* being considered of lesser stability.



(±), *trans*, β

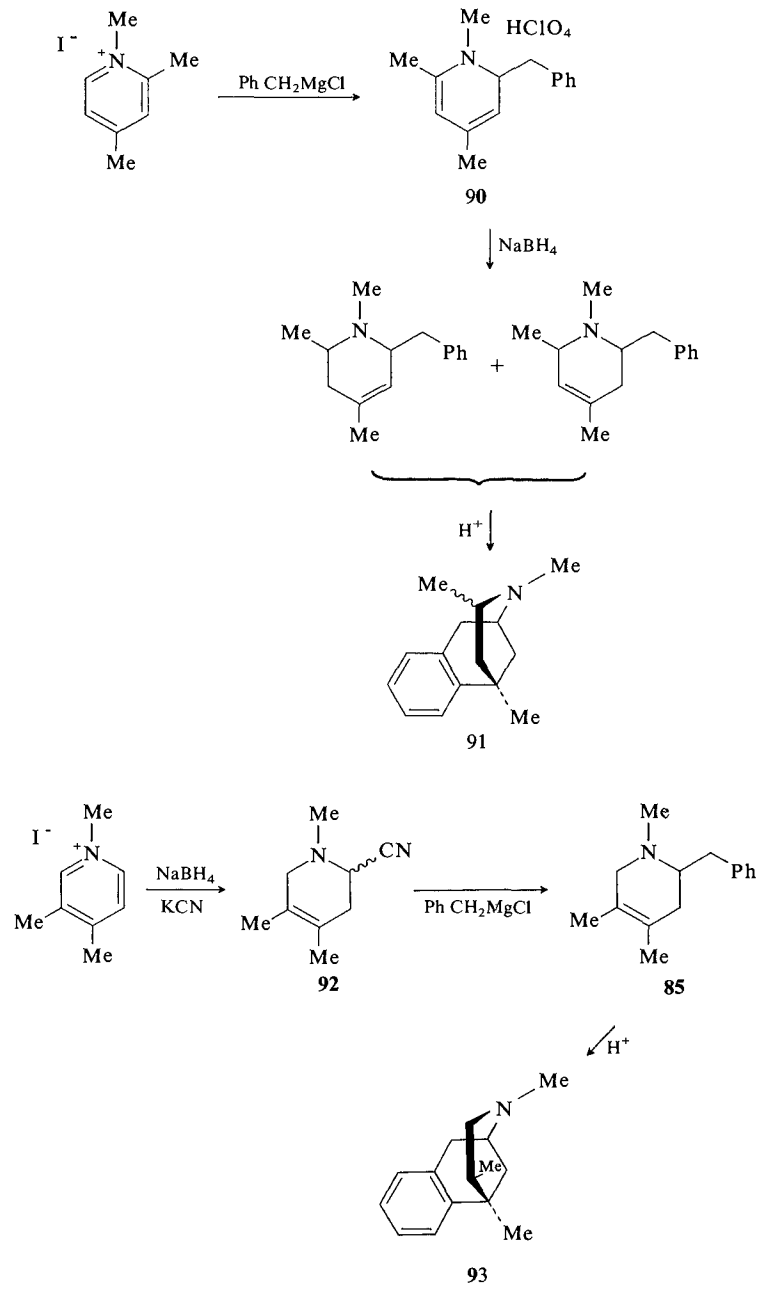
Although the α-isomers are similar to morphine in their vestigial (6,11-*cis*) stereochemistry, the β-isomers exhibit analgesic activity in rodent screens several times greater than the α.[32]

Fry, in a search for an intermediate capable of undergoing stereospecific cyclization to 11β-alkylbenzomorphans, studied the 2,3-*cis* and *trans* isomers of 2-benzyl-1,3,4-trimethyl-1,2,3,6-tetrahydropyridine (Scheme 4.11). These were prepared from the iminium dienes (**80** and **81**) isolated as crystalline perchlorates from benzyl Grignard attack on 1,3,4-trimethylpyridinium bromide. The isomeric dienes were differentiated through their cyano derivatives (**82** and **83**), which on borohydride reduction gave the isomeric tetrahydropyridines, **84** and **85**. Elimination of HCN from **82** gave the iminium diene (**86**) isomeric with **81**. Addition of nitrile to **81** followed by borohydride reduction resulted in the appropriate *trans* tetrahydropyridine (**88**) that cyclized to the 11β-methylbenzomorphan (**89**).



Scheme 4 11

In a similar manner, May and Jacobson[33] exploited this method in the synthesis of the 11β-epimer of 3-methyl-6,11-diethylbenzomorphan. 3,4,6-Trimethylbenzomorphan (**91**) has been prepared from **90** by standard procedures.[27] The same authors exploited an intermediate cyanotetrahydropyridine (**92**), previously described by Fry[26] to secure 3,5,6-trimethylbenzomorphan (**93**) (Scheme 4.12).

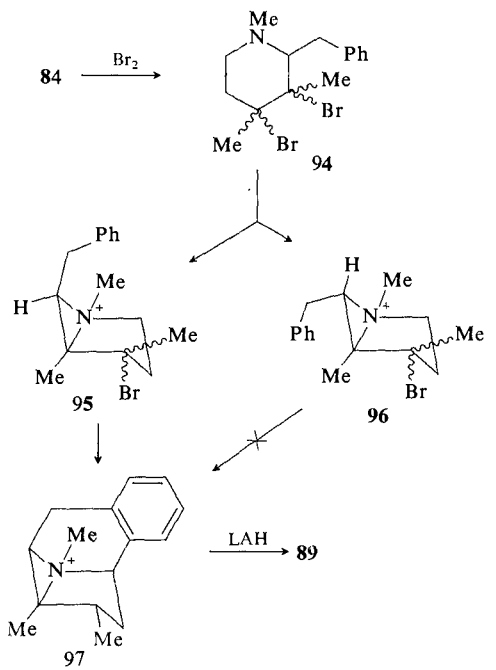

I⁻
Me
N
Me
Me
Ph CH2MgCl
HClO4
Ph
90
NaBH4
+
H+
91
NaBH4
KCN
CN
92
85
93

Scheme 4.12

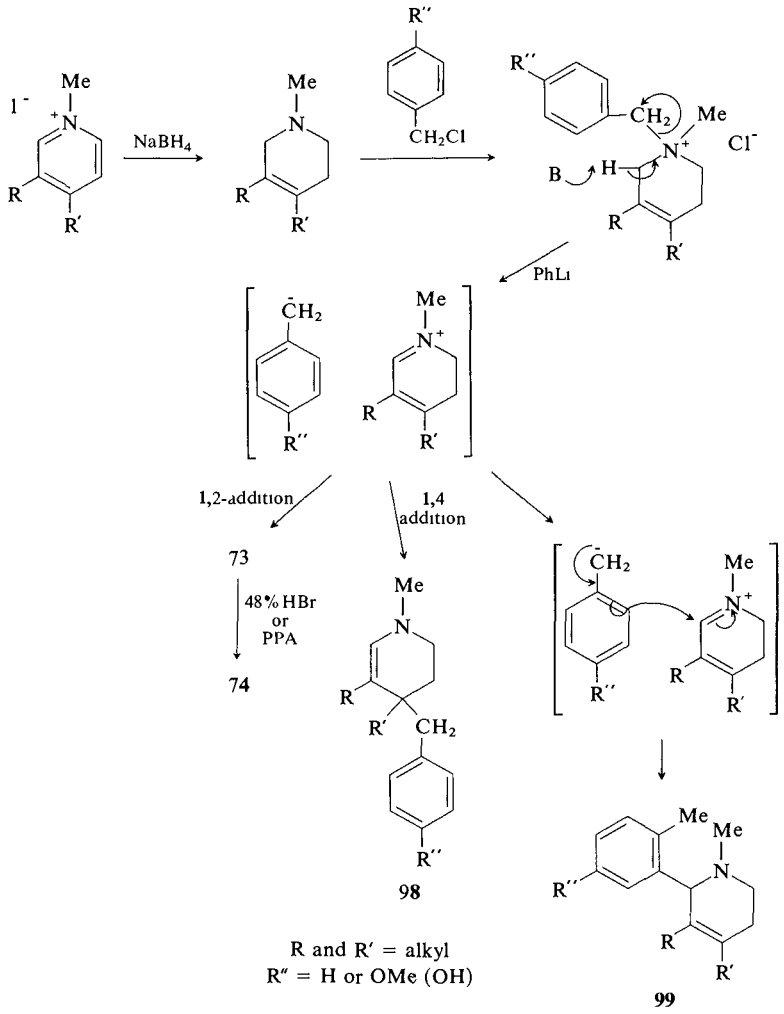
An alternative stereospecific route[34] to 11β-alkylbenzomorphans from 2-benzyltetrahydropyridines (e.g., **84**) (Scheme 4.13) is achieved by bromination to the dibromo intermediate **94**, which with mild base yields, presumably, the isomeric aziridines **95** and **96**. Only **95** affords a conformation capable of cyclizing to the benzomorphan-aziridinium ion (**97**) which may be reduced to the 11β-benzomorphan (**89**).

An alternative approach to 2-benzyl-1,3,4-trialkyltetrahydropyridines (**73**) from the phenyllithium-induced Stevens rearrangement of the corresponding 1-benzyl-1-methyltetrahydropyridinium salt was introduced by Fry and May.[35] Rearrangement occurs predominantly to the 2-position and cyclization of **73** is effected under standard conditions.

During early Stevens-rearrangement studies in this series only 1,2-rearrangement products were isolated.[35,36] Subsequently, large-scale benzomorphan synthesis (Scheme 4.14) afforded, from the rearrangement of 1-(4-methoxybenzyl)-1-methyl-3,4-diethyl-1,2,5,6-tetrahydropyridinium chloride (**73**, R = R^I = C_2H_5; R^{II} = OMe) by phenyllithium, a mixture of products.[37,38] The major components were the anticipated 1,2- and 1,4-addition products **73** and **98**, respectively. In addition, the 2-aryl derivated **99**



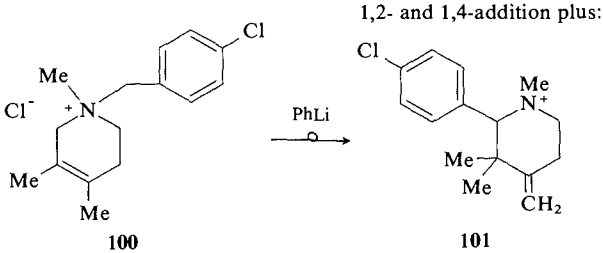
Scheme 4.13



Scheme 4.14

was recovered, formed presumably via the mechanism illustrated (Scheme 4.14).

Jacobson,[38] examining the phenyllithium-induced rearrangement of 1,3,4-trimethyl-1-(4-chlorobenzyl)-1,2,5,6-tetrahydropyridinium chloride (**100**), isolated the expected 1,2-rearrangement product corresponding to **73** (15%) and the 1,4-rearrangement product corresponding to **98**. In addition, he isolated a further rearrangement product, 1,3,3-trimethyl-2-(4-chlorophenyl)-4-methylenepiperidine (**101**).



100 **101**

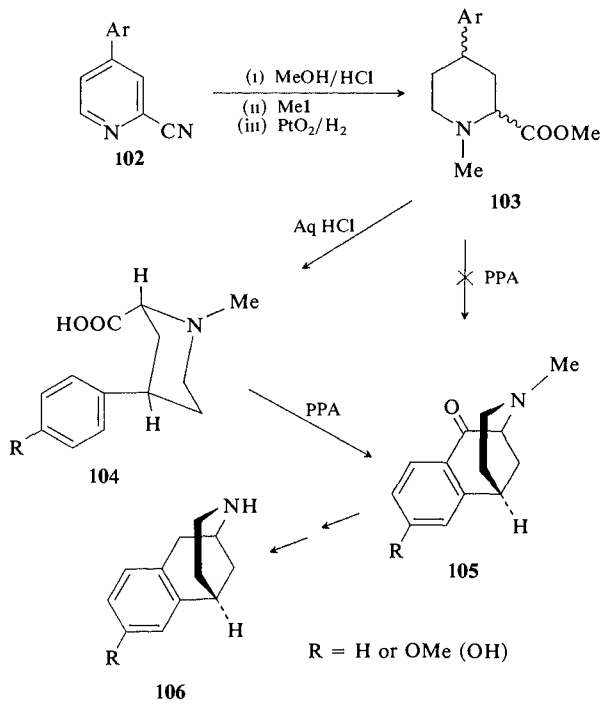
Similarly, Bosch and co-workers[39] isolated from the potassium hydroxide-induced rearrangement of 1,3,4-trimethyl-1-(3,4,5-trimethoxybenzyl)-1,2,5,6-tetrahydropyridinium chloride, products corresponding to **73**, **99**, and by inference **101**, together with a Hofmann-elimination product. An unambiguous method for preparing 2-benzyltetrahydropyridines from 2-bromopyridine, thus affording a wide selection of substituted benzomorphans has been published.[39a]

Although the 11α- and β-epimers of 3,11-dimethyl-6-propyl-8-hydroxybenzomorphans were synthesized and evaluated as analgesics in the early 1960s,[40,41] the corresponding 6-methyl-11α and 11β-propyl isomers were not synthesized until 1975, when May's group[42] prepared the key pyridine intermediate, 4-methyl-3-propylpyridine, from the condensation of cyanoacetamide and ethyl 2-propylacetoacetate in methanolic potassium hydroxide.

Other substituted piperidines, particularly piperidinols, have been exploited as benzomorphan precursors. The first 6,7-benzomorphan lacking a 6-alkyl substituent, the parent heterocycle, was reported by May *et al.* in 1968[43,44] in a synthesis from 2-cyano-4-phenylpyridine (**102**) (Scheme 4.15). The 2-carbomethoxypiperidine (**103**) was prepared readily, but it proved resistant to direct cyclization to 3-methylbenzomorphan-1-one (**105**) with polyphosphoric acid, presumably because the more stable 2,4-diequatorial isomer is not favorable for ring closure for geometric reasons. Hydrolysis to the corresponding acid (**104**), however, gives an intermediate that closes to **105** in 94% yield. The parent heterocycle **106** is produced by standard techniques.

A pentazocine (**109**) synthesis has been reported by Kametani and coworkers[45] from the methyl ester of tyrosine methylether (**107**) via the piperidinol intermediate **108**, according to Scheme 4.16. Other piperidinol syntheses have been published by Kametani[46-49], Janssen,[50] and Henecka and Schubert.[51]

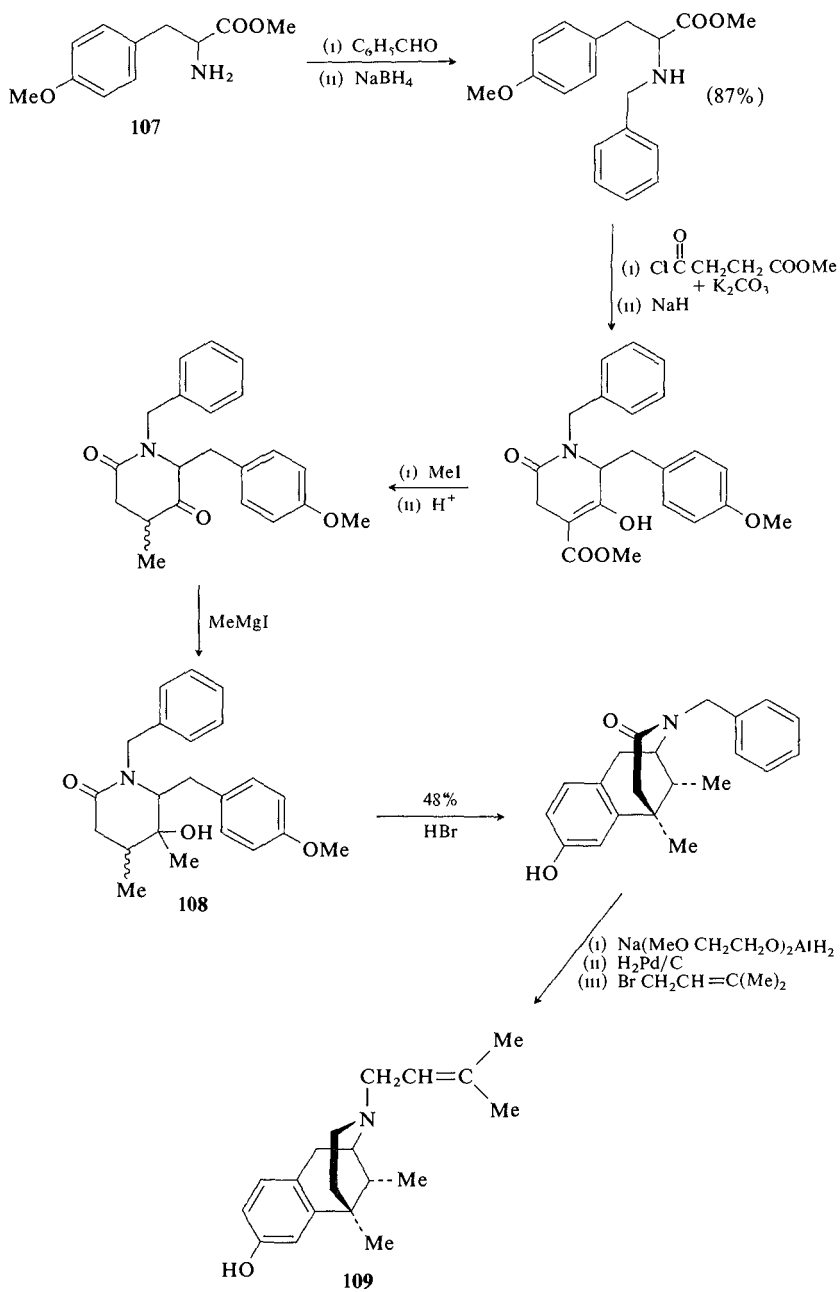
An eight-stage synthesis of 2-methylbenzomorphan (**115**) from benzaldehyde via diethyl benzylidene malonate (**110**) in 19% overall yield has been reported[52] (Scheme 4.17). The amino radical precursor, *N*-chloramine (**111**),



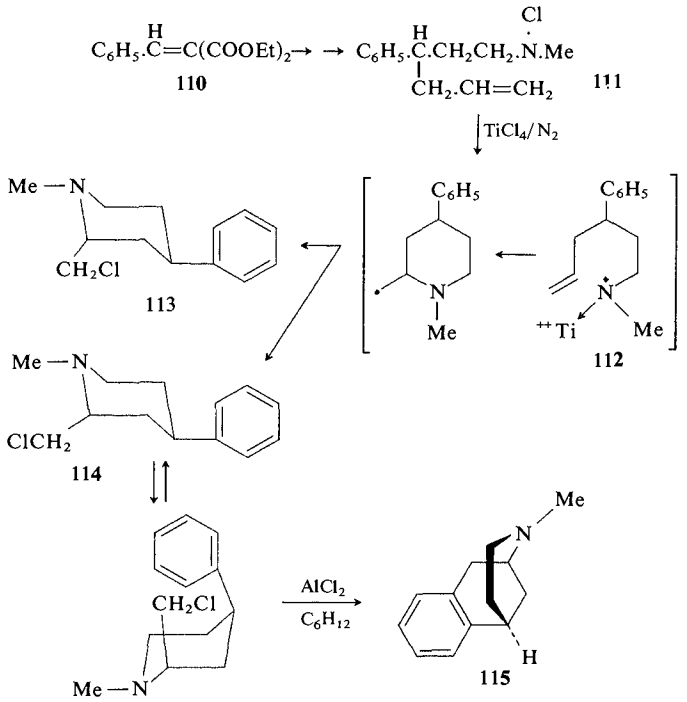
Scheme 4.15

is prepared in five steps from **110**. Addition of titanium dichloride solution to an aqueous acetic acid solution of **111** gave the amino radical-titanium complex (**112**), which cyclized by intramolecular addition to the ethylenic bond, followed by chlorine abstraction from **111** to a *cis-trans* mixture of isomeric 2-chloromethyl-1-methyl-4-phenylpiperidines (**113** and **114**). The favorable conformer of **114** ring closed in 60% yield on treatment with aluminium trichloride in cyclohexane to the benzomorphan (**115**).

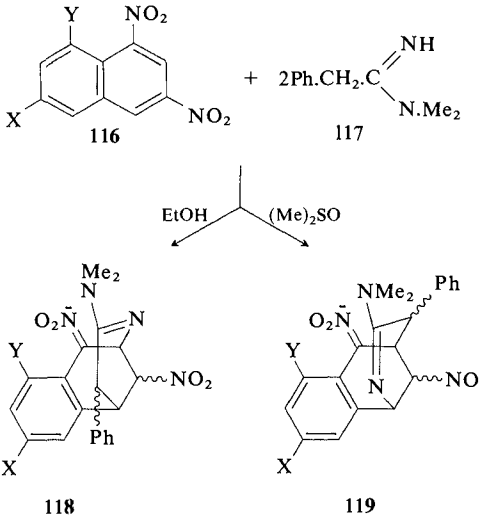
A series of unusual amidinium benzomorphans has been described by Strauss *et al.*[53-55] where some members of the series exhibit narcotic antagonist properties. Their synthesis involves a *meta* bridging process of di- and trinitronaphthalenes (**116**) with α-phenyl *N,N*-dimethylacetamidine (**117**) to produce two isomeric benzazocine amidinium nitronates as their α-phenyl-*N,N*-dimethylacetamidinium salts (AmH^+). The benzomorphan **118** is formed in ethanolic solution, whereas the isomeric benzazocine (**119**) results from reaction in dimethylsulfoxide.


COOMe
NH2
MeO
107
(i) C6H5CHO
(ii) NaBH4
COOMe
NH
MeO
(87%)
(i) Cl C CH2CH2 COOMe
O
+ K2CO3
(ii) NaH
N
O
OH
COOMe
OMe
(i) MeI
(ii) H+
N
O
O
OMe
Me
MeMgI
N
O
OH
Me
Me
OMe
108
48%
HBr
N
O
Me
Me
HO
(i) Na(MeO CH2CH2O)2AlH2
(ii) H2Pd/C
(iii) Br CH2CH=C(Me)2
Me
CH2CH=C
Me
N
Me
Me
HO
109

Scheme 4.16



Scheme 4.17

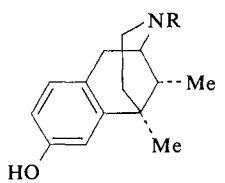


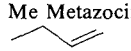
4.3. SUBSTITUTED BENZOMORPHANS

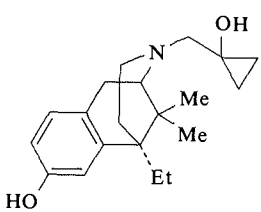
4.3.1. Substitution on Nitrogen

Variation of substituents on the benzomorphan nucleus, particularly on nitrogen, results in significant changes in biological response. The requirements of the tertiary amine in the pharmacological activity of morphine has been systematically investigated.[56] Although replacement of *N*-methyl by ethyl, *n*-propyl, and *n*-butyl resulted in a loss of analgesic responses at subtoxic doses, more hydrophobic groups, such as pentyl, hexyl, and phenethyl, gave an increase in activity.[56a,56b] Replacement of *N*-methyl by *N*-phenethyl in morphine had been shown in 1956[56c] to result in an increase in antinociceptive potency. May and Eddy[74] followed this observation with the synthesis of phenazocine (**123**), which has an enhanced activity relative to morphine. Very much earlier, Pohl[57] observed that *N*-allylnorcodeine antagonized the respiratory depressant effects of morphine, and this led to the development of nalorphine as a morphine antagonist.[58]

In the mid-1950s it was reported that nalorphine not only possessed opiate antagonist properties, but was also a potent analgesic in humans.[59,60] This analgesia had not been seen in rodent tests available at that time and suggested the potential for developing a powerful analgesic free from the dependence properties exhibited by morphine and related "agonists." This observation resulted in the development, ten years later, of first *N*-allylnormetazocine[75] and then the *N*-dimethylallyl- and *N*-cyclopropylmethylbenzomorphans, pentazocine, (**120**), and cyclazocine (**121**), respectively.[61]



120 R = Pentazocine
121 R = CPM Cyclazocine
122 R = Me Metazocine
122a R =  *N*-Allylnormetazocine
123 R = $-CH_2CH_2Ph$ Phenazocine



121a Bremazocine

Pentazocine (*Fortral*), manufactured via a modified Grewe synthesis,[61a] behaves pharmacologically in humans like other opiates. At normal doses (30–50 mg parenteral equivalent to 10 mg morphine; 50 mg oral, equivalent to 60 mg codeine) it is analgesic, is sedative, and depresses respira-

tion. It differs from morphine in that at high doses blood pressure and heart rate are increased and psychotomimetic effects similar to those recorded for nalorphine are seen. The latter are consistent with its properties as a weak morphine antagonist. The synthesis of some pentazocine metabolites and related benzomorphans has been published.[61b] The psychotomimetic effects of cyclazocine have prevented its clinical use as an analgesic. However, it has long-acting antagonist properties that have been exploited in the treatment of opiate dependence. An interesting compound with structural features reminiscent of cyclazocine is the 11,11-dimethylbenzomorphan known as *bremazocine* (**121a**).[217] Although its level of side effects in humans militates against therapeutic use, bremazocine has a high specific affinity for opioid κ-receptors and is likely to prove a valuable pharmacological tool. Its synthesis and actions are covered in detail in Chapter 12.

Generation of benzomorphan secondary amines, for conversion to appropriate *N*-substituted derivatives, usually requires *N*-demethylation of the corresponding tertiary amine. This may be effected by the von Braun reaction with cyanogen bromide or by the use of alkyl-, halogenated alkyl-, and arylchloroformates or diethylazodicarboxylate. Methods for *N*-demethylation in the series have been summarized by Rice.[62] Removal of an *N*-benzyl substituent affords an alternative path to norbenzomorphans and is exemplified by Michne and co-workers[63] and Kametani and Aoyama.[64]

Standard techniques are used to substitute on nitrogen. Allyl and substituted allyl halides substitute directly, whereas alkyl and CPM functions are best introduced via the acyl halide followed by LAH reduction.[61] Reaction of norbenzomorphans with *N*-nitrourea or with urea, acetic acid, and HCl affords *N*-carbamoylbenzomorphans.[65,66] *N*-Arylamidinobenzomorphans have also been reported.[67]

Michael addition of a norbenzormorphan to methylvinylketone[68] affords a method of varying the substituent on nitrogen, and much earlier Fry and May[69] exploited a modified Mannich reaction to give *N*-(3-phenyl-3-oxypropyl) benzomorphans.

Benzomorphans bearing a tertiary nitrogen are readily generated from corresponding quaternary salts. This is referred to in Schemes 4.1 and 4.4 (pp. 156 and 159), where *N*-dimethyl quaternary benzomorphans are converted to the corresponding tertiary bases either by dry distillation or by heating in octanol or nonanol.[7] *N*-Debenzylation of quaternary benzomorphans by sodium thiophenoxide[70] and by catalytic hydrogenolysis[71] have also been reported and dimethylallylbenzomorphans have been prepared by Hofmann elimination of corresponding *N*-cyanoethyl quaternary benzomorphans.[72]

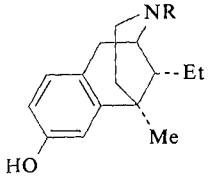
The replacement of *N*-methyl by *N*-phenethyl in morphine increases analgesic potency by up to sixfold.[73] The corresponding change from metazocine (**122**) to phenazocine (**123**)[74] results in a similar increase in potency in both animal models and humans. Clinically, phenazocine (*Narphen*) is

about 3–10 times more potent than morphine (1–3 mg = 10 mg morphine) with similar respiratory depression and dependence properties. In a series of *N*-aralkyl benzomorphans prepared by May's group,[75] analgesic activities greater than that of morphine were usually achieved with arylethyl analogs; however, extension of the alkyl chain invariably led to a dramatic drop in potency.

N-(2,4,5-Trihydroxyphenethyl)normetazocine was prepared by the NIH group[76] from normetazocine as a potential, irreversible, opioid-receptor inhibitor. This is, in effect, a 6-hydroxydopamine benzomorphan analog that unfortunately had only a weak affinity for the opioid receptor.

Following the observation of strong analgesic activity in humans in compounds bearing what were previously considered to be "antagonist" *N*-substituents many variants of *N*-substituted benzomorphans were reported, including pentazocine (**120**) and cyclazocine (**121**) during an extensive investigation by Archer *et al.*[61] As well as being analgesics, these derivatives exhibited variable antagonist activities. Cyclazocine (**121**) is a good analgesic and antagonist (mixed agonist/antagonist) that also gives rise to significant psychotomimetic effects, and both the cyclobutylmethyl and cyclopentylmethyl homologs are antagonists about one-half as potent as nalorphine. In contrast, the cyclohexylmethyl homolog is almost devoid of activity.

During their continuing study of benzomorphans and in an attempt to find improved analgesics, May *et al.*[77] synthesized several *N*-substituted 11α-ethyl-8-hydroxy-6-methyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocines.



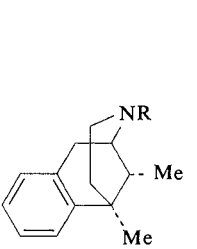
124 R = CH_3
125 R = C_2H_5
126 R = n-C_3H_7
127 R = n-C_4H_9
128 R = $CH_2.CH{=}CH_2$
129 R = $(CH_2)_3.CH{=}CH_2$
130 R = CPM

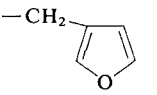
Compounds **124** and **125** were equipotent with morphine in the phenylquinone writhing (MW) and mouse hot-plate (MHP) tests, and compounds **126–130** inclusive exhibited a greater antagonist potency than nalorphine.

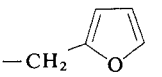
Bellora and co-workers[205] have also prepared a range of *N*-substituted compounds with unsaturated or aromatic characteristics some of which exhibited good activities in the MHP and MW tests.

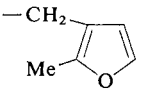
Curious variations in biological response have been observed by substituting on nitrogen, furfuryl, and methylfurfuryl groups,[78] where the substitution pattern about the furan ring dictates the nature of the observed activity.

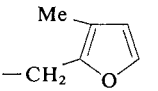
Compound **131** behaves as an antagonist, about one-half as potent as nalorphine;



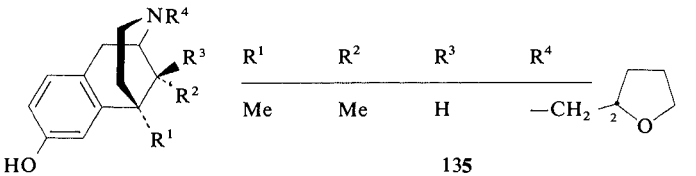
R =  **131**

R =  **132**

R =  **133**

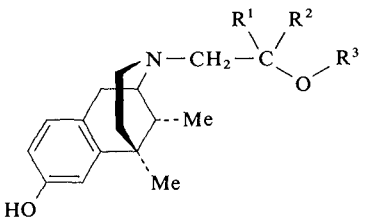
R =  **134**

132 is a mixed agonist-antagonist and **133** is an agonist about $\frac{1}{2}\times$ morphine in analgesic potency with an antagonist component in its pharmacological profile. The most interesting derivative, **134**, appears to be a pure agonist ($\frac{1}{2}\times$ morphine) that does not suppress an abstinence syndrome. The same group[79] extended its investigations to tetrahydrofurfuryl derivatives, where the configuration was established. Compound **135** (2*R*, 6*R*, 11*R*, 2″*R*) was reported as being an agonist (50 × morphine, MW), but it did not possess a demonstrable antagonist activity, nor did it suppress the morphine abstinence syndrome in dependent monkeys.



135

Analgesics such as **134** and **135** may be described as opioid κ agonists (p. 405), and Merz and Stockhaus[80] simplified the *N*-substituent to a series of *N*-(alkoxyalkyl) derivatives of normetazocine in an attempt to define more closely the structural requirements for such activity. They concluded that when a two-carbon chain separated the nitrogen and oxygen functions morphine agonist (μ) or nonmorphine agonist (κ), activity of maximum potency occurred (e.g., **136**, 10 × morphine, MHP). In compounds chiral about position 2″, the 2″*S* forms are very much more potent as agonists than their 2″*R* counterparts (e.g., **137**, 100 × morphine, MHP). Recently, Merz[218] has reviewed structure-activity relationships in these series.

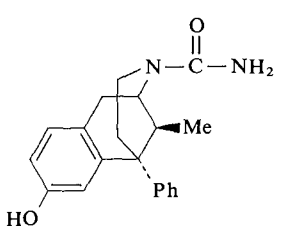


R^1	R^2	R^3	
H	H	Me	136
H	Me	Me	137

To investigate the effect of reducing the opiate nitrogen basic strength without affecting significantly the involvement of the nitrogen with its receptor sterically, several *N*-fluoroalkyl derivatives of normetazocine have been synthesized.[81] All *N*-β-fluoroalkyl derivatives reported had, at best $\frac{1}{10}\times$ morphine activity (MHP) and had dramatically lower opioid receptor binding levels than morphine.

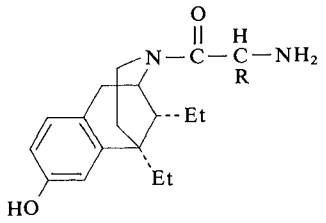
8-Hydroxy-3-cyanoalkyl-6,11-dimethylbenzomorphans have been examined for analgesic potency (MHP).[81a] Earlier[81b] it had been demonstrated that the *N*-(β-cyanoethyl)-analog of (±)-normetazocine was about 1.5 × morphine and the corresponding *N*-(γ-cyanopropyl)-derivative about $\frac{1}{2}\times$ morphine in the MW test. It appeared that neither compound gave rise to an abstinence syndrome. The later NIH study showed that the (−)-N·CH_2CH_2CN compound was about 30 × morphine (MHP) and did not substitute for morphine in dependent monkeys. Similar activity was seen in the corresponding analog of the morphinan, levorphanol; both compounds had excellent therapeutic ratios. Most interesting was the observation that the *N*-cyanoethyl substituent appeared to enable the receptor to differentiate more readily between optical antipodes. In contrast opiates with an intact 4,5 oxygen bridge bearing a cyanoethyl substituent on nitrogen exhibited little change in pharmacological activity relative to the *N*-methyl counterparts.

The carbamoyl derivative[82] **138** has been evaluated clinically as an oral analgesic and has been shown to be similar to codeine with a low dependence liability.



138

A report that *N*-arginylmethionine enkephalin was as active an opioid as methionine enkephalin[83] prompted the preparation, by standard methods of a series of amino acid derivatives of (−)-6,11α-diethyl-8-hydroxybenzomorphan (**139**).[84] All compounds were inactive *in vivo* (RTF and MHP), but binding activities were retained.



139 R = H
= $CH_2CH_2.S.CH_3$
= $CH_2CH.(Me)_2$
from (−) phenylalanine R = $CH_2.C_6H_5$
from (+) phenylalanine R = $CH_2C_6H_5$

Substitution of the alkylating functions bromoethyl- and bromopropyl- on nitrogen[209] to prolong activity and possibly afford a receptor label gave only weak analgesics (MHP), with some prolongation of hypothermia and depression.

4.3.2. Aromatic Substitution

The presence of a phenolic hydroxyl function in the 8 (or 2^1) position of benzomorphans, as a general rule, increases analgesic potency.[1,33] This change is in parallel with changes in biological response observed for morphine and morphinans. Conversion of hydroxyl to methoxyl results in a significant reduction in analgesic response, whereas acetylation of the phenolic function usually increases activity.[75]

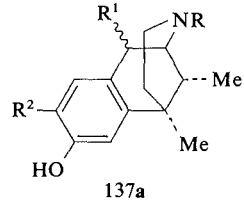
The possibility that benzomorphans lacking an 8-hydroxyl group might afford analgesics as potent as morphine but without dependence liability stimulated a study by Jacobson and May.[33] Their tentative conclusion was that with benzomorphans the presence of the 8-hydroxyl group enhances analgesic potency and, if anything, reduces toxicity and dependence.

Benzomorphans bearing an 8-OH substituent are readily synthesized by conventional tetralone, Grewe and Stevens rearrangement routes described earlier, but in addition, conversions of benzomorphans unsubstituted in the aromatic ring to corresponding 8-OH derivatives have been described.[24,33]

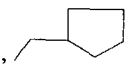
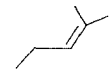
Encouraged by the potential of the 8-position to influence both analgesic potency and toxicity in benzomorphans, Jacobson and May[85] prepared a series of 8-nitro, 8-amino-, and 8-halogeno-substituted compounds by standard methods. All derivatives reported were weaker analgesics and were more toxic than the corresponding 8-OH or unsubstituted compounds.

8-Hydroxy-6,11-dimethylbenzomorphans, with or without a methyl or phenyl substituent in the 1-position, are readily aminoalkylated in the 9-position to afford, for example, 9-dimethylaminomethylbenzomorphans (**137a**, $R^2 = CH_2N{\cdot}(Et)_2$, R = Me). Hydrogenolysis of this product gave the corresponding 9-Me derivative (**137a**), (R and R^2 = Me). All compounds exhibited, at best, weak analgesic activity.[85a]

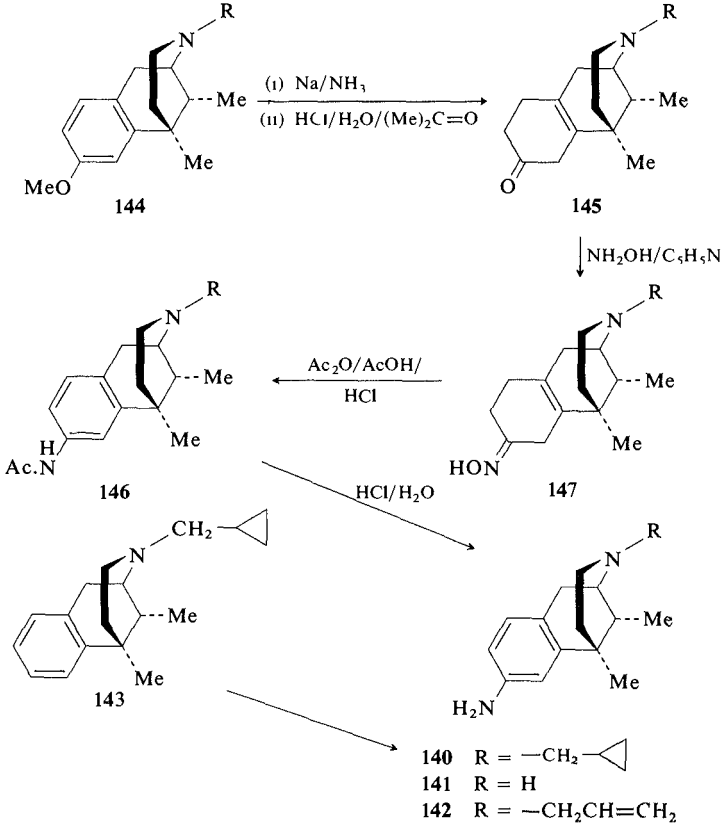
The observation that 8-hydroxybenzomorphans were inactivated and eliminated *in vivo* by conversion to a corresponding glucuronide stimulated



137a

R = CPM, CBM,  ,  , 
R^1 = H, Me, Ph
R^2 = $-CH_2.N(Et)_2$, Me

Wentland *et al.*[86] to investigate 8-aminobenzomorphans related to cyclazocine in an attempt to minimize such effects. The 8-NH_2 cyclazocine analog (**140**) is a strong oral analgesic agonist with antagonist properties somewhere between pentazocine and cyclazocine in potency. Two routes to **140** were published, the first following May and Fry's approach of direct nitration, followed by reduction of *volazocine* (**143**). Alternatively, Birch reduction of **144** gave the ketone **145**, which was converted to its oxime (**147**) and subjected to Semmler–Wolff dehydration to the acetanilide **146**. Hydrolysis gave **140** or **141**, depending upon the nature of R in **144**. Intermediate **146** (R = H) gave the *N*-allyl



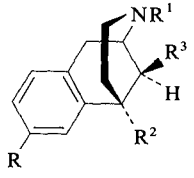
derivative **146** (R = $CH_2{\cdot}CH{=}CH_2$) when treated with allyl bromide to afford ultimately **142**. The diamine **141** may be exploited as an intermediate for various *N*-substituted analogs.

Unusual nitroaromatic benzomorphans have been described earlier,[53-55] and some 8-(1,5-benzodiazepin-3-yl)sulfanyl-benzomorphans have been reported[206] as analgesic and anticonvulsant.

4.3.3. 6-Substituted Benzomorphans

Major synthetic routes to the benzomorphans have dictated that a substituent appears in the 6-bridgehead position (5-position in earlier numbering). Synthetic difficulties were encountered where pyridine starting materials were not equipped with an appropriate 4-substituent (Scheme 4.9, p. 165) or where 2-tetralones were not disubstituted in the 1-position (Scheme 4.1, p. 156). During early studies the 6-substituent was usually a low alkyl function (Me, Et, or *n*-Pr). This work has been reviewed thoroughly by Eddy and May.[1]

Considerable difficulties were encountered in attempts to apply standard synthetic routes to the synthesis of the parent nucleus, 1,2,3,4,5,6-hexahydrobenzazocine (or benzomorphan) (**106**). Ultimately, a route based upon 2-cyano-4-phenylpyridine (**102**) was successful (Scheme 4.15, p. 173).



	R	R^1	R^2	R^3
106	H	H	H	H
148	H	Me	H	H
149	H	Me	Me	H
150	H	Me	H	Me
151	OH	Me	H	Me
152	H	Me	Ph	H
153	OH	Me	Ph	Me
154	OH	$-CH_2CH{=}CH_2$	Ph	Me
155	H	Me	COOEt	H
156	H	Me	$CONH_2$	H
157	H	Me	CH_2NH_2	H

Contrary to expectations, the *N*-Me analog (**148**) proved to be as active (MHP) as the corresponding compound bearing a 6-Me substituent (**149**) that is about equivalent to codeine in potency.

Reinvestigation[87] of the Grewe/Stevens routes to **106**, **148**, and the corresponding 8-OH, 8-OMe, and 8-OAc homologs demonstrated that cyclization of 2-benzyl-1-methyl-1,2,5,6-tetrahydropyridine to **148** occurs in PPA at an optimum temperature of 155°. At higher temperatures, degradation occurs in competition with cyclization, rendering the isolation of products difficult.

A 1-tetralone route was employed by May's group[88] to synthesize compounds related to **106** bearing an 11β-methyl substituent (**150**). Such substitution is known to enhance analgesic activity. Again, activities equivalent to

codeine were observed together with some antagonist responses.[88,89] A modification of the tetralone route[90] facilitated the preparation of the 8-OH compound **151**. Compounds **150** and **151** are about equipotent with codeine and morphine, respectively, as analgesics (MHP and Nilsen) and appear to be devoid of a PDC in monkeys.

The 11α-epimer of compound **151** has been synthesized via a 1-tetralone route in 49% yield (Scheme 4.5, p. 160).[91] Cyclization of **41** to **42** was effected by mercuric acetate, and in addition, 5% of the 11β-epimer was isolated. In the MHP test, 3,11α-dimethyl-8-hydroxy-**1**,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine had an ED_{50} of 4.3 mg/kg, whereas the corresponding 11β-Me analog (**151**) was as active as morphine with an ED_{50} of 1.1 mg/kg (cf. morphine, 1.2 and pethidine 4.5 mg/kg). Like **151** (11β-Me), the 11α-Me epimer behaved as an antagonist and precipitated an abstinence syndrome in dependent monkeys.

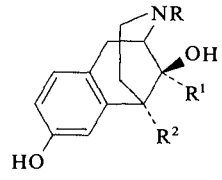
6-Phenylbenzomorphans, having a structural relationship with 4-phenylpiperidine analgesics, with and without an 11-position substituent, have been synthesized via a modified 1-tetralone approach[16] (Scheme 4.6) or from 1,3-dimethyl-4-phenyl-1,2,5,6-tetrahydropyridine by quaternization, Stevens rearrangement and cyclization.[92] Although compound **152** exhibited only weak activity,[16] (ED_{50}, 25 mg/kg MHP), the 6-phenyl analogs possessing an 8-OH and 11β-Me gave a MHP ED_{50} of 0.5 mg/kg when evaluated as the racemate. The *l*-enantiomer was more than twice as potent (ED_{50}, 0.18 mg/kg) as racemate and partially antagonized the analgesia of morphine.

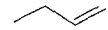
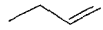
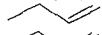
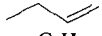
An extensive series of 6-arylbenzomorphans and their 1-methyl-2-benzyl-6-aryl-1,2,5,6-tetrahydropyridine precursors has been reported.[93] Compound **153** (*l*-isomer), the absolute configuration of which was established by X-ray crystallography,[92] is not only a potent oral analgesic, but is also an opioid antagonist. The N-allyl homolog (**154**) is a long-acting pure antagonist. Absolute configurations of the 8-deoxy and 11-desmethyl series were established from ORD and CD comparisons with **153**. Several 6-allyl-8,11β-dihydroxybenzomorphans (**157a–h**) that mimic structurally the 3,14-dihydroxymorphinans, butorphanol and oxilorphan, have been synthesized via the 2-tetralone route.[94a,210,211] Compounds bearing *N*-cyclopropylmethyl or cyclobutylmethyl substituents possess the highest antagonist or mixed agonist–antagonist activities.

Compound **157e** is equipotent with butorphanol as an analgesic and more potent as an antagonist. Similarly, **154g** is more potent than oxilorphan as an antagonist but less potent as an analgesic. In this series, activity resides exclusively in the (−)-enantiomers.

6-*t*-Butylbenzomorphans have been synthesized[94] from 4-*t*-butylpyridines but have only weak pharmacological activities.

A benzomorphan analog of pethidine, bearing a 6-ethoxycarbonyl group (**155**) was prepared by May *et al.*[95] by a modified 1-tetralone synthesis. It



	R	R^1	R^2
157a	CPM	H	
157b	CBM	H	
157c	CPM	H	n-C_3H_7
157d	CBM	H	n-C_3H_7
157e	CPM	Me	
157f	CBM	Me	
157g	CPM	Me	n-C_3H_7
157h	CBM	Me	n-C_3H_7

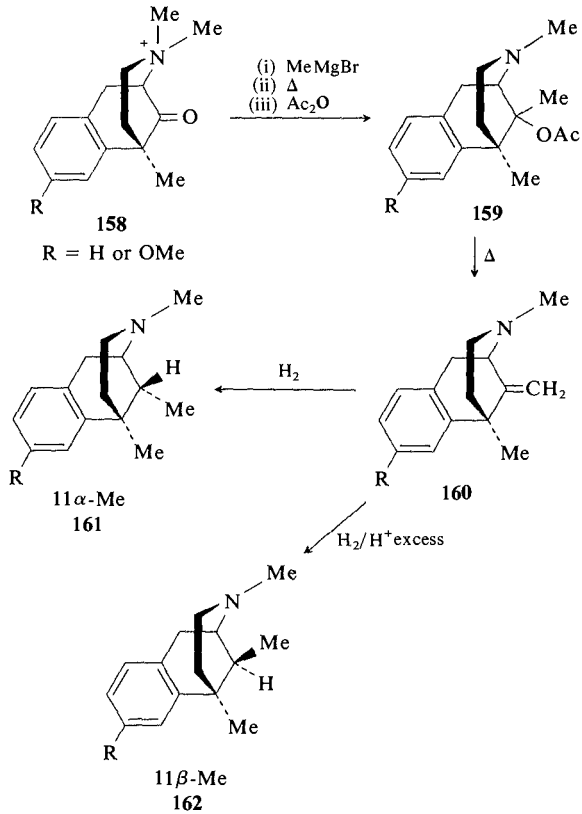
possessed only weak analgesic properties (ED_{50}, 10 mg/kg, MHP), as did the related compounds **156** (ED_{50}, 18.3) and **157** (IA). The corresponding 6-nitrile and 6-carboxylic acid were reported but not evaluated.

4.3.4. 11-Substituted Benzomorphans

Benzomorphans substituted in the 11-position are readily derived via the 2-tetralone route (Scheme 4.1, p. 156) or from pyridines possessing a 3-substituent, usually alkyl (Scheme 4.9, p. 165). Synthesis from 1-tetralones is less useful. Compounds without an 11-position substituent are best prepared by the Grewe route (Scheme 4.9, p. 165), although the 1-tetralone route may be exploited. Eddy and May[1] have summarized work prior to 1965.

During syntheses from 2-tetralones, 11-oxobenzomorphans result and the carbonyl function was exploited in earlier work for the insertion of an 11-methyl group[10,30,96,96a] by treatment with methylmagnesium bromide, followed by acylation, pyrolysis, and hydrogenation. Hydrogenation of **160** base or HCl salt over platinum oxide in ethanol afforded high yields of the corresponding 11α-methylbenzomorphan (**161**). In contrast, the fully protonated form in ethanol containing 15% HCl gave on hydrogenation a high yield of the 11β-epimer (**162**). The carbinol precursor of **159** may be converted more efficiently (75% yield) to the methylene intermediate (**160**) by treatment with thionyl chloride and pyridine.[96]

Addition of methylmagnesium halide, methyllithium, or hydrogen to the 11-oxo group of N-quaternary benzomorphans affords what have been designated 11α-hydroxy derivatives. Unfortunately, this is the opposite of the designation of 11-alkyl substituents. In contrast, addition to11-oxobenzomorphan bases results in the reverse configuration, affording 11β-hydroxy derivatives.[97-99] The nitrogen nonbonding electrons clearly participate in the transition state, permitting hindered face attack. The 11-OH designation was based upon the observation of a strong —OH···N bonding band at 3450 cm^{-1} in the ir spectrum. Confirmation of the proximity of the ring nitrogen to the 11α-OH came from degradation of quaternary salts of each of the 11-epimeric methylcarbinols by two Hofmann elimination reactions[10,100] according to Scheme 4.18. The product from the 11α-OH compound (**163**) proved to be

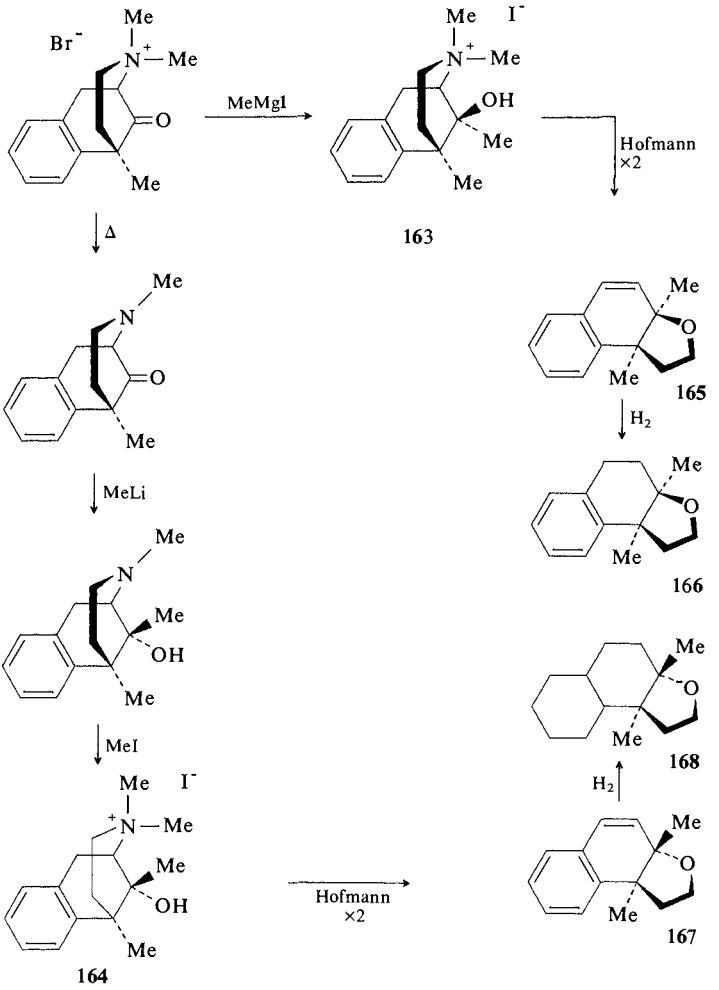


1,2,3a,9b-tetrahydro-*cis*-3a,3b-dimethylnaphtho[2,1-*b*]furan (**165**), which was hydrogenated to **166**. These degradation products were identical with those synthesized by Fry.[101] The corresponding *trans*-fused derivatives **167** and **168** were derived from the 11β-OH compound **164**.

Benzomorphans possessing an oxygen function in either the 11- or 1-position offer the means of constructing an "acetylcholine" moiety on a sterically constrained support. Such α- and β- pairs of 11-acetoxy and 1-acetoxybenzomorphan quaternary salts (**174** and **175**) have been synthesized[116] (see also p. 191).

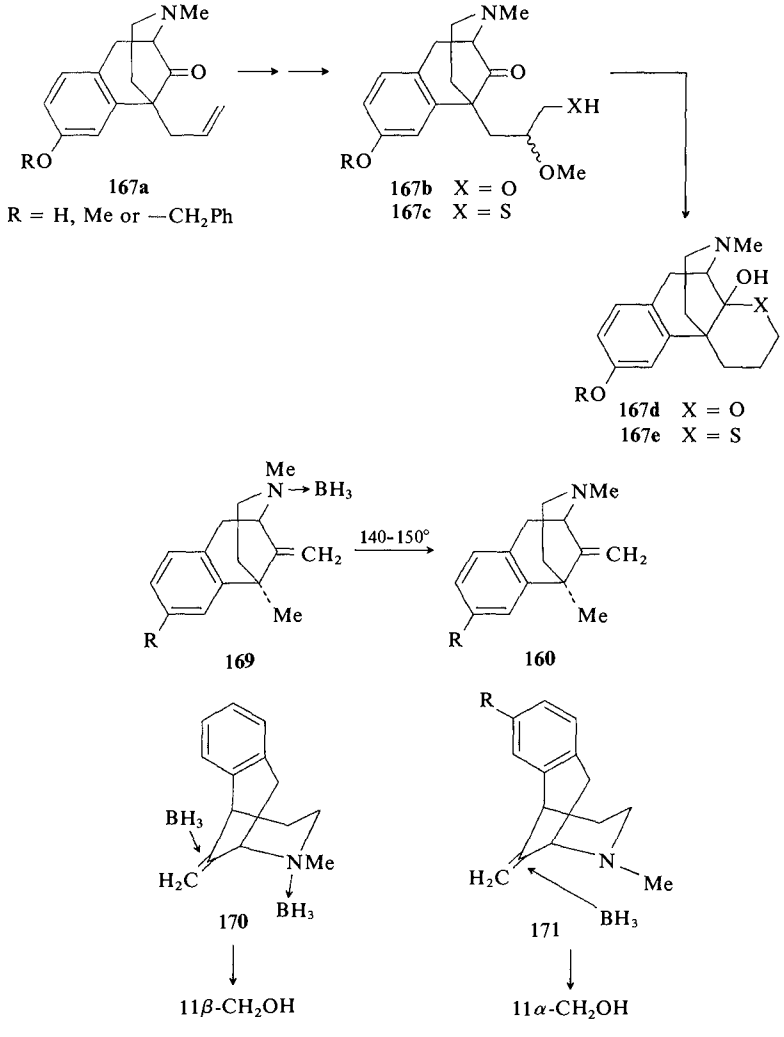
The 11-oxo function has also been exploited in the synthesis of C-ring oxomorphinans and thiomorphinans.[204] 6-Allyl-11-oxobenzomorphan (**167a**) was converted, by way of the 11-methylhemiketal, to **167b** and **167c**, which exists as the cyclic hemiketal (**167d**) and thiohemiketal (**167a**). The latter are moderately active analgesics in the MW test.

Cyclizations of 2-benzyl-3,4-dialkyl-1,2,5,6-tetrahydropyridines have been exploited to give benzomorphans with a variety of 11-alkyl substituents.[30,33,77,102,103]

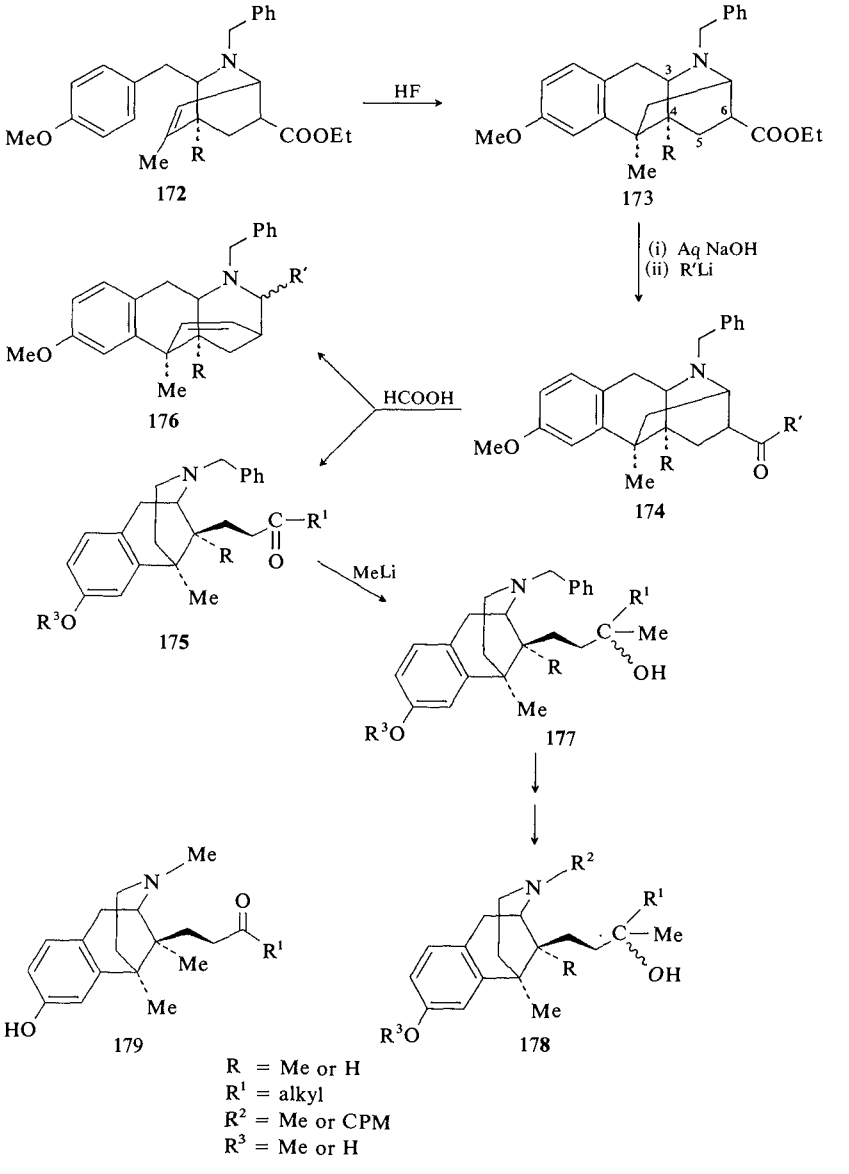


Scheme 4.18

Hydroboration of 11-methylene-3,6-dimethylbenzomorphans (**160**) with diborane followed by H_2O_2 oxidation affords, stereospecifically, the corresponding 11β-hydroxymethyl derivatives.[104,105] If, however, the amine-borane complex (**169**) is heated to 140–150° prior to peroxide treatment, the corresponding **11**α-hydroxymethyl results in addition to the 11β-epimer. Kugita and Takeda[106] propose stereocontrolled attack from the nitrogen side or β-face (i.e., **171**) by borane for the free base, but α-face attack by borane in the case of the amine-borane complex.



Benzomorphans bearing 11-propanol substituents are analogous to the potent analgesic oripavine-7-methanols first described by Bentley and his co-workers (Chapter 2). Such derivatives have been synthesized in a stereospecific manner by Michne.[107,108] The mixed dihydropyridines that result from the reaction of 3,4-dimethylbenzylpyridinium chloride and 4-methoxybenzyl magnesium chloride add ethyl acrylate to afford the adduct **172**. Clearly, only one 3-position stereoisomer will cyclize on HF treatment to give **173**, which in turn is converted to the ketone **174**. Mesitylene/formic acid cleavage affords predominantly the benzomorphan **175**, together with byproduct **176**, isolated as its picrate. Standard conversions yield **177** and **178**. In



R = Me or H
R^1 = alkyl
R^2 = Me or CPM
R^3 = Me or H

general, these compounds do not behave pharmacologically like the corresponding oripavines, being only weak agonists but fairly potent antagonists. Resolution of **178** (R = Me, R′ = *t*-butyl, R^2 = CPM, R^3 = H), which corresponds to buprenorphine, indicates that the activity resides in the (−)-isomer. Replacement of *N*-CPM by *N*-Me results not in the expected agonists, but in potent antagonists.

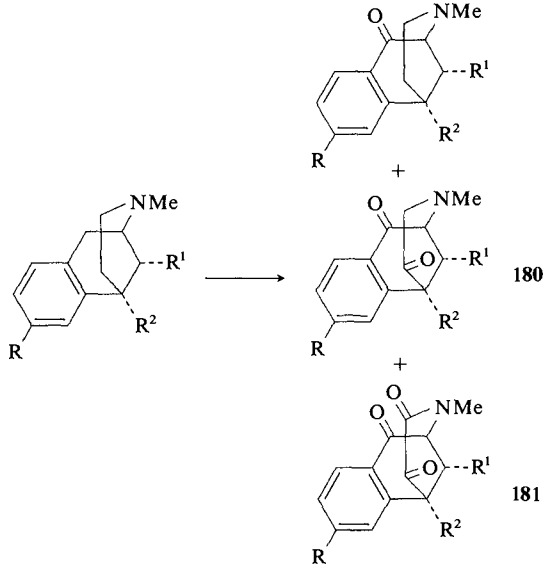
Biological evaluation of a series of 11β-alkanones (**179**) prepared by a similar route[110] has demonstrated analgesic agonist potencies of up to 100 × morphine (RTF) (**179**, R = n-C_4H_9) in the absence of antagonist activity. In contrast, extension of the alkyl chain to pentyl (**179**, R = n-C_5H_{11}) results in naloxone-like antagonist activity in the (−)-isomer, in spite of the presence of an *N*-Me substituent. Contrary to the rationale for developing these series, it is likely that such compounds interact with opioid receptors in a manner that differs from that of the potent oripavines.

May's group[32] has established methods for determining the absolute configuration about the 11-position based upon methiodide formation rates and ^{1}H nmr.

Benzomorphans with an 11-nitro substituent have been reported.[55]

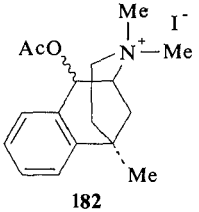
4.3.5. 1-*Substituted Benzomorphans*

Benzomorphans prepared by a 1-tetralone pathway afford a carbonyl function in the 1-position, available for further elaboration. Hydrogenation of 1-oxobenzomorphans over platinum oxide gives the corresponding carbinol,[1,7,90,91] the stereochemistry of which may be determined by chemical means[112] or by ^{1}H nmr.[113] 1-Oxobenzomorphans, which are devoid of analgesic activity, may also be prepared by oxidation of a dihydroprecursor when high yields of 1-oxobenzomorphans[85a,112-114] result together with the di- and trioxo-derivatives (**180** and **181**).[115]

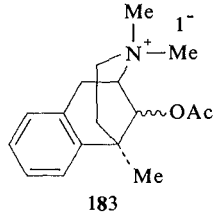


Aryllithium or alkyllithium treatment gives the corresponding tertiary carbinols, which may be converted to 1-aryl and 1-alkyl analogs by standard methods.[85a]

The benzomorphan structure with an oxygen function in either the 1- or 11-position offers a means of building an "acetylcholine" moiety onto a sterically constrained support, and such compounds could afford evidence for the steric requirements of acetylcholine at its nicotinic and muscarinic receptors. Pairs of α- and β-isomers of 1- and 11-acetoxybenzomorphan quaternary salts **182** and **183** have been synthesized and their stereochemistry established by ^{1}H nmr spectroscopy.[116]

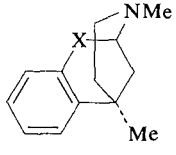


182



183

For each compound only weak cholinergic responses were observed. Oxime (**184a**) formation from 1-oxobenzomorphans has been reported[112,114] for use in ring expansion studies (p. 195). Reduction of the oxime with LAH affords the 1α-amino derivative **184b**.



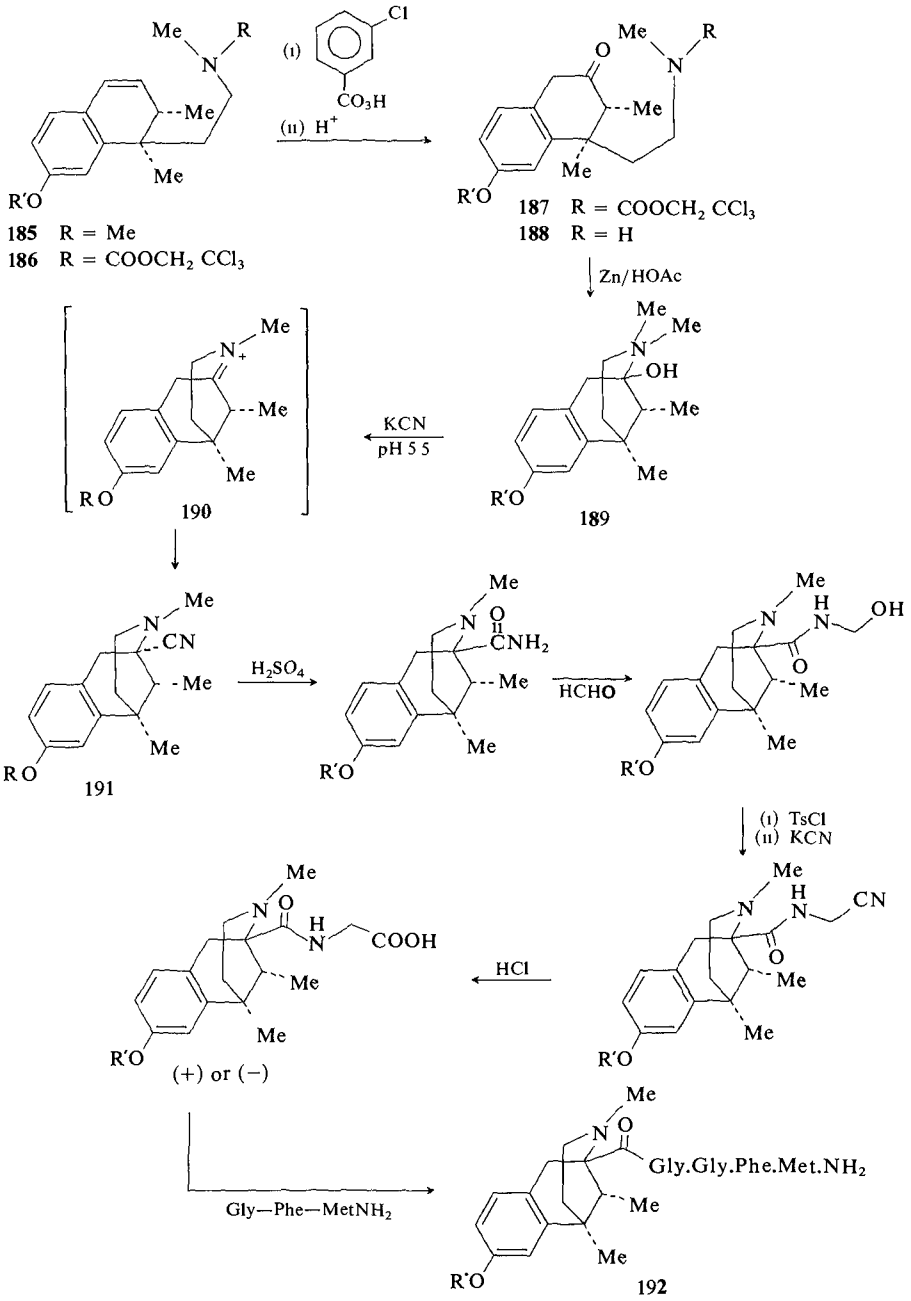
X = =NOH **184a**

X = —NH$_2$ **184b**

Evaluation of a series of 1-oxobenzomorphans[112] for analgesic agonist and antagonist activity demonstrated that in 8-phenolic compounds, agonist potency is maintained, whereas there is a marked reduction in antagonist activity where the 8-OH is absent. This is particularly so where allyl, CPM, and *n*-propyl *N*-substituents are present.

4.3.6. 2-Substituted Benzomorphans

Functionalization of the bridgehead 2-position in benzomorphans by standard synthetic approaches is not easy. This led Portoghese and Ramakrishnan[117] to devise a new 2-tetralone synthesis from a conventional benzomorphan Hofmann elimination product (**185**). Demethylation of **185** was effected by trichloroethylchloroformate to **186**, which, in turn, was oxidized to the 2-tetralone (**187**). Removal of the trichloroethyl carbamate protecting group gave **189**, presumably via **188**. Treatment of **189** with KCN in weak


(i)
(ii) H+
185 R = Me
186 R = COOCH2 CCl3
187 R = COOCH2 CCl3
188 R = H
Zn/HOAc
KCN
pH 5 5
189
190
191
H2SO4
HCHO
(i) TsCl
(ii) KCN
HCl
(+) or (−)
Gly—Phe—MetNH2
Gly.Gly.Phe.Met.NH2
192

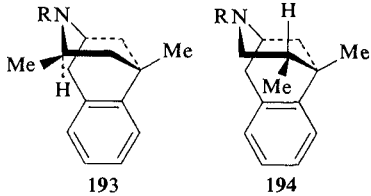
Scheme 4.19

acid gave the 2-functionalized benzomorphan **191** with the iminium ion **190** being proposed as the probable intermediate.

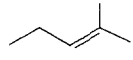
The 2-nitrile derivative **191** was exploited subsequently[118] to give a methionine enkephalin analog with either (−)- or (+)-metazocine in place of the enkephalin tyrosine unit, by standard chemistry (Scheme 4.19). Each compound was, at best, weakly antinociceptive.

4.3.7. 4- or 5-Substituted Benzomorphans

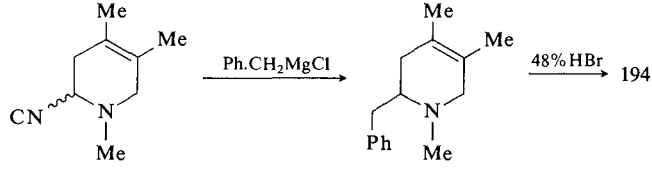
Few benzomorphans substituted in the piperidine bridge 4- and 5-positions have been reported. 4,6-Dimethyl- and 5,6-dimethylbenzomorphans with both agonist and antagonist *N*-substituents have been synthesized[119] and the products demonstrated by ^{1}H-nmr to bear the 4- and 5-methyl substituents in an equatorial conformation on the piperidine chair (**193** and **194**, respectively.) Traces of the axial epimers were also detected.



193 **194**

R = Me, CH_2CH_2Ph,  , CPM

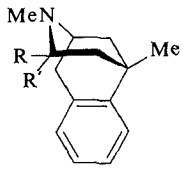
Syntheses of **193** and **194** were by modified Grewe routes. The former was derived from 2,4-dimethylpyridinium methiodide, whereas the latter resulted from treating 3,4-lutidine methiodide with $NaBH_4$ and KCN[26] to afford **195**, which with benzyl magnesium chloride gave **196**. Although Fry[26] reported the isolation of **194**, the product was not characterized.

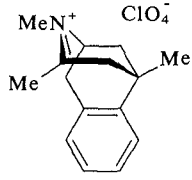


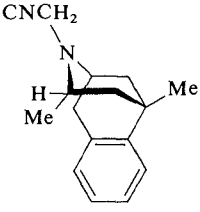
195 **196**

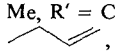
During studies on the functionalization of the benzomorphan 2-position, Portoghese and co-workers[117,120] reported the preparation of a 4-cyanobenzomorphan from the treatment of the corresponding *N*-trifluoroacetate with aqueous KCN. Another study[121,122] demonstrated that cyanation α- to nitrogen in benzomorphans bearing a 4-methyl group may be used to insert a second alkyl substituent in the 4-position. The nature of the cyanation product

is dictated by the configuration of the 4-methyl substituent. Cyanation of **197** proceeded smoothly to the 4β-cyano-4α-methylmethanobenzazocine **199**, whereas **198** gave a 60% yield of the *N*-cyanomethyl derivative (**201**). Both **197** and **198** afforded, on Hg(II) acetate oxidation, the iminium salt (**200**), which underwent cyanation readily to **199**.







197 R = Me, R' = H
198 R = H, R' = Me
199 R = Me, R' = CN
202 R =  , R' = Me

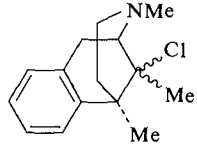
200 **201**

A series of 4-substituted and 4,4-disubstituted benzomorphans has been evaluated for analgesic activity (MHP).[122] The best activity (ED_{50}, 3.7) was exhibited by **202**. Several 5-ethyl and one 5-methylbenzomorphan also exhibited low analgesic activity.[123]

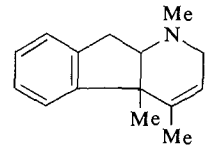
4.3.8. Benzomorphan Rearrangement Products

The synthesis of benzomorphans substituted in the 11-position from a 2-tetralone (Scheme 4.2, p. 157) involves either thionyl chloride dehydration of an 11-methylcarbinol (**13a**)[9] or a pyrolysis of the corresponding acetate perchlorate (**136**)[10] to afford an 11-*m*ethylene derivative (**14**). Carbocation-mediated processes in bridged compounds of this type are likely to give rearrangement byproducts. Kugita and Takeda[124] isolated from the thionyl chloride route an unstable chloride (**203**), and the indenotetrahydropyridine (**204**). Other reports[30,96a,125] of unidentified products from these reactions resulted in an investigation[126,127] of both pathways (Scheme 4.20).

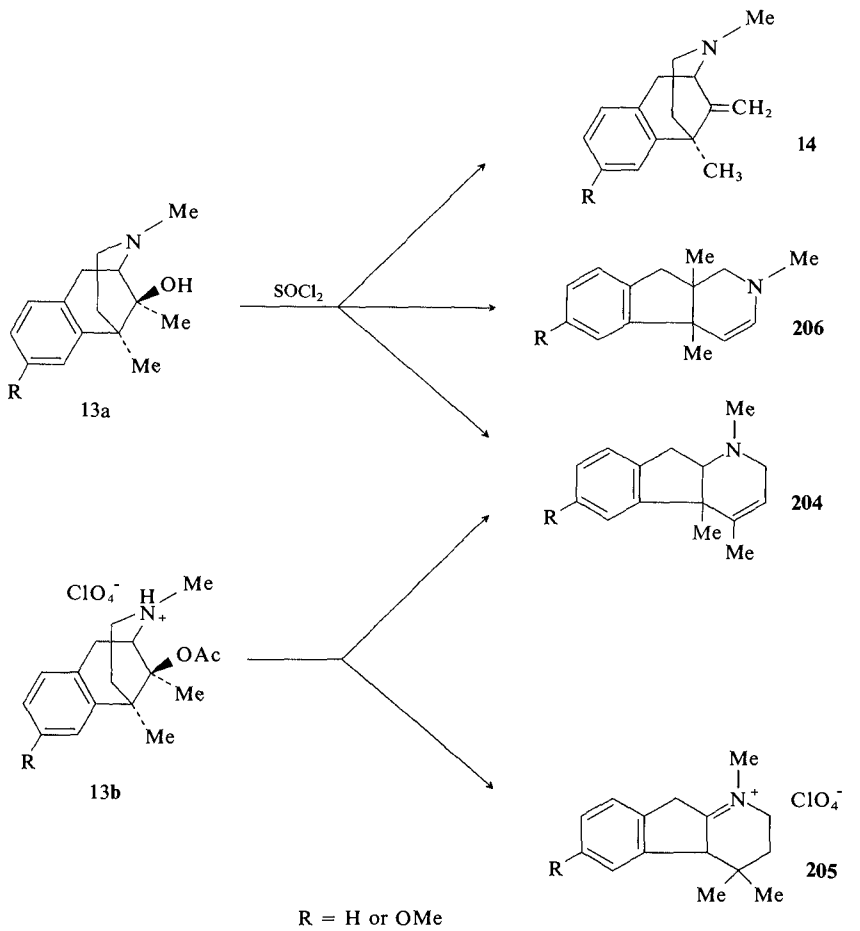
Thionyl chloride treatment of **13a** gave, in addition to the required 11-methylene intermediate (**14**), the indenotetrahydropyridines **204** and **205**, but **203** was not detected. Controlled pyrolysis of the perchlorate of **13b**, on the



203



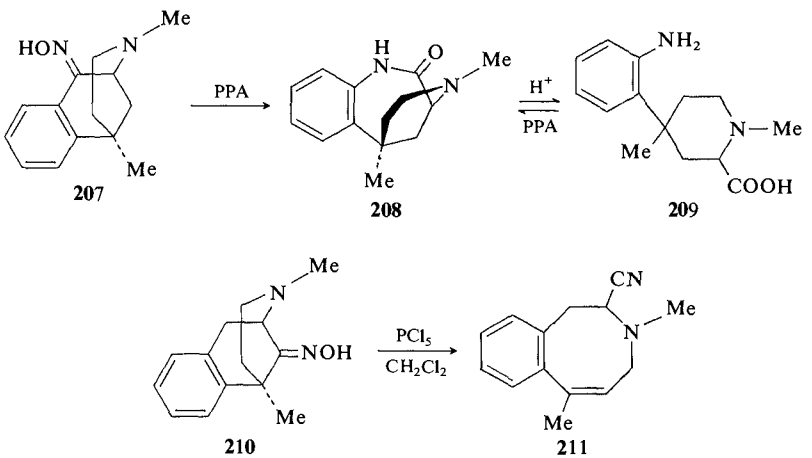
204



Scheme 4.20

other hand, gave no **14** but **204** together with a new indenotetrahydropyridine **205**. The products are readily rationalized by conventional carbocation mechanisms.

Beckmann rearrangement[128,129] of the oxime of the 1-oxobenzomorphan **207**, gave 1,3,4,5,6,7-hexahydro-4,7-dimethyl-3,7-methano-1,4-benzodiazin-2-one (**208**) in 59% yield. On hydrolysis this B-ring expanded benzomorphan analog affords the 4-arylpiperidinecarboxylic acid **209**. The oxime from the 11-oxobenzomorphan, **210** undergoes a second-order Beckmann rearrangement to the 3-benzazocine-2-carbonitrile **211** also in 59% yield.[130]



4.3.9. Benzomorphan Ring Variants

Numerous compounds analogous[3,134a] to benzomorphans with changes in the rings or the position of the hetero-atom have been reported. Few possess significant analgesic properties. Table 4.1 lists examples of such structures.

4.4. SPECTROSCOPY

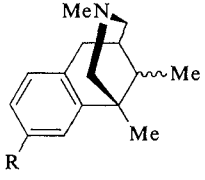
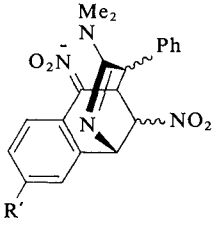
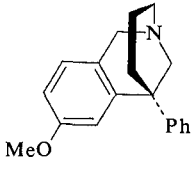
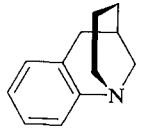
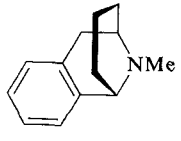
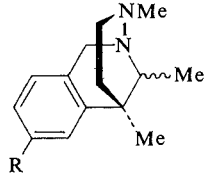
In this section only those studies offering collations of spectroscopic data useful for characterization purposes, or designed to establish conformation or configuration, will be discussed.

4.4.1. ^{1}H-NMR

Early benzomorphan syntheses afforded compounds with 6-alkyl or 6,11-dialkyl substituents. As the configuration of an 11-alkyl substituent in benzomorphan affected pharmacological responses both qualitatively and quantitatively, it was important to have a means of establishing geometry. May's group[111] employed methiodide formation rates and ^{1}H nmr in fixing configuration about C-11 in 8-hydroxy-3-methyl-6,11-dialkylbenzomorphan. In 3,6,11-trimethylbenzomorphan, the 11α-methyl signal appeared 25 Hz upfield of the corresponding 11β-methyl resonance, suggesting significant diamagnetic shielding of the 11α-methyl protons by the aromatic ring (**212**).

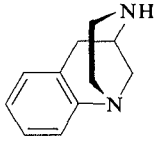
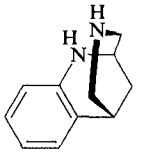
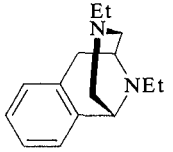
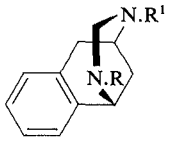
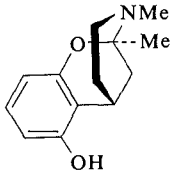
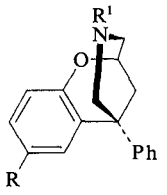
Similarly,[31] in 6-phenyl-11-alkyl derivatives, May's observations were confirmed. Both studies hinted of 11α-methyl proton shielding from the 1,3-diaxial relationship with the nonbonding electrons of nitrogen in the free

Table 4.1

Structure	Pharmacology	References
 R = H, OH, OMe	Maximum analgesic potency = codeine[a]	130a 131 132
 R and R' = H or NO_2	Some antagonist activity	53 54 55
	Inactive	132a 132b 133
	Not reported	163
	Not reported	164 164a
 R = OH, OMe	Not reported	134 (for a review on the synthesis of benzodiazocines, see ref. 134a)

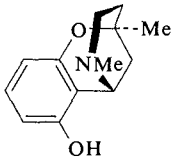
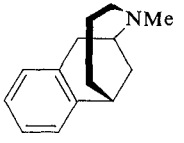
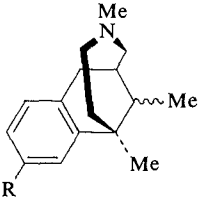
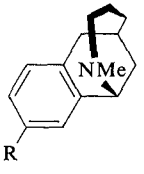
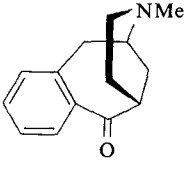
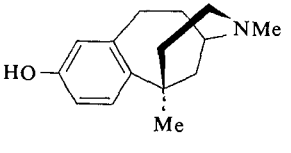
(continued)

Table 4.1 (continued)

Structure	Pharmacology	References
	Not reported	135
	Agonist/antagonist	136 212
	Not reported	137
	Not reported	138 138a
	Not reported	139
	Not reported, "analgesic"	140
	Weak analgesic, eliminated when phenolic OH is introduced	141, 142

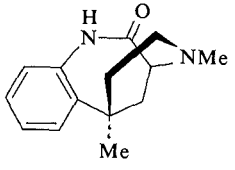
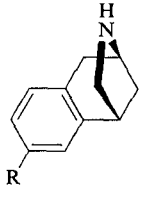
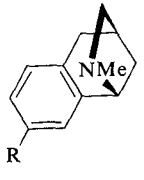
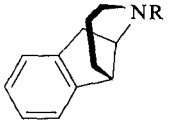
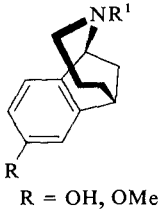
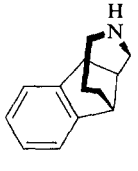
(continued)

Table 4.1 (continued)

Structure	Pharmacology	References
	Not reported, "analgesic"	140, 143
	Analgesic[b] ≡ morphine	144, 145, 199
 R = H, OH, OMe Also, (+) and (−)	Equivalent morphine as an analgesic[a] in mice, some members do not suppress morphine abstinence in the monkey	145 146 147 148 193 194 195 213 214 215
 R = H, OH, OMe	Weak analgesic[a]	149
	Not reported	165
	Weak analgesic	166

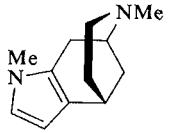
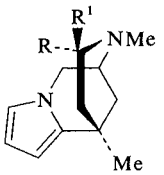
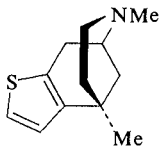
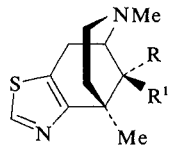
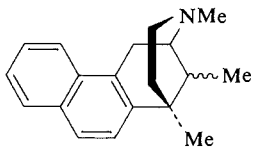
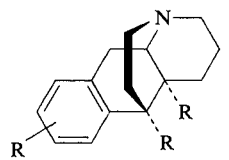
(*continued*)

Table 4.1 (continued)

Structure	Pharmacology	References
	Not reported	129
 R = H, OH, OMe	Weak analgesic[a]	149
 R = H, OH, OMe	Weak analgesic[a]	149
 R = H, OMe	Weak analgesic[b] ≃ one-third codeine	150, 151
 R = OH, OMe	Best ED_{50}^{b}, 12	152
	ED_{50}^{b}, 4.9; nondependent in mice and monkeys	153

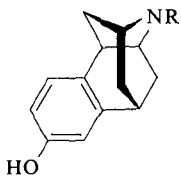
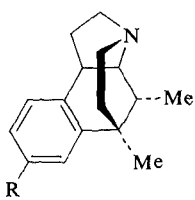
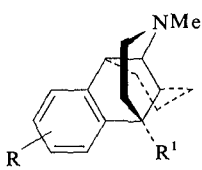
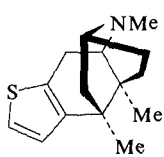
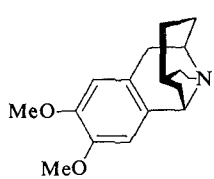
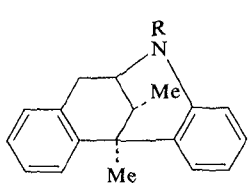
(continued)

Table 4.1 (continued)

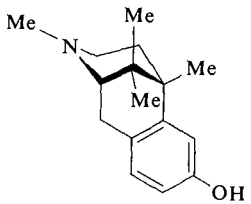
Structure	Pharmacology	References
	Not reported	154
 R = R′ = H, or R = Me, R′ = H	Not reported	155
	Weak[b]; no antagonist activity	156 157 158 196 see also 197
 R & R′ = H or Me	(R = Me, R′ = H) ×10 codeine MW	198
	Inactive	159
 R-wide claims	High potency claimed	160 160a

(continued)

Table 4.1 (continued)

Structure	Pharmacology	References
	Weak analgesics and moderate antagonists	161
	Inactive	167
 R = H, OMe; R′ = H, Me	Not reported	168
	Not reported	162
	Not reported	192
	Inactive	200 201

[a] Mouse tail pressure test.
[b] Mouse hot plate test.



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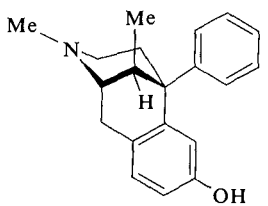

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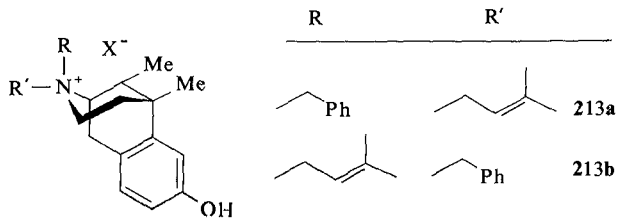
bases. Shift differences between protonated and nonprotonated forms for the 11α-Me (7–11 Hz) and 11β-Me ($\simeq$5 Hz) were smaller than might be expected for a regular piperidine chair, and it was proposed that a skew-boat conformation minimizing 1,3-diaxial interactions could explain this. The observation that the 11β-Me signal in **213** has an upfield shift similar to that of the 11α-Me indicated that the 6-phenyl ring was oriented perpendicular to the benzomorphan aromatic ring, resulting in a diamagnetic shielding of the 11β-Me group. Variable temperature ^{1}H-nmr confirmed this.

X-ray crystallographic studies confirmed the preceding conclusions.[169-171]

Diamagnetic shielding by the benzomorphan aromatic ring was also exploited[119] to determine configuration of 4- and 5-methyl substituents (**193** and **194**). An equatorial 4-methyl group on a regular piperidine chair resonates at δ0.6, whereas an equatorial 5-methyl signal occurs at δ1.0, uninfluenced by aromatic ring shielding.

Benzomorphans lacking a 6-substituent and diastereomeric about positions 1- and 2- have been reported.[172] The 1-position substituent configuration was fixed from the coupling constant between the protons at the 1- and 2-positions ($J_{H_{1\alpha}}$, H_2 = 6 Hz; $J_{H_{1\beta}}$, H_2 = 1.0 Hz). Other 1-substituted series have been examined in this manner.[115,116,128]

Configuration examination[173] by ^{1}H-nmr of the quaternary precursor of pentazocine (**213a** and **b**) and related compounds demonstrate that during quaternary salt formation, axial attack of the electrophile (from 3-methyl-2-butenyl bromide) occurs to yield predominantly **213b**. This was consistent with earlier observations.[174,175] An extensive study of the metazocines (base, HCl salt, and methiodide) has been published,[176] some results of which were later revised.[177,178]



4.4.2. ^{13}C NMR

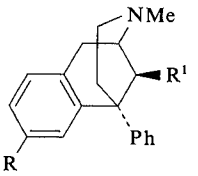
Benzomorphans variously substituted at C-6 and C-11 by methyl and at C-4 by cyano, alkyl, aralkyl, allyl, and benzyl and some quaternary salts, have been investigated[178] at 22.5 MHz in $CDCl_3$ solution. Conclusions regarding configuration and conformation paid particular attention to γ-shielding, *syn*-diaxially deshielding effects, *N*-lone pair orbital-shielding effects, and the anisotropic influence of the aromatic ring on ^{13}C signals.

4.4.3. ORD/CD

Benzomorphan pharmacodynamics is dictated by molecular geometry. (±)-11β-Alkylbenzomorphans are more active analgesics or mixed agonist/antagonists than their (±)-11α-alkyl counterparts, and the *levo* antipode is very largely responsible for the narcotic properties of both α- and β-racemates. This is hardly surprising, as α-(−)-8-hydroxy-3-methyl-6,11-diethylbenzomorphan has been shown to have a configuration identical to that of (−)-morphine.[179]

Casy and Parulkar[180] assigned from optical rotatory dispersion (ORD) curves the absolute configuration of α-(−)- and β-(+)-metazocine as bases, hydrobromides, and methiodides, and a comparison was made with the curves of levorphanol of known configuration.[181] The Cotton effects seen in all samples were attributed to the phenolic chromophore since midpoints between peak and trough wavelengths approximate to the uv-maxima of simple phenols. The sign of the Cotton effects is governed by the local geometry of the chromophore, thus reflecting stereochemistry at C-6 rather than C-11. α-(−)-Metazocine was assigned the absolute configuration 2*R*:6*R*:11*R* and the mirror image relationship between the α(−)- and β-(+)-metazocine curves fixed the α-(−)- and β-(−)-configurational relationship and indicated the C-11 had little influence on benzomorphan ORD characteristics in the 240–350 nm region. The configuration of β-(−)-metazocine was deduced to be 2*R*:6*R*:11*S*.

The absolute configuration of (−)-6-phenyl-11β-methylbenzomorphan has been shown to be identical to that of (−)-morphine.[31] An ORD-CD study[93] of (+) and (−)-6-phenylbenzomorphans lacking a C-11 substituent demonstrated the configurational relationship of the (−)-isomer of **214b** to that of **214a**. The absolute configuration of the latter has been established by X-ray crystallography of its *O-p*-bromobenzoate ester.[31,182] Although curves are complicated by the presence of a second aromatic ring, compound **214c** lacking the 8-hydroxyl function affords curves without $\pi \rightarrow \pi^*$ transitions (above 280 nm). In all three compounds (**214a**, **b**, and **c**), there are three well-defined, negative Cotton effects in the 250–270 nm region, confirming that their absolute configurations are identical.



214 **a** R = OH, R′ = Me
b R = OH, R′ = H
c R = H, R′ = H

There were similar findings[183] from the circular dichroism (CD) curves of (−)-6-ethyl- and (−)-6-phenylbenzomorphan, and although the geometry of the C-**11** substituent has little effect on ORD curves, in the CD curves below 240 nm, large differences in amplitude and rotational strength were observed. In the 6-phenyl series, intense Cotton effects are seen at 191 nm.

4.5. X-RAY STUDIES

Several X-Ray crystallographic studies affording valuable geometric, bond-length and bond-angle data have been reported.[169,171,179,184] Clarke *et al.*[31,182] generated configurational and conformational data for 3,11-dimethyl-8-hydroxy-6-phenylbenzomorphan and offered a relationship between it, other synthetic analgesics, and the enkephalins. Single-crystal analyses on HBr salts of racemic methanobenzazocines and other structures related to benzomorphans have been performed.[185]

4.6. STRUCTURE–ACTIVITY RELATIONSHIPS

The relationship between structure and pharmacological activity of benzomorphans reported to 1966 has been reviewed by Eddy and May.[1] Molecular geometry is the major structure-activity influence, although the nature of the *N*-substituent imparts significant qualitative and quantitative variations in biological response. As with most other analgesic series related to morphine, most studies report analgesic agonist and antagonist responses in a variety of tests, with "side effects" such as dependence being considered under specific circumstances and respiratory depression being considered only rarely. There are great difficulties, as a consequence of this, in collating biological responses and structure in a multiple-receptor context.

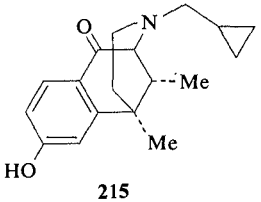
In morphine and morphinan series, the introduction of a hydroxyl group in the position equivalent to C-8 causes a significant increase in analgesia and the same is generally but not always true for benzomorphans. Acetylation of the 8-OH maintains or increases analgesic potency, but formation of the methyl ether reduces activity. Other groups at C-8 (e.g., halogen) usually result in a significant reduction in activity,[85] although a group capable of hydrogen bonding such as NH_2 afforded a good level of agonist activity.[86]

For many years the presence of a substituent at C-6, the "quaternary carbon atom" was considered an essential prerequisite for analgesic activity. The synthesis of compounds with hydrogen at the C-6 bridgehead position demonstrated that that conclusion was incorrect and that good analgesic activity may be retained without C-6 being quaternary.[43,44] However, a methyl function at C-6 usually enhances activity and the level of activity is retained with small alkyl functions. More bulky substituents, such as *t*-butyl reduces the level of activity considerably.[29] Potency may be enhanced by COOEt or $CO{\cdot}N(Me)_2$ at C-6.

The configuration of an 11-alkyl substituent (p. 185) has a marked influence on pharmacological responses. Me, Et, and *n*Pr groups oriented α are about one fifth as active as correpsonding 11β-epimers. However, compounds lacking a substituent at C-11 still exhibit good levels of activity. A ketonic group at position 3 on a β-alkyl side-chain increases activity to about 100 × morphine.[110] Although a C-8 OH normally enhances activities in these series, this does not occur when an 11-OH group is present.

Activities no greater than that of morphine have been observed in benzomorphans bearing 2-, 4-, or 5-substituents, and in general, substitution in these positions tends to reduce responses in 6-alkyl and 6,11-dialkyl species (p. 193).

A ketonic function at C-1 may afford, dependent upon other substituents, analgesics that neither precipitate nor depress an opiate abstinence response. Ketocyclazocine[213] is an example of such a compound that is believed to act at κ receptors rather than the usual morphine receptors. These will be discussed later in Chapter 12 (p. 405).



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Profound effects on pharmacological activity in benzomorphans are exerted when changes in the *N*-substituent are made (p. 176). These changes parallel those seen in morphinan and morphine series. Although agonist potency increases somewhat when the *N*-substituent chain length is extended from Me to hexyl (with a slight reduction for Et), *N*-phenethyl affords a significant increase in agonist potency.[56] More important are the changes that occur on the introduction of so-called antagonist substituents, such as allyl, dimethylallyl, cyclopropylmethyl, and cyclobutylmethyl, when resultant compounds are mixed agonist-antagonists. These effects were discussed earlier (p. 178), and their significance to receptor theory is discussed on p. 405.

A variety of instrumental and chemical methods have been employed to establish the stereochemistry of benzomorphans (pp. 203–205). Configuration

about C-11 has been discussed (p. 185) and as a general rule 11β-alkyl derivatives are up to 5× more effective as analgesics than their 11α- counterparts. Bridgehead (C-2, C-6) geometry is of much greater significance.

Several benzomorphan series have now been resolved into their (−)- and (+)-antipodes, and ORD/CD studies (p. 204) have demonstrated that (−)-series have a configuration identical to (−)-morphine. In addition, Sawa *et al.*[202,203] have prepared (−)- and (+)-8-hydroxyl-3-methyl-6,11-diethylbenzomorphans from thebaine and sinomenine, respectively. It is largely in the (−)-series that narcotic properties reside, but some curious activities are seen in (+)-series.

May and Eddy[186] were first to report that (−)-8-hydroxy-3,6,11α-trimethylbenzomorphan was responsible for the analgesic activity exhibited by the corresponding racemate, and later[187] they noted the high potency without physical dependence capacity (2 × morphine; MHP) of the (−)-6,11α-dimethyl and diethyl compounds. In contrast to all earlier observations, certain (+)-isomers were shown to be codeine-like in both analgesia and physical dependence properties.[188] May's group[188] further noticed that other (−)-isomers in the 3-methyl-6,11-dialkyl and 6-alkyl series not only failed to suppress abstinence in morphine-dependent monkeys, but behaved as morphine antagonists. In contrast, (+)-isomers possessed mild physical dependence capacities and appeared, in the racemate, to be antagonized by their (−)-counterparts. Furthermore, if C-6 bears hydrogen rather than alkyl, the racemate becomes a mixed agonist/antagonist, with each isomer exhibiting both agonist and antagonist properties. although the former is almost 4× greater in the (−)-isomer than in the (+)-isomer.[189] In the 8-hydroxy-3,6-dimethyl-11-propyl series,[190] the (−)-11α-propyl isomer was equipotent with morphine as an analgesic (MHP and Nilsen) and the (−)-11β-epimer equipotent po, but significantly more active sc. None of the isomers, (+)- or (−)-, α- or β-, exhibited a physical dependence capacity; on the contrary, the (−)-11β-propyl isomer exacerbated withdrawal. The (+)-isomer did not exhibit significant analgesic properties. Clearly, the (−)-11β-propyl derivative demonstrates potentially useful agonist–antagonist properties.

Benzomorphans bearing antagonist *N*-substituents[191] show a similar separation of activities. Where antagonist properties are found predominantly within the (−)-isomers, some activity is seen in the (+)-antipodes. However, the level depends very much upon the nature of the *N*-substituent and the geometry at C-11. In several series, activity of the (−)-isomer is consistently more than 2× that of the racemate, suggesting antagonism of the analgesic properties of the (−)-isomer by the (+)-isomer.

An extensive investigation of 6-phenylbenzomorphans[93] also showed (−)-isomers to be considerably more potent than corresponding (+)-isomers. However, the absence of an 11-alkyl substituent reduces considerably the activity difference. (−)-Compounds in series with alkyl at C-6 and with

antagonist *N*-substituents are better analgesics than those without a C-6 function. Where the 11β-side chain possesses a 3-carbonyl function,[110] (−)-isomers show almost all the analgesic activity of the racemate, an observation that remains when the carbonyl is reduced to the corresponding propanol.[109]

Extensive studies of *N*-tetrahydrofurfuryl optical isomers have been published,[79,80] and some homobenzomorphans have been resolved and their activities evaluated.[147]

The benzomorphans illustrate the problems surrounding considerations of the nature of opioid receptors. How does one reconcile agonist activities, albeit of apparently different types, in both antipodes of a structure? There appears to be a complex interdependence of substituent effects, and subtle changes in any substituent may alter profoundly the complex of biological responses. Within this series compounds of high analgesic activity and negligible physical dependence capacity occur. However, from a clinical standpoint, it is to be regretted that more compounds have not been examined for their effects on respiration.

Two groups of workers[207,208] have suggested that binding sites selective for benzomorphans occur in rodent-brain membranes. Chang *et al.*[207] drew their conclusion from [^{3}H]diprenorphine-displacement studies. Diprenorphine appears to bind to a receptor that differs from μ (morphine) and δ (enkephalin) receptors but to which benzomorphans bind with high affinity. Although this observation would seem to cloud the opioid-receptor issue, it may suggest a selective receptor conformational adaptation.

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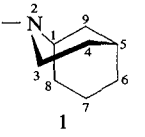
5

Arylmorphans and Related Compounds

5.1. INTRODUCTION

In the previous chapter benzomorphan analgesics were considered. They may be thought of as sterically constrained piperidines bearing an axial aromatic ring. Without the fused aromatic ring a 2-azabicyclo[3.3.1]nonane structure (**1**) remains for which the trivial name *morphan* was suggested by Robinson.[1]

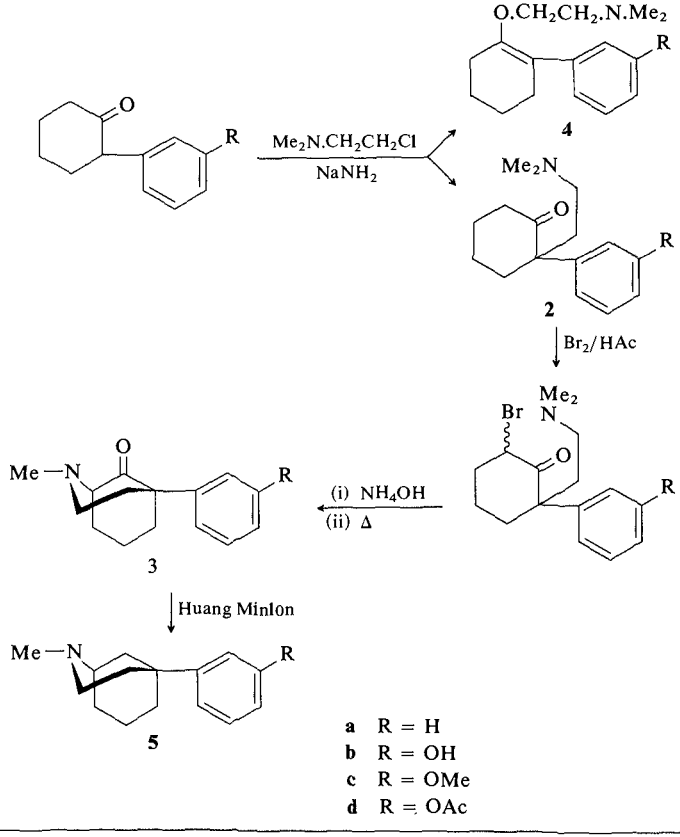


1

Clearly, aryl groups may be positioned on the morphan nucleus in several positions to afford possible analgesic relationships for the nitrogen and aromatic pharmacophores. There have been relatively few studies of arylmorphans and related structures; those compounds with aryl substituents at C-5 (i.e., equatorial on a partially constrained piperidine) have received most attention.

5.2. SYNTHESIS OF 5-ARYLMORPHANS

5-Arylmorphans were prepared first by the NIH group[2,3] following a route similar to a tetralone synthesis for benzomorphans (Scheme 5.1). Alkylation of 2-(3-methoxyphenyl)cyclohexanone by 2-chlorodimethylaminoethane and sodamide afforded the aminoketone (**2**), which was converted to 2-methyl-5-phenylmorphan (**5**). Yields of **5** were relatively low, due largely to the formation of *O*-alkylated material (4) (75%). Improvement of the yield of *N*-alkyl product to 40% was achieved[4] by performing the reaction in DMF/NaH with chlorethylamine hydrochloride rather than the volatile base.



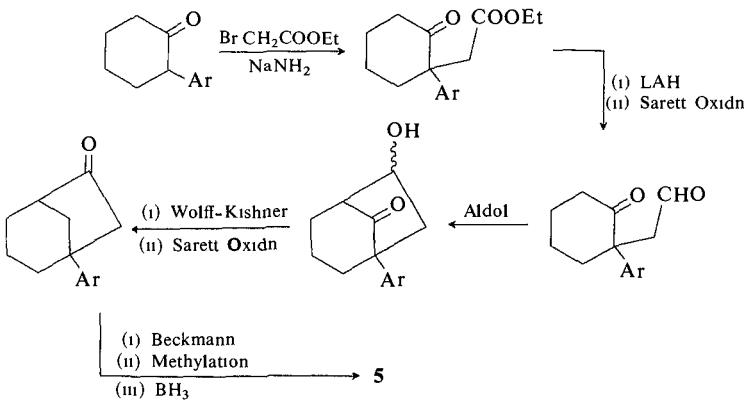
Scheme 5.1

An alternative synthesis[4] giving an alkylation yield of 80% is outlined in Scheme 5.2. Here the Beckmann rearrangement proceeds in only 8% yield, thus reducing the overall yield of **5** to around 1%.

A much improved route[5] to 5-phenyl-2-methylmorphan (**5a**) exploited readily available 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (**6**) as starting material (Scheme 5.3). The enamine (**7**) was cyclized to the unsaturated phenylmorphan (**8**) in 91% yield by H_3PO_4/HCOOH at ambient temperature over 66 h and this was reduced to **5a**.

5.3. PHARMACOLOGICAL ACTIVITY AND STEREOCHEMISTRY

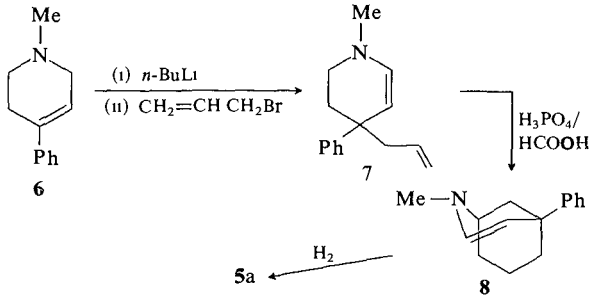
Racemic **5b** and **5d** exhibited analgesic activity equivalent to that of morphine (sc, MHP) with a significant reduction in overall toxicity. Oral



Scheme 5 2

activities of **5b**, **c**, and **d** were equivalent to the potency of pethidine, again with reduced general toxicity.

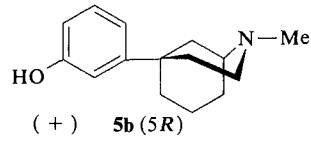
Resolution of racemic 5-(3-hydroxyphenyl)-2-methylmorphan (**5b**) has been effected with *d*-mandelic acid.[6] The (+)-phenylmorphan (**5b**) was found to possess a fourfold greater activity (ED_{50}, 0.4 mg/kg, MHP) than the racemate or morphine. In addition it was capable of substituting for morphine in the Rhesus monkey. The (−)-antipode has an analgesic potency about equivalent to that of morphine (ED_{50}, 1.5 mg/kg, MHP) and is a moderately potent antagonist (abstinence precipitation, monkey, 8 mg/kg). It possesses only a minor PDC.[4,29] Because the racemate is a morphine-like analgesic, there would appear to be some antagonism of the (+)-enantiomer by the (−)-enantiomer.



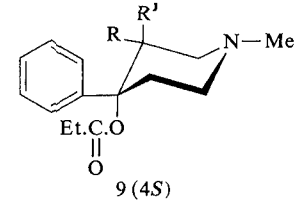
Scheme 5.3

A comparison of the absolute configurations of (−)-**5b** and morphine is not possible because of the difference in the orientation of their aromatic rings. Cochran[7] investigated the absolute configuration of (−)-5-(3-hydroxyphenyl)-2-methylmorphan by single-crystal, X-ray analysis of the HBr salt and found it to be 1*R*, 5*S*. He discovered that both rings of the morphan-fused system existed in chair conformations with the 2-methyl and 5-aryl substituents equatorial.

A comparison[7] of the geometry of the more analgesically potent enantiomer, (+)-**5b** (1*S*, 5*R*), with those of α- and β-prodine (**9**) suggested that the same enantiotopic edge of the piperidine ring bears substitution. It has been established[8] that compounds with 4*S* configuration in the prodines possess significantly higher levels of analgesic activity than the corresponding 4*R* isomers. Thus, it is possible that the arylmorphans and prodines offer the same leading edge when binding to the appropriate receptor.



(+) **5b** (5*R*)



9 (4*S*)

R = Me, R^1 = H. α-Prodine

R = H, R^1 = Me. β-Prodine

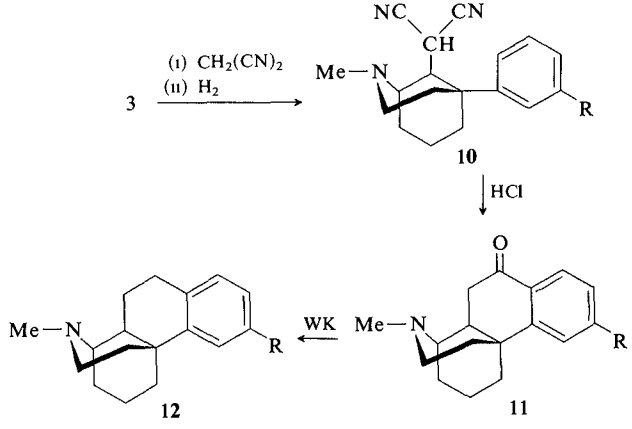
Arylmorphans possessing a *m*-OH group on the 5-phenyl ring have been converted by standard means to *N*-propyl, *N*-allyl, and *N*-CPM derivatives in the (+) and (±)-series.[9] None of the compounds with "antagonist" *N*-substituents exhibited significant antagonist properties and, at best (*N*-allyl), gave an analgesic activity equivalent to pentazocine. This pharmacological profile is similar to that seen with 4-phenylpiperidines. Arylmorphans lacking a *meta* substituent in the 5-aryl ring have also been synthesized[2].

5.4. SUBSTITUTED 5-ARYLMORPHANS

The observation[28] that 4β-(*m*-hydroxyphenyl)1,3β,4α-trimethylpiperidine was a "pure" antagonist and that this unusual property for a piperidine appeared to be endowed by the 3-Me substituent, prompted May *et al.*[29] to explore corresponding arylmorphans with Me in the equivalent position (C-9 or C-4). Because of the availability of a synthetic precursor, C-9 was chosen. Intermediate **3** (R = OMe) was prepared according to Scheme 5.1 and converted to the corresponding 9-methylene compound by a modified Wittig reaction.[30,31] Standard HBr treatment cleaved the methyl ether to give 2,9α-dimethyl-5-(*m*-hydroxyphenyl)morphan. The 9α-assignment for the methyl

group was from ^{1}H nmr Eu(Fod)$_3$ data. Attempts to prepare the 9β-Me epimer, which bears a closer geometric relationship to the antagonist 3β-methylpiperidine, failed. Only the (−)-enantiomer exhibited analgesic activity (≃ codeine, MHP) and this contrasts markedly with activities observed for the enantiomers of **5b** that lack the 9-Me function. However, the activity resembles that observed by Zimmerman *et al.*[28] in that in the (+) series the introduction of a 9-Me group gave rise to antagonist activity in the RTF/A test versus morphine.

5-(3-Methoxyphenyl)-2-methylmorphan-9-one (**3c**, Scheme 5.1) serves as an intermediate in the synthesis of arylmorphans. It undergoes a Knoevenagel reaction with malononitrile[10] readily to give 84% of the corresponding condensation product, which may be hydrogenated to the dinitrile **10**. The bridged 5-arylmorphanones (**11a** and **b**) were derived from **10** by acid treatment and removal of the carbonyl afforded **12a** and **b** corresponding to **12a** reported earlier.[2] These compounds (morphinan isomers) were, at best, weak analgesics.

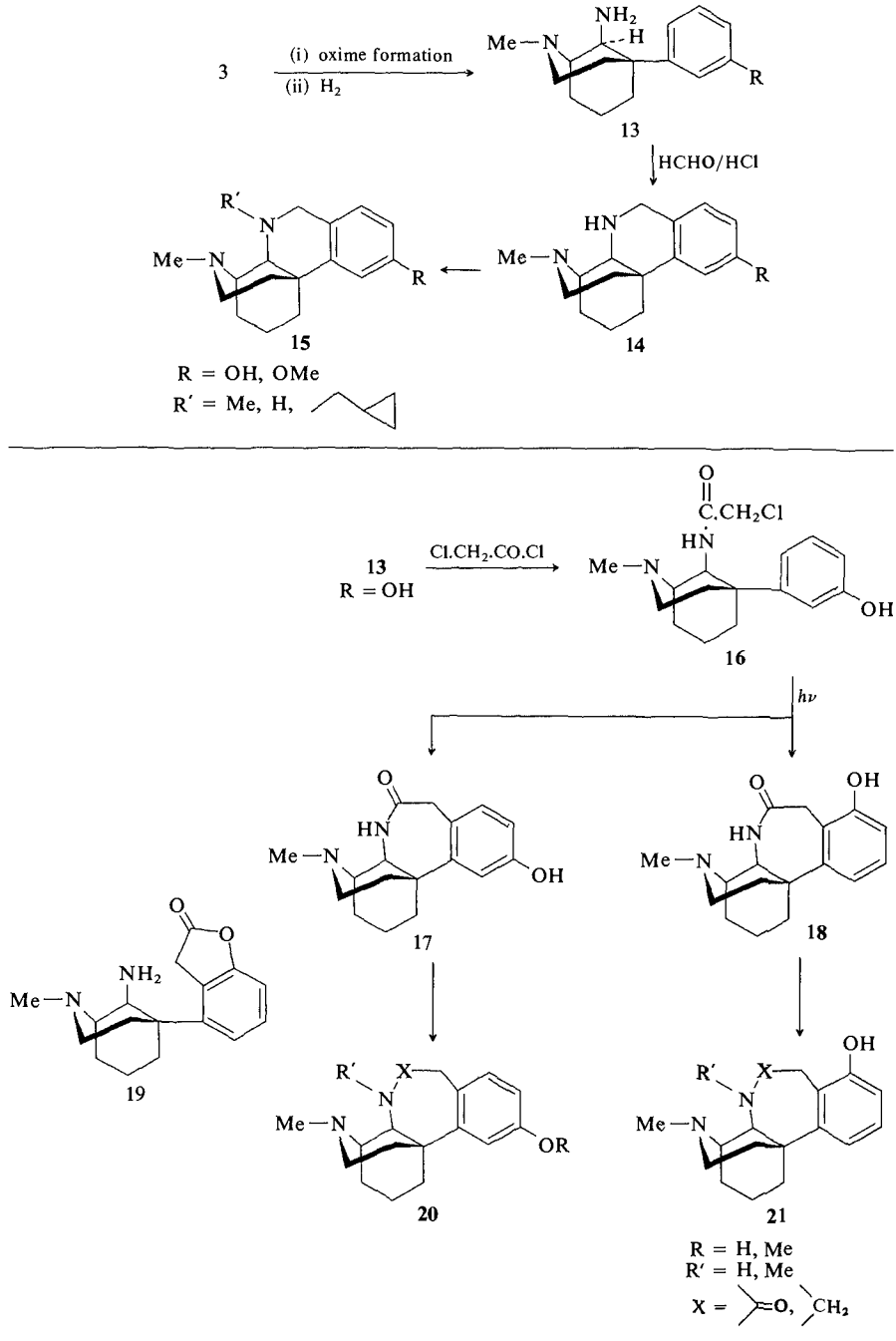


a R = H
b R = OH
c R = OMe

A similar series of bridged arylmorphans was prepared via the 9-aminoarylmorphan (**13**) formed from the oxime of **3c**. Ong and May[11] assigned the 9-amino group of **13** as *cis* to the aromatic ring by virtue of steric approach control during the hydrogenation process. Pictet-Spengler cyclization of **13** afforded the iminoethanophenanthridine (**14**), which was converted by conventional chemistry to a range of derivatives, **15**.

As an analgesic, **13** was inactive and the best compounds **14** (R = OH) and **15** (R = OH; R^1 = CPM) were only one-seventh codeine (MHP).

Extending their study of arylmorphan bridging reactions Ong and May[12] chloracylated the 9-aminoarylmorphan (**13**, R = OH) and hydrolyzed selectively the phenolic ester to give **16**. Irradiation of a dilute aqueous solution

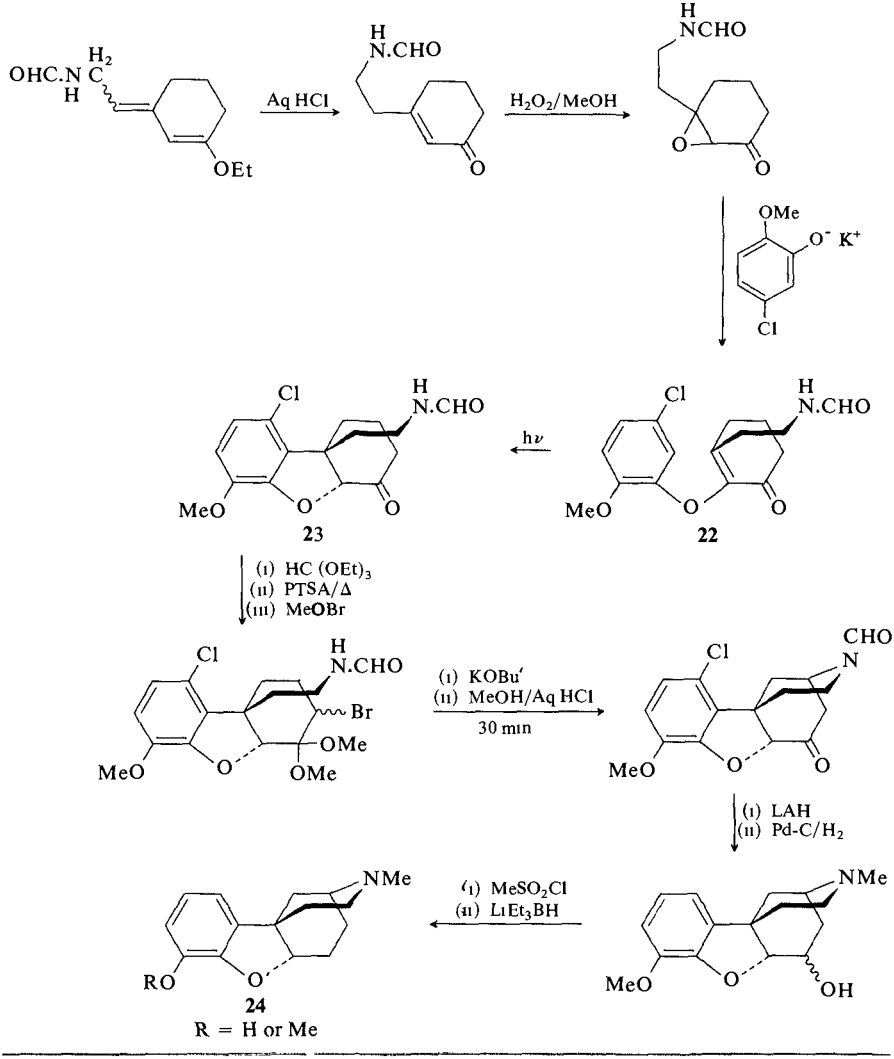

3
(i) oxime formation
(ii) H_2
13
HCHO/HCl
14
15
R = OH, OMe
R′ = Me, H,
13
R = OH
$Cl.CH_2.CO.Cl$
16
$h\nu$
17
18
19
20
21
R = H, Me
R′ = H, Me
X =

Scheme 5.4

of **16** hydrochloride gave a high yield of **17** and **18** (1 : 1) from *ortho* and *para* cyclization within 90 min. The photocyclization was pH independent. The products were converted to a selection of reduced pyridobenzazepines (**20** and **21**). Rearrangement of **18** to the arylmorphan **19** occurs in aqueous acid.

No pharmacological data have been reported for these series.

In 1981 Portoghese[32] proposed the existence of two aromatic ring binding sites on the morphine μ-receptor. These may be the individual recognition sites for the tyrosine (T) and phenylalanine (P) moieties of the endogenous



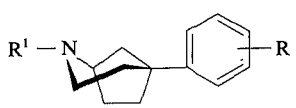
Scheme 5.5

enkephalins. Thus, the T-site would accept axially oriented aryl groups on the piperidine ring of rigid opiates such as morphine, whereas the P-site would accommodate the equatorial aryl functions that occur in 4-phenylpiperidine analgesics.[33]

A study of the limits of rotational mobility of the aromatic ring relative to the piperidine unit and commensurate with opioid pharmacological responses has been commenced at NIH.[34] The importance of the torsion angle between these moieties has been a point of comment in the prodine series.[35,36] By formally joining the 2′ position of the phenyl ring of a 5-arylmorphan to the 6-position of the morphan moiety, a rigid congener would result (**24**). The NIH synthetic pathway to such a compound is outlined in Scheme 5.5. The key step is a photocyclization from **22** to the partially reduced dibenzofuran **23**.

On the basis of X-ray data the target compound (±)-2,3,4,5,6,6a-hexahydro-3-methyl-8-hydroxy-1H,4,11b-methanobenzofuro[3,2d]azocine (**24**, R = H) has a torsion angle between the phenyl ring and the plane of the piperidine ring of 86°. In view of the lack of analgesic, antagonist, and receptor binding capacity of **24** (R = H), it would seem that such an angle is incompatible with opioid responses. 5-Arylmorphans have five other possible sites for oxygen bridge attachment, and biological data on these may help to clarify the torsion angle question.

5.5. AZABICYCLO[3.2.1]OCTANES



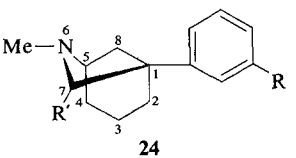
23
R = OH, OMe, OAc
R^1 = various

The good levels of analgesic activity exhibited by (−)-, (+)-, and (±)-5-(3-hydroxylphenyl)-2-methylmorphan (**5b**) and the clinical potential of the (+) enantiomer prompted interest in related bicyclic structures. Replacement of the cyclohexane ring by cyclopentane will increase molecular rigidity and will change, somewhat, the spatial relationship between the nitrogen and aromatic ring pharmacophoric centers. Synthetic approaches[13-15] to the 5-aryl-2-azabicyclo[3.2.1]octanes represented by the general structure **23** follow those for arylmorphans by May and Murphy.[2,3]

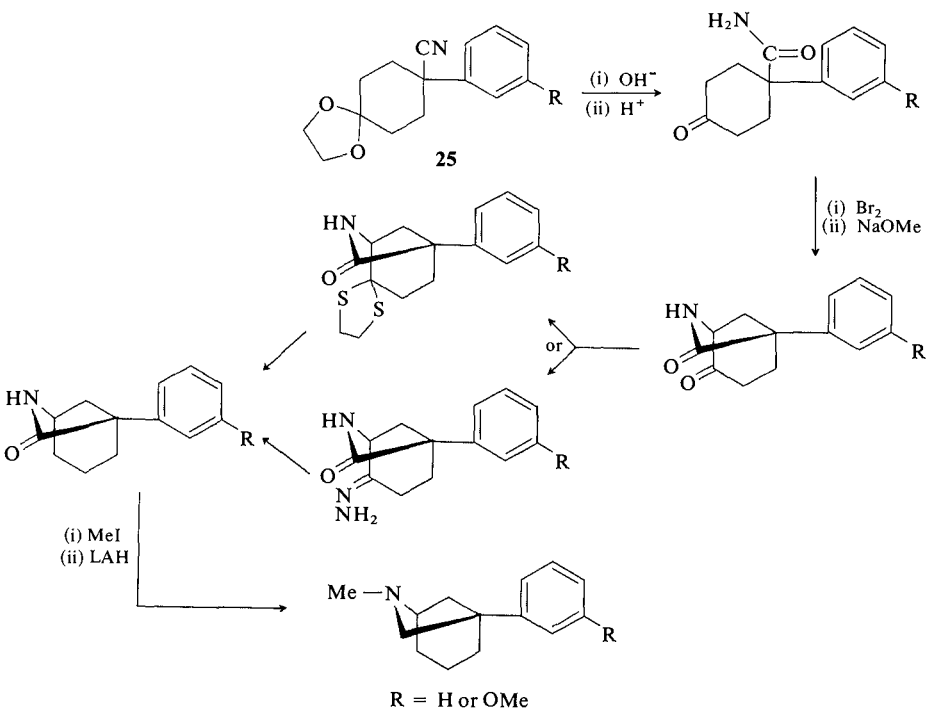
Most compounds tested in these series were without significant analgesic activity in the RTF assay but they often exhibited good inhibition in the MW test. This has suggested possible mixed agonist/antagonist activity. In the *meta* substituted 5-aryl series, **23** (R^1 = CH_2CH_2.Ph; R = OH) was about $\frac{1}{2}$ ×

morphine (RTF, ED_{50} 6.45 mg/kg) and appeared to be devoid of a PDC. Acetylation of the phenolic group increases analgesia (RTF) almost threefold. The best *para* substituted 5-arylazabicyclooctanes in this series were **23** (R = OH; R^1 = .CH_2.CH_2Ph, or .CH_2CH_2.CO.Ph-p-F), but they were found to bind only weakly to opioid receptors. In view of these relatively low levels of biological activity it is surprising that the series has been used as a model for theoretical systematic drug design.[37]

Isomeric 1-aryl-6-azabicyclo[3.2.1]octanes (**24**) that possess a five-membered heterocyclic ring and that may be thought of as bridged analogs of profadol[16] have been described and evaluated for analgesic responses.[17-20] Synthesis was from a previously reported arylcyclohexanone ketal (**25**) according to Scheme 5.6.



24

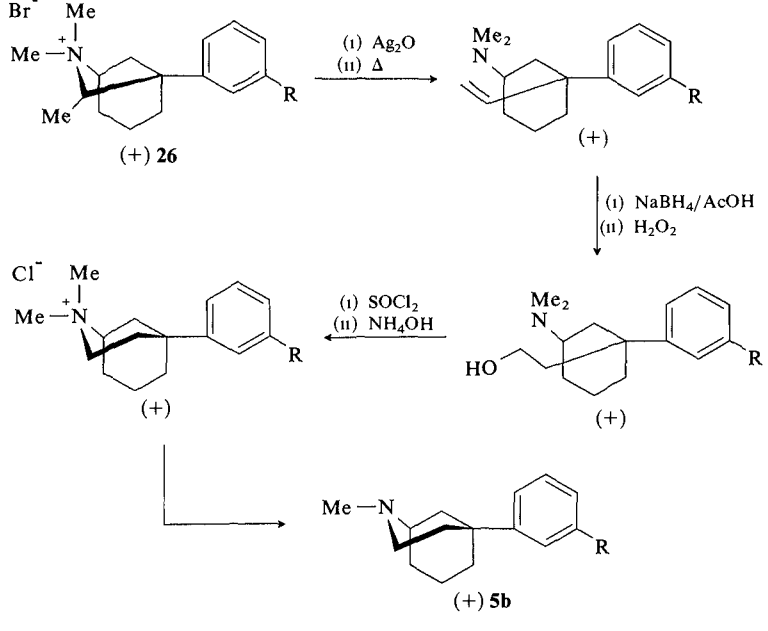


Scheme 5.6

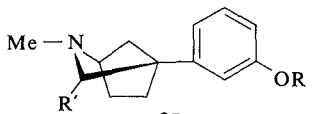
Activities in the MW and MHP tests for (±) **24** (R = OH; R^1 = Me) suggested a codeine-like analgesic. The racemate gave rise to only a mild PDC, whereas the (+)-isomer produced a significantly greater level of morphine-like dependence with analgesia about $\frac{1}{2}$ × morphine. Interestingly, the (−)-enantiomer was devoid of analgesic activity. This observation is in marked contrast to findings with arylmorphans (p. 217).

An X-ray study[20] of (+)-**24** (R = OH; R^1 = Me or H) (1.*R*) suggested a configurational relationship between it and (+)-**5b** (5.*R*) (p. 218). Thus, the dominant biological activity resides in compounds that are stereochemically related. This relationship was confirmed by the chemical conversion, with retention of configuration, of the quaternary 1-aryl-6-azabicyclo[3.2.1]octane (**26**) to (+)-**5b**, Scheme 5.7.

A methyl substituent at C-7 in this series of azabicyclo[3.2.1]octanes invariably increases both agonist and antagonist responses; both 7-*endo* and *exo* methyl substituents are effective in this regard. Because of the similarity in onset, peak levels and duration of these responses in both 7-Me and 7-H derivatives, it is likely that the 7-Me group is involved in some way in events at the receptor. No activity is observed in 8-*endo* or *exo* methyl derivatives.

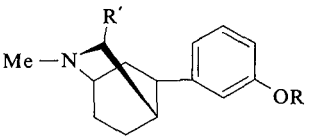


Scheme 5.7



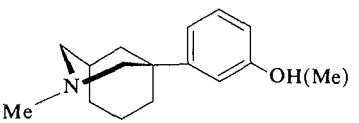
27

R = H or Me
R′ = H or Me (21)



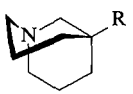
28

R = H or Me
R′ = H or Me (19)



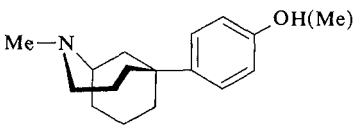
29

(22)



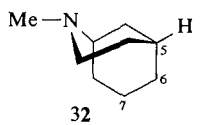
30

R = H, Me, Et (23)



31

(24)



32

(25, 38, 39, 40)

5.6. OTHER ANALOGS

4-Phenyl-2-azabicyclo[2.2.1]heptanes (**27**) have been synthesized via conventional routes by Takeda's group[21] as an extension of their arylmorphan and arylazabicyclo[3.2.1]octane studies. When R = H no analgesic activity was exhibited in the MW test; however, curiously, the corresponding methyl ethers [e.g., **27** (R = Me)] were about $\frac{1}{4}$ × pentazocine as agonists. Some derivatives were moderate antagonists (≃ pentazocine).

4-Aryl-2-azabicyclo[2.2.2]octanes (**28**) show a similar pattern of activities.[19] Although these compounds are not analgesic in the MW test, some of them (**28**, R and R^1 = H; and R = H. and R^1 = Me) have pentazocine-like antagonist properties.

Displacement of the nitrogen from its morphan position, as in the 1-phenyl-3-azabicyclo[3.3.1]nonanes (**29**), afforded compounds without MW analgesic activity, but where, again, some antagonist activity was detected.[22]

Although isomorphans with bridgehead nitrogens (**30**) have been synthesized,[23] none have appropriately positioned aryl substituents.

During early studies by May,[24] 6-aryl-2-azabicyclo[4.3.1]decanes (**31**) were synthesized following the route illustrated in Scheme 5.1, but no analgesic properties were found in the few compounds tested.

The necessity for having an appropriately positioned aromatic ring on a morphan nucleus for narcotic analgesic activity has been demonstrated.[25] 2-Methylmorphan (**32**) and the corresponding 6- and 7-enes were found to be devoid of MHP activity. Several substituted analogs of **31** have been reported more recently.[38-40] Some of these were synthetic precursors of benzomorphan-like compounds with a heterocyclic A-ring.

5.7. SUMMARY

Arylmorphans and closely related compounds are capable of producing analgesia with potencies at least equivalent to the potency of morphine. There appears to be a stereochemical relationship between (+)-5*R*-arylmorphans and 4*S*-prodines; however, the orientation of the aromatic ring in 5-arylmorphans (*eq.* piperidine chair) differs fundamentally from that in benzomorphans (*ax.* piperidine chair). In spite of this their analgesic potencies are similar. Portoghese[26,27] has suggested that these activities may be explained by a pivot model receptor (p. 476), where fixing of the *N*-pharmacophore at the receptor permits two possible modes of π-receptor interaction. More recently,[32] he has proposed the existence of two aromatic ring receptor binding sites. This model could imply, of course, an adjustment in receptor conformation to accept either aromatic group orientation, each mode of binding leading to a similar gross response.

Before meaningful structure–biological activity correlations may be drawn in these series many more arylmorphan studies are needed. Alternative arrangements of the aryl group relative to nitrogen require exploration, as does the necessity for a 3 aryl oxygen function.

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6

Pethidine and Related 4-Phenylpiperidine Analgesics

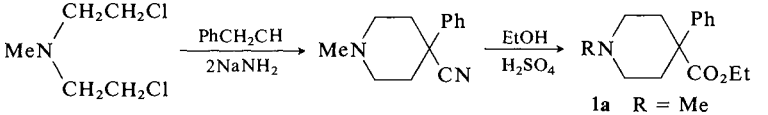
6.1. INTRODUCTION

During the late 1930s some 4-phenylpiperidine derivatives were examined as potential spasmolytics on the basis of their chemical relationships to atropine. The antinociceptive properties of one member, ethyl 1-methyl-4-phenylpiperidine-4-carboxylate (**1a**), were detected during screening tests and the compound was subsequently introduced clinically by Eisleb and Schaumann in 1939.[1] The ester **1a**, well known as *pethidine* in Europe and *meperidine* in North America (proprietary names include Demerol, Dolantin, and Dolosal), was soon in widespread use for the relief of pain and it is remarkable how pethidine, the original nonopioid-derived analgesic, has retained its popularity in the face of competition from other synthetic analgesics marketed over the past 40 years.

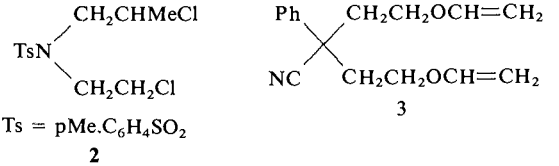
In potency, pethidine is graded between codeine and morphine (50–100 mg is equivalent to 10 mg morphine in man),[2] and it is useful for the management of mild to moderate pain, especially in patients intolerant to opioids. Its toxicity is relatively low and its duration of action is somewhat shorter than that of morphine. At equivalent dosage, pethidine is at least as depressant as morphine upon respiration and while morphinelike side effects such as nausea and vomiting frequently occur, it produces little disturbance of urinary function or bowel action. It is extensively used for the relief of labor pain even though it increases the incidence of delay on the first breath and cry of the neonate;[3] several critical reports on the efficacy of the drug in obstetrics have been made.[4] Tolerance to pethidine develops slowly, and its dependence liability is claimed to be lower than that of morphine.[5] Full accounts of the clinical use of pethidine are available.[4,6]

Eisleb's original synthetic procedure[7] consisted of treating benzyl cyanide with two molar proportions of sodamide and then condensing the resultant dianion with bis(2-chloroethyl)methylamine (a compound with highly vesicant properties) and converting the intermediate cyanide to the

corresponding ethyl ester by acid-ethanol. Less toxic nitrogen mustards with *N*-benzyl,[8] arylsulfonyl,[9] or carbalkoxy substituents (later removed by hydrogenolysis or hydrolysis) may be used in large-scale processes but the original Eisleb procedure is still employed by at least one major U.K. manufacturer.[11] Janssen[10] used the unsymmetrical *N*-tosyl derivative **2** to prepare the isomeric 3-methyl analogs of pethidine. When the secondary amine **1b** (norpethidine) is an intermediate, an *N*-methylation step is required to produce pethidine, but access to **1b** provides a route to a variety of *N*-substituted analogs as will be described. Several alternative syntheses of pethidine have been reported,[12] such as one in which the piperidine ring is closed by reaction of a **1**,5-dichloro compound with methylamine.[13] Benzyl cyanide is condensed with 2 mol of 2-chloroethyl vinyl ether (formed by dehydrohalogenation of di-2-chloroethyl ether). Mild acid hydrolysis of the product **3** gives the bis-2-hydroxyethyl compound, which is converted to the dihalide and cyclized with methylamine.



1a R = Me
b R = H



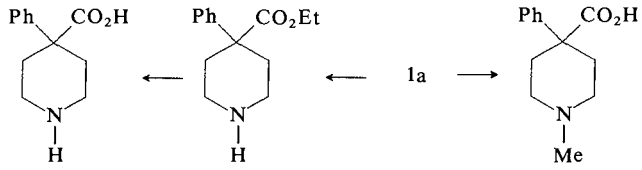
Ts = pMe.$C_6H_4SO_2$

2

3

Some pharmacopoeial specifications for pethidine hydrochloride[14] now include a tlc limit test for related substances as a result of the detection by glc of homologs formed by exchange of alkyl groups between the nitrogen atom and ester function of pethidine base[15]; some samples contained up to 9% impurity even though their melting points lay within the range for the pure salt. 1-Benzylnorpethidine has also been identified as a contaminant of pethidine pharmaceuticals.[16]

When interest in drug metabolism arose during the 1950s, pethidine was one of the first subjects of investigation and there are many reports of both its *in vivo* (animals and man) and *in vitro* (liver homogenates) biotransformation.[17] Pethidine is extensively degraded by *N*-demethylation and hydrolysis, with acidic products excreted in the free form and as conjugates with glucuronic acid (Scheme 6.1); there is nothing remarkable about its metabolism in the light of present knowledge. An aryl-hydroxylated derivative has been detected as a minor component of rat and human urine after dosage with tritiated pethidine by gc–ms analysis,[18] a technique now in common



Scheme 6.1

use for metabolic studies. Norpethidine and other metabolites are feebly active or inactive as analgesics.[19] The absorption of pethidine is rapid by all routes of administration and peak plasma levels are obtained in man 1–2 h after oral administration. The drug penetrates the CNS more readily than more polar analgesics such as morphine, passes the placental barrier, and appears in breast milk.[4] Intravenous to intraventricular ED_{10} potency ratios in rabbits (pethidine 8.5; morphine, 910) illustrate the relative ease with which pethidine penetrates the blood-brain barrier,[20] and this fact helps to explain the apparent discrepancy between the weak affinity of pethidine for opioid receptors and its potency relative to morphine (analgesic potency 10% and affinity only 0.2% that of morphine).[21] Other workers found the IC_{50} value of pethidine to be 50× that of morphine (versus [^{3}H]naloxone) and to be raised 80-fold in the presence of NaCl, typical of agonist binding (p. 334).[21a] Binding studies involving displacement of specific ligands show that pethidine has a high selectivity for μ-receptors and only interacts weakly with δ- and κ-sites (see p. 353)[22]; the activity profile of the drug against various nociceptive stimuli confirm pethidine as μ-agonist.[23]

6.2. *N*-SUBSTITUTED NORPETHIDINES

A discussion of the host of synthetic modifications of pethidine is conveniently made under five subdivisions (one class is discussed in Chapter 7), some overlap of data being unavoidable.

The structural variation of pethidine most thoroughly investigated is that of replacement of *N*-methyl by other groups, notably phenalkyl, synthesized in most cases by alkylation of norpethidine with the appropriate alkyl or aralkyl halide in the presence of base (Table 6.1). These studies follow the observation made in 1956 by Perrine and Eddy[25] that *N*-phenethylnorpethidine is twice as active as pethidine in mice (2-phenylethyl is commonly abbreviated to phenethyl). In the unsubstituted phenalkyl series activity increases as the alkyl chain between ring nitrogen and the aryl group is lengthened from one to three carbons and declines on extension to four carbons,

Table 6.1. Relative Analgesic Activities of N-Substituted Norpethidines in Rats[a]

Item number	R (in 1)	Activity (pethidine = 1)	Item number	R	Activity (pethidine = 1)
1	$PhCH_2$	0.25	13	p-$MeO.C_6H_4.(CH_2)_2$	3
2	$Ph(CH_2)_2$	2	14	4-(C_5H_4N)[b]$(CH_2)_2$	9
3	$Ph(CH_2)_3$	13	15	$PhCH{:}CH.CH_2$	29
4	$Ph(CH_2)_4$	2	16	$PhNH.(CH_2)_2$	100
5	p-$NH_2.C_6H_4.CH_2$	1	17	$PhNH.(CH_2)_3$	30
6	p-$NH_2.C_6H_4.(CH_2)_2$	11	18	C_6H_{13}	6.7
7	p-$NH_2.C_6H_4.(CH_2)_3$	6	19	C_7H_{15}	3.3
8	p-$NH_2.C_6H_4.(CH_2)_4$	2	20	C_8H_{17}	4.0
9	p-$NO_2.C_6H_4.CH_2$	0	21	C_9H_{19}	2.5
10	p-$NO_2.C_6H_4.(CH_2)_2$	6	22	$C_{10}H_{21}$	0
11	p-$NO_2.C_6H_4.(CH_2)_3$	5	23	BuCHMe	5.8
12	p-$NO_2.C_6H_4.(CH_2)_4$	0.5	24	BuCHEt	1.7

[a] From Ref. 24.
[b] 4-pyridyl.

with *N*-benzylnorpethidine the weakest derivative (Table 6.1, items 1-4). In the *p*-amino and *p*-nitro-phenalkyl series, maximum activity occurs with the 2-ethyl compounds (items 6 and 10). Chain branching severely reduces activity. *p*-Substituents in the benzene ring such as amino, nitro, methoxy, and ring nitrogen (4-pyridyl) enhance activity in the phenethyl but not always in other series. *N*-*p*-aminophenethylnorpethidine (*anileridine*, Leritine, item 6) is two to three times as potent as pethidine in man and has been used clinically.[3,26] Some derivatives of anileridine that incorporate various alkylating functions have been made with a view to designing a molecule capable of bonding covalently (and hence irreversibly) with opioid receptors—an example of the affinity labeling approach to receptor studies (p. 449).[27] The most promising candidate was the furanilate **4**, which elevated the ED_{50} of morphine twofold in mice; its mode of action was not of the simple noncompetitve type but its duration of blocakade (over 6 h) indicated that it had a high affinity for the receptors.[28,29] An earlier attempt to exploit affinity labeling in analgesics involved the *N*-2-bromoethyl derivative of normetazocine (p. 181).

In *N*-3-phenpropyl analogs of norpethidine activity is further raised when the 3-carbon chain contains a double bond (item 15) but is lost when a triple bond is present.[30] An imino group placed between the aryl and alkyl portions of the *N*-substituent is advantageous in terms of potency, and one such derivative (item 16, *piminodine*, Alvodine) has been marketed in the United States.[31] The related amide 1 (R = $PhNHCOCH_2CH_2$) is eight times as potent as codeine in mice.[32]

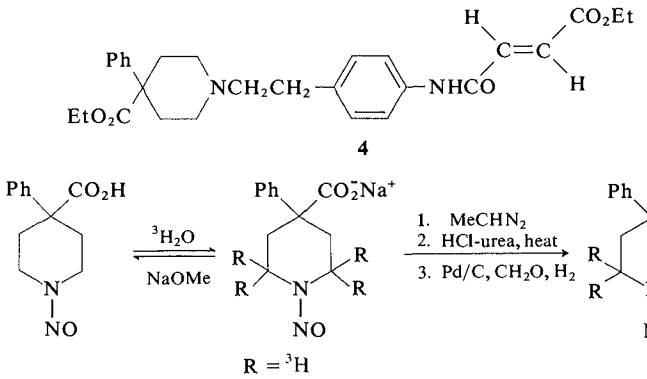
Interesting potency variations are seen in norpethidines with straight-chain alkyl substituents (*N*-R); activity falls to about one third that of pethidine

Table 6.2. Comparison of Analgesic Potencies of *N*-Alkylnorpethidines and Brain Concentrations[a]

N-alkyl substituent	Partition coefficient[b]	Relative iv potency (pethidine = 1)	Cumulative brain level (5–60 min)[c]	Relative potency from brain conc.
methyl	19	1.0	854	1.0
n-propyl	70	0.7	828	1.0
n-butyl	136	1.7	274	3.1
n-hexyl	608	8.8	126	6.8

[a] From Ref. 36.
[b] From octanol-phosphate buffer pH 7.4.
[c] nmol min/g.

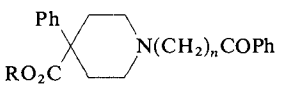
with ethyl and propyl, rises to exceed the parent six- to ninefold with hexyl, with a potency decline on further extension of the chain.[9,33] The *N*-allyl analog is about half to a third as active as pethidine in animal tests,[33,34] a finding to be discussed later. Abdel-Monem and Portoghese[35] found a striking similarity between the curves relating *in vitro* *N*-dealkylation rates and hot-plate ED_{50} potencies in mice to chain length for a series of *N*-alkylnorpethidines (methyl to *n*-nonyl); the least potent member (*n*-nonyl) was the most extensively *N*-dealkylation while the most potent (*n*-hexyl) suffered the least metabolic attack. If *N*-dealkylation is the major metabolic pathway for these compounds *in vivo*, the results suggest that the differences in analgesic potency that they exhibit are due chiefly to differences in their metabolism (affecting transport of the intact drug to the receptor site) rather than differences in the drug-receptor interactions. However, a later study of brain levels of pethidine and three *N*-alkyl homologs determined at equal analgesic iv doses in mice established that the relative levels of the four compounds were closely proportional to their ED_{50} doses even though the group showed a wide range of partition coefficients and metabolic *N*-dealkylation rates (Table 6.2).[36] Peak brain levels of all compounds occurred within the first 5 min after administration; hence, it was concluded that lipid solubility and metabolism, while undoubtedly important factors in the overall time course of drug concentration in the CNS, do not profoundly affect the relative brain levels. Consequently, observed ED_{50} potencies appear to provide a fair approximation of the relative receptor affinities of the four homologs (cf. similar studies of prodine isomers discussed later, p. 254). Direct assay of affinity for opioid receptor binding sites in the presence of Na^+ by displacement of [^3H]naloxone provided further evidence for this view in the case of pethidine analogs with *N*-substituents of six or fewer carbon atoms.[21] These pharmacokinetic studies were aided by a facile method of labeling pethidine and its analogs with tritium that depends on base-catalyzed exchange in ^3H_2O of the α-hydrogens of



Scheme 6.2

N-nitrosonormeperidinic acid for ^3H; the sequence for pethidine is shown in Scheme 6.2.[37]

A variety of pethidine analogs with oxygen-containing *N*-substituents have potencies in excess of the parent analgesic, as illustrated by the alicyclic and acyclic ethers of Table 6.3. Janssen and others struck a rich vein of activity when they investigated Mannich bases prepared from norpethidine, formaldehyde, and acetophenone, or a substituted acetophenone. Highest activity was found in the 2-propiophenone compound 5 (R = Et, n = 2, R951), which was about 60 and 200 times more active than pethidine in mice and rats, respectively.[39] Increase of the alkyl chain to three carbon atoms reduced potency, as did substitution in the aryl group (the decrease was minor with *m*-F), but all variants were much more potent than pethidine. The secondary alcohol **6** (*phenoperidine*, Operidine) derived from R951 has a similar potency to its parent in animals[39] and is in clinical use.[4] There is a modest (four-fold) activity difference between *R*(+)- and *S*(−)- enantiomers that probably reflects pharmacokinetic rather than receptor events since both isomers possess high levels of potency (the weaker dextro antipode is seven times as active as morphine).[40]



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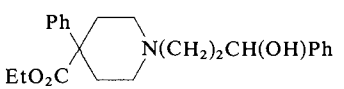
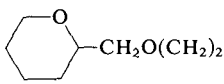
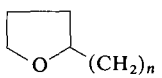


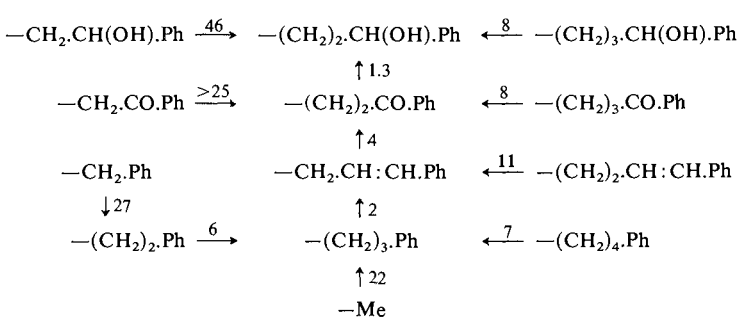
6

Janssen and Eddy[41] have given a semiquantitative estimate of the influence of systematic chemical modifications on analgesic potency in mice and rats of a series of *N*-substituted norpethidines and reversed esters of pethidine. Their estimates, based on the results of the hot-plate test obtained in three separate laboratories, are illustrated in Scheme 6.3.

Table 6.3. Analgesic Activities of *N*-Substituted Norpethidines with Oxygenated *N*-Substituents in Mice or Rats[a]

R (in 1a)	Activity (pethidine = 1)
 [b]	2.5
$EtO(CH_2)_2$	5
$EtO(CH_2)_4$	10 (20)
$PhO(CH_2)_2$	7
$PhCH_2O(CH_2)_2$ [c]	7
 [d]	25 (80)
	10
	
(n = 3 or 4)	30
$HO(CH_2)_2O(CH_2)_2$ [e]	5
$PhOCH_2CH(OH)CH_2$	12

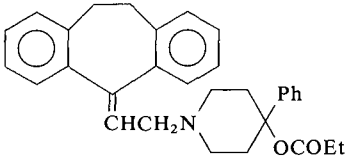
[a] From Ref. 38.
[b] Morpheridine.
[c] Benzethidine.
[d] Furethidine.
[e] Etoxeridine.



Potency relationships among a series of *N*-substituted norpethidines
(The formulas represent *N*-substituents. Arrows point to compounds of increased activity and the potency ratio of adjacent derivatives is given by the numeral next to the linking arrow, i.e. $A \xrightarrow{X} B$; $X = \frac{\text{P.R.B.}}{\text{P.R.A.}}$)

Scheme 6.3

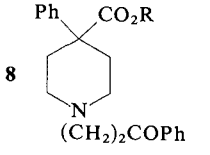
Some labile amide derivatives of norpethidine have been tested in the expectation that they might hydrolyze readily to norpethidine in the CNS; the carbonate 1 (R = CO_2Et) and pethidine were equipotent in rats while the monosuccinimide 1 (R = $CO(CH_2)_2CO_2H$) and pyruvamide 1 (R = COCOMe) were inactive in mice.[42] Linkage of norpethidine and its reversed ester to the dibenzocycloheptene nucleus (the latter structure is the basis of psychotropic agents such as amitriptyline) led to several compounds that showed morphinelike potencies in animal tests for analgesia, for example, **7**.[43]



7

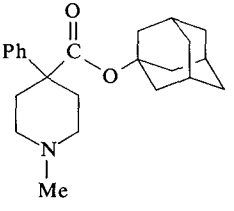
6.3. VARIATION OF THE OXYGEN FUNCTION AT C-4 OF THE PIPERIDINE RING

Investigation of 4-carbalkoxy congeners of pethidine was made soon after the introduction of the drug, and carbethoxy identified as the substituent of optimal size.[12] Later comparisons substantiate the superiority of CO_2Et over CO_2Me by a factor of 4,[41] while data on Mannich-base analogs of pethidine provide potency rankings of a wide range of esters (see **8**). Bulky ester functions usually reduce activity but incorporation of the adamantyl moiety into the ester function of pethidine (**9**) is claimed to be advantageous both in terms of potency and duration of action.[44]

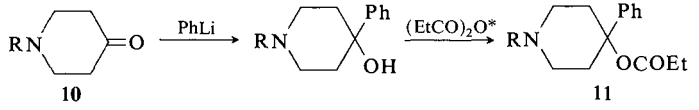


8

R	Molar potency ratio[39]
C_2H_5	1
CH_3	0.42
iso-C_3H_7	0.18
n-C_5H_{11}	0.05
sec-C_4H_9	0.04
n-C_3H_9	<0.01
n-C_6H_{13}	<0.01



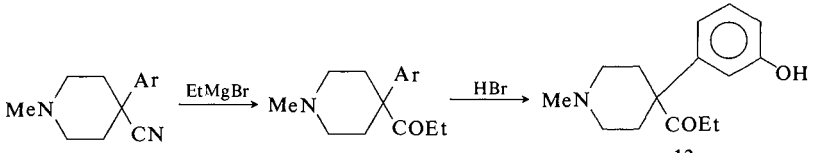
The original observation[45] that replacement of 4-carbethoxy by 4-propionyloxy (OCOEt), to give the so-called reversed ester of pethidine (**11**, R = Me), is attended by an increase in potency has since been confirmed many times. Such a change usually produces an up to 20-fold elevation of activity regardless of the nature of the *N*-substituent.[41] Reversed esters of pethidine are made by treating a 4-piperidone **10** (synthesis p. 266) with an aryl organometallic reagent (often a lithium aryl) and decomposing the complex so-formed with an acid anhydride or acid halide.[46,47] Corresponding 4-piperidinols, available directly by the aminomethylation of α-methylstyrene,[48] are inactive,[41] as is meperidinic acid, also with an acidic hydrogen C-4 function. Discussion of the 3-methyl (prodines) and other 3-alkyl substituted analogs of **11** is given in Chapter 7.



10 **11**

* or treat isolated 4-piperidinol with acid anhydride-pyridine

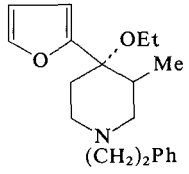
Analogs of pethidine with keto (4-propionyl) and ether (4-ethoxy) oxygen functions also display analgesic properties, as in *ketobemidone* (**13**) and the 4-(2-furyl)ether **14** respectively. Ketobemidone, made from the 4-cyano intermediate **12**,[49] has had much clinical use in Germany and Scandinavia in spite of its high dependence liability.[3] *N*-Demethylated, ring-hydroxylated and *O*-methylated products together with appropriate conjugates were recovered from the urine of patients after iv and oral administration of the drug.[50] The ether **14** is discussed later; lower and higher alkoxy analogs are far less active than the 4-ethoxy compound.[51]



12 **13**

Ar = 3-MeO.C_6H_4

10 × pethidine in mice[12]
(4-Ph analog, 0.5 × pethidine)



14

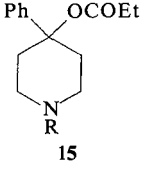
1.2–2.5 × morphine in mice

Table 6.4. Analgesic Activities of *N*-Substituted-4-phenyl-4-propionoxypiperidines in Mice[a]

R(in 11)	ED_{50} μmol/kg	Molar potency ratio (pethidine = 1)
Me	11	7.4
$Ph(CH_2)_2$	3.2	25
$Ph(CH_2)_3$	0.5	162
$Ph(CH_2)_4$	0.65	125
$PhCH=CHCH_2$	0.31	261
$PhCH(OCOEt)(CH_2)_2$	0.054	1500

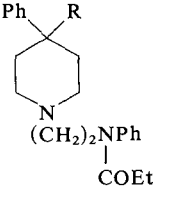
[a] From Ref. 41.

N-Substituted variants of ketobemidone[52] and particularly of the reversed ester of pethidine have been reported, and potency changes seen generally concur with those found in the related pethidines. A few examples from the study of Janssen and Eddy[41] are shown in Table 6.4. It is clear that remarkably potent 4-phenylpiperidine analgesics may be obtained by chosing the appropriate *N*-substituent. The reversed ester analog of phenoperidine (**15a**), for example, is reported to be over 3000 times as active as pethidine in rats[53]; the related diester (OCOEt) is of like potency while the precursor Mannich base **15b** is about half as active as the secondary alcohol. The β-anilinoethyl derivative **15c** (related to piminodine) is also highly active (13,000 × pethidine) but suffers a 100-fold potency fall when the anilino nitrogen is methylated.



15

a R = $(CH_2)_2CH(OH)Ph$
b R = $(CH_2)_2COPh$
c R = $(CH_2)_2NHPh$



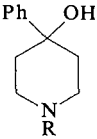
16

Activity (pethidine = 1)

a	R = OH	50
b	R = OCOEt	3
c	R = H	11

Normally, *t*-alcohols corresponding to reversed ester analgesics are inactive, but the free alcohol **16a** is highly potent in rats and its activity is in fact reduced on esterification (**16b**).[54] *N*-Acetyl (6 × pethidine), *N*-butanoyl (32 × pethidine), and 3-methyl (12 × pethidine) analogs of **16a**, and the 4-phenylpiperidine **16c** (4-OH absent) are all significantly active. Even higher-potency levels are reached in the branched-chain congeners **17**, the activity of the first member being specially noteworthy.[55] Analogs of **17a** and **17b** with OH replaced by H are less active but still superior in potency to morphine. Replacement of *N*-phenyl by benzyl in **17b** reduces activity to half that of morphine. All the active derivatives are antagonized by nalorphine, and mice

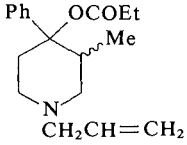
develop tolerance toward their action. Structure-activity relationships in these *N*-substituted propionanilides resemble those of acyclic basic anilides such as diampromide (p. 311) rather than reversed esters of pethidine, and the derivatives **16** and **17** are more appropriately classified with the former. On this basis the entire 4-phenylpiperidin-4-ol moiety (and modifications) serves as the basic unit with acyclic *N*-phenyl rather than *N*-piperidylphenyl as the prime aromatic feature of the molecule.



17

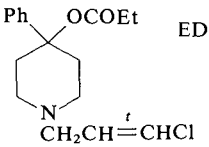
	R =	Activity in mice (morphine = 1)
a	$CH_2CHMeN(COEt)Ph$	150
b	$CHMeCH_2N(COEt)Ph$	20
c	$CH_2CHMeN(CO_2Et)Ph$	35
d	$CH_2CHMeN(CO\text{-}2\text{-}furyl)Ph$	70

Most attempts to design narcotic antagonists based on 4-phenylpiperidine by linking the basic center to groups such as allyl, substituted allyl, and cyclopropylmethyl (CPM) that confer such properties on fused cyclic systems as possessed by morphine and 6,7-benzomorphans have led to agonists that have no power to block opiate receptors; examples include *N*-allyl derivatives of norpethidine and norprodine (**18**)[34] and the *N*-3-chloroallyl reversed ester **19**.[56] Essentially similar results were found for a group of *N*-substituted



18

ED_{50}[a]
α, 1.25
β, 0.63

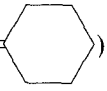


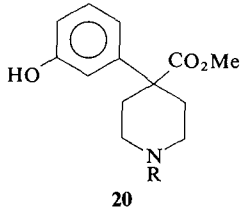
19

ED_{50},[b] 4.0

[a] mg/kg in rats, tail withdrawal (pethidine = 10).
[b] mg/kg in mice, HP (pethidine = 4.7).

norketobemidones.[52] In the last series, reasonable degrees of potency were retained when *N*-methyl of the parent was lengthened (except for the ethyl derivative) while a two-fold activity rise was seen in the *N*-pentyl analog (cf. the superior activity of *N*-hexylnorpethidine over pethidine (p. 233). The pentyl, hexyl, and heptyl members showed weak inhibition of morphine dependence in monkeys in addition to agonist properties, and the antagonistic properties of two of these derivatives were confirmed in the GPI and MVD preparations (*n*-hexyl, 8%, *n*-heptyl, 4% of the potency of nalorphine).[57] The *N*-allyl analog, however, behaved as a pure agonist in accord with findings in the pethidine and prodine series. A German group had more success in producing antagonists when the methyl ester analog of bemidone (**20**, R = Me) was modified rather than ketobemidone;[58] their most potent compound

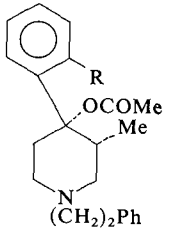
(**20**, R=CH_2CH= ) had one third the activity of nalorphine against morphine in mice but *N*-allyl, *N*-CPM, and *N*-2-furylmethyl (p. 427) derivatives were inactive or feeble in this respect. It is still true to state, therefore, that morphine antagonists based on 4-arylpiperidines with a nonphenolic aromatic feature have yet to be described (cf. also p. 431).



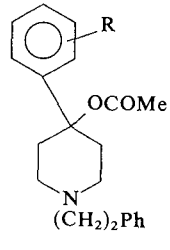
20

6.4. VARIATION OF THE 4-ARYL GROUP

Most data concerning the effect of variations of 4-phenyl on potency in 4-arylpiperidine analgesics relate to reversed esters as a result of the versatility of 4-aryl-4-piperidinol syntheses. Gross increases in size of the aryl group as in naphthyl derivatives[59] lead to inactive compounds, while even 4-tolyl analogs are less active than the parent compounds in almost all cases as shown in Table 6.5, which presents results for isomeric tolyl and xylyl derivatives. There is no consistent relationship betwen potency and position of substitution and only general trends may be discerned. Thus *para* substitution usually results in the greatest, and *ortho* in the least, fall in activity. In *o*-tolyl derivatives the adverse effect of aryl group enlargement on drug–receptor contact may be offset by the shielding action that *ortho* groups have on the ester function in terms of metabolic attack; this effect may also account for the high degrees to which activity is retained in *o*-methyoxy congeners (**21**).



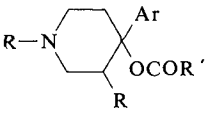
	Activity[46]
R = H	3.9
R = OMe	4.0
morphine	1.0



	Activity[61]
R = H	5.7
R = *o*-OMe	3.0
R = *m*-OMe	0.5
pethidine	1.0

21

Table 6 5 Effect of Substitution in the 4-Phenyl Group of Reversed Esters of Pethidine[a]

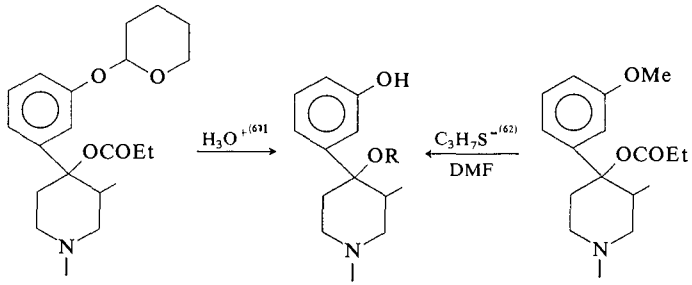


			Analgesic activities (morphine = 1)			
R	R'	R''	Ar = Ph	Ar = *o*-MeC_6H_4	Ar = *m*-MeC_6H_4	Ar = *p*-MeC_6H_4
Me	Me	Me	—	0 75	<0 2	0 3
Me	Me	Et	2	0 85	0 5	1 5
$(CH_2)_2Ph$	Me	Me	3 85	13	1 8	0 9
$(CH_2)_2Ph$	Me	Et	4 3	2 6	0 4	0 2
$(CH_2)_2Ph$	H	Me	6 3	1 2[b]	—	0 5
$(CH_2)_2Ph$	H	Et	3 5	3 4	4 7	0 3

[a] From Refs 46, 60
[b] 2,3 $Me_2C_6H_3$ analog 0 3, 2,4 1 0, 2,5 2 2

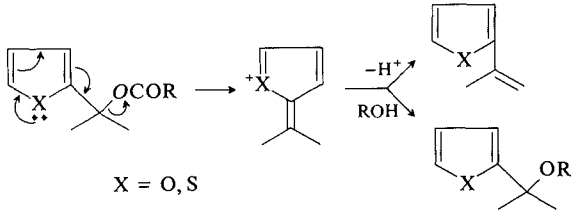
The influence of few substituents other than methyl and methoxy has been reported; a nitro group, as in the 4-nitrophenyl analog of α-prodine, abolishes activity.[61] In analgesics with a rigid skeleton like morphine and levorphanol, the presence of a free phenolic group is a prerequisite for high potency (pp. 26, 468). Such is not the case for most 4-arylpiperidine analgesics, although the presence of a *meta* phenolic hydroxyl elevates potency in the cases of bemidone (activity elevated 13–14 times after metahydroxylation to ketobemidone) and, to a smaller extent, pethidine (both with C_4-carbon functions, cf. p. 275). Only recently have phenolic analogs of reversed esters of pethidine been reported, a delay probably due to synthetic difficulties. The compounds may be made by blocking the phenolic group with either methyl or tetrahydropyran, protective entities removed under mild conditions that leave the acyloxy function intact (Scheme 6.4). *m*-Phenolic analogs of the reversed ester of pethidine, α- and β-prodine, and α- and β-allylprodine all proved inactive in *in vitro* (GPI) and/or antinociceptive tests for analgesia.[62,63] These results substantiate the view that the 4-aryl features of 4-phenylpiperidine analgesics (certainly those with C_4-oxygen functions) and the morphine group interact at different aromatic binding subsites of opioid receptors (cf. results on phenolic analogs of fentanyl, p. 294). The claim that the phenolic analog of β-prodine antagonizes responses to morphine[64] could not be repeated in rats narcotized with fentanyl.[63]

Isosteric replacement of phenyl, that is, replacement of phenyl by other aromatic groups of similar size such as furyl, pyridyl, and thienyl, is generally disadvantageous in analgesics (the thiambutenes are a special exception, p. 310). Thus, the 2-thienyl analogs of pethidine[65] and its seven-membered ring

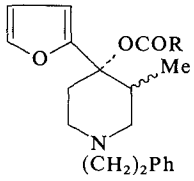


Scheme 6.4

congener (*ethoheptazine*),[66] and the 2-furyl, 2-pyridyl, and 2-thienyl analogs of reversed esters of pethidine[51,59,66a] are all much weaker than the parent compounds. These results have been interpreted in terms of the bulky heteroatom (probably solvated) interfering with the fit of the aryl group at the flat portion of the receptor site.[59] However, the high activities of certain 2-furyl and 2-thienyl isosteres suggest that adequate association between these aryl groups and the receptor is possible and that low activity, where it occurs, is due to other factors (e.g., the facilitation of ester hydrolysis in reversed esters of pethidine as mentioned below). Esters of the *O*- and *S*-heterocyclic 4-piperidinols are made by decomposing the lithium 4-piperidone complex with an acid anhydride; treatment of the corresponding 4-piperidinol with reagents such as pyridine-acid anhydride give alkenic products due to the π-excessive nature of the 4-aryl substituent. The 4-acyloxy derivatives are likewise labile, particularly the 2-furyl analogs, and are converted to tetrahydropyridines and/or 4-alkoxypiperidines by alcoholic-HCl (Scheme 6.5).[51,59,61] Esters of this nature may undergo *in vivo* hydrolysis more readily than 4-phenyl counterparts and have reduced activity on this account; the 2-furyl esters **22** (R = Me and Et) are both inactive while the related 4-ethoxy derivative **14** exceeds morphine in potency as earlier stated.



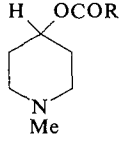
Scheme 6.5



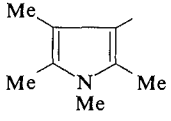
22

The few analogs of pethidine-reversed esters in which phenyl is replaced by nonaromatic groups capable of providing π-electrons such as $-C\equiv CH$ and $-C\equiv N$ have proved inactive.[67]

Complete removal of the 4-phenyl substituent of the reversed ester of pethidine results in a drastic fall in potency as judged from tests in mice (see **23**, R = Et). However, certain esters of 1-methyl-4-piperidinol formed from aromatic acids display antinociceptive activities in the morphine to codeine range of potency (**23**).[68] A QSAR study of such esters has been made and a substitution pattern of the phenyl group defined for optimal activity.[69] The relevance of these compounds to morphine-type analgesics is doubtful since the more active members show marginal or no affinity for opioid receptors of rat brain homogenates and display no physical dependence in monkeys.



23

R	ED_{50} mg/kg sc (mice HP)
Et	20.2
Ph	9.6
2,6-diOMe.C_6H_3	3.9
	4.9
Morphine	1.2
Codeine	7.5

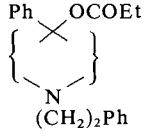
6.5. ANALOGS WITH C-METHYL (AND OTHER HYDROCARBON) SUBSTITUENTS IN THE PIPERIDINE RING

Discussion of this group of variants, which includes such well-known analgesics as α- and β-prodine and promedol, is deferred to Chapter 7 because of the extent and complexity of the work involved.

6.6. MISCELLANEOUS VARIATIONS

A study of heterocyclic ring contraction and expansion upon activity in reversed esters of pethidine has shown that analgesic properties are retained

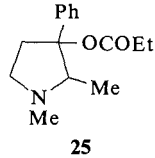
(although in reduced degree) in seven-membered ring analogs of active piperidine derivatives but are absent or weak in five-membered congeners.[70] Some typical data are shown (**24**); similar results were earlier found for



24

Ring size	ED_{50} mg/kg sc mice HP
5(Pyrrolidine)	Inactive at 100
6(Piperidine)	1.5 (17 × pethidine)
7(Azacycloheptane)	3.4 (7 × pethidine)

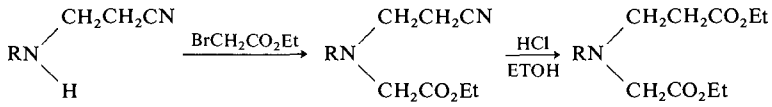
4-carbethoxy (pethidine) analogs. The azacycloheptane related to pethidine (ethoheptazine, Zactane) is one third as active as pethidine in rats and has been used clinically in combination with aspirin for relief of postlabor and arthritic pain.[71,72] 3-Methylated seven-ring analogs of reversed esters have potencies in the morphine range and *cis* and *trans* isomers have similar activities, unlike analogous prodines.[73] As stated, pethidine analogs based on pyrrolidine are feeble analgesics; prodilidine, the 2-methyl reversed ester **25**, has a potency close to that of codeine.[88]



25

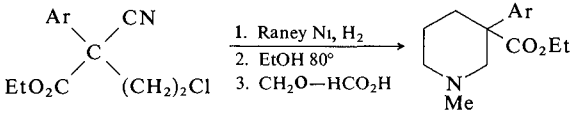
Ring size influence upon activity in the pethidine class of analgesic is probably related to the relative orientation and separation of the basic center and aromatic group of such compounds. These structural parameters appear to be optimal in a six-membered ring. The relationship of the two features will be modified when an additional methylene group is included in the heterocyclic ring but since the molecule is flexible it is free to adopt a wide range of conformations, some of which are likely to approach those of six-ring analogs. In contrast, the distance between the nitrogen atom and the aromatic group in pyrrolidine derivatives must of necessity be less than that obtaining in piperidine analgesics and the orientation of the two features is restricted to narrower limits because of the more rigid (near-planar) nature of the five-membered ring. Certain 3-aryl-3-alkylpyrrolidines show significant activity both as analgesic agonists and antagonists and in such cases it may be argued that the compounds associate with opioid receptors in a manner that differs radically from that of pethidine and its congeners (p. 281).

Azacycloheptan-4-one intermediates required for these studies were made by ring expansion of 4-piperidones with diazomethane; *N*-substituted 3-pyrrolidones were made by the Dieckmann procedure from acyclic precursors of type **26**.[70,74]



26

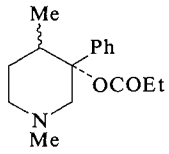
In β-pethidine (**27a**) aromatic and basic features of the molecule are closer than in the parent, a change detrimental to potency as noted for 3-pyrrolidines.[12,87] The 3-*m*-hydroxyphenyl analog **27b** behaved as an agonist in a writhing test (0.1 × morphine) and weakly antagonized morphine analgesia (AD_{50} μmol/kg, 24.4; nalorphine, 0.08) with a potency somewhat less than that of the N-CPM derivative (AD_{50} 18.8 μmol/kg).[75] Binding affinities of **27b** and its analogs (vs. ^{3}H-DADL) were low.[86]



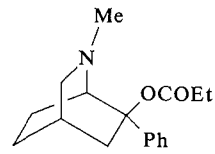
a Ar = Ph (0.5 × pethidine)
b Ar = 3-OH.C_6H_4

27

Isoprodines (**28**), related to β-pethidine, are inactive in mice in doses up to 100 mg/kg[76]; the bicyclic analog **29** with the piperidine ring constrained to a boat conformation is about half as active as α-prodine in rats while its diastereoisomer is inactive.[77] Results on β-pethidine and isoprodine should be compared with data on 3-aryl-3-methylpiperidines that lack an oxygen substitutent in the piperidine ring but possess one in the aromatic moiety (p. 279).

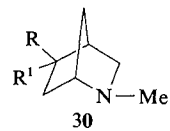


28



29

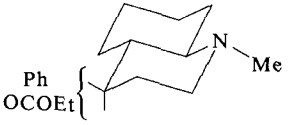
Other conformationally restricted forms of pethidine are the endo and exo isomeric azabicyclo[2,2,1]heptanes **30**, which have similar orders of potency in mice (benzoquinone writhing test) after allowance is made for the greater ease with which the exo isomer penetrates the brain.[78] Reversed ester



30

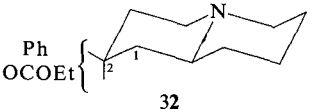
endo(R = CO_2Et, R^1 = Ph) 2 × pethidine
exo (R = Ph, R^1 = CO_2Et) 12 × pethidine

analogs based on decahydroquinoline (**31**) and quinolizidine (**32**) have also been reported.[79,78]



31

Both isomers 0.5 × pethidine



32

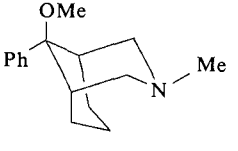
ED_{50} mg/kg sc mice, hotplate

2-*ax* Ph 8.0

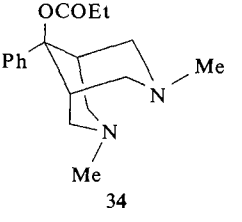
2-*eq* Ph 3.1

Codeine 7.5

Some extremely potent pethidine analogs result when the 3,5-positions of the piperidine ring are bridged with trimethylene. The azabicyclane **33** is reported to be six to eight times as active as pethidine[81] (the pethidine ether analog, 4-methoxy-1-methyl-4-phenylpiperidine is itself inactive).[61] Its potency in mice was dramatically raised when Ph was replaced by *m*-hydroxyphenyl (500 × morphine), while the same change coupled with replacement of *N*-methyl by *N*-phenethyl gave a product 1600 times as active as morphine. The *N*-allyl analog of **33** failed to exhibit narcotic antagonism, and agonist-antagonist properties of its diastereoisomer were of a low order.[82] The related 3,7-diaza derivative **34** was devoid of analgesic properties.[83] Bicyclic ketones formed by a Mannich reaction between cyclohexanone,

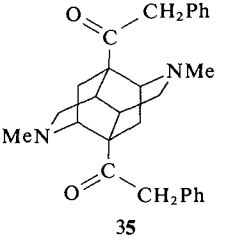


33



34

methylamine, and formaldehyde were the synthetic intermediates of this series.[84] Surprisingly, the chemical curiosity diazatwistane provides the skeleton of a potential analgesic. The derivative **35** was about 1.5 times more effective an antinociceptive agent than morphine in the rat paw pressure test (sc route) and showed a high degree of receptor stereoselectivity (ED_{50} levo



35

isomer, 0 6, dextro, 80 mg/kg) [85] According to the authors, a space-filling model of **35** shows structural similarities with morphine and bridged-thebaine analgesics Mono and bis *N*-demethyl analogs of **35** were only feeble analgesics while the bis *N*-allyl derivative was neither an analgesic nor an antagonist.

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84 H O House and W M Bryant 3rd, *J Org Chem* **30**, 3634 (1965)
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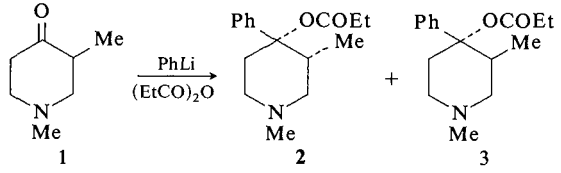
7

Further Analgesics Based on Piperidine and Related Azacycloalkanes: Prodines, Promedols, Profadol, and Their Derivatives

7.1. INTRODUCTION

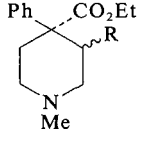
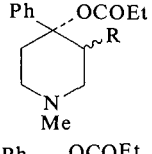
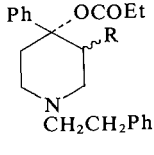
The major part of this chapter is devoted to 4-phenylpiperidine analgesics with *C*-alkyl substituents in the piperidine ring and to a consideration of their stereochemical structure–activity relationships. The effect of alkyl substitution in the piperidine ring of 4-phenylpiperidine analgesics has attracted much interest ever since the 3-methyl analogs of the reversed ester of pethidine were described by Roche workers in the late 1940s.[1] Since that time many 3-alkyl and all possible mono- and di-*C*-methyl derivatives of the reversed ester have been reported, and much evidence of potency variation amongst stereoisomers disclosed. The ease of synthetic access and the fact that replacement of 4-carbethoxy (CO_2Et) by 4-propionyloxy (OCOEt) usually produces a major increase in potency (up to 20-fold regardless of the nature of the *N*-substituent)[2] are probable reasons why the bulk of the investigations have been of derivatives of the reversed ester rather than pethidine itself.

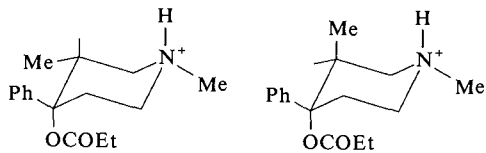
Alkyl-substituted derivatives of 4-phenylpiperidine analgesics present two intellectual challenges, namely, that of solving stereochemical problems of relative and absolute configuration, and that of relating molecular geometry to potency variations among stereoisomers. These aspects are well exemplified by the original 3-methyl reversed esters derived from 1,3-dimethyl-4-piperidone (**1–3**). Such esters have relative *trans* or *cis* 4-Ph/3-Me geometry, corresponding IUPAC nomenclature being *c*-3-Me, and *t*-3-Me, *r*-OCOEt, respectively; furthermore, each diastereoisomer is chiral and may be resolved to give a total of four stereoisomers. Ziering and Lee[3] succeeded in isolating a major (α)



and minor (β) racemic ester, termed α- and *β-prodine*, respectively, and partly resolved the minor component with (+)-tartaric acid. The α-racemic mixture was found to be as potent as morphine in animal tests, while β-prodine was almost five times as active as the standard agent.[1] Later studies confirmed these findings and showed, in addition, that a significant potency rise over that of the parent reversed ester (3-desmethylprodine) only occurred in the case of the β-isomer.[4] The same relationships were found for *N*-phenethyl analogs of the prodines, and for pethidine and its 3-methyl congeners (Table 7.1). All the α-3-methyl isomers have a *trans*, and all β-forms a *cis* 4-Ph/3-Me configuration. The configuration of the prodines remained controversial for some years until the validity of arguments that reversed the original assignments[9] were substantiated by X-Ray crystallographic analyses[10]; the solid-state conformations of α- and β-prodine are shown in formulas **4** and **5**, respectively; equatorial (*eq*) 4-phenyl chairs are preferred in each case. Stereochemical evidence relating to the prodines and other methyl substituted analogs is given later.

Table 7.1. Antinociceptive Activities (MHP) of Some des-3-Methyl, α- and β-Methyl 4-Phenylpiperidine Triads

Type	R = H	R = α-Me (*t*-3-Me/4-Ph)	R = β-Me (*c*-3-Me/4-ph)
	1.0 (Pethidine)	1.3	11.0
	9.2 (pethidine = 1)	7.1	34.0
	3.5 (morphine = 1)	4.5	22.0



α-4 β-5

The original Roche papers also reported that resolved forms of β-prodine differed in potency [racemic mixture 5.5, (+) 3.5, (−) 7.9, relative to morphine = 1], a result that led some 20 years later to a thorough investigation of antipodal forms of the prodines and their relatives, as will be recounted.

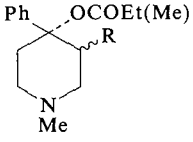
The enhanced activity of α-prodine over that of pethidine in animals holds also in man (40–60 mg ≡ 100 mg pethidine with brief duration of action)[11] and the compound (now withdrawn) was marketed as Nisentil. *Trimeperidine* (*γ-promedol*), a 2,5-dimethyl analog of 3-desmethylprodine described later, is also more active than pethidine and has been in clinical use in the USSR since the 1950s.[12]

7.2. STEREOCHEMICAL STRUCTURE–ACTIVITY RELATIONSHIPS

To reiterate, it has long been known that the potency of the reversed ester of pethidine is little changed after insertion of 3-methyl *trans* to 4-phenyl (as in α-prodine) but is elevated severalfold when the substituent is *cis* to the aromatic group (as in β-prodine). It was only later appreciated, however, that the case of methyl is unique and in pairs with larger alkyl substituents, the α-isomer (*trans* 3-R/4-Ph) is the more potent.[8] Receptor affinities measured by determining the concentration of 3-alkylated ester to displace 50% of specifically bound [^{3}H]dihydromorphine from rat brain homogenates have confirmed the higher affinity of β- over α- (**6**, R = Me, Table 7.2), and α- over β- (**6**, R = Et, allyl and *n*-hexyl) (both prodines and even the highly potent α-3-allyl congener have affinities inferior to that of morphine, reflecting the generally poor correlations between the binding and *in vivo* activities of 4-phenylpiperidines relative to polycyclic analgesics, see below).[13]

In this chapter an interpretation of the structure-activity relationships of reversed esters of pethidine with *C*-alkyl substituents (i.e., compounds of close or isomeric molecular structure) will be made in terms of events at the analgesic receptor rather than pharmacokinetic factors that govern drug absorption and transport to the active sites. Justification for such an approach will now be given. A study of brain levels of pethidine and three *N*-alkyl homologs (in which hot-plate activities in mice and *in vitro* *N*-dealkylation rates were inversely related) determined at equal analgesic iv doses in mice established that the relative levels of the four compounds were closely proportional to their ED_{50} doses even though the compounds exhibited a wide range of

Table 7.2. Antinociceptive Activities (ED_{50} mg/kg, sc MHP) of Some Reversed Esters of Pethidine[a]



6

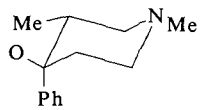
R	α(*t*-3R/4Ph)	β(*c*-3R/4Ph)
H	0.85 (3.62)	0.85 (3.62)
Me	0.92 (6.0)	0.18 (0.98)
Et	0.4 (2.1)	3.5 (15.9)
Pr^n	2.0 (10.4)	14.7 (23.4)
allyl	0.09	11.7
Bu^n	54.7 (29.3)	12.8 (26.5)
$C_6H^n_{13}$	Inactive at 80	54.4

[a] From Ref. 8; acetate data in parentheses.

partition coefficients (between octanol and phosphate buffer pH 7.4) and metabolic *N*-dealkylation rates.[14] Peak brain levels of all compounds occurred within the first 5min after administration; hence, it was concluded that lipid solubility and metabolism, while undoubtedly important factors in the overall time course of drug concentration in the CNS, do not profoundly affect the relative brain levels. Consequently, observed ED_{50} potencies appear to provide a fair approximation of the relative receptor affinities of the four homologs. Direct assay of affinity for opioid-binding sites in the presence of sodium by displacement of [^{3}H]naloxone provided further evidence for this view in the case of pethidine homologs whose *N*-substituent had six or fewer carbon atoms.[15] The apparent discrepancy between the weak affinity of pethidine and related drugs for opioid receptors (e.g., the affinity of pethidine is only 0.2% that of morphine as judged by IC_{50} values against [^{3}H]naloxone, whereas its pharmacological potency as an analgesic is about 10% that of morphine) may be explained by pethidine's efficient penetration of the CNS.[16] A similar case may be made for the SAR interpretations of C-methy-substituted reversed esters of pethidine on the basis of receptor binding data of the kind already mentioned[13] (and most recently on antipodal forms of β-2-methyl analogs)[17] and the fact of small variations of times of onset, peak, and duration of action among a wide range of the 3-alkyl esters of Table 7.2. Support also comes from a detailed study of the metabolism and distribution of prodine isomers in mice, facilitated by the use of analogs labeled in the aromatic part of the molecule with tritium.[18] In no case were the differences in analgesic potency between isomers fully accounted for by metabolism or distribution. At identical

doses, the racemic prodine diastereoisomers and 3-desmethylprodine differed significantly in brain levels attained after 15 min but the magnitudes of difference were not large. Thus, the analgetically more potent β-prodine gave rise to 12% higher brain concentration than did α-prodine, which in turn achieved 11% higher levels than its similarly potent 3-desmethyl analog. If two analgesics penetrate the CNS with similar ease, then when given at equieffective dose levels, the higher-to-lower brain level ratios should approximate the ratio of the greater-to-smaller ED_{50} values. Such was found to be the case in general and only racemic β-prodine and its desmethyl parent showed significantly different brain level and potency ratios. Drug uptake by plasma protein was also investigated and the prodine isomers (racemic mixtures and antipodal forms) differed in extents by less than 10%; it is improbable, therefore, that plasma binding plays an important role in promoting the stereoselective access of these analgesics to the CNS.

Hence, taking the unsubstituted esters (**6**, propionyloxy and acetoxy) as standards, the drug–receptor interaction appears to be enhanced by α-ethyl and impeded by α-*n*-propyl (moderately) and α-*n*-butyl (severely) while all β-substituents except methyl have detrimental influences (the case of 3-allyl is discussed separately below) (Table 7.2). The chief exceptions to receptor preference for α-diastereoisomers are the 3-methyl pairs, where the β-members are not only distinctly more potent than corresponding α-isomers but also more active than their C-3 unsubstituted parents. Assuming close correspondence of binding and preferred conformations, the influence of a β-3-methyl may be achieved *directly* through interaction with a binding site on the receptor specific for axial methyl (the γ-2,3-dimethyl analog, also with an axial 3-methyl group in the preferred conformation, is the most potent of this particular diastereoisomeric set, see later). Larger hydrocarbon groups of the same, axial, orientation are not accommodated at this site and act against drug–receptor association. An alternative explanation, however, is that a β-3-methyl group has an *indirect* influence on ligand–receptor association by facilitating a rise in the population of reversed-ester conformations that bind more effectively than the equatorial 4-phenyl chairs favored for unsubstituted and 3-α-substituted derivatives. Thus, the axial 4-phenyl chair (**7**) (more favored although not preferred for β-esters through the relief of axial 3-methyl interactions) may well have greater receptor affinity than equatorial 4-phenyl analogs. α-Promedol (**8**), for example, an isomer in which the axial 4-phenyl form may be preferred, is about 10 times more potent than the γ-isomer (**9**), in which an axial 4-phenyl orientation is unfavored as discussed later. This argument requires the assumption that the arrangement (**7**) loses its superiority over equatorial 4-phenyl conformers when the 3-substituent exceeds one carbon in chain length. A similar case may be advanced if flexible (boat) forms are conformations most favored by the receptor. As will be seen, the former interpretation of the role of β-3-methyl is considered the more probable



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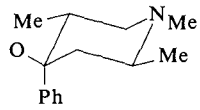

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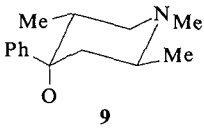


9

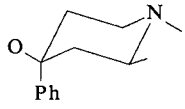
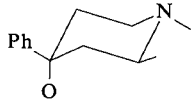
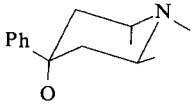
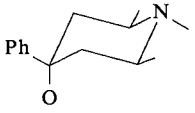
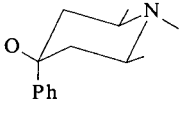
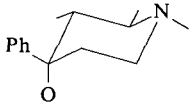
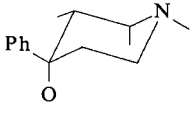
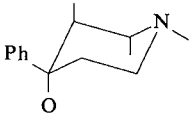
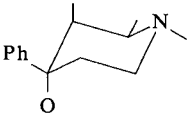
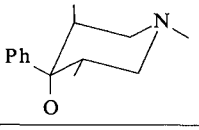
(OCOEt represented by O in these and other formulations)

because it does not require the proposal of a radical difference in the ligand-receptor interactions of α- and β-prodine or of α-promedol and its diastereoisomers.

The case of 3-allyl analogs of the parent reversed ester is of special interest. The stereochemistry of the allylprodines (**6**, R = $CH_2CH{=}CH_2$)[19] has been clarified by concurrent reports from two groups.[20,21] The ^{1}H-nmr characteristics of the isomeric esters and the behaviour of related 4-piperidinols towards dilute acid establishes that the more potent α-diastereoisomer has a *trans*- and the β-isomer a *cis*-3-allyl/4-phenyl configuration. These assignments have been confirmed by X-ray crystallography and the solid-state conformations established for hydrochloride salts.[22] In mice (HP test), α-allylprodine was about 13 times and the β-isomer about one-tenth as active as morphine, results that confirm the superiority of the α-form as an analgesic but give the β-compound a much lower potency than that originally reported.[19] The allylprodines therefore concur with the structure-activity relationship pattern of 3-alkyl reversed esters of pethidine (*trans*-3-R/4-Ph isomer the more potent except for 3-methyl).[18] The strikingly high potency of the 3-allyl derivative (10 times that of the unsubstituted ester) and far lower activity of its reduced 3-*n*-propyl analog demonstrate the large contribution to binding made by the carbon-carbon double bond of the allyl group when present in an α-3-substituent.

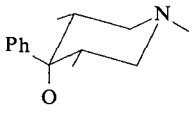
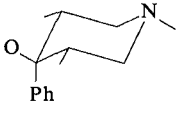
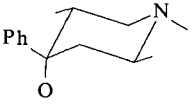
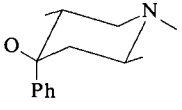
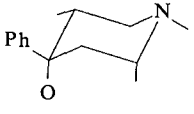
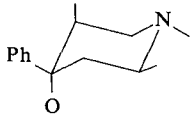
Over the past 20 years or so mono- and di-C-methyl analogs of the reversed ester of pethidine have been reported in addition to 3-alkyl derivatives of the prodine type already discussed; these include 2-methyl, 2,6-, 2,5-(promedol series), 2,3- and 3,5-dimethylpiperidines. In each case stereochemical problems arise that were not solved conclusively in most of the original reports, and since 1970 efforts have been made to isolate all possible isomeric species, to compare them pharmacologically, and to establish configurations unambiguously. A summary of the references and stereochemical data is given in Table 7.3. It turns out, in fact, that wide-ranging potency variations are found not only among the various positional isomers but also within isomeric sets, and it is of great interest to discover whether activity variations may be accounted for by stereochemical demands of the receptor that are valid for the entire group and whether the effects of methyl in its different positions and orientations about the piperidine ring are additive. To this end a

Table 7.3. Stereochemical Data on *C*-Methyl Derivatives of Reversed Esters of Pethidine

Substituent	Isomer designation or characteristic	Configuration[a,b]	Ref.
2-Me	α		23–25
	β		
2,6-di-Me	mp 198–199° (HCl)		26, 27
	mp 203–204° (HCl)		
	mp 145–154° (acid succinate)		
2,3-di-Me	β		28–31
	α		
	γ		
	δ		
3,5-di-Me	γ		41–43

(*continued*)

Table 7 3 (Continued)

Substituent	Isomer designation or characteristic	Configuration[a,b]	Ref
	meso		
	meso		
2,5-di-Me	γ		32–40[c]
	α		
	β		
	δ[d]		

[a] Depicted in most cases as the preferred chair conformation, only one enantiomorphic form is shown for chiral molecules

[b] To simplify these and subsequent formulas, methyl groups are denoted by a single line defining the position and orientation (axial or equatorial) of substitution, and acyloxy (mostly OCOEt) functions by O

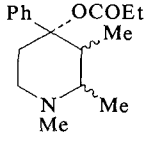
[c] In some of these references α and β are interchanged as a result of an error in an abstract of the original paper,[32] in this review the original designations of Nazarov are employed Initial interpretations of some of the ^{1}H nmr data in terms of configuration were incorrect [33 34]

[d] Configuration originally assigned incorrectly,[40] now established by elimination

comprehensive study of stereochemical structure-activity relationships of 4-phenylpiperidine analgesics is required. Such a study requires knowledge of (1) the relative configuration of the substituents in the piperidine ring, (2) the conformational equilibrium of each isomer, preferably in the protonated state as solute in water, and (3) separation of chiral diastereoisomers into antipodal forms followed by establishment of the absolute configuration and the analgesic potency of each member of enantiomorphic pairs.

Items 1 and 2 have been established chiefly by nmr (^1H and ^{13}C) studies for solutes and X-ray crystallography for solids. All data on optically active forms are due to the elegant work of Portoghese and his colleagues, who eludicated absolute configurations chiefly by correlations with or conversions to chiral molecules of known stereochemistry.

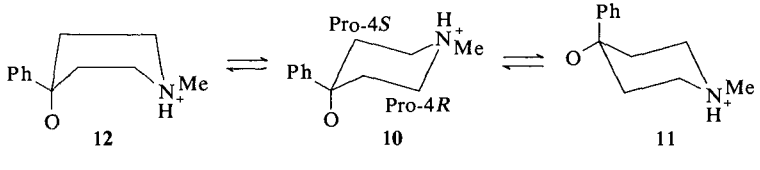
The interpretations of stereochemical structure-activity data that follow are based almost entirely on assay ED_{50} values of the hot-plate test in mice after subcutaneous injection of the test substance. In many cases compounds have been examined in the medicinal chemistry section of the National Institutes of Health under the direction of Dr. E. L. May, and later of Dr. A. E. Jacobson, a fact that permits meaningful comparisons among the various derivatives and especially of isomeric sets. Where *in vitro* assay data on isomeric sets are available, correlations with *in vivo* potency rankings are found even though 4-phenylpiperidines generally have rather low orders of activity/affinity in these tests. Results for a triad of 2,3-dimethyl analogs of the reversed ester of pethidine with MHP rankings $\gamma > \alpha > \beta$ illustrate this point.[91]



	IC_{50}, nM (GPI)	IC_{50}, nM (MVD)	K_1, nM^a
γ	196 ± 46	234 ± 24	19.5 ± 3.8
α	1750 ± 470	234 ± 24	186 ± 39
β	30-35% inhibition at 10,000	Inactive at 10,000	1903 ± 422

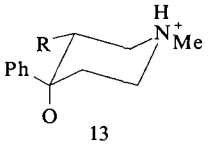
[a] Displacement of μ-ligand [^{3}H-D-Ala^2, MePhe^4, Gly-ol^5]enkephalin.

In most isomers investigated a piperidine chair with an equatorial 4-phenyl substituent (**10**) is highly preferred although there are cases (e.g., the α-2,5-dimethyl derivative) of a possibly favored axial phenyl chair (**11**) and several where populations of flexible (boat) forms (**12**) are likely to be significant. As a starting point to the analysis, Portoghese's treatment of the reversed ester of pethidine in its preferred equatorial 4-phenyl chair conformation is followed.[44] Borrowing biochemical nomenclature,[45] the two sides of the nondissymmetric (achiral) reversed ester (**10**) may be differentiated as prochiral-4*S* and prochiral-4*R*. If an alkyl group is inserted in the Pro-4*S* side, the formerly symmetric C-4 atom becomes asymmetric and acquires an *S* configuration in terms of the Cahn-Ingold-Prelog convention[46]; insertion of alkyl in the Pro-4*R* side gives C-4 an *R* configuration.

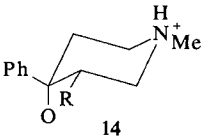


12 10 11

The question now arises as to whether the opioid receptor discriminates between the two sides (or enantiotopic edges)[44] of the molecule in the same sense as enzymes differentiate chemically alike paired groups of substrates of the Caabc type such as citrate (Ogston effect).[47] Data on the antipodal forms of 3-alkyl derivatives of the prodine type strongly suggest that the opioid receptor does indeed show discrimination of this nature. Thus, it is found that the more potent antipodal forms of α-3-methyl(α-prodine), α-3-ethyl, and α-3-propylpiperidines all have the same configuration; **13** depicts the more (3*R*,4*S*) and **14** the less (3*S*,4*R*) potent enantiomer. The same configurational



13

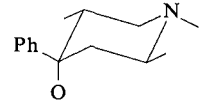


14

R	3*R*,4*S*	3*S*,4*R*
Methyl	0.91	22.4(cf. R = H, 1.3)[44]
Ethyl	0.9	25(cf. R = H, 0.85)[48]
n-Propyl	1.0	25.2[48]
Allyl	0.03	7.8[48]

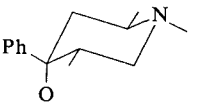
(ED_{50} mg/kg, sc MHP)

pattern is displayed, moreover, by the α-3-allylprodines[48] even though potency levels are much higher than in the preceding examples, and also by (+)- and (−)-γ-promedol (**15**).[49] One interpretation of these findings[4] is that the pethidine-reversed ester presents the Pro-4*R* rather than Pro-4*S* side of the molecule to the receptor. Substituents positioned in the 4*S* side are remote from the receptor surface and do not hinder approach of the ligand to receptor binding sites—the similar orders of potency of α-4S (**13**, R = Me, Et and *n*-Pr) and the unsubstituent ester support this proposal. In the α-4R antipodes the ring alkyl substituent (at least when equatorial and adjacent to C-4) prevents effective drug-receptor association because it is now immediately adjacent to the receptor surface. These arguments are given further weight by the fact that the *cis*-3,5-dimethyl analog (**16**) lacks analgesic properties.[42] The α-3-allylprodines are accommodated by the same proposals except that in this case the 3-alkyl substituent plays a significant positive role in enhancing drug-receptor binding when present within the 4*S* edge.

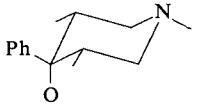


ED_{50}, 0.94

γ-Promedol
15



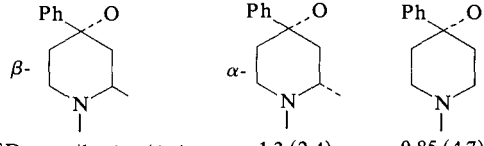
8.8[51]



16

(In these and subsequent formulas methyl substituents are represented by a single line and ED_{50} data are in mg/kg, sc, MHP.)

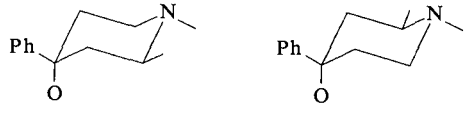
Turning now to derivatives with substituents adjacent to nitrogen, the racemic α-and β-2-methyl-reversed esters prove to have similar activities (in contrast to the prodine diastereoisomers) and are somewhat less potent than the parent desmethyl derivative (see **17**).[23] The β-2-methylpropionate, with



ED_{50} mg/kg 1.4 (4.9) 1.3 (2.4) 0.85 (4.7)
(Acetate data in parentheses)

17

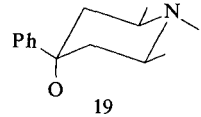
preferred equatorial 4-phenyl chair conformation,[23] has recently been resolved and a tenfold potency difference between antipodes revealed.[17] The more active (levo) isomer was shown to have the 2*S*,4*R* configuration by X-ray analysis (see **18**). It is interesting to note that stereoselectivity toward equatorial



(−)-2*S*,4*R* (+)-2*R*,4*S*
ED_{50} mg/kg 0.53 5.5

18

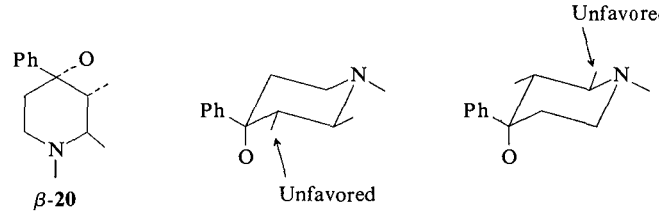
ring-methyl groups α- to nitrogen is the reverse of that toward those placed adjacent to the 4-phenyl substituent in reversed esters. α-*eq*-Methyl within the 4*R*-enantiotopic edge has little influence on activity as judged by concurrent assay data on the desmethyl parent (ED_{50} 0.4–0.6 mg/kg),[50] while a similarly oriented group in the 4*S* edge significantly impedes drug-receptor binding as confirmed by IC_{50} values of 1.2 μM for the levo and 11.0 μM for the dextro isomer (concentrations required to displace 50% of stereospecifically bound [^{3}H]etorphine from opioid-binding sites in guinea pig brain homogenates).[17] The inactivity of the *cis*-2,6-dimethyl analog (**19**) conforms to this interpretation.[26]



19

Reversed esters with equatorial methyls adjacent to both 4-phenyl (as in α-prodine) and nitrogen (as in **17**) are next considered. The activity of the racemic γ-2,5-dimethyl derivative mixture (promedol, trimeperidine), of like potency to the unsubstituted reversed ester, proves to reside chiefly in the (+)-isomer of 2*S*,4*S*,5*R* configuration (see **15**).[49] Note that the methyls are

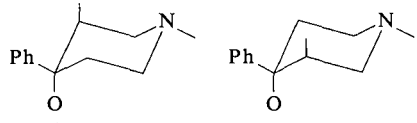
placed in favorable and unfavorable enantiotopic edges in (+)- and (−)-isomers, respectively, as judged by results on the 2- and 3-monomethyl derivatives. The corresponding 2,3-dimethyl isomer (*β*-**20**) has a very low potency (ED_{50} 30.7 mg/kg in mice by the HP test)[31] in accord with the fact that a favorable placement of both methyls is impossible in either of the isomers (see **20**).



β-**20**

Thus, in 2- and 3-monomethyl, and 2,5- and 2,3-dimethyl derivatives with preferred equatorial hydrocarbon substituents, consistent and additive stereochemical structure–activity relationships are found. Furthermore, the more active antipodal forms have potencies close to that of the desmethyl parent ester, in support of an essentially passive role for methyl substituents of this type in the drug–receptor interactions.

β-Prodine presents a case where the 3-methyl substituent has a preferred axial orientation, and in this instance the (+)-3S,4S isomer is the more potent antipode.[44] Hence, in terms of equatorial 4-phenyl chairs, the Pro-4S edge is still the preferential substitution site (as in *α*-prodine) but the receptor is not as selective toward axial 3-methyl (13-fold antipodal activity difference) as it is toward equatorial groups (25-fold difference) (see **21**). In addition, axial 3-methyl placed along the Pro-4S edge raises potency (4×) so its role is not passive as is a similarly positioned equatorial group.

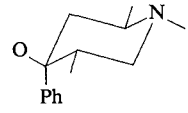


(+)-3*S*,4*S*
ED_{50} mg/kg 0.25

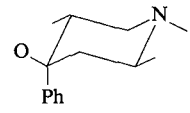
(−)-3*R*,4*R*
3.3

21

From the viewpoint of preferred conformation a stereochemical correlation between the more potent antipodal forms of *β*-prodine and the *α*-2,5-dimethyl derivative (*α*-promedol) is not immediately apparent. In the latter compound the dextro isomer, depicted in its axial 4-phenyl chair form (preferred for *α*-4-piperidinol base, X-ray evidence),[38] is about 20 times more active than the desmethyl parent while the levo form is inactive (see **22**).[51] The inverted chair form of (+)-*α*-promedol (**23**) clearly reveals a stereochemical kinship with (+)-*β*-prodine in respect to C-3(5) geometry, and furthermore points to the activity-raising role of axial methyl adjacent to nitrogen when

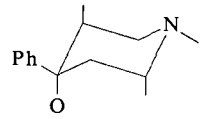


(+)-
ED_{50} mg/kg 0.06



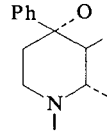
(−)-
Inactive to 50

22

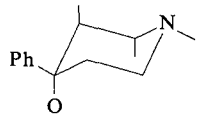


23

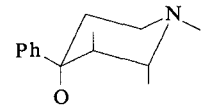
located in the front edge of the molecule as depicted. The conformation (**23**) may seem unlikely as the active (receptor-bound) form of the molecule, since it requires three axial substituents in comparison with the single axial phenyl of (**22**), but there is evidence from conformational energy calculations that it is in fact the preferred form[92] (^{13}C-nmr evidence of solute conformation is equivocal).[36] Furthermore, not only is the equatorial 4-phenyl chair (with axial Me and OCOEt substituents) preferred to the axial 4-phenyl chair conformation of β-prodine, it is also favored in the case of the γ-2,3-dimethyl analog of promedol (**24**) and the corresponding 4-piperidinol hydrochloride.[30,31] Antipodal forms of γ-(**24**) have not yet been examined, but the racemic mixture is about four times as potent as the reversed ester of pethidine and 100 times that of the corresponding β-isomer (**20**). It is highly probable that the 4*S* isomer will prove the more active antipode, and it follows that the receptor can accommodate axial methyl adjacent to nitrogen within either enantiotopic edge (cf. 2-Me configuration in **23** and 4*S*-**24**). The last point is supported by the retention of activity in the tropane analog of the acetoxy-reversed ester of pethidine (**25**)[52,66] and stands in contrast with receptor sensitivity toward equatorial α-methyl substituents, as discussed earlier.



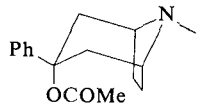
γ-**24**



4*S* isomer



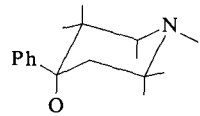
4*R* isomer



ED_{50} mg/kg 3.4
(4.7 for reversed acetoxy ester of meperidine)[66]

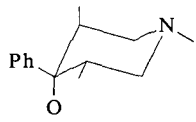
25

The absolute orientations of methyl substitution that favor or have minor influence on the ligand–receptor interactions of the reversed ester of pethidine identified by the preceding analysis are summarized in terms of the equatorial 4-phenyl chair (**26**), and the concordance of the stereochemical SAR of the remaining C-methyl derivatives with these deductions may now be examined.

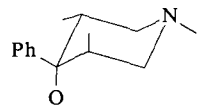


26

A detailed study of 3,5-dimethyl analogs has been made.[41] Of the three diastereoisomers only the γ-isomer (*t*-3Me, *c*-5Me, *r*-OCOEt) is active (at least twice as potent as pethidine in mice), and the more active (+)-antipode has an axial 3-methyl group advantageously, and an equatorial 5-methyl disadvantageously placed (see **27**). Because axial 3-methyl placed as in dextro- (**27**) has a potency-raising influence (cf. discussion of β-prodine), activity is retained in spite of the unfavorably positioned equatorial methyl but at a lower level than that of the desmethyl parent.



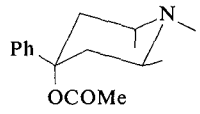
(+)-3*S*,5*S*
ED_{50} mg/kg 4.91
(pethidine 28.8)



(−)-3*R*,5*R*
25.01

27

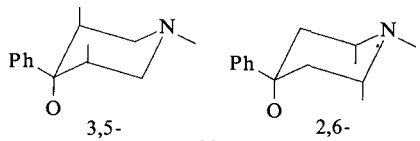
The 2,6-dimethyl triad of diastereoisomeric esters presents a case similar to the 3,5-dimethyl derivatives. The sole active member is the *trans*-2,6-dimethyl-*eq*-4-phenyl chair (examined as acetate ester)[26] and the more active antipode deduced as (**28**) with equatorial methyl within the front enantiotopic edge (cf. data on β-2-methyl antipodes). Unlike the (+)-γ-3,5-dimethyl isomer (**27**), structure (**28**) contains no unfavorable element and its potency is clearly



28

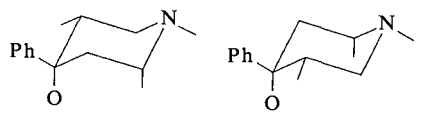
superior to the desmethyl parent. The inactivities of *cis*-3,5- and 2,6-*eq*-dimethyl analogs of equatorial 4-phenyl chairs have already been interpreted. *cis*-Diaxial analogs (**29**), especially the 2,6-dimethyl derivative, might be expected to show activity and the fact that they fail to do so may be attributed to

the highly unfavored nature of the conformations as shown, which entail severe syn-diaxial Me-Me interactions.



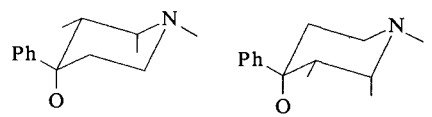
29

The β-2,5- and α-2,3-dimethyl-reversed esters are both represented by equatorial 4-phenyl chair conformations with one *eq*-3(5)- and one *ax*-2-methyl substituent; of these, **30** and **31** with *eq*-Me within the rear edge should be active forms in terms of the general structure (**26**), and both racemates are, in fact, reasonably potent—close to or somewhat weaker than the desmethyl parent.[30,34]



Racemic mixture ED_{50} mg/kg 0.6 (2.6, acetate)
Desmethyl analog 0.85 (4.7)

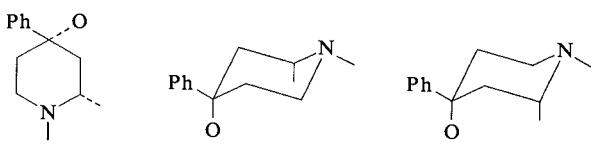
β-2,5-**30**



Racemic mixture ED_{50} mg/kg 1.6 (6.5, acetate)
Desmethyl analog 0.4–0.6 (4.9) (1980 data)

α-2,3-**31**

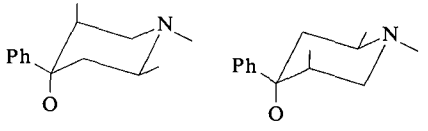
Neither antipode of the α-2-methyl derivative (**32**) (shown in the *eq*-4-phenyl chair conformation) has an unfavorably placed methyl substituent, and a hot-plate ED_{50} value of 1.3 mg/kg (racemic mixture, 2.4 mg/kg for acetate),[23] which is close to that of the reversed ester of pethidine itself, presents no problem of interpretation. As the two antipodes differ in the configuration of an axial methyl adjacent to nitrogen, the isomeric potency ratio is likely to approach unity.



α-**32**

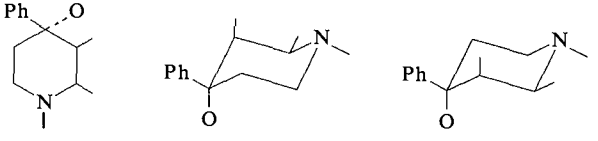
Finally, δ-diastereoisomers of the 2,5- and 2,3-dimethyl series need consideration. The δ-analog of promedol was reported in the original Russian

literature as a potent analgesic, twice as active as the γ-isomer (promedol).[32] Its configuration has not been established but by elimination it must be the *t*-2Me, *t*-5Me, *r*-OCOEt isomer, one antipodal *eq*-4-phenyl chair form (**33**)



δ-2,5-**33**

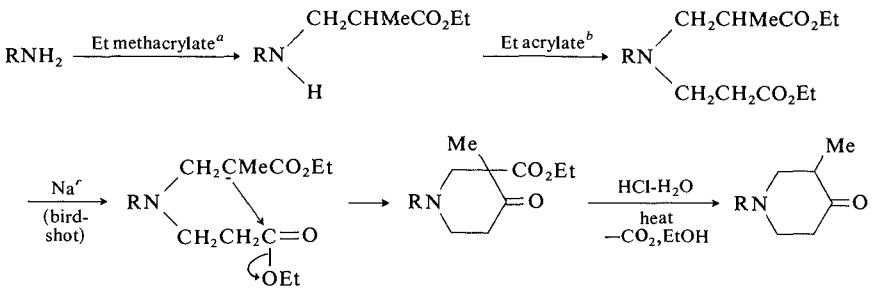
of which should be active (probably more so than the desmethyl parent) because it contains favorably placed axial 5-methyl and *eq*-2-methyl substituents. In contrast, the δ-2,3-dimethyl derivative (configuration **34**, again by elimination) is inactive,[28] as anticipated from the fact of unfavorable methyl substitution in each antipode (2-Me in 4*S*, 3Me in 4*R*).



δ-2,3(**34**) 4*S* 4*R*

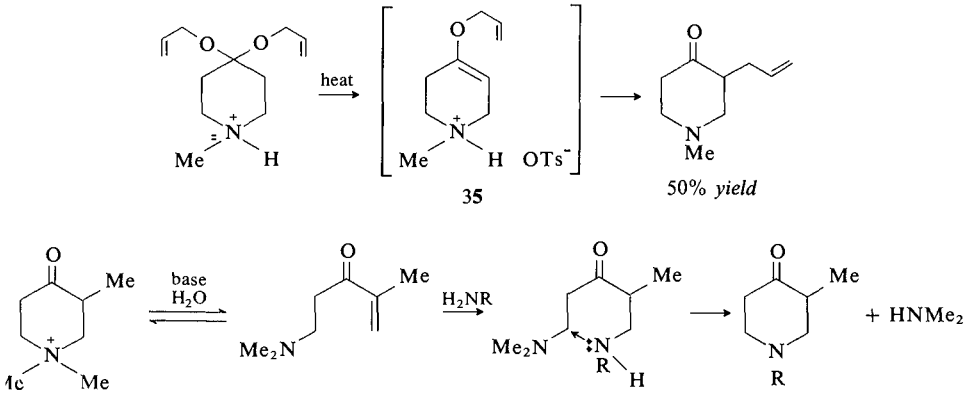
7.3. SYNTHETIC AND STEREOCHEMICAL METHODOLOGY

The key intermediates for reversed esters of pethidine are 4-piperidones as illustrated at the outset of this chapter (see **1**); these aminoketones are usually made by a Dieckmann cyclization of a bis-β-carbalkoxyethylamine with sodium or a related agent and decarboxylation of the resultant 3-carbalkoxy-4-piperidone.[53] The fact that Michael condensations of this type may be carried out stepwise makes possible adaptation of the route to the synthesis of 2- and 3-methyl-4-piperidones (Scheme 7.1). Substituted 4-piperidones with 3-alkyl groups larger than methyl, such as ethyl and allyl,[19] may also be made by the Dieckmann procedure but not so conveniently because the appropriate 2-substituted acrylates are not commercially available. An alternative route to 3-allyl-1-methyl-4-piperidone is the Claisen rearrangement of the allyl vinyl ether formed from the product of exchange between **1**-methyl-4-piperidone and acetone diallyl ketal (see **35**).[20] The Dieckmann route works best with methylamine as the starting primary amine, and 4-piperidones with larger *N*-substituents are often more conveniently obtained by utilizing an exchange reaction between the methiodide salt of the *N*-methyl ketone and the appropriate primary base[54]; a probable mechanism is shown in an example (**36**). The reaction must be promoted by a strong base such as tetramethylammonium hydroxide in the absence of a methyl substituent α- to C-4, since the ketone function is then deactivated by hydration.



[a] Use of ethyl or methyl crotonate at this stage leads to a 2-methyl-4-piperidone.[23]
[b] 1(Amine) to 1(acrylate), R°, 10 days; when R is $PhCH_2$ or $Ph(CH_2)_2$, reactants need to be heated under reflux.
[c] Bases such as NaOEt, NaH and $NaNH_2$ may be used; also potassium metal.

Scheme 7.1



35

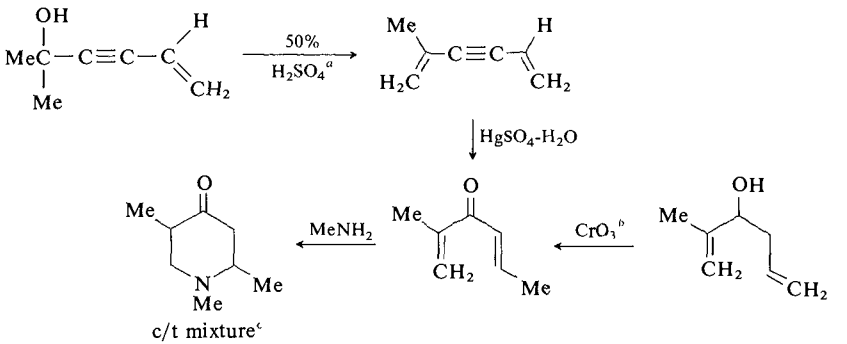
50% *yield*

R = isoPr, *t*-Bu, etc.[54]

36

Several 4-piperidone syntheses are based on the addition of a primary amine to a divinyl ketone and methods for the preparation of 1,2,5-trimethyl-4-piperidone (the precursor of the promedols) and the 2,3-dimethyl analog by this means are shown (Schemes 7.2 and 7.3). 3,5-Dimethyl-4-piperidone is prepared on a similar basis,[41] while the 2,6-dimethyl ketone is made either by a Mannich procedure from dimethyl acetonedicarboxylate and acetaldehyde (leading to *c-t* mixtures)[26] or by catalytic reduction of 1,2,6-trimethyl-4(1H)-pyridone (**37**) and oxidation of the resultant 4-piperidinols, giving a *cis* product.[58]

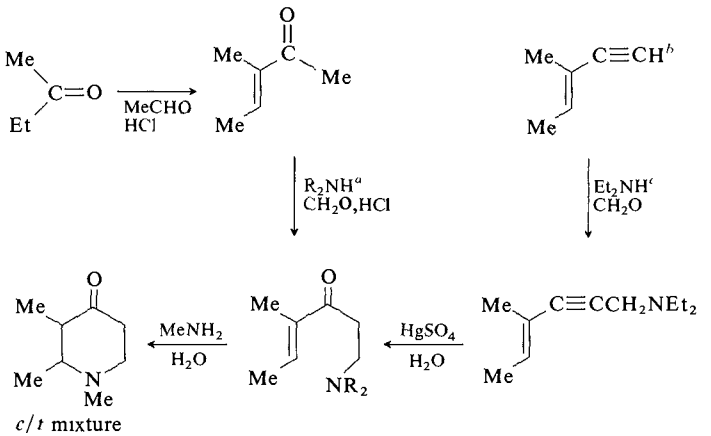
There are no special synthetic features to the conversion of 4-piperidones to corresponding reversed esters (phenyl lithium is generally preferred to a phenyl Grignard as the organometallic reagent, while dehydration products are sometimes encountered when the 4-piperidinols are esterified), but a



[a] Refs 32, 55, [b] Ref 49, [c] Ref 56

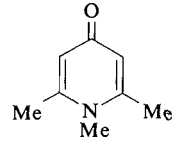
Scheme 7 2

one-step alternative route to the parent alcohol of the reversed ester of pethidine is worth mentioning. The method involves amino-methylation of α-methylstyrene and gives the 4-piperidinol in 30% yield together with a substituted oxazine (see **38**); use of ammonium chloride as the basic salt gives the *N*-desmethyl analog while higher α-substituted styrenes are claimed to lead to prodine alcohols and higher analogs.[59]

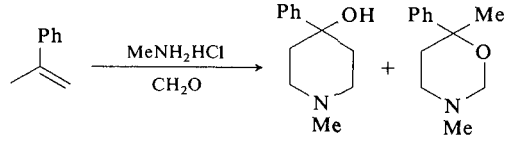


[a] Refs 30, 31, R = Me or Et
[b] Treat 2-butanone with acetylene and dehydrate the resultant *t*-alcohol
[c] Ref 57

Scheme 7 3



37



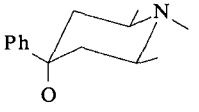
38

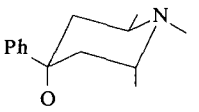
7.3.1. Stereochemistry

Separations of diastereoisomeric forms (racemic mixtures in most cases) of mono-*C*-methyl (two isomers) and di-*C*-methyl (three or four isomers) analogs of the reversed ester of pethidine have been achieved in various ways, for example, by fractional crystallization of propionate ester hydrochlorides (α- and β-prodine),[3] fractional crystallization of the precursor 4-piperidinols followed by chromatography (2-methyl and 3,5-dimethyl analogs),[23,41] fractional crystallization of 4-piperidinols first in the free-based form and then as hydrochlorides (2,3- and 2,5-dimethyl congeners).[29,34] Minor isomers of both 2,3- and 2,5-dimethyl derivatives have been secured by chemical inversion and other transformations.[29,40] Resolutions of chiral diastereoisomers, chiefly the work of Portoghese and his group, have been achieved by treating corresponding 4-piperidinols with a variety of resolving agents, all derivatives of (+)- and (−)-tartaric acid or the acid itself.[60]

Initial stereochemical interest in the field centered on the prodines, and configurational conclusions of the late 1950s were based mainly on chemical evidence such as rates of ester hydrolysis, the likely course of addition of aryl lithiums to the precursor 4-piperidone, and the reaction of the 4-piperidinols with thionyl chloride and the ease and direction of their dehydration.[9,61] The assignments *c*-3Me, *r*-4OCOEt to α- and *t*-3Me to β-prodine were substantiated by X-ray crystallographic analyses in the early 1960s, which also established the solid-state conformations (4 and 5).[10] With the advent of the nmr era, a powerful technique for the study of solute conformation became available, and preferred conformations of α- and β-prodines and related compounds (base and conjugate acids) as solutes in a variety of solvents were proposed on the basis of isomeric differences between ^{1}H-nmr spectra.[62] The technique, together with that of ^{13}C-nmr (since 1970), has now been applied to all isomeric reversed esters and a few examples that illustrate the principles are now given.

^{1}H-nmr spectroscopy readily enables the differentiation of chiral from achiral (meso) diastereoisomers of 3,5- and 2,6-dimethyl-4-phenylpiperidines because in the meso forms the two methyls have identical environments and give rise to the same resonance, while chiral isomers involve an axial-equatorial pair that results in two separate methyl signals (see **39**). The configurations of both the chiral 2,6- and 3,5-dimethyl reversed ester analogs of pethidine have been confirmed by X-ray crystallography.[27,41]





	cis	*trans*
2,6-di-Me ^{1}H-nmr signal	δ1.58 Doublet HCl in $CDCl_3$	δ1.2, 1.07 Pair of doublets base in $CDCl_3$

(Data refers to acetoxy esters)[26]

39

Coupling constant data of vicinal protons often yield direct information about stereochemistry as a result of the relationship between the ^{3}J magnitudes and dihedral angle between the coupled protons.[63] Thus, for γ-promedol alcohol (a 2,5-dimethyl derivative) a two-proton doublet of quartets anticipated for the 3-CH_2 of the coupled system 3-H_a, 3-H_e, 2-H is present in the spectrum near δ2 ppm (Fig. 1).[34] First-order analysis gives ^{2}J 14 (identified by its occurring four times within the eight-line signal) and ^{3}J **11** and 3.5 Hz. The vicinal values are typical of a/a and e/a (or e/e) coupling, respectively; thus, the arrangement (**40**) must occur in the γ-isomer with 2-methyl positioned equatorially in the preferred 4-phenyl chair conformation. Resonance assignments to the 3-methylene protons were validated by the absence of such signals

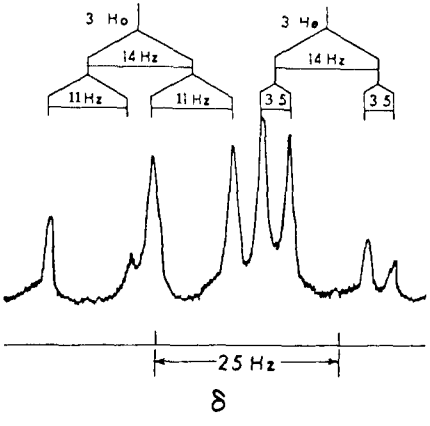
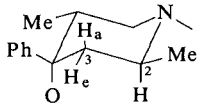


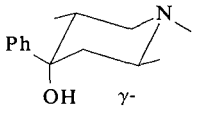
Fig. 7.1 Part of the ^{1}H-nmr spectrum of γ-promedol alcohol recorded at 100 MHz in $CDCl_3$ (signal falls between δ2.0 and 1.5 ppm).

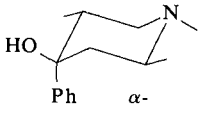


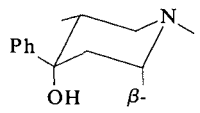
40

in the spectrum of the γ-deuterated analog obtained from the 3,3,5-trideuterated 4-piperidone.

Turning now to some ^{13}C-nmr examples, chemical shifts of *ax*- and *eq*-2-methyl carbons may be assigned by study of spectra of the chiral forms of 2,6-dimethyl-4-phenylpiperidin-4-ol and related acetate (see **39**). Of the two C-2(6)-methyl resonances seen in the spectrum of the *trans* isomer, the higher field (near 13 ppm) is assigned to the axial group and the lower field (near 20 ppm) to equatorial methyl on the principle of the more sterically compressed group having the higher field position (an *ax* group is in a more hindered environment than an *eq* group).[25,64] The ^{13}C-nmr chemical shift comparisons between the three promedol alcohol isomers (**41**) then show that 2-methyl has





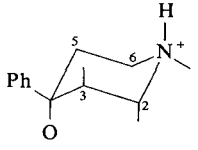


^{13}C chemical shift[36]	γ-	α-	β-
C-2	20.1	20.6	13.0
C-5	12.0	14.5	15.0
C-q	147.2	144.9	147.4

(ppm from TMS)

41

an equatorial conformation in the γ- and α-isomers and an axial orientation in the β-isomer. The similar C-q (quaternary aromatic carbon) chemical shifts of the γ- and β-isomers and the higher field C-q resonance of the α-isomer enable 4-phenol conformational assignments to be made as shown.[36] Similar evidence establishes the relative configurations of 2,3-dimethyl analogs.[30,31] The γ-ester hydrochloride of this series is of special interest; its diaxial methyl conformation (**42**) is supported by the marked upfield shifts (5–6 ppm) of both the C-5 and C-6 carbons compared with corresponding shifts of the unsubstituted reversed ester (diagnostic of steric compression due to opposed axial methyls),[65] and the unusually low field positions of the *C*-methyl signals.



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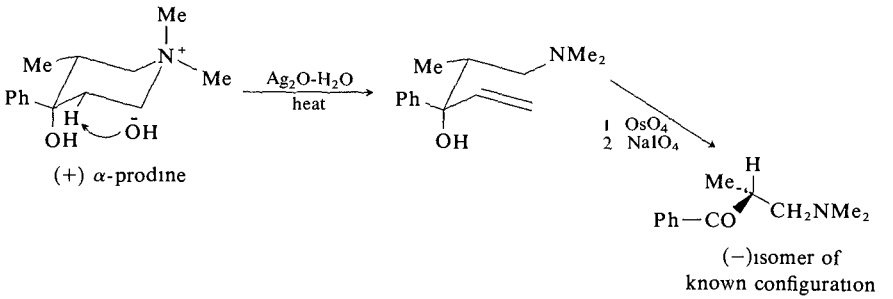
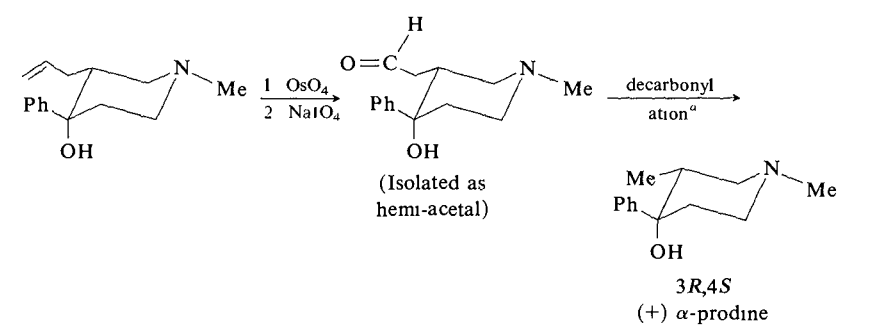


Scheme 7 4

Absolute configurational assignments to chiral reversed esters of pethidine have been accomplished by reaction sequences leading to degradation products of known chirality, by schemes linking *C*-methyl analogs of known with those of unknown configuration, and by application of the crystallographic technique of anomalous dispersion whereby absolute geometry is directly derived from the X-ray data.

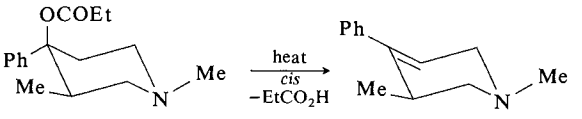
A sequence in which a metho salt of (+)-α-prodinol is converted to a phenyl ketone of known configuration is shown (Scheme 7.4)[44]; (+)-γ-promedol is likewise degraded to the same levo ketone; hence, the two dextro 4-piperidinols have identical C-3(5) configurations.[49] The chirality of the antipodal 3-allylprodines is determined by their conversion to corresponding prodinols, now of established configuration (Scheme 7.5).[48]

The more active antipodal forms of α- and β-prodine are neatly linked as follows: pyrolysis of (+)-α-prodine (*cis* steric pathway) gives the (−)-tetrahydropyridine (**43**) with preservation of C-3 chirality, while dehydration of (+)-β-prodinol (*trans* steric course also leaving C-3 geometry intact)[61]



[a] Reagent tris(Ph_3P) rhodium(I)chloride

Scheme 7 5

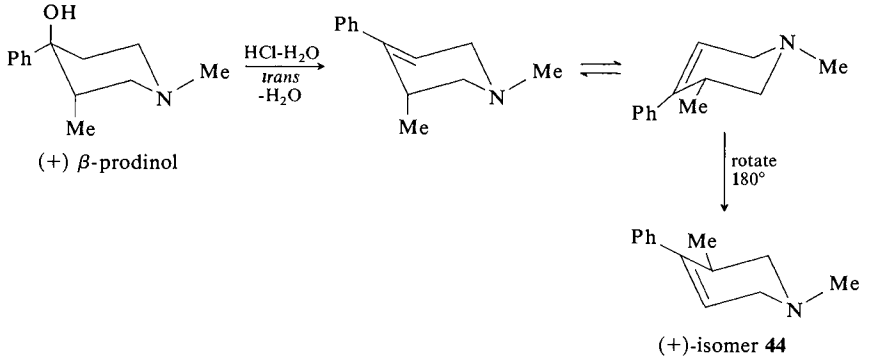


(+) 3*R*,4*S* α-prodine

(−)-isomer **43**

gives the (+)-alkene. Manipulation of structures as shown reveals that (+)-α- and (+)-β-prodine must therefore have opposite configurations at C-3.[44]

Finally, the absolute configuration of (−)-β-2-methyl-4-phenyl-4-piperidinol has been established by X-ray analysis of the hydrochloride (the salt provides the heavy atom necessary to the anomalous dispersion technique).[17] This physical procedure is the method of choice because it avoids problems of racemization and inversion inherent in all chemical transformations however well conceived.



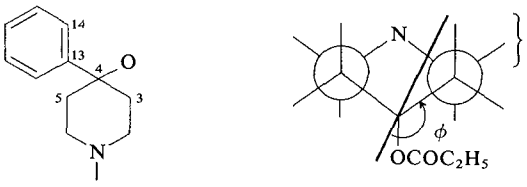
(+) β-prodinol

(+)-isomer **44**

7.4. CONCLUDING REMARKS

A consistent stereochemical structure-activity pattern may be built up on the basis of the 4-phenylpiperidine ligands associating with the opioid receptor in the form of equatorial 4-phenyl chair conformations. Other conformations (i.e., axial 4-phenyl chairs or flexible boat forms) could have been employed as the basic active species but greatest adherence to probable conformations is possible by the approach adopted; furthermore, no need arises to assume a major difference in the binding modes of the few examples of esters in which axial 4-phenyl chair conformations may be favored.

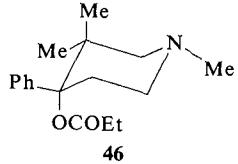
Portoghese[60] has interpreted potency differences between *C*-methyl pethidine-type antipodes in terms of the sign and magnitude of C(14)-C(13)-C(4)-C(5) torsion angles (all fall in the range −128 to −167° for the more active antipodes of α- and β-prodine, 5-methylprodine, α- and γ-promedol, and α-allylprodine), and steric hindrance between the *C*-alkyl substituent and the receptor when the ligand is in a pharmacophoric conformation. The



45 Projection formula of reversed ester of pethidine

significance of the orientation of the phenyl and piperidine rings in absolute terms is doubtful, however, since, as has been pointed out,[22] the corresponding value of the relatively weak and non stereoselective analgesic (+)-β-allylprodine is also negative and within the range found for potent agents. Furthermore, activity differences between antipodal forms of the β-2-methyl reversed ester cannot be accounted for in this manner because the *C*-methyl substituent is too far removed from C-4 to influence the orientation of the aromatic substituent.[17]

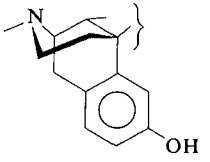
Whether or not the topography of the opioid receptor in its binding conformation will in fact prove capable of accommodating reversed esters of pethidine in equatorial 4-phenyl chair conformations and bearing *C*-methyl substituents oriented as in the general structure (**26**) must await the technological advances that will permit direct observation of opioid ligands bound to their receptors (cf. work on the enzyme lysozyme and its substrates). For the present, conclusions reached from stereochemical structure-activity analysis may find utility in the design of novel agents and the correlation of the 4-phenylpiperidine class with other families of analgesics (see studies of relative stereochemistries of 3-substituted fentanyls and prodines, p. 291). As an example of the predictive value of the analysis, the case of the 3,3-dimethyl analog of the reversed ester of pethidine may be given.[67] According to the analysis, the analgesic activity of the racemic mixture of this derivative should reside in the R-isomer **46** and the S-isomer should be inactive. Results of antinociceptive tests on RS, R, and S forms (obtained from 1,3,3-trimethyl-4-piperidone, 4-piperidinols resolved using dibenzoyl-L-tartaric acid, absolute configurations by X-ray crystallography) validated these predictions.



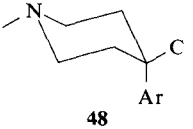
46

Early attempts to account for the analgesic properties of pethidine and its reversed ester[68] involved the assumption that the active conformations of 4-phenylpiperidines mimic rigid analgesics of the morphine, morphinan, and

6,7-benzomorphan class (see 47).* Ample evidence, in addition to the stereochemical analysis, is now available to discount this viewpoint—certainly for derivatives of 4-phenylpiperidines with C-4-oxygen substituents. Thus, there is a striking difference between the pharmacological properties of *N*-allyl (and *N*-CPM, etc.) analogs of normorphine (antagonists) and corresponding norpethidine-reversed esters (agonists, p. 239), while inclusion of meta-placed hydroxy in the phenyl substituent of the parent reversed ester and diastereoisomeric forms of prodine and 3-allyl prodine leads to a virtual loss of activity (p. 241). In contrast, most active 4-arylpiperidines with C_4-carbon substituents such as CO_2Et and COEt (and methyl and other alkyls, see p. 276), are of low potency or inactive without such a phenolic function. This radical difference in the structure-activity relationships between 4-arylpiperidines with C_4-O compared with C_4-C substituents may be a result of differences in conformational preferences. Energy calculations for pethidine (4-CO_2Et) and bemidone (4-COEt) reveal little difference between axial and equatorial 4-arylpiperidine chairs, while in the case of 1,4-dimethyl-4-phenylpiperidine the axial form is actually preferred.[70] For pethidine-reversed esters (and C_4-O derivatives with 3-Me substituents) the *eq*-4-phenyl conformers are the low-energy form, and hence favored, a finding consistent with nmr evidence;[25,62] the same conclusions were reached in an earlier quantum-chemical study of the prodines.[93]



(Partial formula)
47



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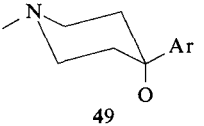


49

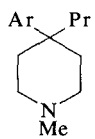
It may be proposed, therefore, that analgesics based on 4-arylpiperidines with C_4-carbon substituents (and unsubstituted at C_3) associate with opioid receptors in the axial-4-aryl chair conformation **48**, which is a mode closely analogous to that of morphine **47**. It is consistent that introduction of meta-OH into such piperidines should enhance analgesic potency. The pethidine-reversed esters, on the other hand, appear to associate with opioid receptors in a different manner involving an *eq*-4-phenyl chair conformation **49** that will not tolerate a phenolic substituent. The lack of antagonist properties in C_4-carbon derivatives such as *N*-allylnorketobemidone,[71] however, remains an enigma, especially since *N*-allyl derivatives of simple 3-*m*-hydroxyphenylpiperidines and pyrrolidines antagonize morphine as anticipated (p. 280).

* Activity profiles of pethidine and α-prodine against different nociceptive stimuli in mice and rats classify these 4-phenylpiperidines as μ-receptor agonists typified by morphine.[69]

Further studies of phenolic analogs of 4-phenylpiperidine analgesics—especially those with preferred axial 4-phenyl chair conformations—are therefore clearly important for the elucidation of the ligand-receptor binding modes of derivatives based on pethidine.

7.5. PHENOLIC PIPERIDINES AND PYRROLIDINES

In the piperidines derivatives so far described, the presence of an oxygenated function at position 4 of the alicyclic ring is an essential feature of all active compounds. As long ago as 1958, however, McElvain and Clemens[72] reported some highly active 4-arylpiperidines that lacked such groups and, instead, carried alkyl substituents at C-4 (see **50**). All compounds with significant activity were phenols with meta-placed hydroxyl, and subsequent studies have shown that the presence of phenolic OH attached to the meta-carbon of the 4-aryl moiety is an essential feature of active compounds of this kind, as it is of the morphine group. Interest in compounds of type **50** was



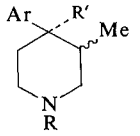
50

2 mg/kg ≡ 2–4 mg morphine sc in rats
(des-OH, *O*Me, 2- and 4-*O*H analogs less active)

Ar = 3-OHC_6H_4 in this and subsequent formulas

revived in 1978 by a paper by Zimmerman *et al.*[73] Previous SA relationships of the series were confirmed (need for a metaphenolic OH, enhanced activity of 4-propyl over 4-methyl derivatives), but of more importance was the discovery that the presence of 3-methyl *cis*-oriented to 4-aryl resulted in an analgesic antagonist rather than agonist. Thus, the β-(*cis*)-3,4-dimethyl derivative (Table 7.4, entry 1) was either half or twice as active as nalorphine (depending on rodent species) and lacked agonist properties, while the corresponding α-(*trans*) isomer behaved as a partial agonist (entry 2). Results for the 4-propyl diastereoisomers were less clearcut; the α-form was primarily an agonist (like the 3-desmethyl derivative, although less potent) and the β-form was a significant antagonist in rats but a weak agonist in mice (entries 3–5). *N*-substituents associated with morphine blockade in polycyclic derivatives, like allyl and CPM, depressed the antagonist potency of the β-**1**,3,4-trimethyl derivative somewhat in rats while 2-phenethyl and 2-benzoylethyl raised activity (to the level of naloxone in the last case) with some evidence of receptor preference for the dextro antipode (entries 6–9). The view that the more potent β-derivatives were pure antagonists was backed by *in vitro* tests (binding IC_{50} values were unchanged in the presence of Na^+ and their rank orders correlated with *in vivo* AD_{50} values).[73] Antagonist properties were also claimed for β-3-methylketobemidone and the phenolic analog of β-prodine (see p. 241).

Table 7 4. Agonist and Antagonist Activities of Some 4-*m*-Hydroxyphenyl-4-alkylpiperidines[a]



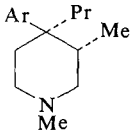
α *trans* 3-Me, 4-Ar
β. *cis* 3-Me, 4-Ar
Ar = *m*-OH C_6H_4

Entry	*N*-R	4-R'	Isomer	Antagonist AD_{50}[b]		Agonist measure	
				Rats	Mice	Rats (ED_{2s})[c]	Mice (ED_{50})[d]
1	Me	Me	β	0 24	1 0	>50	>50
2	Me	Me	α	13	45	33	15
3	Me	Pr	β	4 6	43	>50	13
4	Me	Pr	α	Additive	45	2 0	2 4
5	Me	Pr	(des 3-Me)	Additive	—	0 89	0 85
6	C_3H_5	Me	β	0 47	0 98	—	—
7	CPM	Me	β	0 72	0 72	—	—
8	$(CH_2)_2Ph$	Me	β	0 11	0 14	—	—
9	$(CH_2)_2COPh$	Me	$\beta(\pm)$	0 056	0 049	—	—
			$\beta(-)$	0 05	0 14		
			$\beta(+)$	0 023	0 025		
Nalorphine				0 4	0 45	>50	1 0
Naloxone				0 022	0 079	—	—
Morphine				—	—	1 8	0 97
Pentazocine				20	14	—	—

[a] From Ref 74
[b] Dose (mg/kg, sc) required for a 50% reduction in the response to morphine in rats (tail heat) and mice (Straub tail and locomotion)
[c] Dose required for a 2 s increase in reaction time in rat tail heat test
[d] Dose required for a 50% reduction in the frequency of writhing

The α-1,3-dimethyl-4-propyl analog **50a** (LY 150720, *picenadrol*, a racemic mixture) was examined in further tests.[74] It was essentially an agonist with about half the potency of morphine and its 3-desmethyl parent with most of its activity residing in the dextro antipode. Surprisingly, the levo isomer (a weak agonist in mice) showed distinct antagonist properties with a potency between that of nalorphine and pentazocine. Since all 4-propyl derivatives differed little in their IC_{50} binding values, their varying pharmacological profiles were attributed to changes in intrinsic activity rather than receptor affinity. The sodium index of the levo isomer was about one fifth that of its antipode and of morphine, in accord with its acting primarily as an antagonist. Picenadrol had a low PDC in monkeys and may have clinical potential.

In an attempt to determine the conformational binding mode (*ax*- or *eq*-4-arylpiperidine chair) some 3,6-dimethyl analogs were tested, and evidence

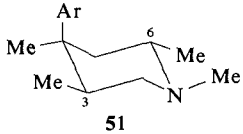


	Agonist activity[a] MWR	RTF	Antagonist activity[a] RTF
(±)	1.6	1.8	41
(−)	8.1	>100	4.4
(+)	0.76	0.78	Additive
Morphine	0.89	0.71	—
Nalorphine	0.65	>80	0.32
Pentazocine	2.0	2.6	20

[a] Footnotes of Table 7.4 apply.

50a

that the axial 4-aryl conformation leads to an agonist response while equatorial 4-aryl geometry causes receptor blockade was obtained.[74] Thus, the *trans*-3,6-dimethyl isomer **51** proved half as active as morphine (inverted chair unfavored by severe *syn*-diaxial 4,6-dimethyl interaction), while the cis derivative (with the *eq*-4-aryl chair **52** probably preferred) was an antagonist almost as potent



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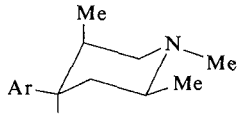
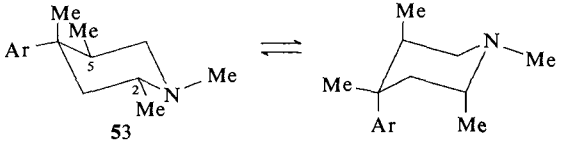


52

as nalorphine and devoid of agonist properties. These ideas require that the agonist 1-methyl-4-propyl-4(3-hydroxyphenyl)piperidine binds in the axial 4-aryl conformation, and there is computational evidence that such a conformer is preferred in this derivative.[70] Results difficult to accommodate in this respect are the agonist properties of isomer **53** in which the axial 4-aryl chair with three axial substituents is unlikely to be highly populated, and the fact

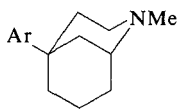


53

(0.75 × morphine, MWR)

that insertion of 3-methyl into the agonist 1,4-dimethyl-4-(3-hydroxyphenyl)piperidine (a change that favors the *eq*-4-aryl conformation in both α- and β-Me orientations),[70] although leading to an antagonist in the β-case, provides a partial agonist in that of the α-isomer. Further, rigid analogs of these 4-arylpiperidines with the aromatic group constrained to either an equatorial (as in the morphan **54** (Chapter 5), or axial conformation as in the pyrindine **55**,[74] have been examined and both compounds behave as agonists. More evidence of the conformational equilibria of piperidines of

this type is required to clarify these issues. If axial-4-arylpiperidine chairs are in fact the active conformational species of 4-(3-hydroxyphenyl--4-alkyl-piperidines with agonist properties, then the close relationship of their binding mode to that of morphine becomes an attractive possibility (see **47** and **48**) and accounts for their need of a phenolic substituent.



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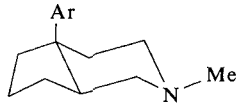
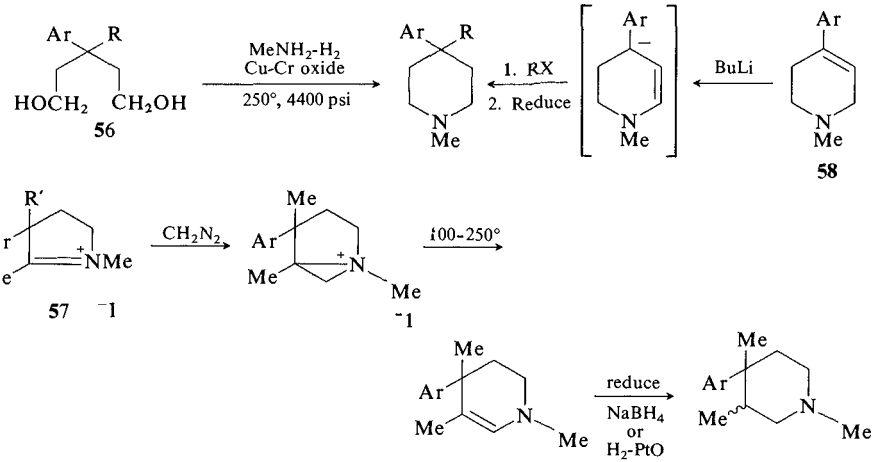


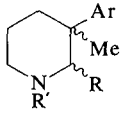
55

The original 4-aryl-4-alkylpiperidines were made by cyclizing 3-aryl-3-alkylpentan-1,5-diols **56** with methylamine,[72] while later described compounds were obtained by ring expansion of 3-arylpyrrolines **57** with diazomethane[75]; the relevant patent gives no details of the precursor pyrrolines nor evidence of the stereochemistry of the products. Another route starts from the tetrahydropyridine **58**.[76] Most recently an SRI International group[90] prepared a series of 4-aryl-4-methyl (and propyl) piperidines by modification of the original route. The most active agonists (MWR) were the 1-phenethyl-4-methyl (14 × pethidine) and 1-methyl-4-propyl (32 × pethidine) derivatives, while the most potent antagonist (*vs.* morphine, Straub tail) was the 1-allyl-4-methyl analog (0.16 × nalorphine). Results were interpreted in terms of multiple modes of binding involving different ligand conformations.



There is evidence that 3-aryl-3-methylpiperidines closely related to the 4,4-disubstituted piperidines also mimic morphine in their associations with opiate receptors. Again all active derivatives of this type are phenols and some possess antagonist properties when carrying an allyl or CPM substituent at the basic center. *N*-Methyl derivatives are feeble analgesics but become more

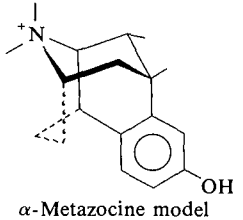
potent when *N*-arylalkyl substituents are present; for example, **59** (R = H, R′ = CH_2COPh) and pethidine are equipotent in mice (HP).[77] Higher potencies were achieved when a 2-methyl substituent was present; one diastereoisomer of the 2-Me-*N*-CH_2COPh derivatives was half as active as morphine (MHP) while the *N*-allyl analog lacked agonist properties but antagonized morphine at one tenth to one fifth of the dose of the analgesic.[78] Further work has clarified the stereochemistry of the α- and β-2,3-dimethyl diastereoisomers and provided pharmacological data that confirm and extend the original reports.[79] Thus, *N*-methyl, *N*-allyl, *N*-CPM, and *N*-3,3-dimethylallyl derivatives **59** (R = Me) were ineffective as analgesics in mice (HP and Nilsen tests) while *N*-phenethyl isomers were significantly active (α, 0.7; β, 0.3–0.4 × pethidine), results substantiated by tests on isolated GPI.[80] In rats, the *N*-allyl and *N*-CPM derivatives antagonized fentanyl-induced narcotic effects with potencies close to that of nalorphine; in both cases the β-isomer was the more potent by a factor of 2 or more (β-*N*-allyl 2×, β-*N*-CPM 2–4 × nalorphine).



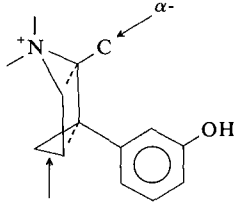
α *c*-2-Me, *r*-3-Ar
β *t*-2-Me, *r*-3-Ar

59

Many conformational options are open to such 3-arylpiperidines, and it is reasonable to believe that some may provide a similar spatial relationship between the charged nitrogen and aromatic features as obtains in the rigid system of morphine (see **60**). Parahydroxyphenyl analogs of the *N*-allyl and *N*-CPM derivatives were much less potent antagonists,[79] results that emphasize the importance of a *m*-hydroxyphenyl moiety for ligands that bind to opioid receptors.



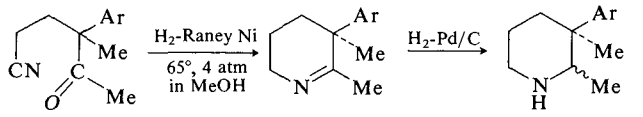
α-Metazocine model



Boat conformation

60

The key intermediate for synthesis of the diastereoisomers **59** (R = Me) is the tetrahydropyridine **61** obtained by hydrogenation of a cyanoketone; a further reduction step using a Pd catalyst gave a separable mixture of isomers **62**, which were converted to *N*-substituted phenolic analogs by standard methods.[81] The configurations α: *c*-2-Me, *r*-3-Ar and β: *t*-2-Me, *r*-3-Ar were



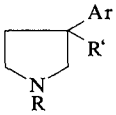
Ar = 3MeO.C_6H_4 **61**

α- isolated as oxalate,
β- as HCl salt

62

established from differences in the ^{1}H-nmr spectra of *N*-benzyl and *N*-acetyl diastereoisomers,[81] and also by ^{13}C nmr.[82]

The 3-arylpiperidines **59** are clearly related to analgesically active derivatives of the 3-arylpyrrolidines **63**, especially as the smaller ring analogs are also converted to morphine antagonists when the ring nitrogen carries an allyl or CPM substituent.[83,84] *Profadol* (**63** R = Me, R′ = Pr), the first notable

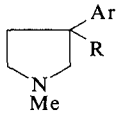


63

R	R′	Activity (codeine = 1)*
Me	Pr	2.5 (1.3)
Me	COEt	1.7
Me	CO_2Et	0.4
$(CH_2)_2Ph$	Pr	4.9 (0.8)
$(CH_2)_2C_6H_4.4NH_2$	Pr	5.8 (0.9)

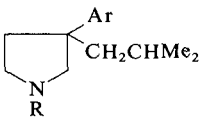
* Methyl ether in parentheses.

compound of this type was about twice as active as codeine in rats by antinociceptive tests and its action was antagonized by nalorphine.[85] It had no PDC in monkeys and remarkably unmasked physical dependence in these animals.[86] In patients with cancer pain, profadol was about one quarter as potent as morphine and produced similar side effects. Antipodal forms differed little in activity. When the 3-alkyl substituent of profadol is replaced by oxygen functions typical of 4-phenylpiperidine analgesics (CO_2Et, COEt) potency falls occur, and the SAR of the profadol group relate to morphine rather than pethidine (see **63**). The influence of size and degree of branching of the 3-alkyl substituent upon activity has also been examined (**64**).[83] The *N*-allyl and



64

R	Me	Et	Pr	Bu	isoPr	secBu	isoBu	CH_2CMe_3
Activity (codeine = 1)	0.2	1.7	2.5	1.7	3.0	3.2	2.7	3.8

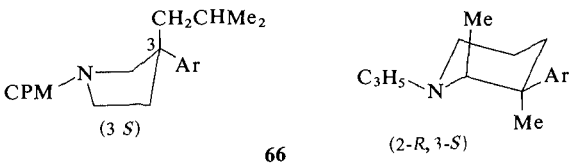


65

R	ED_{50} (WR, mice)	ED_{50} (antag)*
C_3H_5	0 35	1.5
CPM	0 11	1.7
Pentazocine	2 7	6 2

* Antagonism of ED_{50} dose of morphine in mice by tail pressure test, all values in mg/kg

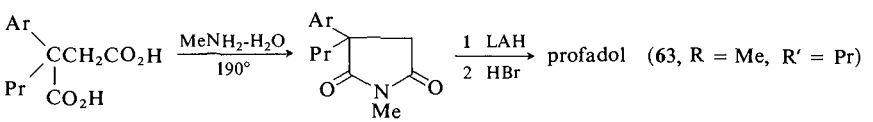
N-CPM derivatives **65** are reasonably potent antagonists of morphine, and their ability to suppress acetylcholine-induced writhing in mice characterizes them as partial agonists. Only the levo antipodes are active antagonists.[84] The pyrrolidine-piperidine pair **66** (both the more potent antipodal form) are related in absolute configuration at the *C*-quaternary chiral center as shown (X-ray analysis of HBr salts).[87] In these compounds, active conformations akin to that of levo α-metazocine may be formulated, a result that supports the idea of their being opioid ligands of similar type.



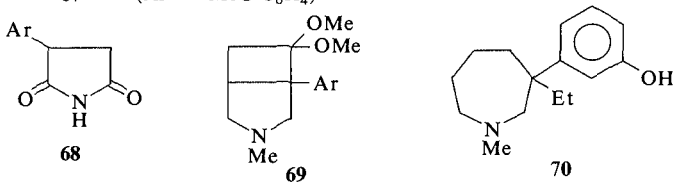
(3 *S*) (2-*R*, 3-*S*)

66

Profadol was first made by cyclizing the substituted succinic acid **67**,[85] but a more versatile route to such derivatives is direct C-3 alkylation of the intermediate **68**.[83] Some bridged profadol analogs that incorporate a ketal function have been studied; of these, the ketal **69** bound to rat brain homogenates with an affinity similar to that of morphine.[88]



67 (Ar = 3MeO C_6H_4)



68 69 70

Another compound closely related to the 3-arylpiperidines and pyrrolidines is the azacycloheptane **70**, recently marketed as *meptazinol* (Meptid). Its potency as an analgesic is moderate (100 mg ≡ 15 mg morphine) and the drug is claimed to be free from respiratory depressant and other side effects.[89]

It also has an antagonist component to its actions, since it inhibits many of the pharmacological effects of morphine and produces withdrawal signs when given to morphine-dependent rats and monkeys.

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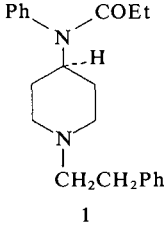
8

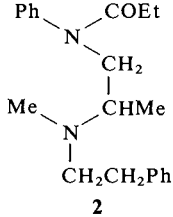
Fentanyl and the 4-Anilinopiperidine Group of Analgesics

8.1. INTRODUCTION

Paul Janssen's exploitation of 4-piperidone chemistry during the early 1960s proved remarkably successful in that it led to the clinical use of both a major tranquillizer (*haloperidol*)[1] and a potent narcotic analgesic, *fentanyl*.[2] Fentanyl (**1**, Sublimaze, Leptanol) is related to pethidine and also to basic anilides with analgesic properties such as diampromide **2** (p. 311) and is characterized by high potency and short duration of action. Thus, in mice (tail-clip method) fentanyl is almost 200 times as active as morphine by the sc route and has a faster onset and shorter duration of action than the standard



1



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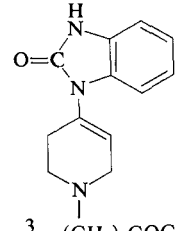


3 $(CH_2)_3COC_6H_4$4–F

drug. It shows the usual morphinelike effects, namely, Straub tails, mydriasis, and constipation in mice; in dogs and cats it causes respiratory depression but is devoid of emetic action.[3] A clinical study in postsurgical patients and healthy volunteers showed 0.2 mg fentanyl to be equianalgesic with 10 mg morphine (im route) and the two drugs had similar side effects.[4] The respiratory action of fentanyl in healthy males was judged to be somewhat greater than that of pethidine at equianalgesic dose levels.[5] The rapid onset and short duration of action of fentanyl make it particularly well suited for use in neuroleptanalgesia and it has now achieved widespread use in surgical analgesia,[6] especially when given in combination with a major tranquilizer such as *droperidol* (**3**) (Thalamontal contains fentanyl, 50 μg, and droperidol, 2.5 mg/ml).[7]

From pharmacodynamic studies using [^{3}H]fentanyl, Hess *et al.*[8] concluded that the brief duration of action of fentanyl in man is due to its redistribution from the brain to other tissues rather than to high rates of metabolism and excretion. Its great ability to penetrate the CNS is revealed by the low order of its ED_{iv}:$ED_{intraventricular}$ ratio (6) compared with that of the far more polar drug morphine (900).[9] Most metabolism studies refer to work in animals since dosage in man is necessarily very small; products of oxidative desalkylation (phenylacetic acid and norfentanyl) and hydrolysis (the NHPh analog) have been detected in rats[10,11] and oxidation of *N*-propionyl to $NCOCH_2CO_2H$ in horses (fentanyl has been used to dope race horses).[12] It is concluded that rat, rabbit,[13] and man all rapidly metabolize fentanyl and that its analgesic effect is probably brought about by the unaltered drug because all metabolites referred to are inactive.[10] In a recent study in man, products hydroxylated in the piperidine ring and *N*-propionyl group of fentanyl were detected.[14]

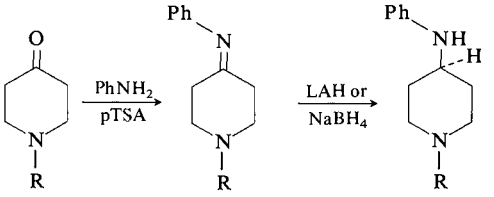
Although fentanyl and its analogs have rarely been encountered as drugs of abuse in man (the low effective concentrations of such agents make them difficult to detect), their illicit use is a potential problem. Recently, a number of unexplained narcoticlike overdose cases occurred in California caused by drugs sold as "China White" thought to be heroin but subsequently identified as α-methylfentanyl (see **5**).[15]

Fentanyl is probably a μ-agonist as judged by *in vitro* smooth muscle assays (IC_{50} n*M*: 0.92 GPI; 26 MVD; 153 rat VD) and the fact that it displaces the μ-agonist DAGO more rapidly than it does DADL (δ) or ethylketazocine (κ) from brain tissue binding sites (see p. 356).[16] However, the analog of fentanyl termed FIT with a 4-isothiocyanate function inserted in the *N*-phenethyl aryl moiety blocked δ- rather than μ-receptors in rat brain membranes; FIT was also a potent inactivator of δ-receptors in NG 108-15 hybrid cell membranes (p. 489).[17] The *in vivo* properties of FIT are under investigation.

8.2. SYNTHETIC METHODS AND SAR DATA

Fentanyl and its analogs are made from *N*-substituted-4-piperidones [i.e., from the same intermediates of the reversed esters of pethidine (p. 266)]. These ketones condense with aniline under the influence of catalysts such as toluene-*p*-sulfonic acid[2] and zinc chloride[18] to give Schiff bases, which are reduced to diamines **4** by $NaBH_4$ or LAH. Recently, the direct conversion of 4-piperidones to 4-anilino derivatives 4 has been achieved by reductive amination with aniline and sodium cyanoborohydride ($NaBH_3CN$).[19] The diamines are acylated with propionic anhydride.

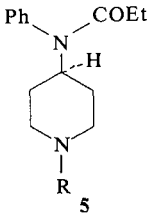
Larger and smaller *N*-acyl functions provide less active analogs (potencies of fentanyl and NCOR analogs, pethidine = 1; NCOMe 50, NCOEt 700,



ν_{CN} 1660 cm^{-1}

4

NCOPr 90).[20] *N*-Phenethyl is clearly the optimal size of unbranched *N*-substituents, and the potency ranking *N*-phenethyl > *N*-benzyl > *N*-methyl of the fentanyl class differs from 4-phenylpiperidine analgesics not only in the placement of the *N*-benzyl derivative, but also in the virtual inactivity of the *N*-methyl member.[18] Furthermore, the *N*-phenethyl is more potent than the *N*-(3-phenpropyl) congener (NCH_2Ph 0.7, NCH_2CH_2Ph 700, $NCH_2CH_2CH_2Ph$ 14, pethidine = 1)[20] (cf. p. 231). Insertion of methyl α- to the piperidine nitrogen elevates, while hydroxyl β- to the same atom depresses potency (in *N*-phenethylnorpethidine, insertion of α-Me abolishes activity).[21] The combination α-Me, β-OH provides the most potent compound of the series (see **5**). The phenethyl side chain is restricted to the extended conformation **5a** in *N*-tetrahydronaphthyl analogs of norfentanyl and its *c*/*t* 3-methyl congeners. The fact that all three compounds had MTF potencies close to that of the parent indicates that fentanyl also binds to the receptor with its *N*-phenethyl group fully extended.[19]

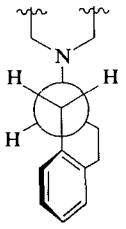


5

R	Potency in mice or rats[20] (pethidine = 1)
$PhCH_2CH_2$ [a]	700 ± 250
$PhCH_2CH(Me)$ [b]	1150 ± 150
$PhCH(OH)CH_2$	150
PhCH(OH)CH(Me)	1300
PhCH(OH)CH(Et)	900

[a] Fentanyl.
[b] α-methylfentanyl.

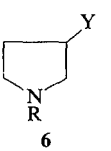
5



5a

In spite of the SAR discrepancies between the fentanyl and pethidine groups so far noted, the agonist (albeit weak) rather than antagonist activities of *N*-allyl and 3,3-dimethylallyl analogs (MHP potencies: fentanyl, 470; *N*-allyl, 0.4; *N*-dimethylallyl, 0.5; pethidine 1)[18] point to a closer relationship of the anilide group with the 4-phenylpiperidine than the morphine class of analgesic.

Both one-carbon expansion and contraction of the piperidine ring of fentanyl diminish potency, but activity levels do not fall much below that of morphine.[22,23] *N*-Benzylpyrrolidino and *N*-benzylazacycloheptane congeners have similar activities (0.5–0.3 × morphine) that surpass that of the *N*-benzyl 6-ring compound, while the 7-ring *N*-allyl derivative is markedly less potent than corresponding 5- and 6-ring compounds (the last two are equally effective in antinociceptive tests). The pyrrolidine analogs were made by displacement reactions between aniline and **6** (*Y* = Br or OTs), and the azacycloheptanes from 1-carbethoxyazacycloheptan-4-one **7**, derived by ring expansion of the lower homolog with ethyl diazoacetate.



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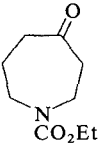
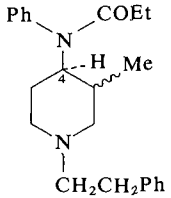


7

Studies of ring-substituted analogs have thrown further light on the relationships between fentanyl and the 4-phenylpiperidine group of analgesics. Riley *et al.*[24] first reported 3-methylfentanyl **8** prepared from a 4-anilinopyridine, which proved to be 10 times more effective than fentanyl in the RTF assay. The configuration of **8** was not established but from its mp (HCl salt) and potency the compound is probably the *cis* diastereoisomer that was later described by Janssen's group[25] along with the *trans* isomer, prepared from a 3-methyl-4-piperidone following the original route of synthesis. The configurations of the diastereoisomers **8** were readily established from the dimensions of the 4-H ^{1}H nmr resonances (see **8**). A similar nmr analysis had already been employed to establish the preferred conformation of fentanyl (4-H resonance near δ5, nonet width 36 Hz, ^{3}J 11.0 and 4.5 Hz, evidence for a piperidine chair with eq-4-NPhCOEt).[18] The *cis* and *trans* 3-methyl analogs were obtained in 70 and 9.5% yields, respectively, results that show that chemical reduction of the Schiff base intermediate is highly stereoselective. The Belgian workers found that *trans* **8** and fentanyl were equipotent while the *cis* isomer was eight times as active as the parent in the rat tail-withdrawal tests[25]; most of the activity of the *cis* racemate resided in the *levo* enantiomer [(−)-*cis* **8** 16 × fentanyl, (+)-isomer inactive]. The stereochemical structure–activity relationships of 3-methylfentanyls thus mirror those of 3-methyl-



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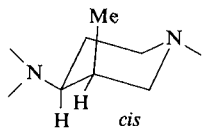
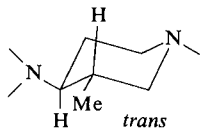
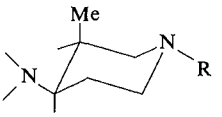


4-H resonance δ4.4 ppm
doublet (12.5 Hz) of
triplets (5 Hz)
(4*S* stereoisomer depicted)

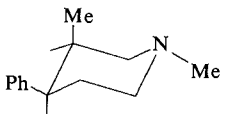


δ4.53 ppm
triplet (12.5 Hz) of
doublets (4.5 Hz)

pethidines and the related prodines (p. 260) in terms of not only relative geometry but probably also of absolute configuration. The configuration of (−)-*cis* **8** has been provisionally assigned as 3S, 4R and is seen to be equivalent to that of the more active antipode of β-prodine (3R, 4S) when allowance is made for the RS stereochemical convention (see **9**). Similar stereochemical SAR results were obtained for *N*-tetrahydronaphthyl analogs of **8** (MTF AD_{50} mg/kg: 3-demethyl 0.012; *cis* 3-Me 0.004; *trans* 3-Me 0.018).[19]



R = $(CH_2)_2Ph$

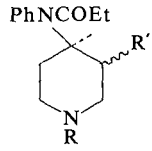


3*R*,4*S* β-prodine

9

These findings, together with other common features of the structure-activity relationships of fentanyl and 4-phenylpiperidine analgesics (see later), suggest that the two analgesic groups share similar drug-receptor association modes. A critical test of this proposal is the examination of isomeric 3-allyl and 3-propyl analogs of fentanyl[26] since the effect on potency of such substituents in reversed esters of pethidine differs radically from that of methyl (e.g., potency raised over 10-fold by 3-allyl *trans* to 4-aryl and depressed by a *cis* substituent).[27] Data on fentanyl and its *cis*-3-allyl congener (Table 8.1, entries 2 & 4) appear at first to correlate with related investigations of the pethidine reversed ester (insertion of 3-allyl *cis* to the 4-aryl substituent causes an approximately 10-fold decrease in potency in both series). However, potency results for the 3-allyl and 3-propyl diastereoisomers reveal a divergence of such relationships in that (1) the *cis* and *trans* isomers have activities in the same range, with the *cis* form the more potent by a factor of only 2, and (2) the reduced analog of the *cis*-3-allyl derivative is more active than that of the alkenic parent (in reversed esters of pethidine, 3-allyl are far more active than corresponding 3-propyl derivatives).[26] To summarize these results in terms of receptor events, it appears that the drug-receptor associations of fentanyl are significantly enhanced only by 3-methyl *cis* to the 4-anilido substituent while hydrocarbon groups at C-3 of three carbon chain length,

Table 8.1. Antinociceptive Activities of Some 4-(*N*-phenylpropionamido)piperidines in the Rat Tail Withdrawal Test after iv Administration[a]



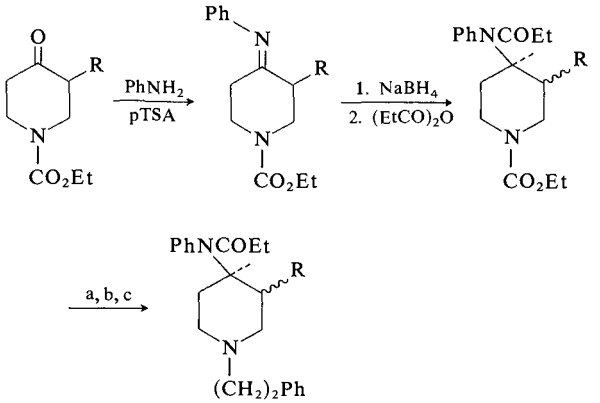
Entry	R	R'	Configuration	ED_{50} mg/kg
1	Me	H	—	inactive (100 mg/kg)[b]
2[c]	$(CH_2)_2Ph$	H	—	0.01[d]
3	Me	$CH_2CH{=}CH_2$	*cis*	10.0
4[e]	$(CH_2)_2Ph$	$CH_2CH{=}CH_2$	*cis*	0.08
5[f]	$(CH_2)_2Ph$	n-Pr	*cis*	0.02
6	$(CH_2)_2Ph$	n-Pr	*trans*	0.04

[a] From Refs. 25, 26, 28
[b] In mice by HP test, sc (28)
[c] Fentanyl
[d] Ref. 25
[e] Janssen (unpublished data) reports both *cis* and *trans* isomers, examined as oxalates, to have ED_{50} values near 0.04 mg/kg in the rat TW test
[f] Compound entry 5 was more potent than compound 4 in displacing DAGO(μ) DADL(δ) and bremazocine (κ) from GP brain homogenates, and both compounds showed preference for μ-sites (H. W. Kosterlitz, private communication)

whether saturated or unsaturated, impair such associations in a manner that is little dependent upon stereochemistry.

It may be concluded, therefore, that fentanyl and 4-phenylpiperidine analgesics such as pethidine represent distinct classes of analgesic. If these analgesics are assumed to interact with the same recognition site (probably the μ-class of opioid receptor),[16,35] they must differ in their modes of association. The fact of their sharing certain structure-activity relationships, notably the agonist properties of *N*-allyl congeners,[18,28] the adverse influence of *m*-hydroxy substitution in the 4-aryl moiety (see later), and the optimal nature of a propionyl structural component (NCOEt/OCOEt) demonstrates that differences in drug-receptor binding are not so radical as those between 4-aryl/4-anilidopiperidines and rigid analgesics of the morphine, morphinan, and benzomorphan class.

The 1-methyl-3-allyl congener of fentanyl was made by application of the routine synthesis to 1-methyl-3-allyl-4-piperidone (p. 267) while 1-carbethoxy-3-allyl-4-piperidone served as intermediate for synthesis of the 3-allyl/propyl-*N*-phenethyl analogs (Scheme 8.1). Reduction of intermediate Schiff bases was highly stereoselective and the *cis* isomers were produced almost exclusively by both chemical and catalytic reduction procedures; low yields of the 3-propyl

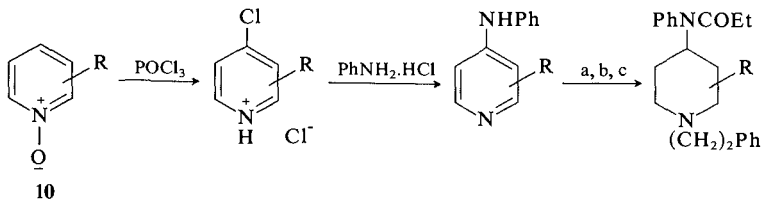


R = $CH_2CH{=}CH_2$ throughout; reagents: a, KOH-isopropanol; b, $Ph(CH_2)_2Br$-K_2CO_3; c, $(EtCO)_2O$

Scheme 8.1

trans isomer were isolated after lengthy chromatographic resolutions. Stereochemical evidence of configuration based on 4-H methine nmr signal dimensions was corroborated by ^{13}C chemical shift data, notably the C-5 shifts. In the minor isomers the C-5 shift was close to that of des-3-alkyl derivatives while upfield shifts of about 3.5 ppm were seen in C-5 resonance of all major isomers, confirming the preferred axial 3-alkyl orientation of these derivatives (axial 3-R groups sterically polarize, and hence shield, C-5 carbon while equatorial substituents have little effect at the same position of the piperidine ring).[29]

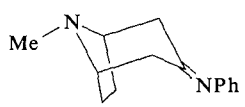
2-Methyl and 2,5-dimethyl analogs of fentanyl have also been reported (derived from methylated pyridine-*N*-oxides **10** as shown) in single isomeric forms of unestablished configurations and have potencies inferior to fentanyl (RTF ED_{50} mg/kg values: fentanyl, 0.04; 2-Me, 0.67; 2,5-diMe, 0.8).[24] One isomer of the 1,2,5-trimethyl analog (prepared from the corresponding 4-piperidone and related to promedol, p. 268) was less active than promedol against thermal and mechanical irritation in rodents but effective against electrical stimulation.[30] Bridged 2,6-dimethyl congeners of fentanyl have been



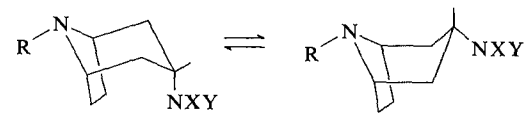
10

R = 2-Me or 2,5-diMe; reagents: a, $(EtCO)_2O$; b, Pd-C/H_2; c, $Ph(CH_2)_2Br/K_2CO_3$

made from 3-tropanone and provide further examples of stereoselectivity of action.[31] The α-form resulted when the Schiff base **11** was catalytically reduced (H_2/PtO_2) while the β-isomer formed the major component of the mixture produced after Na/EtOH reduction. ^{1}H-nmr data (similar to work on 3-methyl-fentanyl and the tropane analog of pethidine)[32] gave evidence of configuration and preferred conformation (boat for α-isomers). α/β pairs with a variety of *N*-substituents were tested as analgesics by the MTF test (Table 8.2), and structure-activity relationships followed previous results. The β-forms of the *N*-benzyl and *N*-phenethyl derivatives were substantially more potent than the α-diastereoisomers, results that support the *eq*-4-NPhCOEt chair as the active conformation of fentanyl. *N*-Allyl and *N*-CPM analogs were devoid of opioid antagonistic activity.

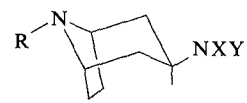


11



α-12

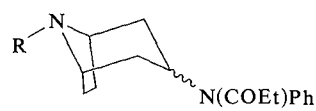
XY = (COEt)Ph



β-12

To test the proposition that one of the phenyl rings of fentanyl was equivalent to the aromatic feature of morphine, Lobbezzo *et al.*[33] prepared analogs of fentanyl with a phenolic OH group in either the *N*-phenethyl side

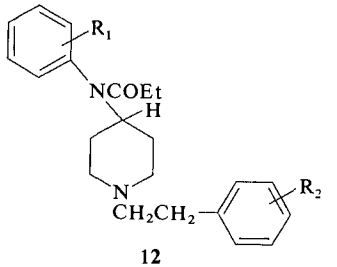
Table 8.2. Antinociceptive Activities of Some Tropane Analogs of Fentanyl in Mice by the Tail-Flick Test.[a]



R	Isomer	AD_{50} mg/kg sc
Me	α	>100
Me	β	>100
CH_2Ph	α	35.2
CH_2Ph	β	1.8
$(CH_2)_2Ph$	α	2.22
$(CH_2)_2Ph$	β	0.047
Fentanyl	—	0.024

[a] From Ref. 31.

chain or the 4-anilido substituent; in morphine and related polycyclic analgesics 3-OH derivatives are far more potent than 3-methoxy or 3-desoxy congeners in both *in vivo* and *in vitro* assays.[34] In binding assays (inhibition of ^{3}H-fentanyl stereospecific binding to the P_2 fraction of rat brain homogenates) none of the phenolic derivatives possessed a higher affinity than fentanyl, and in general the methoxy analogs had only slightly lower affinities than the free phenols. A few results are shown (**12**). The anomalous result for the 2-methoxy derivative (**12**, R_1 = H, R_2 = 2 − OMe) prompted the examination

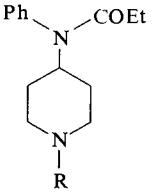


12

R_1	R_2	Relative affinity (morphine = 1)
H	H	3
3-OH	H	0.44
3-OMe	H	0.37
H	2-OH	0.33
H	2-OMe	4.0
H	3-OH	1.4
H	3-OMe	0.79

(Compounds made by standard methods of fentanyl synthesis)

of a series of 2-substituted derivatives of this type; relative affinities were low except for the 2-Me (2.2) and 2-Cl (2.1) analogs. The 3-NPhCOEt piperidine congener (isofentanyl), also included in this series, was virtually inactive. Data on the phenolic analogs therefore substantiate the view that fentanyl and its active derivatives differ in their ligand-receptor interactions from those of the morphine group (cf. related studies of phenolic analogs of reversed esters of pethidine, p. 241). In a similar vein, it is unlikely that the two aromatic residues of fentanyl bind with complementary subsites that accommodate the Tyr[1] and the Phe[4] residues of the enkephalins (p. 336), since the analogs of fentanyl (**12a**) that incorporate appropriate aminoacid residues all lacked significant activity in the GPI and MVD assay procedures.[35]

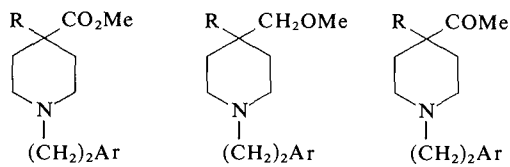


R = Tyr, Tyr-Gly, Tyr-Gly-Gly

12a

Only a few fentanyl analogs of type **12** with an R' substituent have been reported. Three other examples are the pyridyl analogs with *N*-Ph of **1** replaced by 2,3, and 4-pyridyl, which had MHP ED_{50} values (mg/kg): 2-py, 0.14; 3-py, 0.26; 4-py, 4.1; fentanyl, 0.09.[36] Thus, replacement of the *N*-Ph of fentanyl by *N*-2-pyridyl has a far less adverse influence upon activity than the same replacement of 4-Ph in reversed esters of pethidine (p. 242).

In further papers from Janssen Pharmaceutica an extensive series of fentanyl analogs substituted at C-4 by carboalkoxy (CO_2R as in pethidine), alkoxymethyl (CH_2OR) and acyl (COR as in ketobemidone) were reported.[37] When alkyl in these groups was methyl, all C-4 additions were advantageous and remarkable orders of potency were achieved in rats (similar, in fact, to those found for certain bridged thebaine analgesics, p. 69) as shown (**13–15**).



13 **14** **15**

a	Ar = Ph	(7862)	(4038)	(4291)
b	Ar = 2-thienyl	(7159)	(3967)	

(Potencies relative to morphine = 1 in parentheses, cf. fentanyl 286)

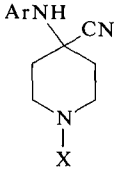
(R = PhNCOEt)

Replacement of methyl by ethyl in **13** caused the potency to fall by a factor of 10, in sharp distinction to potency rankings found for pethidine and its methoxycarbonyl analog.[38] The *cis*-3-methyl derivative of **13a** (5625 × morphine) was 15 times more potent than the corresponding *trans* isomer but fell below that of the unsubstituted ester, a result at variance with findings for fentanyl and *cis*-3-methylfentanyl. The detailed pharmacology of the more potent members of this group in mice, rats and dogs has been presented,[39] and the derivative of most clinical promise was considered to be (**13b**, R30730, *sufentanyl*) on account of its high potency, short duration of action, and high safety margin.[40] The use of sufentanyl-O_2 anesthesia for coronary artery surgery has been described.[41] Like fentanyl, sufentanyl displays the characteristics of a μ-agonist and is more potent than the parent in *in vitro* tests.[16] The corresponding *N*-phenethyl derivative **13a** (*carfentanil*), which exceeds the clinical potency of sufentanil, has been used for the immobilization of wild animals.[43]

Janssen's philosophy for the design of analgesics has always been to make compounds of high potency because of their potential of high specificity and low toxicity.[44] This approach carries the problem of respiratory depression, and patients receiving high doses of powerful analgesics of the fentanyl and other classes during surgery often require reversal of such depression or postoperative ventilation. Use of *lofentanil* (the levo antipode of the *cis* 3-methyl analog of carfentanil), five times as potent as fentanyl with a remarkably long duration of action,[45] is thus only justified when respiration can be assisted for long periods. An analog of the 4-methoxymethyl derivative **14** with the unusual 4,5-dihydro-5-oxo-tetrazolethyl *N*-substituent **17** may offer a solution to this problem. The compound, termed *alfentanil*, is a highly active

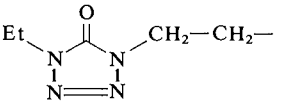
morphinelike agent in animals (137 × pethidine in rats, iv tail-withdrawal test) with a duration of action shorter than that of fentanyl and sufentanil.[46] There are reports of its use as an anesthetic induction agent[47] and of its effects on human volunteers.[48] The prolonged activity of lofentanil correlates with its binding properties; it bound with high affinity to rat brain homogenates to form a very stable complex as shown by the very slow dissociation of specifically bound drug in the presence of a large excess of dextromoramide. Its binding affinity was not depressed by Na^+.[49] The dextro antipode of the drug had only feeble activity in the rat tail-withdrawal test (ED_{50} values, mg/kg: levo, 0.0006; dextro, 2.2; fentanyl, 0.011) and antagonized fentanyl-induced respiratory depression in rats with an ED_{50} of 0.45 mg/kg (cf. naloxone, 0.03 mg/kg), a property unique to the group.

The 4-substituted fentanyls **13–15** were prepared by manipulations of the cyano function of intermediates of type **16**, themselves made by treating a 4-piperidone with aniline HCl and KCN.[42]



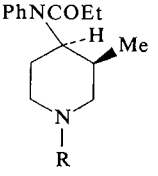
16

X = $(CH_2)_2Ph$, CH_2Ph, CO_2Me



17

A QSAR study[50] of the series **13–15** showed that their analgesic action was positively dependent on the lipophilicity and molecular mass of the *N*-substituent but negatively dependent on the lipid affinity of the 4-substituent additional to the anilido function. A Chinese group has studied a variety of *cis*-3-methylfentanyl derivatives with modified *N*-phenethyl substituents. Some of the compounds approached the potency of the parent and one exceeded it (see **18**).[51] All compounds had high lipid solubilities as judged



18

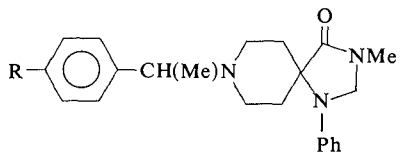
R	Potency ratio (fentanyl = 1)	log P[a]
$PhCH_2CH_2$	5.6 (1.5 for trans)	3.08
$PhCH_2CH(Me)$	3.3	3.52
$PhCH(OH)CH_2$	28.0	2.97
$PhCH(OCOMe)CH_2$	4.4	—

[a] Methanol-water/octanol partition ratio (fentanyl 2.72).

by log P values (methanol–water/octanol), but the values did not correlate with potency rankings. A good correlation was found between receptor binding IC_{50} and analgesic ED_{50} values.

Cyclic analogs of fentanyl in which the *N*-acyl group is joined to *N*-phenyl,[52] *N*-phenyl linked to C-3 of the piperidine ring,[53] and the *N*-phenethyl substituent incorporated in a ring system[54] were all of low potency or inactive. Analogs based on 2-azabicyclo[2.2.2]octanes also lacked measurable analgesic activity.[55]

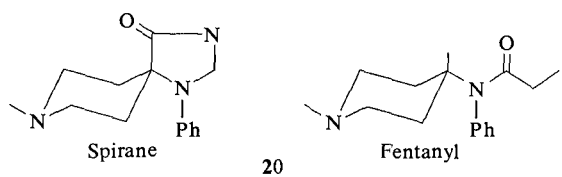
In contrast to these failures, several derivatives in which the anilido nitrogen of fentanyl is doubly linked to C-4 of the piperidine ring, forming a spirane (**19**), are highly potent, although unusual in requiring an α-methylbenzyl rather than phenethyl substituent attached to the piperidine nitrogen.



R = H 450 × pethidine
R = Me 410 × pethidine

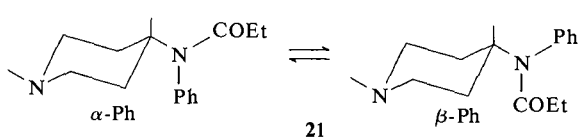
19

The spirane ring is formed by treating amides derived from **16** with formamide and reducing the product.[20,56] In the solid state the 4-NPh moiety adopts an equatorial rather than an axial conformation in relation to the piperidine ring,[57] akin to the solid and probable solute state conformation of fentanyl, for which there is X-ray[58] and ^{1}H-nmr evidence (see **20**). The activities of the spiranes **19** also provide evidence that anilido phenyl is α- rather than β-oriented in active conformations of fentanyl derivatives (**21**). This aromatic feature is confined to the β-orientation in the bicyclo analogs **22**, neither of



20

(Partial solid-state conformations)



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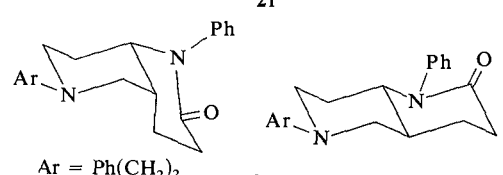
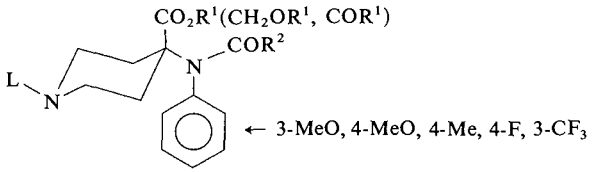


22

which showed analgesic properties in mice (TF test)[59]. Further speculations on the active conformation of fentanyl and its relationship to other classes of analgesic are made in Chapter 13 (p. 485).

The affinities of the structural assembly **23** for the analgesic receptor are superior in greater or lesser degree to that of morphine over a wide range of structural variation at L, R^1, and R^2 (see legend) and to extents of structural change not tolerated in other classes of analgesic (notably 4-arylpiperidines). Of the 47 compounds of type **23** examined, only two were inactive (see legend) while carfentanil (7682 × morphine) and its *N*-methyl analog (2 × morphine) represent the activity extremes among compounds superior to morphine.[37]



23

L: C_nH_{2n+1} n = 1–7 (8, inactive); CPM, *i*-Pr; many variants of $ArCH_2CH_2$ (β, α) including β-OH and α-Me

R^1: Me, Et, Pr, *i*-Pr, allyl, CH_2Ph (H, inactive)

R^2: Et, Pr, cyclopropyl

Derivatives of fentanyl and sufentanil with chemo- and photoaffinity functionalities attached to the anilido nitrogen (e.g., $NCOCH_2Br$, $NCOCH{=}N_2$) have been reported, but affinity labeling experiments performed with theses compounds on brain tissue met with little success. Some of the compounds, notably the diazoacetyl analog of *cis* 3-methylfentanyl, displayed high binding affinities.[60]

Compounds that may be regarded as open-chain analogs of fentanyl are discussed in Chapters 6 (p. 238) and 9 (p. 311).

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9

Methadone and Related 3,3-Diphenylpropylamines

9.1. INTRODUCTION

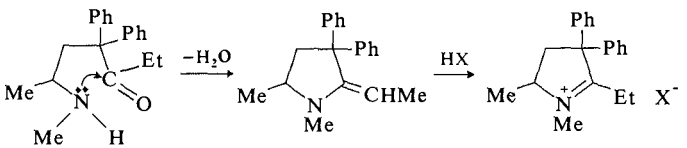
During World War II, chemists working in the Hoechst Laboratories of I. G. Farbenindustrie discovered that certain derivatives of 3,3-diphenyl-*N*,*N*-dimethylpropylamine had analgesic properties. Details of this work, acquired by the Allies as one of the fruits of victory,[1] provided a lead to a novel class of analgesic that was followed with vigor on both sides of the Atlantic. The best-known member of the group is 6-dimethylamino-4,4-diphenylheptan-3-one (**1**, *methadone*, *amidone*, Physeptone), which was introduced into clinical practice in 1946; several variants obtained by modifying the basic group and/or ketone function have also been marketed as analgesics.

1 $Me_2NCHMeCH_2CPh_2COEt$

Methadone is classified as a strong analgesic in man, being assessed as potent as morphine both by controlled clinical trial[2] and by ischemic[3] and visceral[4] pain methods. Its duration of action is at least as long as that of morphine and it is well absorbed from the GI tract with onset of action of about 15 min after sc and 45 min after oral administration. It is a far less polar drug than morphine (log partition coefficients between heptane and phosphate buffer pH 7.4 are 1.65 for methadone and −5.0 for morphine)[5] and becomes widely distributed throughout the body. Absence of appreciable sedative action makes it of little value in obstetrics (as does its ability to cross the placenta and depress respiration of the neonate) or as a preanesthetic analgesic.[6,7] It is a powerful antitussive (it is used as a linctus to control nonproductive cough), and its spasmolytic properties make it useful against bladder spasm and renal cholic. Side effects of methadone are similar to those of morphine with less incidence of constipation. Tolerance to its therapeutic action develops after repeated administration, and it sustains addiction at lower than the required dose of morphine with a longer-lasting effect. After withdrawal, physical signs are slower to develop and are judged less severe than those

after morphine withdrawal.[8] These last properties form the basis of the now common use of methadone for the ambulatory maintenance of patients dependent upon narcotics such as heroin that are associated with severe abstinence phenomena.[6,9,117,119] In the light of this development, Martin and others[10] reevaluated the pharmacological effects of methadone in man and found that the hydrochloride in dose levels of 100 mg orally produced physical dependence similar to that following morphine except that onset of the abstinence syndrome was slower. The syndrome was moderate to severe in intensity (qualitatively akin to that following morphine withdrawal) and the acute syndrome was followed by a protracted abstinence syndrome. The related derivative α-methadyl acetate (racemic and levo forms; see later) has also been used to maintain addicts; both forms of the acetate are safe and as effective as methadone in aiding the social rehabilitation of heroin users.[11]

Metabolic *N*-demethylation of methadone occurs since incubation of levo methadone with rat liver slices results in the formation of formaldehyde at a rate only marginally less than that obtained with pethidine as substrate.[12] The reason for the failure of early attempts to isolate the corresponding secondary amine is now well established as due to the facile cyclization of *N*-desmethylmethadone to a pyrroline derivative. Chemical studies have confirmed the cyclic structure **3**;[13] the corresponding free base is an exocyclic alkene **2** that exists as an approximately 50:50 mixture of *c-t* isomers.[14]

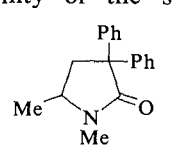


2 **3**

Synthetic **3** was shown to be identical with one of the two basic excretion products detected in the urine of males given methadone orally (the other base was unchanged drug).[13] In more recent metabolic studies no fewer than eight products were identified, results that illustrate the power of the combined GCMS technique.[15] In maintenance subjects, major metabolites were the pyrrolines **3** and *N*-demethyl-**3** and their aryl-ring hydroxylated analogs. Small amounts of 4-dimethylamine-2,2-diphenylvaleric acid **4** (formed by side-chain oxidation), the pyrrolidone **5** (resulting from subsequent *N*-demethylation and cyclization of **4**), ring-hydroxylated methadone and *N*-desmethylmethadol **6** were also found. The stability of the secondary amine **6** (an active

$Me_2NCHMeCH_2CPh_2CO_2H$

4



5

$MeNHCHMeCH_2CPh_2CH(OH)Et$

6

metabolite)[17] has been established by synthesis.[16] In the metabolism study just detailed, methadone *N*-oxide was not detected in fresh or frozen urine samples, a result at variance with earlier reports of the *N*-oxide as a metabolite;[18] samples kept at room temperature did, however, develop a component that had properties similar to those of the oxide. The most recent evidence on this point relates to work in Rhesus monkeys, where the *N*-oxide was judged a genuine metabolite when procedures aimed at minimizing its formation as an artefact of sample preparation were employed.[19] A comparison of methods used in the detection of methadone and its primary metabolite **2**, which include radioimmune assay, TLC, and GLC, has been reported.[20]

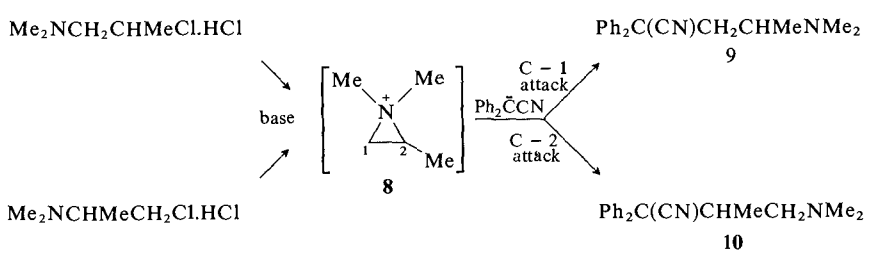
When examined by *in vitro* procedures, methadone behaved as a typical μ-agonist, as judged by its power to inhibit contractions of electrically stimulated smooth muscle (IC_{50} n*M*: 22 GPI, 523 MVD, 1650 rat VD; corresponding values for oxymorphone were 12, 833, and >5000). It displaced the μ-ligand DAGO more efficiently than it did DADL(δ) or ethylketazocine(κ) and hence showed a preference for μ-sites.[118]

9.2. SYNTHETIC METHODS

The general process for the synthesis of methadone and its analogs is most simply illustrated by the case of normethadone **7** (6-dimethylamino-3,3-diphenylhexan-3-one), which is made by nucleophilic attack of diphenyacetonitrile (as anion generated by strong bases such as sodamide or sodium hydride) on 2-chloro-l-dimethyaminoethane. The precursor aminonitrile that results is converted to the ethyl ketone by ethyl magnesium bromide under vigorous conditions (reflux with excess of reagent in toluene).[21] The last step proceeds via a ketimine[$-CPh_2C(Et)=NH$] that is readily hydrolyzed to the ketone by cold aqueous acid except when hindered by a β-methyl substituent (as in the preparation of isomethadone) when more extreme conditions are necessary to complete the reaction. Ketimines of this type are characterized by absorption bands near 1630 (C=N) and 1715 cm^{-1}.[22] Use of 2-chloro-l-dimethylaminopropane in the reaction leads to the precursor of methadone (**9**) but it also yields a similar amount of the isomethadone intermediate (**10**) that has a methyl substituent β- rather than an α- to the basic center. The same mixture of isomeric nitriles (termed methadone basic oil in the pharmaceutical industry) results when 1-chloro-2-dimethylaminopropane is employed, and an ethyleneiminium salt (**8**) (formed

$$Ph_2CHCN \xrightarrow[2.\ ClCH_2CH_2NMe_2]{1.\ NaNH_2} Me_2NCH_2CH_2CPh_2CN \xrightarrow[2\ H_3O^+]{1.\ EtMgBr} Me_2N\overset{\alpha}{C}H_2\overset{\beta}{C}H_2CPh_2COEt$$

7



Scheme 9.1

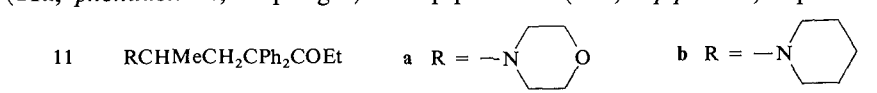
when the chloroamine base is liberated from its hydrochloride) has been proposed as the intermediate responsible for the isomeric nature of the reaction product (Scheme **9.1**). Several degradative schemes were devised during the late 1940s to prove the structure of each isomeric nitrile,[23] as were unequivocal syntheses that do not produce isomers such as that of Scheme **9.2**.[24,25]

Details of syntheses of methadone and its congeners prior to 1960 are available in Janssen's extensive compilation of chemical and pharmacological data on diphenylpropylamine analgesics.[26]

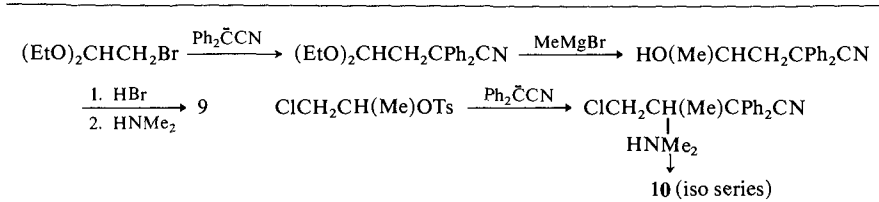
9.3. STRUCTURE–ACTIVITY RELATIONSHIPS

A veritable host of methadone-related structures has been investigated and the resultant structure–activity data are conveniently discussed (with some inevitable overlap) under the subdivisions of changes in (1) the basic group, (2) the $NCCCPh_2$ chain, (3) the oxygen function, and (4) the aromatic groups.

1. Variation of the basic group of methadone has led to the morpholino (**11a**, *phenadoxone*, Heptalgin) and piperidino (**11b**, *dipipanone*, Pipadone)



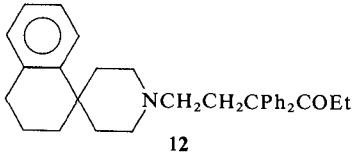
analogs, both of which have been employed clinically. The latter is no longer marketed, but dipipanone is still frequently prescribed in the United Kingdom



Scheme 9.2

as a tablet formulation with the antiemetic cyclizine (Diconal). The morpholino derivative *dextromoramide* (Table 9.1, Palfium, Jetrium) is related to isomethadone (see later). In general, dimethylamino is the basic group that gives optimum activity in 3,3-diphenylpropylamine analgesics. Diethylamino analogs are markedly less active, while 5- and 6-membered alicyclic basic units yield compounds comparable in activity to the NMe_2 derivatives.[27] Activity is lost again when the basic function is azacycloheptyl or azacyclo-octyl.[28] Replacement of one *N*-methyl of methadone or isomethadone by 2-phenethyl abolishes activity,[29] a result that differentiates 3,3-diphenypropylamines from 4-phenylpiperidines and basic anilides such as diampromide (p. 231, 311).

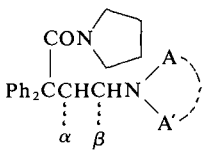
These results appear to reflect the steric limitations of the opioid anionic site (at least in regard to receptor interactions with diphenylpropylamine analgesics), the more compact medium-sized alicyclic basic groups fitting the site better than the flexible NMeR (R = Et, CH_2CH_2Ph) functions of greater van der Waals' radii. Methyl substituents in positions 2 and 3 of the piperidine ring increase the width of the basic group and activity falls, whereas a 4-methyl substituent does not adversely affect activity in normethadone analogs[30] (cf. a similar study of thiambutene derivatives, p. 310). In normethadone, replacement of the metabolically labile NMe_2 group by a bulky piperidinospiro function unexpectedly yielded a highly potent analgesic of long duration of action. In the rat tail-withdrawal test, **12** was about 200 and the corresponding normethadol (carbonyl of **12** reduced to sec-OH) and acetyl normethadol derivatives were about 100 times as effective as methadone.[31]



12

2. The $NCCCPh_2$ chain feature of methadone with a methyl substituent adjacent (α) to nitrogen is usually optimal in regard to potency for 6-amino-3,3-diphenylhexan-3-one analgesics. The β-methyl analog isomethadone retains about two thirds, and the desmethyl derivative normethadone one to two thirds of the activity of methadone as judged by a variety of animal tests.[26] The potency raising role of α-methyl is even more clearly revealed from activity comparisons of levo methadone (1.5-2.4) and normethadone (0.3-0.75; racemic methadone = 1), but it is to be noted that the group must be correctly oriented with respect to the other substituents about the α-carbon (cf. dextro methadone 0.03-0.15). The stereochemistry of the methadone group is discussed later. Normethadone is marketed as an analgesic and is an ingredient of a popular antitussive linctus (Ticarda) used in Germany and neighboring countries that has presented problems of abuse.[6]

Table 9.1 Hot-plate Activities in Mice of Some Tertiary Amides Related to Methadone[a]



α	β	NAA'	Isomer	ED_{50} mg/kg	Potency (methadone = 1)
Me	H	NMe_2	(±)	16.3	0.32
H	Me	NMe_2	(±)	>100	<0.05
Me	H	$N(CH_2)_4O$	(±)	1.7	3.6
Me	H	$N(CH_2)_4O$[b]	(+)	0.12	13
Me	H	$N(CH_2)_4O$	(−)	85	0.07
H	Me	$N(CH_2)_4O$	(±)	57	0.09
Me	H	NC_5H_{10}	(±)	13.2	0.39
Me	H	NC_5H_{10}	(+)	7.8	0.66

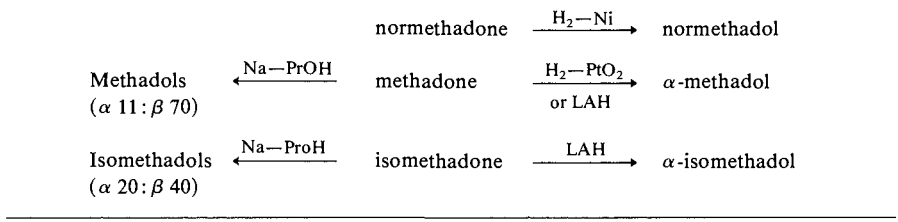
[a] From Ref. 71.
[b] Dextromoramide.

Surprisingly, a methyl group β- to nitrogen is superior to an α-placement in basic amides **13** related to methadone, made by treating appropriate acid chlorides with a secondary amine. Table 9.1 shows data for some amides derived from pyrrolidine. The morpholine group confers highest potencies in this series, while in the β-methyl derivatives, activity resides mainly in the (+) isomer. Dextromoramide (R-875, Palfium, Jetrium) is especially potent, being 20–40 times more active than morphine in animal tests. Clinically, it is an analgesic of high potency, although not as active as in animals; one study of postoperative pain relief equates 5 mg with 10 mg morphine with a shorter duration of action than the standard drug.[33] Dextromoramide, like methadone, is effective by mouth.[6] The 5- and 6-methyl analogs of methadone are discussed later.

$$R_2NCH_2CH_2CPh_2CN \xrightarrow[\substack{2.\ SOCl_2\\ (\not>60°)*}]{1.\ H_2SO_4} R_2NCH_2CH_2Ph_2COCl \xrightarrow{HN\diagup} \underset{\textbf{13}}{R_2NCH_2CH_2CPh_2CON\diagup}$$

* To avoid pyrrolidone formation.[132]

3. Variants of the ethyl ketone function of methadone, an aspect already broached with mention of dextromoramide, include ester, sulphone, and secondary alcohol functions in addition to *t*-amides. The ethyl ester analog **14a** obtained by treating the acid chloride derived from methadone cyanide with ethanol is markedly inferior in potency to methadone, while the sulfone **14b** (obtained by aminoalkylation of benzhydryl ethyl sulfone) is equipotent



Scheme 9.3[37]

with the same standard in animals.[35] The sulfone is labile and readily hydrolyzed to the corresponding diphenylcarbinol.[36]

14 $Me_2NCHMeCH_2CPh_2R$ **a** R = CO_2Et, ED_{50} 18 mg/kg, sc, MHP (methadone 1.6)[34]
b R = SO_2Et

Much study has been made of the reduction of methadone, isomethadone, and normethadone to corresponding secondary alcohols (—$CPh_2CHOHEt$). The varying success of catalytic reduction among the trio reflects the differing degrees to which the ketone function is hindered (iso>methadone>nor) (Scheme **9.3**).

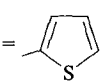
LAH reduces all three ketones and gives only one of the two possible diastereoisomeric alcohols designated the α-racemate in the cases of the branched chain ketones. The branched ketones give α/β mixtures after treatment with sodium propanol from which the major (β) isomer may be isolated. Similar results follow reduction of antipodal forms of methadone and isomethadone.[38] Both racemic *methadols* are inferior in potency to methadone (α, 0.08; β, 0.2; methadone, 1) in the MHP test, but activity is more than restored on *O*-acetylation (α-acetate, 1.3; β-2). Racemic α-acetylisomethadone (the most active member of the isomethadone series) is about half as active as the parent ketone. Complexities of activity variations among resolved forms of the methadols and acetylmethadols are described in the stereochemical section of this chapter.

There has been revived interest in α-acetylmethadol as a result of its use in the maintenance of addicts (p. 304) and several pharmacokinetic[19] and pharmacological studies of the ester have been made. The acetate is characterized by a slow onset of action, a feature attributed to its conversion to an active metabolite,[40] and this proposal is supported by the isolation of two metabolic products from rats[41] and opioid addicts[42] that are effective analgesics. The compounds are the secondary and primary amines corresponding to α-acetylmethadol formed by successive *N*-demethylation and were detected by GCMS after conversion to trichloroacetamide derivatives. Authentic primary amine **15** was initially prepared by oxidizing α-(−)-acetylmethadol

15 $H_2NCHMeCH_2CPh_2CH(OCOMe)Et$

with neutral permanganate and reducing the resultant 6-nitro derivative, but a one-step procedure (reaction of the *t*-amine with mercuric acetate) was later described along with the other methods.[43] Smits[44] found α-(−)-acetylmethadol and the primary amine **15** to be equieffective in the MWR test, while the corresponding secondary amine was about seven times more potent than the other two. Both lower amines proved 15 times more potent than the parent compound by the GPI procedure, in which metabolic *N*-demethylation is negligible.[45] The great majority of narcotic analgesics are tertiary amines, and the few examples of lower amines examined usually prove less active than the parent compounds (e.g., normorphine and norpethidine), a result possibly of their more rapid metabolic conjugation and reduced ability to cross lipid barriers. It is of interest, therefore, that *N*-demethylation of α-acetylmethadol gives amines of similar or superior potency to the original tertiary amine. *N*-allyl and *N*-CPM analogs of (−)-α-acetylmethadol and (−)-α-methadol possess weak analgesic activity in mice (the *N*-allyl derivative and morphine were equipotent in the MTF test). All four compounds had the characteristics of agonists in binding experiments (binding ability decreased in the presence of Na^+), although the *N*-allyl analog of acetylmethadol partially antagonized morphine-induced TF analgesia.[46]

4. Little variation of the diphenylcarbon ($-CPh_2$) unit of methadone has been reported. Removal of one phenyl abolishes activity[47] while its isosteric replacement by 2-thienyl gives a feebly active product.[27] Strangely, some related 3-amino-1,1-di(2-thienyl)but-1-enes **16** (analogs of methadone with

16 $Ar_2C{=}CHCH(Me)NR_2$ Ar = 

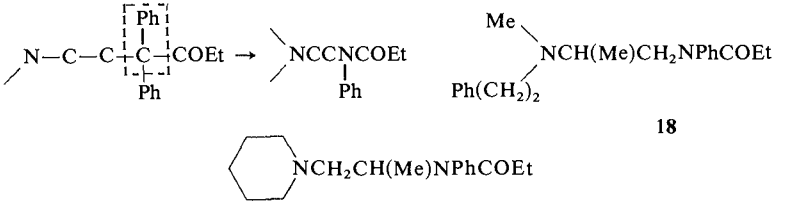
the oxygenated function eliminated) are potent analgesics with orders of activity similar to those of morphine in animals,[48] and they have been used, for example, in veterinary practice (**16** R = Et, Themalon).[49] In contrast, 3,3-diphenyl analogs of **16** lack analgesic properties. The tolerance of thiambutenes to basic groups of increased size over NMe is greater than that found for methadone and its congeners, although general trends of S-A relationships are similar. Some potencies in rat by heat and pressure methods (morphine = 1) are NMe_2, 1; NEt_2, 1; NEtMe, 1.7; piperidino, 1.1; 2-methylpiperidino, 0.5-0.6,—all in reference to structure **16**.[28] The thiambutene analgesics are made from esters of methyl crotonate as shown (Scheme 9.4); the *t*-carbinol **17** readily dehydrates when treated with cold ethanolic HCl.

$$MeCH{=}CHCO_2Et(Me) \xrightarrow{R_2NH} MeCH(NR_2)CH_2CO_2Et \xrightarrow{\text{2-thienyl Li}} MeCH(NR_2)CH_2CAr_2OH$$

17

Scheme 9.4. (Ar = 2-thienyl)

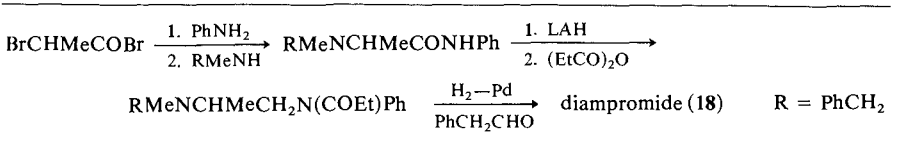
The formal modification of methadone by replacing one phenyl group and its attached quaternary carbon with nitrogen is also appropriate to this section. Such analogs are acyclic basic propionanilides and a few are analgesics with modest levels of potency. The most active is the *N*-methyl phenethylamine **18** (*diampromide*), which approximates to the potency of pethidine and morphine in mice and rats, respectively[50] (**18** is four times as potent as pethidine by the MHP test).[51] Activity is retained when anilino-phenyl is replaced by 2-thienyl.[52] Direct comparison of diampromide with its dimethylamino analog has not been reported, but the fact that the NMe_2 compound is less than one third as effective an analgesic (MHP) as the $NMeCH_2Ph$ analog (itself about half as active as diampromide in rats)[53] indicates that the basic propionanilides are better classified with the pethidine (and more particulary with fentanyl) than the methadone group (low potencies of *N*-phenethyl analogs of methadone have already been mentioned, p. 307). Configurational studies of antipodal forms of methadone and diampromide and its congeners emphasize this point, as will be discussed. *Phenampromide* **19** also lacks an *N*-aryl component to its basic function and falls in the codeine-pethidine range of potency in animals and man.[54] *Propiram*, a 2-pyridyl analog of **19**, is discussed on p. 315. Synthetic methods for the group are illustrated by the case of diampromide (Scheme 9.5).[50] Reversal of the sequence of reactions of aniline and secondary amine with α-bromopropionyl bromide leads to analogs with chain branching β-to basic nitrogen as in phenampromide.



18

19 (activity 0.7, pethidine 1.0, MHP)[51]

The final aryl modification conveniently included in this section concerns the compound *propoxyphene* **20**, in which the two phenyl groups are on adjacent carbon atoms in a structure akin to acetyl isomethadol. Although this compound (specifically the α-racemate) is only a weak analgesic (20–40 mg/kg ≡ 2 mg methadone in rats; activity, 0.4, compared with 1 for



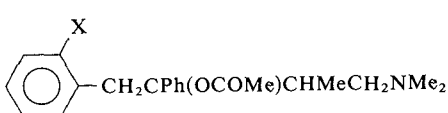
Scheme 9.5

pethidine and 0.8 for codeine; MHP),[51] analgesic preparations of the corresponding dextro isomer (dextropropoxyphene; activity, 1.3; levo inactive in mice) with aspirin or paracetamol such as Doloxene, Darvon, and Distalgesic have been widely prescribed for the relief of mild to moderate chronic pain for many years. The ready availability of such mixtures is emphasized by their frequent use in self-poisoning and attention has been drawn to the dangers of acute overdoses.[55] The dependence liability of dextropropoxyphene is judged to be less than that of codeine,[56] and its preparations are exempt from international narcotics legislation. *N*-Desmethylpropoxyphene has been identified as a biotransformed product and a procedure for determining plasma levels of the parent drug by GLC described.[57]

20 $Me_2NCH_2CHMeCPh(OCOEt)CH_2Ph$

$$PhCOEt \xrightarrow[CH_2O]{HNMe_2} \underset{\textbf{21a}}{Me_2NCH_2CHMeCOPh} \xrightarrow{PhCH_2MgCl} \underset{\textbf{21b}\ (\alpha\text{-major})}{Me_2NCH_2CHMeCPh(OH)CH_2Ph}$$

The carbinol precursor of propoxyphene is made by treating the Mannich base **21a** with a benzyl Grignard reagent. The major (α) diastereoisomer **21b** is separated, resolved with (+)-camphor-10-sulfonic acid, and finally acylated to yield the active drug. Pyrrolidino analogs of propoxyphene are more potent than the parent (acetate, 2 × , propionate,**1** × pethidine in mice),[51] while the halogenated acetates **22** (X = F or Cl) have similar activities to morphine in mice.[58] Replacement of terminal phenyl of propoxyphene by 2-pyridyl achieves a potency rise, as occurs also in the cyclic analog **23**.[59]



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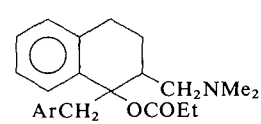
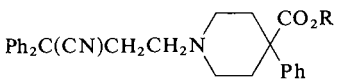


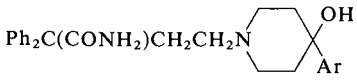
23

Ar = 2-pyridyl
5 × morphine

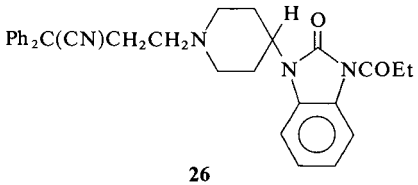
To conclude this section, a few compounds made with the probable aim of combining the best features of both diphenylpropylamine and 4-phenylpiperidine analgesics are worthy of mention. Linkage of the nitrile precursor of normethadone to norpethidine gives *diphenoxylate* **24a**, a compound that is not an analgesic but has the constipating activity of morphine and is used as an antidiarrheal agent (marketed as Lomotil).[6,60] The active metabolite of diphenoxylate is the free acid **24b**, reported to be five times more potent than the parent drug.[61] Analogs have been described in which the 4-carbethoxy group is replaced by hydroxyl[61]; of these, **25a** and **25b** proved more specific and twice as active as diphenoxylate in preventing diarrhea caused by castor oil in rats; the former compound has since been marketed as Imodium. *Benzitramide* **26**, an analog of diphenoxylate that incorporates a 2-oxobenzimidazolinyl substituent (the same as that present in the tranquilizer



24 a R = Et
b R = H

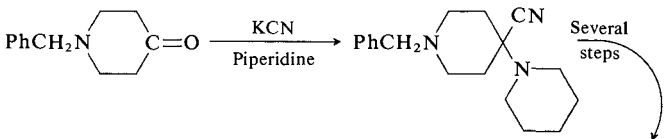


25 a Ar = 4 − $Cl.C_6H_4$
b Ar = 3 − CF_3, 4 − $Cl.C_6H_3$



26

droperidol), is a potent analgesic five to nine times as active as morphine in rats (TW test) with effects antagonized by nalorphine and has given promise in a man as an effective, long-acting analgesic.[62] It is made by suitable *N*-alkylation of the benzimidazole derivative derived from 1-benzyl-3-carbethoxy-4-piperidone and *o*-phenylenediamine.[63] An earlier analog, *piritramide* (pirinitramide) **28**, obtained from *N*-benzyl-4-piperidone via the cyanoamine **27**, is twice as active as morphine (MHP); it causes Straub tails, excitement, and mydriasis in mice and is antagonized by nalorphine.[64] In an extensive clinical evaluation lasting nearly 5 years, piritramide (marketed in Sweden as Piridolan) effectively relieved pain in postoperative patients at dose levels of about 15 mg.[65] It was long-acting and its side effects were comparable with those of morphine; physical dependence and tolerance were not experienced.



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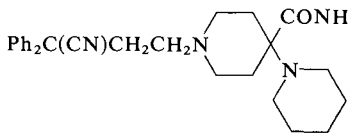


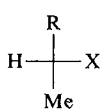
28

9.4. STEREOCHEMISTRY

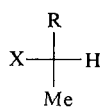
Methadone and most of its congeners possess a single chiral center and provide a rich field of examples of stereochemical selectivity in analgesics, with potency and morphinelike side effects residing mainly in one antipode of each enantiomorphic pair. Antipodal forms of methadone are best obtained

by performing a Grignard reaction on the precursor nitriles that are readily obtained by resolving the racemic mixture with (+)-tartaric acid. (The process is almost ideal. Crystals that separate from acetone-water are chiefly the levo base-dextro tartrate, and the dextro base may be recovered from the mother liquors in a high state of optical purity.[66]) Thorp and Ofner[67] were the first to report the superior activity of the levo form of methadone, a fact soon confirmed by others; in Janssen's compilation[26] the potency ranges 1.4-2.3 are given for (−)-methadone and 0.06-0.15 are given for (+)-methadone (racemic methadone = 1) in a variety of animal tests. MHP data obtained at the National Institutes of Health, Maryland (ED_{50} values, mg/kg, recorded in a well-standardized and reliable procedure, were racemate, 1.6; levo, 0.8; dextro, 25.7) showed the levo to be twice as active as the racemate and gave an isomeric potency ratio of 32, a reasonably high value in view of the possibility of nonideal optical purities.[51] In man, 4–6 mg of (−)-methadone were found to be as effective as 7-9 mg of the racemate against postoperative pain.[2] A number of authors have studied the comparative pharmacology and pharmacokinetics of (−)- and (+)-methadone. Misra and Mulé[68] have challenged the generally accepted view of the potency difference between the two isomers being due to receptor events and claim that the phenomenon may be attributed

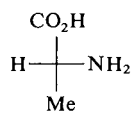
Table 9.2 Activities in Mice and Configuration of Methadone and Thiambutene Analgesics[a]



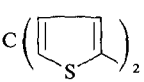
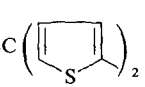
R-series



S-series

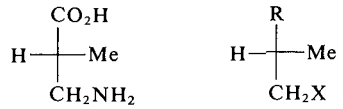


R-(−)-alanine

R	X	Isomer	Activity[b]	Ref.
CH_2CPh_2COEt (methadone)	NMe_2	R-(−)	180	26,67
		S-(+)	10	
$CH_2CPh_2SO_2Et$	NMe_2	R-(−)	180	72
		S-(+)	10	
CH_2CPh_2COEt (phenadoxone)		R-(−)	195	73
		S-(+)	5	
	NMe_2	S-(−)	30	48
		R-(+)	170	
	NEt_2	S-(−)	50	74
		R-(+)	120	

[a] From Ref. 80.
[b] (±)-Methadone = 100.

Table 9.3. Antinociceptive Activities in Rodents and Configuration of Isomethadone and Analgesics with Related Chiral Centers



R-(−)-α-methyl-β-alanine

R	X	Isomer	ED_{50} mg/kg[a]	Ref
CPh_2COEt (isomethadone)	NMe_2	*R*-(−)	1.2	51
		S-(+)	49.8	
$C(OCOEt)PhCH_2Ph$ (propoxyphene)	NMe_2	α-(±)	25.4	77
		α-3*R*-(+)	7.5	
N(COEt)Ph (phenampromide)	$N(CH_2)_5$	*R*-(−)	9.0	50
		S-(+)	36.0	
$CPh_2CON(CH_2)_4$ (moramide)	$N(CH_2)_4O$	*R*-(+)	0.12	71
		S-(−)	85	
2-Pyridyl analog of phenampromide (propiram)	$N(CH_2)_5$	*S*-(+)	13	78
		R-(−)[b]	18	

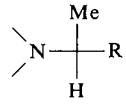
[a] Mouse hot-plate test except for phenampromid antipodes, which were tested by the rat tail-flick procedure, and propiram isomers, examined by a radiant heat method in mice

[b] Although the marginally weaker antipode, it showed the greater pharmacological resemblance to morphine

to (1) formation of an apparently active metabolite in rat brain from the levo but not from the dextro isomer, (2) a significant difference between the half-lives of the isomers in rat brain and plasma, and (3) differential stereospecific *N*-dealkylation (a major route for levo but not for dextro methadone). Sullivan and others[69] found, however, that at equal analgesic dosage, brain and plasma concentrations of (+)-methadone were at least 25 times greater than those of the levo isomer, while no qualitative differences were observed between isomers with respect to *in vivo* metabolic pattern or *in vitro* *N*-demethylation rates. The weight of evidence, including measurements of isomeric affinities for opioid binding sites,[46,70] therefore, comes down firmly in support of the original interpretation of the isomeric potency difference.

Antipodal activity differences are also found for congeners of methadone and for isomethadone and related compounds (Tables 9.2 and 9.3).

The significance of stereoselectivity in drug action in terms of drug-receptor interactions only becomes established when the more active isomers of groups of enantiomorphic pairs are shown to possess identical configurations. Stereochemical correlations within the methadone and isomethadone group are justified because the members of each possess chiral centers of similar nature (methadone type **29**; isomethadone type **30**) and subsequent



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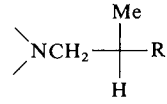
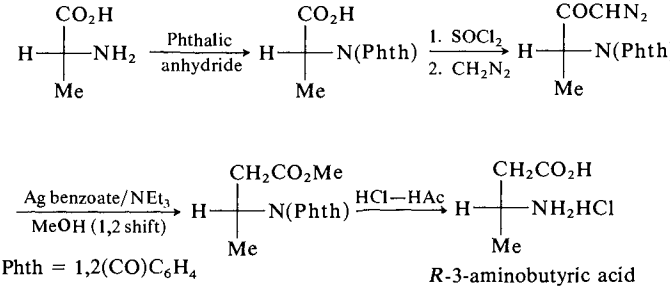
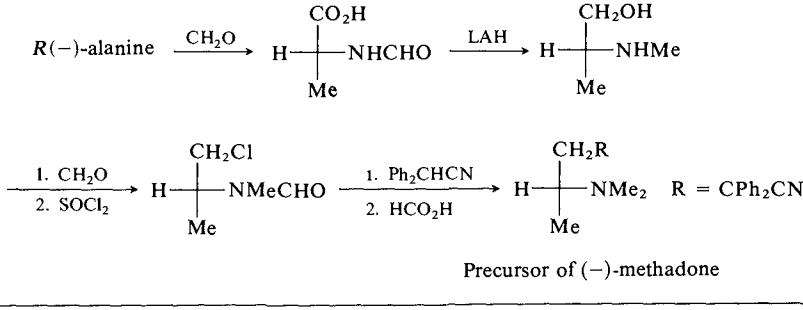


30

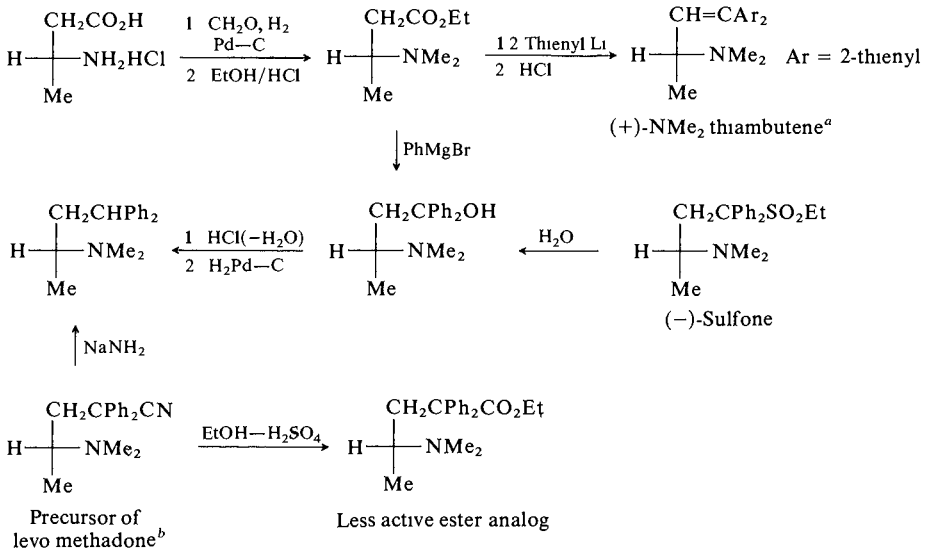
studies of both series established the like configuration of the more potent antipodes. Work on the methadone series is of particular historical interest, since it was one of the first configurational correlations of its kind and focused attention on the importance of stereochemistry in medicinal chemistry.[79] The key intermediate for the methadone studies was optically active 3-aminobutyric acid derived from *R*-(−)-alanine by the sequence of Scheme 9.6. Rearrangement of the diazoketone in the 1,2-shift step was subsequently shown to proceed with retention of configuration by synthesis of (−) methadone nitrile from *R*-(−)-alanine by reactions that did not involve the chiral center as shown in Scheme 9.7. Scheme 9.8 summarizes use of optically active *R*-3-aminobutyric acid in correlating the more potent antipodal forms of methadone, its sulfone analog, and the thiambutenes.



Scheme 9.6 (ref. 80)



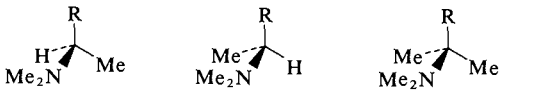
Scheme 9.7 (ref. 81)



[a] NEt_2 analog obtained by replacing CH_2O by MeCHO in the reductive alkylation step
[b] (−)-phenadoxone, the morpholino analog of levo methadone, was 64 times as active as its (+)-antipode (electric grid assay), it was correlated with levo methadone by study of molecular rotations in various solvents [73]

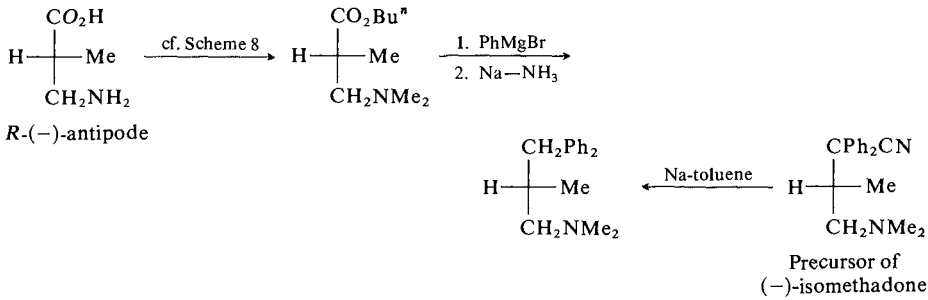
Scheme 9 8

When these relationships were first established the concept of a three-point fit of ligand molecule at the receptor surface provided a simple interpretation of the antipodal potency ratios seen for methadone and its congeners. In such a situation only one member of an antipodal pair will be able to present the required configuration to the receptor surface. Hence, if Me, NMe_2, and R are taken as the significant pharmacophoric groupings of methadone, chiral methyl is correctly oriented in the *R*-(−)-isomer and incorrectly in *S*-(+)-methadone (Fig. 9.1). To test this concept, 6-methylmethadone[74,82] (which contains methyl oriented both as in *R*- and *S*-methadone) was examined and its inactivity (as agonist and antagonist) provided evidence that an incorrectly placed methyl prevents drug-receptor interaction. The role of the α-methyl



R = CH_2CPh_2COEt

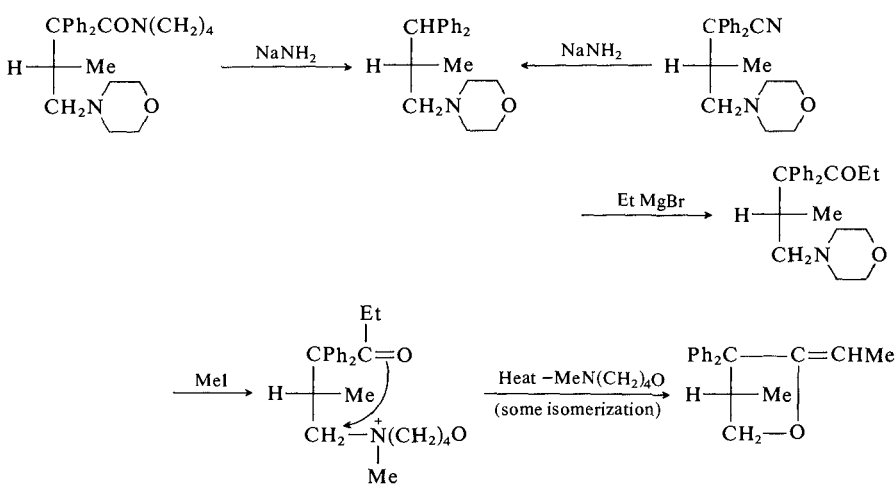
Fig 9.1. Tetrahedral representations of *R*-(−), *S*-(+) methadone and 6-methylmethadone.



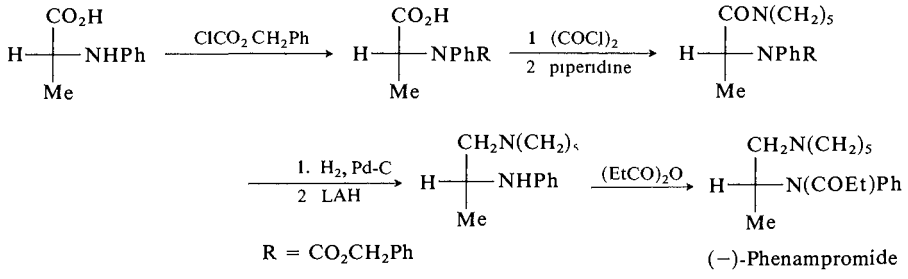
Scheme 9.9

group in *R*-(−)-methadone was thus deduced as minor in terms of ligand binding, although it may have an advantageous influence on the attainment of the active conformation of the drug, since the desmethyl analog, normethadone, is significantly less potent than methadone itself.

Similar configurational studies have been carried out in the isomethadone series (Table 9.3). A sequence involving *R*-(−)-α-methyl-β-alanine was used to establish the configuration of isomethadone itself[83] (Scheme 9.9); some of the steps recall the strategy of the methadone work. The approach to the configurational assignment of dextromoramide was first to relate it to the corresponding ethyl ketone and then to show that both the ketone and (−)-isomethadone gave identical (−)-tetrahydrofuran derivatives on pyrolysis of the methiodides (Scheme 9.10); these transformations supported earlier assign-



Scheme 9.10

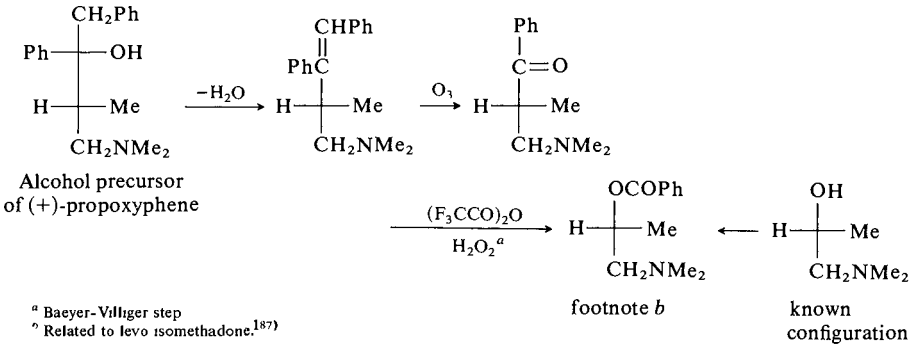


Scheme 9.11

ments based on the evidence of molecular rotational changes with solvent polarity.[84] The more potent antipode of phenampromide also fits the configurational pattern of levo isomethadone and dextromoramide, relationships in sharp contrast with those of (+)-diampromide and (−)-methadone (see later). Portoghese's route starts from an antipode of *N*-phenylalanine of known configuration (Scheme 9.11).[85]

Propoxyphene has chiral centers at both C-2 and C-3, with the latter equivalent to that of isomethadone. Pohland and others[86] showed the C-3 centers of (+)-propoxyphene and (−)-isomethadone to be identical (3*R*) by a sequence that rests upon retention of configuration during a Baeyer-Villiger oxidation step (Scheme 9.12). In subsequent work, this assumption was justified by a correlation that did not involve the C-3 center and employed a Mannich base intermediate.[87] The C-2 configuration of (+) propoxyphene was established by a lengthy sequence that required degradation of the compound to (+)-2,3-diphenylpropane of known (*S*) configuration.

The configurational studies so far outlined neatly correlate the more active antipodal isomers of the methadone and isomethadone type, respectively.

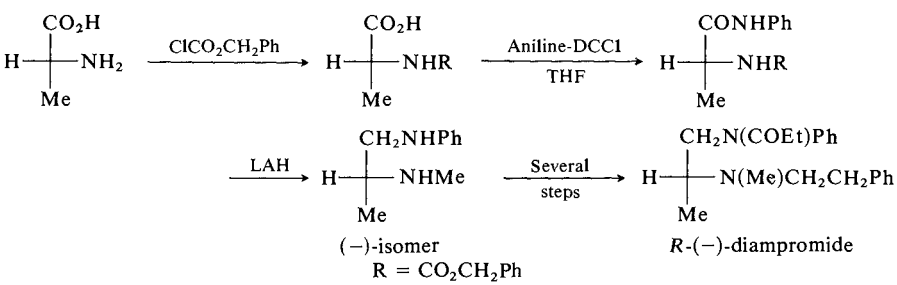


Scheme 9.12

(Correlations between the two classes are not meaningful because two different kinds of chiral center are involved.) Evidence of deviations from configurational identity among analgesics with apparently close relationships to methadone was available, however, early in the postwar investigations of acyclic analgesics, when it was discovered that the more active antipodal form of the ethyl ester analog of methadone was formed from the nitrile precursor of the *less* active (+)-isomer of methadone (Scheme 9.8).[88] Several studies have confirmed these findings and established that the ester is a true morphine-like analgesic.[75] The α-methadols provided another example of analgesics that fail to correlate stereochemically with methadone, as will be discussed.

Anomalies of this kind, although noted,[74] did not receive serious consideration until Portoghese provided yet another example in his stereochemical studies of diampromide (p. 311), an analgesic designed as a methadone analog and hence with a chiral center similar to that of the parent. It turns out, however, that the more potent antipode of diampromide is identical in configuration with *S*-(+)-alanine, and hence has an opposite chirality to that of levo methadone.[89] The configurational sequence (Scheme 9.13) involves one-step amide to amine and *N*-carbobenzyloxy to *N*-methyl interconversion and links *R*-(−)-alanine to the less potent antipodal form of diampromide. These configurational relationships extend to several analogs of diampromide (Table 9.4); note, however, that configurational preferences of the opioid receptor for phenampromide (a basic anilide related to isomethadone) and the parent diphenylpropylamine analgesic are the same.

Configurational data on diampromide and its relatives indicate, therefore, that the assumed analogy with the methadone class is not justified and that the two classes probably differ in their binding modes at the receptor.[91] Degrees of receptor stereoselectivity are generally less in the anilides (Table 9.4) than in the methadone group, where the *R*:*RS* potency ratio is usually close to 2. Further, the arylalkyl nature of the basic function in the anilides is of a type unusual (and indeed detrimental to potency) to diphenylpropylamine analgesics. This fact does not help explain the configurational results



Scheme 9.13

Table 9.4. Antinociceptive Activities of Enantiomorphs of Diampromide and Related Compounds

$$\begin{array}{l} \text{MeN.CHMe.CH}_2\text{.N.COEt} \\ \quad\;\; | \qquad\qquad\;\; | \\ \quad\;\; \text{R} \qquad\quad\;\; \text{Ph} \end{array}$$

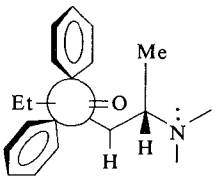
R	Form[a]	AD_{50} values (mg/kg)[b]	*S*/*RS* potency ratio	Ref.
$PhCH_2$	*RS*-(±)	8	1.86	50[c]
	S-(+)	4.3		
	R-(−)	inactive (50)		
$Ph(CH_2)_2$	*RS*-(±)[d]	3.7	1.0	50
	S-(+)	3.6		
	R-(−)	11.7		
$Ph(CH_2)_3$	*RS*-(±)	12.5	1.4	90
	S-(+)	8.9		
	R-(−)	11.9		
p-$MeC_6H_4.CH_2$	*RS*-(±)	1.6	1.14	90
	S-(+)	1.4		
	R-(−)	inactive (50)		
Me	*RS*-(±)	50[e]	1.7	92
	S-(+)	35		
	R-(−)	40		

[a] $[a]_D$ Sign of base given.
[b] Tail-flick method.
[c] Hot-plate ED_{50} values in mice are (±) 15, (+) 12 and (−)≥40 (Ref. 92).
[d] Diampromide.
[e] Hot-plate ED_{50} values in mice.

because the more active antipode of the analog with the "normal" dimethylamino function also has an *S* configuration (Table 9.4).

Probable conformations for methadone (**31**) and the *N*-benzylmethylaminoanilide **32**, based upon spectroscopic and X-ray crystallographic studies, have been proposed.[92,93] If it is assumed that these conformations are likely to resemble those adopted by the analgesic at the receptor site, and further that the phenyl-*sec*-methyl-basic center orientation of the methadone

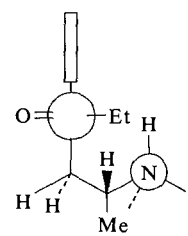
31



Representation of a probable conformation of methadone hydrochloride (N.Me groups are omitted).

conformation **31** is particularly inducive to drug–receptor association, a possible reason may be advanced for the differing stereochemical and basic group features of the two classes of analgesic. Although the spatial arrangement of the three groups specified in **31** is not favored in the basic anilide **32**, this compound is nevertheless an active analgesic, and it is therefore probable that its mode of binding to the receptor differs markedly from that of methadone. Hence, the stereospecificity of the receptor toward enantiomorphic forms of the anilide is not necessarily the same as that which it exhibits toward methadone isomers, and binding sites additional to those operating in the case of the methadone–receptor association may be required for the effective uptake of basic anilide molecules upon the receptor surface. Such sites could be provided by the aryl feature of the basic group of active anilides, which is absent in methadone and related compounds. It is significant in this respect that the NMe_2-substituted anilide (Table 9.4 R = Me) has a low order of analgesic potency, whereas methadone and isomethadone analogs with benzylmethyl- and phenethylmethyl-amino functions are inactive.[29,92]

32



Representation of a probable conformation of *N*-[(2-benzylmethylamino)-propyl]propionanilide hydrochloride Note (1) End-on view of aromatic ring is shown (2) Amido-carbonyl carbon eclipses amido-nitrogen (3) H and Me on C-2 may be interchanged (4) For clarity, N·Me and CH_2 Ph substituents have been omitted

As already mentioned, the greater analgesic potency of α-(−)-methadol over its antipode is another anomaly in the study of configurational relationship among diphenylpropylamine analgesics, since the more potent levo form is derived from the feeble analgesic (+)-methadone rather than from levo methadone (Table 9.5). Evidence of the configuration of the C-3-OH center of the methadols has been obtained by ^{1}H-nmr analysis of derived 2-ethyl-3,3-diphenyl-5-methyltetrahydrofurans,[95,96] and the application of Prelog's rule.[97,98] Such indirect evidence of C-3 stereochemistry is obtained from the fact that reaction of α- and β-methadol with cyanogen bromide gives two different tetrahydrofurans, respectively, as are also produced by pyrolysis of corresponding methiodides. The configurations of the cyclic products (*c* or *t* 2-Et/5-Me) may be deduced from chemical shift differences between the α/β 4-CH_2 protons and the findings applied to the configurations of the precursor alcohols, making the likely assumption of the reactions proceeding with inversion at C-6 (see **33**).[95] Similar arguments were advanced by

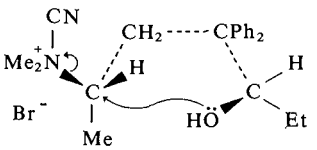
Table 9.5. Hot-plate Activities in Mice of Some Methadols and Normethadols (sc Route)

$Me_2N.CHR.CH_2.CPh_2.CHEt$
$|$
OR'

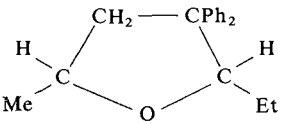
(methadols, R = Me, normethadols, R = H)

Precursor	Form	Configuration	ED_{50} values (mg/kg)	
			Methadols (R′ = H)	Acetylmethadols (R′ = $COCH_3$)
R-(−)-Methadone	α-(+)	6*R*:3*R*	24.7	0.3
(0.8)[b]	β-(−)	6*R*:3*S*	7.6	0.4
S-(+)-Methadone	α-(−)	6*S*:3*S*	3.5	1.8
(25.7)[b]	β-(+)	6*S*:3*R*	63.7	4.1
(±)-Normethadol HCl		*RS*	9.88	—
(±)-Normethadol-(±)-tartrate		*RS*	10.3	—
(+)-Normethadol-(+)-tartrate[c]		*R*	17.7	—
(±)-Acetylnormethadol HCl		*RS*	—	4.44
(+)-Acetylnormethadol HCl		*R*	—	2.7

[a] From Refs. 38, 94.
[b] ED_{50} value.
[c] α-(+)-Methadol and (+)-normethadol correlated sterically at C-3 by fact of their near-identical ORD curves.[94]



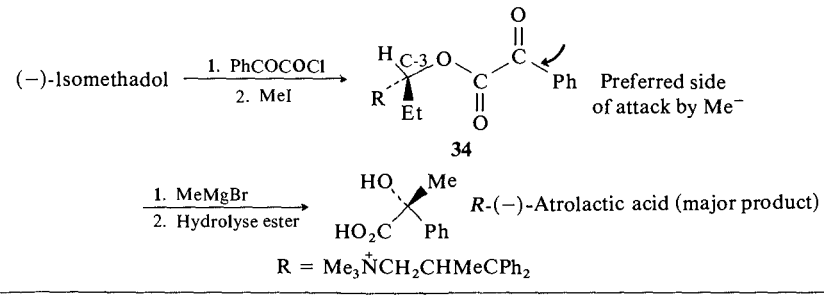
α-(−)-Methadol cyanobromide



cis-2-Et,5-Me isomer

33

Portoghese and Williams,[96] and the *cis* geometry of the tetrahydrofuran produced from α-methadol was subsequently confirmed by *X*-ray crystallography.[99] Inspection of chiral centers shows that reaction leading to a *cis* product requires a 6*S*,3*S* configuration of α-(−)-methadol. Scheme 9.14 illustrates how Prelog's rule of asymmetric induction has been applied to establishing the C-3 configuration of the methadols and isomethadols.[97,98] The optically active secondary alcohol is first coverted to a phenylglyoxylate ester by reaction with benzoylformyl chloride. This ester (after *N*-methylation) is assumed to favor a conformation in which the carbonyl groups are anti-parallel and the smallest group of alcoholic chiral center (C-3) is eclipsed by the ketone carbonyl. A methyl carbanion, from a Grignard reagent, will prefer to approach the ketone carbonyl from the side of the smaller of the two



Scheme 9.14

remaining groups attached to C-3 (i.e., Et in **34**). Hence, *R*-(−)-atrolactic acid is the major product if the C-3 configuration is as shown (*R*), while the *S*-(+)-antipode results if opposite chirality applies.

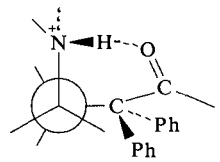
The complete configurational relationships of the methadone, methadols, and acetyl methadols are shown in Table 9.5 together with MHP data. From these results it appears that the C-3 rather than C-6 configuration is of prime importance respecting the activities of the methadols. Thus, the two more active isomers α- and β-(−)-methadol both have the 3*S* configuration, while the most active isomethadol, β-(+)-, belongs to the same C-3 steric series.[100,101] It follows that the *S*-member of methadol enantiomers lacking asymmetry at C-6, the normethadols, should be the more potent antipode, and this prediction has been confirmed (Table 9.5). The relative activities of (+)- and (−)-α-methadol are reversed when the alcohols are acetylated (Table 9.5), and the α-(+)-isomer derived from levo methadone is the more potent ester. This remarkable inversion of stereoselectivity may be interpreted in terms of the C-6 center asserting its dominating role. Alternatively, it may be considered due to esters requiring a *R*- C-3 center for optimal activity. The latter is more probable because the same steric reversal occurs in the case of normethadols and their acetate esters, with the less active *R*-alcohol yielding the more active acetate (Table 9.5). Although the methadols and acetylmethadols are closely related in structure, their conformations at the receptor may well differ as a result, for example, of a hydrogen bond donor group (OH) in one ligand being replaced by an acceptor group (OCOMe) in the other. Strong intramolecular hydrogen bonding has been demonstrated in diastereoisomeric methadol bases (in CCl_4) and hydrochlorides (in $CHCl_3$), and preferred conformations have been proposed on this evidence.[102] This interpretation of differing stereoselectivites of structurally related analgesics in terms of differing binding modes is akin to that proposed in the case of the more active enantiomorphic cholinergic agents (+)-muscarine and (−)-muscarone, which have opposite configurations at the C-5 center.[103] It is interesting that α-(−)-acetylmethadol (6*S*,3*S*) is far less potent than the dextro isomer after intraventricular

administration, and it has been suggested that the analgesic effects of the levo isomer are due to a metabolite rather than the intact drug itself.[104]

Sullivan and others[17] found that α-(−)-*N*-desmethylmethadol and (−)-methadone were similarly potent as analgesics; hence, the former represents an active metabolite of methadone (see p. 309). It is possible that the *in vivo* formation of the methadol (and the *N*-desmethyl analog) may account for the relatively better effectiveness of (+)-methadone as an analgesic when given orally rather than parenterally.[105]

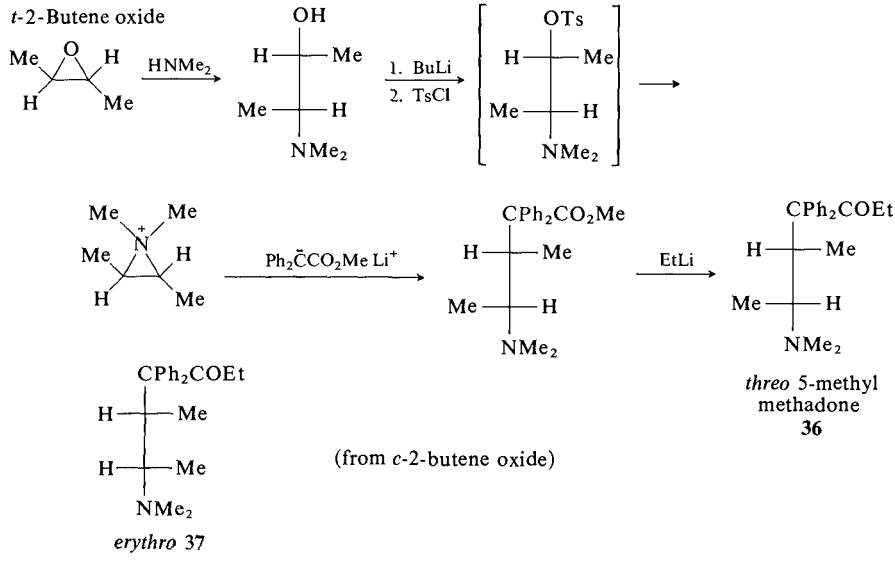
Several papers dealing the conformation of methadone and its relatives have been published in attempts to justify or refute hypotheses about the "active" forms adopted by the highly flexible molecules of this type at opioid receptors. Of the various techniques employed, X-ray crystallography provides information about solid-state conformation that may give clues to probable or possible molecular orientations in solution and at the receptor site. Conformations of methadone and its congeners that mimic morphine require close approach of the C-3 oxygen function and amino nitrogen atom. N/C_3-O proximity is only possible if the C(4)-C(5)-C(6)-*N* torsion angle (τ) is less than 120° (**35**). This parameter is therefore of special significance in detecting

35



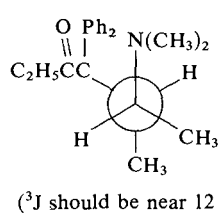
Newman diagram, molecule viewed along C(6)—C(5) bond (also applies to formulae **38** and **39**).

intramolecular nitrogen-oxygen interactions, and data on this point are summarized in Table 9.6. Only in the case of methadone base (item 1) is the torsion angle τ of a value consistent with close *N*/C-O contact; the *N* to carbonyl carbon (C-3) distance of 291 pm is, in fact, almost 30 pm less than the sum of the van der Waals radii of carbon and nitrogen. This distance is only possible at the expense of introducing other interactions in the molecule that are repulsive and the conformation is probably stabilized by the electronic attraction between the nitrogen lone-pair of electrons and the carbonyl carbon atom (*N*:...C = O). The *N* to O(3) distance and torsion angle found for α-methadol hydrochloride (item 4) is also indicative of an interaction between nitrogen and oxygen functions and there is pK_a[97,98] and IR[102] evidence of intramolecular hydrogen bonding (N^+—H···O—C_3) in this salt. In all other cases, however, torsion angles have values that show that the C(4)-C(5)-C(6)-*N* chain is fully extended with oxygen and nitrogen functions well separated. There is now evidence, in fact, that an antiperiplanarlike disposition of Ph_2COEt and $^+NHMe_2$ groups is one of the pharmacophoric dispositions of methadone and related analgesics. This conclusion was reached from studies



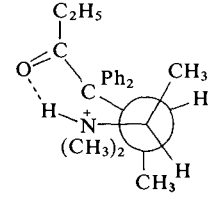
Scheme 9.15 (only one antipode depicted)

of the *threo* (**36**) and *erythro* (**37**) 5-methylmethadone diastereoisomers prepared by stereospecific reaction sequences (Scheme 9.15).[109] The authors of this work suggest that the striking difference in analgesic potency between the isomers (*erythro* 5.4 × methadone, *threo* inactive, MHP) might be traced to a difference in the conformational equilibria. As in previous investigations of acyclic diastereoisomers,[110] ^{1}H nmr spectroscopy provided key data on this point. The magnitudes of the vicinal coupling constants between the C-5 and C-6 protons ($^3H_{5,6} \leqslant 1$ Hz for *threo*, 6-8.3 Hz for *erythro*) show that, whereas the contribution of the antiplanar form **38** must be small for *threo*, it is probable that all three staggered or near-staggered conformers of the *erythro* isomer are significantly populated. Nmr and pK_a data suggest that the inactive *threo*-racemate (**36**) exists chiefly in a hydrogen bonded conformation **39** that does not possess the requisite geometry for association with the opioid receptor



(^{3}J should be near 12 Hz)

38



39

Table 9.6. C(4)-C(5)-C(6)-N Torsion Angles (τ) and N to O(1) Distances of Certain Diphenylpropylamine Analgesics[a]

Item	Compound	$\tau°$	N to O(1) in pm
1	(−)-Methadone (1) base	−68.5 −69.8	3.43
2	(−)-Methadone HBr	−146.3	3.81
3	(−)-Isomethadone[b] HCl	−152.5	3.69
4	α-Methadol[c] HCl	116.1	3.159
5	α-Methadyl acetate HCl	−146.2	4.88
6	Dextromoramide[d] acid tartrate	−166.5	Not reported
7	Dextromoramide base	−159.4	Not reported

[a] From Refs. 106-108.
[b] $Me_2NCH_2CHMeCPh_2COEt$.
[c] $Me_2NCHMe\ CH_2CPh_2CH(OH)Et$.
[d] Table 9.1.

(this arrangement was not, however, found in the solid state).[116] In contrast, the *erythro* isomer offers much greater latitude for effective binding because of its increased conformational flexibility. A circular dichroism and nmr investigation of methadone and isomethadone gave evidence of the greater conformational flexibility of the former analgesic, and this conclusion was advanced as a possible cause for the two-fold greater enantiomeric potency ratio of (−):(+) isomethadone, and also the observation of inversion of receptor stereoselectivty in the methadone series ($NCHMeCH_2C$) but not in the isomethadone (NCH_2CHMe) group of analgesics.[111] The CD data shown in Figure 9.2 illustrates the radical solvent-induced inversion of the sign of the Cotton effect of methadone, a phenomenon not seen for isomethadone base or salts of the two ketones in demonstration of methadone's high degree of conformational mobility. Similar sign inversions are anticipated from optical rotatory dispersion (ORD) measurements, but available data are confined to a single solvent (dioxane).[112] The results of quantum chemical studies of methadone add further support to the experimental evidence that methadone has several low-energy and therefore readily interconvertible conformers[113] and to Portoghese's proposals about receptor interactions of methadone, 5-methylmethadone, and isomethadone.[115] It is instructive to note that the inactive *threo* isomer of 5-methylmethadone contains the 5*S*,6*R* stereoisomer, which combines the configurations found in the more active enantiomers of

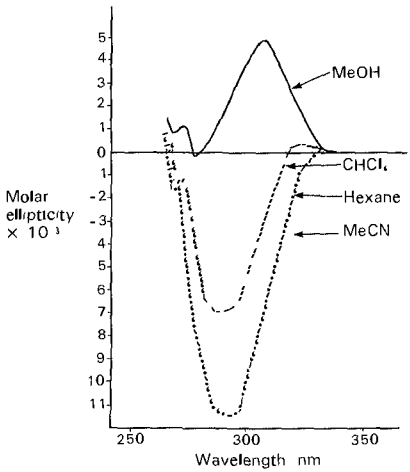


Fig 9.2. CD spectra of (+)-6*S*-methadone (0.1% in solvents noted)

methadone and isomethadone.[109] This observation indicates that the chiral centers do not behave as independent units but interact with other groups to afford a conformational population that strongly influences the potency of the diastereoisomers. In other words, conformational factors have greater weight than those of absolute configuration in governing drug-receptor binding in diphenylpropylamine analgesics. The antipodal forms of the *erythro* isomer **37** show an isomeric potency ratio of about 6 in the MHP procedure (relative potencies: levo, 11.3; dextro, 1.8; morphine, 1) and the more active levo isomer has a 5*S*,6*S* configuration (X-ray evidence).[114] More pronounced activity differences were seen after *in vitro* tests while GPI:MVD potency ratios indicated that (−)-**37** was primarily a μ-agonist in contrast with (+)-**37** and levo isomers of methadone and isomethadone, which interacted with both μ- and δ-sites.

In summary, it is evident that the 3,3-diphenylpropylamine system provides the basis for a variety of compounds of significant analgesic activity, and development of the group has led to several clinically useful agents. Potency levels of the more active derivatives are generally close to, or a few times greater than, that of morphine, and no agents of superpotency (with the exception of the spirane **12**) have been described, possibly a result of the extremely flexible nature of molecules of this group. Stereochemical studies of methadone and its analogs have been notably extensive, and the results have provided impetus for many of the original speculations upon the nature of ligand-receptor interactions in the opioid field.

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10

Enkephalins, Endorphins, and Other Opioid Peptides

10.1. INTRODUCTION

The isolation of naturally occurring peptides with morphinelike properties and the subsequent investigation of synthetic analogs are direct consequences of two major developments in the methodology of study of opioid receptors and their ligands made since 1970. These are (1) the introduction of *in vitro* testing procedures, notably inhibition of the contraction of electrically stimulated guinea pig ileum (GPI) and mouse vas deferens (MVD), and (2) the detection of opioid receptors in brain and other tissue by binding studies with radiolabeled opioids and the measurement of specific drug-receptor binding constants.

Although the existence of opioid receptors has been inferred for many years from the structure-activity relationships (especially stereochemical) of narcotic analgesics and their antagonists,[1] it was not until the early 1970s that direct evidence of their existence and location came to light. A direct approach to detecting receptors is to bind radioactive opioids to brain membranes, but this is made difficult by the fact that opioids, like most polar drugs, bind nonspecifically to many membrane sites whose numbers greatly exceed the specific opioid receptors. To differentiate between specific and nonspecific binding, Goldstein *et al.*[2] introduced the principle of stereospecific binding (SSB). This requires measuring the difference in binding of a radioactive opioid such as levorphanol under two conditions: condition A in the presence of a large excess of nonradioactive dextrorphan, and condition B in the presence of a large excess of nonradioactive levorphanol with the total drug concentration the same in both cases. If there were no stereospecific binding, there should be no difference in bound levorphanol radioactivity because the binding sites would not distinguish the two isomers. If some binding were stereospecific, there would be less bound levorphanol radioactivity in B than in A, provided the fractional occupancy of the sites were sufficiently great.[3] Success in identifying specific opioid receptor binding depends on the use of opioids of

high specific radioactivity so that low concentrations can be employed favoring binding to high-affinity, specific rather than nonspecific sites.[4] The original system of Goldstein[3] did not meet these requirements, since less than 2% of the total binding of levorphanol was SSB. Pert and Snyder,[5,6] however, used ^{3}H-naloxone with a specific radioactivity 1000 times greater than the opioids employed by Goldstein and were able to demonstrate high-affinity SSB in rat brain homogenates (SSB was about 3 times greater than nonspecific binding) using the originally described displacement conditions A and B. Techniques have been developed to permit rapid and extensive washing of membranes with the aim of removing nonspecifically bound drugs without affecting a radioactive drug bound to the opioid receptors. SSB was shown to be present in neural (rat brain and guinea pig myenteric plexus) but not in other tissues. Terenius[7] also devised methods for the demonstration of SSB by measuring the displacement of ^{3}H-dihydromorphine by the antipodal forms of methadone.

In addition to the use of SSB measurements for the detection of opioid receptors, other aspects of this technique include the correlation of ligand affinity, usually expressed as the concentration of drug that displaces 50% of the radioactive label (IC_{50} or ID_{50}), with pharmacological potency,[8] and the differentiation of agonists, antagonists, and dualists. This last application utilizes the observation that low concentrations of sodium selectively decrease the binding of opioid agonists but enhance that of the antagonist used as displacement label.[9,10] Thus, opioid agonists that lack an antagonist component to their activity become 12–60 times more weakly bound in the presence of sodium, whereas pure antagonists such as naloxone are not influenced; wide-spectrum ligands such as nalorphine and pentazocine become 3 to 7 times less well bound. The degree of decrease after sodium is termed the sodium index (Table 10.1).

With the tangible demonstration of opioid receptors accomplished, the question of their normal physiological role clearly required consideration. It is unlikely that the receptors should have evolved uniquely for reaction with substances exogenous to the body, and it is logical to postulate the existence of natural morphinelike substances that associate with opioid receptors in an interaction that has some normal physiological function such as the transmission or modulation of nerve impulses. This prediction, first made by Goldstein,[11] stimulated an intensive search for substances of natural occurrence with opioidlike properties, and an account of such natural opioids and their synthetic analogs forms the main topic of this chapter.

During 1974–1975 several groups isolated substances from brain tissue that acted as agonists at opioid receptor sites. A single issue of *Life Sciences* included reports by British, Swedish, and American groups on this topic, all being papers read at the May 1975 meeting of the International Narcotics Research Club.[12] The isolation techniques of Hughes *et al.*[13] are typical. Pig brain was extracted with acetone and the residue after evaporation of solvent

Table 10 1 Effect of Sodium Ions on the Ligand Affinity of Certain Narcotic Analgesics and Analgesic Antagonists[a]

Compound	IC_{50} (n*M*)[b] No NaCl	100 m*M* NaCl	IC_{50} ratio NaCl/no NaCl
Naloxone	1 5	1 5	1 0
Diprenorphine	0 5	0 5	1 0
Cyclazocine	0 9	1 5	1 7
Levallorphan	1 0	2 0	2 0
Nalorphine	1 5	4 0	2 7
Pentazocine	15	50	3 3
Metazocine	10	60	6 0
Etorphine	0 5	6 0	12
Phenazocine	0 6	8 0	13
Pethidine	3,000	50,000	17
Levorphanol	1 0	15	15
Methadone	7 0	200	28
Oxymorphone	1 0	30	30
Morphine	3 0	110	37
Dihydromorphine	3 0	140	47
Normorphine	15	700	47

[a] From Ref 9

[b] Concentration of drug that produces 50% inhibition of control stereospecific binding of [^{3}H]naloxone to rat brain homogenates

was treated with methanol to remove protein and salt and with ether/ethyl acetate to remove lipids. The product was subjected to a series of fractionations by ion exchange and gel (Sephadex G-15) chromatography. Fractions were monitored by MVD assay, a specific action at opioid receptors being assumed if the depression of neurally evoked contractions was antagonized by naloxone or diallylnormorphinan, quantitative data were obtained by running parallel assays with normorphine. The peptidic nature of active material was established by its positive reaction with reagents such as cadmium ninhydrin and the Royden-Smith test for NH groups (UV absorption at 280 nm suggested the presence of an aromatic amino acid), and the molecular weight judged to be about 800 from electrophoresis experiments. The British group termed the active material enkephalin and followed up its initial report by full characterization of the material.[14] Acid hydrolysis of pig brain enkephalin gave five amino acids, namely (nmol): Gly (36.5), Met (12.3), Tyr (16.9), Phe (22.5), and Leu (4.2). The peptide sequence was established by degradation (dansyl-Edman) and MS (originally by application of the use of *N*-acetylpermethylated derivatives, which are suitably volatile and yield mass spectra that provide sequential information on the basis of favored fragmentation at the peptide bonds - more recently, the fast-atom bombardment (FAB) technique has been found to provide data of equal utility and may be applied to the underivatized

Tyr-Gly-Gly-Phe-Met(OH) Tyr-Gly-Gly-Phe-Leu(OH)
1 2

$PhCH_2CH(CH_2SH)CONHCH_2CO_2H$
3

peptides).[15] From this evidence enkephalin was deduced to be a mixture of the two peptides **1** and **2** in the ratio of 3 or 4 to 1. This conclusion was confirmed by electrophoretic, MS, and biological comparisons between natural and synthetic peptides, the latter being obtained by classical solution methods (see later). Peptide **1** is generally referred to as methionine-enkephalin (*Met-enkephalin*) and **2** as leucine-enkephalin (*Leu-enkephalin*). The same enkephalin mixture has been isolated from bovine brain, but in this case Leu-enkephalin preponderates by a factor of 4.[16] Sensitive and specific HPLC procedures are now available for the detection and quantification of the enkephalins and related peptides in biological extracts.[17] Both Met- and Leu-enkephalin produced dose-related inhibition of electrically evoked contractions of the MVD and GPI, and the inhibitory effects were completely reversed by naloxone. Met-enkephalin was 20 times more active than normorphine in the vas deferens and equipotent with the same standard in the GPI (morphine and normorphine are equiactive in these preparations but the nor-derivative has a quicker onset of action and is easily washed out), facts later correlated with the subclassification of opioid ligands, as will be discussed. Leu-enkephalin was weaker than the methionine peptide in both MVD (0.5×) and GPI (0.2×); later experiments confirmed the weaker activity of Leu-enkephalin in GP ileum but gave the leucine peptide a higher potency in the MVD test.[18] Met-enkephalin also proved effective, in degree at least 3 times more than morphine, as an inhibitor of the stereospecific binding of ^{3}H-naloxone to sodium-free homogenates of guinea pig brain, and exhibited cross tolerance in morphine-tolerant mice.[19] In general, the two enkephalins behaved like an agonist in binding experiments; sodium decreased the binding of ^{3}H-met-enkephalin while the sodium index for the two peptides lay between that of naloxone and dihydromorphine.[16] Belluzzi *et al.*[20] first reported analgesic activity following central administration of enkephalins to rats (via in-dwelling cannulae implanted stereotaxically with the tips located in the lateral ventricle). In tests for analgesia using the tail-flick (RTF) method, the enkephalins were less potent and had shorter durations of action than morphine; they were ineffective unless applied directly to the brain. Several groups subsequently performed similar tests of enkephalins in animals and the data has been collated by Malik and Goldstein.[188]

10.2. ENZYMATIC DEGRADATION

The transient nature of the pharmacological actions of the enkephalins was noted early in opioid peptide studies, a fact that was soon correlated with

the rapid deactivation of enkephalins by plasma and tissue homogenates.[21] The primary mode of degradation was shown to be cleavage of the Tyr-Gly amide bond (shown by release of Tyr from radio-labeled substrates).[22] Peptides are liable to attack of this kind by many nonspecific aminopeptidases arising from broken cells and plasma, and which are present in the tissues and surrounding organ bath fluid of the pharmacological assay procedure. These aminopeptidases are inhibited by working at 4° or adding bacitracin or puromycin, and the actions of enkephalins are enhanced when assay conditions are so modified.[23] Recently, aminopeptidases have been isolated from both human brain[24] and plasma[25] with marked preferences for Met- and Leu-enkephalin (a D-Ala^2 analog was resistant to the brain-derived enzyme). In contrast, a carboxypeptidase (termed *enkephalinase* and obtained from the particulate fraction of mouse striatum) has been identified that specifically cleaves the Gly^3-Phe^4 bond of the enkephalins.[26] It is a membrane-bound enzyme localized in the vicinity of opioid receptors and may therefore play a role in the physiological control of endogenous opioid peptide activity. The enzyme is not inhibited by puromycin but is blocked by (DL-3-mercapto-2-benzylpropanoyl)glycine (**3**, *thiorphan*), a compound designed on the basis of a proposed mode of enkephalin/enkephalinase uptake.[27] Thiorphan protects enkephalins under both *in vitro* and *in vivo* conditions and itself displays significant antinociceptive activity, attributed to the potentiation of endogenous enkephalins released in response to the noxious stimuli.[28]

The resistance of enkephalins to enzyme attack may be increased by substituting D-amino acids for glycine at the 2-position, by converting terminal CO_2H to an amide function, and by other modifications (see later).

Recent work on enzymes of this kind is included in reports of the 1982 and 1983 International Narcotics Research Conference.[189]

Other sources of peptides with opioid properties are the pituitary gland, in which the so-called endorphins are found, and the adrenal medulla (see p. 359). Speculations have been made on whether such tissues are the source of enkephalins found centrally[4] and on the ability of small peptides of the type to cross the blood-brain barrier. Met-enkephalin itself combines marked hydrophobic properties (its water solubility is less than 0.7%, according to Roques *et al.*[29]) with a low affinity for lipid as judged by its heptane-phosphate buffer pH 7.4 partition coefficient of 0.0001 (identical with that of morphine). However, there is evidence, using isotopically labeled Met-enkephalin, that the peptide rapidly enters the brain following iv administration.[31] [D-Ala^2]Met-enkephalinamide and three analogs of endorphin (all synthetic and radiolabeled to allow sensitive detection) were found to have moderate cerebrovascular permeability that was sufficient to produce significant brain uptake within 3–11 min after a step rise in plasma concentration, and the findings were considered in accord with the observed central effects of such peptides after systemic administration. On the other hand, only very low amounts of

the metabolically stable enkephalin analog FW 33-824 of Sandoz (p. 350) compared with morphine were detected in CSF by an immuno assay technique after iv infusion (cf. iv and icv potencies of this peptide shown in Table 10.3).[32]

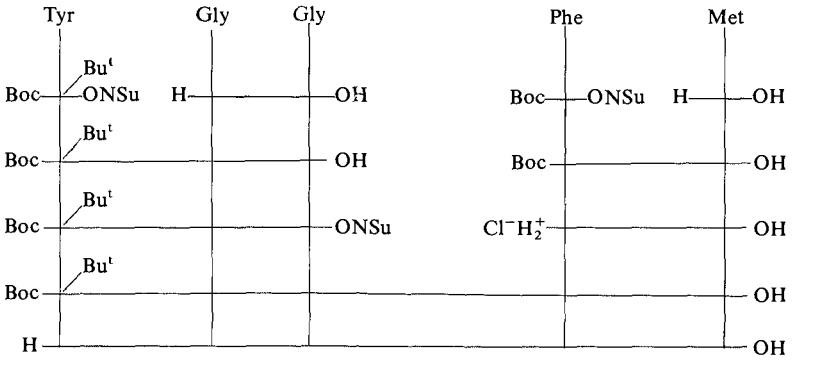
Hopes that natural peptides or their analogs might provide the long-sought nonaddicting analgesic have not been encouraged by reports that tolerance and physical dependence can be produced by chronic perfusion of rat cerebral ventricles with enkephalin or by repeated injection of β-endorphin.[33] Furthermore, rats made tolerant to morphine proved cross-tolerant to β-endorphin as well as to synthetic Met-enkephalin, while naloxone given to rats repeatedly pretreated with endorphins precipitated a withdrawal syndrome similar to that induced in rats treated with normorphine.[34] Heroin addicts, however, preferred morphine to the synthetic opioid FK 33-824 (of high PDC)[81] and asserted that the peptide evoked intoxication without euphoria.[35]

10.3. SYNTHETIC METHODS

Very soon after it became known that small peptides were capable of interacting with opioid receptors the investigation of analogs of the natural enkephalins commenced on an ever-increasing scale, and today literally hundreds of such derivatives have been tested for opioid properties. Before embarking on an account of the structure–activity relationships that have emerged, a short account of synthetic methods used in this field will be given.

The many syntheses of enkephalins, endorphins, and their variants carried out since 1975 have been achieved by standard methodology, full advantage being taken of the major development in peptide synthetic chemistry seen over the past 30 years [e.g., use of *t*-butoxycarbonyl (Boc) as an amino protecting group and dicyclohexylcarbodiimide (DCCI) as a coupling reagent].[36] Both solution and solid-phase procedures are represented in this work, each of which involve the well-known steps of NH_2 protection, CO_2H activation, coupling, and deprotection. In the solid-phase technique the initial *N*-protected amino acid is attached to a synthetic resin (usually a copolymer of styrene and divinylbenzene) that bears reactive chloromethyl groups. The great advantage of the method over solution procedures is the fact that purification at intermediate stages is achieved merely by washing and filtration of the insoluble resin.[37] However, all reactions must proceed to 100% completion if a homogeneous product is to result.

Many strategies have been employed to achieve the attachment and removal of amino and carboxylate protecting groups and formation of the peptide bond by methods that proceed in high yield and do not imperil optical purity. The former aim is especially important in the case of a solid-phase synthesis because there is no purification of intermediates during the synthesis. Avoidance of racemization is also of major concern because of the high level of stereoselectivity of most peptide–receptor interactions.

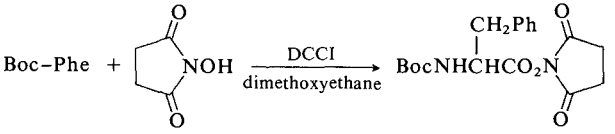


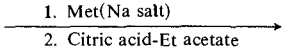
Scheme 10.1. Synthesis of Met-enkephalin

To illustrate these preparative methods the synthesis of natural enkephalins and the potent synthetic analog FX 33-824 are outlined. Scheme 10.1 depicts the original synthesis of Met-enkephalin.[38]

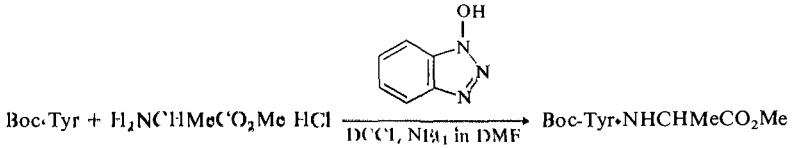
Points to note are:

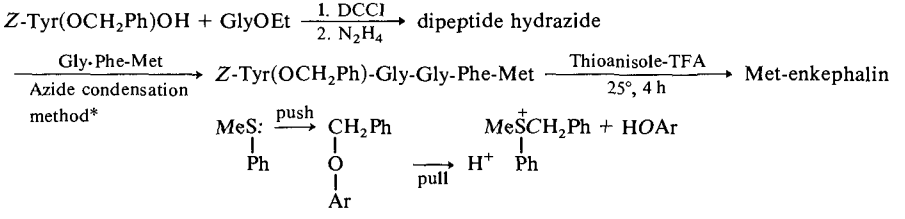
1. Use of Boc *N*-protected amino acids throughout and the masking of the Tyr phenolic OH by conversion to the *t*-butyl ether; both amino and OH functions were subsequently deprotected by treatment with HCl in peroxide-free dioxane.
2. Activation of carboxylate groups by formation of the *N*-hydroxysuccinate ester (ONSu):





Condensation of peptide units is also often carried out in one step by treating the two components with *N*-hydroxysuccinimide or *N*-hydroxybenzotriazole and DCCI since coupling with DCCI alone, as originally described,[39] may entail a significant degree of racemization[40]; an example is shown.[41]





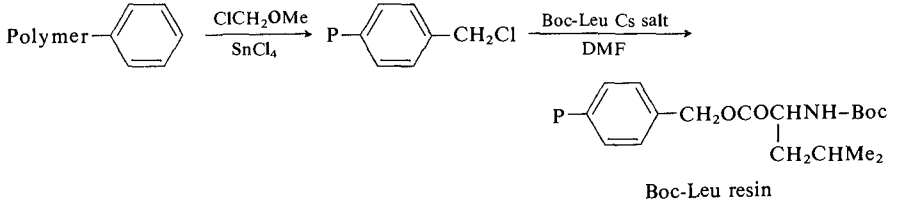
* Little risk of racemization[136]

Scheme 10.2

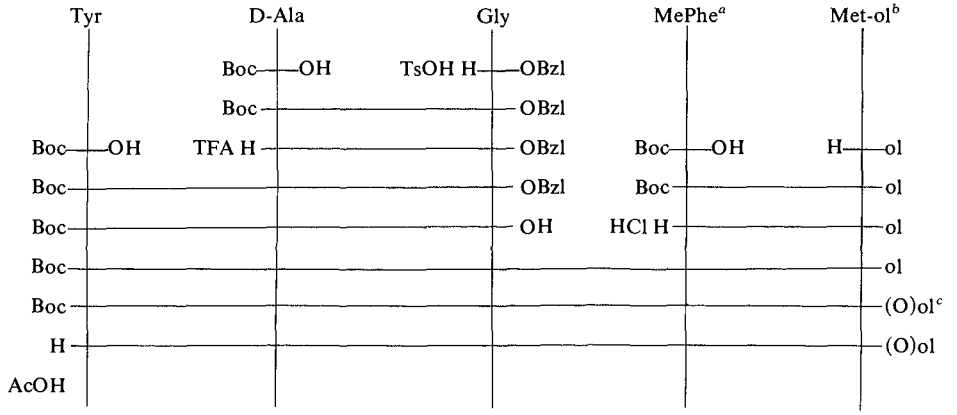
3. Purification of the pentapeptide by passage of the HCl salt in pH 6 buffer (1% pyridine in 0.04% acetic acid) through a column of sephadex; the free peptide is isolated from the eluate, which is monitored by UV absorption at 280 nm and optical rotation at 546 nm.

The use of benzyl and benzyloxycarbonyl (Z) blocking functions is usually precluded when peptides containing methionine are being assembled because of the vulnerability of Met to catalytic hydrogenolysis, the common deprotecting process associated with such blocking groups. Kiso,[42] however, has found that treatment of blocked peptides of this type with thioanisole-trifluoromethanesulfonic acid (or TFA) smoothly cleaves N-CO_2CH_2Ph, O-CH_2Ph, and O-Me functions but not S-Me under mild conditions and has applied this technique to the synthesis of Met-enkephalin and its analogs. A "push-pull" mechanism for the deprotection reactions is proposed (Scheme 10.2).

The preparation of FX 33-824, a typical variant of Met-enkephalin, is set out in Scheme 10.3.[43] Couplings were carried out by the mixed carbonic anhydride method using isobutyl chloroformate[44]; Boc derivatives were used to protect amino groups while Met-ol and Tyr-OH were unprotected. The risk of racemization was minimized by building up fragments stepwise with Boc-amino acids and by fragment coupling to achiral glycine residues. Furthermore, only weak bases such as *N*-methylmorpholine were used, and in equimolar amounts. The Boc-protected pentapeptide (penultimate stage of Scheme 10.3) was deprotected by treatment with TFA at 0°; the TFA salt precipitated on dilution of the reaction solution with ether and was converted to the corresponding acetate by passage of an aqueous solution through Amberlit IRA 410 in the acetate form.



Boc-Leu resin

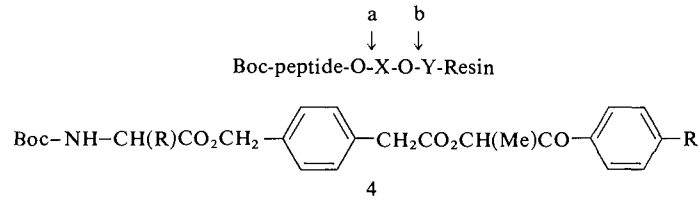


[a] Treat Phe with MeI-NaH
[b] Reduce Met with $NaBH_4$ (no racemization)
[c] Oxidize Met residue with H_2O_2—HAc

Scheme 10 3 Synthesis of FX 33-824

The preparation of Tyr-D-Ala-Gly-Phe(-Me)-Leu provides an example of the solid-phase procedure.[45] The starting material, Boc-Leu-resin, was obtained by chloromethylation of polystyrene-co-1% divinylbenzene resin with chloromethyl methyl ether and $SnCl_4$, and then by reacting equivalent amounts of the chloromethyl resin and the cesium salt of Boc-Leu (Cs salts react better than Na or K salts possibly because of their greater lipophilicity).[46] After several swelling and shrinking steps, to allow effective penetration of solvents and reactants to reactive sites on the insoluble matrix, the resin was deprotected with 50% TFA in toluene. The resin (now with free terminal NH_2 functions) was then coupled with a six-fold excess of Boc-Phe (α-Me) in toluene together with an equivalent amount of DCCI for two successive 4-h periods with the usual shrinkage-swelling cycles. Prior to coupling, acid was neutralized with triethylamine. Repetition of the procedure using the Boc amino acids Gly, D-Ala, and Tyr successively led to the Boc-pentapeptide resin. The free peptide was released by treating the resin with anhydrous HBr in TFA in the presence of excess of anisole (the latter removes bromine, which would brominate Tyr residues), and purified by countercurrent distribution in 1-butanol, ethyl acetate, acetic acid, water (2:2:1:1).

A recent development of solid-phase peptide synthesis is the use of multidetachable resin supports (**4**). The Boc-amino acid or peptide is attached to the resin via a spacer group (X) and may be detached as the Boc-peptide-O-X-OH by photolytic cleavage at (b), as the Boc-peptide-OH by basic cleavage at (b) and (a), or the unprotected peptide by cleavage with acid at (a).[47] Its application to the synthesis of Leu-enkephalin involved the use of the so-called



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pop-resin 4 obtained by esterification of Boc-Leu-acyloxymethylphenylacetic acid with a 2-bromopropionyl resin. After chain extension the completed peptide was cleaved from the resin by acidolysis with HF/10% anisole to give free Leu-enkephalin, photolysis at >350 nm, 72 h, 25° to give Boc-Leu-enkephalin-OMPA, or transfer hydrogenolysis (18 h, 50°, H_2, 1,4-cyclohexadiene) to give Boc-Leu-enkephalin.

10.4. STRUCTURE–ACTIVITY RELATIONSHIPS

Identification of the peptide nature of the enkephalins stimulated an extensive amount of SAR studies throughout the world, and the amount of data reported is now so large as to make the presentation of a comprehensive account of the SAR of opioid peptides impossible in a general text of this nature. Instead, samples of available results will be presented selected mostly on the basis of various aspects of their pharmacological significance. This account has been guided by several reviews of the topic, notably those of Morley of ICI,[48,49] Beddell *et al.* of Wellcome Research,[50] and Hardy,[51] which cover the literature up to early 1981. Major innovations from results published subsequently will also be included. Classification of the SAR studies is difficult because of the various viewpoints and objects of the investigators (e.g., search for stable derivatives of potential clinical value, or agents specific for a particular subclass of opioid receptor). Hence, some overlap in presentation is inevitable.

In assessing the potency of analogs, three *in vitro* test systems have been widely employed: the opioid binding assay,[5,54] inhibition of electrically stimulated guinea pig ileum (GPI),[52] and mouse vas deferens (MVD)[53] with agonist activity expressed by IC or ID_{50} values relating to 50% reduction of bound radiolabel or muscle twitch as appropriate (see Glasel and Venn[190] for a critique of binding measurements). The behavior of peptide derivatives in antinociceptive tests, a more direct measure of the potency of the compounds as analgesics, is less frequently available and in many cases is seen only after central administration (by icv and related routes) because of the instability of most of the peptides. With many analogs a lack of correlation between individual *in vitro* assays and between *in vitro* and *in vivo* assessments of potency is observed and has been interpreted in terms of the existence of

different types of opioid receptor, populations of which vary from tissue to tissue, as will be discussed. Evaluation of assay data is complicated in particular by the lability of peptide material to enzymes and the probability of endopeptidase activity playing a major role in determining the observed activity. Taber *et al.*[55] have stressed the need for care in interpreting both *in vivo* and *in vitro* results of the SAR studies of opioid peptides.

In the account of the influence of structure upon the activity of enkephalins that follows, the approach is broadly that of examining the effect of single changes of amino acid residue commencing at the amino terminal (position 1).

10.4.1. Structural and Configurational Requirements at Tyr[1]

There is no doubt of the central role played by the Tyr unit and the need for its having free phenolic and amino functions. Thus, desamino-Tyr is inactive, as is the Phe congener (phenolic OH absent). Masking Tyr-NH_2 by *N*-acylation, or Tyr-OH by *O*-alkylation also have pronounced adverse effects on activity. Deletions and substitutions that reduce activity relative to Met-enkephalin are shown below, chiefly taken from Wellcome group data[50]:

D-Tyr	β-homo-Tyr	*O*-alkyl-Tyr
Phe	*N*-acyl-Tyr	*N*-alkyl-Tyr
des-Tyr	Arg-Tyr	*N,N*-dialkyl-Tyr
des-NH_2		

Morley[48] gives data at variance with some of the above items in that addition of Arg to the *N*-terminal residue (giving a hexapeptide) causes little loss of activity in the case of Met-enkephalin by the GPI test (Tyr-NH_2 may be freed enzymatically), while the *N*-methyl Tyr[1] analog is at least as active as the parent in the same test. *N,N*-Dimethylation, which removes hydrogen-bonding capacity on the part of the *N*-terminus, has a distinctly adverse effect on potency. *N*-Allyl analogs are described on p. 434. Configurational requirements at position 1 are precise, as is clear from the inactivity of D-Tyr and α-Az-Tyr (α-CH replaced by *N* with resultant stereochemical and electronic change) analogs. A cyclic enkephalin (p. 374) in which Tyr is replaced by Phe is a rare example of a potent enkephalin that lacks a tryosine residue.[211]

10.4.2. Variation of Gly[2]: Analogs with Enhanced Resistance to Proteolytic Enzymes

Early SAR investigations revealed that the amide of Met-enkephalin was several times as active as the parent with a longer duration of action and that replacement of Gly[2] by D-Ala had a similar influence on peptide stability.[62,63] It was later shown that a variety of D-amino acids in place of Gly[2] caused a marked increase in potency both in GPI and MVD assays, results presumed

to be in consequence of enhanced stability GPI potency data on such analogs of Leu-enkephalin methyl ester (0 2 × Met-enkephalin, GPI) are shown below,

D-Ser 11 0, D-Met 8 0 D-Ala 5 6, D-Leu 1 3, D-Phe 1 3, D-Pro 0 002

D-Ser being the most effective replacement [56] Note that D-Pro at residue 2 is detrimental, as is also *N*-methylation (Sar^2 analog 0 01) All L-amino acid analogs had low activities

The potency of [D-Ala^2]Leu-enkephalin in GPI and MVD assays is differentially altered when L-Leu is replaced by the D-amino acid, [D-Ala^2-D-Leu^5]enkephalin (DADL) is half as effective as the parent in the ileum test but three times more active in the MVD procedure (see data) [57] DADL is now commonly employed as a selective δ-agonist (see p 356) Thus,

IC_{50} n*M* values	GPI (μ)	MVD (δ)
[D Ala^2]Leu enkephalin	28 7	1 63
DADL	47 8	0 54

vas deferentia chronically treated with DADL became 8000-fold less sensitive to this peptide but showed no cross-tolerance to μ-receptor agonists The amide of [D Ala^2]Leu-enkephalin (DALAMID) is considered to have similar affinities for μ- and δ-sites[191] and is a useful dual agonist [192]

Frederickson of Lilly reported that the D-Ala^2-$MeMet^5$ analog of Met-enkephalinamide (with a methyl substituent on the Met nitrogen) was active after systemic administration, its ED_{50} in the MHP test (μM/kg, sc, hind-

Table 10 2 Stability and Antinociceptive Potency of Some Peptides

Pentapeptide (Tyr[1] Gly[3] Phe[4] common)	Stability (% intact peptide)		Potency (10^3 divided) by ED_{50} μM/kg) RTF iv
	in brain extract after 0 5/2 h	in human serum after 4 h	
1 Gly^2 Pro OH^2	10/0	0	64
2 D Ala^2 Pro OH^5	78/54	—	83
3 D Ala^2 Pro NH_2	85/62	89	89
4 D Eth^{2b} Pro NH_2	88/63	—	235
5 D Met^2 Pro NH_2	92/78	100	3125
6 D Nle^2 Pro NH_2	93/74	100	222

[a] From Ref 61
[b] D Eth = SEt analog of Met

paw-like response) being 1.5 compared with 4.8 for morphine and 11.3 for pethidine. It was at least 100 times more potent than morphine after central administration and considered to act at both δ- and μ-opioid receptor sites with a preference for the former.[58] In a double-blind clinical trial on surgical patients, the analgesic activity of 70 mg of this derivative (termed *metkephamid*) given by im injection was significantly greater than that of placebo and not less than that of 100 mg pethidine.[59] Side effects unusual to narcotic analgesics were observed (heaviness of the extremities and nasal congestion), and the study was not large enough to judge effects on respiration or development of tolerance. D-Thr^2 and Phe(p-F)^4 congeners of metkephamid surpassed the activity of the parent both in *in vitro* and *in vivo* tests (see data).[60]

	MVD IC_{50} (nM)	MHP ED_{50} (mg/kg sc)
Tyr-D-Ala-Gly-Phe-MeMet-NH_2	12.2	0.36
D-Thr^2 analog	1.2	0.3
Phe(p-F)^4 analog	0.77	0.022

Cross tolerance between metkephamid and morphine was not seen in rats.[193]

Bajusz *et al.*[61] believe that although the factor of enhanced resistance to enzymes is an important aspect of the design of enkephalin analogs, its significance has been overestimated and that raised activities of many D-amino acid^2 derivatives may also be due to the provision of extra binding sites in consequence of such substitutions. These opinions were based on the poor correlation found between analgesic potency and metabolic stability. Some examples are shown in Table 10.2; note that peptides 1–3 have similar potencies, although varying greatly in stability, while the influence of D-Met on analgesic activity is exceptional and significantly higher than that of D-Nle, although both substitutions lead to peptides of high stability.

10.4.3. Variation of Gly^3

The sensitivity of residue 3 is second only to that of Tyr^1 in regard to structural variation. Almost all changes lead to a drop in potency, which in most cases is marked or complete. Morley[48] gives data that include replacement of Gly^3 by D- and L-Ala, D- and L-Pro, des-Gly and Gly-Gly. One exception is the change of CH_2 of Gly to NH, which gives an analog (AzGly^3) that is four times more potent than the parent in the GPI test. *N*-Methylation gives inactive compounds, possibly due to loss of hydrogen bonding ability. Chipkin *et al.*[64] claim that the potency loss that follows removal of Gly^3 from Met-enkephalin may be largely attenuated by substituting D-Ala in position 2 and derivatization to the amide. The tetrapeptide Tyr-D-Ala-Phe-Met-NH_2 and the parent amide had similar activities in GPI (see below) and MTF tests. The

natural and potent peptide dermorphin also has a D-Ala^2-Phe^3 sequence (p. 363). Structure-activity relationships deduced from single residue changes are

	Relative potency (GPI)
Met-enkephalin	1.0
Met-enkephalinamide (parent amide)	1.6
[D-Ala^2]-Met-enkephalinamide	1.4
Tyr-Gly-Phe-Met-OH	0.004
Tyr-Gly-Phe-Met-NH_2	0.02
Tyr-D-Ala-Phe-Met-NH_2	1.2

often upset when multiple alterations are made, an example pertinent to this section being the high potency of [D-Ala^2-D-Ala^3]-Met-enkephalinamide (10 × normorphine in GPI test)[65] in spite of replacement of Gly^3 by D-Ala.

10.4.4. Variation of Phe^4

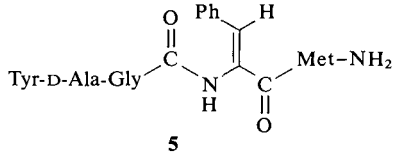
Requirements for activity at residue 4 are decidedly stringent both structurally (Gly^4, D- and L-Ala^4, Tyr^4 and Trp^4 analogs are inactive) and configurationally (D-Phe^4 inactive).[48] The AzPhe^4 (α-CH changed to N) and MePhe^4 (NH of Phe methylated) analogs of leu-enkephalin retain 25% of the activity of the parent in the GPI assay, the latter change being advantageous in the potent Sandoz derivative FK 33-824 (see later). The aromatic nature of residue 4 is desirable but not essential, since activity is retained, albeit at low levels, in hexahydro Phe derivatives of [D-Ala^2]Leu-enkephalin methyl ester and [D-Met^2-Pro^5]-enkephalinamide.[48] Data on some D-Ala^2 or Met^2-Pro-NH_2^{5} congeners emphasize this point[66]:

	$IC_{50}nM$[a]	$AD_{50}nM/kg$[b]
Tyr-D-Ala-Gly-Phe-Pro-NH_2	340 ± 90	2.6
(6H)-Phe^4 analog	1510 ± 310	21.5
Tyr-D-Met-Gly-Phe-Pro-NH_2	82 ± 23	1.3
(6H)-analog	735 ± 105	5.0
morphine	170 ± 10	77.0

(a: displacement of ^{3}H-etorphine; b: MTF, icv)

Some *p*-substituted Phe^4 analogs are also active (NO_2, Cl, Br, very effective; CF_3, SO_2Me, SOMe, SMe, moderately effective; NH_2, OH, inactive; data on D-Ala^2 series),[48] cf. *p*-F Phe analog of metkephamid, p. 345. The imposition of rigidity within the Phe^4 unit, as in the Δ-Phe^4 analog **5** (five times D-Ala^2-Met-NH_2 in GPI assay), elevates activity.[66] Further, such analogs (all of Z-configuration with Ph turned away from the $CONH_2$ terminus of the

peptide) appear to be favored ligands for δ-receptors as judged by binding assays involving displacement of DADL (**5** is twice as active as the saturated analog).[67] It is to be hoped that comparative data on E-Δ Phe isomers will be forthcoming, since E/Z isomeric pairs of this type should prove valuable probes of μ- and δ-receptors and the active conformations of their ligands.[68] Dehydropeptides of type **5** are resistant to enzymic hydrolysis. Other double-bond isosteres of the enkephalins are described in the conformation section of this chapter (p. 371).



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A large series of D-Ala^2 enkephalins has been prepared with Phe^4 (and residue 5, see next section) replaced by the artificial amino acids *t*-butylglycine (Bug), 4-NO_2Phe (Nip), carboranylalanine (Car, **6**) and adamantylalanine (Ada), sometimes called "fat" or "super" amino acids because of their steric bulk and hydrophobicity properties.[69] In these analogs binding and pharmacological potency increased in the order Ada, Phe, Car, and Nip (all L acids), the Nip analog of Met-enkephalinamide being 25 times as active as the parent.[70]

6 $\underbrace{1,2\ C_2B_{10}H_{11}}$-$CH_2CH(NH_2)CO_2H$

o-carborane moiety with icosahedral geometry

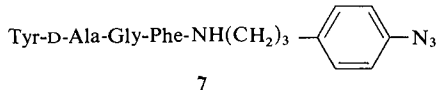
10.4.5. Variation of Met^5/Leu^5

In contrast with positions 1, 3, and 4, more scope for structural change with retention of activity is seen at residue 5. A few such analogs, mostly with reduced but significant potencies in the GPI test, are shown:[48] Ala, 0.03; D-Ala, 0.07; Gly, 0.02; Nle, 0.3–0.5; Phe, 0.11 (MVD); Pro-NH_2, 0.02; Pro-NHEt, 0.86 (Leu^5, 0.2; Met^5, 1.0). Substitution by Pro^5 provides analogs of high potency when the second amino acid is D-Ala or D-Met, and peptides of this kind were some of the first examples of systemically active enkephalins (p. 352). The role of the proline residue (perhaps that of protecting the fourth amide link from proteolysis) cannot be attributed to its cyclic nature because open-chain analogs (Pro^5 replaced by Nval) are even more potent than the cyclic derivatives in binding and GPI assays.[30] The "super" amino acid analog [D-Ala^2-Bug^5]-enkephalinamide has similar *in vitro* potencies to natural enkephalins, while the Ada^5 congener is three times as potent as the D-Ala^2-Leu^5 peptide and is strongly resistant to proteases.[71]

Stereochemical requirements at residue 5 are minimal for Leu- but more demanding for Met-enkephalin, as is clear from the GPI activities of D-Leu (0.15) and Leu (0.2), and D-Met (0.1) and Met (1.0). The special properties of the D-Ala^2, D-Leu^5 peptide (DADL) have already been mentioned.

Many variations of Leu^5 and Met^5 themselves are permissible with retention or elevation of activity [e.g., esterification (Leu-OMe, 0.2), amidation (Leu-NH_2, 0.5; Leu-NHEt, 0.34; Met-NH_2, 1.3–3.0; Met-NHEt, 2.5; see also section (b)), reduction of terminal CO_2H to CH_2OH (Leu-ol, 0.13 MVD; Met-ol, 8.2 binding assay)[48] and replacement of terminal CO_2H by $COCH_2Cl$, which causes a several-fold potency rise.[72] Changes that increase resistance to proteases such as amidation (and the presence of D-amino acids at residue 2) also result in an increased μ- over δ-receptor specificity.[73] In tests on a series of Met-enkephalinamide analogs poor correlation was found between binding and MHP (icv) potencies. The NHEt analog was the most potent in the former test (7 × Met-enkephalin); the *N*-isopropylamide was the most potent in the latter (700 × standard).[74] The sulfoxide analog of Met-enkephalin was active [Met (0), 0.2], but the sulfone was very feeble [Met (O_2), 0.01]. *N*-Methylation of Leu-OH and -NH_2 raised potency (MeLeu-OH, 0.3, 0.74, respectively), while replacement of the α-CH by N (AzLeu-NH_2, 0.56) did not depress activity (all GPI data).[48]

The conclusion from these SAR analyses that residue 5 is not a major determinant of opioid peptide activity is supported by the fact that the tetrapeptide Tyr-Gly-Gly-Phe (des-Leu/Met) has significant (if weak) activity in both GPI and MVD assays, while the derivative Tyr-D-Ala-Gly-$NH(CH_2)_2$Ph is almost as potent as [D-Ala^2]-Met-enkephalin in the GPI test (it is feeble in the MVD assay).[48] Gorin *et al.*[45] provide similar data on Tyr-D-Ala-Gly-phenethylamine and the corresponding benzylamine (0.19 and 0.14 × [D-Ala^2]-Leu-enkephalin, respectively, GPI assay). Some compounds of this type carry azide functions and were designed as affinity labels (e.g., **7**), the principle being that the photosensitive azide group forms a covalent bond with the receptor upon exposure to UV radiation.[65] In fact, irradiation of membrane suspensions from bovine caudate nuclei in the presence of peptides of type **7** resulted in an irreversible inactivation of opioid binding activity; the receptors were protected by prior treatment with normorphine.



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A further modification of enkephalins at residue 5 is replacement of Met or Leu by a hydrazide group. Several tetrapeptides so terminated proved significantly active as analgesics in mice (MHP, sc), especially when D-Met^2 was present [e.g., Tyr-D-Met-Gly-Phe-NHNHCOEt and its D-Met (O), MePhe analog were 4.4 and 5.7 times more potent than morphine, respectively].[75]

Related peptides with terminal Phe reduced to phenylalaninol (Pheol) or replaced by *N*-phenethylamide also show potencies of the morphine order in the GPI assay. The derivative Tyr-D-Met(O)-Gly-*N*-methylphenethylamide, termed *syndyphalin*, is about as potent as morphine in mice after sc injection by MTF and WR tests with selectivity for μ-sites.[76,77,194] A Reckitt and Colman group[78] has described some similar derivatives **8** based on the protected tetrapeptide Tyr-D-Ala-Gly-MePhe; the GPI and MVD potencies reveal their potent μ-receptor activities. The compound terminated by a reduced Gly residue (DAGO) is in fact one of the most selective μ-ligands available (see p. 356). All three peptides **8** were much more stable to brain and plasma enzymes than Leu-enkephalin, and two had activities close to or better than that of morphine in a rat *in vivo* test.

		Relative potencies		
8	Tyr-D-Ala-Gly-N(Me)PheNHR	GPI[a]	MVD[b]	Rat tail-flick ED_{50} mg/kg iv[c]
	R = CH_2CH_2OH(DAGO)	6.5	0.3	2.9
	R = $CH_2CH_2NMe_2$	9.3	0.36	1.4
	R = $CH_2CH_2N(O)Me_2$	12.5	0.76	0.32

[a] Normorphine 1.
[b] Met-enkephalin 1.
[c] Morphine 1.65.

Finally, Bajusz *et al.*[79] have examined peptides bearing the sulfonic or phosphonic acid analogs of norleucine at the carboxyl terminus (**9**), the rationale being that δ-receptor affinity may be related to the presence of a terminal acidic group. These changes produced carboxypeptidase-resistant peptides; only unchanged peptides could be detected in 2-h digests of $NleS^5$, D-$NleS^5$, $NleP^5$, and D-Nle^5 enkephalins, while 60–70% of Nle and Phe were released from [Nle^5]-enkephalin under identical conditions. Some of these derivatives had significant *in vivo* analgesic potencies [e.g., [D-Met^2, D-$NleP^5$]-enkephalin: half (iv) and one fifth (icv) as active as morphine (RTF)].

9 Rest of peptide-NHCH(Bu^n)X
X = CO_2H(Nle); SO_3H(NleS); PO_3H_2 (NleP)

10.4.6. Changes at More Than One Residue: Parenterally Active Derivatives

Many analogs involving multiple residue changes have been examined, chiefly with retention of the original amino acids at residues 1(Tyr), 3(Gly), and 4(Phe) because of their established need to sustain or enhance opioid

activity. As noted in section (c), structural changes are not necessarily consistent in their effects. Thus, replacement of D-Ala by D-Ser in Tyr-D-Ala-Gly-Phe-Leu-OMe (potency 5.6 relative to Met-enkephalin = 1) raised potency to 11, while the same change in the Pro-NH_2^5 analog caused a sharp fall in GPI activity.[48]

An important aim of the multiple-change work is the design of analogs with systemic and enteral activities. The derivative metkephamid has already been mentioned in this respect (p. 344), but the first significant advance in developing a stable pentapeptide of this kind was made by a Sandoz group in 1977.[43,80] It was found that the potency and duration of action of Met-enkephalin could be increased after icv administration by altering Met^5-CO_2H to $CH_2OH(Met^5\text{-ol})$ and substituting Gly^2 by D-Ala. (The effects of individual changes of these kind have already been described.) The combination D-Ala^2-Met^2-ol gave a peptide that showed sc activity as well as prolonged icv and iv analgesic potency. Other advantageous changes were oxidation of Met-sulfide to sulfoxide and *N*-methylation of the Phe^4 residue. The peptide that incorporated all these variations, namely, D-Ala^2-$MePhe^4$-Met-$(O)^5$-ol(FX 33-824, DAMME), showed definite analgesic activity even after oral administration and on a molar basis was 30,000 and 1000 times as active as Met-enkephalin and morphine, respectively, after icv injection (Table 10.3). It displayed the highest affinity for rat membranes of all compounds tested; of these only Met-enkephalin and Met^5-ol-enkephalin had reduced IC_{50} values in the presence of the enzyme inhibitor bacitracin (i.e., all the others were resistant to proteases). Other properties of FK 33-824 establishing its pharmacological kinship to morphine were displacement of its dose–response curve (parallel to that of morphine) in the tail-flick test by naloxone, its induction of the Straub tail effect in mice and tolerance in rats, and its support of addiction in morphine-dependent rhesus monkeys. The PDC of a series of the more potent enkephalins has been judged in rats by the dose required to inhibit shaking episodes after immersion in ice-cold water and the chronic dose needed to produce escape behavior after naloxone; FX 33-824 scored highly in both tests.[81]

In a double-blind study against experimental pain the compound gave dose-dependent analgesia, but its side effects (face flushes, heaviness of muscles, etc.) limited the dosage level.[82] Morphinelike euphoria was not experienced and the analgesia was abolished by high doses of an antagonist. The side effects mentioned together with an impressive increase in bowel sounds were also reported in an earlier study in man after parenteral administration of the peptide by various routes.[83] The derivative was a moderate to good analgesic in patients with postoperative pain. However, unpleasant peripheral side effects dominate and limit the therapeutic use of the compound, as a result possibly of poor transfer of the drug to central areas after im or epidural injection, and clinical tests have now been abandoned.[84]

Table 10 3 Analgesic Activity in the Mouse of Met-enkephalin and Its Analogs[80]

Compound	Tail-flick test ED_{50}					
	icv 15 min (μg per mouse)	iv 15 sec (mg kg ^{1})	iv 30 min (mg kg^{-1})	sc 30 min (mg kg^{-1})	po 120 min (mg kg^{-1})	Relative molar dose (icv)
Met-enkephalin	68[b]	153				1
Met^5-ol	43	52				0 6
D-Ala^2, Met^5	0 7	51				0 01
D-Ala^2, Met^5-ol	0 04	12	13	59	>640	0 0006
D-Ala^2, Met(O)^5-ol	0 01	12	3 5	3 9	319	0 0001
D-Ala^2, MePhe^4, Met-(O)^5-ol (33-824)	0 002	0 7	0 4	1 4	102	0 00003
β-Endorphin	0 3					0 0007
Morphine HCl	1 0		1 8[c]	3 0	20 5[d]	0 03

[a] From Ref 80
[b] At 2 min
[c] At 15 min
[d] At 30 min

The *N*-methyl (Tyr) analog is even more active than the parent in mice (sc and oral route) and is orally equipotent with morphine.[85] A Japanese group[76] confirmed the advantageous influence upon potency of blocking terminal amino by *N*-methylation and terminal CO_2H by reduction; in the GPI test MeTyr-Gly-Gly-Phe-Met-ol and the H-Tyr analog had potencies of 66 and 0.96, respectively (morphine = 1), with *N*-methylation responsible for all the potency rise. The D-Ala^2 variant was not as active as the most effective peptide in the *in vitro* test, but exceeded the activity of both this compound and morphine after central administration.

Further progress toward a stable enkephalin of high potency followed the finding that the introduction of proline or prolinamide at position 5 increased receptor binding and stability to carboxypeptidases.[61,86,87] An increase in analgesic activity after parenteral administration was obtained when D-Met was simultaneously incorporated at position 2 with a corresponding increase in the degree of receptor binding. The progressive increases in *in vivo* antinociceptive activities achieved by this sequence of substitutions are shown. [D-Met^2, Pro^5]-enkephalinamide is thus comparable in activity with the

Potency[a]	iv	Centrally
Met-enkephalin	0	0.02
D-Ala^2, Pro-NH_2^5	0.22	3.9
D-Met^2, Pro-NH_2^5	5.5	49.8

[a] Morphine = 1, RTF.

Sandoz peptide FX 33-824 after iv administration. A report of the *in vitro* pharmacology of [D-Met^2, Pro^5]-enkephalinamide shows that the amide interacts preferably with μ-receptor sites; it is less potent than Met-enkephalin in the MVD test and much less effective than β-endorphin at rat VD sites (this tissue shows selectivity toward β-endorphin).[88] Tolerance toward the analgesic effects of the proline derivative in mice develops rapidly, and its PDC in rats is high.[81,89] Naloxone effectively antagonized the analgesic effects of the peptide in RTF and MHP tests so there is no doubt of its morphinelike nature.[90] Clinical trials of the peptide are in progress, and a report on its autonomic effects and influence upon some hormone levels in man has been made.[213]

Wellcome Research Laboratories has also described a series of potent Pro-NH_2^5 analogs;[195] the D-Met^2, Phe(4-NO_2)^4, Pro-NH_2 derivative was twice as active as morphine in the MHP test after sc injection and caused physical dependence and respiratory depression.

Replacement of Pro^5 by its sulfur analog, thiazolidine-4-carboxylate (Thz), a strategy that led to enhanced activities in oxytocin derivatives, yielded the potent peptide [D-Met^2, Thz^5]-enkephalinamide, 4 to 5 times as potent as morphine (MTF, iv).[91]

Both FK 33-824 and [D-Met^2-Pro^5]-enkephalinamide induce hormonal changes, such as release of prolactin and growth hormone, and are useful as tools for endocrinological studies.[82,92]

10.5. RECEPTOR MULTIPLICITY

Opioid peptides have given a major impetus to the ideas of the existence of more than one variety of opioid receptor. Prior to 1977 evidence had been available for some years that certain benzomorphan derivatives do not interact with the same receptors as those that accommodate morphine and the majority of synthetic analgesics. Thus, Martin *et al.*,[93,217] on pharmacological grounds, described three different syndromes produced by congeners of morphine in the nondependent chronic spinal dog that were attributed to the interaction of agonists with three distinguishable receptors, namely, μ- (morphine is the typical agonist), κ- (activated by ketoclazocine), and σ- (activated by the *N*-allylanalog of α-metazocine), all of which are blocked by naltrexone (see p. 434). Kosterlitz[94] extended these concepts by using the approach of assaying a set of agonists, which included peptide and nonpeptide derivatives, simultaneously in several biological systems. If the rank order of potency varies in parallel in the different procedures, then the assay tissues may be assumed to have identical receptors. If there is a lack of correlation, however, the receptor populations of the bioassay tissues cannot be identical.[95] The assay systems were depression of electrically induced contractions in GPI and MVD muscle preparations and inhibition of specific binding of the radiolabeled ligands ^{3}H-naloxone and ^{3}H-Leu-enkephalin to GP brain homogenates in a sodium-free medium. Specific binding was the difference between values obtained in the absence and presence of 50 n*M* of the potent antagonist levo 3-(3-furylmethyl)-6,11-diethyl-8-hydroxy-6,7-benzomorphan (Mr2266) and was 50–60% of the total; at the same concentration the dextro isomer had no significant effect on specific binding.

The potencies of morphine and a series of peptides in these assays are shown in the bar diagram (Fig. 10.1). Note that Leu-enkephalin comes first (closely followed by the Met-analog) and morphine last in the potency rank order for the MVD preparation, while reverse placements hold for morphine and Leu-enkephalin in respect of GPI activities (Met-enkephalin ranks just below morphine in this tissue and does not suffer so great an MVD to GPI potency fall as does the Leu^5 peptide). Inconsistent rankings are also seen in the ligand displacement activities as shown: β-endorphin > Met-enkephalin > morphine > Leu-enkephalin (against naloxone), and Met-Leu-enkephalin $\equiv$ β-endorphin $\gg$ morphine (against Leu-enkephalin). Note that morphine is a much more efficient antagonist of naloxone than Leu-enkephalin binding, while the reverse is true when Leu-enkephalin is the competing ligand.

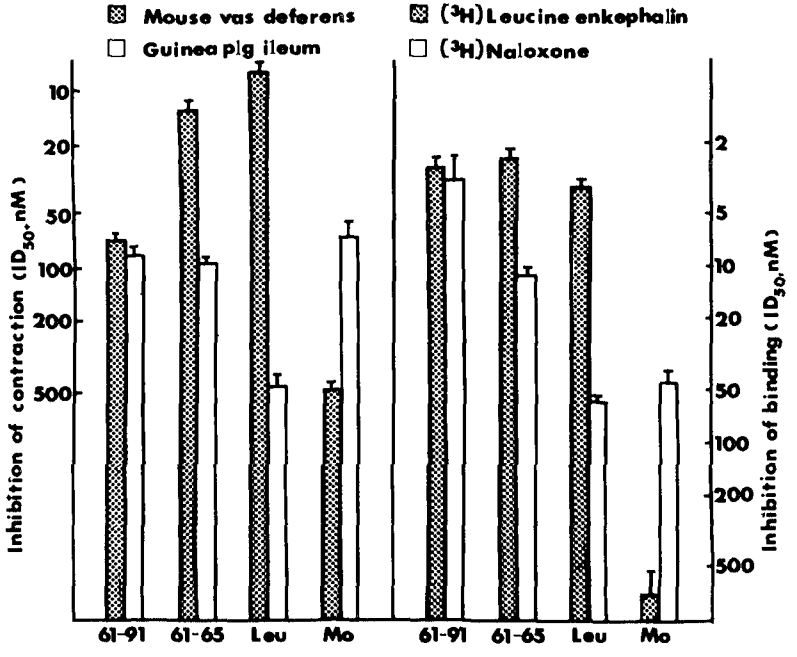


Fig 10 1 The agonist activities of various compounds in the mouse vas deferens and guinea pig ileum and their potencies to inhibit ^{3}H-Leu-enkephalin and [^{3}H]naloxone binding in homogenates of guinea pig brain (pH 7 4 at 0°C, no Na^+, 150 mm) The numbers on the absiccsa indicate the amino acid sequence of β-lipoprotein, Leu, leu-enkephalin and Mo, morphine All peptides are synthetic (61–91, ovine β-endorphin, 61–65, met-enkephalin and leu-enkephalin)

Analogs with weak antinociceptive potencies, as judged by *in vivo* tests, generally resembled Leu- and Met-enkephalin in being more potent in the vas than the ileum assay, while the potency of peptides and conventional synthetic agents with higher analgesic activities was similar in both assays, although superior values were often found in the GPI test. Two receptors, designated δ- and μ-, were therefore postulated as appropriate to natural enkephalins and synthetic and morphine-related opioids, respectively (both distinct from κ- and other receptors; see p. 434), the GP ileum being regarded as a tissue rich in μ-, and the mouse vas deferences in δ-sites.

Since the rank orders of activity in relation to analgesic potency in man and inhibition of the contraction of the GPI concurred for morphine, normorphine, and a wide range of synthetic opioids,[96] it was concluded that the μ-receptors must be associated with analgesia. The role of δ- and other putative receptors is uncertain and is the subject of much speculation.[97]

In a later paper[98] activity patterns were characterized by the ratio of GPI to MVD potencies and by the ratio of potency in inhibiting ^{3}H-naloxone

binding to that against ^{3}H-Leu-enkephalin (Nal/Leu) in guinea pig brain homogenates. The enkephalins had low GPI/MVD (0.02–0.09) and low Nal/Leu (0.05–0.18) ratios, whereas corresponding values for morphine were 7.0 and 7.5. Analogs resistant to enzymatic degradation (amidation of C-terminal carboxyl and/or *N*-methylation of Tyr^1) had GPI/MVD ratios of 1.2–5.5 and Nal/Leu ratios of 0.5–21. High values (2.1 and 3.4) were found for the potent Sandoz peptide FK 33-824 indicative of its morphinelike nature; the same peptide displaced labeled naloxone or dihydromorphine from rat brain membrane sites more efficiently than it replaced [^{125}I-D-Ala^2, D-Leu^5]-enkephalin,[99] results that complement those of Kosterlitz. Binding Nal-Leu ratios for morphine and a range of synthetic analgesics are shown.[98] The potent peptide developed by Bajusz, [D-Met^2, Pro^5]-enkephalinamide, also appears to be more morphinelike than enkephalinlike in nature, since it is readily antagonized by naltrexone but less so by Met-enkephalin.[100]

	Nal/Leu ratio
Morphine	7.7
Normorphine	12.0
Naloxone	11.0
Ketobemidone	2.8
Levorphanol	2.6
Methadone	1.0
Etorphine	1.8

The variations in potency rankings observed in the GPI and MVD tests are thus accounted for by assuming that while each tissue contains both types of receptor, the μ-preponderates in the ileum and the δ-receptor is the chief species in the vas. The fact that enkephalins are less effective in displacing ^{3}H-naloxone from rat brain membranes than in detaching labeled enkephalins accords with the idea of naloxone, of structure typical of morphine and many synthetic opioid ligands, binding preferentially to μ- rather than δ-sites in brain tissue. Antagonist studies in the ileum and vas preparation complement these results: in the GPI (high μ-population) morphine and the enkephalins are readily antagonized by naloxone, while the MVD (high δ-population) naloxone is a much poorer antagonist of enkephalins than it is of morphine.

More direct evidence for the existence of subtypes of opioid receptors has been obtained from experiments investigating selective protection of the binding sites against inactivation by alkylating agents such as phenoxybenzamine.[196,197] The latter causes a long-lasting inactivation of receptors of the μ- and δ-type in homogenates of guinea pig brain. This effect is selectively prevented when, before exposure to phenoxybenzamine, the homogenate is preincubated with ligands of high affinity for either of the two binding sites

(e.g., dihydromorphine for the μ-receptor and DADL for the δ-site). In contrast, DALAMID, which has high affinities for both binding sites, protects both receptor types. Other irreversible inhibitors used in such experiments are *N*-ethylmaleimide and chlornaltrexamine (p. 449).

The work of Vaught *et al.*,[215] in which natural enkephalins are shown to have much lower affinities for μ-sites than generally believed, and evidence presented of Leu-enkephalin potentiating and Met-enkephalin attenuating morphine analgesia in mice are discussed in Chapter 13 (p. 490).

Many peptide studies are now directed at the discovery of specific ligands for use in the characterization of opioid binding sites. Progress toward this goal is summarized in the histogram of Figure 10.2, taken from a 1982 review,[101] which displays the relative effectiveness of various peptides in inhibiting the binding of a μ-, δ-, and κ-ligand to their respective recognition sites. The hexapeptide Tyr-D-Ser-Gly-Phe-Leu-Thr (DSLT) and DADL have fair selectivities for the δ-binding site in accord with original reports (DSLT is 620 times as potent in the MVD compared with the GPI assay and is about 15 times as active as Leu-enkephalin in the vas with high enzyme resistance).[102] [D-Ala^2, MePhe^4, Gly-ol^5]-enkephalin (DAGO) provides an agent highly selective for μ-binding sites,[78] while etorphine is a universal ligand.

Other peptides with δ-selectivity have also been reported (e.g., the heptapeptide[Arg^6, Phe^7]-Met-enkephalin present in rat, bovine, and human brain in amounts comparable with those of Leu-enkephalin).[103] Among the most specific so far described is a dimeric tetrapeptide amide in which the monomer units (Tyr-D-Ala-Gly-Phe-NH) are linked by a 12-carbon chain.[104] The monomer itself shows μ-selectivity, but this changes to a preference for δ-receptors when two units are linked by a bimethylene chain; δ-selectivity increases as the length of the chain link increases and shows a dramatic rise when a 10-chain is replaced by a 12-chain link (Table 10.4). The dimer DTE_{12}

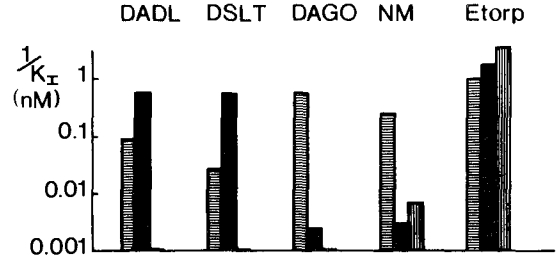


Fig. 10.2. Inhibition of binding of the μ-ligand [^{3}H]-[D-Ala^2, MePhe^4, Gly-ol^5]enkephalin (1.0 n*M*; first column), the δ-ligand [^{3}H]-[D-Ala^2, D-Leu^5]enkephalin (1-1.8 n*M*; second column) and κ-like ligand [^{3}H]-(±)-ethylketazocine (0.65 n*M*; third column). Ordinate: log of reciprocal K_I (n*M*). DSLT: [D-Ser^2, L-Leu^5]enkephalyl-Thr^6; DADL: [D-Ala^2, D-Leu^5]enkephalin; Etorph: etorphine; DAGO: [D-Ala^2, MePhe^4, Gly-ol^5]enkephalin (Ref. 101).

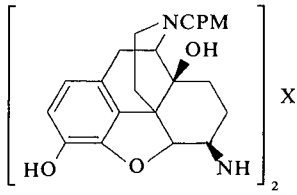
Table 10.4. δ/μ Selectivity Ratios[a]

Monomer Tyr-D-Ala-Gly-Phe-NH_2 (DT)		0.1
Dimers DT-$(CH_2)_n$-DT	$n = 6$	0 62
	$n = 8$	1 8
	$n = 10$	4 7
	$n = 12$	91

[a] δ-Activity assays using ^{3}H[DADL] and NG 108-15 cell membrane (neuroblastoma-glioma hybrid cells, which bear only δ-receptors)[106], μ-activity assay using [^{3}H]naloxone and membranes from whole brain

and DADL have similar orders of potency at δ-sites. When longer monomer units (Tyr-D-Ala-Gly-Phe-Leu-NH) were employed, the most potent pentapeptide dimer had the shortest methylene bridge ($n = 2$).[105] The authors interpret their findings in terms of the dimers serving as bivalent ligands that bind simultaneously to two distinct but closely clustered δ-receptors but fail to bridge a pair of μ-receptors. Bridged D-Pen^2, D- or L-Pen^5 enkephalin analogs are also δ-agonists of high selectivity (p. 373).

The concept of bridging has also been applied to antagonists; bivalent ligands containing β-naltrexamine pharmacophores (p. 67) linked by an oligoethylene glycol spanner have been described that differentially block μ, κ, and δ-opioid receptors.[198] Thus, **10a** (with a six-ethylene-units spanner) most effectively blocks δ-receptors (DADL on MVD), while **10b** (with shorter spanner) acts preferentially at κ-sites (ethylketazocine on GPI).



10

a X = $(CH_2CH_2OCH_2CH_2OCH_2CH_2)_2O$

b X = $CH_2CH_2OCH_2CH_2OCH_2CH_2$

Another μ-agonist of high specificity has been developed as a result of the observation that extracts of lyophilized bovine milk display opioid activity in binding and GPI assays, and the subsequent isolation of a heptapeptide named β-casomorphin from enzymatic digests that exhibited low opioid activity.[107] It turned out that the synthetic tetrapeptide fragment of β-casomorphin had much greater morphinelike properties than the parent and was specific for μ-receptors; this tetrapeptide is named morphiceptin. Table 10.5 shows some illustrative data. Morphiceptin has an affinity for μ-receptors that is at least 10^3 times that for δ-receptors as judged from relative IC_{50} values relating to displacement of the morphinelike peptide FK 33-824 and the δ-agonist

Table 10.5. Potency Data (in μM) for β-Casomorphin and Morphiceptin[a]

	$IC_{50}(\mu)$[b]	$IC_{50}(\delta)$[c]	ED_{50} GPI	ED_{50} MVD
Tyr-Pro-Phe-Pro-Gly-Pro-Ile (β-casomorphin)	1 8[d]	15	10	no effect (10)
Tyr-Pro-Phe-Pro-NH_2[d] (morphiceptin)	0.019	30	0.13	15
Morphine	0 0004	0.035	0.1	0.9

[a] From Ref 199
[b] Displacement of [^{125}I]FK 33-824
[c] Displacement of [^{125}I]DADL
[d] The D-Pro^2 analog is feeble or inactive in all tests

DADL, and the GPI/MVD ED_{50} values. Morphiceptin (of high peptidase resistance) was one third as active as morphine in an assay for opioid agonists based on a fall in heart rate in urethane-anesthetized rats after iv administration.[108] The low absolute potency of morphiceptin (about a fifth that of DADL, itself only weakly active at μ-sites), may be due to its lack of Gly^3, a residue usually essential for activity in enkephalins (p. 345).

Another means of enhancing μ- at the expense of δ-specificity is to replace Phe-Met(Leu) of D-Ala^2 or D-Met^2-enkephalin by a hydrophobic alkyl chain; some data, including those for the δ-agonist DSLT, are shown.[102] δ-Selective peptides of this group had potencies in the GPI test (measure of μ-activity) and *in vivo* antinociceptive assays in the same range as those of the μ-selective peptides, results that support the idea of μ- rather than δ-receptors being involved in analgesia.

	IC_{50} GPI/IC_{50} MVD	icv dose nM, MHP
Tyr-D-Ala-Gly-NHCH(Me)CH_2CHMe_2	0.15	1.98
Tyr-D-Met-Gly-NHCH(Me)CH_2CHMe_2	0.09	1 77
Morphine	0 18	2.66
Met-enkephalin	15 0	—
DSLT	620	1.46

In a 1981 analysis, Roques and colleagues[109] emphasized the following features for specificity:

μ-:

1. Shorten enkephalin sequence and remove or neutralize (e.g., by amidation) the terminal CO_2H.
2. Replace Phe^4 with a lipophilic alkyl chain.
3. Replace Gly^2 by a hydrophobic amino acid of D-configuration (side chain probably interacts with a stereospecific μ-receptor subsite).

δ-:

1. Residue 4 must be aromatic.
2. Amino acid(s) following Phe^4 have a key conformational influence in facilitating the fit of the Phe^4 side chain at a specific δ-subsite and must be of D-configuration.
3. Lengthen the enkephalin sequence by addition of a hydrophilic moiety such as Thr^6 and introduce a hydrophilic side chain (e.g., D-Ser) into position 2 to decrease μ-specificity.

The authors believe that oripavines such as etorphine and the Sandoz peptide FK 33-824 (a compound active at both sites although with μ-preference) owe the universality of their actions to the presence in their structure of all the critical components required for interaction with both μ- and δ-receptors.

The so far neglected κ-receptors also appear to relate to specific peptides, namely, dynorphin$_{1\text{-}8}$ and its 1–9 analog, which are selective ligands for such sites, more fully discussed elsewhere (p. 361, 439).[110]

Belief in the existence of yet another variety of opioid receptor, designated ε, is gaining ground.[228,240] This species was originally postulated to account for the unique characteristics of opioid receptors in the rat vas deferens.[229] β_h-Endorphin is a potent agonist in this tissue, but its effects do not appear to be mediated at μ-, κ-, or δ-sites. Specific benzomorphan sites in rat brain membranes have been described that also do not seem to be of the κ-variety,[230] and since β_h-endorphin is likewise a potent ligand for these sites,[231] they may well correspond to the putative ε-receptors.

10.6. ENDORPHINS[200] AND OTHER NATURAL PEPTIDES WITH OPIOID PROPERTIES[201]

Brain tissue is not the only source of natural opioids. The pituitary gland and more recently the adrenal medulla have also been shown to contain a variety of such compounds. Like the enkephalins, the active materials are peptides but composed of more than five amino acid residues. The pituitary gland was recognized as a source of opioid peptides soon after discovery of the enkephalins. Many so-derived materials prove to be fragments of β-lipotropin (LPT), a peptide containing 91 amino acids characterized in 1965,[111] and are termed *endorphins*; β-LPT itself has no opioid properties.[112] The fragment composed of residues 61–91 (**11**), designated β-endorphin[113] or C-fragment,[114] is much more potent than Met-enkephalin under conditions of both *in vivo* and *in vitro* tests.[114,115] Thus, potencies of β-endorphin in mice relative to morphine (1) after icv injection were 19.5 (WR), 17.5 (MHP), and 33 (RTF); 10^3-fold greater doses of Met-enkephalin were necessary to elicit analgesia in the same tests, and the effects were weak and of short

61 65 70
Tyr-Gly-Gly-Phe-Met-Thr-Ser-Glu-Lys-Ser-Glu-Thr-Pro-

75 77 80 83 85
Leu-Val-Thr-Leu-Phe-Lys-Asn-Ala-Ile-Val-Lys-Asn-Ala-

87 89 90 91
His-Lys-Lys-Gly-Gln

11 β-endorphin (porcine)

duration.[115] Binding IC_{50} values (nM) against naloxone of 2.6 (β-endorphin), 90 (Met-enkephalin), and 25 (morphine) have been reported.[114]

Clearly, it is significant that the first five residues of β-endorphin are identical with Met-enkephalin, and of the many fragments of β-LPT examined only those with an intact 61–65 amino acid sequence had opioidlike properties as judged by ability to displace the stereospecific binding of ^{3}H-naloxone and ^{3}H-dihydromorphine.[114] β-Endorphin not only is a potent analgesic after icv and iv administration (e.g., icv MTF ED_{50}, 0.3 mg/kg; morphine, 1.0 mg/kg), but also has a prolonged duration of action due most probably to its relative stability to peptidases.[116] The influence of the carboxyl terminal tetrapeptide (see **11**) of β-endorphin has also been studied; removal of residues **90** and **91** brought about a moderate reduction and of **88–91** a severe reduction of opioid activity (binding and TF assays).[117]

Endorphins from a variety of species (even ostrich)[118] have now been isolated.[50,200] Human β-endorphin (β_H), which differs from most animal untriakontapeptide in having Tyr at position 87 instead of His, and Glu at 91 in place of Gln, has been synthesized by the solid-phase procedure.[119] When applied centrally, β_H-endorphin was 17–48 times more potent than morphine in mice and 3.4 times more potent after the iv route by MTF, MHP, and WR tests; naloxone blocked the analgesic responses.

The structure-activity relationships of the endorphins largely mirror those of the enkephalins. Thus, masking Tyr-NH_2 by *N*-carbamylation or Tyr-OH by *O*-benzylation abolishes or reduces the opioid properties of β-endorphin,[120,121] while stereochemical requirements are identical for the two groups (D-Tyr^1, D-Phe^4, and D-Met^5 endorphin analogs are feeble or inactive).[122] The stepwise substitution D-Ala^2 and D-Ala^2-MePhe^4 produced progressive increases in potency in the rat but decreased potency in the GPI, while oxidation of Met^5 to the sulfoxide was without effect.[123] [Leu^5]-β_H-Endorphin (synthetic) was one fifth as active as the parent Met compound in the GPI test but only slightly less active in MVD and binding assays.[124] *N*-Terminal acetyl β-endorphin (Ac61-91) is inactive, as is the same derivative of fragment 61–87.[125] These derivatives (along with β-endorphin) have been identified in rat brain, a fact indicative of acetylation being a controlling mechanism whereby the natural peptides may be reversibly inactivated. Salmon endorphin, in fact, has been characterized as an *N*-α-acetyl peptide.[126] β-Endorphin inhibits contractions of GPI, MVD and rat VD smooth muscle at similar potency levels; the last named tissue, which is insensitive to morphine and

relatively so to Met-enkephalin, is reported useful as a preparation selective toward β-endorphin.[202]

It is evident that β-LPT is not the sole source of endogenous opioid peptides found in the pituitary gland now that *dynorphin*, an active peptide isolated from this organ as early as 1975, has been characterized.[127] This peptide differs from the β-endorphins (lower mol wt, more basic, more persistent effect in GPI assay, and resistant to CNBr) and its first 13 residues (established by a microsequencing technique) commence with Leu-enkephalin at the *N*-terminal. The absence of Met^5 accounts for its insensitivity toward CNBr. The synthetic tridecapeptide (**12**, dynorphin 1-13) and dynorphin itself

$$\overset{5}{\text{H-Tyr-Gly-Gly-Phe-Leu-Arg-Arg-Ile-Arg-Pro-Lys-Leu-}}\overset{13}{\text{Lys-OH}}$$

12

(with four extra residues: Trp-Asp-Asn-Gln^{17}) have similar activities and show remarkably high levels of potency in the GPI test; dynorphin 1-13 is 700 × Leu-enkephalin, 200 × normorphine, and 50 × β_c-endorphin with effects blocked by naloxone, and three times as effective as Leu-enkephalin in the MVD assay. No degradation occurred in the *in vitro* preparation, but ^{125}I-labeled material was rapidly attacked after central administration (analgesia was seen in rats after injection of 50 n*M* into the lateral ventricle). The Arg^6-Arg^7 unit of 12 should make the peptide vulnerable to many peptidases and facilitate release of Leu-enkephalin. A peptide termed α-neoendorphin, isolated from porcine hypothalami, resembles dynorphin 1-13 in its possession of a Leu-enkephalin *N*-terminal sequence followed by Arg and has a similar amino acid composition.[128] The peptide, now fully sequenced (**13**), had 6.7

$$\text{Tyr-Gly-Gly-Phe-Leu-Arg-Lys-Tyr-Pro-}\overset{10}{\text{Lys}}$$

13

times the GPI activity of Met-enkephalin (21 × Leu-enkephalin) and suffered a three-fold drop in potency when Lys^{10} was deleted to give β-neoendorphin.[129] Dynorphin and its 1-9, 1-8, and 1-13 analogs are of special interest in that they show selectivity for the κ-subclass of opioid receptor, as based on the evidence of binding assays (displacement of κ-agonists such as ethylketoclazocine) and inhibition of electrically induced muscle contractions.[110,130,131] Thus, all these peptides are effective inhibitors of contractions of rabbit, but not of rat, vas deferens (remarkably, rabbit muscle is sensitive to κ- but not to μ- or δ-agonists, while the rat tissue shows a low sensitivity to κ-ligands).[132] Some data are shown. Activity in the rabbit preparation was

IC_{50} nm	GPI (μ, κ)	MVD (δ)	Rat VD	Rabbit VD
$dynorphin_{1-13}$	0.31	0.33	10,000	2.43

lost progressively as CO_2H terminal residues were removed, the IC_{50} value of [Arg^6]-Leu-enkephalin being 3000 n*M*.[110] In 1982 Udenfriend's group reported the characterization of *rimorphin*, another pituitary-derived opioid peptide;

like dynorphin it commences with a Leu-enkephalin sequence and is highly active in the GPI test.[203]

Attention has also been directed to the adrenal medulla as a source of opioid peptides following immunohistological evidence of relatively large amounts of enkephalin immunoreactive material in this tissue. Udenfriend's group, using HPLC monitored by radioreceptor assay (involving neuroblastoma-glioma hybrid cells with [^{3}H-Tyr] Leu-enkephalin as the competing ligand) and two radioimmuno assays, isolated a heptapeptide from bovine adrenal medulla cells plus several proteins and polypeptides that showed opioid activity after treatment with trypsin.[133] The active peptides were distinct chromatographically from β-LPT (61-69) generated by trypsin digest of pituitary endorphins and their precursors. The heptapeptide was shown to be [Arg^6, Phe^7]-Met-enkephalin and thus resembles dynorphin (1-13) and α-neoendorphin in having an *N*-terminal enkephalin sequence (Met- rather than Leu-) followed by Arg; the peptide was also detected in striata from bovine, rat, and human brain and in amounts comparable with those of Leu-enkephalin.[134] Its *in vitro* potencies (Met-enkephalin = 1) were 0.7 (GPI) and 1 (MVD), and it had a four- to fivefold greater activity at vas sites.

In related studies on the adrenal medulla, Japanese workers have isolated three so-called big Met-enkephalins, each of which yields Arg^6-Met-enkephalin after tryptinization, and determined most of the amino acid sequences.[135] The smallest peptide (BAM-12P) is the dodecapeptide **14**; in BAM-20P and 22P this sequence is extended. All contain the Arg^6-Arg^7 unit and are thus readily cleaved by trypsin. The three peptides were highly active *in vitro*, especially the larger two (see **14**).

Tyr-Gly-Gly-Phe-Met-Arg-Arg-Val-Gly-Arg-Pro-Glu^{12}
Relative potencies (GPI, Met-enkephalin = 1): BAM-12P 2.1, BAM-20P 15, BAM-22P 26; β-endorphin 1.2)

14

The function of opioid peptides in the adrenal medulla (localized in chromaffin granules) is unknown, but such peptides may be the source of enkephalins found centrally, especially as there is evidence that pituitary opioid peptides do not fulfil this role (e.g., hypophysectomy has little effect on the enkephalin content of brain).[115] The small peptide content of bovine adrenal medulla cells after 6 days in culture has been analyzed in detail and the results are shown.

Met(O)-enkephalin	0.82 (ng/10^6 cells)
Met-enkephalin-Lys^6	0.12
Met-enkephalin-Arg^6	0.18
Met-enkephalin	0.88
Leu-enkephalin	0.33
Met-enkephalin-Arg^6-Phe^7	1.53

Yet another adrenal-medulla-derived peptide (peptide E) has been isolated; it contains 25 residues and is remarkable in having both a Met-enkephalin amino and a Leu-enkephalin carboxy terminus. It is 30 times as potent as Met-enkephalin in the GPI test.[136]

The skin of certain South American frogs is the unlikely source of another group of opioid peptides, termed the *dermorphins.*[137] These are heptapeptides of remarkably high potencies in both *in vitro* and *in vivo* tests (see data). Like enkephalins, they have an amino terminal Tyr residue, but the rest of their amino acid sequences differs radically from those of opioid peptides from mammalian sources. Residue 2 is D-Ala (a replacement that confers peptidase resistance on enkephalins, p. 343) followed by Phe^3-Gly^4, in reversal of the usual order. Residue 5 is another Tyr, leading to Pro (or 4-hydroxyproline, Hyp) and Ser-NH_2. The minimal requirement for opioid activity is the *N*-terminal tetrapeptide. [L-Ala^2]-Dermorphin is practically inactive, and the D^2-Ala residue is probably important for the resistance of dermorphin to enzymatic degradation. A variety of structural analogs of dermorphin have been examined and structure-activity relationships reviewed. As in enkephalins and endorphins, the Tyr^1 OH is vital to activity (relative GPI potencies: dermorphin, 1440; Phe^1-dermorphin, 0.026; morphine, 1).[138] Dermorphin and its $Tyr(Me)^1$ analog were both effective at 10^{-5} *M* concentration in displacing ^{3}H-naloxone from striatal homogenates.

	Relative potencies			
	GPI	MVD	HP (rats icv)	Tail-flick
Tyr-D-Ala-Phe-Gly-Tyr-Pro-Ser-NH_2 (dermorphin)[a]	100	100	100	100
Hyp^6-dermorphin	85–90	85–90	90–110	70–80
Pro-NH_2^6 analog	44–52	35–40	25	14
Tyr-NH_2^5 analog	40–45	54–62	27	12
Gly-NH_2^4 analog	2.5–3.5	3–3.5	22	12
Tyr-D-Ala-Phe-OH	<0.03	<0.05	<0.2	<0 1
Metenkephalin	1 5–2	110	0.01	0 01
β-Endorphin	5–7	6	—	4
Dynorphin (1-13)	300–500	40–70	<0.1	<0.1
Morphine	2 5	2 5	0.05	0.13

[a] 10 × morphine in MHP (iv) and 3 × morphine in rat tail-pinch test (sc), all effects blocked by naloxone.[137]

In a section chiefly devoted to peptides substantially larger than the natural enkephalins, the properties of the dipeptide Tyr-Arg are worthy of note. This small molecule, termed *kyotorphin* and found in bovine brain, produces dose-dependent analgesia after central administration (four times as potent as Met-enkephalin) but is only feebly active in *in vitro* assays. It is believed to act by inducing release of Met-enkephalin and possible inhibition of

enkephalinases.[139] It has also been suggested that part of the analgesic action of morphine may be due to release of endogenous opioid peptides.[220,221]

Major advances have been made in identifying the prohormone precursors of enkephalins and dynorphins.[222] These materials were initially detected by use of antisera to the opioid peptide, which also recognized the larger prohormone forms. The technique is to separate tissue extracts according to size either by gel-exclusion chromatography or by gel electrophoresis and subject fractions to radioimmunoassay using the relevant antisera. Isolation and amino acid composition and sequence analysis of fractions with prohormone activity follow. Another approach depends upon modern nucleic acid technology and overcomes the problem of the small quantities of prohormone available in normal tissues. It is possible to isolate and purify the prohormone mRNA from hormone-rich tissues. A complementary DNA sequence is then prepared through reverse transcriptase manipulation and the resultant cDNA is cloned to yield sufficient material for deoxyribonucleotide sequencing. Another method is to prepare a synthetic oligonucleotide sequence corresponding to a unique amino acid sequence of the hormone. This nucleotide may then be used to identify, by hybridization, the specific hormone cDNA prepared from a total tissue mRNA extract. Use of these techniques has led to the total sequencing of the prohormones proenkephalin-A and prodynorphin.[223,226] These proteins, together with pro-opiomelanocortin[227] provide the basis for three separate opioid peptide families.

Proenkephalin-A contains six copies of Met-enkephalin and one of the Leu-analog. Some of the probable cleavage products (e.g., Met-enkephalin-Arg-Gly-Leu) occur as normal constituents of adrenal chromaffin cells. β-Endorphin originates from a prohormone which is the common precursor of ACTH, α-, and β-melanocyte-stimulating hormone and β-endorphin (the prohormone also includes the β-lipotropin sequence).[227]

10.7. CONFORMATIONAL STUDIES OF OPIOID PEPTIDES

Much time has been devoted to the conformational analysis of natural opioids and their analogs in a search for evidence of a topographical analogy between active peptides and rigid analgesics of the morphine and related groups. The problem is a difficult one because of the open-chain nature of peptide molecules and their many conformational options, especially in the solute condition. One solid-state study has been reported, namely, that of Leu-enkephalin by X-ray diffraction.[140] Crystals grown from dimethylformamide–water contain four independent enkephalin molecules with solvent in the asymmetric unit. All four enkephalins have extended peptide backbones with the amino acid side chains oriented alternately above and below the plane; the asymmetric unit form is a slightly irregular antiparallel β-pleated sheet held together by intermolecular NH–CO hydrogen bonds. An earlier

study erroneously concluded a β_1-bend conformation stabilized by a pair of intramolecular hydrogen bonds due to the incorrect characterization of the unit cell.[141]

Considerable efforts have been made to analyze both ^{1}H- and ^{13}C-nmr spectra of opioid peptides in a pursuit of clues of solute conformation. Spectra are complex and may show poorly resolved and broad resonances even when recorded on spectrometers operating at especially high frequencies (220–400 MHz for ^{1}H) and present problems of assignment that have been solved in various ways, including selective decoupling, the monitoring of chemical shift change with pH (pD) changes, and the use of specifically deuterated analogs.[142] Interpretation of the data adds another dimension to the complexity of the work, and the various contributors to the field are by no means unanimous in their conclusions. Most regard the data as evidence of the peptides having preferred conformations in the solute state (studies have been largely confined to work in DMSO, a solvent that, although polar, differs from water), while others deny this[143]; the existence of folded conformations is advocated by many, but some find the evidence to favor extended conformations.[144] A brief resume of the nmr work follows to provide insight into the approaches taken and to illustrate its controversial nature.

Anteunis and his colleagues[29,145] have reported a 300 MHz ^{1}H nmr study of Met-enkephalin in DMSO-d_6; this solvent ensures resolution of the NH signals (exchangeable, hence otherwise lost in D_2O) but may influence conformation in a manner different from that of water as a result of its disruption of intra- and intermolecular H-bonding interactions of the peptide molecules. Evidence of conformation was derived by measuring all the ^{3}J (NH–CH_α) and ^{3}J (CH_α–CH_β) coupling constants. Reference to the ^{3}J/dihedral angle (θ) curves developed for peptides[146] led to the relevant dihedral angle magnitudes, which in turn (from the relationship $\theta = \phi - 60°$ for L-amino acids) provided a measure of the N–C_α (ϕ) and C_α–C_β (Ψ) torsion angles, which define the conformation of peptides.[147] Many proton assignments were possible from selective irradiation experiments, while solution of the problem of identifying the Gly^2 and Gly^3 NH proton bands (which arose because of the coincidence of the two α-CH_2 resonances) was based on the fact that the nearer *N*-terminal NH proton in oligopeptides displays a broadened signal as a result of its proximity to the $^+NH_3$ group.[148] Large differences were found for the various NH–CH_α J values, a fact that pointed to the existence of a preferred conformation rather than a random-coil structure that would have averaged all the couplings. Figure 10.3 illustrates the appearance of NH and α-CH resonances in the case of the spectrum of the D-Nle^2, L-$NleS^5$ enkephalin analog, recorded at 400 MHz in DMSO-d_6.[149] Another approach was to study the temperature dependence of the amide NH shifts; this was least for the Met-NH proton, suggesting its involvement in an intramolecular hydrogen bond or being in a buried position. From the data, a folded conformation with a β_1-bend relating to the sequence of Gly-Gly-Phe-Met was deduced with an H-bond between

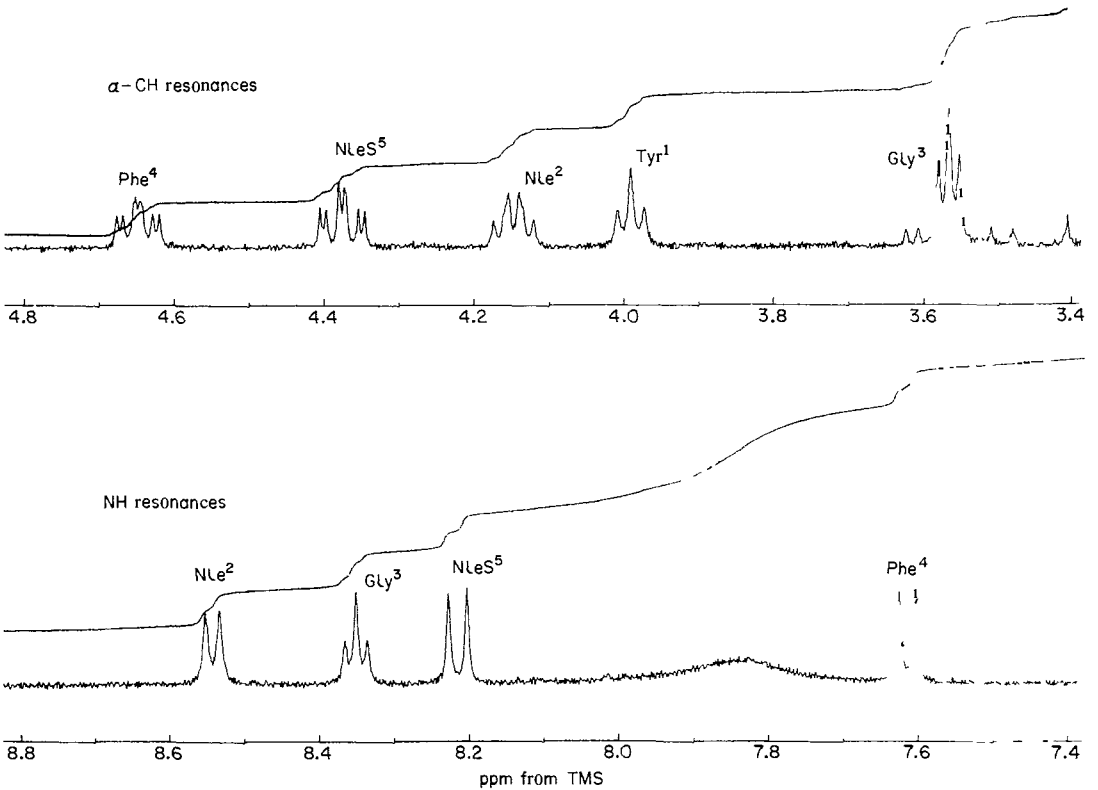


Fig. 10.3. Part of the 400 MHz ^{1}H-nmr spectrum of the tyr-amino terminal peptide Tyr-D-Nle-Gly-Phe-L-NleS in DMSO-d_6 at 23°C (Ref. 149).

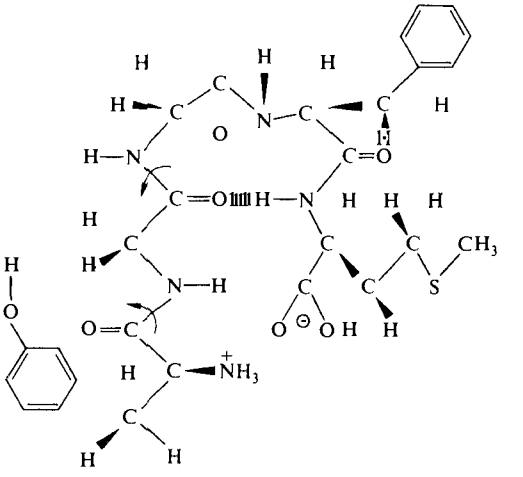


Fig 10.4 Diagrammatic representation of one conformation of Met-enkephalin (Ref 150)

HN of Met^5 and CO of Gly^2. In this conformation the two aromatic residues are pseudo-equatorial and the side chain Met^5 pseudo-axial to the mean plane of the peptide backbone, while the *N*-terminal Tyr-Gly moiety is relatively unrestrained. A head-to-tail interaction of the *N*- and *C*-terminal ionized functions was also proposed. Jones *et al.*[150] made a similar (simultaneously reported) study of Met-enkephalin at 270 MHz; they considered that analysis of the NH-CH_2 spin system of the Gly residues was not possible but that $^3J(NH\text{-}CH_\alpha)$ values for the Phe^4 and Met^5 preclude a γ- and support a β_1 turn. Other evidence, including the small temperature dependence of the NH proton of Met^5, led them to advance the preferred conformation of Fig. 10.4, which is similar to that suggested by the Europeans. The Belgian and French investigators made a similar study of the Leu-enkephalin and concluded that it shared the same conformation preference as that of its Met-analog.[151] Similar nmr evidence of a conformational preference of this kind has been found for D-Ala^2-D/L-Leu^5 and D-Nle^2-D/L-Nle^5 analogs, that is, for peptide pairs, including one that displays distinct diastereoisomeric differences in enkephalinlike properties; hence, the relevance of their solute geometry in DMSO-d_6 appears doubtful.[214]

Relaxation times (T_1) of carbon nuclei were also applied to the problem. The T_1 times of the CH_α backbone were of the same order, a result that implies the same correlation time for the motions of these carbons, including those of the terminal residues. T_1 data for the Phe^4, Leu^5, and Tyr^1 side-chain carbons indicated that the motion of the Tyr side chain was relatively unrestricted. Similar conclusions were drawn earlier by an American group[152] and from ^1H relaxation time data.[153] Uncertainties in determining the $^3J(NH\text{-}CH_\alpha)$ values of the Gly residues of the enkephalins have been resolved by a study of specifically deuterated analogs, but the results were considered to provide

no evidence of a favored conformation and, rather, to indicate the presence of a number of rapidly interconverting conformers in aqueous solution.[143] The ^{1}H nmr features of metenkephalin examined as the hydrochloride (cationic) form differ from those of the zwitterion, and no conclusion of conformation for the former species could be drawn from the data.[150,152] In a related study of the δ-selective peptide [D-Nle^2, L-NleS^5]-enkephalin (p. 349), NH/α-CH coupling constant magnitudes were consistent with an extended conformation but could also be accommodated by one involving a β-turn about the Nle^2 N-C_α bond and a head-to-tail $^+NH_3/SO_3^-$ interaction.[149] The latter arrangement was supported by evidence of an intramolecular hydrogen bond between Phe^{4}NH and Tyr^{1}CO and X-ray crystallography.[204] There was no evidence that the less potent D^{2}D^5 isomer favored a β-bend structure.

Khaled *et al.*[154] found a concentration dependence of nmr and other spectral parameters for the enkephalins that they felt might invalidate some of the reported conformational studies, and they proposed both monomeric (containing a β-turn between Gly^3 and Phe^4, an H-bond between Gly^3-NH and Tyr-CO, and a folding of the Tyr aromatic side chain over the molecule that is stabilized by an interaction of the phenolic OH proton with Gly^3-CO) and associated conformational forms of enkephalins to account for their observations. The same group[155] presented a complete assignment of the ^{13}C-nmr spectra of the two enkephalins in D_2O and other solvents; correct assignment of carbon resonances is essential if T_1 data (providing evidence of molecular motion as described earlier) is to be applied meaningfully. In this work an important aid was the evidence of chemical shift changes induced by pD variation. Thus, the CO resonance that showed a pronounced upfield shift when the pD fell below 5 must be due to that of the terminal (Met^5) residue ($CO_2^- \rightarrow CO_2H$, upfield shift), while that which moved to low field above pD 9 must be the Tyr^1 CO resonance because deprotonation of terminal amino ($^+NH_3 \rightarrow NH_2$) induces widespread downfield shifts, particularly at the α- and β-carbons (Fig. 10.5). Since protonation of the *C*-terminal carboxyl group of a peptide causes a downfield shift of the CO carbon of the preceding amino acid residue,[156] the titration curve that is deflected to low field below pD 5 must be due to carbonyl of Phe^4. Titration changes in the pD range 9–12 of the Tyr^1 C-quaternary aromatic carbon appear to correlate with those of Gly^3-CO and support the idea of an H-bond between the latter carbonyl and the phenolic function of Tyr^1.

Nmr studies of Phe^4 and Tyr^1 side-chain conformations have been possible with the aid of deuterated analogs.[157] In the case of Tyr^1 the conformers **15a** and **15b** had the higher populations in aqueous solution; the former corresponds to the local conformation of the tyramine moiety of crystalline morphine hydrochloride.[158]

Finally, reference is made to nmr work on enkephalin analogs with terminal Pro residues that are highly active at μ-receptors (p. 352). Both ^{1}H

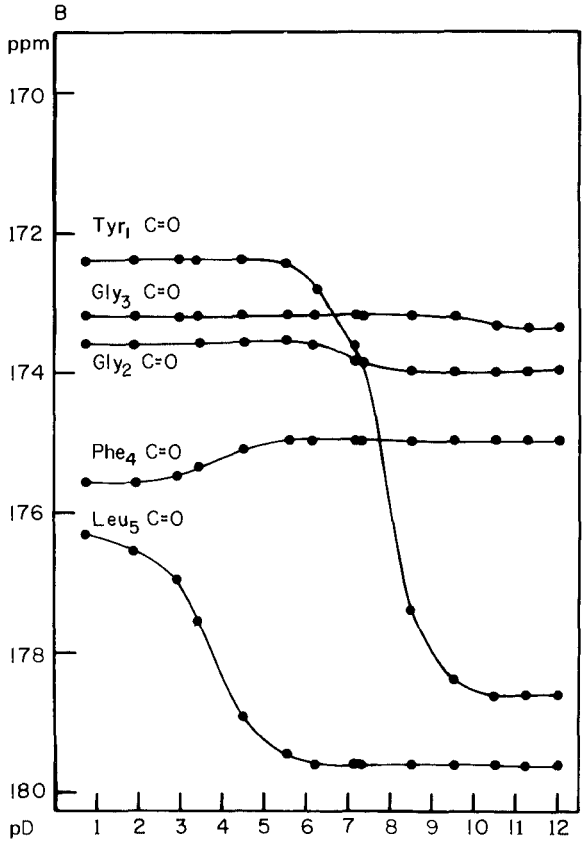
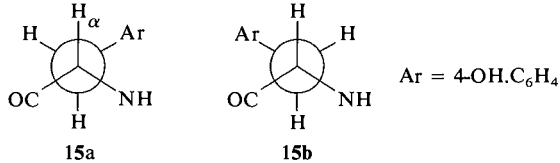
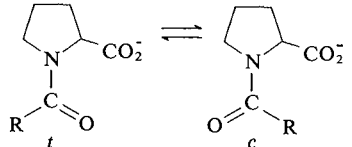


Fig. 10.5. pD titration curves of carbonyl carbon resonances of Met-enkephalin (Ref. 155).



and ^{13}C spectra of [D-Met^2, Pro^5]-enkephalin and its amide showed sets of well-separated signals corresponding to *cis* and *trans* conformers that arise as a result of restricted rotation about the Phe-Pro peptide bond (**16**).[159] Resonances were assigned on the basis of established differences in ^{13}C chemical shifts between the C-β and C-γ resonances of the prolyl ring in *cis* and *trans* rotomers of proline-containing peptides,[160] and the *trans* form was found to preponderate in the enkephalinamide. The usual analysis (e.g., use



16

R = Tyr-D-Met-Gly-Phe[4]

of vicinal coupling constants and T_1 measurements) indicated that despite the absence of a β-turn (as proposed for Met- and Leu-enkephalin and not possible in the Pro[5] derivatives because the presence of a tertiary peptide bond in the fifth position of the chain precludes the stabilizing H-bond to Gly[2]), the compounds exhibited folded structures induced by their high content of hydrophobic side chains.

The technique of circular dichroism (CD), much applied to study of the conformation of peptides and proteins,[161] has also been used to investigate enkephalins and endorphins.[162] Large positive molar ellipticity ($\Delta\varepsilon$) peaks occur in the CD spectra of enkephalins in the 220–250 nm region because of the Tyr and Phe aromatic chromophores. Soós *et al.*[163] estimated the contribution of folded (β) and random conformers of the CD curves of several enkephalins by subtracting curves due to the tripeptides Tyr-Gly-Gly and Gly-Gly-Phe (assumed to be entirely random) from the pentapeptide curve. The resultant had the form predicted for a peptide in a β-bend,[164] and a close correlation was found between the corrected $\Delta\varepsilon_{225}$ values and potency for a series of enkephalins in the GPI assay (a μ-receptor preparation) but not in the MVD (δ-receptor) test. The CD curves of Met-enkephalin and its analogs were sensitive to pH change as followed by titration of cationic forms in acetonitrile with aqueous NaOH.[165] Not all derivatives could be deprotonated with equal ease; thus, [D-Met[2], Pro[5]]-enkephalinamide required five equivalents of base to achieve this, while the corresponding D-Nle[2] analog showed the same spectrum in acetonitrile both with and without a large excess of alkali, results that suggest that the terminal $^{+}NH_3$ group is highly shielded by the hydrophobic side chains of the peptide. The observation that Na^+ and K^+ differentially affect the intensities but not the positions of ellipticity bands of Met-enkephalin in water has been advanced as evidence that these ions induce conformational change.[166]

Energy transfer experiments by spectrofluorimetry enable an estimate to be made of the Tyr-Trp separation in Trp[4]-Met-enkephalin, an analog that is about a quarter as active as the parent in the MVD test. The value obtained (~10 Å) is close to the phenol–phenyl separation in a potent oripavine derivative in support of peptide β_1-bend conformations.[167]

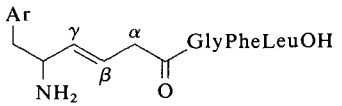
Quantum mechanical calculations have been applied to opioid peptides in attempts to identify low-energy conformers and to study their relationships to rigid opioids. Of the 52 conformations reported for met-enkephalin,[205] the lowest-energy structures (those with $\Delta E \leq 2.5$ kcal/mol) were found to have

βII[1] bends[206] about the Gly[3] and Phe[4] residues. The lowest-energy structure appeared to be stabilized by a hydrogen bond between Tyr[1] OH and Gly[3] or Phe[4] CO, as was also concluded from an nmr study.[154] From similar calculations, Loew and Burt[207] concluded that Met-enkephalin (and its D-Ala[2] analog) conformers with maximum resemblence to rigid opioids had the highest energies but considered that certain of the low energy forms allowed overlap between the NH_2-terminal Tyr residue and the phenethylamine moiety of rigid opioids. βII[1] Bend geometry was also proposed for the active conformers of Tyr-Gly-Gly-Phe-OH and related tetrapeptides (all of low potencies), stabilized by a hydrogen bond between Tyr[1] OH and Phe[4] CO rather than a **1**-4 bond.[208]

10.8 CONFORMATIONALLY RESTRAINED ANALOGS

The simplest way of reducing the conformational options of an enkephalin peptide is to include an alkene link in the molecule and several such variants have been examined. That with rigidity imposed upon the side chain of residue-4 has already been noted (p. 346); the compound [D-Ala[2], ΔPhe[4]]-Met-enkephalinamide (**5**) of Z-configuration is five times more active than its saturated (Phe) analog in both *in vitro* (GPI)[67] and *in vivo* (MTF, intracerebral route)[64] assays and is not attacked by chymotrypsin. The amide 5 ranked above D-Ala[2]-Met-enkephalinamide in binding assays respecting μ- and δ-sites, and its Z-configuration (Ph/CO *trans*) was considered of special importance for interactions with δ-receptors.[168] Since [D-Phe[4]]-enkephalins have binding activity,[50] the Δ-Phe[4] moiety must maintain stereochemical requirements satisfied by the natural amino acid. Substitution of D-Ala[2] by Δ-Ala[2] and Leu[5] by Δ-Leu[5] also preserved almost full receptor activity in binding tests. The Δ-Phe[4] and Δ-Leu[5] analogs showed preference for δ-sites as judged from activity ratios in displacing labeled DADL and dihydromorphine,[68] as did also the D-Ala[2], Δ-Ala[3] peptide.[169]

British workers have made the Δ-analogs **17** and **18** in which rigidity is built into the peptide chain.[170] The β,γ-derivative **17** had a similar binding potency as Leu-enkephalin against the ^{3}H-Leu-enkephalin but was less effective against [^{3}H]naloxone, while the α,β-isomer **18** was a tenth as active as its parent in displacing the peptide. The reduced analog of these peptides had negligible activity, so the steric constraints imposed by the β,γ-double bond are important for activity. Cox and others[209] found that the racemic methyl



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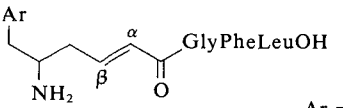
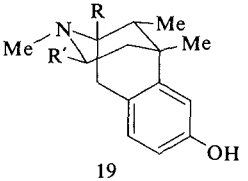


18

Ar = 4-OH.C_6H_4

ester of **17** was 3 and 0.25 times as active, respectively, as the parent (Leu-enkephalin OMe) in the GPI and MVD tests. It was suggested that hydrogen bonds formed by the Tyr^1-Gly^2 amide function are not important conformationally and that the amide link serves principally as a steric spacer. An analog of Tyr-Gly-Gly-Phe-Pro-NH_2 similar to **18** also proved to be inactive (GPI test),[209] while leu-enkephalin with amide functions connecting Tyr-Gly and Gly-Gly replaced by ketomethylene groups had a much lower binding affinity than the parent but was more effective in an *in vitro* test (mice TF, icv).[210] The full significance of these data in terms of the active conformations of natural enkephalins has yet to be analyzed.

Enkephalins with Tyr^1 restrained within the skeleton of a benzomorphan have been reported by two groups. Ramakrishnan and Portoghese[171] prepared antipodal forms of the regioisomeric derivatives **19a** and **19b** by routes based on corresponding 1- and 3-cyanides. All compounds



19

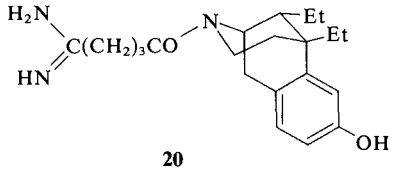
a R = COGlyGlyPheMetNH$_2$, R′ = H
b R′ = COGlyGlyPheMetNH$_2$, R = H

were either inactive or of low potencies in GPI and MVD tests, results that lent no support to the hypothesis that the tyramine moiety in morphine fulfills the same role as Tyr^1 in opioid peptides. An objection to this view has been advanced on the grounds of differing absolute chirality of L-Tyr and C-9 of morphine.[172]

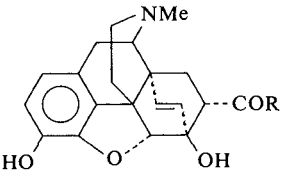
The fact that *N*-arginyl-Met-enkephalin(β-lipotropin 60–65) has an activity comparable with that of the parent by *in vitro* tests,[173] prompted the examination of benzomorphan derivatives in which the piperidino nitrogen was linked to a variety of amino acids (Gly, Met, Leu, Arg). The Arg derivative **20** was close in potency to Met-enkephalin in a binding assay against [^{3}H]naloxone (as was the nor-base) and all others had very low activities.[174] Peptidase action, liberating the active drug from Arg derivatives of both the enkephalin and benzomorphan, may explain these results, although there is contrary evidence in the case of peptide.

The thebaine-derived compound **20a**, which contains three leu-enkephalin residues but can hardly be regarded as an enkephalin analog, was highly potent in displacing ^{3}H-etorphine from rat brain membranes (IC_{50} 0.019 n*M*, morphine 28.3 n*M* in presence of NaCl), behaved as a dualist (weak agonist, potent antagonist) in the MVD assay, and had a MHP ED_{50} 1.1 mg/kg (NIH data).[219]

Restraint by cyclization has also been applied to enkephalins. Cyclo-Leu^5-enkephalin itself with Tyr^1-NH_2 joined to Leu^5-CO_2H has been reported but



20



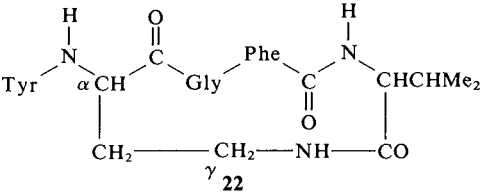
20a R = Gly-Phe-Leu-OEt

was found too insoluble to permit biological evaluation.[175] Canadian workers have cyclized enkephalins in a variety of manners and obtained some highly active analogs and evidence that the levels of potency achieved are a consequence of the conformational restraints imposed by cyclization. Thus, the derivatives **21** obtained by oxidative disulfide bond formation of 2,5-dicysteine analogs of enkephalinamide were both much more active than Met-enkephalin in the GPI assay.[176] The reduced pentapeptide D-Cys^2, D-Cys^5-enkephalin was somewhat less active (57.8 × metenkephalin) than the cyclic form to which it rapidly reverts on oxidation. Corresponding disulfides made with D-penicillamine (β,β-dimethylcysteine) as residue 2 displayed significant activity (ED_{50} 3.3 μg, icv) in the rat HP test, which was blocked by naloxone, with *in vitro* evidence of high δ-site selectivity.[177] In a recent comparison of δ-agonists, the penicillamine analogs proved the most selective with δ-binding 99% of the total.[218]

Tyr-D-Cys-Gly-Phe-L(or D)-Cys-NH_2

$D^5L^2$37.9x, D^2D^5 73 × Met-enkephalin in GPI test

21



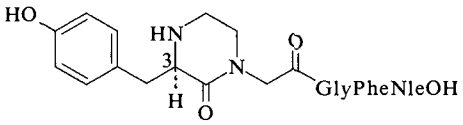
22

Another cyclic enkephalin of high potency is H-Tyr-cyclo(-N$^\gamma$-D-A_2bu-Gly-Phe-Leu-) (**22**), made by substituting α,γ-diaminobutyric acid (A_2bu) for Gly^2 of Leu-enkephalin and linking the γ-NH_2 of residue-2 to CO_2H of Leu^5.[178] The D-A_2bu derivative was 17.5 and the L-A_2bu diastereoisomer 0.2 times as potent, respectively, as Leu-enkephalin by GPI assay with lower potencies recorded in binding assays against [^{3}H]naloxone. Further studies confirmed the high activity of **22**, and GPI : MVD potency ratios revealed its selectivity for μ-sites.[180] The open chain congener with D-norvaline as residue-2 was somewhat less active than **22** (10.6 × Met-enkephalin, GPI) and showed a reduced specificity for μ-sites, evidence that μ- and δ-opioid subsites differ in their conformational requirements.[179] Extension of the bimethylene bridge

of **22** to $(CH_2)_4$ and use of Leu^5 in the D-configuration gave the most active compound of the series at GPI sites (IC_{50}, n*M* 2.4; Leu-enkephalin, 246), which, again, was more potent than the open-chain analog [D-Nle^2-Leu^5]-enkephalinamide (IC_{50}, 24.6 n*M*, GPI). In general, greater activity was found at μ-sites. The cyclic compounds, including the Cys^2-Cys^5 derivative, were highly resistant to enzymaytic degradation. It was noted that some of the compounds (e.g., **22**), do not permit formation of a 4-1 or 5-2 hydrogen bonded β_1 bend or β-bend stabilized by two antiparallel H-bonds between Tyr^1 and Phe^4, features advanced for the solute conformations of acylic enkephalins (p. 365), although such bends become possible in analogs of greater ring size.

The GPI activity of the tetramethylene analog of **22** (Tyr-c-[-N^{ϵ},D-Lys,Gly,Phe,Leu-]) fell 20-fold when Tyr^1 was replaced by Phe, but the nonphenolic derivative was still twice as effective as Leu-enkephalin at GPI sites with its action fully reversed by naloxone; it is thus notable as the first example of a potent opioid peptide lacking an intact Tyr^1 residue (the cyclic nature of the compound may be significant since its linear analog was virtually inactive).[211] *p*-Nitration of Phe in the μ-selective tetramethylene cyclic peptide produced a potency rise in the GPI test, as was also the case for δ-selective DSLT, while κ-selective dynorphin 1-13 suffered a potency fall after such alteration. The results point to differing electronic requirements of the Phe^4 binding site at μ/δ and κ-receptors.[212] German workers have prepared further analogs of **22** and report that Tyr-cyclo-[-N^{ϵ}-D-Lys-Gly-Phe-Pro] and Tyr-cyclo-[-N^{ϵ}-D-Lys-Gly-Tic-Pro] are three and one and a half times as potent, respectively, as morphine at GPI sites (Tic = tetrahydroisoquinoline carboxylic acid); they also presented conformational evidence based on Nmr data.[181]

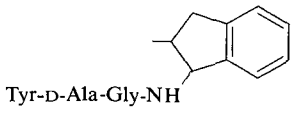
DiMaio prepared some cyclic analogs in which Tyr-NH_2 was linked to Gly^2-NH by bimethylene (to form a 2-oxo-piperazine ring).[182] The compound **23** (D-configuration at C-3) was active in mice at a dose level of 50 μg in the hot-plate test and was blocked by naloxone, whereas the corresponding L(C-3) diastereoisomer was inactive. However, the compound failed to displace [^{3}H]naloxone in a binding assay and showed no GPI activity.



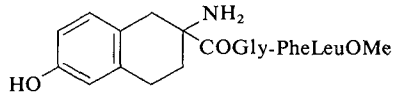
23

Aminoindane and related ring systems have also been employed as conformational restraints of enkephalins. The analog **24** in which 1-aminoindane replaces residues 4 and 5 of the pentapeptide retains half the GPI activity of DADL,[45] while the peptide **25** modified at the Tyr residue exceeds Leu-enkephalin in potency seven to eight times, but is 30 times less effective at MVD sites.[183] The last derivative showed no activity in mice, using the

hot-plate assay, after sc and icv administration. A variety of nonphenolic analogs related to **25** had no *in vivo* or *in vitro* activity.[184]

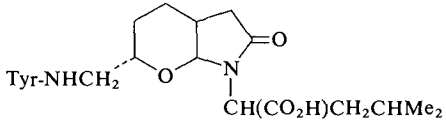


24

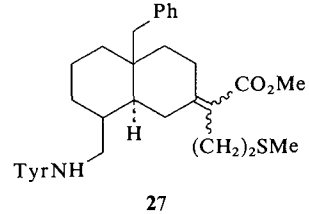


25

Many conformations of natural enkephalins with β-bends (stabilized by the Phe^{4}NH-Tyr^{1}CO or Leu/Met^{5}NH-Gly^{2}CO hydrogen bonds) have been proposed (see ref. 185 for review), some of which have already been discussed. Krstenansky and coworkers claim that analogs based on a saturated pyrano-pyrrole ring system mimic certain of these β-bend conformers.[185] The one example so far reported (**26**) represents a 5-2 β-bend system (identified as the preferred conformation of Met/Leu-enkephalin by nmr, p. 365); it had one third of the potency of morphine in the GPI test even though it lacks a Phe residue. In further pursuit of compounds that mimic enkephalin conformations, Bélanger and others prepared a series of isomers **27** based on a perhydronaphthalene backbone.[186] Rationale for the work was derivation of an enkaphalin model with a 5-2 β-bend that was considered to resemble opioids (morphine and etorphine) in the disposition of key groups and the design (by aid of computer graphics) of a nonpeptide model. The four isomers of **27** obtained had only weak binding activities versus naloxone, but the approach provides a useful guide to future work of this kind.



26



27

It is evident that the imposition of conformational restraints upon enkephalin molecules leads, notably in cases of cyclic analogs, to high levels of potency coupled with (and in part consequent upon) enhanced resistance to enzymic degradation. The significance of the data in terms of the conformational demands of opioid receptors for their ligands had yet to be established and will require, among other things, knowledge of the conformation of the cyclic forms themselves (see ref. 241 for recent work of this kind). The complexity of the conformational comparisons that will need to be made may well necessitate increasing application of computer graphics to the problem.

In the course of less than 10 years the study of opioid peptides has become a discipline in its own right and monographs devoted solely to the topic are now appearing. The monograph on endorphins has already been cited.[200]

Most recently, the Hungarian workers Szekely and Ronai have published three volumes on opioid peptides that cover the literature to the end of 1980.[187] A useful 1983 summary of work on opioid peptides that includes clinical and many other aspects has been edited by Hughes.[216]

After the discovery of the endogenous opioid peptide system there was tacit assumption that an undertstanding of the anatomy, physiology, and adaptive regulatory mechanisms of these systems would lead to some understanding of the mystery of tolerance and dependence to opioid analgesics that has so long eluded solution even after many years of intensive biochemical investigation.[232] Proposals made in the light of the discovery of opioid peptides by Kosterlitz and Hughes[233] and by Snyder[4] rest upon the assumption that the perception and response to pain are modulated (inhibited) under normal conditions by enkephalins and other opioid peptides; in this respect the report of a stress-induced increase in endogenous opioid peptides concurrent with a decrease in pain responsiveness in the rat is of interest.[234] If opioids are administered, control of these inhibitory mechanisms may pass from the endogenous peptides to the exogenous opioid. Since diminution of pharmacological response (tachyphylaxis) is a characteristic of all opioids, a state of tolerance will arise in which increasing amounts of opioid will be required to maintain the inhibitory mechanism, a situation that may be aggravated by a feedback mechanism (possibly with cyclic nucleotides playing a second messenger role) activated by the constantly stimulated opioid receptors that cuts off release of enkephalins. The CNS will then be wholly dependent on the exogenously supplied opioid, and if this is suddenly withdrawn, the inhibitory mechanism will be inoperative and symptoms of the withdrawal syndrome will appear. The duration of this syndrome will depend on the rate at which the opioid receptors regain their sensitivity and on the restoration of normal enkephalin synthesis and release. Evidence supporting this sequence is (1) the overall increase in enkephalin levels in rat brain during the course of chronic administration of morphine (a paradox explained by assuming that the peptides are stored in the brain cell terminals—and hence protected from enzyme attack—rather than released after synthesis)[4] and (2) signs of inactivation of the inhibitory mechanism in nondependent animals after administration of antagonists.[233] Other workers, however, have reported evidence on the effect of naloxone on pain in laboratory animals that is conflicting and even positive results have been less than dramatic.[238] Martin *et al.*[93] failed to detect antimorphine activity in the chronic spinal dog and also in man after treatment with naltrexone as judged by pupillary diameter changes, respiration and pulse rates, and hyperalgesia, while naloxone effects on electric shock,[235] ischemic and cold water pain[238] judgments could not be demonstrated in healthy subjects. Other examples are given by Melzack and Wall.[239] These results may merely reflect the less dramatic effects of antagonists expected in nondependent than in dependent subjects. Buchsbaum *et al.*[236] found that

normal adult volunteers could be divided into those sensitive and those insensitive to a standard electric shock, the pain-sensitive subgroup found shock less painful after naloxone (2 mg i.v dose), while the pain-insensitive subgroup experienced more painful shocks after the antagonist. The bidirectional nature of the results was interpreted as supporting a modulatory rather than strictly analgesic role for opioid peptides. Changes in the number of binding sites or of the affinity of opioid receptors for ligands might be a likely consequence of the development of tolerance, but so far evidence of such change has not been observed after chronic opioid treatment, although a 10% fall in ligand binding capacity was noted in brain homogenates from mice reared in isolation compared with that of brain material from mice reared as normal in aggregate [237]

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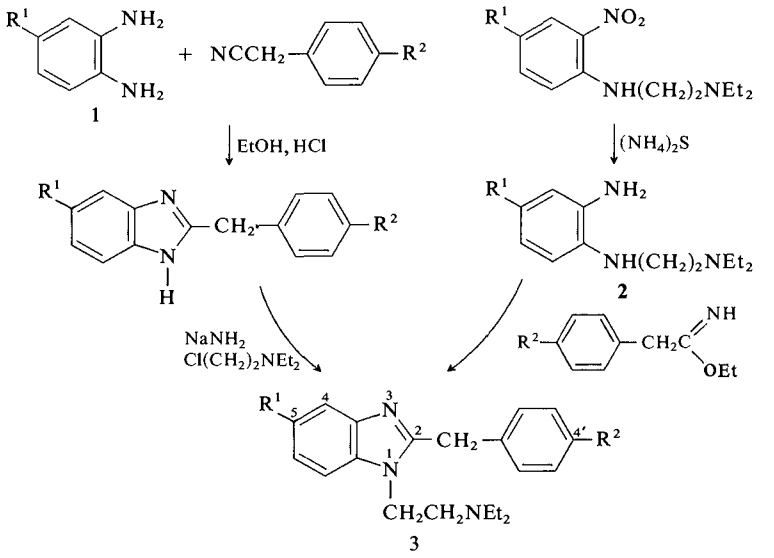
11

Miscellaneous Groups of Analgesics

11.1. BENZIMIDAZOLE DERIVATIVES

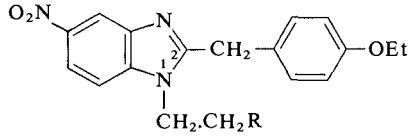
Up to the late 1950s the goal of potency in the development of novel analgesics was that of the classic opiate morphine. However, in 1957 it was made apparent from reports from CIBA on analgesics based on benzimidazole that levels of activity several orders above this standard could be achieved, and the group is of historical importance on this account.[1,2] The compounds of general formula **3** carry a 2-aminoethyl substituent at N-1 and a benzyl substituent at C-2 with further substituents at C-5 and C-4′ in the more potent derivatives. Two synthetic routes were employed (Scheme 11.1)[3]: (a) condense



Scheme 11.1

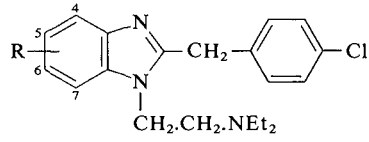
substituted *o*-phenylenediamines with a substituted benzyl cyanide (or related compound) and alkylate the product with a 2-*t*-aminoethyl chloride (**1–3**), and (b) (appropriate to derivatives with R′ substituents) condense 1-amino-2-diethylaminoethane with a 2-nitrochlorobenzene, reduce the nitro group with $(NH_4)_2S$ (a 5-NO_2 substituent is unchanged), and condense the product **2** with an iminoether formed from a benzyl cyanide and EtOH-HCl.

Table 11.1. Analgesic Activities in Mice of Benzimidazole Derivatives (Relative to Morphine = 1)[a]



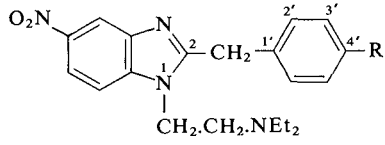
4

R	NMe_2	NEt_2	NC_5H_{10}	$N(C_2H_4)_2O$	CH_2NEt_2
Activity	20	1,000	100	2	0.2



5

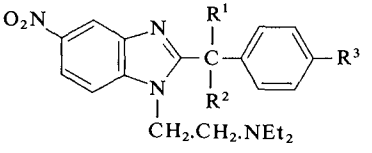
R	H	4-NO_2	5-NO_2	6-NO_2	7-NO_2
Activity	0.1	0	3	0.1	0



6

R	H	OMe	OEt	OPr^i	OPr	OBu	4′-Cl
Activity	2	100	1,000	500	200	5	3
R	H	SMe	SEt		SPr	SBu	4′-F
Activity	2	50	30		2	0.25	1
R	H	Me	Et		Pr	Bu	4′-OH
Activity	2	10	20		50	1	1

Table 11.1. (Continued)



7

R^1	H	Me	Et	Me	$CONH_2$	H	Me	$CONH_2$
R^2	H	H	H	Me	H	H	H	H
R^3	H	H	H	H	H	4′-OEt	4′-OEt	4′-OEt
Activity	2	2	0.5	0.7	2.5	1,000	50	200

[a] From Refs. 2 and 3.

Structure-activity relationships established from the Swiss data are as follows (Table 11.1):

1. The structure of the basic side chain at N-1 is 2-diethylaminoethyl for optimal activity although high activities are achieved with other basic groups such as 2-dimethylamino- and 2-piperidino-ethyl (see 4). Chain lengthening drastically reduces activity. The superiority of NEt, over NMe_2 in this respect is in sharp contrast to other analgesics that carry noncyclic NR_2 basic functions such as methadone (p. 307).

2. While the 4′-chloro analog (**3**, R′ = H, R^2 = Cl) is only one tenth as active as morphine, a 5-nitro group in the benzimidazole nucleus raises activity by a factor of 30 (see **5**); nitro groups placed elsewhere in this nucleus are ineffective. The only other active analgesics with nitro functions are a tetrahydroisoquinoline and some NO_2-Phe[4]-enkephalins (p. 346).

3. Substitution in the 4′-position of the benzyl fragment is advantageous particularly with alkoxy groups (highest activity results with 4′-OEt) while thioethers and lower alkyl groups also give compounds of high activity (see **6**). Chlorine is less effective, nevertheless 3(R′-NO_2, R^2 = Cl) is three times as active as morphine; 4′-fluoro and hydroxyl groups are disadvantageous.

4. The methylene group linking the benzimidazole and phenyl nuclei is best left unsubstituted although the effect of substitution on activity appears to be dependent on other substituents; for example, the carbamoyl ($CONH_2$) group has little influence on the activity of the unsubstituted methylene derivative when R^3 = H (see **7**), but causes a fivefold reduction when R^3 = OEt.

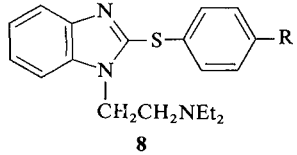
While the 5-nitro and 4-ethoxy groups both enhance activity separately, their effect together is additive and the compound **3** (R′ = NO_2, R^2 = OEt) proved the most powerful analgesic known at that time. Eddy[4] stated that this derivative, termed *etonitazene*, was about 1500 times as active as morphine

in mice, with an ED_{50} value of just over 1 μg/kg. In man, Bromig[5] found the 4′-chloro-5-nitro derivative **3** to be three to five as potent as morphine against postoperative pain, in close agreement with activity found in mice. Its duration of action was shorter than that of morphine while undesirable side reactions such as respiratory depression and constipation were noted in only a small percentage of cases. In the same trial the 4′-methoxy analog was 10 times as potent as morphine but produced greater incidence of side reactions, especially severe respiratory depression. The action of orally administered benzimidazole analgesics, both in animals and man, is rather weak and irregular while by injection the therapeutic ratio between analgesic and respiratory depression activity is narrow and does not offer any advantage over morphine. For these reasons clinical trials were not pursued. In addicted monkeys, etonitazene and its 4′-chloro analog were 1500 times and twice as potent as morphine respectively in alleviating abstinence[6] while in addicts both compounds had addiction potentials comparable to that of morphine.[7] Etonitazene is useful in experiments designed to condition drug-seeking behavior in rats.[8] Previous attempts failed because of adverse reactions induced by the bitter taste of morphine and other opioids. The benzimidazole derivative, however, is effective at great dilutions (3 to 10 μg/l) and water-deprived rats accept solutions at these drug concentrations; morphinelike effects develop within 4–7 min after the rats begin to drink.

The benzimidazole analgesics are best classified with methadone and other members of the diphenylpropylamine group in that both types possess a 2-*t*-aminoethyl side chain linked to a nonprotonated center (N and C respectively) and two aromatic rings. They differ in the optimal size of the *t*-amino function (see above) and the need for aryl-placed substitutents in active benzimidazoles. Analogs with branched 2-aminoethyl side chains have been reported but not tested for analgesic properties.[9] Distribution factors must contribute greatly to the high potency levels of the benzimidazoles since active derivatives have very high partition coefficients (cyclohexane favored over pH 7.4 aqueous buffer) compared with that of morphine.[10] Substituents must also influence receptor binding, however, as is apparent from the 70-fold activity difference between **3**($R' = H$, $R^2 = OEt$) and its less active 4-OMe analog, a pair that would be expected to have similar lipid solubility properties (see **6**). The binding affinity of etonitazene to rat brain membranes was 14 times that of morphine and approached that of etorphine, another analgesic of superhigh potency.[60] It is principally a μ-ligand since it more readily displaced [^{3}H]DALAMID from sites of this type rather than the δ-variety, while it displaced [^{3}H]morphine (μ) but not labeled DADL(δ) at n*M* concentrations.[61] Its variant with 5-nitro replaced by isothiocyanato (BIT, **3**, $R' = NCS$, $R^2 = OEt$), designed as an irreversible ligand (p. 453), reduced rat brain μ-receptors by 45% but δ-receptors by only 4%.

A few structural variants of **3** have been described but interest in the

group has faded since the late 1960s. Activity is retained, although at low levels, when the methylene group linking the two ring systems is altered to NH[11] or CH_2O.[12] Structure-activity relationships of the 2-phenoxymethyl derivative mirror those of the original molecules. Thus, 5-NO_2 and 4'OEt substituents are specific for high activity while a 2-diethylaminoethyl basic side chain at C-1 is far more effective than dimethylaminoethyl. The 5-methyl, 4'-ethoxy derivative is morphinelike in potency. Seki *et al.*[13] made a series of 2-arylthiobenzimidazoles **8**, several of which were superior in potency to



8

R	ED_{50} mg/kg, ip mice
OEt	4.3
OPr	4.5
NHEt	3.1
NHPr	7.6
Morphine	7.3

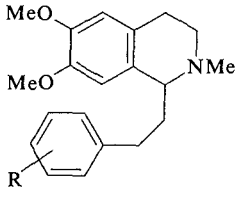
morphine. A detailed study of the 4'-ethoxy congener showed it to be typical narcotic analgesic; it caused addiction and Straub tails in rats and its analgesic and respiratory depressant actions were antagonized by levallorphan. The NEt_2 group was replaced to advantage by pyrrolidino but other *t*-amino groups such as piperidino, $EtN(CH_2)_2Ph$, and N-diallyl were potency lowering. The allyl derivative was not an analgesic antagonist. Some 2-benzylindenes (heterocyclic nitrogens of **3** replaced by CH_2/CH) based on benzimidazole analgesics have been reported,some of which have potencies in the codeine-pethidine range.[14] A *p*-OEt group in the benzyl moiety depressed potency so the relation of these indenes to etonitazene and its congeners is doubtful.

A possible relationship between benzimidazole and fentanyl-like analgesics is discussed on p. 485; the high potencies seen in both series may be related to the presence of a nonbasic N-Ar pharmacophore.

11.2. TETRAHYDROISOQUINOLINE DERIVATIVES

Another heterocyclic nucleus investigated as a basis for analgesics is isoquinoline with a fully reduced heterocycle moiety and carrying a 1-phenethyl substituent. The series was reported by Hoffman-La Roche in 1960[15] but no further information has appeared since 1965, when a full account of the work appeared in deStevens book *Analgetics.*[16] 1-Benzyltetrahydroisoquinoline alkaloids such as papaverine occur in opium but lack analgesic properties, while others, for example, α-narcotine (noscapine), have antitussive activity. Some of the novel 1-phenethyl analogs **9** behaved as analgesics in mice after sc administration when tested by the tail-flick assay, but potency levels were mostly low and close to that of codeine. Details of the most active compounds are shown in Table 11.2. All have 6,7-methoxyls and 4'-substituents with

Table 2. Analgesic Activities in Mice (sc route) of Some 1-Phenethyl-1,2,3,4-tetrahydroisoquinolines[a]



9

R	Isomer	Activity (codeine = 1)
4′-Cl	(±)	1.4
4′-Cl	(−)	3.0
4′-Cl	(+)	Inactive
3′,4′-di-Cl	(±)	1
3′,4′-di-Cl	(−)	2.1
4′-F	(±)	1.9
4′-Br	(±)	0.8
4′-NO_2	(±)	20

[a] From Ref. 16.

potency rankings $NO_2 > F > Cl > Br$; activity fell when the 4′-groups were moved to the 2′- or 3′-positions. Stereochemical specificity in the series has been established in three cases (4′-NO_2, 4′-Cl and 3′,4′-dichloro derivatives) with activity restricted to the levo (*R*) enantiomers.[17] Spasmolytic properties were independent of configuration. No substitutent was found that replaced *N*-methyl with retention of activity. Lengthening or shortening the phenalkyl side chain or aromatization of the nitrogen ring both resulted in loss of activity. Sadove *et al.*[18] studied the relative effectiveness of the racemic 4′-chloro compound (*methopholine*) and codeine by a double-blind trial in 40 postoperative orthopedic patients. They concluded that the analgesic potencies of the two drugs, given orally, were similar. In monkeys the physical dependence capacity of methopholine was low. Other details of the pharmacology of this derivative are available.[16]

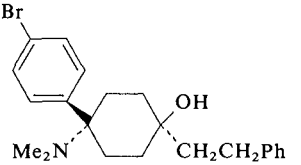
The isoquinolines **9** were synthesized from acetophenone precursors, quaternary 1-methylisoquinolines, or by the Bischler–Napieralski procedure.

11.3. CYCLOHEXANE DERIVATIVES

From a structural point of view, cyclohexane forms the common element of a variety of analgesics that are otherwise difficult to classify. The alicyclic

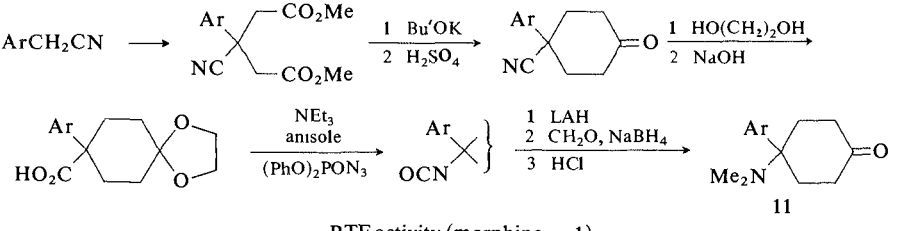
ring system serves to restrict conformational options in all derivatives that contain it and in most examples only a few conformations are likely to be significantly populated.

The most notable analgesic of this class, certainly, from the viewpoint of activity, is the 4-aryl-4-dimethylaminocyclohexane **10**.[19] Its potency is at least 10^4 times that of morphine on a weight basis, and hence it may be classified among the relatively small group of extremely potent narcotic analgesics typified by etonitazine, etorphine, and fentanyl. The ED_{50} values of **10** in tail-flick, tail-pinch, and HCl-induced writhing tests in mice (sc route) were all close to 0.1 μg/kg, corresponding values for morphine being 1.5, 1.6, and 0.6 mg/kg, respectively, and its antinociceptive effects were blocked by naloxone. It displaced [^{3}H]naloxone from brain binding sites 30 times more effectively than did morphine, the discrepancy in relative binding and antinociceptive activities probably reflecting the greater facility with which **10** enters the CNS.



10

Discovery of **10** grew out of the idea of examining compounds in which aromatic and basic features (both critical structural requirements of narcotic analgesics but usually separated by two or three carbon atoms) are linked to the same quaternary carbon. The precursor ketone **11** and its analogs were described in the first full report of the series,[20] made by the route of Scheme 11.2 or from the monoketal of 1,4-cyclohexadione. Several of the ketones **11** were active in mice by a variety of pain tests; the *p*-tolyl and *p*-bromophenyl



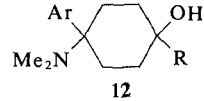
11

RTF activity (morphine = 1)
Ar = Ph, 0.02
Ar = *p*-MeC_6H_4, 1.5
Ar = *p*-BrC_6H_4, 0.4

Scheme 11.2

analogs showed potencies in the morphine range and activity rankings of *p*-substituted aryl derivatives were Me ≅ Br > Cl > MeO > F > H. Effects of the compounds were reversed by naloxone and they did not themselves behave as antagonists in a test involving blockade of morphine-induced elevation of tail-flick latency. The 4-deoxy analog of **11** (Ar = Ph), itself of low potency, was inactive in all tests. Most of the activity of the ketones **11** was retained in corresponding ketals.

Potencies were enhanced when the ketone function of **11** was converted to a secondary or tertiary alcohol, and remarkably high levels of activity were found when R in **12** was an arylalkyl substituent, as the data demonstrates.[21] Diastereoisomeric alcohols were isolated in most cases (~1:1 mixtures separated by chromatography on silica gel) and high isomeric potency ratios observed with the *trans* (N/O) isomers the more effective. Configurational assignments were based on ^{1}H-nmr evidence for isomers carrying 4-CH_2R substituents with resolvable methylene proton signals and assumption of a preferred axial conformation of the 4-aryl substituent.[22] An X-ray analysis of the 4-*p*-bromophenyl,1-phenethyl derivative supported assignment of the more potent isomers.

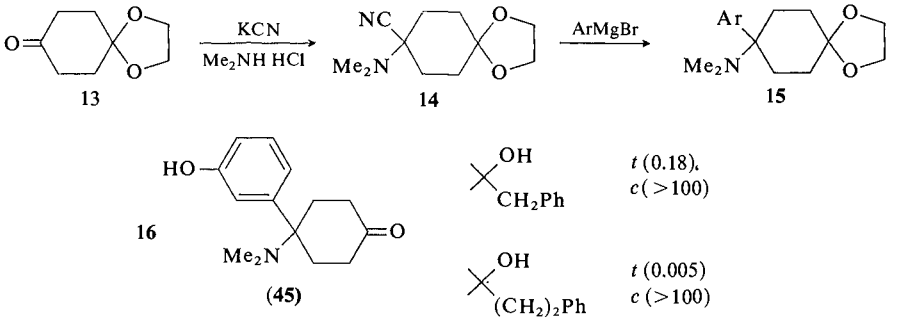


12

Ar	R	Me_2N/OH configuration	ED_{50} mg/kg sc mouse TF[a]
p-ClC_6H_4	Me	*t*	1.0
p-ClC_6H_4	Me	*c*	2.0
p-ClC_6H_4	CH_2Ph	*t*	0.0056
p-ClC_6H_4	CH_2Ph	*c*	63
p-ClC_6H_4	$(CH_2)_2Ph$	*t*[b]	0.0014
p-ClC_6H_4	$(CH_2)_2Ph$	*c*	>100
p-ClC_6H_4	$(CH_2)_3Ph$	*t*	0.11
p-ClC_6H_4	$(CH_2)_3Ph$	*c*	32
p-BrC_6H_4	$(CH_2)_2Ph$	*t* (**10**)	0.0001
p-BrC_6H_4	$(CH_2)_2Ph$	*c*	7 9

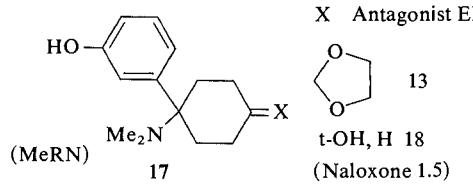
[a] Morphine SO_4 1 5
[b] $CH_2CH_2C_6H_{11}$ analog 0 014

4-(*m*-Hydroxyphenyl) analogs were prepared from the monoketal of 1,4-cyclohexadione **13** by its conversion to the α-aminonitrile **14** followed by displacement of the cyano group by an aryl Grignard reagent, giving **15** as in the synthesis of phencyclidine.[23] Use of the Grignard from the THP ether of *m*-bromophenol (cf. p. 242) led to the phenolic ketone intermediate **16** and corresponding *t*-alcohols. High orders of potency were recorded for 1-benzyl



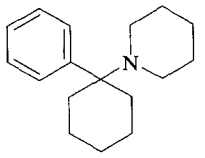
Mouse TF ED_{50} values, mg/kg in parentheses.

and 1-phenethylcyclohexan-1-ols (data on corresponding 4-phenyl analogs is not available for comparison) and preference for *trans* stereochemistry maintained, but actual orders were not superior to those of the nonphenolic derivatives already noted. A few of the phenols were weakly active as antagonists (see **17**). Hence, in these cyclohexanes a phenolic OH is not essential for high agonist potency but may be a minimal requirment for antagonist activity. When R in **17** (ketal variant) was allyl or a long-chain alkyl group, antagonist properties were lost while agonist activity in the tail-flick test rose in the order Me ≅ Pr ≅ « Bu < C_5H_{11}.



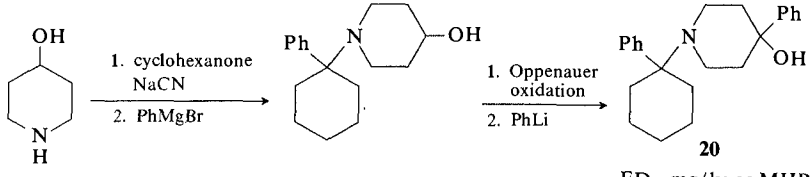
According to the Upjohn workers, Dreiding models of the potent compounds **10** and fentanyl may be arranged to give point-for-point coincidence of all salient structural features including the basic centers, the 4-aryl (**10**) and *N*-phenethyl aryl ring of fentanyl, and the 1-phenethyl (**10**) and *N*-anilido (fentanyl) aryls.[19] Conformations of **10** required to achieve this superposition are not the preferred ones, but energy increases on this account could be offset by that released on formation of the ligand receptor complex. These ideas are attractive but need to be supported by comparative structure-activity analyses. It is to be noted that phenolic analogs of fentanyl have low potencies (p. 294) while those of **10** (in respect of 4-aryl) retain activity.

Aromatic and *t*-basic features are also linked to a quaternary center in *phencyclidine* (**18**, PCP), a well-known drug of abuse.[24] In the MHP test, PCP was not active up to 9 mg/kg sc (higher doses caused ataxia) but its analog **20** proved about twice as effective as morphine.[25] The activity of **20** fell 10-fold after esterification with propionic acid so the compound appears



18

unrelated to the reversed ester of pethidine (p. 243); significant potency (0.3 × morphine) was retained, however, when it was combined with 3,4-dimethoxybenzoic acid (*cf.* p. 243). The 4-deoxy analog of **20** had a very low potency. The derivative **20** was also active in the MVD test (IC_{50}, 0.082, μM morphine, 0.5 μM) and both its *in vivo* and *in vitro* actions were reversed by naloxone. The compound was made from piperidin-4-ol (**19**) by adaptation of the PCP synthesis (**19**→**20**).



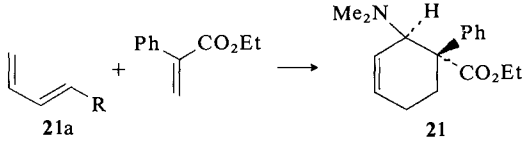
19

20

ED_{50} mg/kg sc MHP
1.3 (morphine 2.5)

PCP binds strongly to a specific receptor present in synaptic membranes from rat brain, less strongly to muscarinic receptors, and weakly to μ-opiate receptors.[26] The specific binding affinity of a variety of PCP analogs with substituents in the homo- and heterocyclic moieties have been examined but no data on their analgesic properties are yet available.[27]

A number of cyclohexane derivatives with *t*-amino substituents, especially NMe_2 as in **10**, have proved to be active analgesics of potencies in the pethidine to morphine range. *Tilidine* **21** is one such compound; its *trans* NMe_2/CO_2Et configuration is important for activity since the corresponding *cis* isomer, although still effective, is less potent.[28] Most of the activity of racemic **21** resides in the dextro isomer (see ED_{50} data) and activity is abolished when the alicyclic ring is saturated. The effective form of the drug may be its metabolite nortilidine (the NHMe analog) as the latter is equiactive with pethidine after central administration, whereas tilidine is without action by this route.[29] Details of the pharmacology of tilidine (Valoran) are available (it is effective in a variety of antinociceptive tests with potencies inferior to



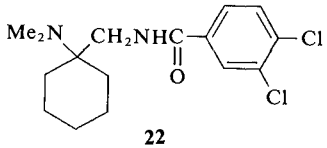
21a **21**

ED_{50} mg/kg MWR
(+) 4.95
(−) 116
(±) 8.8
Pethidine 6.3[30]

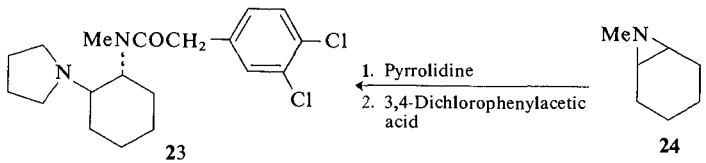
those of pethidine)[30] as are reports of its clinical use as an oral analgesic.[31] Its PDC is low[32] and 50–100 mg produced less respiratory depression than 10 mg morphine after iv administration.[33] Some "*p*-tilidine" analogs (1-NR_2, 4-CO_2Et) were active in the writhing test, and in these cases *cis* isomers proved superior to *trans*.[34]

Tilidine is the minor component of the product of cycloaddition of *trans* 1-dimethylamino-1,3-butadiene (**21a**, R = NMe_2) to ethyl atropate, a reaction with favored *cis* stereochemistry. When the butadiene **21a** (R = $NHCO_2CH_2CCl_3$) was employed, the *trans* isomer was obtained exclusively and was converted to tilidine in two steps (Zn dust–HAc followed by CH_2O–$NaBH_4$).[35] Stereochemistry in the series was established by spectroscopic methods, X-ray crystallography, and chemical transformations. *t*-1-Dimethylamino-*r*-3-propionyloxy-3-phenylcyclohexane, a saturated reversed-ester analog of tilidine, was only feebly active in the MHP test.[62]

Two other *t*-aminocyclohexanes of relevance here are the aminoamides **22** and **23**, both of which include a 3,4-dichlorophenyl moiety. The dimethylamino derivative **22** (the most potent of a series) was reported almost equieffective with morphine in mice WR and HP assays[36] even though it failed to elicit a Straub tail response. The absence of this and other μ-behavioral properties was also noted for the pyrrolidine **23**, a compound about half as active as morphine in tail-flick and tail-pinch tests and a quarter as active as morphine against HCl writhing.[37] The dimethylamino analog showed similar potencies in mice and the actions of both compounds were blocked by naloxone. Further biological evaluation[38] suggests that **23** (U-50488) and its analog are κ-rather than μ-agonists (see p. 438). The synthesis of **23** from the aziridine **24** is shown.

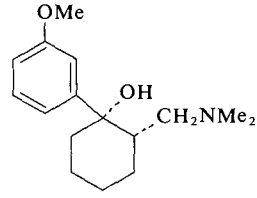


22



23 **24**

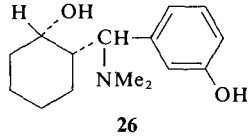
Tramadol (**25**, Tramol), another cyclohexane with opioid properties, has *trans* 1-*m*-methoxyphenyl,2-dimethylaminomethyl substituents and is in clinical use in West Germany. It was extensively described in a supplement of Arneimittel Forschung.[39] In animal tests its potency is closer to that of codeine than morphine and relatively high clinical doses (50–100 mg) are necessary for pain relief. Side effects are generally minor and the compound



25

has a low physical dependence capacity (it is not subject to the Narcotics Act in Germany). It is metabolized by *O*- and *N*-demethylation, the free phenol being more potent than the parent drug.[40] Activity fell when the alcoholic function was esterified, while a Δ-1,2 double bond shortened duration of action but had little influence on potency. The *cis* analog of **25** is a feeble analgesic. Stereoselectivity typical of opioids is displayed by tramadol as seen by ED_{50} values (mg/kg) measured in mice by an electroshock test: *trans* **25** (±) 10.3, (−) 67 (+) 6.2; *cis* **25** 78; morphine 1.8. Some nonphenolic analogs of tramadol were reported in 1964[41] but all proved inactive in the hot-plate test. The importance of a phenolic function suggests that analgesics of this type are closely related to morphine and that the orientation of their basic group-aromatic features mimics that of the alkaloid. The compounds were made from the Mannich base derived from cyclohexanone, formaldehyde, and dimethylamine.

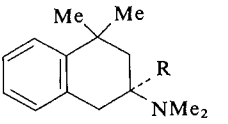
To confuse the structure-activity relationships of analgesics even more, it turns out that transposition of aryl (*O*-demethylated) and one of the α-hydrogens of the aminomethyl side chain of tramadol also yields an active compound. The formally derived analgesic *ciramadol* (actually made by reducing the unstable adduct formed from a benzylidine cyclohexanone and dimethylamine) is the levo antipode of the *cis* diastereoisomer **26**. It is about twice as potent as morphine in the rat tail-flick assay and classified as a partial agonist, since it antagonizes morphine in rats with a potency near that of nalorphine. The corresponding (+)-antipode and *trans* racemic mixture are inactive as agonists in rats.[42] Several clinical trials of ciramadol have been reported and evidence of its oral efficacy as an analgesic obtained.[43]



26

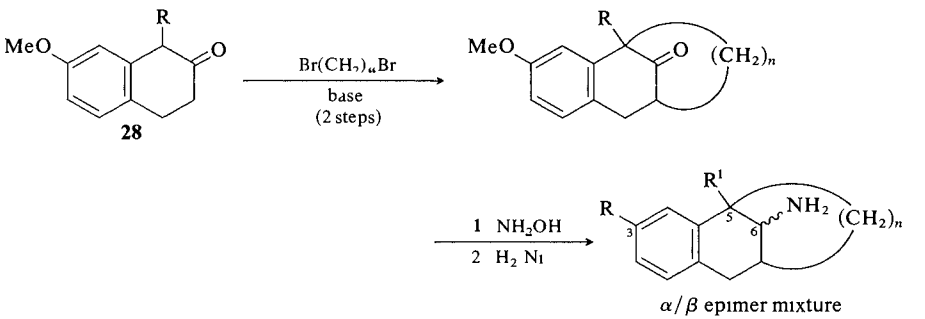
11.4. AMINOTETRALINS

The 2-aminotetralin skeleton has attracted several groups as a basis for potential analgesics. Martin *et al.*[44] succeeded in obtaining several derivatives



27

with pethidinelike potencies, for example, **27** (R = H, Me, CH_2Ph) while bridging the carbons that flank the amino function led to compounds that match or exceed the activity of morphine.[45] The bridged compounds **29** bear some resemblence to benzomorphans but differ in having a noncyclic amino function, which, furthermore, is primary in most active examples. All the active derivatives are β-epimers (6-NR_2 above mean plane of the tetralin system) and highest potencies occur when n = 5 with Me or Et C-5 and OH/OMe substituents at C-3. A free phenolic function is not essential for activity and may in some cases be masked to advantage. Some potency data are shown alongside **29**. The action of the most effective racemic mixture **29** (n = 5, 3-OH, 5-Me, 6-NH_2) is due to the levo antipode [ED_{50}, mg/kg (±)-1.11, (−)-0.53, (+)- > 100] and this form (WY-16225, dezocine) has been evaluated clinically by parenteral routes. It is judged an effective analgesic with a potency in the morphine range and with the usual side effects of opioids.[46] In healthy men its potency as a respiratory depressant was 8.6 times that of pentazocine.[47] *Dezocine* is rapidly distributed throughout the body after iv and im injection to monkeys; it readily penetrates the brain in spite of its primary amino function, which may be shielded from solvation by the flanking pentamethylene bridge.[48] Glucuronidation is its major metabolic pathway.



α/β epimer mixture

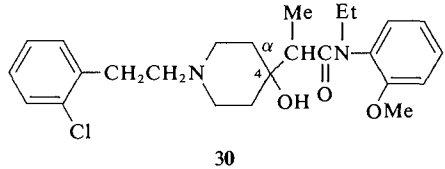
29

n	R	R′	Activity RTF (morphine = 1)
5	OH	Me	2.8
5	OMe	Me	0.63
5	OMe	Me	0.46 (6-NHMe)
4	OH	Et	0.8
4	OMe	Et	0.9

The animal pharmacology of dezocine is unusual in that it acts as an agonist in opioid-naive animals (**17** × morphine in mice, sc HP, 8 × in rats, ip TF), and an antagonist in morphine-dependent rhesus monkeys with a potency in precipitating a withdrawal syndrome close to that of nalorphine.[49] Such dual activity is shared by the four-chain (n = 4) congener. It is strange that opioid receptor blockade should be a property of these primary amino derivatives. Another unusual finding is that dezocine is devoid of agonist effects in the GPI test as is the pure antagonist naloxone but not nalorphine, which proved twice as active as morphine in the hands of these workers. The synthetic route from a 2-tetralone **28** is illustrated.

11.5. 4-PIPERIDINOLS

In 1983 Sandoz chemists reported yet another class of analgesic based on piperidine. They found that the compound **30** was about 50 times more potent than morphine in rats by the TF test (sc route) while many of its congeners also showed activities superior to or comparable with that of the standard analgesic[50]; the compounds were also active in MWR tests. The series defies classification with other piperidine analgesics in spite of possessing a 2-arylethyl substituent at basic nitrogen and an anilino moiety recalling that of fentanyl. Activity in the series falls or is lost when α-methyl of the 4-substituent is replaced by hydrogen, when the α-carbon carries geminal methyls, and when the 4-OH is acylated (the solid-state conformation of the N-Pr analog of **30** is stabilized by a strong hydrogen bond). The N-Et group may be varied with retention of most of the activity: ED_{50} mg/kg (as in **30**) N-Et, 0.07; N-allyl, 0.09; N-Pr, 0.11; N-$CH_2C{\equiv}CH$, 0.13. Ethoxy analogs of **30** (anilinoaryl substituent) are also potent.



ED_{50} mg/kg RTF
0.07 (morphine 3.4)

30

When the terminal anilino moiety of the 4-substituent of **30** is replaced by methylaminocyclohexane, a compound as active as morphine results (ED_{50} 3.2 mg/kg); the dextro antipode (ED_{50} 42 mg/kg) is distinctly less active than the racemic mixture, but the levo form (ED_{50} 3.8 mg/kg) does not show the expected doubling of potency. The more potent members of the group effectively displace [^{3}H]naloxone from rat brain membranes provided NaCl is absent, while the N-propyl analog of **30** (a typical member) produced mydriasis accompanied by a Straub tail response and CNS depressant effects

at higher doses, effects all abolished by naloxone. Hence, there seems little doubt of these compounds being opioid agonists with μ-receptor selectivity.

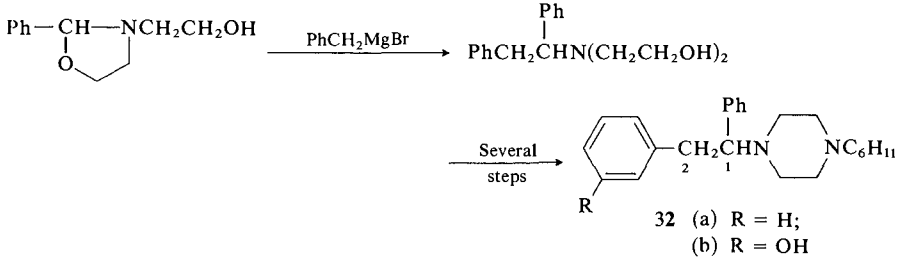
Synthesis routes used in the work involved condensation of 1-benzyl-4-piperidone with an appropriately substituted propionamide promoted by a strong base (lithium diisopropylamide, LDI), with subsequent alkylation of anilino nitrogen (if necessary) and replacement of *N*-benzyl by the 2-arylethyl substituent. Direct use of the *N*-arylethyl-4-piperidone was also made.

11.6. (1,2-DIPHENYLETHYL)PIPERAZINES AND OTHER PIPERAZINES

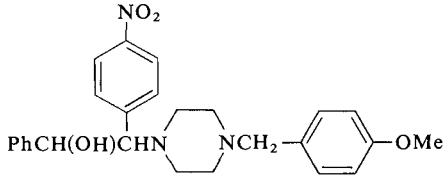
The starting point for this group is the tertiary amine **31**, the levo isomer of which was found to possess weak morphinelike activity.[51] When a piperazino unit replaces the NMe_2 group of **31** potency rises sharply, especially when cycloalkyl groups are attached to the terminal nitrogen as in **32a** (ED_{50} mg/kg RTF, heat sc 3.09, morphine 2.39, **31** 46.6).[52] Most of the activity of **32a** is due to the *S*(+) isomer. When a *m*-OH is present in the C-2 aromatic group, a compound over 20 times more potent than morphine results activity falls to the level of **32a** after *O*-methylation while *o*- and *p*-placed hydroxyls depress activity. The *S*(+) form of **32b** is again the more active antipode but the *R*(−) isomer retains significant potency (ED_{50} as before except tail-pressure test: *S*, 0.027; *R*, 0.35; morphine, 1.17).[53] The analog of **32b** with a terminal *N*-3,3-dimethylallyl substituent (as present in pentazocine) provided another *S*(+) antipode of high potency (ED_{50} 0.031 mg/kg) while its *R*(−) form (ED_{50} 2.99 mg/kg) along with that of **32b** were capable of reversing the analgesic effects of morphine, and were considered to have some clinical potential on this account. Derivatives with hydroxyl substituents at C-2 were mostly weak or inactive as analgesics, the most potent being those with benzyl substituents attached to terminal nitrogen, for example, **33** (ED_{50} 8.1 mg/kg, as before). A synthesis of **32a**, typical of the series, proceeds via the oxazolidine derived from benzaldehyde and diethanolamine (see formulae).

$PhCH_2CH(Ph)NMe_2$

31



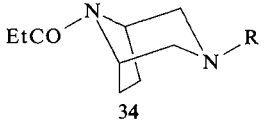
32 (a) R = H;
(b) R = OH



33

The analgesics appear to relate to morphine in respect of phenolic influences on their activity but it is difficult to formulate a more specific relationship.

The piperazine unit is a common feature of the analgesics **32** and a series **34** developed by an Italian group. These are piperazines linked across α-carbons by a bimethylene bridge.[54] Nitrogen closest to the bridge is amidated while the terminal (basic) atom carries a variety of substituents. Some of the compounds, notably those with *N*-phenalkyl substituents of proven efficacy in other analgesic classes, had activities superior to that of morphine (see data). The assay data refer to a test specifically designed to detect anti-inflammatory drugs and the characterization of the piperazines as narcotic analgesics was not established, although the more potent produced excitation and Straub tails in mice.

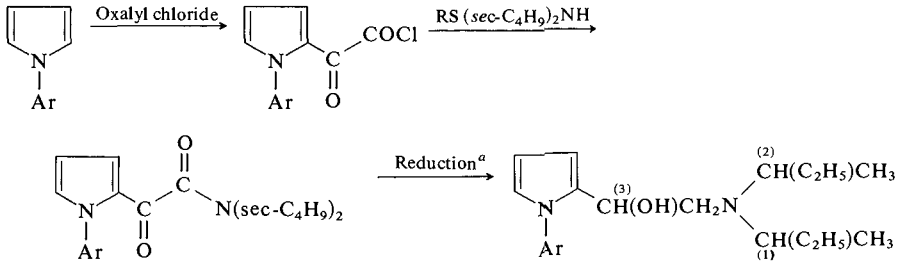


34

R	ip dose (mg/kg)	% Increase in pain threshold
$PhCH{=}CHCH_2$	0.1	46.5
$PhCO(CH_2)_2$	0.1	11
Morphine HCl	1.5	31.5

11.7 VIMINOL

This analgesic is a mixture of diastereoisomers obtained by the reaction sequence shown preceding formula **35**.[55,56] The molecule has three asymmetric centers and viminol is a mixture of the five detailed; individual isomers are accessible by using *R* or *S* sec-butylamine in the synthesis and resolving the secondary alcohol formed at the end of the sequence. The configuration of the C-3 center was established by X-ray crystallography.[57] In the RTF test, isomer R_2 was the most potent (ED_{50} 0.9 mg/kg ip, morphine 5.0 mg/kg). Other isomers had ED_{50} values greater than 20 mg/kg while the mixture itself was about one third as effective as morphine. The superiority of isomer R_2 over morphine as an analgesic was confirmed by tail-clip and HP assays in mice. Only the R_2 isomer produced physical dependence in mice (the PDC for viminol was very low), and naloxone caused comparable jumping responses in mice administered with morphine or isomer R_2 over a two-day period. Remarkably, isomer S_2 also antagonized R_2 (and morphine) as judged by the jumping response in tolerant mice; it also partially reduced the analgesic



35

Isomer	Configuration (1)	(2)	(3)
R_1	*R*	*R*	*R*
R_2	*R*	*R*	*S*
S_1	*S*	*S*	*R*
S_2	*S*	*S*	*S*
meso	*RS*	*RS*	*RS*

Ar = *o*-Cl.C_6H_4 (asymmetric centers in parentheses)

[a] Using sodium bis-(methoxyethoxy)aluminum hydride.

effectiveness of R_2 in the tail-clip test but strangely not that of morphine. Viminol thus contains both an agonist and antagonist component, a combination that leads to the mixture having moderate analgesic potency coupled with a low order of physical dependence capacity. May[58] found that none of the isomers had dependence capacity in morphine-dependent monkeys. There is evidence that the blocking mechanism of the S_2 isomer differs from that of competitive antagonists such as nalorphine since this isomer, unlike the R_2 species, does not bind to synaptosomal binding sites.[59] There are several reports of the clinical promise of viminol as an oral analgesic of codeinelike potency.[58]

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12

Antagonists, Dualists, and Kappa Agonists

12.1. INTRODUCTION

The aim of this chapter is to bring together data on opioid ligands that (1) antagonize the actions of morphine and its surrogates, (2) possess both agonist and antagonist properties, and (3) possess the unique pharmacological profile of the so-called kappa (κ) agonists. The majority of these compounds fall within the morphine, morphinan, or benzomorphan groups of opioid ligands (Chapters 2, 3, and 4). The topic of narcotic antagonists and dualists has been extensively reviewed up to 1976[1] and only a resumé of the earlier work is presented here.

Original reports of the arousal properties of *N*-allylnorcodeine in dogs narcotized with morphine[2] went unnoticed until the synthesis and pharmacological properties of *N*-allylnormorphine (**1** nalorphine, Lethidrone) were announced.[3] The dramatic effects of nalorphine are worth recounting. Dogs remained alert and showed no signs of depression after sc doses of 10–20 mg/kg of nalorphine, and morphine (5–10 mg/kg) given 20–60 min later failed to produce its usual effects (vomiting, drowsiness, and muscular uncoordination). Dogs intoxicated with morphine were promptly aroused by a subsequent injection of nalorphine and regained their normal behavior completely after about 15 min. Similar results were obtained with cats. Nalorphine produced no Straub tail effects in mice and was effective in counteracting morphine poisoning in the same species. After the prior administration of nalorphine, morphine failed to depress the respiration of rabbits even when given iv in large doses (20 mg/kg); the respiration rate, markedly depressed when morphine was given first, was rapidly restored to normal after subsequent injection of nalorphine. In mice, the threshold for pain perception in abdominal skin after electric shock was not raised significantly by nalorphine. Morphine was ineffective in raising the pain threshold in mice previously treated with nalorphine; when given first, its analgesic effect was rapidly abolished after administration of nalorphine.

The remarkable antagonism of the depressant actions of morphine upon pain perception and respiration observed by Unna is now well known and has been confirmed in many other animal species and in humans.[2] Nalorphine antagonizes a wide spectrum of morphine effects, including excitation of cats, antidiuresis in rats, the hyperglycemic response in rabbits, and intestinal and biliary spasm in humans.[4] Until superseded by more potent agents (e.g., naloxone and naltrexone), nalorphine was the agent of choice for treating morphine poisoning and for counteracting the depression of neonates' respiration caused by opioids given to the mother.[5] It also found use in the diagnosis of addiction to morphine-type drugs as a result of its ability to precipitate an acute abstinence syndrome; in the so-called allyl test for the addiction liability of drugs, use of nalorphine enables assessment to be made after relatively short withdrawal periods.[6]

Most attempts to demonstrate the antinociceptive properties of nalorphine in animals failed (see also below). In the mid-1950s, however, two reports were made of its relieving postoperative pain in man;[7,8] it thus proved to be the first example of an opioid drug with both agonist and antagonist properties dependent on the circumstances of its use. The discovery of its near morphine-like potency was made accidentally during studies of morphine–nalorphine mixtures aimed at achieving analgesia with minimal respiratory depression. Many such mixed-acting agents (dualists) are now known, and it is presently usual practice to screen novel agents for activity in both pharmacological senses. One attraction of a dualist is the likelihood of its having a low physical dependence capacity (PDC). This is essentially true of nalorphine,[9] but the drug cannot be used clinically because of its undesirable psychotomimetic side effects (hallucinations and feelings of unreality), which, unfortunately, are characteristic of many mixed-acting agents. Nevertheless, the approach has led profitably to the introduction of several novel analgesics, notably pentazocine, buprenorphine, butorphanol, and nalbuphine, as will be described.

In addition to its effects on morphine, nalorphine also antagonizes other potent analgesics, encompassing members of the morphine, morphinan, 8-benzomorphan, 4-phenylpiperidine, 4-anilopiperidine, and diphenylpropylamine groups.[2,10] Indeed, the antagonism of analgesia by nalorphine and its congeners is accepted as one of the criteria by which morphinelike analgesics may be differentiated from other CNS depressants. The wide range of compounds susceptible to its action has encouraged the view of competitive nalorphine–agonist interactions at a single receptor species, a concept supported by quantitative studies utilizing Schild's pA_2 value (the negative logarithm of the dose of antagonist that reduces the effect of a double dose of agonist to that of a single dose)[11] and the Gaddum drug ratio (molar ratio of agonist and antagonist producing a 50% analgesic effect)[12]; both parameters were constant for a variety of nalorphine-analgesic combinations, as is required for the competitive condition (see also Chapter 13).

Table 12.1. Writhing Test Analgesia and Clinical Potency[a]

Compound	ED_{50} values (mg/kg) Mouse	Rat	Analgesic potency in man
Naloxone	>82	>41	0
Levallorphan	26	1.7	0[b]
Pentazocine	3.8	0.95	0.2
Nalorphine	0.48	0.20	0.9
Cyclazocine	0.028	0.012	30
Cyclorphan	0.019	0.018	30
Morphine	0.59	0.20	1.0

[a] From Ref. 13; see also Ref. 1 for similar data.
[b] In another clinical report, levallorphan (8 mg/70 kg) approached but was not equivalent to a 10 mg/70 kg dose of morphine.[55]

Since the mid-1950s many narcotic antagonists—often with marked agonist properties and of potential value as clinical analgesics—have been discovered. The pharmacological spectrum of such agents may now be established by a variety of *in vivo* and *in vitro* tests. Dualists fail to display antinociceptive action in many animal (particularly rodent) test procedures as commonly applied, but effectively reduce abdominal constrictions in rodents induced by various chemical irritants (e.g., phenylquinone, acetylcholine, and bradykinin) in so-called writhing (WR) tests.[13] These tests have been criticized on the grounds of lack of specificity (drugs as diverse as ephedrine, pilocarpine, and meprobamate also block the response), sensitivity to experimental conditions, and animal welfare.[14] Reasonable correlations between writhing prevention ED_{50} values and analgesic properties in man have been found for a series of morphine antagonists (Table 12.1), and the procedure is still widely used. Apparent pA_2 values of naloxone in the writhing assay fell in the range 6.98 ± 0.06 for the agonists morphine, levorphanol, and methadone, and 6.32 ± 0.11 for the narcotic-antagonist analgesics pentazocine, nalorphine, and cyclazocine, and it is claimed that the two groups of analgesics may be differentiated on this basis.[126] It is claimed that the usually ineffective physical nociceptive tests detect dualists if modified (1) by testing reaction times within a few minutes of administration,[15] or (2) by use of low stimulus intensities[16]; thus, nalorphine behaved as an agonist in the hot-plate test run at 50° (ED_{50}, 2.5 mg/kg; morphine, 0.8 mg/kg) but not at 55°. Electrically induced pain applied to the tail of a mouse with a vocal response (the Nilsen test) is also believed capable of detecting agents of mixed action but correlations with clinical potencies are sometimes poor.[1,17]

The guinea pig ileum (GPI) test (inhibition of the contraction of electrically stimulated longitudinal muscle by opioid agonsts, p. 3) is a most useful *in vitro* procedure for dualists since it may be adapted to assess both their agonist and antagonist properties. The agonist activity is measured by

Table 12.2. Kinetic Parameters of Some Agonists and Antagonists in the GPI Assay[a]

Drug	ID_{50} (nM)	K_e(nM)	P_a
Morphine	68.2	87.5	0.8
Codeine	10,300	8840	1.2
Pentazocine	250	150	1.7
Cyclazocine	3.60	1.48	2.4
Levallorphan	4.28	1.12	3.8
Diprenorphine	0.68	0.13	5.2
Nalorphine	24.3	4.7	5.4
Naloxone	68,000	1.22	56,000

[a] From Ref. 18.

finding the concentration of drug that causes 50% depression of the twitch induced by coaxial stimulation (ID_{50} value) and the antagonist activity from the equilibrium constant (K_e). The latter is obtained from the expression $K_e = a/\mathrm{DR} - 1$, where a is the molar concentration of antagonist and DR is the ratio of the concentration of agonist (e.g., morphine) required to depress the twitch to the same extent in the presence or absence of a given concentration of antagonist (the smaller K_e, the more potent the antagonist). The ratio ID_{50}: $K_e(P_a)$ is another useful parameter; its value is found to be less than 2 for pure agonists, greater than 2 for dualists, and much greater than 2 for pure antagonists; that is, the larger P_a, the greater the antagonist component of activity. Some typical data are shown (Table 12.2). There is a good correlation between the ID_{50} values of many dualists and their clinical potency.[18] Mouse deferens muscle was found to be a more suitable preparation for assessing the antagonist potencies of compounds that are also potent agonists such as cyclorphan, because of flatter dose-response curves.[19] The cat nictitating membrane, although activated by an adrenergic rather than cholinergic mechanism, has also been used to assess agonist-antagonist properties (p. 416).

Routine binding assays (p. 333) measure the affinity of opioid ligands of all types but may be modified to discriminate between agonists and antagonists. Thus, sodium ions have pronounced moderate and minor influences, respectively, on the binding affinities of agonists, partial agonists, and antagonists. Other criteria are also available, for example, decrease of agonist binding in the presence of guanine nucleotides.[20,142]

The antagonist potency of an opioid ligand is only rarely determined as a pA_2 parameter; more commonly the dose (e.g. AD_{50}) that abolishes the antinociceptive action of a fixed amount of an agonist such as morphine or pethidine is measured and compared with that of a standard antagonist. In Janssen's procedure,[21] fentanyl (the agonist) is injected sc into rats at the

very high standard dose of 0.63 mg/kg, which results in pronounced respiratory depression, loss of righting reflex, lead-pipe rigidity, and analgesia (as judged by the tail-withdrawal test). The test compound is then given iv and the dose needed to reverse the effects of fentanyl is determined. Prevention of oxymorphone-induced Straub tails in mice (OMST) is also employed as a criterion of antagonist potency.[22]

Another test for antagonists lies in their ability to prevent the depressant effect of morphine on basal and PGE_1-stimulated cAMP levels in neuroblastoma × glioma hybrid cells.[23] Thus, adenylate cyclase activity (responsible for cAMP conversion from ATP) was unaffected by morphine ($2 \times 10^{-5}\ M$) in the presence of levo-naloxone ($5 \times 10^{-7}\ M$), but was not protected from inhibition by dextro-naloxone.[37] Discussion of the use of these cell lines in receptor studies is given elsewhere (p. 489).

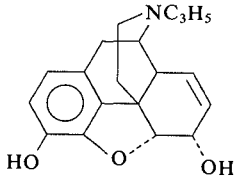
12.2. STRUCTURAL CLASSES OF ANTAGONIST

Structure–activity relationships of the many antagonists and dualists developed since the revival of interest in nalorphine are dominated by (1) the nature of the supporting skeleton, (2) the influence of the *N*-substituent on the pharmacological profile, and (3) the concept of a "pure antagonist."

Apart from a few notable exceptions (see later), all known narcotic antagonists are based on the morphine, morphinan, or benzomorphan polycyclic systems, that is, on three closely related groups of opioid ligands that share many structure–activity relationships (see Chapters 2, 3, and 4). Details of antagonist representatives of each group will now be given, chiefly confined to *N*-allyl and *N*-cyclopropylmethyl (CPM) derivatives, with minimal chemical details.

12.3. MORPHINE DERIVATIVES

Without exception, *N*-allyl analogs of ring-modified normorphines behave as opioid antagonists (see **1**), and usually the more potent the *N*-methyl parent as agonist, the more potent its *N*-allyl counterpart as antagonist. This is particularly true for 6,14-endoethanotetrahydrothebaine derivatives (p. 69) in which *N*-methyl compounds of notably high analgesic activities yield very potent antagonists when the basic center carries an allyl or CPM substituent. Thus, cyprenorphine **2** (R = Me; pA_2, 8.2) is several hundred times as potent an antagonist as nalorphine (pA_2, 5.6),[25] while diprenorphine (**2**, R = Me with reduced 6,14 bridge) ranked above naloxone, naltrexone, and oxilorphan (all potent agents, see later) in antagonist potency assessed by the GPI test.[18] Diprenorphine also behaved as a potent agonist in the GPI (100 × morphine);



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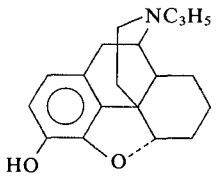

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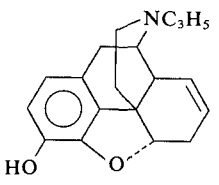

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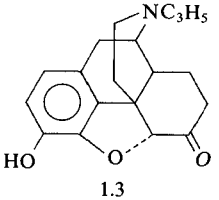

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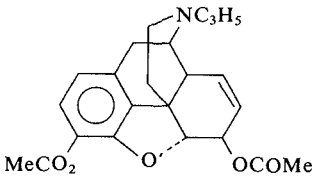
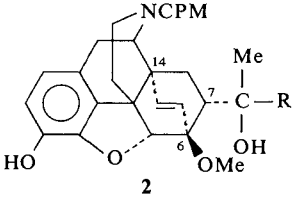


0.5 (Heroin analog)

(Activities as antagonists, nalorphine = 1)[24]

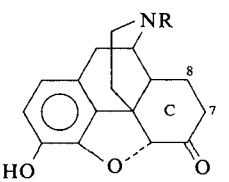
it is marketed as Revivon to reverse the immobilization of game animals and large domestic animals brought about by etorphine (Immobilon).[26] An unusual feature of these compounds is the influence of the R substituent of the C-7 *t*-carbinol group upon the pharmacological spectrum of activity. Potent antagonists-feeble agonists are only seen when R = methyl; when larger alkyl groups are present the compounds behave primarily as analgesics. For example, the *N*-allyl analog of etorphine (**2**, *N*-allyl, R = Pr) retains much of the agonist activity of the parent, while the *N*-allyl analog of **2** with R = *n*-pentyl is a potent analgesic, not an antagonist.[27] Similarly, the antagonist potency of diprenorphine is much reduced when one of the C-7 carbinol methyls is replaced by a larger group; the Pr analog, for example, is more than 200 times as active as morphine in rats but only one-sixth as potent as nalorphine as an antagonist. Corresponding figures for the tertiary butyl derivative (**2**, bimethylene bridge, R = *t*-Bu) named buprenorphine, are 75 × morphine (as agonist) and 4 × nalorpine (as antagonist).[26] Nalorphine and buprenorphine were equipotent as antagonists of phenazocine in rats.[28] Buprenorphine failed to produce physical dependence after chronic administration to monkeys and mice and showed a longer duration of action than morphine,[29] facts that have led to its introduction as a clinical agent (Temgesic).[5] It is used as an



2

injection (dose 0.3-0.6 mg im every 6-8 h) or as sublingual tablets. Care must be taken in administering analgesics like buprenorphine (and butorphanol, see later) that have a significant antagonist component to their action to patients who have recently been receiving another class of analgesic since pain may be aggravated rather than alleviated under such circumstances. Buprenorphine is the most lipophilic of the thebaine-derived analgesics; its partitioning between heptane and phosphate buffer, pH 7.4, gave the coefficient 60, corresponding values for etorphine being 1.4 and morphine 0.0001.[30] Sodium had little influence on the kinetics of reaction between buprenorphine and opioid receptors, evidence that the drug behaves predominantly as an antagonist in binding assays.[31] The pharmacokinetics of buprenorphine[156] and its breakdown under autoclaving conditions have been reported.[157] Irreversible ligands based on *endo*-ethenotetrahydrooripavines with *N*-allyl, propyl, or CPM substituents[127] are discussed in Chapter 13 (p. 453).

Kotick's group have studied a number of dihydromorphinone derivatives (**3**) with *N*-CPM and *N*-CBM substituents.[32,33] The parent compounds have dual actions, the CPM member being the more potent antagonist and the CBM



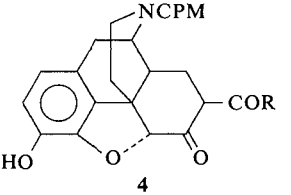
3

R	Ring C substituent	Analgesic ED_{50} [a]	Antagonist ED_{50} [b]
CPM	—	4.12	0.58
CBM	—	0.21	5.01
CPM	8β-Et	20.8	0.66
CBM	8β-Me	1.72	4.74
CPM	7,7-diMe	Inactive at 28	1.2
CBM	7,7-diMe	2.2	>24

[a] MWR mg/kg sc, dihydromorphinone = 0.25.
[b] RTF vs. morphine, nalorphine = 2.47.

derivative the more potent agonist. The same properties are seen in corresponding ring *C*-alkylated congeners; alkyl substituents generally diminish potency but 8-Et raises antagonist activity in some cases. The 8-alkyl derivatives were made by treating codeinone with a lithium dialkylcopper reagent, while the 7,7-dimethyl analogs were derived from the corresponding bis(hydroxymethyl) derivative, product of an aldol condensation between dihydrocodeinone and formaldehyde catalyzed by calcium hydroxide. 7-Alkanoyl derivatives of hydromorphone with an *N*-CPM substituent had mixed actions of variable

agonist-antagonist potency ratios (see, e.g. **4**).[34] They were made by alkylation of the pyrrolidine enamine of the dihydrocodeinone.

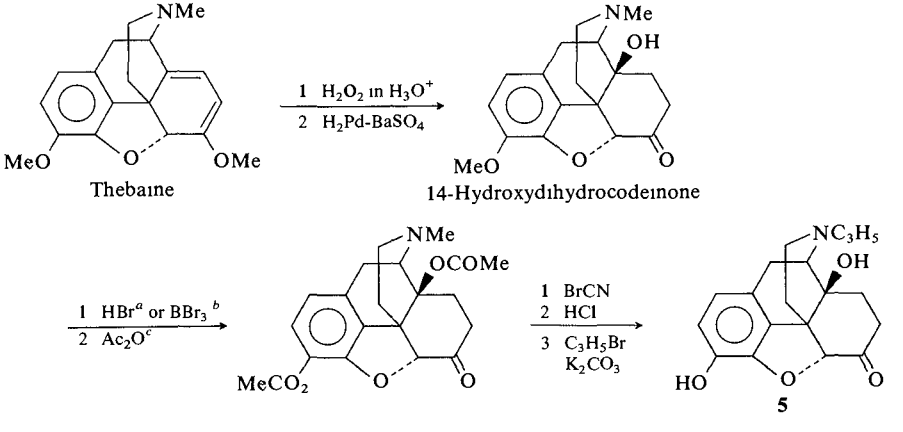


4

R	Analgesic ED_{50} [a]	Antagonist ED_{50} [a]
C_5H_{11}	0 29	22
C_6H_{13}	0 4	Inactive
C_3H_7	10 0	0 81
Et	Inactive	0 52

[a] As in **3**, except that dihydromorphinone = 0 08 as agonist

Study of 14-hydroxymorphine derivatives deserves special note because it led to the concept of the existence of "pure" antagonists, that is, antagonists entirely devoid of agonist activity. The *N*-allyl analog of noroxymorphone (**5**), made as shown in Scheme 12.1 and termed naloxone (Narcan), proved to be a potent antagonist in animal tests (up to 20 times nalorphine depending on the test employed—pA_2, 0.01; nalorphine, 6.7) and to lack antinociceptive actions in MHP, RTF, and phenylquinone writhing tests (it antagonized



[a] Ref 35, [b] Ref 37, [c] Ref 36

Scheme 12 1 (See Ref 128 for suggested variations of the reaction sequence, and Ref. 155 for application of vinyl chloroformate to the *N*-demethylation step)

mixed-acting agents in the latter tests).[38] Naloxone had only a negligible agonist component in the GPI and MVD assay procedures but was highly active as an antagonist.[18,39] It also had zero activity as an inhibitor of adenylate cyclase in neuroblastoma × glioma hybrid cells.[134] The most that has been reported to refute the mid-1960 view of naloxone being a "pure" antagonist are a few reports of its showing antinociceptive actions in tests run at low stimulus intensities.[16] In humans the drug is inactive as an analgesic[40]; it does not induce respiratory depression and is more effective than nalorphine or levallorphan in reversing narcotic-induced effects of this kind.[41] Neither psychotomimetic effects nor the mild abstinence syndrome that follows chronic administration of nalorphine or cyclazocine was seen after naloxone.[42] It is used clinically as a specific narcotic antagonist, chiefly to reverse respiratory depression in cases of opioid overdosage and obstetrics and to produce narcotic blockade for the maintenance of addicts during narcotic withdrawal.[5] The 7,8-di-tritiated derivative of naloxone (**6**), of high specific radioactivity, is commonly used in binding assays as the displaceable ligand.[43] A 7,8,19,20-tritiated analog of naloxone (*N*-$CH_2CT{=}CHT$) of even higher specific activity has also been described.[129]

14-Hydroxynormorphinone $\xrightarrow[2.\ C_3H_5Br\text{-}NaHCO_3]{1.\ ^3H,\ Pd\text{-}C}$ 7,8-[^{3}H]naloxone specific activity 40 Ci/mmol (≡ 97% pure) after tlc or partition chromatography

6

(+)-Naloxone, prepared in eight steps from (+)-7-bromodihydrocodeinone dimethyl ketal (26% overall yield), proved virtually inactive in three test systems (binding, GPI, and neuroblastoma × glioma hybrid cell adenylate cyclase assays) and can thus be used to establish the stereospecific binding of the natural levo isomer.[37] Both antipodes of naloxone are available from a total synthesis of morphinans starting from optically active 1-benzylisoquinolines.[128]

Measurements of the potency of naloxone (K_e or pA_2) versus a variety of agonists has been employed to provide evidence of the receptor subsites at which the latter act (p. 451).[18,126,153] Dualists such as nalorphine, pentazocine, and cyclazocine require a greater amount of naloxone for reversal than do pure agonists such as morphine, levorphanol, and methadone; hence, the two types are believed to induce agonism at different sites. These are taken to be non-μ for the agents with dual effects and are possibly κ-receptors in view of the fact that the pA_2 of naloxone versus ketazocine (7.58) (a κ-agonist, p. 434) is also distinctly lower than that against morphine (8.82)[148]; another study confirms this difference.[149] Further evidence on this point derives from the observation that β-FNA, a selective μ-blocker fails to reverse the agonist actions of nalorphine and ethylketazocine in the GPI.[152] Data provided by Sterling-Winthrop[154] emphasize the kinship between nalorphine and

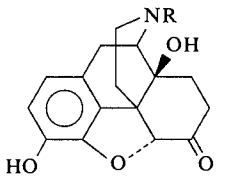
κ-agonists. Speculations on the modes of action of agonists, both pure and of mixed action, are presented in Chapter 13.

Summary of Effects of Some Opioids in Isolated Tissue Preparations[a]

Agonist	Guinea pig ileum		Rabbit vas deferens[b]	
	IC_{50}	K_e vs naloxone	IC_{50}	K_e vs naloxone
Normorphine	212	3 7	>100,000	—
Morphine	171	2 0	—	42 2
Ketazocine	6 3	13 1	16 8	18 6
Ethylketazocine	2 2	18 5	18 5	18 6
U50488[c]	12	—	196	36 6
Nalorphine	10	19.3	1 27	20 2
Nalbuphine	20	7 0	Antagonist	—
Butorphanol	4 2	5.7	Antagonist	—

[a] All IC_{50} values are expressed in n*M*
[b] Considered to possess κ-receptor only (ref 111)
[c] See p 438

N-R Variants of naloxone include the 3,3-dimethylallyl (**7a**, nalmexone), CPM (**7b**, naltrexone) and cyclobutylmethyl (**7c,d**) derivatives.[1,44] Of these, only naltrexone may be rated a "pure" antagonist; it is highly potent (pA_2, 7 76; naloxone, 7.06 vs. morphine) and shares the clinical applications of naloxone where advantage is taken of its longer duration of action.[125] See ref. 158 for pharmacokinetic studies. The dihydro analog of the *N*-CBM derivative with a 6-α-OH is *nalbuphine* (**7d** Nubain, also a dualist) and is in clinical use in the United Kingdom and United States. It is effective and has the same potency as morphine, and its clinical advantages appear to be low incidence of nausea and vomiting, a ceiling effect on respiration (depression reaches a level beyond which additional depression does not readily occur), low frequency of psychotomimetic reactions, and an abuse potential similar to that of pentazocine.[46]

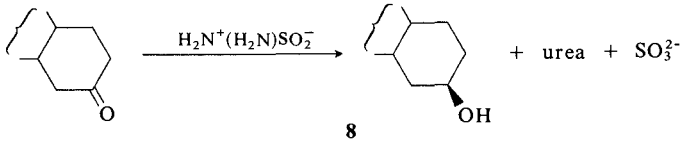


7

	R	Activity[a]
a	$CH_2C{=}CMe_2$	0 5 × nalorphine 0 3 × morphine
b	CPM	39 × nalorphine 2–3 × naloxone
c	CBM	5 × nalorphine 1 × morphine
d	CBM(6-α-OH)	0.25-0 5 × nalorphine 1 × morphine in man[46]

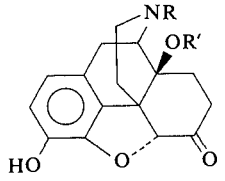
[a] Comparisons with morphine relate to agonist activity, others to antagonist properties

Replacement of 6-keto by methylene is claimed to enhance the oral potency of naloxone and naltrexone (the *N*-CPM analog, Nalmefene, is under clinical trial and is detectable by radioimmunoassay),[47,143] while its reduction to a secondary alcohol depresses activity.[48] A pure antagonist results when OH is β-and a dualist if OH is α-oriented (as in morphine); such alcohols have been identified among the metabolic products of the 6-keto antagonists.[49] Most chemical reducing agents yield the α-isomer exclusively,[50] but the less usual reductant thiourea dioxide (from thiourea and H_2O_2, see **8**) gave 6-β-OH derivatives as sole product.[48] It is notable that the dual-acting agent butorphanol is a 6-α-OH derivative.[51]



8

The presence of an acidic hydrogen in the 14-oxy substituent of naloxone and naltrexone has no special significance in regard to the pharmacological profiles of these drugs since corresponding *O*-methyl and *O*-ethyl ethers (**9**) behave like their parents and have similar or greater potencies as antagonists.[39] There is evidence (from the ratios of activities versus metenkephalin and normorphine, MVD test) that the CPM derivatives have the greater affinity for μ-receptors. The key step in the synthetic sequence was the alkylation of 14-hydroxycodeinone, achieved by treating the sodium salt in DMF with a dialkyl sulfate.



9

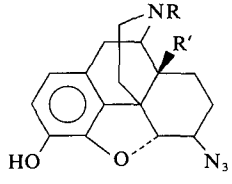
R	R'	Concentration required to give a dose ratio of 2 vs. normorphine (MVD) ng/ml
C_3H_5	Me	0.46
C_3H_5	Et	0.33
CPM	Me	0.26
CPM	Et	0.07
Naloxone		0.51
Naltrexone		0.17

6-Amino analogs of naloxone and naltrexone are, like the 6-OH derivatives, less potent antagonists than the parents.[45] They are made by reductive amination of the ketones with $NaCNBH_3$ when 2:1 α/β mixtures result. The 6-β-NH_2 analog of **7b**, termed naltrexamine, is the more potent of the two epimers. It forms the basis of several affinity-site directed ligands as described in Chapters 2 and 13, and of selective μ- and κ-antagonists that involve two naltrexamine units linked by "spanner" groups (p. 67).

Hydrazone derivatives of naloxone and naltrexone produce a remarkably long blockade of opioid receptors as judged by binding and antinociceptive tests[52] (oxymorphazone, the *N*-methyl analog, produced prolonged analgesia

in rats).[130] However, no change in the LD_{50} value of morpine was found after naloxazone treatment. Further work suggests that the hydrazones act via corresponding azines (dimers linked by $=N-N=$) which are 20-40-fold more potent blocking agents than related hydrazones. Lethality of opioids is largely linked to their respiratory effects so it is highly significant, in terms of separate receptor sites for mediation of analgesia and respiratory depression, that the azine of naloxone has no effect on morphine's respiratory depressant action.[53] ^{13}C-nmr evidence shows the hydrazones to be 4:1 mixtures of *anti-syn* isomers.[131] Other 14-substituted analogs or morphine are discussed later (p. 429).

6β-Azido analogs of dihydronalorphine and its congeners have been examined by Knoll *et al.* (cf. p. 39).[144] All the compounds **9a** proved potent antagonists versus morphine in the rat (HP) with COAM the most effective (≡naloxone after sc and four times as potent after central administration).



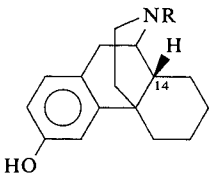
9a

	R	R'	MWR ED_{50} (mg/kg) (morphine 0.69)
NAM	C_3H_5	H	17.5
NOAM	C_3H_5	OH	inactive
CAM	CPM	H	0.51
COAM	CPM	OH	inactive

Agonist properties were recorded for CAM (WR, HP, and TF) and NAM (WR, HP) but not for the 14-OH analogs. All except NOAM were more potent agonists than morphine in the GPI test and were feeble antagonists, even the 14-OH derivatives. On the cat nictitating membrane agonist rankings were CAM > morphine > COAM = naloxone, and antagonist, COAM > CAM > naloxone. Differing mechanisms of humoral transmission in the smooth muscle preparations were advanced as the reason for CAM being a potent antagonist of morphine in cat muscle (adrenergic)[145] but lacking such properties in the GPI/MVD (cholinergic). A two-receptor theory was developed in which type A (cholinergic) are stimulated by CAM, leading to behavioral disturbances and some antinociceptive responses, and type B (adrenergic) are blocked, leading to reversal of analgesic, antitussive, cataleptic, and respiratory depressant effects of morphine.

12.4. MORPHINANS

Not surprisingly, *levallorphan* (**10a**, Lorfan), related to levorphanol as nalorphine is to morphine, is also a narcotic antagonist while its dextro antipode

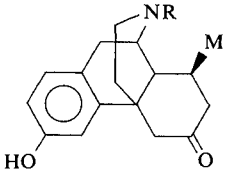


10 (Levo isomers)

R	AD_{50} (mg/kg)[a]	ED_{50} (mg/kg)[b]
a C_3H_5	0 39	0 29
b CPM	0 25	0 036
c $CH_2CH{=}CMe_2$	Inactive	0 3
d $CH_2C{\equiv}CH$	see text	

[a] Antagonism of morphine, MTF
[b] Analgesia MWR

(readily available synthetically) is devoid of such properties.[54] Levallorphan is similar to nalorphine in action and clinical use, and judged more potent in counteracting respiratory depression.[5] The GPI test reveals both its agonist and antagonist actions, which exceed those of nalorphine (ID_{50} 4.28 (24.3), K_e 1.12 (4.47) in n*M*, nalorphine data in parentheses).[18] The compound is also active in the writhing test (rat) and as an analgesic in man (8 mg/70 kg approached but were not equivalent to a 10 mg/70 kg dose of morphine).[55] The *N*-CPM (**10b**, cyclorphan), dimethylallyl (**10c**) and propargyl (**10d**) analogs of levorphanol all have mixed actions, with cyclorphan the most potent both as agonist and antagonist[56,57] **10b** and **10d** were effective in relieving postoperative pain, with the former being more potent than morphine.[132] As in the dihydromorphinones, Kotick[58] has reported ring C-alkylated derivatives of 3-hydroxymorphinan-6-ones (derived from thebaine). Consistent superiority of *N*-CBM over *N*-CPM congeners as analgesics (and inferiority as antagonists) was seen, but ring alkyl influences upon activity were not well defined. Some examples are shown (**11**).



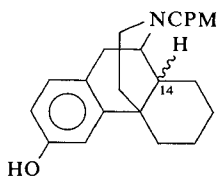
11

R	Analgesia ED_{50}	Antagonist ED_{50} (mg/kg)[a]
CPM	10 2 (2 4)	1 8 (14 4)
CBM	0 29 (0 35)	2 79 (>30)

Data for 7-Me analogs in parentheses

[a] Footnotes of **3** apply

Stereochemically, the fusion of rings B/C is *cis* in the morphinans (as in morphine) and *trans* in the isomeric isomorphinans. Formation of the B/C ring junction by Gate's procedure (Chapter 3, p. 133) gives a *trans* closure and thus entry to isomorphinan derivatives.[59] Isocyclorphan (**12**, 14α-H)



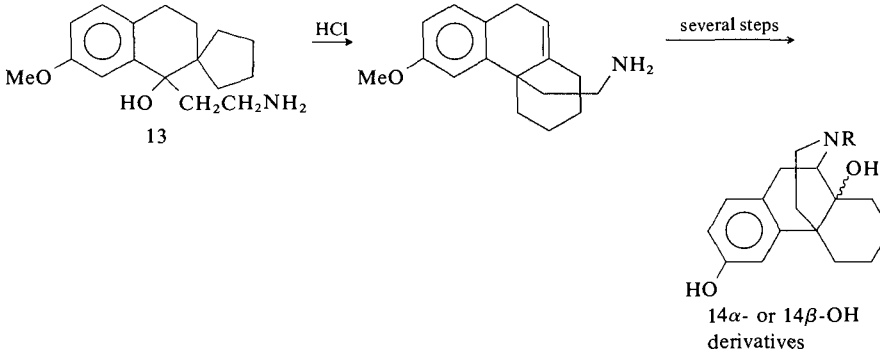
12 (Levo isomers)

	MWR[a]	OMST[b]	RTF[b]
Cyclorphan(14β-H)	0 031	0 32	0 032
Isocyclorphan(14α-H)[c]	8 7	0 67	0 057

[a] Analgesic ED_{50} mg/kg
[b] Antagonist ED_{50} mg/kg
[c] The iso derivative was the more potent in antagonizing pethidine in mice (14β 11 4 ×, 14α H 7 × nalorphine)[60]

retains the antagonist potency but loses most of the agonist activity of the 14β-H epimer; in contrast, the agonist activity of levorphanol (RTF test) is undiminished (even enhanced) after C-14 inversion.[59] Kotick's morphinan-6-one series provides some stereochemical comparisons of the same kind; the analgesic potencies of derivatives of type **11** invariably fall after B/C ring inversion while the antagonist activity is often enhanced.

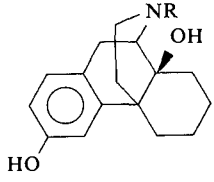
Belleau and a Bristol Laboratories group developed a novel morphinan synthesis which leads to 14-hydroxy derivatives.[62] The procedure rests upon rearrangement of the spirane **13** and may be adapted to provide either 14-β- or 14-α-hydroxy (iso) diastereoisomers (see **13** and p. 110). Out of this work



13

14α- or 14β-OH derivatives

were developed the compounds oxilorphan (**14a**), weakly active as an analgesic but as potent as naloxone as an antagonist, and butorphanol (**14b**), which displays both agonist and antagonist actions (see legend).[63]

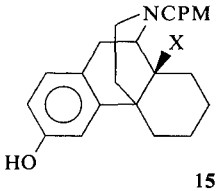


mg/kg	Analgesic ED_{50} MWR	Antagonist ED_{50} OMST	RTF
a) R = CPM	13	0.3	0.012
b) R = CBM	0.05	0.1	0.043
Naloxone	>80	0.09	0.01
Morphine	0.56	—	—

14 (Levo isomers)

Subsequent animal tests indicated that butorphanol is about 4 times more potent than morphine as an analgesic and equivalent to nalorphine as an antagonist. Clinical evaluation shows that butorphanol is also an effective analgesic in man (approximately 5 times more potent than morphine), and the tartrate is now marketed as an injection (Stadol). In animals its PDC is low (less than that of pentazocine) as it is in man, and this fact and its ceiling rather than dose-related effect on respiration (see p. 414) are recommendations for clinical use of the drug.[5,64]

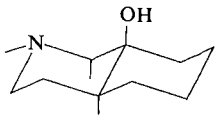
The importance of a β-oxygen at C-14 for analgesia in these morphinans may be linked to its hydrogen-bonding capacity (O > S in this respect) because the 14-β-thiol analog of oxilorphan, while still an antagonist, is far less potent an agonist (see **15** and p. 429).[61] When the hydroxy function moves to a



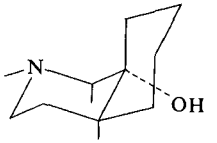
ED_{50} mg/kg (agonist or antagonist)
X = OH 8.7 (ag.), 0.03–0.3 (antag.)
X = SH > 40 (ag.), 0.9 (antag.)

15 (Racemic mixture)

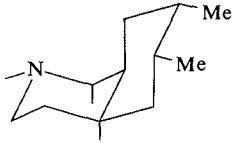
α-position as in the isomorphinan analog of butorphanol **16** a >100-fold drop in agonist and a much smaller fall (3×) in antagonist potency results. In addition to the change in 14-OH orientation, one may argue, carbons 6 and 7 of butorphanol (β-**16**) directly affect the agonist response and these centers cannot interact with the receptor when in the iso configuration. It is of interest that agonist properties are partially restored in the *cis*-6,7 dimethyl analog **17** in which the methyls extend into a region that overlaps C-7 of butorphanol.



β-**16** (14β-OH)



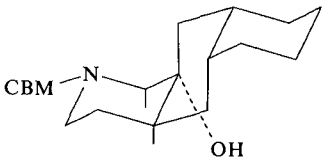
α-**16** (14α-OH, iso)



17
MWR ED_{50} 0.32 mg/kg
(±butorphanol, 0.06)

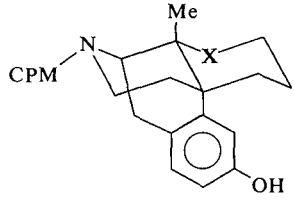
Partial formulas, NCBM in all cases.

Epimerization at C-14 and 6,7-dimethyl substitution had no pronounced effects on the antagonist potencies of oxilorphan and butorphanol. Similarly, *cis* fusion of an extra cyclohexane ring to C-6 and C-7 of isobutorphanol (**18**) (MWR ED_{50}, 23.0 mg/kg) is less detrimental to agonist activity than a *trans* attachment (MWR ED_{50}, 80 mg/kg).[61]



18 (Partial formula)

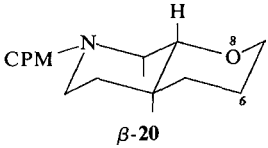
Incorporation of an 14-α-oxygen into the normal morphinan skeleton was achieved by synthesis of the tetrahydropyran (**19**, X = O) with a 14-β-methyl group.[61] This compound is a potent agonist (100 × the deoxy analog),



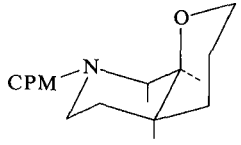
19

	ED_{50} mg/kg (agonist or antagonist)
X = O	0.19 (ag.), 0.6 (antag.)
X = CH_2	20.0 (ag.), 0.16 (antag.)
Oxilorphan	8.7 (ag.), 0.03-0.3 (antag.)

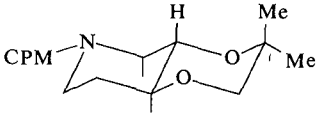
evidence that loss of analgesic potency of isobutorphanol is due principally to the change in ring C configuration. The high antagonist potency of **19** (X = CH_2) shows that a 14-β-OH substituent is not essential for activity of this kind. Similar patterns of activity were seen for 8-oxy analogs of cyclorphan (β-**20**) and isocyclorphan (α-**20**). The 6-oxa analog of cyclorphan had agonist-antagonist potencies close to those of the parent. The dual activities of the 8-oxa derivative (β-**20**) were little changed when an extra oxygen was inserted at position 6, while the corresponding 7,7-dimethyl derivative **21** proved an especially potent agonist-antagonist. In this series the 6-oxa derivative displayed the best oral profile and was free from undesirable properties associated with narcotic analgesics; canine delerium and psychotomimetic effects in man were strongly induced by cyclorphan but absent after the 6-oxa analog. Iso forms of 6,8-dioxamorphinans proved feeble analgesics, in accord with results already given.[61]



β-**20**
0.02 (ag.)
0.22–0.32 (antag.)



α-**20**
4.8 (ag.)
1.25 (antag.)

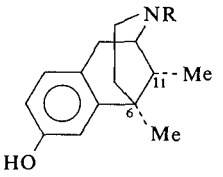


21
0.005 (ag.)
0.03-0.09 (antag.)

ED_{50} mg/kg values, agonist or antagonist in parentheses.

12.5. BENZOMORPHANS

The *N*-allyl analog of normetazocine (**22a** SKF-10047) was an early investigated member of the benzomorphan group and it was shown to antagonize phenazocine, morphine, and pethidine,[65] to be of superior potency to nalorphine versus pethidine, and to relieve postoperative pain (5 mg/kg = 10 mg/kg morphine).[66] Clinically, it caused psychic and other effects similar to those seen after nalorphine and is, in fact, the prototype sigma (σ) agonist of Martin's classification of opioid ligands (p. 353). The pA_2 value of naloxone versus the agonists morphine (8.82), ketazocine (7.58), and **22a** (7.74) is



		ID_{50} (nM)	K_e (nM)	P_a
a	SKF-10047 (R = C_3H_5)	—	—	—
b	Cyclazocine (R = CPM)	3.6	1.48	2.4
c	Pentazocine (R = $CH_2CH{=}CMe_2$)	250	150	1.7
	Nalorphine	24.3	4.7	5.4

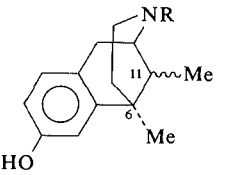
22

evidence that the agonist site of the *N*-allyl benzomorphan differs from that of morphine and may in fact be of the κ-variety.[148] In the mouse writhing test, the compound is half as potent an agonist as morphine.[67] Among the many *N*-R variants of **22** examined (see later), cyclazocine (**22b**) and pentazocine (**22c**) (both used as racemic mixtures) are especially notable. Both have agonist-antagonist properties with cyclazocine the more potent in either respect (see GPI data)[18] and provide effective relief in a variety of pain situations.[42,57] Cyclazocine is not used clinically because of its undesirable psychic effects. Psychic experiences are rarely reported after pentazocine and this drug (Fortral, Talwin) has achieved widespread use as a clinical analgesic in spite of its rather low potency.[5,68] Although pentazocine is exempt from international narcotics legislation, many cases of pentazocine-induced drug dependence have been reported and the need for caution in its use for the treatment of chronic pain has been emphasized.[133]

In mixed agonists-antagonists based on the benzomorphan nucleus, a number of 6,11-dimethyl *cis-trans* isomeric pair comparisons of activity have been made equivalent to those of morphinan-isomorphinan pairs. Antagonist activity is retained after inversion at C-11 from the α-(*cis*) norm, at similar, elevated or depressed levels (Table 12.3).[69] In all but one case c/t potency differences are small, the exception being the CBM derivative, which carries a substituent that usually enhances the analgesic rather than antagonist behavior as judged from studies of morphinans. The same configurational change disadvantages the more potent *N*-CPM and *N*-CBM derivatives as agonists but elevates the potencies of the weaker 3,3-dimethyl congeners. By and large the stereochemical SAR of benzomorphans and morphinans correlate in these respects. In all cases agonist-antagonist activity differences between antipodes are consistent, levo isomers of configuration related to morphine and levorphanol being by far the more potent (data for c/t cyclazocine are given in Table 12.3).

Benzomorphans with a β-OH at C-11 are analogous to naloxone and oxilorphan. Such derivatives of pentazocine and cyclazocine were more potent

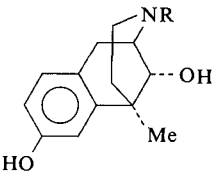
Table 12.3. Diastereoisomeric Benzomorphan Analgesic-Antagonists (Racemic Mixtures Unless Otherwise Stated)[a]



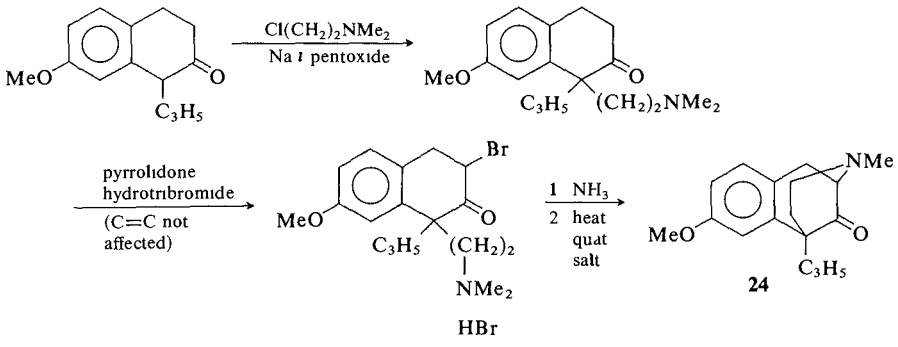
R	6/11 config.	Antagonist activity[b] AD_{50} (mg/kg)	Writhing test ED_{50} (mg/kg)
$CH_2CH{=}CMe_2$	c	3.9	3.1
	t	3.3	1.9
$CH_2CH{=}CMe_2$	c	10.9	4.1
(6-Et)	t	equivocal	0.32
CPM	c	0.019	0.1
	t	0.014	2
	(−)-c	0.006	0.005
	(−)-t	0.005	—
	(+)-c	2.5	inactive
	(+)-t	19	—
CBM	c	0.37	0.08
	t	0.06	0.61
$CH_2CH{=}CHCl$	c	0.018	peak activity at 3
	t	0.047	—
Nalorphine		0.13	0.54

[a] From Ref. 69.
[b] Versus pethidine in RTF test.

as antagonists of pethidine (3× and 10× respectively) than the parent compounds; in contrast α-11-OH in the derivatives **23** (R = allyl, dimethylallyl and CPM) had no influence on antagonist action.[70] Some potent analgesics with mixed action profiles have been derived from the 6-allyl-11-oxobenzomorphan **24** by selective reduction or methyl Grignard attack of the carbonyl function, processes that introduce a β-OH at C-11.[71] The *N*-CPM and CBM derivatives **25** were effective agonists in mice (writhing test) and antagonists

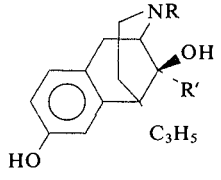


23



Scheme 12 2

of oxymorphone, with the CPM compound the more effective in both tests (cf. related oxilorphan-butorphanol comparisons). Reduction of *C*-allyl to propyl produced little potency change, but insertion of α-methyl at C-11 (**25**, R′ = Me) abolished the analgesic properties of the *N*-CPM derivative and enhanced its action as an antagonist. The 11-α-methyl *N*-CBM derivative was somewhat more potent both as agonist and antagonist than the parent. Synthesis of the intermediate **24** is outlined in Scheme 12.2.

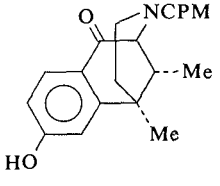


25

	Agonist	Antagonist ED_{50} [a]
R = CPM, R′ = H	0 08	0 5
R = CBM, R′ = H	0 3	1 8
Oxilorphan	13	0 19
Butorphanol	0 05	0 98

[a] mg/kg, see 12

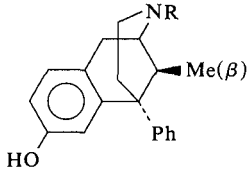
Oxidation of the benzylic carbon (C-1) of **22** (R = H) gave the 1-oxo derivative from which ketazocine (ketocyclazocine, **26a**) is derived.[72] This compound equals cyclazocine as an agonist but is a much feebler antagonist (**26a** and its *N*-allyl and *N*-propyl analogs were all about 100 times less potent than cyclazocine versus pethidine).[69] Its chief interest lies in its designation as the prototype kappa (κ) agonist, as discussed later (p. 434). 1-β-Hydroxy



26a

AD_{50} vs pethidine 7 2 mg/kg (0 02)
ED_{50} MWR 0 16 mg/kg (0 15)
Cyclazocine data in parentheses

analogs of **26a** are of low agonist-antagonist potency.[72,73] Levo isomers of the 6-phenyl benzomorphans **26b** all proved to be antagonists while analgesic properties were demonstrated for all except the *N*-propargyl member.[74] In the GPI test both the propargyl and allyl analogs behaved as pure antagonists, while the rest had agonist activity.[18] "Purity" of the *N*-propargyl derivative was also apparent in its zero activity as an inhibitor of adenylate cyclase activity in hybrid cells (p. 489).[134]



R = (i) $CH_2C{\equiv}CH$ (GPA 2663), (ii) $CH_2CH{=}CH_2$, (iii) $CH_2CH{=}CMe_2$, (iv) CPM, (v) CBM

26b

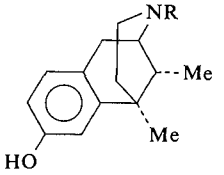
12.6. BASIC NITROGEN AND C-14 SUBSTITUENTS

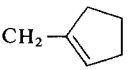
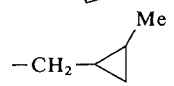
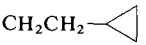
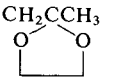
More detailed consideration will now be given to the influence of N- and C-14 (≡C-11 in benzomorphans) substituent structure upon the pharmacological profile of opoid ligands.

The first *N*-substituted series to be examined in any detail was that of normorphines from which it emerged that antagonist properties were associated with a 3-carbon (mostly linear) *N*-substituent.[24] In this series propyl and allyl were ranked equipotent versus morphine while small branched chain (isoPr, 2-methylallyl) analogs were also effective. The *N*-butyl congener was inactive (2-butene conferred some activity) and the pentyl and hexyl derivatives behaved as agonists (0.7 × morphine). With increased sophistication of pharmacological methods, it is now clear that the *N*-allyl and related groups may also evoke an agonist response.

It is of interest that two reports upon *N*-cyclopropylmethyl (CPM) derivatives appeared in the same edition of the *Journal of Medicinal Chemistry* (March, 1964).[60,75] Gates exploited the chemical analogy between vinyl and cyclopropyl groups (the latter more closely resemble the C=C double bond than the cyclobutyl ring)[76] by design of the potent antagonist cyclorphan **10** (R = CPM). However, many *N*-CPM derivatives also behave as agonists. A Sterling Winthrop group[75] greatly extended knowledge of *N*-R influence by study of a large series of α-metazocine analogs including the *N*-CPM derivative (Table 12.4). Antagonist activity was conferred by straight 3-carbon chains attached to nitrogen with *N*-propyl ranking above *N*-allyl (in view of this result it is strange that *N*-propyl analogs of opioids have been largely neglected). Variable results followed substitution of the chain—terminal dimethyl (No. 5 pentazocine) or dichloro (No. 6) groups depressed potency 80- to

Table 12.4. Antagonist Activities of Some *N*-Substituted Racemic *cis*-6,11-Dimethylbenzomorphan Derivatives[a]



No.	R	AD_{50} (mg/kg)[b]	No.	R	AD_{50} (mg/kg)
1.	Me	>10	17.	$CH_2c-C_6H_{12}$	14.58
2.	Pr	0.019	18.	$c-C_5H_{10}$	0.15
3.	$CH_2CH=CH_2$	0.047			
4.	$CH_2C\equiv CH$	0.078[c]	19.		2.7
5.	$CH_2CH=CMe_2$	3.9			
6.	$CH_2CH=CCl_2$	5.1			
7.	$CH_2CH=CHCl(c)$	0.018[c]	20.		0.17
8.	$CH_2CH=CHCl(t)$	0.039			
9.	$CH_2CMe=CH_2$	0.094			
10.	$CH_2CCl=CH_2$	4.2	21.		0.026
11.	$CH_2CH=CMeCl(Z)$	0.48			
12.	$CH_2CH=CMeCl(E)$	1.4	22.		0.092
13.	$CH_2CMe=CMe_2$	0.62			
14.	CPM	0.019	23.		0.07
15.	CBM	0.37			
16.	$CH_2c-C_5H_{10}$	0.28			

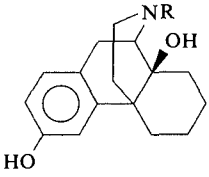
[a] From Ref. 75.
[b] Versus pethidine in RTF test.
[c] See ref. 159 for data on antipodal forms.

100-fold, while the derivatives with a single 3-chloro group were among the most active of the series (Nos. 7 and 8). The reasonable activity of the 2-methyl variant (No. 9, cf. the same analog of normorphine) contrasts with the poor performance of the 2-chloro derivative (No. 10). Dual 3-Me, 3-Cl substitution depressed activity at least 10-fold (Nos. **11** and 12). Strangely, further methyl substitution of the pentazocine *N*-chain restored activity (No. **13**). Of the four cycloalkylmethyl derivatives, the CPM member (No. 14, cyclazocine) stood out as the most potent; the CBM and cyclopentylmethyl analogs were reasonably active but further increase in ring size seriously lowered potency (Nos. 15–17). Direct linkage of cyclopentyl to nitrogen was advantageous (No. 18), while a double bond was an advantage to No. 16 but not to No. 18 (cf. Nos. 20 and 19). One antipode of the *t*-2-methyl CPM analog was almost as potent as cyclazocine (No. **21**); other potent agents were the 2-cyclopropylethyl and dioxolane derivatives (Nos. 22 and 23). Some information on the agonist

properties of these benzomorphans is given in a 1965 review[1] where the *N*-CBM derivative (No. 15) is reported half as active as pethidine in the RTF assay.

NIH groups have also examined *N*-substituted normetazocines, and later a series of the 11-propyl analogs. In the metazocines, replacement of *N*-methyl by saturated alkyls from Et to Bu caused a diminution or loss of analgesic action and a concurrent gain in antagonist activity, which was maximal with *N*-Pr. Analgesia was restored in the *N*-pentyl and *N*-hexyl derivatives. In the 11-propyl series a similar pattern of activity was seen except that analgesia did not reappear in the *N*-pentyl and *N*-hexyl congeners, which behaved as antagonists with long durations of action. The *N*-allyl and *N*-CPM members were, as usual, potent antagonists with prolonged actions. The compounds with antagonist components to their actions did not substitute for morphine in dependent monkeys and precipitated abstinence syndromes in these animals.[77]

Table 12.5 Antagonist and Agonist Activities of Some *N*-Substituted 14-Hydroxymorphinans (racemic mixtures except where indicated)[a,b]

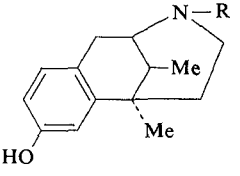


No	R	Antagonist[c] ED_{50} (mg/kg)	Agonist[d] ED_{50} (mg/kg)
1	H	>40	40
2a	Me	>40	0.15 (levo 0.1)
2b	Et (levo)	3	0.6
3	Pr	1.2	40
4	$CH_2CH{=}CH_2$	0.5	46
5	$CH_2C{\equiv}CH$ (levo)	0.7	40
6	$CH_2CH{=}CMe_2$ (levo)	>20	0.1
7	CPM	0.3 (levo 0.2)	9 (levo 13)
8	CBM	3 (levo 0.1)	0.06 (levo 0.05)
9	$CH_2CH_2C(OH)Me_2$ (levo)	>20	8
10	$CH_2CH_2CH{=}CH_2$	0.5	4.5
	cyclazocine	0.81	0.047
	naloxone	0.09	>80
	morphine	—	0.56

[a] From Ref. 63.
[b] Agonist activity was considerably reduced in the isomorphan analogs of Nos. 2 (NMe) and 8 (NCBM), most dextro isomers had very low potencies in either test.
[c] Versus oxymorphone in mouse Straub tail test (OMST).
[d] Mouse writhing test.

N-Substituent influence on antagonism is also well documented in a report on 14-hydroxymorphinans, which also includes agonist data (Table 12.5).[63] In general, structure-activity conclusions concur for the two series, notably the importance of 3-carbon chains and the CPM group for antagonism, and the depressed activities of 3,3-dimethylallyl derivatives. Agonism is especially notable in the *N*-CBM (racemic butorphanol) and dimethylallyl (as in pentazocine) derivatives, while the activity of the *N*-ethyl member (≡morphine) is surprising in view of the reported low potency of *N*-ethylnormorphine. It is of interest that the *N*-allyl and 3-butene analogs are equivalent as antagonists and that the latter is significantly active (0.1 × morphine) as an agonist. Almost all the compounds, however, must be classified as mixed-action agents and it is clear that no one *N*-substituent generates a pure antagonist.

A notable addition to *N*-substituents that confer antagonist properties on the polycyclic opioids is the 2-furylmethyl (2-furfuryl) group.[141] The 2-arylethyl derivative **27a** is a potent analgesic (30 × morphine)[78] but the lower homolog **27b** has only feeble analgesic properties and is as potent an antagonist as nalorphine.[79] The activity profile of **27b** may be varied by simple structural changes, as shown below its formula. Behavior of these derivatives in the GPI test was in reasonable accord with the *in vivo* findings, except that the 2-furfuryl derivative displayed very little antagonist activity.[18] In sharp distinction, the *N*-tetrahydrofurfuryl benzomorphans **28** prove to be analgesics, not antagonists.[80] Both antipodal forms of the related naloxone derivative **29**, however, supressed morphine analgesia (at potency levels below that of nalorphine); the *R*-isomer was also a potent analgesic but the *S*-form was devoid of agonist properties. The 6,11-diethyl analog of **27** (R = furfuryl) is a selective κ-antagonist (MR 2266, p. 439).



a R = CH_2–CH_2–(2-furyl)

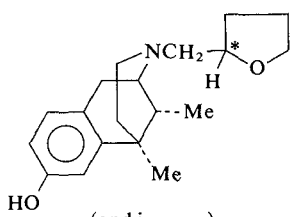
b R = CH_2–(2-furyl)

27

R	$-CH_2$–(2-furyl)	$-CH_2$–(2-furyl)	$-CH_2$–(3-methyl-2-furyl)	CH_3–CH_2–(2-furyl)
Antagonism[a]	+ + +	+ + +	+	none
Analgesia[b]	none	+	+ +	+ + +

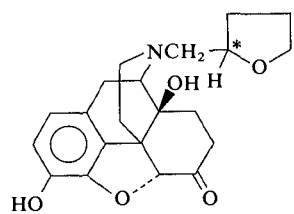
[a] 50% suppression of morphine analgesia in mice in tail-clip test.

[b] Tail-clip, MLD, and MWR tests.



(and isomers)

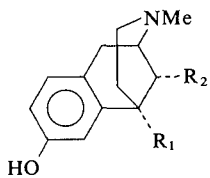
28



*(*RS* center)

29

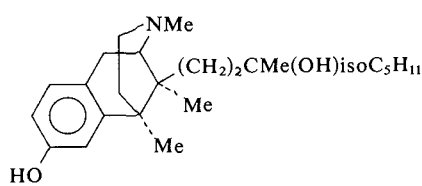
Although methyl is generally regarded as the *N*-substituent most commonly associated with pure agonism, unusual antagonist properties have been reported for certain *N*-methylbenzomorphans. Thus, levo isomers of the benzomorphans **30a–d**, although displaying antinociceptive actions in mice (MHP), failed to substitute for morphine in dependent monkeys and gave evidence of antagonist behavior in precipitating abstinence syndromes.[81,82] In the case of **30e** the racemic mixture and antipodal forms all showed antagonist activity of this kind, while corresponding forms of **30f** did not, although none could



	a	b	c	d	e	f
R_1	Et	Me	Et	Pr	H	Me
R_2	Et	H	H	Me	H	Pr

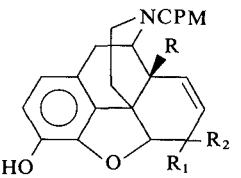
30

substitute for morphine. Further, the analgesically active (4–6 × morphine) levo isomer of the 11-β-methyl-6-phenylbenzomorphan **26b** (R = Me) precipitated withdrawal symptoms in morphine-dependent monkeys.[74] Kosterlitz found the compound to have both agonist (potency = morphine) and weak antagonist activity in the GPI.[18] The buprenorphine analogs **31** provide final examples; the compounds are isomeric about the carbinol carbon and antagonize phenazocine in the RTF test with potencies three to five times that of nalorphine (their agonist activities are low).[83] An 11α-Me-11β-$(CH_2)_2CO n C_5H_{11}$ analog of **31** termed *Tonazocine* equaled naloxone in potency in the same test.[84] Tonazocine was less potent versus morphine ($\frac{1}{25}$ × naloxone), possibly reflecting a specificity for benzomorphan receptors, while its isopentyl analog *Zenazocine* was an even weaker antagonist but with



31

Table 12 6 Agonist-Antagonist Parameters of Some *N*-CPM 14-Substituted Normorphines in the GPI Test (similar results were found in the MVD)[a]



No	R	R_1-R_2	IC_{50} (n*M*)	K_e (n*M*)
1	H	H, OH	2 16	0 8
2	OH	H, OH	∞	2.35
3	SH	H, OH	39 1	1 69
4	NO_2	=O	41 2	4 44
5	Br	=O	∞	1 36
6	Cl	=O	∞	3 92
	Naloxone			1 22
	Naltrexone		max inhib 25%	0 38
	Nalorphine		24 3	4 47
	Morphine		68 2	none

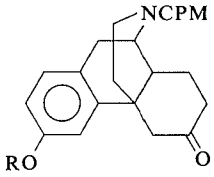
[a] From Ref 85

pronounced agonist activity (6 × morphine, Ach-MRW).[146] Both were agonists in GPI/MVD tests and believed to act on μ-sites in the ileum and δ in the vas on the basis of K_e values for naloxone determined with normorphine, DADL, and the two novel benzomorphans as competing agonists. (See p. 439 for a related κ-antagonist.) More examples of *N*-methyl antagonists are given in the account of non-morphine-based antagonists.

The influence of a 14-hydroxyl substituent in elevating antagonist potency and, in the examples of naloxone and naltrexone, leading to essentially pure antagonists, has already been described. It must be appreciated, however, that the combination of a 14-OH with *N*-allyl or *N*-CPM is not a guaranteed recipe for pharmacological purity. It is not easy to account for the role of 14-OH. The high activities versus morphine of methyl and ethyl ethers of naloxone and naltrexone show that its acidic hydrogen is not essential (p. 415); on the other hand, its electronegativity may be important since other, similarly placed, electronegative substituents also influence the potency and pharmacological profile of morphine-based antagonists, as is clear from work on *N*-CPM normorphines (Table 12.6).[85] In this series the antagonist activity of the parent compound (No. 1) was, in fact, depressed by 14-OH but its action was "purified" in the process. The thiol analog (No. 3) had mixed actions with high antagonist (close to naloxone) and better than morphine agonist potencies; hence, the hydrogen-bonding capacity of oxygen does not appear to be

significant because that of the more active sulfur analog is less. In 14-OH/SH morphinans, the thiol was the less active agonist-antagonist (p. 419). Replacement of 14-OH in 7,8-dehydronaltrexone by NO_2, Br, or Cl (Nos. 4-6) depressed potency versus normorphine with one exception, both halo derivatives behaving, like naltrexone, as pure antagonists. The 14-*R* compounds were all made from thebaine; thus, treatment of the alkaloid with N_2O_4, thiocyanogen followed by LAH, and *N*-Br/Cl-succinimide led to the 14-NO_2,SH and halo derivatives, respectively. Some highly potent 14-amidomorphine derivatives (*N*-CPM antagonists, *N*-Me agonists) have also been reported.[161]

Agonist and antagonist ligands are influenced in the same way by the presence of a phenolic hydropxyl at C-3, as is evident from relative potencies of many free phenol-*O*-methylated pairs of antagonists (e.g., **32**).[32] However, like 3-deoxymorphines and morphinans (p. 119), absence of this feature in antagonists may be compensated by a 4-methoxy substituent. Thus the 4-methoxy derivatives **33** all have had narcotic antagonist action with at least pentazocine-level antinociceptive effects in mice.[86]

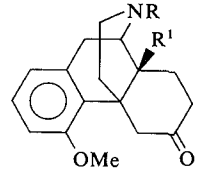


	ED_{50} mg/kg Antagonist	Agonist
R = H	0.5 (5.01)	4.12 (0.21)
R = Me	7.9 (inactive)	39.6 (20.3)

N-CBM data in parentheses.

32

A hypothesis has been advanced to explain the different pharmacological response to opioid agonists and antagonists in terms of conformational differences about the basic center, as discussed in Chapter 13. However, a study by ^{13}C-nmr of two such pairs (morphine-nalorphine, oxymorphone-naloxone) revealed little difference between agonist and antagonist molecules in either piperidine ring conformation (chairs only) or ratio of *N*-R axial to equatorial forms (83:17 for morphine, virtually 100% eq *N*-R for 14-OH derivatives).[135]

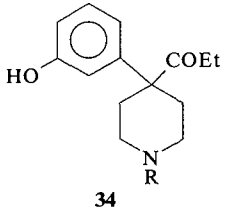


R = C_3H_5, CPM or CBM
R^1 = H or OH

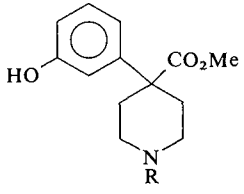
33

12.7. NONMORPHINE-BASED ANTAGONISTS

With a few exceptions, no antagonists of remarkable potency have been designed from classes of analgesic other than the morphine, morphinan, and benzomorphan groups. For example, replacement of one of the *N*-methyl groups of (−)-α-acetylmethadol by allyl or CPM gave products that showed agonist activity in mouse HP, TF, and WR tests (1–0.3 × morphine), while the *N*-allyl analog partially antagonized morphine-induced RTF analgesia.[87] Most *N*-allyl (and related "antagonist" substituted) analogs of the 4-arylpiperidine group of analgesics proved to be agonists with no power to block opioid receptors; examples include *N*-allyl derivatives of norpethidine and norprodine and the *N-trans*-3-chloroallyl-reversed ester of pethidine (p. 239).[88] Essentially similar results were found for a series of *N*-alkylnorketobemidones **34**, although the pentyl, hexyl, and heptyl members showed weak antagonism of morphine dependence in monkeys in addition to agonist properties.[89] Kosterlitz *et al.* confirmed that (**34** R = hexyl and heptyl) were weak antagonists (with 8 and 4%, respectively the potency of nalorphine) in the GPI and MVD preparations.[90] It is to be noted that these piperidines possess a phenolic function essential to potent antagonists of the polycyclic class. Merz and colleagues[91] had more success in producing antagonists when the methyl ester analog of bemidone (**35** R = Me) was modified rather than



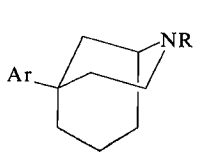
34



35

R = a Me; **b** CH_2CH=

ketobemidone; their most potent compound (**35b**) had one third the activity of nalorphine versus morphine in mice but *N*-allyl, *N*-CPM and *N*-2-furylmethyl derivatives were inactive or feeble in this respect. Bridged (*m*-hydroxyphenyl) piperidines of the 5-arylmorphan type **36** with *N*-propyl, allyl, and CPM side chains had only weak activity as opioid antagonists,[92] while the *N*-allyl congener of the 3,5-trimethylene bridged derivative **37** (6–8 × pethidine as analgesic) was not an antagonist.[93]



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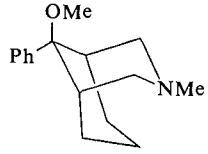
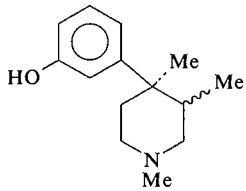
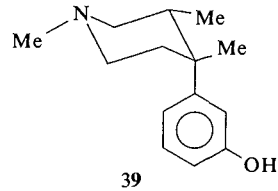


37

4-Arylpiperidines with 4-alkyl substituents behave as analgesics provided a phenolic (*m*-OH) group is present (p. 276). However, antagonist properties are found for the 1,3-dimethyl derivative **38** when C-methyl is *cis* to 4-aryl (the α-diastereoisomer has mixed actions).[94] The antagonist potency of the β-derivative (0.5–2 × nalorphine) fell when *N*-Me was replaced by allyl or CPM but was raised by the typical "agonist" substituents phenethyl and 2-benzoylethyl, with the latter yielding a product that approached naloxone in potency. Antagonist properties were also claimed for β-3-methylketobemidone and the phenolic analog of β-prodine. It is tempting to explain the activities of these compounds in terms of mimicry of the morphine skeleton, possible when an axial arylpiperidine conformation (**39**) is adopted, but this viewpoint does not account for the antagonist role of *N*-methyl. Further discussion of this group is given in Chapter 13.

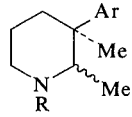


38



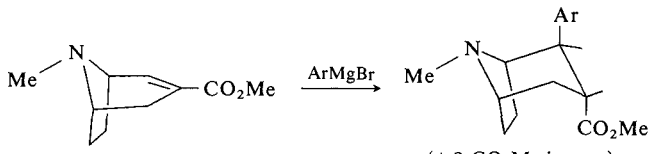
39

There is a stronger case for accounting for the antagonist properties of certain 3-aryl(*m*-OHC_6H_4)piperidines **40** in terms of mimicry of morphine because the *N*-substituent exerts its normal influences in these compounds (Me,CH_2CH_2Ph, CH_2COPh: agonists; allyl, CPM: antagonists).[95] The *N*-allyl and *N*-CPM derivatives antagonized fentanyl-induced narcotic effects with potencies close to or greater than that of nalorphine, and receptor stereoselectivity has been established for the levo isomer of the α-*N*-allyl antipodal pair.[96] The tropanes **41** made by Clarke *et al.*[97] may be regarded as bridged analogs of 3-arylpiperidines, with the aromatic group constrained to an axial conformation. The compound **41** antagonized phenazocine in the RTF test at



40

Ar = *m*OHC_6H_4
α: *t* Me, Me
β: *c* Me, Me

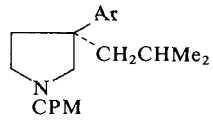


(+β-CO_2Me isomer)

41

about a quarter the sc potency of nalorphine, and provides another example of an *N*-Me antagonist. Data on *N*-allyl or -CPM congeners were not reported.

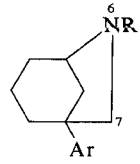
The 3-arylpiperidines **40** are clearly related to 3-arylpyrrolidines such as **42** that provide antagonists when the ring nitrogen carries an allyl or CPM substituent.[98] The absolute configurations of the more active antipodal forms of α-**40** (R = allyl) and **42** have been determined by X-ray crystallography and probable "active" conformations proposed with features akin to those α-(−)-cyclazocine.[96] 3-Arylpiperidines and pyrrolidines are further discussed in Chapter 7. Bridged 3-arylpyrrolidines **43** provide (unlike related 5-arylmorphans) both agonists and dualists; for example, the 6-CPM, 7-Me congener has a potency close to nalorphine as antagonist and twice pethidine as agonist.[99] The order of activity for antagonism (*N*-Pr > 2,2-dimethylallyl > CPM > allyl = propargyl) is unusual, particularly in the ranking of dimethylallyl (see p. 424).



(−) > RS > (+) as antagonist

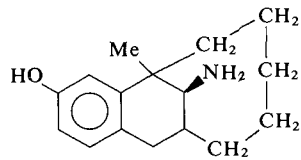
42

(Ar as for **40**)



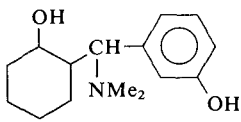
43

The bridged aminotetralin **44** (dezocine, p. 397) is a potent agonist in animals (reports of its agonist actions in the GPI conflict) but has antagonist properties in morphine-dependent monkeys, as shown by its precipitation of a withdrawal syndrome at a potency close to that of nalorphine.[100] Dezocine appears to be the only example of an antagonist with a primary amino function and particular aspects of its pharmacological profile may be related to the nitrogen lone-pair orientation as proposed by Belleau (p. 464).

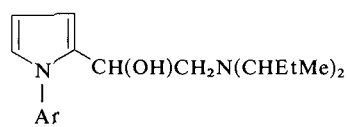


44

The analgesics ciramadol **45** and viminol **46** (Chapter 11) also display antagonist behavior when examined in appropriate tests.[101,102] Viminol is a



45



46

Ar = *o*ClC$_6$H$_4$

diastereoisomeric mixture of five isomers, only one of which appears to contribute antagonist activity (the S_2 isomer causes jumping responses in morphine-dependent mice).

With the increased sophistication of pharmacological methodology available today, most compounds designed as analgesics are now screened for agonist and antagonist properties on a routine basis. Hence, we must anticipate continuing reports of opioid ligands with mixed actions rather than "pure" agonists or antagonists, which are now seen to be exceptional.

Final to this section is a description of opioid peptides with *N*-allyl Tyr^1 residues, which have been examined as potential narcotic antagonists. The mono *N*-substituted derivative *N*-allyl-D-Ala^2-metenkephalin had a reduced affinity for opioid receptors as compared with metenkephalin, and did not decrease the antinociceptive response in mice (TF test) obtained after D-Ala^2-metenkephalinamide.[103] *N*-Allyl-leu-enkephalin, however, is claimed to behave as an antagonist in the GPI.[104] Surprisingly, more definite evidence of antagonism has been found for *N,N*-diallyl derivatives.[105] Two such compounds made by ICI, namely 154129 *N,N*-diallyl-Try-Gly-Gly-ψ-(CH_2S)-Phe-LeuOH(Gly^3-Phe^4 peptide bond replaced by CH_2S), and 174864 (*N,N*-diallyl-Tyr-Aib-Aib-Phe-LeuOH: Aib = α-aminoisobutyric acid) selectively antagonize δ-agonists such as leu-enkephalin and DTLET (D-Thr^2, Leu^5, Thr^6 enkephalin) in the MVD test, the latter at potencies close to those of naloxone. The activities of typical μ- and κ-agonists were little changed. Binding studies confirm this work.[150]

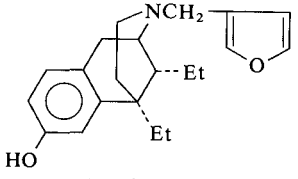
Material of as yet unproven peptide nature was isolated from instant coffee powders by an Australian group prompted by the identification of opioid-active peptides in casein and gluten hydrolysates, and morphine in milk.[136,137] A product that bound to rat brain homogenates was found with characteristics of opioid antagonists (its binding ED_{50} value was little changed in the presence of Na^+) and with an activity at 1.2 mg/ml equivalent to that of naloxone at 3.4 n*M*.[137]

12.8. KAPPA-AGONISTS AND ANTAGONISTS

As already mentioned, oxidation of C-1 methylene of cyclazocine to carbonyl abolishes the antagonist but retains the agonist actions of the parent compound (p. 423). The behavioral and pharmacological effects of the oxidized product ketazocine **26a** in the chronic spinal dog were subsequently compared with those of morphine by Martin, and as a result of differences observed, he dubbed the two compounds κ- and μ-agonists, respectively.[106] Thus, while morphine induced analgesia, meiosis, bradycardia, hypothermia, and indifference to environmental stimuli, ketazocine produced meiosis, general sedation, and depression of flexor reflexes but did not alter the skin twitch reflex or pulse rates.

Although ketazocine and its close analog ethylketazocine (EKC, **26a**, β-6-Me replaced by 6-Et) have *in vito* activities in antinociceptive tests (MHP, RTF, and MW),[72,107] they differ from most other agonists in failing to elicit Straub tails and mydriasis in mice or to substitute for morphine in withdrawn morphine-dependent monkeys.[108,109] Further, while morphine (10 mg/kg sc) caused marked respiratory depression in rats, ketazocine (32 mg/kg) had no such effect and the same is true for other κ-agonists.[110] Ketazocine also has agonist properties when examined by *in vitro* procedures; it is more potent in the GPI than MVD preparation (62 and 10 × normorphine, respectively) suggesting that it acts at both μ- and δ-sites with a preference for the former.[107] The additional fact of its activity in the rabbit VD (a preparation insensitive to μ- and δ-agonists)[111] supports the idea of its action at yet another (κ) subspecies of receptor.[110]

Discovery of an antagonist that selectively blocks putative κ-agonists adds further weight to arguments for opioid receptor species of this nature. The compound Mr 2266 (**47**), the levo isomer of the *N*-3-furylmethyl analog of 1-deoxyethylketazocine, acts as a highly effective antagonist in organ models and binding assays (of potency equal to naloxone in some cases) but displaying selectivity for presumed κ-agonists (dextro **47** is inactive).[112] Thus, Mr 2266 is a far more efficient antagonist of ethylketoclazocine than is naloxone in both GPI and MVD preparations (see data).[113]



levo isomer

47

Effectiveness (K_e, nM) of naloxone and Mr 2266 in antagonizing a μ-ligand and two putative κ-ligands

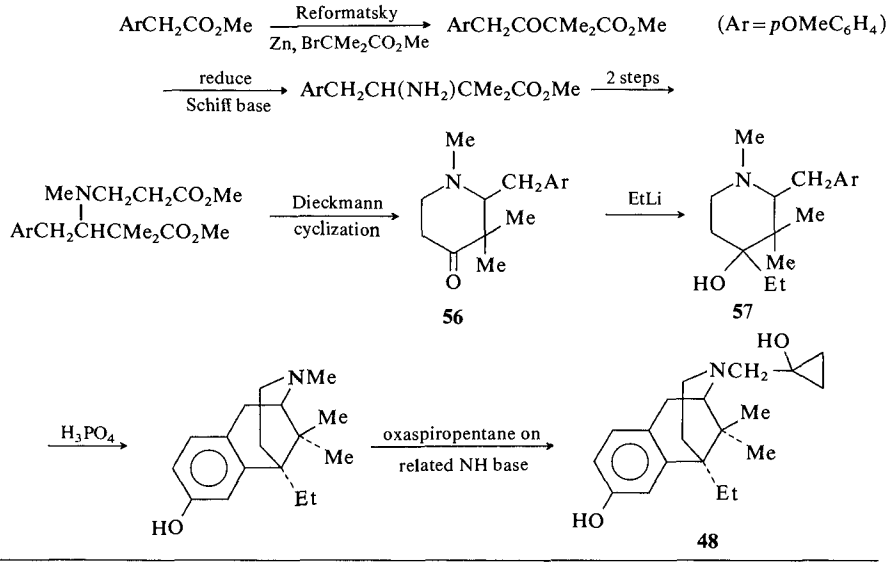
Compound	vs. naloxone		vs. Mr 2266	
	GPI	MVD	GPI	MVD
Normorphine	1.89	3.1	1.93	1.50
(−) Ethylketazocine	14.9	11.0	2.53	4.51
Mr 2034	10.4	9.1	3.34	8.4

Likewise κ-ligands displace ethylketazocine from brain tissue at concentrations marginally lower than those necessary to expel the μ-ligand dihydromorphine and considerably lower than those required to remove DADL, a selective δ-ligand.[107] In other competitive experiments[114] the high affinity binding of [^{3}H]ethylketazocine was readily displaced by other κ-agonists

but not by the selective μ-ligand DAGO or the δ-ligand DADL. κ-Agonists exhibited a high degree of cross-reactivity with the μ-binding site but somewhat less with the δ-site. The results of protection assays provide further evidence for a receptor subspecies additional to the μ- and δ-types.[114] In these tests the potency of ligands in protecting GP brain binding sites from inactivation by the irreversible alkylating agent phenoxybenzamine is measured (p. 355). About 30 times more dihydromorphine than levo-ethylketazocine was required to protect 50% of the binding while very high concentrations of DADL protected only 20–40%. Relative inhibitory potencies of prototype ligands at the three sites are judged to be:

	μ	δ	κ
μ (DAGO)	1	0.01	0.01
δ (DADL)	0.1	1	0.01
κ-(−) ethylketazocine	0.8	0.2	1

A number of κ-agonists, characterized in the outlined ways, have now been identified, and the majority are benzomorphan derivatives (The analogous 10-keto analog of naltrexone has little affinity for κ-sites).[160] Several non-keto derivatives have been described but all such compounds include an oxygen feature in their *N*-substituent that may be able to occupy a similar position in space as the C-1 oxo group. *Bremazocine* (**48**), which carries an hydroxyl substituent in its CPM side chain and is a 6-ethyl-**11**,**11**-dimethyl derivative, is a potent, long-acting agonist of κ-classification.[107] In mice it was three to four times as potent (sc) as morphine in HP and TF tests, and its TF activity was reversed more effectively by MR 2266 than by naloxone. It produced no mydriasis or Straub tails in mice and did not depress respiration in rats. Chronic administration to monkeys did not lead to a morphinelike withdrawal syndrome although tolerance to its analgesic effects occurred; morphine remained an effective analgesic in such animals. Conversely, treatment of morphine-tolerant animals with bremazocine did not cause analgesia. These data suggest that μ-receptors are largely undisturbed by bremazocine and that κ-receptors do not mediate analgesia. Bremazocine is made from the 3,3-dimethyl-4-piperidone **56** via the tertiary alcohol **57**, which may be cyclized to a 11,11-dimethylmorphinan derivative; *N*-demethylation and treatment of the resultant secondary amine with oxaspiropentane gave **48** (Scheme 12.2).[115] Somewhat conflicting evidence was found by Spencer and coworkers, who demonstrated that bremazocine had an analgesic profile in mice closer to that of pentazocine than ethylketazocine in four antinociceptive tests.[138] The results were held to provide evidence for bremazocine being active at μ- as well as κ-sites, as was the fact of its precipitating a withdrawal syndrome in morphine-dependent

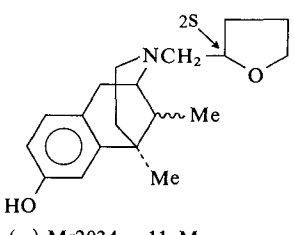


Scheme 12.3. Synthesis of Bremazocine

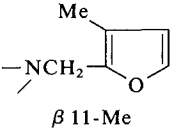
rats.[139] Bremazocine has no future as a clinical analgesic because of its psychotomimetic side effects.[140]

Binding experiments using levo[^{3}H]bremazocine coupled with autoradiography show that guinea pig cerebellum is an ideal tissue for the isolation and investigation of κ-receptors. Binding of this agent to tissue with μ- and δ-sites blocked by unlabeled ligands of appropriate selectivity comprised 84% of that found when all sites were available.[151]

Other κ-agonists are the tetrahydrofurfuryl derivative **49**, the 3-methylfurfuryl derivative **50**, and the open chain ether **51**, all made by Boehringer Ingelheim.[116,117] Structural features of κ-agonists based on the benzomorphan skeleton, including conformational reasons for activity differences

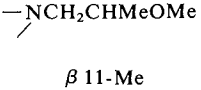


(−) Mr2034 α 11-Me
(−) Mr2184 β (more potent)
49



β 11-Me

(−) Mr1353
50

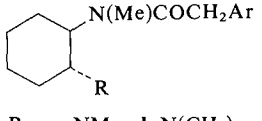


β 11-Me

(±) MRZ 2549
(no cross tolerance
with racemic Mr 2033)
51

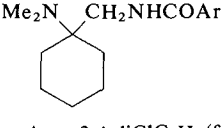
between 2*S* and 2*R* *N*-tetrahydrofurfurylmethyl diastereoisomers, have recently been summarized by Merz.[141]

Several types of κ-agonists unrelated to benzomorphans are claimed. The first comprise some diaminocyclohexane derivatives **52** made by Upjohn, and the second, peptides that may represent endogenous ligands of κ-receptors. The pyrrolidine derivative **52b** (U-50,488) is an analgesic that lacks morphine-like behavioral effects in mice (Straub tails, arched backed, increased locomotor activity).[118] It was up to half as potent as morphine in mice and rats in a variety of antinociceptive tests, and its actions were reversed more effectively by Mr 2266 than by naloxone. Its TF ED_{50} values in chronic saline- and chronic morphine-treated mice were 3.0 and 4.4 mg/kg, respectively, corresponding values for morphine being 1.4 and 8.2 mg/kg, and it lacked antagonist actions as judged by its failing precipitate withdrawal jumping in morphine-dependent mice (jumping was caused by naloxone and, unexpectedly, bremazocine at similar low dose levels). In binding assays, U-50,488 bound primarily to a subpopulation of [^{3}H]EKC sites that were not blocked by dihydromorphine; it showed reduced affinities for μ-sites as compared with those of bremazocine and Mr 2266. In studies reported by Romer, the Upjohn compound **52b** (32 mg/kg) had no effect on the respiration of rats and did not reverse or inhibit the morphine withdrawal syndrome in dependent monkeys.[110]



R = a NMe_2, b $N(CH_2)_4$

52



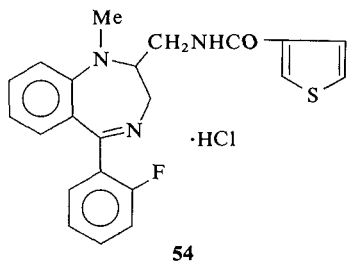
Ar = 3,4-diClC_6H_3 (for both)

53

The 3,4-dichlorophenyl unit of U-50,488 also appears in the cyclohexane derivative **53** (p. 395), and in view of its morphinelike potencies in mouse WR and HP tests and failure to give Straub tails, there is a good case for its further examination as a putative κ-agonist.[119]

Most recently certain benzodiazepines have been discovered that fail to bind to sites typical of the class but with selective actions on subpopulations of opioid receptor dependent upon their substituents. One agent, *tifluadom* (**54**) acts selectively on κ-receptors as judged by the usual criteria.[120] Thus tifluadon displaced the κ-ligand ^{3}H(−)-bremazocine from GP brain and inhibited GPI contractions with IC_{50} values intermediate between those of ketazocine and bremazocine, and was also active in the rabbit VD preparation (believed rich in κ-sites). It was three times as potent as morphine in mice by the TF test and its action was more readily blocked by Mr 2266 than naloxone. It did not depress respiration in rats and had a low PDC in monkeys.

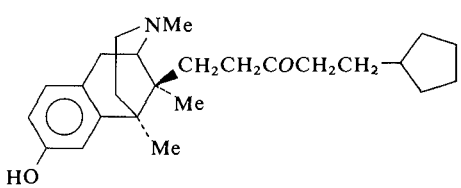
There is evidence that dynorphin and related opioid peptides (p. 361) are the endogenous ligands for κ-receptors. Thus, dynorphin 1-13 and EKC



54

had equally poor sensitivity to naloxone antagonism in the GPI assay, while in binding experiments the two compounds were more potent in displacing [^{3}H]EKC than expelling typical μ- and δ-agonists, and showed selective cross protection in receptor inactivation experiments with β-chlornaltrexamine (p. 449).[121] Kosterlitz's group[122] found dynorphins **1**-17, 1-13, and 1-9 especially active at rabbit VD sites (a tissue insensitive to μ- and δ-ligands) and inactive at the rat VD preparation, which has low sensitivity to κ-agonists. Rabbit VD was insensitive to leu-enkephalin and its Lys^6 analog. The dynorphins listed were also potent displacers of [^{3}H]bremazocine from GP brain after suppression of μ/δ-binding sites with DAGO (μ) and DADL (δ).

Clearly, selective antagonists are valuable tools for the study of κ-receptors and the compound MR 2266 (**47**) has already been mentioned in this respect. The Sterling Winthrop compound **55** (Win 44,441-3) is more potent than naloxone at κ-receptors but its relative selectivity ($\mu > \kappa > \delta$) is similar to that of the standard antagonist[123]; it is notable in having an *N*-methyl substituent and carrying its oxygen function in a β-C-11 side chain. The antagonist β-naltrexamine pharmacophores when linked by an oxymethylene ($CH_2CH_2OCH_2CH_2OCH_2CH_2$) spanner selectively blocked the actions of the κ-agonist EKC in the GPI (see Chapter 2 and Chapter 10).[124,147]



55

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13

Opioid Receptors: Facts and Speculations

13.1. INTRODUCTION

Opioid receptors were originally conceived as specific sites in the CNS that form a crucial link in the mechanism of pain perception and that fail to function in this respect when bound to certain ligands termed *analgesics* or *analgetics.* Substances that block the action of such opioid agonists ligands in a competitive manner were termed *opioid antagonists* and the two classes of ligand were assumed to compete for the same receptor. Up to the early 1970s there was no direct evidence of opioid receptors; speculations on their existence rested upon classical pharmacology (specificity of action and structure activity analyses, especially stereochemical, of agonists) and the identification of specific antagonists. Over the last 10 years or so, however, the application of radioactive labeled ligands to binding studies and autoradiography has yielded a large body of direct evidence and provided information about the location and general chemical nature of the receptors. Complementary to this evidence and of crucial support to the existence of opioid receptors was, undoubtedly, the discovery and identification of endogenous ligands (enkephalins, endorphins, etc.) since it was inconceivable that such receptors should have evolved on the off chance of interactions with exogenous ligands.

An account of the principles and methods of binding experiments has been given in Chapter 10 of this book, and the topic has been extensively reviewed.[1-3] It suffices here to stress the need to establish the specific nature of the binding parameters (by use of ligands of high specific radioactivity in Goldstein's stereospecific binding technique) and the avoidance of the pitfalls of erroneous interpretation of the data.[3] There is reasonable correlation between clinical and/or antinociceptive potencies and binding site affinities of opioid ligands[4] (e.g., data of Table 13.1),[6] but correlations between analgesic classes of high and those of low affinity (such as the methadone and pethidine groups) are generally poor. The large number of nonopioid drugs that are ineffective in altering [^{3}H]-dihydromorphine binding[5] adds confidence

Table 13 1 Displacement of [^{3}H-]Naloxone Binding by a Series of Opiates[a]

Drug	IC_{50} (nM)
(−)-etorphine	0 3
(−)-Levallorphan	1
(−)-Levorphanol	2
(−)-Nalorphine	3
(−)-Morphine	7
(−)-Cyclazocine	10
(−)-Naloxone	10
(−)-Hydromorphine	20
(−)-Methadone	30
(±)-Pentazocine	50
(+)-Methadone	300
Meperidine	1,000
(±)-Propoxyphene	1,000
(+)-3-Hydroxy-N-allylmorphinan	7,000
(+)-Dextrorphan	8,000
(−)-Codeine	20,000
(−)-Oxycodone	30,000

[a] The above IC_{50} values were determined by log probit analysis and are taken from Ref 5

to the claimed specificity of the technique. The procedure also lends itself to the differentiation of agonist and antagonist ligands. Thus, low concentrations of sodium ions usually decrease the binding of agonists while enhancing or affecting little those of antagonists (see the sodium index, p. 334). Agonist but not antagonist binding is also decreased by other cations, enzymes, and certain reagents and nucleotides.[6] Much study has now been made of the effects of divalent and monovalent cations, GTP (and analogs), and thiol reagents on the binding of opioid ligands to receptors, and the complex and sometimes contrary results have been reviewed.[120,130] Although the differential effects of some of these agents upon binding serve to differentiate agonists from antagonists, it is likely that they reflect differentiation of receptor subtypes rather than agonist-antagonist receptor states.[120]

Radiolabeled ligands have also enabled development of the technique of *autoradiography*, a method of great sensitivity that can provide anatomical resolution in the micron range and hence yield evidence about the location of receptors superior to that derived from binding experiments.[7]

13.2. LOCALIZATION OF RECEPTORS

First, radiolabeled ligands are bound to receptor material in as specific a manner as possible; ligands of high affinity are required with dissociation

constants lower than 10 nM. Next, 4–10 μm sections of the tissue are placed in contact with emulsion-coated cover slips (in the dark) and the film is developed after a suitable time interval. The preparation is then examined by light (and sometimes electron) microscopy. Either *in vivo* or *in vitro* procedures may be used; in each case care must be taken to minimize diffusion of ligand from the receptor, especially if electron microscopy is to be applied (use of irreversible ligands avoids this problem). Several reports of opioid receptor localization by autoradiography have been made. For example, Atweh and Kuhar[8] found that receptors were highly concentrated in the substantia gelatinosa of the dorsal horn of rat spinal cord, as judged from the autoradiographic grain density, confirming results of Pert *et al.*[9] using [^{3}H]diprenorphine as ligand.

The results of histochemical and immunofluorescent mapping of neurotransmitter-containing neurones often complement receptor distributions established by autoradiography. A case in point is that of the dorsal horn of the spinal cord in which high concentrations of both opioid receptors and enkephalin-containing nerve terminals are found.[10] An immunofluorescent technique may be used to map enkephalins.[11] First, Met- or Leu-enkephalin is coupled to a protein (keyhole limpet hemocyanin or BSA) by use of a carbodiimide derivative or gluteraldehyde, and rabbits or guinea pigs immunized with the complex over several months. An antiserum is raised in the animals' blood and its titre is judged from the ability of blood sera to bind enkephalins in a radioimmune assay. When antisera levels are adequate, the antisera is incubated with rat brain sections, which are then washed and reincubated with goat antibody, which reacts against rabbit or guinea pig IgG and which has been conjugated with a fluorescent molecule such as fluorescein. The preparation is then washed and viewed with a fluorescence microscope; areas of fluorescence correspond with locations of the enkephalins.

Positron-emission, transaxial tomography (PETT) is a recent extension of these visualization techniques,[12] and a study of a ^{19}F derivative of phenazocine (*fluorophen*) has been made with a view to employing the ^{18}F congener, the form required for a PETT scan.[13]

13.3. ISOLATION OF RECEPTORS

If one accepts that the concept of an "isolated" receptor is meaningful (i.e., that a receptor retains its integrity outside its *in vivo* environment), then attempts to achieve this condition must form an important step in receptor investigations. To date, only modest progress has been made in attempts to isolate opioid receptor material as characterized by its ability to bind ligands in a manner similar to that of intact nervous tissue. The problem is to devise a method of solubilizing the receptor from its supporting tissue (usually assumed to be a cell membrane) in a manner in which it retains its ability to

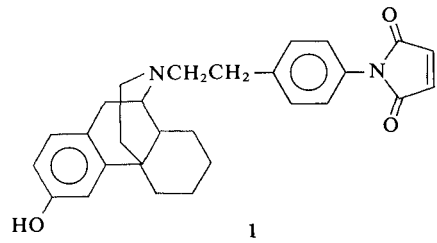
bind ligand.[14] Mild solubilization techniques such as repeated washing in isotonic buffer solutions are ineffective while use of detergent (ionic and nonionic) usually yields materials of impaired binding ability. There is plenty of evidence of the protein nature of opioid receptors; active material loses its binding power in the presence of proteolytic enzymes and reagents for thiols such as *N*-ethylmaleimide, and when heated (denatured).[15] There is also evidence for a lipid component in that phospholipase A (but not C or D) inhibits receptor binding.[16] An artificial tetracontapeptide, in fact, has been synthesized in an attempt to design an opioid receptor mimetic peptide; opioid ligands had only weak affinities for the peptides, a finding considered not too discouraging in view of its small size relative to natural receptors.[108] Some success has been achieved in receptor isolation, however, and a few details are given here. Simonds *et al.*[17] obtained active material from neuroblastoma-glioma hybrid NG 108-15 cells and rat brain membranes by use of the novel detergent CHAPS (a zwitterionic derivative of cholic acid), and their procedure is typical. The biological material was homogenized in the presence of 10 n*M* CHAPS and then centrifuged for 60 min at 160,000 g. Aliquots of the supernatant were incubated with 2 n*M* [^{3}H]DALAMID(D-Ala^2-leu-enkephalinamide) or 5 n*M* [^{3}H]etorphine with or without excess of unlabeled opioid (to assess total and nonspecific binding, respectively). The mixture was applied to a Sephadex column and the high molecular weight fraction, which eluted in the initial 4.5 ml, examined for radioactivity. Specific opioid binding was demonstrated that was optimum at a CHAPS concentration near 10 n*M*, and equivalent to 20% of the original capacity of the NG cells. The solubilized protein retained the high stereoselective characteristics of membrane-bound receptors as demonstrated by the effective displacement of [^{3}H]DALA amide by (−), but not by (+)-morphine. Binding activity was destroyed by trypsin and *N*-ethylmaleimide. No active receptors were obtained after solubilization experiments with sodium cholate, digitonin (a nonionic steroid detergent), or Zwittergent 3-10 (an *n*-decyl zwitterionic detergent). Bidlack *et al.*[18] used affinity chromatography to isolate an opioid receptor–levorphanol complex, which was resolved by electrophoresis into three major proteins with molecular weights 43,000, 35,000, and 23,000. Protein material from rat neural membranes was solubilized with Triton X-100[19] and applied to a column of ω-aminohexyl sepharose beads conjugated to 14-β-bromoacetamidomorphine (prepared from 14-β-nitrocodeinone[20] or 14-β-aminomorphine[21]); after 30 min incubation time, the morphine and corresponding morphinone derivatives were shown to bind irreversibly to neural membranes. Nonspecific proteins were eluted with buffer and receptor protein with 1 μM levorphanol. The binding properties of the purified receptor (free from ligand by dialysis) were similar to the intact and solubilized neural membranes but the resolved fractions failed to bind opioids.[22]

Recent work on receptor solubilization, including successful use of digitonin in the presence of 0.5–0.1 *M* NaCl,[23,118] is described in the 1982 and 1983 reports of the International Narcotic Research Conference.[24] Fractionation of the digitonin–NaCl extracts of guinea pig brain on a sucrose gradient allowed separation of two distinct binding components characterized as κ-sites and a mixture of μ- and δ-sites, respectively.[119] Extracts of guinea pig cerebellum gave a single peak of activity that exhibited κ-characteristics only, confirming an earlier report of the Kosterlitz group made to the 1983 INRC; in this case solubilization did not require NaCl. The extracts retained 28.5% of binding present in the intact membrane preparations. κ-Ligands (bremazocine, trifluadom, EKC, and U50488) were potent displacers of [^{3}H]bremazocine from GP cerebellum fractions, while DAGO (μ) and DSLT (δ) were ineffective. Barnard and others also used digitonin to solubilize brain membranes (rat) but included Mg^{2+} in the extraction medium since this ion has been shown to stabilize receptor activity.[127] Improved yields of solubilized binding sites were obtained (90% for [^{3}H]etorphine and 45% for [^{3}H]DADL) and high-affinity μ-, δ-, κ-, and antagonist sites were detected. The stability of the material at room temperature makes it potentially useful for purification and characterization.

A 1983 review of the molecular properties of opioid receptors that includes an account of solubilization and purification procedures is available.[120]

A diversion on *affinity labeling* as a general approach to opioid receptor studies is appropriate at this point.[14,25] The object of such work is to incorporate various alkylating functions into opioid ligands in the hope of obtaining a molecule that will bond covalently (and hence irreversibly) to opioid receptors. The location of such a ligand, and thus also the receptor, may be monitored by use of radiolabeled material. As alkylating functions, both classic nitrogen mustards (NCH_2CH_2Cl, which acts via an aziridine ion) and fumaramate and maleimides (involving Michael addition of thiol and other nucleophiles across activated carbon–carbon double bonds) have been employed. The earliest work included examination of *N*-2-bromoethylnormetazocine (p. 181) and a fumaramate based on anileridine (p. 232). Neither of these compounds could be classified as noncompetitive antagonists, although the latter blocked morphine and other agonists (it behaved as an agonist in the single-dose suppression test performed on morphine-dependent mice and in the GPI test).

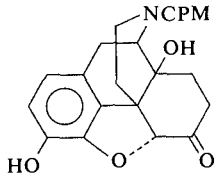
The morphinan **1** with a maleimide function attached to the *N*-phenethyl side chain was five times as potent as morphine as an agonist in mice by the D'Amour Smith test.[26] Mice pretreated with the compound at 2 mg/kg were less responsive to morphine given after the analgesia to the morphinan had disappeared, but unequivocal classification of the mode of antagonism was not possible.



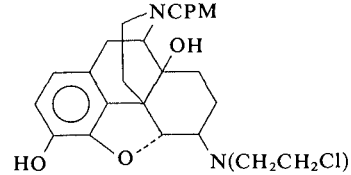
1

(Treat corresponding *p*-NH_2 derivative with maleic anhydride)

Recent interest in affinity binding ligands has centered on 6-amino derivatives of naltrexone and oxymorphone (Chapter 2, p. 64). Reductive amination of naltrexone **2** with $NaCNBH_3$ and diethanolamine gave the precursor of chlornaltrexamine (**3**, CNA of β-configuration).[27] The compound **3** had no analgesic activity in mice after icv injection in doses up to 4.8 nM/mouse. It produced long-lasting (3–6 days) narcotic antagonism in mice and its effects



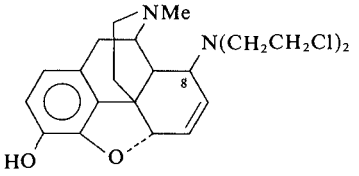
2



3

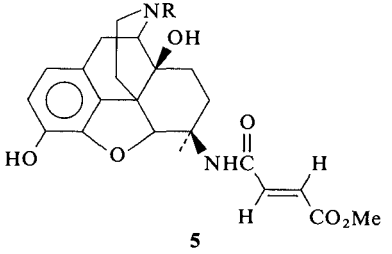
were blocked by pretreatment with naloxone. Inhibition of [^{3}H]naloxone binding by naltrexone or levorphanol was rapidly lost following washing; in contrast, β-CNA continued to inhibit 40% of the binding. All results are good evidence that β-CNA acts by selective covalent association with the receptors. Complexes of [^{3}H]CNA bound to brain membranes, in fact, have been isolated by solubilization with Triton X-100 and chromatography on an Ultrogel column after dialysis and precipitation. Resolution of the complex into at least four fractions was achieved.[28] There is evidence that β-CNA irreversibly alkylates μ-, κ-, and δ-receptor subtypes. The α-isomer (obtained by reductive alkylation of α-naltrexamine with glycoaldehyde and $NaCNBH_3$)[29] also produced irreversible blockade of the same three receptor subtypes but was distinctive in having an irreversible agonist action on the GPI (22 times that of morphine's reversible effect), although it lacked such action on the MVD.

β-COA, the *N*-methyl analog of β-CNA, bound covalently to opioid receptors[112] *in vitro* and *in vivo* (behaving as an agonist rather than as an antagonist), but its 8β-[bis(2-chloroethyl)amino]analog 4 proved to be only a feeble reversible agonist at GPI and MVD sites and showed no evidence of alkylating ability.[126]



4

The related fumaramate methyl esters (**5a** β-FNA and **5b** β-FOA), analogs of naltrexone and oxymorphone, respectively, both behaved as reversible agonists on the GPI (β-FNA 5 × β-FOA = morphine).[30] When ileal tissue was incubated with β-FNA for 30 min or more, it became nonresponsive to morphine, even after thorough washing or treatment with naltrexone. The time-dependent irreversible antagonist actions of β-FNA were very selective. Pure μ-agonists were blocked but little effect was seen against mixed agonists-antagonists such as nalorphine or κ-agonists. β-CNA, with the more reactive alkylating function, did not show such specificity, and β-FNA is deemed a



a R = CPM (β-FNA)
b R = Me (β-FOA)

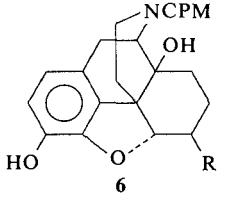
5

valuable agent for the selective blockade of μ-sites. Similar results were found for the action of β-FNA and β-CNA on the MVD preparation. The 6α-isomer of **5a** (α-FNA) shared the reversible agonism of β-FNA at GPI sites (α:7 ×, β:5 × morphine) but lacked alkylating properties.[31] It protected the GPI against alkylation by β-FNA, suggesting that the two epimers bind to the same receptor. Epimeric 6-isothiocyanates (6-NCS) differed in similar ways (all epimeric pairs were made from corresponding epimers of naltrexamine). The action of affinity labels is presumed to involve (1) a primary recognition step of forming a reversible ligand-receptor complex, followed by (2) a secondary step requiring proper alignment of the electrophile with a proximal nucleophile on the receptor. Data on the epimers examined suggests that only the β-isomers provide the correct geometry for step 2. Irreversible blockade of nalorphine (dualist) or ethylketazocine (κ-agonist) by β-FNA did not occur, establishing the selectivity of the β-isomer for μ-sites. Further, the reversible agonist activities of α- and β-FNA in β-FNA-treated ileum were not significantly different from those exhibited in the untreated tissue; hence, these activities may be mediated through κ-receptors. In the MVD, β-FNA but not the

α-epimer irreversibly antagonized morphine while neither isomer blocked the δ-agonist DADL. The two FNA isomers and related epimeric pairs behaved as reversible agonists in the vas but maxima equal to that of morphine could not be achieved. Portoghese and Takemori presented a full discussion of their results at a 1981 Cambridge symposium.[32]

The differing properties of β-FNA and its *N*-methyl analog (β-FOA), both of which contain an identical electrophilic moiety, may be explained either by a difference in the nature of the interaction of agonist and antagonists with a single receptor type or by the existence of distinct receptor sites for μ-agonism and antagonism. The differing pA_2 values of naloxone in reversing the effects of β-FNA (8.06 ± 0.02) and β-FOA (8.62 ± 0.06) in the GPI were taken as evidence that the former resembled pure agonists and the latter, dualists.[32] The fact of antagonists being more effective than agonists in protecting GPI sites from irreversible blockade by β-FNA has been advanced in support of linked agonist-antagonist sites, as will be further discussed (p. 457).[33]

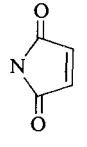
In studies of a further range of β-FNA analogs that contained a variety of electrophilic groups attached at the 6β-position, several agents were discovered that mimicked the parent compound in behaving as reversible agonists at κ-receptors and irreversible antagonists at μ-sites.[113] The rank order of irreversible antagonism for a series of related Michael acceptors did not parallel their intrinsic chemical reactivity (judged by rates of reaction with cysteine), indicating that the degree of covalent binding is related to the spatial disposition of the electrophilic center relative to the receptor nucleophile in the secondary recognition step. Both the maleamate ester **6a** (the *cis* analog of β-FNA)[31] and dihydro-β-FNA(6-NHCO-$CH_2CH_2CO_2Me$, not a Michael acceptor function) showed little evidence of alkylation ability in the GPI.



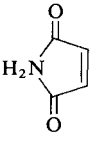
6

a R = NHCOCH=$CHCO_2Me$ (*cis*)

b R =



c R = $NHCOCH_2$

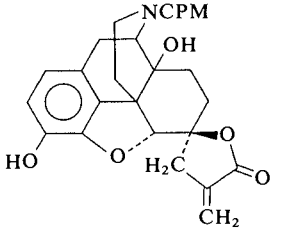


The 6β-NHCOCH=CHCOMe(*t*) and 6β-NHCOCCl=CH_2(*t*) analogs were more potent than β-FNA as irreversible antagonists of GPI μ-sites (κ-sites were little affected) while the highly reactive maleimides (**6b** and **6c**) were much less effective in this respect. The *N*-allyl analog of β-FNA was

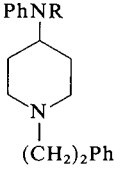
several fold less active as an antagonist at GPI sites but displayed persistent agonist activity (β-FNA is a *reversible* agonist). No evidence for covalent attachment of the benzoylformamide (6β-NHCOCOPh) or bromoacetamide (6β-NHCOCH$_2$Br) analogs in the GPI was found. The former agent was a potent agonist (24 × morphine), while its benzamide congener (6β-NHCOPh, synthesized for comparative purposes) proved over 200 times more active than morphine; κ-sites are probably involved because potencies were unchanged after treatment with β-FNA.

The maleimidoacetamide **6c** differed from β-FNA in showing considerably greater irreversible μ-antagonism in the MVD relative to μ-blockade in the GPI. It was proposed, on this basis, that different proportions of μ-receptor subtypes (μ_M and μ_G) exist in the two tissues. Receptor models were advanced in which μ-receptors are subject to regulatory subunits ρ, which differ in the two muscle preparations.

Another group[114,117] studied the binding of β-FNA and other affinity ligands to rat brain membranes and obtained results somewhat at variance with the smooth muscle data. Thus, β-FNA lacked irreversible binding properties (inhibition of [^{3}H]naltrexone binding: unwashed, 22% of control; washed, 101%) in contrast to its irreversible antagonism of smooth muscle receptor sites. The 6β-chloroacryloyl amide (NHCOCHCl=CH$_2$) analog (see also above) was similarly effective in displacing [^{3}H]naloxone but had a marked degree of irreversible action, especially in the presence of NaCl (% control: unwashed, 9; washed, 39; no NaCl: unwashed, 21; washed, 73). Other compounds examined were the α-methylene lactones **7** and fentanyl derivatives **8**, of which only the lactone **7** (6β-O epimer) had irreversible effects (% inhibition: 40 with NaCl, 66 without). Some correlation among the antagonists was found between the degree of irreversible binding and rate of Michael addition to *p*-methoxybenzene thiol, again in contrast to previous observations.



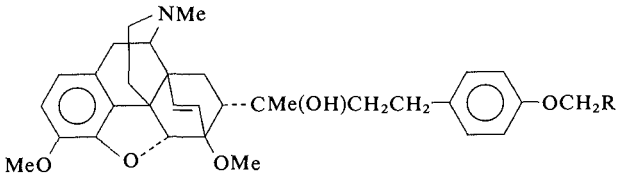
7 (and 6α-O epimer)



8

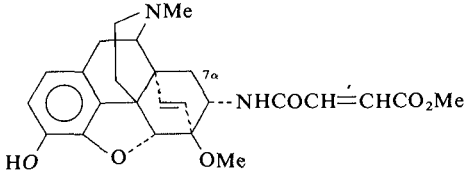
R = COCl=CH$_2$
COCH=CHCl(*t*)

Hybromet **9b**, an oripavine derivative, was designed for use in affinity chromatography.[115] A 500-fold purification relative to a crude solubilized extract[116] was achieved by use of a column prepared by condensing its precursor **9a** with Affigel-401, a sulfhydryl-containing derivative of Agarose. The product was μ-selective. Data on **9b** itself is awaited.

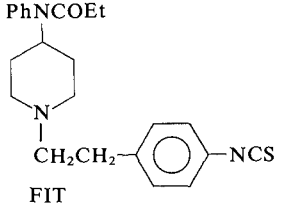


9 a R = $CH{=}CH_2$
b R = $CH(OMe)CH_2HgBr$

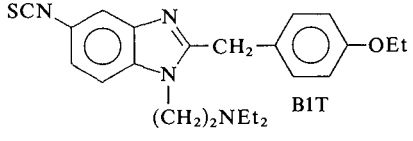
An NIH group has examined irreversible ligands based on oripavine, etonitazene (p. 387), and fentanyl (p. 287), termed FAO, BIT, and FIT, respectively (see **10**). Of these, FIT and FAO proved highly selective alkylators of δ-receptors, while BIT was equally specific toward μ-sites.[34] The *N*-CPM analog of FAO also had δ-selectivity and displayed the properties of a narcotic antagonist as judged by its effect on the adenylate cyclase activity of hybrid



FAO



FIT



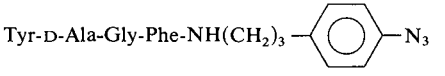
BIT

10 (NIH irreversible ligands)

cell homogenates. The corresponding 7α-isothiocyanate (also an antagonist) specifically alkylated μ-sites in brain tissue.[35] Tritiated FIT has been used to identify an M_r 58,000 subunit of the opioid receptor that is alkylated by this ligand in the presence of dextrorphan but not levorphanol.[36] When a $NHCOCH_2C_6H_4$-*p* group was inserted between C-7 and *N* of FAO, the product bound specifically to μ-receptors, while the analog with a 7α-$NHCOCH_2C_6H_4p$-NCS function bound equally well to μ- and δ-sites.[134] Thus, the selectivity of a receptor subclass does not appear to be mediated by the type of alkylating function (NCS is present in both μ- and δ-selective labels) or by the agonist or antagonist nature of the alkylating opioid. The whole matter is complex and requires further study.

DALECK(Tyr-D-Ala-Gly-Phe-Leu-CH_2Cl), an enkephalin affinity reagent, also bound irreversibly to a 58,000-dalton subunit of a rat brain preparation with subsequent blockade of μ- but not δ-ligands.[128]

Photoaffinity labels have also been investigated. These are enkephalin analogs containing a photosensitive group [e.g., 4-azidophenyl or 2-nitro-4-azidophenyl (NAP)] that form a covalent bond upon irradiation with UV light. Thus, both the peptide **11**[37] and the Leu-enkephalins **12**[38] bind strongly to brain membranes on photolysis, and the latter pair have been shown to cause a 20–30% inactivation of opioid receptors. Further work on affinity labels and related topics is described in the 1982 and 1983 reports of the International Narcotics Research Conference.[39]



ID_{50} (GPI, μM) 0.028, cf. D-Ala^2-metenkephalinamide, 0.012

11

D-Ala^2-Leu^5-enkephalin-NAP-EDA
D-Ala^2-Leu^5-enkephalin-NAP-β-Ala-EDA
(EDA: ethylene diamine, links Leu^5 carbonyl to NAP or NAP-β-Ala)

12

13.4. RECEPTOR SCENARIOS

Earlier chapters of this book demonstrate the extensive variety of organic molecules that may be identified with confidence as ligands capable of binding to opioid receptors. Indeed, a case may be made for the extent of structural variation among opioids being greater than that of any other pharmacological class of agents with specific effects such as those that activate cholinergic, adrenergic, or histaminic receptors. This observation may merely reflect a greater concentration of effort in the search for novel analgesics; but whatever its absolute truth, it points to opioid receptors having an unusually high degree of adaptability toward ligand structure and molecular geometry. This diversity of ligand structure poses one of the main problems of formulating the molecular characterization of the opioid receptor on the basis of complementary relationships with its ligands—the only approach presently open to us, however deficient, until advances in technology permit direct study of receptors and receptor–ligand interactions. A further problem is that of accounting for the mechanism of action of opioid antagonists and agents with mixed agonist–antagonist effects.

It is generally agreed that opioid receptors are flexible macromolecules, chiefly protein in nature, sited on membrane surfaces and capable of adopting a variety of conformations that are triggered and stabilized by ligand uptake. Links between the receptor and protein-enzyme effectors are made or broken according to the particular conformation assumed with consequent changes in pharmacological response. The possibility that exogenous opioids act

indirectly by bringing about release of endogenous opioids (p. 363) seems improbable in view of the numerous qualitative differences that they display.

Overall speculations on receptor situations (scenarios) devolve on whether multiple or single receptor species are to be considered. The multiple condition in its extreme form requires a collection of distinct (and possibly linked) receptors, each being specific for a particular response (involving pain perception, respiration, etc.) and for a closely related group of ligands, and all susceptible to blockade by a narrow range of antagonists. There can be little doubt that compounds with opioid activity interact with a variety of receptor subtypes, three or four of which (μ, δ, κ, σ) have been well defined (see p. 353). Our concern here, however, is with ligands that induce analgesia and the common side effects of analgesics, and most evidence available links these actions specifically to the μ-receptors (there is some evidence for the coexistence of μ- and δ-receptors in a complex site and that occupancy of both is important for analgesia, p. 490). Thus, the multiple receptor concept calls for an even further classification of a receptor type already defined as a subspecies of opioid receptor, an improbable and unnecessarily complex view.

The alternative concept specifies a *single* receptor species at which all ligands bind and all pharmacological responses typical of central analgesics are mediated. There are two possibilities in regard to receptor–ligand interactions for this model. The simplest (and earlier) view is that all ligands adopt the same binding mode, but this idea is no longer tenable in view of the wide range of molecular species and geometries tolerated by the receptor. It is far more reasonable to believe that a variety of binding modes are possible, probably pivotal about the basic nitrogen function (essential to all ligands) as proposed in 1965 by Portoghese.[40] Such a view accounts for the diversity of ligand structure and allows the possibility of differential perturbation of receptor conformation to which differences in the *quality* of the receptor response may be attributed.

Belleau has offered a detailed consideration of the single receptor situation which allows explanation of the actions of agonists, antagonists and agents of mixed activities.[41]

In its normal resting (unperturbed) state the receptor most likely adopts an ordered conformation (closed state A, Fig. 13.1) in which all links to other macromolecule effectors are intact; this state accommodates and is stabilized by antagonist ligands. Another receptor conformation may be proposed, described as an open or disordered state (B in Fig. 13.1), in which links to other effector molecules are weakened or broken or new ones created. The population of the open state is normally low unless stabilized by interaction with an agonist ligand. Agonist uptake triggers perturbation of the closed to the open state, provided the former is not stabilized by an antagonist. Hence, states A and B represent the classic two-state model accounting for the existence of competing agonist and antagonist ligands.[42] The model also allows for

ligands displaying affinity for both states and thus for the existence of partial agonist-antagonists. In Belleau's opinion, any stabilization of the open state B should result in manifestation of *all* the typical pharmacological consequences of central analgesics. He points out that certain agents with mixed properties are devoid of some of these responses, notably the lack of dependence liability (understood by him as a narcotic property), and terms such agents "metagonists." He therefore proposes a third conformational state (C), also ordered, stabilized by such metagonists in which linkage change is similar to that of state A with the special exception of lesions that lead to dependence phenomena. If conventional (pure) agonists have reduced affinity for state C, the antagonist properties of metagonists (which stabilize this state) may be understood.

The need for the separate classification of agents with both agonist and antagonist properties into dual agonists/antagonists and metagonists may be challenged, since dependence phenomena in the majority of mixed-acting agents are either of a low order, absent, or different in kind from those

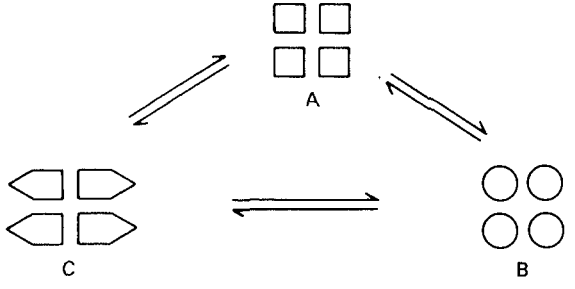


Fig. 13.1. Hypothetical conformational states of the opiate receptor; A, closed state (antagonists); B, open state (agonists); C, allotropic state (metagonists).

associated with morphinelike agonists. State C may nevertheless be usefully retained and may have a wider relevance than that originally intended.

In terms of this receptor situation mixed agonists-antagonists exert their dual effects at the *same* molecular species at which pure agonists associate (however conformationally perturbed). In contrast, some workers advocate the idea that agents with dual action exert their agonist and antagonist effects at *separate* sites. Thus, such agents are considered to block the sites appropriate to pure agonists, which are probably of the μ-variety, but to induce agonism at different (non-μ) sites, and there is evidence that these may be of the κ-subtype (p. 435). If this is the case, then the different quality of agonism induced by pure and dual-action agents may be understood, since the receptor subtypes may be expected reasonably to differ in their links to pharmacological effectors.

Returning to the model of Fig. 13.1, even the view of an agonist-antagonist interaction at the same site remains an assumption, although a likely one on the basis of stereochemical and structure-activity analyses of agonist-antagonist pairs and quantitative studies of their interactions (p. 406). Contrary views have, however, been expressed. Thus, Portoghese and Takemori,[33] from experiments using agonist and antagonist ligands with identical affinity-site functions, have advanced evidence for a specific acceptor of antagonists with allosteric modulation of the agonist site conformation. Their work stemmed from the observation of the differing properties of β-FNA and β-FOA (p. 451)—both contain an identical electrophilic moiety, yet only β-FNA irreversibly blocks μ-sites. The unreactivity of β-FOA in this respect is consistent with its interaction at a site that does not possess an accessible nucleophile requisite for covalent association, and hence to the possibility of the two compounds interacting at separate sites. Protection studies provide further evidence for distinct agonist and antagonist sites. In these experiments GP ileal muscle (for which a control IC_{50} value of morphine was measured) was incubated with the protecting compound followed by addition of 20 n*M* β-FNA. After thorough washing the IC_{50} of morphine was redetermined. The effect of the protector was expressed as the morphine IC_{50} ratio (IC_{50} after treatment/IC_{50} control); values close to unity revealed high protection, and values >1, low protection. It turned out that antagonist ligands were far more effective protectors than agonists and in degree related to their potency as antagonists (nalorphine < naloxone < naltrexone < diprenorphine). If agonists and antagonists occupied the same site, high-affinity ligands of the two types would be expected to have similar protecting abilities, and the fact that such is not the case supports proposals of dual sites. The fact of antagonists of β-FNA sharing common "antagonist-type" *N*-substituents may, however, play some role in making antagonists the superior protectors.

An opioid μ-site model was advanced consisting of μ-subsite (at which agonists associate) linked to a regulatory ρ-subsite. Antagonists bind preferentially to the ρ-sites, which, when occupied, induce a unidirectional (vectorial) decrease in the affinity of the agonist binding site (in contrast, binding of a μ-agonist is held to produce minimal conformational change at the ρ-site, hence competitive kinetics established for agonists and antagonists may be more apparent than real in the classical sense).[139] The authors point out that a dual model of this kind provides a basis for rationalizing the differential effects of various types of treatment on the binding of opioid agonists and antagonists (p. 408, 413) and differing pA_2 values of antagonists dependent on the nature of the competing ligand. The concept also allows explanation of ligand "purity" (a result of relative affinities for μ- and ρ-subsites) and the complex structure-activity relationships of ligands that reflect affinity at two sites rather than one on this basis (cf. also proposals for linked μ-δ-receptors and the regulatory influence of δ- upon the μ-site, p. 490). This

model has been developed further to account for the selective covalent affinity of different μ-receptor subtypes in the GPI and MVD.[113]

Although the evidence for the dual model is compelling and difficult to explain on the basis of the single receptor scenario, it must be borne in mind that the use of ligands that bind in a covalent manner in receptor studies inevitably involves displacement of normal equilibria in an irreversible sense. Conclusions drawn from such experiments may therefore not be relevant to the natural physiological conditions.[43]

Although we are now confident about the existence of receptors that mediate analgesia and have some evidence of their location, our knowledge of the molecular structure of such receptors is limited to the fact of their protein nature with possible inclusion of lipid components (see isolation section). The goal of full characterization (as is that of any protein even when available in the pure form) is an ambitious one and clearly outside our present technological competence. As already stressed, proposals about the molecular features and topography of opioid receptors (more specifically, those at which analgesia is mediated, deemed the μ-type) are therefore limited to inferences that can be drawn in a complementary sense from knowledge of the relatively small ligands with which they interact. A vast fund of structure-activity data, which continues to grow, is available, and many authors have advanced receptor models on the basis of such analyses. These will be reviewed later in the chapter. As a preliminary to these discussions, overall comments and summaries of the structure-activity relationships of μ-opioid ligands will be presented.

13.5. OVERALL STRUCTURE–ACTIVITY RELATIONSHIPS OF OPIOID LIGANDS

In spite of the wide variation in size, molecular skeleton, and functionalities seen in opioids, prerequisites for all authentic analgesics are the presence of a basic center of pK_a permitting extensive protonation at physiological pH and an aromatic feature. Given these essentials, it is clear that a wide range of structures provide orientations of such pharmacophoric groups that allow the primary ligand-receptor interactions that may be enhanced or impeded in varying degree by secondary features of molecules. It is often difficult to discern common molecular features and orientations among agonists of diverse structure; careful examination of accurate molecular models over a range of conformation options is essential, an approach for which the technique of computer graphics offers a powerful tool for the future.

In an attempt to impose some order upon the heterogeneous molecular nature of opioids, it is convenient to subdivide them broadly into five groups, as follows, of which the peptide category has come to the fore only since 1975:

1. Polycyclic molecules of the morphine, morphinan, and benzomorphan type.
2. Derivatives of 4-substituted piperidines typified by pethidine and fentanyl.
3. Acyclic diarylamines such as methadone and dextromoramide, and possibly the benzimidazole derivative etonitazene and its relatives.
4. Enkephalins, endorphins, and related peptides.
5. Miscellaneous examples such as the potent 4-aryl-4-dimethylaminocyclohexanols of Upjohn (p. 391) that fail to fit obviously into any of the preceding categories.

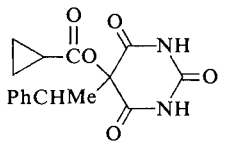
Within each group evidence that members associate with the same receptor and/or exhibit similar modes of binding may be advanced in greater or lesser extent on the basis of comparative structure-activity relationships and direct assessments of receptor affinities; by these means it may also prove possible to classify more specifically some members of the miscellaneous group. Factors governing the spectrum of activity of individual compounds and the definition of "pure" or "mixed" agonists-antagonists add a further dimension to the structure-activity analyses.

Groups (1) and to a lesser extent (2) comprise relatively rigid molecules or structures with well-defined preferred conformations and may be presumed to combine with receptors according to the classical "lock-and-key" model in which all favorable interactions between the different parts of the ligand and the corresponding subsites on the macromolecule may be formed simultaneously. Opioids with flexible molecules, notably the peptides and the acyclic arylamines of group (3), may bind via the so-called zipper mechanism as proposed for peptides.[44] For enkephalins and related compounds, this involves formation of the initial nucleation complex by interaction of the Tyr^1 residue with its corresponding subsite on the receptor followed by a series of conformational rearrangements of the partially bound peptide chain leading to full binding of the remaining amino acid chains and/or functionalities to the appropriate subsites.

13.6. BASIC NATURE

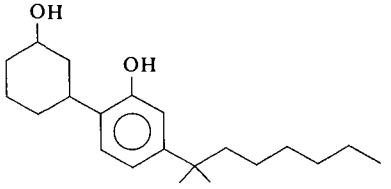
All compounds that behave as narcotic analgesics characterized by the usual criteria contain a basic nitrogen center that either forms parts of an alicyclic ring system, as in morphine and pethidine, or terminates an acyclic chain, as in methadone, etonitazene, and the enkephalins. Nonbasic compounds of high activity in antinociceptive tests invariably fail to satisfy criteria for narcotic analgesics, such as reversal of effects by naloxone or nalorphine or evidence of binding to opioid receptors; recent examples are the barbiturate

13[45] and the cannabinol-related cyclohexane **14**, which is of morphinelike potency in five *in vivo* tests.[46]



13

ED_{50} mg/kg sc MHP, 0.5(morphine 4.8)



14

In most cases the base is tertiary, but there are a few examples of primary and secondary amines with analgesic properties. Most peptides with opioid properties are primary amines, a type of analgesic base rarely encountered prior to 1975. The ionization constants of a number of analgesics representative of the chief groups have been reported (Table 13.2), and all except etonitazene lie in the range pK_a 7.8–9.6 after correcting for solvent effects; this range corresponds to the bases being about 86–99% ionized as cations at physiological pH (7.2 approximately).[52] The protonation of ligand molecules near the receptor surface is thus extensive if not essentially complete, and it has been generally concluded that one of the primary modes of ligand-receptor association is the formation of an electrostatic bond between the cationic center of the ligand and the center of high electron density on the macromolecule termed the anionic site (Fig. 13.2).[53] The relative importance of the electrostatic bond itself and the $^{+}N-H$ proton to ligand-receptor binding at the anionic site is discussed later (p. 465). On the basis of molecular orbital calculations upon the ammonium ion,[55] the positive charge may be distributed over the atoms directly attached to the nitrogen atom. If this is so, the onium group as a whole will be involved at the anionic site and the magnitude of the interaction will be influenced by electron densities on carbons close (α-) to nitrogen as well as by the overall dimensions of the cationic group. Ion pairing electrostatic interactions of this kind are a common feature of pharmacological agents with specific actions, such as adrenergic, cholinergic, and histaminic agonists and antagonists, and form one of the most universal interactions of biological systems.

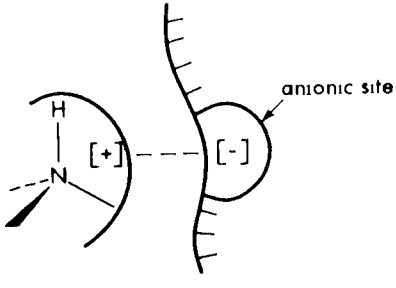


Fig. 13.2. Binding energy for $CO_2^-...^+NH_3$ (a typical ionic interaction) is −5 kcal/mol.[54]

Table 13 2 Ionization Constants of Various Opiate Ligands[a]

Compound	pK_a	Ref
Morphine	8 05	47
Diamorphine	7 6	109
Hydromorphone	8 2	109
Oxymorphone	8 5	109
Nalorphine	7 73	51
Naloxone	7 94	51
Naltrexone	8 38	51
Buprenorphine	8 5	109
Levorphanol	8 18	47
Levallorphan	8 81	51
Cyclazocine	9 78	51
Pentazocine	8 76	48
Phenazocine	8 5	109
Pethidine	8 72	47
Ketobemidone	8 7	109
α-Prodine	7 7 (8 51)[b]	48
β-Prodine	7 75 (8 56)[b]	48
Methadone	8 62	49
Normethadone	8 18	48
Isomethadone	8 21	48
Dipipanone	9 08	48
Dextromoramide	7 1	109
α-Methadol	7 86	49
Fentanyl	7 34	48
Etonitazene	6 36[c]	50

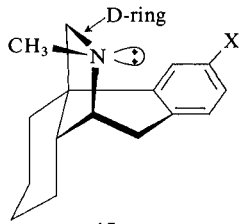
[a] For solubility reasons most of the data refers to solutions of salts (usually HCl) in 50% EtOH—H_2O at 20-25°C, values in water are assumed to be at least 0 5 units higher (see data for α- and β-prodine) pK_a values are uncorrected for ionic strength

[b] In water

[c] Side chain nitrogen

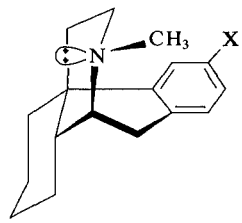
Although conjugate acid forms of opioids are generally regarded as the active species, the existence of small amounts of nonionized base is almost certainly necessary if the drug is to penetrate the CNS as is emphasized by the inactivity of morphine methochloride (in which ionization is complete and irreversible) when given by usual routes.[56] Analgesics with pK_a values at the lower end of the quoted range should be able to concentrate centrally more readily than those with values near the upper limit. A case in point is fentanyl (pK_a 7.3), which has both a high lipid solubility[57] and a high analgesic potency. Etonitazene (about 50% ionized at pH 7.2) is an even more extreme example and is 10^3 times more active than morphine in mice.

In the case of rigid opioids there is good evidence that a specific stereochemical orientation of the nitrogen feature in respect to the rest of the molecule (notably the aromatic group) is important for a productive interaction of the ligand with its receptor. Belleau and his colleagues first drew attention to this aspect when they discovered that the five-membered ring D analog of racemorphan (**15**) was devoid of analgesic agonist or antagonist activities.[58] The compound was made by a general procedure described for ring-D-contracted congeners of morphinans.[121] X-Ray analysis of the HBr salt revealed that its *N*-methyl substituent is directed away from the aromatic ring, while the $^{+}N-H$ (and hence the lone pair orbital in the corresponding base) points toward this structure. In morphinan analgesics with a six-membered D-ring (see **16**), and morphine and benzomorphan derivatives, the reverse



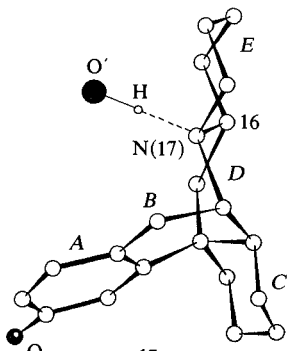
15

(One antipode shown, X = OH)



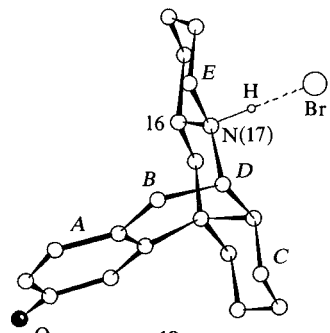
16

stereochemistry obtains—at least in the solid state and probably in the solute condition. Belleau, in fact, attributed the inactivity of **15** to its inappropriate nitrogen lone-pair orbital orientation (for reasons discussed later) but incorrect ^{+}NH and/or ^{+}NMe positioning could equally well be the key factor involved. A similarly ring-contracted analog of a benzomorphan analgesic proved to be of low potency as well but the example lacked a phenolic hydroxyl.[59] The 16,17-butanomorphinans **17** and **18** present examples of isomers of even greater



17

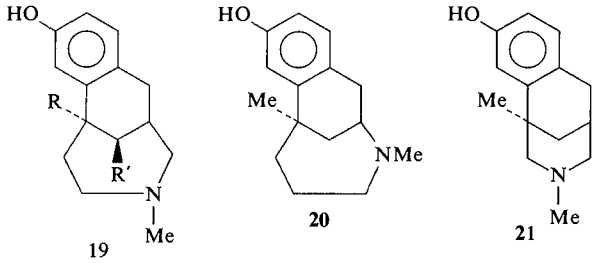
(*syn*, boat ring D)



18

(*anti*, chair ring D)

rigidity that differ in their $^{+}$NH orientations; of these only the *anti* $^{+}$NH/Ar isomer **18** had analgesic properties in mice (WR ED_{50} 3 ± 0.5 mg/kg, pentazocine ED_{50} 5.0 mg/kg).[41,60,122] The $^{+}$NH (lone pair)/aryl orientations of the potent (morphinelike) seven-membered ring benzomorphan congeners **19a** and **19b** are also *anti* (X-ray analysis of HBr salts).[61] It is *syn*, however, in the derivatives **20** (morphinelike in potency) and **21** (codeinelike), but the flexibility of the heterocyclic rings might allow solute molecules to adopt the *anti* conformation.[41]



19

20

21

a R = R′ = H
b R = R′ = Me

Apparently serious objections to the view of the stereoelectronic importance of the nitrogen lone pair of electrons in the productive interaction of an opioid ligand with its receptor are the claims made for the activity of a variety of *N*-methyl quaternary analogs of opioids. Thus, *N*-methyl morphine was reported to be similar in potency to morphine itself when administered directly into brain ventricles,[56,62] while the methiodide of levorphanol (but not the dextrorphanol salt) produced a dose-dependent inhibition of contraction of GP ileum that was completely reversed by naloxone.[63] Binding of [^{3}H]etorphine by GP brain homogenates was also depressed by the levo methiodide, the dextro isomer being less effective. However, Belleau has pointed out that absolute potencies of quaternary salts examined by *in vitro* and rat central routes are low,[65] while the axial *N*-methyl analog of nalorphine retains only 30% and the equatorial *N*-methyl isomer only 1% of the antagonist activity of the base in the MVD test (both isomers lacked agonist effects).[64] More recent work on quaternary salts support Belleau's contention.[66] This evidence suggests that ion-pairing without direct proton involvement can lead to the activation or inhibition of the receptor, albeit inefficiently (indirect action

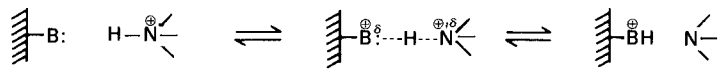
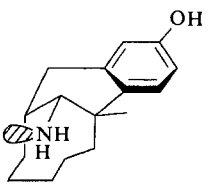


Fig. 13.3. Schematic representation of proton transfer between an acceptor base of the opiate receptor and a protonated morphinan. Position of equilibrium strongly dependent on relative basicities of acceptor and donor.

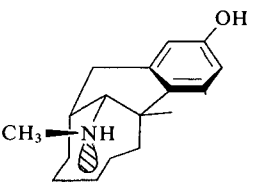
involving displacement of endogenous effectors from storage sites is an alternative explanation). The reduced activity of quaternary salt forms of opioid ligands could, of course, be attributed to the extra *N*-substituent leading to steric hindrance at the anionic site. However, Belleau's evidence of stereoelectronic lone-pair involvement is difficult to refute and leads to the attractive concept of a protein transfer reaction occurring when an agonist ligand binds to the receptor (Figure 13.3).

In this scheme (referred to as clastic binding),[125] the morphinan (for example) acts as a potential proton donor and binds in the cationic form in an initial electrostatic interaction. Transfer of the proton to a nucleophilic site on the receptor can then occur; if proton transfer one way or the other is the key trigger of analgesia, the equilibrium position of the proton will necessarily depend on the lone-pair orientation and the basicity of the nitrogen. In these terms a distinction between protonated and nonprotonated ligands as "active species" does not arise. The influence of nitrogen basicity is nicely illustrated by comparing an *N*-methyl analgesic with its *N*-CD_3 analog, since replacing hydrogen by deuterium elevates basicity (by 20–25%) without altering the steric requirements of the basic function. In fact, the ND_3 analogs of both morphine and levorphanol are about half as active as their protio parents as analgesics.[125,67] Activity differences cannot be attributed to metabolic effects because replacement of *N*-H by *N*-D slows oxidative *N*-dealkylation[68] and the results suggest that displacement of the equilibrium of Fig 13.3 from left to right favors the induction of analgesia.

The lone-pair orientation factor also serves to account for the unusual activity relationships of the bridged aminotetralins **22** (see p. 397), the primary amine being more potent than the *N*-methyl congener (the hydrocarbon bridge encases the amine group and probably limits solvation—a factor detrimental to the transfer of free amines to the CNS).[41] In **22a** there should be a significant population of a conformation in which a solvent-exposed *N*-lone pair projects away from the aromatic ring in a relationship akin to that of levorphanol and its analogs. When an *N*-methyl group is present, its steric demands (greater than those of the *N*-protons) prevent it fitting into the polymethylene cavity and render the form **22b**, with change in lone-pair orientation to a position unfavorable for agonism, the lower-energy conformation. The reason **22a** also acts as an antagonist (p. 398) may be due to its binding to the receptor in an alternative form with the lone pair oriented as in **22b**.

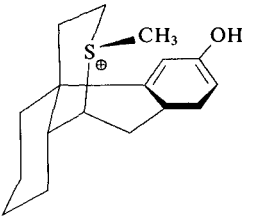


22a

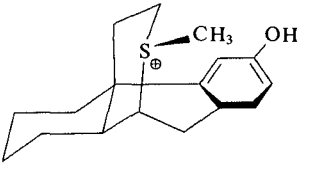


22b

In an attempt to distinguish between electrostatic-pairing and proton-transfer phenomena, Belleau prepared the sulfonium analogs of levorphanol **23** and isolevorphanol **24**; the levorphanol analog was isolated as a mixture of *S*-Me isomers with **23** preponderating while **24** (and its *N*-CPM congener) were obtained as single species.[58,123] Because of their pyramidal geometry sulfonium cations are virtual isosteres of tertiary amine salts except for their



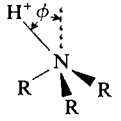
23 (S-Me mixture)



24 (Single isomer)

inability to accept a proton. Results of preliminary pharmacological studies were unexpected in that both compounds behaved as agonists (analgesics) in the CNS by an *in vivo* test, and antagonists in the GPI preparation; **23** approached both the *in vivo* and *in vitro* potencies of levorphanol in these tests. The interpretation is that the opioid CNS and ileum receptors are activated by mechanisms that fundamentally differ. Electrostatic ion-pairing at the GPI site, while sufficient for agonism in the CNS, is not sufficient in the ileum, where intervention of a proton (as in proton transfer) is essential for the triggering of the agonist response. In the absence of the proton the electrostatic interaction leads only to blockade of the site. A hydrogen bond complex also appears important for agonism at MVD sites, since **23** and **24** (although agonists in this preparation) had very low activities. The results imply that pharmacological events following the primary interaction of opioid agonists with the GPI receptor may have no pharmacological bearing on their actions on the CNS receptor and that correlations between ligand action at the two sites are purely fortuitous (cf. differing effects of β-FNA and other affinity labels on brain and smooth muscle preparations, p. 452). The data do not, unfortunately, support the idea of hydrogen-transfer interactions at the CNS receptor, as developed to account for the lack of central activity of the D-normorphinan **15**. It would be of interest to find out if this compound (and also the butanomorphinan **17**) behaves as an antagonist at GPI sites.

The energetics of the interaction of the nitrogen lone pair with a proton (taken as the simplest model of an electrophilic site upon a receptor) have been calculated by molecular orbital techniques.[69] In the cases of proton interaction with ammonia and trimethylamine, the lowest-energy structure was one in which the proton lay directly along the lone pair axis with $r = 1.02$ Å (the equilibrium N—H bond length, see **25**). Energy rose as the angle ϕ increased but was less sensitive at longer values of r, indicating that "bent"



25 (R = H or Me)

complexes might be significant for ligand–receptor interactions where close approach of nitrogen to the electrophilic site is not possible. A similar computational study has been made of NH_3–H_2O, taken as a model for the clastic binding hypothesis.[124]

13.7. *N*-SUBSTITUENT STRUCTURE

It is not possible to make clear-cut statements about the role of *N*-substituent structure upon the biological response to opioid ligands. One reason is the fact that influences upon both ligand affinity for, and intrinsic activity at, the receptor are involved, and these cannot be differentiated except in the rare cases where the ligand is a pure antagonist of presumed zero intrinsic activity (binding experiments probably provide the closest approach to affinity data). The problem is compounded by the influence of other regions of the ligand upon the action profile whereby, for example, a pure antagonist may be converted to a mixed-acting agent by structural change remote from the basic center. Yet another aspect must be the pharmacokinetic one in that passage of lipid barriers is facilitated by the presence of long hydrocarbon chains and/or aromatic features and by a shift in ionization equilibrium toward the free base species. A detailed account of basic group structure associated in particular with antagonism has been given in Chapter 12, and a summary of salient points is listed here.

1. *N*-Methyl remains the substituent most commonly associated with agonism, although there are a few examples of *N*-methyl antagonists and mixed-acting agents (p. 428).
2. Receptor uptake of most ligands is enhanced by unbranched *N*-substituents larger than methyl, particularly those with a two or three methylene chain terminated by an aryl group. *N*-Arylalkyl derivatives of this kind seldom, if ever, display antagonist properties and hence may be regarded as pure agonists. Such groups are mandatory for significant activity in 4-anilidopiperidines like fentanyl and the acyclic base diampromide. In contrast, the methadone and 2-benzylbenzimidazole classes demand small alkylamine or medium-sized alicyclic basic groups for optimum activity. α-Branching of the *N*-substituent, as in *N*-tert-alkyl and *N*-*sec*-alkylnormorphines, usually leads to low levels of potency.[110]

3. With few exceptions, antagonist properties are specifically associated with three-carbon substituents (propyl, allyl, and propargyl) or methylene linked to a small cycloalkyl ring (notably cyclopropylmethyl, CPM) (p. 424). It must be stressed, however, that bases carrying these substituents only behave as antagonists when part of the polycyclic morphine, morphinan, or benzomorphan systems; otherwise activity (if present) is that of an agonist. Further, most polycyclic bases of this kind display mixed actions dependent on the circumstances of their use, and some are much more potent agonists than antagonists (e.g., certain *N*-CPM oripavines) (p. 410).

It is probable that all opioid ligands have the potential of activity at either extreme of the agonist-antagonist spectrum. To date the majority of compounds developed and used as analgesics have been presumed to behave solely as agonists although pharmacological evidence for such assumptions is lacking in all but a few cases (eg morphine and a few recently reported analgesics). While relatively pure agonists may be common, antagonists without agonist properties are rare. The only well-documented examples are naloxone and naltrexone (p. 55) both of which possess a 14β-hydroxyl substituent. The recipe *N*-allyl/CPM-14β-OH does not guarantee pharmacological purity, however, and it is evident that overall molecular structure is crucial to the pharmacological profile of opioid ligands, the relevant SAR principles of which are still poorly understood.

The 30-year old proposal that *N*-demethylation(dealkylation) of morphine and its congeners is involved in the pharmacological activity of opioids[142] was based upon the evidence of metabolic studies in the liver and, in consequence, received much criticism. Recent work of Hahn and his colleagues[143] has revitalized the hypothesis since their data relate to central metabolic processes. Significant facts established by double isotope (6-^{3}H, *N*-$^{14}CH_3$ morphines) techniques are:

1. The reaction is localized in brain regions which are associated with the presence of opioid receptors and with opioid sites of action.
2. The enzyme responsible for brain *N*-dealkylation is different from the liver enzyme (a cytochrome P-450 mixed function oxidase).
3. Dextrorphan and (+)-morphine are not *N*-demethylated while the corresponding potent levo agonists are biotransformed.
4. The reaction *in vivo* is very rapid and takes place well within the time frame of receptor binding and the onset of opioid action.
5. Enzymatic *N*-demethylation of morphine also occurs in other opioid target tissues such as the GPI and hybrid cell lines but is absent in non-target tissue such as the diaphragm muscle.
6. The antagonist naloxone inhibits *N*-demethylation of morphine (*in vivo* and *in vitro*) in specific brain sites but does not affect the course of the reaction in the liver.

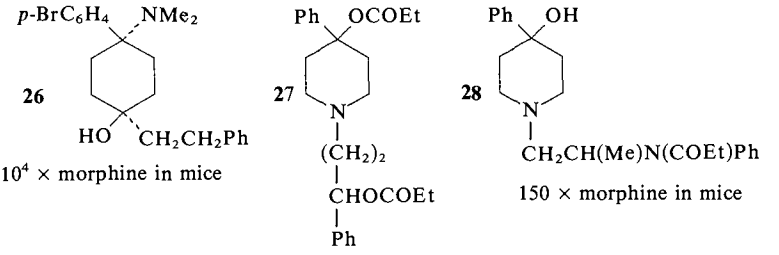
7. Acute morphine increases while opioid tolerance results in a relative decrease in the brain microsomal *N*-demethylation of morphine.
8. Naloxone and naltrexone (pure antagonists) are not *N*-dealkylated in the brain although they are metabolized in this manner in the liver.
9. Increased *N*-dealkylation in the brain is associated with greater biological effectiveness of morphine.

The authors favour a mode of opioid action in which an "*N*-dealkylase" enzyme is first activated either by an endogenous substrate (such as an enkephalin or endorphin which lack *N*-alkyl substituents) or an exogenous opioid-receptor complex (the enzyme incidentally *N*-de-alkylates the opioid). The activated enzyme then acts upon an unknown physiological substrate to yield a product which ultimately produces biological responses typical of opioids. Opioid antagonist-receptor complexes fail to activate the enzyme in this scheme.

13.8. AROMATIC FEATURES

All active compounds possess at least one aromatic ring (see p. 75 for one minor exception). The most common aromatic entity is the phenyl ring as in pethidine (one ring) and methadone (two rings), while in morphine, the morphinans, and the benzomorphans a phenyl ring forms part of a polycyclic skeleton. Substituents in the benzene ring are generally disadvantageous, but a correctly placed hydroxy group (phenolic) is a requirement for high activity in morphine and its congeners while several potent 2-tolyl analogs of pethidine are known. In certain cases, phenyl may be replaced by a heteroaryl ring as in the thiambutene analgesics and a 4-(2-furyl) analog of pethidine; in etonitazene and its relatives the aromatic feature is an imidazole nucleus fused to a phenyl ring. A 2-fold role is likely for the aromatic moiety of opioid ligands. First, its facilitation of penetration of the CNS by virtue of the lipid-solubility-endowing nature of aromatic hydrocarbon features, and second, contribution to receptor binding via collective van der Waals bonds. These bonds are best developed at complementary flat areas as provided, for example, by aromatic amino acid residues of the receptor protein.

Most analgesics of exceptionally high potency such as those shown (**26**–**28**) possess at least two aromatic features, and it is likely that these ligands utilize more than one set of aromatic van der Waals bonds when they bind to the receptor. The fact that most opioid peptides of significant potency also have two aromatic features (Tyr^1 and Phe^4) lends encouragement to this view, and it has been further proposed that analgesics with dual aryl substituents provide structures that mimic the related residues of the peptides. If such mimicry is valid, the aryl feature that stands in lieu of Tyr^1 should benefit (in terms of receptor interactions) by insertion of a correctly placed phenolic OH. Fentanyl



(Potent analgesics with dual aromatic features)

and reversed esters of pethidine have been modified accordingly to test this idea, but results obtained did not support the concept (pp. 241, 295).

In the case of methadone and its congeners, the dual diphenyl system (CPh_2) does not lead to specially elevated potencies, and it is possible that one phenyl ring serves as a steric restraint for the other in achievement of an active conformation. High orders of activity are found in oripavine derivatives without inclusion of extra aromatic elements, but all potent derivatives have extensive additional hydrocarbon elements attached to the morphine skeleton.

There is ample evidence of the importance of the relative placement and orientation of aromatic features to the rest of the molecule (notably the basic area) in active derivatives, and binding interactions involving the basic and aromatic features of the ligand must be of primary importance in opioid receptor–ligand interactions. One example of the influence of phenyl orientation relative to the rest of the molecule is Portoghese's explanation of structure–activity variations among antipodal prodinés and related compounds, as discussed in Chapter 7.

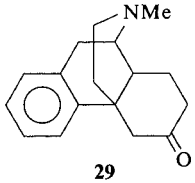
13.9. OXYGEN FUNCTIONS

The oxygen function of greatest influence upon most opioid ligands of the polycyclic class is undoubtedly the phenolic hydroxyl. In morphine and its congeners a free phenolic OH is present at C-3 in all potent members whether agonist or antagonist in nature. On the other hand, it is detrimental to activity in many piperidine-base analgesics such as fentanyl and reversed esters of pethidine. Support for the classification of small cyclic molecules with opioid properties within the morphine group rests largely upon their possession of a phenolic function and vice versa (e.g., 3-arylpiperidines, p. 279). In morphine and its relatives removal of C-3 OH or its masking by alkylation always results in a sharp fall in potency (acetylation is ineffective in masking 3-OH, since derivatives such as heroin suffer rapid *in vivo* break-

down to the free phenol, p. 27). These observations point to a hydrogen bonding subsite on the receptor adjacent to the area complementary to the aromatic ring. Moving the phenolic group to the 1- or 2-position has been shown, at least for 6-ketomorphinans, to produce compounds of low potency.[70] Activity is retained in some 4-OH phenols related to morphine, but in these cases *O*-methylation *elevates* activity, demonstrating that hydrogen bonding is not important to the binding of such ligands.[144]

Recent work indicates that the phenolic 3-OH of morphine does not play as vital a role as previously thought. Morphinan analogs that lack it have unchanged or elevated potencies provided a 4-phenolic (or better, 4-methoxy) substituent be present to compensate for the absence of the 4,5-oxide bridge of the natural alkaloids (p. 125).

A variety of oxygen functions in ring C (C-6 OH, C=O, C-14 OH, OCOR) and a few nitrogen functions (C-6 azide, amino) also enhance the activity of the morphine group in varying degree, but none is vital to activity. These groups may strengthen ligand binding by hydrogen bonding acceptor or donor interactions with appropriate subsites of the receptor. The presence of polar functions in both rings A and C sometimes is detrimental to activity as in the morphinan-6-one **29**, probably a result of impaired transport across CNS barriers (cf. also the relative iv and central activities of morphine and levorphanol[57]).



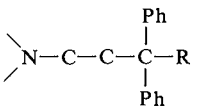
29

Ar substituent	MHP ED_{50}(mg/kg)
None	0.33
3-OH	1.9
4-OH	1.6

In analgesics with nonrigid or semirigid (cyclic) skeletons the presence of a phenolic group usually depresses potency, and the few cases where it is advantageous (such as ketobemidone and 4-aryl-4-alkylpiperidines) are those of compounds considered to mimic the morphine conformation. On the other hand, nonaromatic oxygen functions are essential. In 4-phenylpiperidine analgesics these include the 4-substituents CO_2Et (as in pethidine), OCOEt (in alphaprodine and other reversed esters), COEt (in ketobemidone), and OEt [in a 4-(2-furyl) piperidine]. Fentanyl requires an *N*-propionyl group. Overall size of such groups is critical for optimum potency (p. 236). Activity is weak or absent in such piperidines when oxygen is linked to an acidic hydrogen as in 4-OH and CO_2H (fully charged CO_2^- anionic species are only encountered in analgesics of the peptide class). Nonaromatic hydroxyl is present, however, in the piperidine **28** and the cyclohexane **26** both of high potency.

A range of oxygen functions is also met in the 3,3-diphenylpropylamine class of analgesic (R in **30**): methadone (COEt, SO_2Et in sulfone analog),

methadols (CHOHEt), acetylmethadols (CHOCOMeEt), dextromoramide [$CON(CH_2)_4$], ester analog (CO_2Et). These functions may provide acceptor or donor terminals of hydrogen bonding interactions with the receptor. Related thiambutenes **31** are rare examples of analgesics devoid of an oxygen function, but they require the sulfur heteroatom because corresponding diphenyl derivatives are inactive. Potent benzimidazole analgesics **32** possess oxygen functions



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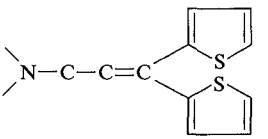

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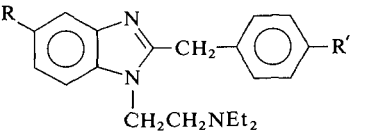


32

in both aromatic regions of their structure, often alkoxy in the benzyl and nitro in the heterocyclic rings. The nitro function is rare to analgesics and may play the same role as ionized carboxylate in opioid peptides. Opioid peptides are rich in oxygen functions of all kinds. Apart from the Tyr^1 phenolic group (essential to activity) and the various peptide carbonyls that may govern conformation through intramolecular hydrogen bonding with NH groups, the terminal carboxylate group (CO_2^-) may be changed in many ways with retention or elevation of activity (e.g., to $CONH_2$, CH_2OH, CO_2Et, SO_2OH, or PO_3H).

The role of oxygen functions in opioid ligands is complex, involving distribution, metabolism (especially conjugation) and binding interactions with the receptor, and assessment of the significance of a particular group requires information on each of these aspects.

13.10. STEREOCHEMICAL FEATURES

Specific arrays of atoms comprising C, H, N, and O have been shown to be essential to ligand uptake at opioid receptors and identified as basic nitrogen, aromatic, and oxygen functions. A molecule that includes all these essentials within its structure may still, however, fail to display opioid properties if the relative arrangement of its pharmacophoric features and the overall absolute geometry of the molecule are inappropriate to ligand–receptor interactions. A host of stereochemical investigations of analgesics dating from the early 1950s has served to underline this fact. Although in any one chiral analgesic or class of analgesic one absolute arrangement is preferred to the corresponding mirror image (in greater or lesser extent dependent on the conformational flexibility of the molecule), quite different arrangements of pharmacophores are compatible with receptor activation in analgesics of different classes. The question of whether these differences are real or apparent and related to different modes of ligand–receptor uptake must be the task of medicinal chemists in compara-

tive stereochemical studies of diverse groups of opioid ligand, aided by modern techniques such as computer graphics.

13.11. RECEPTOR MODELS

Until it becomes technically possible to examine opioid receptors and their complexes with ligands directly, knowledge of receptor structure must be inferred from that of the ligands with which they interact. Many proposals of opioid receptor structure and topography have been advanced on the basis of the vast fund of structure-activity relationship data now available respecting opioid agonists and antagonists. The early concept (1954) of a single receptor at which all ligands associate in manners that are essentially alike now appears improbable, and the view of multiple modes of ligand-receptor interaction, whether at a single receptor or a variety of linked receptor sites, is a more reasonable one in the light of the present body of structure-activity analyses and receptor affinity evidence. There are basic similarities in enzyme, antibody, and receptor specificities involving the binding of small molecules to macromolecules.

It is, however, intellectually satisfying to formulate a receptor model that accounts for as much of the experimental information as possible, and for this reason a review of such proposals is made here. A further complication to receptor speculations of this kind is the fast-accumulating evidence of the existence of subpopulations of opioid receptors, and most proposals are best viewed in terms of μ-receptors that associate with morphine as the prototype agonist.

In 1954 Beckett and Casy developed a hypothesis concerning the nature of the analgesic receptor on the basis of stereochemical evidence and structural features common to analgesics and their antagonists known at that time.[53] They considered the stereoselectivity of analgesics and the results of configurational studies (limited then to a few methadone- and morphinan-type analgesics) to be indicative of a "three-point association" between drug molecule and receptor site. Belief in a single receptor was encouraged by the common antagonistic action of nalorphine against a variety of analgesics. A basic group and a flat aromatic ring structure were postulated as two of the active areas of the molecule while the third was held to be a hydrocarbon entity. Some idea of the arrangement of active sites on the receptor was gained by consideration of the actual shape of rigid analgesic molecules, since their "active features" should be complementary to corresponding features of the receptor surface. Natural (−)-morphine served as a model because it had a rigid skeleton and its conformation was known (the absolute configuration of morphine was established subsequent to 1954). The relationship between (−)-morphine and

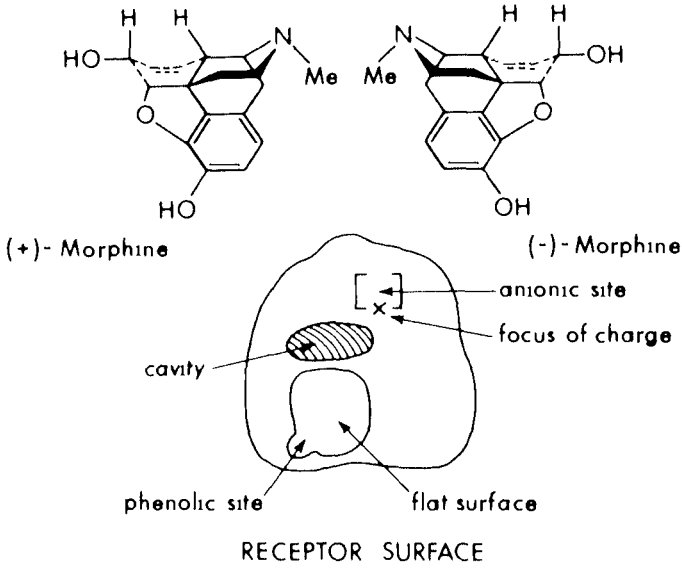


Fig. 13.4. Diagrammatic representation of the three-dimensional arrangement of morphine and the analgesic receptor site. The diagrams represent the lower surface of the drug and the upper surface of the receptor; complementary surfaces in front of, behind, and in the plane of the paper are represented by—, ---, and —, respectively. This drawing is a modified form of the original diagram to take into account the true configuration of morphine, which was unknown in 1954.

(+)-morphine and the receptor are shown in Fig. 13.4; note that the agonist molecules must be turned over (mentally) before fitting them to the receptor. The three essential sites described were:

1. A flat portion that allows binding with the aromatic ring of the analgesic drug through van der Waals type forces. The rigid model also fixes the location of the phenolic binding site.
2. An anionic site that associates with the positively charged basic center of the ligand.
3. A cavity suitably oriented with sites (1) and (2) to accommodate the projecting bimethylene (C-15, C-16) portion of the piperidine ring D that lies in front of the plane containing the aromatic ring and the basic center.

It was argued that association of ligand donor groups with sites (1) and (2) represents the primary binding interaction, while correct alignment of a projecting hydrocarbon residue with the cavity in one enantiomorph enhances the drug-receptor contact and consequently the pharmacological response; in the opposite enantiomorph, the projecting group impairs the drug-receptor contact because it fails to coincide with the depression in the surface.

In the original paper the proposition was made that the receptor of Fig. 13.4, formulated on the basis of the morphine molecule, was capable of accommodating other structural types of analgesic, and a common mode of drug-receptor interaction for both cyclic and acyclic analgesic molecules was implied. These aspects are now examined in the light of the more extensive evidence and data now available.

The model adequately accommodates most structural variants of morphine and the morphinan and benzomorphan groups of analgesic. All such ligands are closely related in the molecular shape and absolute configurational relationships of the more active antipodal forms. Additional receptor sites are required to interact with:

1. *N*-Substituents larger than methyl, especially 2-arylethyl, allyl, and CPM, with the possibility of sites for the latter two being specifically associated with narcotic antagonism. These sites may be regarded as extensions of or additions to the anionic site of the 1954 model.
2. C-14 (or equivalently placed) substituents, as in β-metazocine and isomorphinan, and the C-6/C-14 ethylene bridge of the potent oripavines.

Separate subsites, both lipophilic in nature, are required to enable these features to reinforce binding, although one site must have a hydrogen bonding acceptor capacity to allow benefit from interaction with the hydroxyl substituent of the bridged compounds. The general location of the new binding areas relative to morphine is shown in Fig. 13.5, assuming an extended *N*-phenethyl conformation for the bound ligand. Since 14β-oxygen functions (OH, OCOR, OR) raise the potency of morphine and its congeners, an appropriate subsite must also be formulated not necessarily with hydrogen bonding acceptor character because many O-acyl and alkyl analogs bind as well or better than the free OH derivative. Subsites that interact with ring-C and otherwise placed oxygen functions (including the 4,5-ether bridge) may likewise be involved in the binding mechanism. Oxygen binding near C-10 may be responsible for the κ-agonist properties of certain C-1 ketobenzomorphan derivatives (p. 434).

Analgesics of the 4-arylpiperidine class mimic the geometry of a large portion of morphine when in the axial phenyl chair conformation **33a** and were thus earlier believed capable of accommodation at the proposed receptor. This view later fell into disrepute as a result of conformational considerations and particularly the radically different structure-activity relationships in regard to *N*-substituents and the influence of phenolic hydroxyl between the 4-arylpiperidine and morphine groups. There is evidence that reversed esters of pethidine and other 4-phenylpiperidines with C-4 oxygen functions bind in the equatorial 4-phenyl chair conformation **33b**, and receptor modifications necessary to allow uptake of both *ax* and *eq* 4-phenyl chairs are discussed

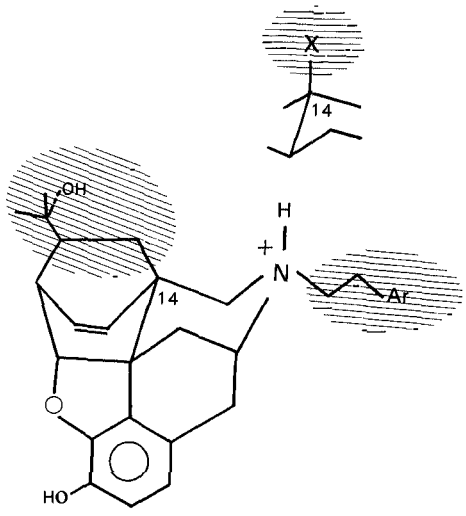
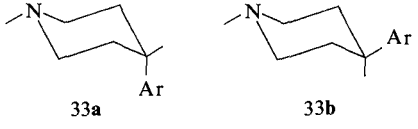


Fig. 13.5. Representation of a morphine-based ligand bound to the receptor surface. Binding sites additional to those of Fig. 13.4 are shaded. X = OH, OR, OCOR, or R, where R is a hydrocarbon radical.



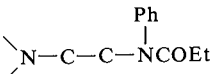
33a 33b

later. However, the original view now appears reasonable for 4-arylpiperidines with C-4 carbon substituents (CO_2Et, COEt, Me etc) on conformational grounds (*ax*-phenyl forms are more favored in C-4 carbon than C-4 oxygen derivatives) and the fact that potent compounds of this type generally require a phenolic *m*-OH substituent (p. 276). In these terms, the agonist properties of the *N*-allyl analog of ketobemidone present a problem, but it is possible that such derivatives bind in the reverse (*eq* 4-Ph) conformation whereby the allyl function is remote from the binding site that triggers antagonism as explained later. The original model is also reasonably appropriate to 3-arylpyrrolidines and 3-arylpiperidines with opioid agonist or antagonist properties, especially as all active derivatives are phenols (p. 279). Fentanyl is unlikely to fit the model of Figure 13.4 because it would need to bind in the axial 4-R chair conformation with the assumption that the anilido function (R = NHCOEtPh) is equivalent to the aryl feature of morphine.

Many conformational options are open to acyclic analgesics like methadone and the thiambutenes, and it is not unlikely that some may have an aromatic and basic group suitably aligned for association at the morphine-

based receptor, with the second aromatic substituent and various N—O intramolecular interactions playing conformational holding roles. Against this view are the facts that, unlike morphine and its congeners, activity in the group is abolished rather than enhanced by an *N*-phenethyl group and that activity does not depend on the presence of a phenolic OH. Both benzimidazole derivatives and 3,3-diphenylpropylamine analgesics possess the feature of a 2-aminoethyl side chain linked via a fully substituted atom (nitrogen in this case) to an aromatic ring, and active molecules are flexible enough to provide a conformation likely to fit the original receptor model. Whatever the binding mode, receptor subsites that interact with oxygen functions vital to activity (NO_2, OEt) must be implicated in benzimidazole binding. Comparative structure-activity relationships, however, point to the benzimidazoles having a different binding mode to that of morphine (p. 387).

The concept of *multiple uptake modes* of ligand-receptor interaction arose from studies of acyclic analgesics of the basic anilide type **34** and was first clearly delineated by Portoghese.[71] These anilides differ from the general



34

methadone-type structure only by replacement of one phenyl group and its attached quaternary carbon by nitrogen. The most potent member is diampromide (p. 311), which carries an *N*-methyl-*N*-phenethylamino and an α-methyl substituent. As in methadone, an antipodal activity difference is found, but the more active antipodes of methadone and diampromide (which possess asymmetric centers of the same kind) *differ* in configuration. It is apparent that the two classes cannot bind in similar manners to the receptor, a view supported by the differing structures of their basic function. Portoghese drew attention to other configurational anomalies among acyclic analgesics (see p. 320 of Chapter 9) and proposed reasons that antipodal selectivity by the receptor for ligands might alter as a result of structural change [e.g., replacement of carbonyl (a hydrogen bonding acceptor function) by a secondary alcohol (CHOH, a donor group)]. He stressed that differences in molecular binding modes could be detected by comparing the variation in activity in two or more different series of analgesics when identical changes of the *N*-substituent are made. Thus, the plot relating to derivatives of pethidine and its reversed ester (Fig. 13.6), based on well-defined data, provides evidence that the two series have similar interaction modes at the receptor and for the consequent existence of a linear free energy relationship. In contrast, *N*-substituents such as cinnamyl and 3-phenylpropyl (which give potent pethidine but inactive morphinan derivatives), phenacyl (potent morphinan, weak pethidine analogs), and allyl (morphinans have antagonist and pethidine derivatives agonist properties) clearly differentiate the morphine from the

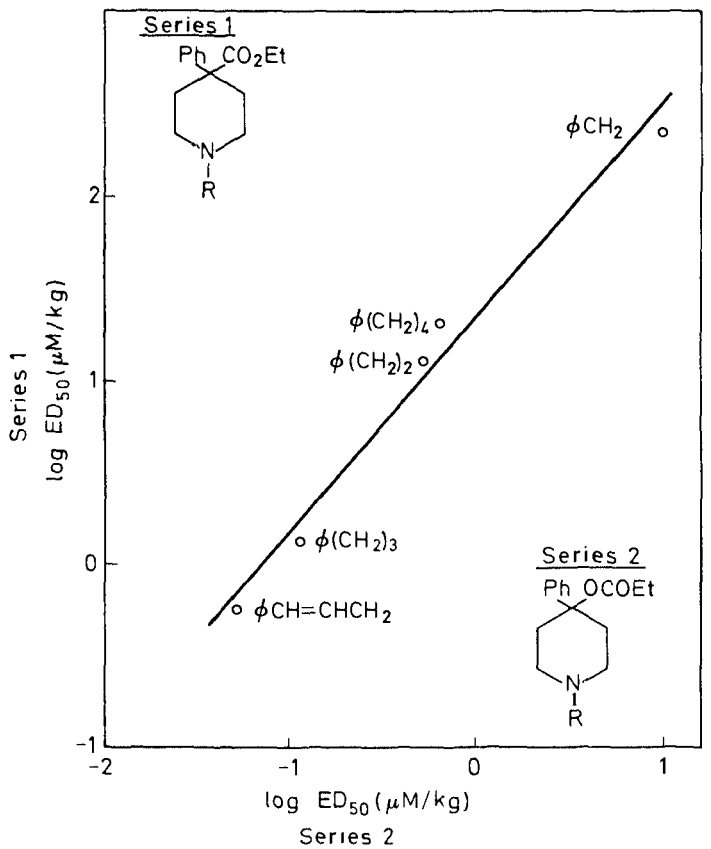


Fig. 13.6 A plot of the log ED_{50} (related antinociceptive assays in rodents) of analgesics in series 1 versus the log ED_{50} of identically *N*-substituted compounds in series 2.

4-phenylpiperidine groups of analgesic terms of receptor interactions. The influence of a phenolic hydroxyl group adds further weight in this respect. Portoghese felt it reasonable to assume that regardless of the binding mode, all analgesics (including competitive antagonists) are involved in ionic bonding with an identical anionic site that may be envisaged as a pivotal point around which the various modes of binding may occur (Fig. 13.7). A more detailed version of this model was later given in which separate subsites were designated to recognize aromatic residues of the morphine and 4-arylpiperidine classes of analgesic.[111] These subsites correspond to those appropriate to the Tyr^1(T) and Phe^4(P) aromatic features of the enkephalins, respectively (Fig. 13.8).

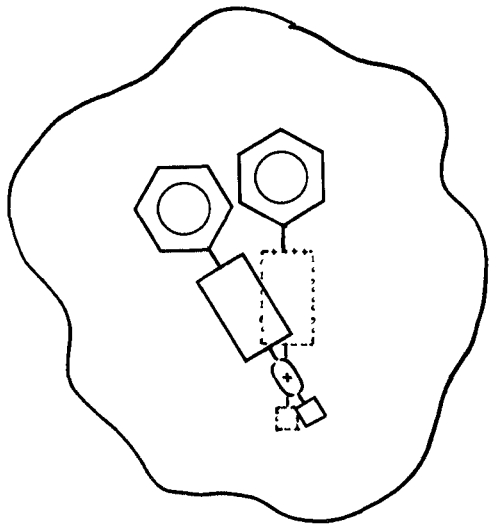


Fig 13 7 A schematic illustration of two different positions of binding to a receptor The protonated amine nitrogen is represented by + and the square denotes an *N* substituent The anionic site lies directly beneath +

In 1976 Snyder and his colleagues[72] made receptor proposals aimed at accounting for analgesics of especially high potencies, the role of *N*-allyl substituents in conferring antagonist properties, and the chemical features that afford "pure" antagonists. They suggested that the opioid receptor exists in two conformational states, which associate with agonist and antagonist ligands, respectively, whose equilibrium is allosterically modulated by sodium ions. Two sites, one of lipophilic (A) and one of anionic character, akin to the sites proposed to accommodate a flat aromatic feature and a charged nitrogen center, respectively, in the original model, are available in either state. Agonists are capable of interaction with a second lipophilic site (F) (complementary to an additional aromatic feature, F, of the ligand) that is not available to antagonists, and when this occurs transformation of receptors to the agonist conformation is triggered. Aromatic ring A and the amine nitrogen are crucial for all opioid actions. When ring A and the basic center are set in a fixed location in models (Dreiding and CPK) of phenazocine, the thebaine derivative PET, etonitazene and fentanyl, only one conformation of benzene ring F can be shared by all four compounds (Fig. 13.9). They proposed that the unusually high potencies of these agents are associated with a common conformational localization of ring F in relation to the ring A and basic nitrogen centers. A conformational similarity between fentanyl and a potent cyclohexane derivative of Upjohn in relation to the two compounds' aromatic and basic features has been pointed out (p. 393); hence the Upjohn compound also may be presumed to satisfy the pharmacodynamic pattern. Such equivalence of aromatic features remains to be established (e.g., by comparative structure-activity and conformational analyses); data available on studies of ring A phenolic

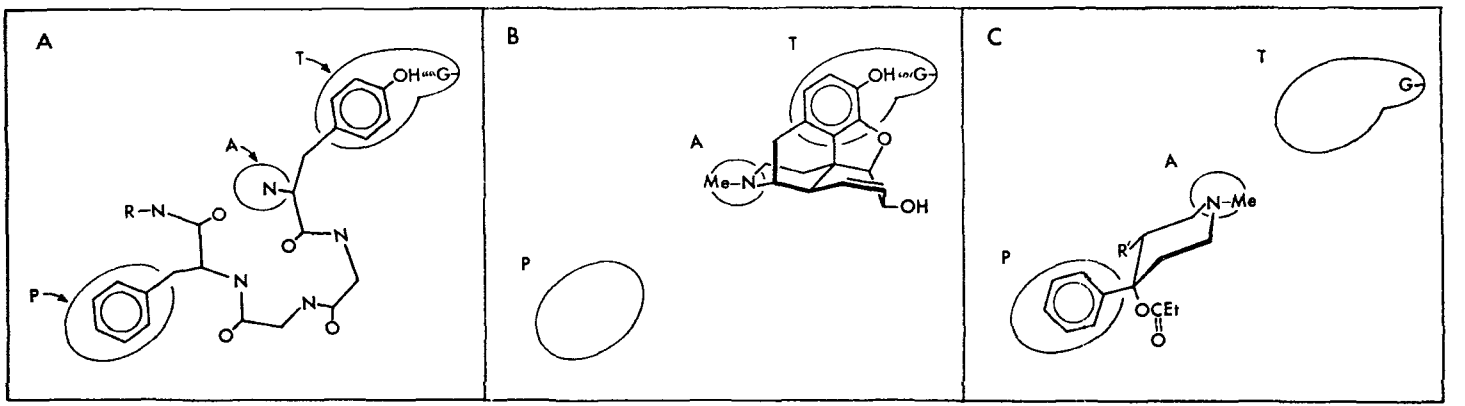


Fig. 13.8. A schematic illustration of the interactions of enkephalins or endorphins (panel A), morphine (panel B), and allylprodine (panel C) with opioid receptor subsites (T and P) which recognize the aromatic residues of Tyr^1 and Phe^4 of the opioid peptides. The anionic site A is ion paired with the protonated nitrogen of the opioids in all three cases. Group G located on subsite T represents a hydrogen-bonding acceptor dipole.

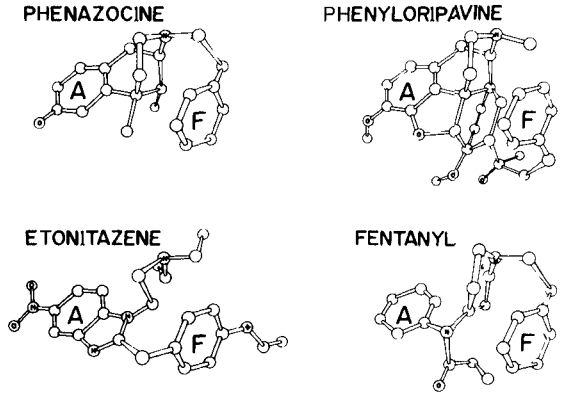
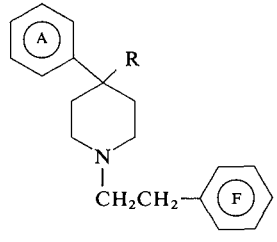


Fig. 13.9. Molecular models of the potent agonists phenazocine, phenyloripavine, etonitazene, and fentanyl. Rings A and F and the amine nitrogen are drawn in common spatial orientation, the hypothetical "agonist conformation" of these drugs.

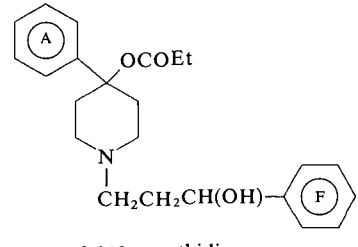
analogs of fentanyl are not encouraging in this respect, and there is no evidence that either Ar ring of fentanyl is equivalent to the phenolic aromatic ring of morphine.

The relatively low potencies of analgesics such as methadone and dextromoramide, also with dual aromatic features, are considered due to the fact that they cannot assume the critical conformation of rings A and F proposed for the potent derivatives. Conversely, however, it is difficult to account for the low orders of potencies (on the scale of the compounds of Fig. 13.9) of the 4-phenylpiperidines **35** that are capable of conversion to conformations appropriate to high activity (provided energy barriers may be overcome and/or compensated for); the derivative **36** presents little difficulty in this respect. There are clearly hazards in attempting the correlation of aromatic molecular features in ligands of disparate structure.



R = CO_2Et 2 × pethidine
R = OCOEt 25 × pethidine

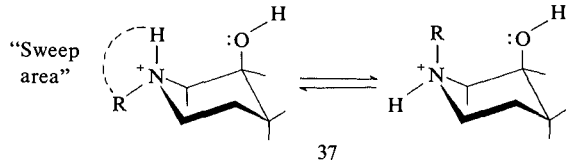
35



3,219 × pethidine

36

In these proposals, antagonists also have a specific binding site capable of linkage to *N*-allyl and like substituents and its occupancy shifts the receptor equilibrium toward the antagonist conformation. Because of the normally prevailing brain Na^+ concentration, it is maintained that the receptor is generally in the antagonist state (cf. p. 334). An essential part of these arguments depends on consideration of the structure of "pure" antagonists. The authors believe it significant that the few antagonists so classified carry a hydroxyl substituent that bears a 1,3-diaxial relationship to protonated nitrogen and cite the examples of naloxone, naltrexone, and oxilorphan (the last named is not a pure antagonist, p. 418). Certain benzomorphans with appropriately placed 11β-OH-groups (p. 423) are also quoted. Introduction of hydroxyl oriented as in **37** modifies the RN^+H feature sterically by reducing the population of axial *N*-R conformers and hence restricting the possible "sweep area"



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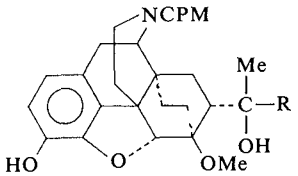
of the R substituents. Mixed agonist-antagonists are considered to interact with both variants of the anionic site, an argument that implies that the *N*-R substituent is axial in the active conformation of agonists and equatorial in that of antagonists, and open to criticism on this score. Thus, the potency of the *N*-methyl derivative hydromorphone is raised (not lowered) after insertion of axial OH at C-14 (giving oxymorphone). Although studies of isomeric methiodides of nalorphine support these ideas, at least as far as the conformation of the antagonist pharmacophore is concerned (the axial *N*-allyl isomer had a third and the equatorial isomer one hundredth of the binding affinity of the parent base),[64] conformational differences between agonist-antagonists pairs (morphine-nalorphine and oxymorphone-naloxone) as studied by ^{13}C-nmr spectroscopy were not found for either base or HCl salt forms.[73,141] The nmr results also provided no support for Kolb's idea[74] of morphine-based agonist-antagonist pairs differing in their piperidine ring conformations (chair for agonists, skew boat for antagonists).

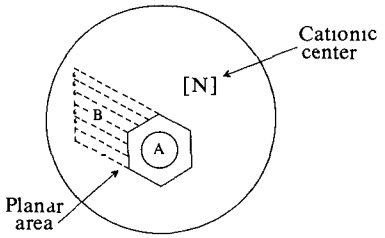
Snyder's model is also used to explain a number of puzzling structure-activity relationships. Thus, the lack of antagonist properties in *N*-allyl and *N*-CPM bridged thebaines of type **38** with R a propyl or larger group is held due to their ability to interact with the agonist site (F), which is not possible when R is a smaller group. The failure of *N*-allyl-like substituents to endow 4-phenylpiperidines of the pethidine, prodine, and phenylmorphan type with antagonist properties is accounted for by the proposition that the inability of phenyl in such structures to assume an axial conformation leads to the aromatic



38

feature associating with the lipophilic site (F) rather than (A); since the former is an agonist site these ligands fail to act as antagonists.

Galt[75] has advanced yet a further variant of the original model that requires an extension of the planar binding area (A) rather than the additional lipophilic region (F) proposed by Snyder's group; this extension is depicted by (B) in the diagram (**39**). He maintains that any molecule that has (by rigidity) or can project (by bond rotation or ring inversion) a planar surface and a cationic center in the same juxtaposition in space as the model (**39**)



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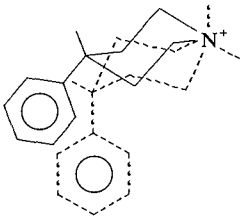
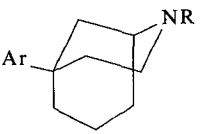
could have opioid properties. In this model 4-arylpiperidine analgesics in which the aromatic group is equatorial may fit the site designed for analgesics that incorporate an axial 4-arylpiperidine moiety (such as morphine) by suitable orientation of the molecule as illustrated (**40**). Galt's main purpose in making these proposals was to account for stereochemical anomalies among certain polycyclic systems where both members of enantiomorphic pairs show significant pharmacological activity [e.g., certain 5-arylmorphans (p. 217) and



The axial 4-phenylpiperidine (broken lines) is superimposed on the cationic site and the planar area A, while the equatorial isomer (full lines) is superimposed on the cationic site and the planar area B of 39

40

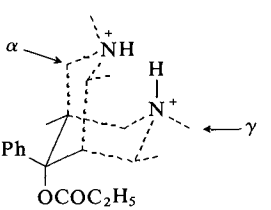
11-methyl-6-phenylbenzomorphans (p. 424)]. Thus, both antipodal forms of the phenylmorphan (**41**) provide the alignment of aromatic and protonated nitrogen features required to fit the new model and differ only in the orientation of the cyclohexane ring in relation to the receptor surface. Presumably, the overall structure of the more active enantiomer (1*S*, 5*R*) provides better contact than that of the 1*R*, 5*S* isomer, but the latter still has sufficient affinity for the receptor to display a significant analgesic potency.



41

R = Me, Ar = *m*-OH.C_6H_4
5*R*(+)-isomer 3–4 × morphine
5*S*(−)-isomer 1 × morphine

Having broached the idea of extending the aromatic site while confining the site of basic nitrogen function binding (as in **40**) to account for the activities of both *eq* and *ax* 4-phenylpiperidine moieties, the reverse proposal may now appropriately be considered. It was first advanced by Fries and Portoghese[76] to explain why both α- and γ-promedol behaved as analgesics. If the α-isomer binds in the axial and the γ-isomer in the equatorial 4-phenyl chair conformation, both may share the same aromatic subsite A of the receptor, provided the anionic binding zone extends over a greater area than that originally envisaged, as shown in diagram **42**, which depicts the two molecules superimposed above the receptor. It is to be noted that, although receptor regions adjacent to nitrogen and its substituent (Me) are different, the $^{+}$N—H protons adopt identical positions. There is now good evidence that both isomeric promedols bind in the *eq* 4-phenyl chair form (p. 273), but the concept depicted in **42** is nevertheless valuable in providing an explanation of how the binding modes of ligands with axial and equatorial 4-arylpiperidine moieties (typified by the morphine and pethidine class, respectively) differ and of *N*-substituent and phenolic influences in the two types.

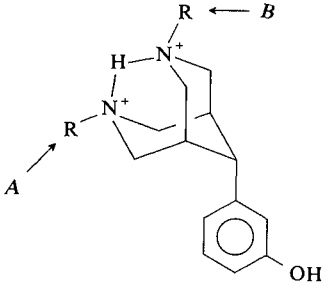


The more potent axial phenyl (α) and equatorial phenyl (γ) promedol diastereoisomers superimposed upon one another. Portions that are not superimposed are shown by dashed lines.

42

When a 4-phenylpiperidine ligand binds in the *eq*-Ph conformation, the position of its *N*-R substituent differs considerably from that of an *ax*-Ph binding analog. Hence, *N*-R substituent influence might be expected to differ

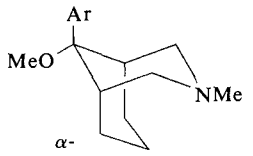
in the two conformational series. In fact, substituents associated with agonism generally have similiar quantitative effects upon potency, in, for example, the morphine and pethidine (and reversed ester) series. This observation would be a cause for suspicion of the concept if it were not for differences in order of effect and some examples of a substituent enhancing potency in one series and abolishing it in the other (p. 475).[77] The influence of *N*-allyl and related groups is of special significance; these groups need to be sited near region A of **43** to produce an antagonist response as judged from the morphine model. Failure of *N*-allyl and related analogs of 4-phenylpiperidines with preferred *eq*-Ph conformations to act as antagonists may thus be understood because their *N*-R substituents are remote from the antagonist trigger zone and located near B of **43**, where they promote agonism in common with the many nonallylic *N*-substituents. By the same token, *N*-allyl congeners of 4-arylpiperidines with significant *ax*-Ph conformations should behave as antagonists. The fact that this is rarely the case for simple piperidine derivatives must mean that the presence of *N*-allyl and like groups in piperidines that favor *ax*-Ph conformations when *N*-methyl is present, results in uptake in the *eq*-4-arylpiperidine conformation with consequent juxtaposition of *N*-allyl with agonist site B.



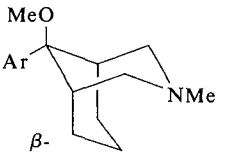
A, agonist–antagonist site
B, agonist site only
(reverse to fit receptor surface)

43

The concept accounts nicely for the pharmacological profiles of certain 4-arylpiperidines, where bridging confines the aryl group to either an axial or equatorial conformation. Thus, 5-arylmorphans (**41**) must bind in the *eq*-Ph mode, whereby the N-R substituent falls in the exclusively agonist zone B, accounting for the nonappearance of antagonist properties when *N*-methyl is replaced by *N*-allyl and the need for a *meta*phenolic OH in active compounds. 4-Arylpiperidines bridged by trimethylene across the 3,5 positions (p. 246) provide both *ax*- and *eq*-4-aryl species termed α-(**44**) and β-azabicyclanes (**45**), respectively.[78] Both isomers have potencies close to that of morphine in mice by the writhing test and similar binding affinities (inferior to that of



44



45

Ar = Ph or *m*-OH.C_6H_4

		IC_{50} (n*M*)[a]	ED_{50} (n*M*/kg)[b]
α-Isomer	Nonphenolic	560	2700
	Phenolic	14	2.8
β-Isomer	Nonphenolic	590	4000
	Phenolic	12	6 1
Morphine		160	3400

[a] Binding assay vs. [^{3}H]etorphine
[b] MW(HAc)

morphine) to rat-brain homogenates (see data alongside formulas). Activities in both respects rise dramatically after insertion of *m*-OH in the phenyl ring. The β-*N*-allyl analog of (**45**) lacked antagonist properties[79] while the corresponding α-derivative behaved as a weak opioid antagonist.[78]

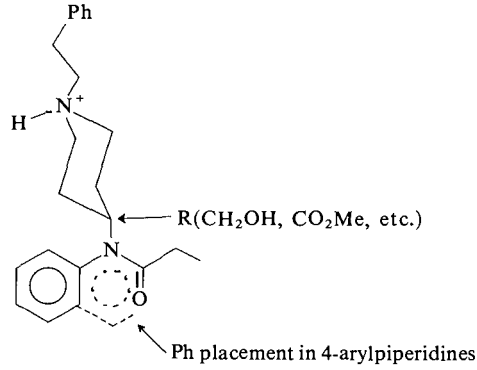
In terms of the model **43**, a *meta*-placed phenolic hydroxyl should enhance activity in both *ax*- and *eg*-phenyl modes of uptake. This is clearly true for the azabicyclanes and in simple 4-arylpiperidines with C-4 carbon substituents that have significant *ax*-aryl populations (p. 275). However, phenolic hydroxyl insertion in 4-phenylpiperidines with preferred *eq*-Ph conformations virtually abolishes activity in the few cases examined (all reversed esters of pethidine). This fact counts against the present arguments but may be explained by a difference in the orientation of the aryl (made nonsymmetrical by *m*-substitution) and piperidine rings in the two-chair conformations. Thus, the arrangement that places the phenolic OH close to the receptor subsite appropriate to the rigid morphine model may be favored in the axial-aryl but not in the equatorial-aryl chair conformations of the flexible piperidine derivatives (cf. the alternative model of Portoghese et al.,[111] which requires a pair of well-separated aromatic subsites, p. 478).

The receptor model **43** has also been discussed by Humblet and Marshall[80] in a review illustrating the application of 3-D computer graphics to drug design.

The scheme of diagram **43** has been developed for ligands based on the morphine and 4-arylpiperidine groups. If additional binding areas as envisaged in Figure 13.5 (including extension of the anionic site) are incorporated into this scheme, most other ligand types may no doubt be manipulated to fit the corresponding receptor surface, but evidence upon the likely existence of such active conformations is probably lacking. These considerations apply in particular to highly flexible acyclic analgesics of the methadone class, the ben-

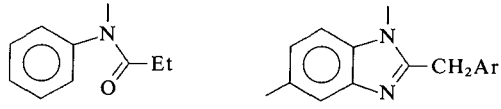
zimidazoles, the fentanyl group, the potent 4-aryl-4-aminocyclohexanols of Upjohn, and the (1,2-diphenylethyl) piperazines (p. 391, 399).

An active binding conformation for fentanyl (with its highly effective 4-anilido-1-phenethylpiperidine pharmacophore) not too dissimilar from those of the morphine and 4-arylpiperidine groups, and one that does not demand a high-energy arrangement (unlike that of Snyder's proposals),[72] may be advanced if one accepts extension of both anionic (Portoghese)[76] and aromatic (Galt)[75] subsites of the receptor. This conformation (**46**) (similar to the solid and probable solute state of fentanyl, p. 298) differs from that proposed for 4-arylpiperidines only in a displacement to the left (in terms of **43**) of Ph equivalent to the 4-aryl group. This model accounts for activity-elevating influences of C-4 carbon substituents (which would be positioned as in 4-arylpiperidines), the adverse influence of phenolic OH, and the failure of the *N*-allyl analog to behave as an antagonist. The *N*-phenethyl conformation of **46** (unlike that of the proposals of Snyder[72] and Upjohn workers)[81] accords



46

with evidence that this feature is fully extended in the active conformation of fentanyl (p. 289). This model may also accommodate benzimidazole ligands if one assumes an analogy between the nonbasic features (**47**) of analgesics related to fentanyl and benzimidazole, wherein might lie the reason for the high levels of activity seen in the two series. Examination of appropriately modified fentanyls with *N*-phenacetyl rather than *N*-propionyl features would provide a test of this idea.



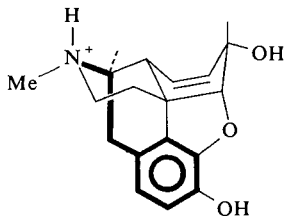
47

A vastly different relationship between the active conformations of fentanyl and pethidine was deduced from a computer matching exercise carried out on these two analgesics (plus morphine) using the basic nitrogen center and three aromatic carbons as reference points.[133] Good matches were

obtained but at substantial energy costs that might be offset by the ligand-receptor interactions. It was concluded that the 4-phenyl of pethidine was equivalent to terminal phenyl of -phenethyl of fentanyl, that is, this substituent must twist above the piperidine ring in a manner similar to that proposed in the Snyder model (Fig. 13.9). This aromatic feature was also matched to the phenolic ring of morphine, which is unlikely on SAR grounds, as already explained.

The relationship of the active conformation of the potent cyclohexanol **26** to those of analgesics so far discussed is not readily apparent, although it is likely that phenyl of the 1-phenethyl substituent is equivalent to anilido phenyl of fentanyl with the 4-NMe_2 basic center positioned close to either ^{+}N of **43**. Lednicer and Von Voigtlander[81] have presented a correlation between **26** and fentanyl based upon what appears to be a high-energy conformation of the latter compound. In view of the unusually high potency of the cyclohexanol **26** and its special utility as a probe of receptor topography, it is a matter of some urgency that further structure-activity analyses of the group be undertaken so that its potential for receptor studies may be exploited fully.

The opioid peptides are especially difficult to correlate with other ligands because of their highly flexible nature and numerous conformational options. Some workers, nevertheless, have attempted to carry out this exercise. Soon after the discovery of the enkephalins, Horn and Rodgers[82] pointed out that a β-(4-hydroxyphenyl)ethylamine unit was common to both morphine and the enkephalins, and subsequent SAR investigations provided evidence of the equivalence of the aromatic features of morphine and the Tyr^1 residue of the natural peptides (p. 343). An objection to these views was raised by the fact of the C-9 chirality of levo morphine being the reverse of the Tyr^1 α-carbon of the enkephalins (see **48**),[83] although peptide flexibility may allow this



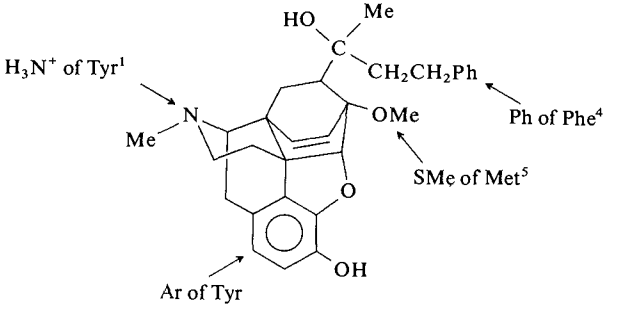
Morphine showing the Tyr moiety (underscored)

48

configurational problem to be overcome (note, however, that D-Tyr^1-metenkephalin is inactive). Furthermore, the inactivity of a hybrid enkephalinamide that contains levo metazocine in place of Tyr^1 adds no support to the hypothesis of identical roles for Tyr moieties in the two types of opioid molecule.[84]

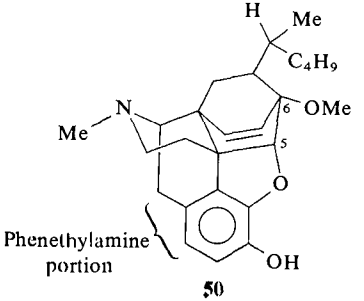
Model building at various levels of sophistication has led to conformational comparisons between enkephalins and rigid analgesics of the morphine

and bridged-thebaine type. Clearly, if an opioid peptide may mimic the spatial array of pharmacophoric groups presented within a rigid opioid, then the peptide is likely to be accommodated at a receptor surface appropriate to the rigid derivative. Use of natural enkephalins in these comparisons may be challenged on account of recent evidence of their low affinity for μ-sites (p. 490), and it may be more meaningful to employ more potent μ-selective synthetic peptides such as the Sandoz compound FX33-824 (p. 350). Bradbury *et al.*[85] compared a Framework molecular model of metenkephalin with that of the endoethenothebaine **49**, which contains both a phenolic (as in morphine) and a nonphenolic aromatic feature. When the peptide was arranged in a conformation with a β-bend about Gly^2 and Gly^3 stabilized by a 1-4 (Tyr^1CO, Phe^4NH) hydrogen bond, coincidence could be achieved between the basic centers, and the phenolic and nonphenolic aromatic rings of the two molecules (see **49**).



49

The derivative **49** is rather a special case, since most potent thebaine-derived analgesics lack a phenyl component in the C-7 substituent. Hence, Hutchins and Rapoports' comparison of metenkephalin and 19(*R*)-butorvinol (**50**) may be of more general relevance.[86] Computer-drawn projections (based on the crystal structure of an analog of **50**, and the data of a conformational search of the Tyr-Gly-Gly-Phe tetrapeptide)[87] provided coincidence between the phenethylamino portions, while the Phe^4 benzene ring of the peptide (in contrast to Bradbury's proposal) corresponded to the C_5-C_6 region of the exogenous opioid. The position of the Met^5 residue reflected the similar



50

orientation of the lipophilic groups of the orvinol (C-7 substituent) and the enkephalin.

Marshall's group, which favors use of the rigid opioids as steric probes to map the active conformation of opioid peptides, derived a structure for the tetrapeptide Tyr-Gly-Gly-Phe similar to the metenkephalin conformation based on the orvinol **50**.[88] Marshall *et al.* maintain that theoretical energy calculations, crystal structure data, and nmr (and other physical) solute studies (p. 494) contribute little to the elucidation of the receptor-bound conformation of flexible molecules such as the opioid peptides. This is because peptide-receptor interactions are likely to induce mutual conformational changes that cannot be accounted for by current conformational techniques. Their advocacy of the systematic exploration of all possible conformations of restricted analogs of enkephalin, made in 1978, is particularly apt at present now that several cyclized derivatives of enhanced potency have been discovered (p. 373). To date such conformational investigation has not been carried out in any detail, but the approach is likely to yield valuable information of active enkephalin geometry, whereby meaningful comparisons with other opioid ligands may be possible.

13.12. SOME ASPECTS OF δ-RECEPTORS

As already stated, speculations presented of receptor topography and ligand-receptor interactions refer specifically to the μ-class of receptor, since this subspecies is most likely to be associated with analgesia. Recent observations, however, suggest that both μ- and δ-receptors are implicated in the mediation of analgesia in a cooperative manner. δ-Receptors themselves are notable in that their action appears to be linked to a specific biochemical event, namely, the interconversion of ATP and cAMP via adenylate cyclase. This biochemical model of opioid receptors evolved from Collier and Roys' observation that morphine and other opioids inhibit the adenylate cyclase-catalyzed conversion of ATP to CAMP.[89] The original work was performed on rat brain homogenates and referred to PGE_1-stimulated rather than basal cAMP formation (formation of radioactive cAMP from its labeled precursor [^{3}H]ATP was measured, the labeled cAMP being isolated by chromatography). The neurones involved had many features in common with opioid receptors, notably their structural and stereochemical requirements for blockade by ligands (rank order for inhibition was heroin > morphine > methadone, with dextrophan inactive), and the fact of restoration of normal activity by anatagonists such as naloxone. The experiments also provided a model for tolerance and dependence in that the tissue became less responsive when exposed chronically to opioids and reacted excessively on drug withdrawal as seen by the production of abnormally high cAMP levels.[90] Later the same

phenomenon was demonstrated in a neuroblastoma × glioma hybrid cell line (NG 108-15 initially prepared by fusion of a rat glioma cell with a mouse neuroblastoma cell) in which both basal and PGE_1-stimulated cAMP production were affected.[91] The tissue is particularly sensitive to enkephalins (in one experiment metenkephalin had more than 100 times the potency of morphine as an inhibitor of adenylate cyclase activity) and is considered rich in δ-receptors.[92] Opioid peptides appear to reduce adenylate cyclase activity by stimulation of GTP hydrolysis. The intrinsic activities of a series of opioids were identical for stimulation of GTPase and inhibition of adenylate cyclase with potency rankings: D-Ala^2-metenkephalinamide > etorphine > morphine > nalorphine > naltrexone (naloxone=O).[93] The study of hybrid cells in terms of the characterization of their opioid receptors[94] and the mechanism of cAMP inhibition is now extensive and cannot be given full justice here (see ref. 129 for review).

Turning now to μ-*d*-receptor interactions, the view of the two types being distinct species of receptor may need revision as a result of evidence that they are capable of interconversion. Binding sites in rat striatum for opioid ligands when visualized autoradiographically display discrete (patchy) and diffuse (even) distribution patterns for ligands of μ- and δ-selectivity, respectively.[95] Tissue pretreated with GTP (known to inhibit μ- more than δ-opioid binding) and cations (Mn^{2+} and Na^+) altered the ligand selectivity pattern in favor of the δ-type, a result taken to indicate that opioid receptors located in striatal patches can shift from μ- to δ-forms as they couple to adenylate cyclase. The authors postulate a three-state allosteric model consisting of μ-agonist-, μ-antagonist-, and adenylate-cyclase-coupled δ-agonist-preferring states, whose equilibrium may be regulated by a sulfhydryl group mechanism.

Vaught *et al.*[96] argue for the integrity of the two receptor species but maintain that they act cooperatively, at least as far as the mediation of analgesia is concerned. These authors commence their discussion by pointing out the apparent discrepancy between the generally believed high affinity of natural enkephalins for μ-sites and their feeble *in vivo* activities after central administration. Since explanations based on the rapid degradation of the peptides are unsatisfactory in their opinion (p. 336), they suggest that it is due to their, in fact, *feeble* affinity for μ-receptors. Previous ligand-binding studies, assuming competitive inhibition, indicate that both natural enkephalins bind to the μ-receptor with a high affinity and are only 2- to 10-fold selective for the δ-receptor.[97] Rothman and Westfall,[98] however, found that leu- and met-enkephalin behaved as noncompetitive inhibitors of [^{3}H]etorphine binding and, allowing for this fact, established that the enkephalins are considerably more selective toward the δ-receptor than previously believed and have very low affinities for μ-sites (Table 13.3).

The fact of δ-site occupancy having an influence upon the analgesic potency of μ-ligand was demonstrated by measurement of the effects of

Table 13 3 K_1 Values[a] of Various Ligands for μ- and δ-Receptors and Their Analgesic ED_{50} Values[b]

Ligand	$K_1\mu$ (nM)	$K_1\delta$ (nM)	ED_{50} (nM/mouse)
Morphine	11	434	5 4
Met-enkephalin	>150	1 5	>100
Leu-enkephalin	>350	3 5	»100
DADL	72	5 0	0 29
β_h-Endorphin	4 7	17 2	0 05

[a] Versus [^{3}H]etorphine, competitive kinetics applied except for met- and leu enkephalin
[b] Icv route, tail flick test

Table 13 4 Effects of Enkephalins on Morphine-Induced Analgesia

Compound	Treatment	ED_{50} [a]
Morphine	Saline	5 4
Morphine	Leu-enkephalin (40 μg)	1 8
Morphine	DADL(10 μg)	1 2
Morphine	Met-enkephalin (40 μg)	12 9

[a] Details as in Table 13 3

subanalgesic doses of enkephalins upon morphine-induced analgesia in mice (Table 13.14); leu-enkephalin and DADL potentiated, and met-enkephalin (surprisingly) antagonized morphine. A model in which μ- and δ-receptors coexist in a complex unit was advanced to account for these data (Fig. 13.10) [cf. the earlier model of Lee and Smith[99]]. Met- and leu-enkephalin interact exclusively with the enkephalin receptor and morphine with the μ-receptor. Occupation of the morphine receptor induces a conformational change in the receptor that allows coupling to its effector leading to analgesia. μ-Occupancy by an antagonist such as naloxone prevents this conformational change. In contrast, occupation of the δ-receptor by leu-enkephalin induces a conformational change in this receptor that results not in analgesia but in a facilitation of coupling between the μ-receptor and its effector (manifested in the potentiation of morphine analgesia). Occupation of the δ-receptor by a ligand such as met-enkephalin also triggers a conformational change but one that inhibits the said coupling (whence antagonism of analgesia is observed). If a peptide binds to both sites and behaves as a potentiator at the δ-site, its *in vivo* analgesic activity will be greater than that predicted by its *in vitro* affinity for the μ-receptor. Thus, results for peptides such as DADL (one seventh the μ-affinity of morphine, 18 times more potent as an analgesic) and β_h-endorphin (Table 13.14) may be explained. In these terms, the enkephalins cannot be endogenous

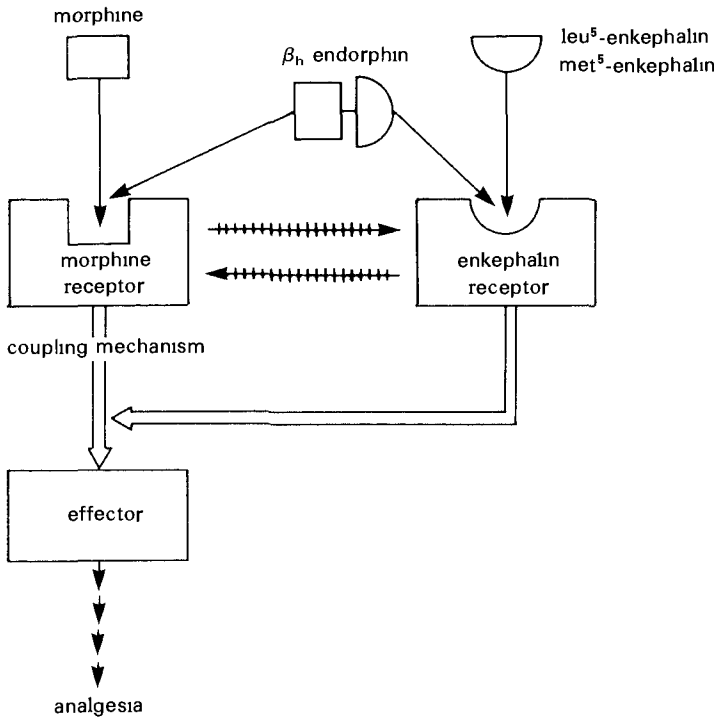


Fig 13.10 μ/δ complex model of the opioid receptor. Hatched arrows symbolize interactions between the two sites (not a thermodynamic equilibrium)

ligands of the μ-receptor but β-endorphin and/or other opioid peptides may fulfil this role. Further evidence for the two-site model has been obtained by use of rat-brain membranes enriched in either μ- or δ-sites by treatment with the selective alkylating agents BIT(μ) and FIT(δ) (p. 453).[100]

Barnard and Demoliou-Mason[120] have pointed out that interpretations of binding data may be invalid if allowance is not made for any variation in the assay conditions, notably the presence or absence of mono and divalent cations. They have shown, for example, that $Mg^{(2+)}$ is essential for DADL binding and a strong promoter of etorphine binding, and it is to be noted that Rothman and Westfall[98] included Mg^{2+} in the assay medium used to measure [^{3}H]etorphine binding but omitted this cation in that employed for receptor uptake of [^{3}H]enkephalins. Barnard[120] carried out direct binding studies on rat brain membranes using a buffer (Tes-KOH), that, unlike the usual agent (Tris-HCl), cannot substitute for divalent cations, and he believes this medium to be particularly suitable for studying the differential effects of cations and other agents on agonist binding to receptor sites. Equilibrium binding studies led to the identification of at least four receptor subtypes, and a model

consisting of an enkephalin dimer (δ_1 and δ_2) and a morphine dimer (μ and κ) has been proposed. In a computer-aided analysis of the binding data, the receptor–ligand system was shown to exhibit complex cooperative behavior that suggested that the functional opioid receptor conforms to a mobile heterooligomeric system. In this model the association-dissociation of the heterologous receptor subunits ($\mu_1 + \mu_2$ or $\kappa + \delta$) are assumed to be required for receptor coupling with effector molecules (E) such as the guanine nucleotide binding proteins of the adenylate cyclase complex (Fig. 13.11). Receptor association-dissociation and coupling with effector subunits are assumed to involve disulfide bridges, the making and breaking of which are regulated by cations and GTP.

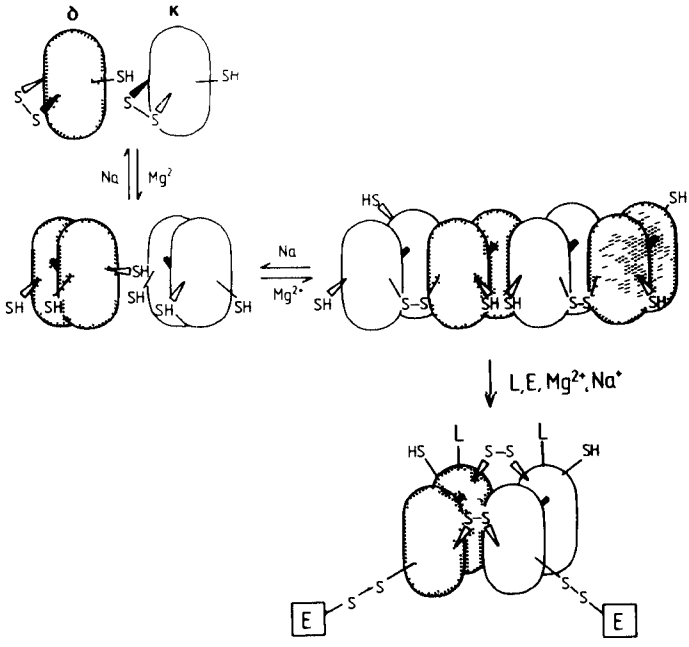


Fig 13 11 Hypothetical model for ligand interactions with the opioid receptor (Only κ-δ hetero oligomers shown, but scheme also applies to the μ_1-μ_2 complex) The interactions between the receptor subunits are considered to be transmitted by interdisulfide bond formation at three distinct domains of each subunit Due to —SH/SS— exchange the interactions between homologous subunits can occur only in a linear sequence upon ligand binding Heterologous subunits are considered to share a mirror-image orientation of their domains so that opioid peptide binding to a pair of adjacent subunits in the complex can stabilize the receptor conformation required for coupling with effector subunits (E) In the above dynamic model of receptor association/dissociation, ligand (L) binding stabilizes rather than induces receptor-effector coupling

13.13. COMPUTATIONAL APPROACH

Over the past decade speculations upon ligand–receptor interactions in the opioid field have been increasingly based upon computational methods, a trend that is likely to continue in the future. Most of the work is directed at predicting the more probable conformations of ligand molecules. Provided sufficient computer resources are available, quantum chemical calculations yield the whole conformation domain of a molecule in the isolated state, the relative stabilities of the various conformers, the energy levels, the charge distributions and other quantities that can be derived from the wave functions.[101,105] The difficulty with a systematic examination is one of cost, and the approach is "governed by compromise between the desire to simulate physical reality in detail and the limitations on computational power available."[102] The assumptions of fixed bond angles and bond lengths are usually made, leaving only torsional variables to specify a conformation.

A bibliography of quantum pharmacological studies of opioids that includes work of the Kaufman and Loeb groups is presented in the text of W. G. Richards[103]; to this must be added recent reports of Froimowitz.[104] Franke's recent book *Theoretical Drug Design Methods* includes a chapter devoted to receptor mapping and pharmacophores in which quantum mechanical and other principles involved are clearly presented.[131]

Marshall[102] has criticized the conformational approach based on crystal structure, nmr solute studies, and theoretical calculations and pointed out that it is not very successful in correlating biological activity with minimum-energy geometry. He believes this is due to the fact that the procedures listed ignore the perturbation caused by interaction between the drug molecule and the asymmetric force field represented by the receptor, when it follows that there is no reason to assume that a receptor binds the low-energy conformer of a ligand. His own approach is to seek out (by computational methods) the presence of common pharmacophore candidates in orientation space within a group of active analogs and, if found, to base the active conformations on these pharmacophores. To date this procedure has not been reported for opioids.

Tollenaere *et al.*[101] have emphasized that as conformational data based on computer technology accumulates, a strong need is felt to visualize the results of the analyses and to be able to manipulate structures in a more sophisticated way than is possible by use of conventional molecular models. Models of the ball and stick and space-filling kind are cumbersome, easily transformed, and do not lend themselves to superposition one upon the other. These problems may be solved by the use of computer graphics, and evidence of the application of this facility is increasingly apparent in the opioid field.

Several review articles on computer graphic systems and their use in drug design are now available[103,106,107,132]; these systems attempt to display a 3-D shape upon a 2-D screen as convincingly as possible. The Merck Molecular Modeling System (MMMS)[106] allows structural representation based upon structure input information (often derived from crystallographic data) and refinement (e.g., avoidance of strain) and molecular display and comparison. The last features aid the operator in the study of 3-D molecular structures (e.g., by stereoscopic representation in any orientation desired). Superposition programs that facilitate the comparison of different structures are also available; the "compare" program allows specified atoms of one molecule to be superimposed on specified atoms of a second molecule by a least-square-fitting routine. This technique is potentially of great value to comparative structure-activity studies (e.g., comparison of fentanyl with the potent cyclohexanol derivative of Upjohn, p. 393) and to pharmacophore searches. Another system, AIDA (Aid in Interactive Drug Analysis), which allows the manipulation, modeling, and display of relatively small molecules containing a maximum of 280 atoms, has been developed by Janssen Pharmaceutica.[101]

13.14 POSTSCRIPT

Advances in the solubilization and fractionation of brain membrane material, coupled with the development of selective affinity labels, are fast reaching the point when relatively pure and viable opioid receptor substances will be available for direct study of ligand–receptor interactions. Amino acid sequencing of active sites will then prove a practical proposition, and knowledge of the molecular features of the receptors may well be aided by recombinant DNA technology following the path of study of proenkephalin-A (p. 135) and the nicotinic[135] and insulin[140] receptors.

Work of this kind may also clarify the complex picture that now obtains of subspecies of opioid receptor, as will also the continuing refinement of selective ligands of both agonist and antagonist nature. The normal physiological roles of such subspecies remain to be established,[136] with the possible exception of the μ-variety, which appears to be linked to the perception of pain and to the development of morphine tolerance and dependence.[137] The study of receptors responsible for side effects of opioids is still poorly developed, and work in the area of receptors inducing respiratory depression (Pasternak's μ_2 receptor)[138] and dependence phenomena is a particularly urgent need. Studies of mechanisms of pain perception and its alleviation by investigation of the biochemical pharmacology of opioids is another approach of promise (e.g., elucidation of the role of Ca^{2+} and cyclic AMP as second messengers or otherwise).[129]

Although biochemical and pharmacological studies now tend to dominate opioid research, a place remains for the design and investigation of ligand molecules by the methods of medicinal chemistry. Medicinal chemists have the ability and expertise to exploit clues provided by biological studies and to generate chemical tools, such as affinity labels and specific ligands, essential for such work. Furthermore, the design of clinical analgesics of low side-effect liability remains a goal of the medicinal chemist in spite of the range of such agents already in general use.

As we more closely approach investigation of the receptor itself, examination of actual ligand-receptor interactions may become a possibility by physical techniques such as X-ray diffraction and high-resolution nmr spectroscopy, and the concept of multiple association modes may be substantiated or refuted. In the meantime it is important that attempts to classify and correlate the various types of opioid ligand continue. This may be achieved by classical structure-activity analyses and stereochemical investigations coupled with computational and molecular graphics techniques. Opioid ligands, because of their structural diversity, are particularly appropriate to study by molecular graphics, a technique that by matching and superimposition operations is likely to reveal novel pharmacophores that are not obvious by other methods. It will be vital, however, to support the significance of any putative pharmacophore by appropriate stereochemical and structure-activity analyses, as is illustrated by the apparent correlation between aromatic entities of fentanyl and morphine (p. 485). Thus, it is important to link and establish harmony between results of the two investigative approaches.

Conventional methods of medicinal chemistry may also be expected to contribute further to identification of structural features that determine whether an opioid ligand behaves as an agonist, antagonist, or dualist. Although it is well established that the substituent attached to the basic center of the ligand plays a key role in this respect, it is evident that other structural factors must be implicated, as is clear from the varying influence of such groups and the fact that antagonists are chiefly confined to the more rigid type of opioid ligand. Another aspect appropriate to the medicinal chemist is the identification of molecular features that determine association of ligands with specific subspecies of opioid receptor, work of value not only in its own right, but also in its provision of specific agents required for corresponding biological investigations.

It is not possible to conclude this book with definitive statements on the many problems posed by the perception of pain and its alleviation, such as reasons for opioid ligand activity, the molecular nature of opioid receptors, and the mechanisms of pain perception and its relief. However, interest in the field of central analgesics shows no sign of diminishing and it is not unduly optimistic to believe that some at least of these enigmas will have been solved by the end of this century.

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