SYNTHETIC ANALGESICS

PART I

Diphenylpropylamines

By

Paul A. J. Janssen
Research Laboratoria
Dr. C. Janssen n.v, Beerse
Belgium

PERGAMON PRESS
NEW YORK · OXFORD · LONDON · PARIS
1960

PERGAMON PRESS INC.
122 East 55th Street, New York 22, N.Y.
P.O. Box 47715, Los Angeles, California

PERGAMON PRESS LTD.
Headington Hill Hall, Oxford
4 and 5 Fitzroy Square, London W.1

PERGAMON PRESS S.A.R.L.
*24 Rue des Écoles, Paris V^e^*

PERGAMON PRESS G.m.b.H.
Kaiserstrasse 75, Frankfurt am Main

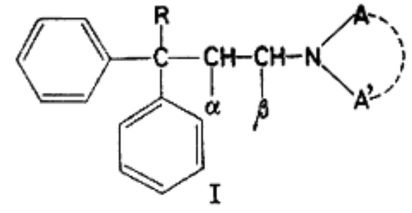
Library of Congress Card No. 59–13814

Printed in Great Britain by
CHORLEY & PICKERSGILL LTD
Leeds and London

Contents

Introduction

THE main purpose of this book is to describe and to discuss our factual knowledge of the methods of synthesis, the physical and chemical properties, as well as the "analgesic" activity of diphenylpropylamines of general structure (I)*. Other pharmacological properties are not discussed in great detail.



I

R = H or radical
α, β = H or CH_3
NAA′ = tertiary amino group

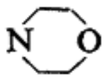
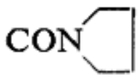
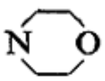
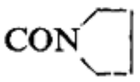
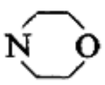
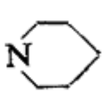
The first chemical and pharmacological experiments in this field were conducted in Germany during the Second World War by BOCKMÜHL, EHRHART and SCHAUMANN. They resulted in the discovery of the analgesics methadone and normethadone, and of several related analgesically and parasympatholytically active compounds.

After the war similar experimental programmes were carried out in several laboratories. Many related basic ketones, such as *iso*methadone, phenadoxone and dipipanone were studied in detail and underwent clinical trial.

Considerable effort was devoted to the development of diphenylpropylamines of structure (I) with analgesic, atropine-like, antihistaminic, local anaesthetic, diuretic, curarizing, ganglion blocking and ocytosic activity (Table I). Experimental work in this laboratory resulted in the introduction in human therapy of the analgesic dextromoramide (R 875, Palfium*), the parasympatholytics *iso*propamide (R 79, Priamide*, Darbid*, Combid*) and Mydriamide* (R 658), and the musculotropic antispasmodic R 253 (Bilagol*).

* The data are derived from the literature, reviewed until July 1958, and from unpublished experiments conducted in this laboratory.

TABLE I—DIPHENYLPROPYLAMINES OF STRUCTURE (I) USED IN HUMAN THERAPY

	R	α	β	NAA′	Isomer, salt	Name	Main property
1.	COC_2H_5	H	CH_3	$N(CH_3)_2$	*dl*, HCl	Methadone	Analgesic
2.	COC_2H_5	H	CH_3	$N(CH_3)_2$	*l*, bitartr.	Levanone	Analgesic
3.	COC_2H_5	CH_3	H	$N(CH_3)_2$	*dl*, HCl	*iso*Methadone	Analgesic
4.	COC_2H_5	H	H	$N(CH_3)_2$	HCl	*nor*Methadone	Analgesic
5.	COC_2H_5	H	CH_3		*dl*, HCl	Dipipanone	Analgesic
6.	COC_2H_5	H	H		HBr	Hexalgon*	Analgesic
7.	COC_2H_5	H	CH_3		*dl*, HCl	Phenadoxone	Analgesic
8.	$-CHOCOCH_3 \cdot C_2H_5$	H	CH_3	$N(CH_3)_2$	α, *dl*, HCl	Alphacetylmethadol	Analgesic
9.	$-CHOCOCH_3 \cdot C_2H_5$	H	CH_3	$N(CH_3)_2$	β, *dl*, HCl	Betacetylmethadol	Analgesic
10.	$COOC_2H_5$	H	H		HCl	Dioxaphetyl butyrate	Analgesic
11.		CH_3	H		*dl*, base	Racemoramide (R 610)	Analgesic
12.		CH_3	H		*d*, base	Dextromoramide (R 875) (Palfium*)	Analgesic
13.	$CONH_2$	H	CH_3	$N(CH_3)_2$	*dl*, HCl	Aminopentamide	Parasympatholytic
14.	$CONH_2$	H	H	$N(i\text{-}C_3H_7)_2$	CH_3I	Isopropamide (R 79) (Priamide*, Darbid*, Tyrimide*)	Parasympatholytic
15.	$CONH_2$	H	H		HCl	R 14	Parasympatholytic
16.	$CONH_2$	H	H		CH_3Br	R 92	Parasympatholytic
17.	$CONH_2$	H	H		base	Mydriamide* (R 658)	Parasympatholytic
18.	OH	H	H		HCl	Parkiphen*	Parasympatholytic
19.	H	H	CH_3	$N(CH_3)_2$	*dl*, HCl	Recipravine*	Antispasmodic
20.	H	H	H	$N(iC_3H_7)_2$	HCl	R 253 (Bilagol*)	Antispasmodic
21.	H	H	H		HCl	Aspasan*	Antispasmodic

Eventually the field was expanded, and interesting antihistaminics, parasympatholytics and analgesics (e.g. Actidyl*, Akineton*, Amolanone, bromprophenpyridamine, chlorprophenpyridamine, cycrimine, hexocyclium, mepiperphenidol, Par KS 12, piperphenidol, procyclidine, prophenpyridamine, propoxyphene, pyrrobutamine, Spalisal*, thiambutene, tricyclamol, tridihexethide iodide and trihexyphenidyl) were developed by changing the basic side chain or the phenyl rings of structure (I).

CHAPTER I

"Analgesic" Activity in Man and in Animals

A COMPOUND is said to possess "analgesic" activity when it is capable of relieving pain. Pain, of course, is a universal subjective experience of mankind, and everybody knows what is meant by it [39]. Hence there is no point in trying to define this basic concept.

In man, pain can be evoked by various "noxious" stimuli, such as heat, pressure, chemicals, electric current, etc. When such stimuli are applied to animals, their behaviour changes in a typical way. Generally speaking the animal either tries to avoid the stimulus by various flight reactions or, when flight is made impossible, it shows a series of reflexes, which are often interpreted as signs of discomfort. In man, the evidence on whether or not pain is relieved, is entirely based on the statement of the subject as expressed in the interview made by the observer. The nature of such statements, however, depends on several factors in constant operation, such as the willingness of the subject to talk about his feelings, the attitude of the observer towards the subject, the influence of the environment on the subject, his immediate problems, his hope or desperation and many other factors.

Obviously, therefore, the study of the influence of one single factor, such as the administration of a drug, on the statements of a given subject necessitates special techniques. The elimination of bias on the part of the subject or the observer emerges clearly as a basic and essential requirement for such studies [39]. Recently, the various problems concerning the measurement of pain and relief of pain were adequately reviewed by Beecher [39].

In view of the fact that pain is, by definition, a subjective sensation of mankind, it can, strictly speaking, only be studied in humans. What we are able to study in animals is not pain itself, but the behaviour of the animal following a stimulus which provokes pain in man and also, of course, the influence of a given factor, such as the administration of a certain drug on the reactions of the animal. Rather full lists of references to the methods of producing "pain" for experimental purposes are given by BEECHER [39] and

O. SCHAUMANN [402]. Numerous ingenious means of inflicting pain which is quantifiable in mechanical, thermal, electrical or chemical units of measurement have been devised.

All possible species, routes of administration, criteria of "effectiveness" or "analgesic activity" and methods of symbolization and statistical analysis have been used, and many other modifications of known methods will undoubtedly be published in the future.

The main difficulty, however, in interpreting the various results obtained by different authors, originates from the fact that the reproducibility and standardization of the methods is a neglected problem. The evidence, presented in the next chapters, shows that significantly different results have often been obtained by investigators, claiming to use the same method. There are several possible reasons for this:

(1) The description of the original method may have been insufficient for the purpose of exact duplication.

(2) Unknown neglected and unexpected factors (race, food, body-weight, handling of the animal, amount and nature of solvent, impurity in sample, previous treatment, season, etc.) may have been responsible.

It should be more generally realized, in our opinion, that the first requirement for an "ideal" pharmacological method is that it should be reproducible by every investigator who follows exactly the directions given in a description of the method. In order to find out whether such descriptions exist at all, the whole problem of standardization of pharmacological methods should be investigated by collaborative experimentation in many laboratories.

These considerations and restrictions should be kept in mind when reading the following chapters.

CHAPTER II

The "Analgesic" Activity of Methadone, Morphine, Pethidine and Codeine in Animals

THE vast majority of published data concerning the "analgesic" activity of diphenylpropylamines of structure (I) are expressed in quantitative symbols, i.e. "equiactive" doses, ED_{50}-doses, "threshold" doses or potency ratios.

The usual standards of reference are morphine, methadone and pethidine. The quantitative results obtained in fifty experimental conditions with these compounds and with codeine by twenty-eight authors, referred to in the following chapters, are listed in Table II. The following experimental factors are summarized in this table:

(1) Species: R (rats), M (mice), G (guinea pig), Rb (rabbit) and D (dog).
(2) Method, characterized by the noxious stimulus used: RT (radiant heat on tail), RB (radiant heat on back), PIT (pinching of tail, Haffner's method), CF (contact heat on feet), CT (contact heat on tail), ET (electric stimulus on tail), ETO (electric stimulus on tooth), PRT (pressure on tail).
(3) Route of administration: s.c., i.p., i.v., oral.
(4) The time of reading or determination of the phenomenon under investigation, in minutes after dosage.
(5) The salt used.
(6) The symbol used for expressing the term "equiactive dose": ED_{50}, ED_{100} or "threshold" dose.

None of the listed methods may be regarded as being adequately standardized.

In forty-six out of these fifty experiments mice and rats were used, the s.c. route being adopted thirteen out of nineteen times in rats and twenty-one out of twenty-seven times in mice.

Nearly all authors find methadone more active than morphine, morphine more active than pethidine, and pethidine more active than codeine by s.c. injection in both species (Table III).

TABLE II

Author	Method	Animal	Route	Time of reading after admin. (min.)	Equiactive doses*				Symbol	Potency ratios											
					Methadone	Morphine	Pethidine	Codeine		Me = 1			Mo = 1			Pe = 1			Cod = 1		
										Mo	Pe	Cod	Me	Pe	Cod	Me	Mo	Cod	Me	Mo	Pe
1. ATTENBURROW *et al.*[12] DUPRÉ *et al.*[126], OFNER, THORP, WALTON [350f]	RT	R	s.c.	30	1·58 1·39–1·77	2·16† 1·92–2·40	17·50 15–20	—	ED_{50}	0·73	0·09	—	1·4	0·12	—	11	8·1	—	—	—	—
2. BASIL *et al.* [18]	RT	R	s.c.	30	2·6 2·24–3·12	3·67 3·14–4·17	—	—	ED_{50}	0·70	—	—	1·4	—	—	—	—	—	—	—	—
3. BIANCHI [46]	PIT	M	s.c.	30	2·5 2·0–3·0	5·7 4·9–6·6	21·5 18·6–24·7	—	ED_{50}	0·44	·012	—	2·3	0·26	—	8·6	3·8	—	—	—	—
	PIT	M	i.p.	30	4·4 3·6–5·2	7·8 6·6–9·4	31·0 23·8–40·3	—	ED_{50}	0·56	0·14	—	1·8	0·25	—	7·0	4·0	—	—	—	—
4. BOCKMÜHL and EHRHART [52], KLEIDERER *et al.* [259], SCHAUMANN *et al.* [390–402]	PIT	M	s.c.	30	5	7	50	—	ED_{100}	0·71	0·10	—	1·4	0·14	—	10	7·1	—	—	—	—
5. BONNYCASTLE *et al.* [54, 55]	RT	R	i.p.	—	1·74	2·04	14·1	—	ED_{50}	0·85	0·12	—	1·2	0·14	—	8·1	6·9	—	—	—	—
6. CAHEN *et al.* [75, 76]	RB	R	s.c.	30	2·4 2·1–2·7	3·0† 2·8–3·2	21 18·2–23·8	24† 19·3–28·7	ED_{50}	0·80	0·11	0·10	1·2	0·14	0·12	8·7	7·0	0·87	10	8·0	1·1
7. DE JONGH, VAN PROOSDIJ-HARTZEMA [111]	CF	M	s.c.	10–60	6·2 5·4–7·0	10·2 9·2–11·4	27 21·7–32·3	—	ED_{50}	0·61	0·23	—	1·6	0·38	—	4·4	2·6	—	—	—	—
	PIT	M	i.v.	30	3·3 2·2–4·4	3·8 3·1–4·5	12·2 9·7–14·7	—	ED_{50}	0·87	0·27	—	1·2	0·31	—	3·7	3·2	—	—	—	—
	PIT	M	s.c.	30	3·3 2·2–4·4	3·7 3·0–4·4	13·9 11·1–16·7	—	ED_{50}	0·89	0·24	—	1·1	0·27	—	4·2	3·8	—	—	—	—
	PIT	M	or.	60	35·7 18–53·4	34·9 23·1–46·7	69·6 50·1–89·1	—	ED_{50}	1·0	0·51	—	0·98	0·50	—	1·9	2·0	—	—	—	—
	RT	R	i.p.	60	4·8 1·5–6·1	7·6 6·5–8·7	27·8 22·8–32·8	—	ED_{50}	0·63	0·17	—	1·6	0·27	—	5·8	3·7	—	—	—	—
8. EDDY *et al.* [138, 144], BRAENDEN [58, 59], LEIMBACH [286], MAY [315–317]	CF	M	s.c.	5–120	1·6 1·5–1·7	2·1 2·0–2·2	9·9 8·3–11·9	14·2 13·1–15·3	ED_{50}	0·76	0·16	0·11	1·3	0·21	0·15	6·2	4·7	0·70	8·9	6·8	1·4
	CF	M	or.	5–120	9·2 7·3–11·6	3·9 3·4–4·5	—	—	ED_{50}	2·3	—	—	0·42	—	—	—	—	—	—	—	—
9. FRIEBLE, REICHLE [162–164]	RT	M	s.c.	10–60	1·4 1·2–1·6	2·3 1·8–3·0	5·8 5·2–6·5	10·8 8·5–13·7	ED_{50}	0·61	0·24	0·13	1·6	0·40	0·21	4·1	2·5	0·54	7·7	4·7	1·9
	ET	M	s.c.	60	1·35 1·2–1·5	5·2 4·5–6·0	—	17·0 15·0–19·2	ED_{50}	0·26	—	0·08	3·8	—	0·30	—	—	—	13	3·3	—
	RB	R	s.c.	30	1·8 1·5–2·1	2·3 2·2–2·4	8·2 7·3–9·2	13·0 11·6–14·6	ED_{50}	0·78	0·22	0·14	1·3	0·28	0·18	4·5	3·6	0·63	7·2	5·6	1·6
	RB	G	s.c.	30	3·7 3·0–4·6	11·5 10·6–12·5	12·3 11·6–13·1	48·5 43·3–54·3	ED_{50}	0·32	0·30	0·08	3·1	0·93	0·24	3·3	1·1	0·25	13	4·2	3·9
10. GREEN [176, 177]	PRT	R	s.c.	30	—	—	—	—	—	—	—	—	2·3	—	—	—	—	—	—	—	—
11. HAAS [181]	RT	M	s.c.	15–180	1·4	1·7	8·6	8·3	ED_{50}	0·82	0·16	0·17	1·2	0·20	0·20	6·1	5·06	1·04	5·9	4·9	0·96
	RB	R	s.c.	15–180	> 20	6·8	16·3	—	ED_{50}	> 2·9	> 1·2	—	< 0·34	0·42	—	< 0·81	2·4	—	—	—	—
	ET	M	s.c.	15–180	2·5	4·5	4·5	9·4	ED_{50}	0·55	0·55	0·27	1·8	1·0	0·48	1·8	1·0	0·48	3·8	2·1	2·1
	ETO	Rb	s.c.	15–120	2·2	3·3	6·3	2·3	ED_{50}	0·67	0·35	0·18	1·5	0·52	0·27	2·9	1·9	0·51	5·6	3·7	1·9
12. HERR *et al.* [191–198]	CF	M	s.c.	30	5	7	40	—	ED_{100}	0·71	0·12	—	1·4	0·17	—	8·0	5·7	—	—	—	—
13. HOUGS-OLSEN [219, 220]	RT	R	s.c.	—	2·7	3·5	—	—	ED_{50}	0·77	—	—	1·3	—	—	—	—	—	—	—	—

* All hydrochlorides, unless otherwise indicated, in mg/kg.
† Sulphate.
‡ Phosphate.

TABLE II—*continued*

Authors	Method	Animal	Route	Time of reading after admin. (min.)	Equiactive doses*				Symbol	Potency ratios											
					Methadone	Morphine	Pethidine	Codeine		Me = 1			Mo = 1			Pe = 1			Cod = 1		
										Mo	Pe	Cod	Me	Pe	Cod	Me	Mo	Cod	Me	Mo	Pe
14. JACKSON [231]	CT	R	i.v.	1–15	0·31 0·20–0·80	2·0 1·7–2·4	2·0 1·8–2·2	—	ED_{50}	0·15	0·15	—	6·5	1·0	—	6·5	1·0	—	—	—	—
	CT	R	i.v.	1– > 15	0·48 0·40–1·4	2·2 1·9–2·8	—	—	ED_{50}	0·22	—	—	4·6	—	—	—	—	—	—	—	—
15. JACOB *et al.* [232]	CF	M	s.c.	30 or 60	—	6·5 5–8·45	24 19–30·2	—	ED_{50}	—	—	—	—	0·27	—	—	3·7	—	—	—	—
	CF	M	s.c.	30	—	10 7·7–13	30 23·7–38·1	—	ED_{50}	—	—	—	—	0·33	—	—	3·0	—	—	—	—
	CF	M	s.c.	30+ 60+90 +120	—	12·5 9·4–16·5	41 33·6–50	—	ED_{50}	—	—	—	—	0·30	—	—	3·3	—	—	—	—
16. JANSSEN *et al.* [237, 241, 242]	CF	M	s.c.	10–240	5·19 4·81–5·61	11·4† 10·8–12·1	25·3 23·2–27·6	53‡ 48·2–58·3	ED_{50}	0·45	0·20	0·10	2·2	0·45	0·21	4·9	2·2	0·48	10	4·6	2·1
	CF	M	or.	10–240	26·5 21·5–32·6	68† 60·7–76·2	65·5 59·5–72·1	—	ED_{50}	0·39	0·40	—	2·6	1·0	—	2·5	0·96	—	—	—	—
	CF	R	s.c.	10–240	5·14 4·59–5·76	14·3† 13–15·7	41 36·6–45·9	142‡ 118·3–170·4	ED_{50}	0·36	0·12	0·04	2·8	0·35	0·10	8·0	2·9	0·29	28	9·9	3·5
17. KASE *et al.* [246]	CF	M	s.c.	—	3·0 2·9–3·1	7·3 6·4–8·2	—	—	ED_{50}	0·41	—	—	2·4	—	—	—	—	—	—	—	—
18. KRAUSHAAR [270]	RT	M	s.c.	15	1·2 1·03–1·4	2·3 2·04–2·4	—	4·9 2·64–9·06	ED_{50}	0·52	—	0·24	1·9	—	0·47	—	—	—	4·1	2·1	—
	ET	M	s.c.	15	1·1 0·85–1·42	2·29 1·86–2·82	—	2·95 2·11–4·13		0·48	—	0·37	2·1	—	0·78	—	—	—	2·7	1·3	—
19. LEWIS [291]	RB	R	s.c.	—	—	10*	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
20. MILOSEVIC [335]	PIT	M	s.c.	30	3·2 2·5–4·0	5·3 3·7–4·0	22·0 18·8–25·7	—	ED_{50}	0·60	0·15	—	1·7	0·24	—	6·9	4·1	—	—	—	—
21. MORREN *et al.* [343]	RT	R	s.c.	—	—	2	—	—	"threshold" dose	—	—	—	—	—	—	—	—	—	—	—	—
			or.	—	—	8	—	—		—	—	—	—	—	—	—	—	—	—	—	—
	CF	M	s.c.	—	—	10	—	—		—	—	—	—	—	—	—	—	—	—	—	—
				—	—	20	—	—		—	—	—	—	—	—	—	—	—	—	—	—
22. OHLSSON [350]	CF	M	s.c.	10–180	5·3	8·6	23	—	ED_{50}	0·62	0·23	—	1·6	0·37	—	4·3	2·7	—	—	—	—
23. PORSZASZ [363–365]	CF	M	s.c.	—	—	—	—	—	ED_{50}	0·71	0·20	—	1·4	0·28	—	5·0	3·6	—	—	—	—
	CF	R	s.c.	30–90	3·35	8·0	22·2	—	ED_{50}	0·42	0·15	—	2·4	0·36	—	6·6	2·8	—	—	—	—
24. RADOUCO *et al.* [367a]	ETO	G	s.c.	—	—	2·5	7·7	—	ED_{50}	—	—	—	—	0·32	—	—	3·1	—	—	—	—
25. SCOTT *et al* [415–419]	PIT	R	i.p.	—	1·0	—	8·0	—	"threshold" dose	—	0·12	—	—	—	—	8·0	—	—	—	—	—
	RB	D	i.p.	—	1·0	—	10·0	—		—	0·10	—	—	—	—	10·0	—	—	—	—	—
26. TYE *et al.* [463]	RT	R	s.c.	40	1·9 1·6–2·2	4·7* 4·2–5·2	—	31·6‡ 28·5–35·0	ED_{50}	0·40	—	0·06	2·5	—	0·15	—	—	—	17	6·7	—
27. WINTER and FLATAKER [509, 510]	RT	R	s.c.	15–120	2	4*	—	—	ED_{100}	0·50	—	—	2·0	—	—	—	—	—	—	—	—
28. YANAI [533]	RT	M	—	—	3·9	8·2	—	23·5	ED_{50}	0·47	—	0·16	2·1	—	0·35	—	—	—	6·0	2·9	—

* All hydrochlorides, unless otherwise indicated, in mg/kg.
† Sulphate.
‡ Phosphate.

TABLE III—"ANALGESIC" POTENCY RATIOS OF METHADONE, MORPHINE, PETHIDINE AND CODEINE AS DETERMINED BY S.C. INJECTION IN MICE AND RATS IN FORTY-SIX DIFFERENT EXPERIMENTAL CONDITIONS

	Mice s.c.				Rats s.c.			
	Average	Minimum	Maximum	*n**	Average	Minimum	Maximum	*n**
Methadone : morphine	1·8	1·1	3·8	17	1·9	1·2	2·8	10
Morphine : pethidine	3·4	1·0	5·7	14	4·5	2·4	8·1	6
Pethidine : codeine	1·7	1·0	2·1	5	2·1	1·1	3·5	3
Methadone : pethidine	5·8	1·8	10·0	12	7·8	4·5	11·0	5
Methadone : codeine	7·0	2·7	13·0	8	16	7·2	28·0	4
Morphine : codeine	3·7	1·3	6·8	8	7·6	5·6	9·9	4

* n = number of comparative results.

The data listed in Tables II and III show:

(a) That the results obtained in mice and in rats are quite similar.

(b) That the variations of the results obtained in methods characterized by similar noxious stimuli, are as large as the variation of the combined results.

(c) That there is no detectable correlation between "equiactive" dose level and potency ratio.

(d) That the potency ratios and "equiactive" dose levels determined after i.p. injection are not significantly different from those obtained after s.c. injection.

(e) That the results obtained after oral or i.v. administration are quite different from the s.c. and i.p. results. The agreement among different authors is very poor.

(f) That too few experiments with other species have been carried out to allow for useful discussion.

(g) That factors, other than those listed in Table II, must play an important role in determining the outcome of the experiments.

CHAPTER III

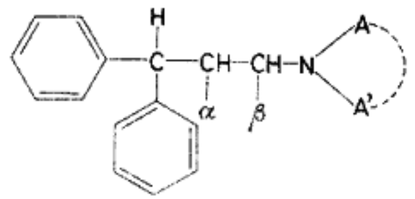
3:3-Diphenylpropylamines (I : R = H)

THE important methods of synthesis of 3:3-diphenylpropylamines (I : R = H [3.1]) may be outlined as follows:

(a) Treatment of basic nitriles (I : R = CN) with excess sodamide leads to replacement of the cyano group by hydrogen. Yields are excellent [236–240, 379].

(b) Dehydration and reduction of basic tertiary alcohols (I : R = OH) in one step, using red phosphorus and hydriodic acid [378] or in two steps, using dehydration in acid medium followed by catalytic hydrogenation [2, 3].

(c) Condensation of a tertiary aminoethylchloride with sodium or potassium diphenylmethide, which are best prepared from diphenylmethane and $NaNH_2$ or KNH_2 in liquid ammonia [185]. Lower yields are obtained with the older methods employing sodium amide in toluene [148] or phenylsodium in benzene [40].



3.1

Less important methods of synthesis include:

(a) The reductive condensation of 2:2-diphenylpropionaldehyde and a secondary amine [52].

(b) Condensation of 3:3-diphenylpropylchloride with a secondary amine [52].

(c) Decarboxylation of aminoacids (I : R = COOH) [92, 93].

(d) Replacement of the ketogroup of basic ketones of the methadone-type (I : R = COalk) with excess Grignard reagent, several reducing agents or boiling alkaline solution [50, 51, 20, 21, 139, 315, 316].

Continued on p. 107

TABLE VI—*continued*

Compound No. (Table IV)	Dissociation pK_a	Refraction $t°$ (°C)	Refraction n_D	Optical rotation: Base or salt	Optical rotation: $[M]$	Optical rotation: $[\alpha]_D$	Optical rotation: $t°$ (°C)	Solvent	Concentration	References
16.4	—	—	—	*l-d*-tartrate	− 111·5	− 22·5	27	CH_3OH–50% H_2O	2·0	462
	—	—	—	*d*-base	− 34·5	− 10	27	CH_3–CO–CH_3	2·0	
	—	—	—	*d*-base	—	0	27	C_2H_5OH	2·0	
	—	—	—	*d*-base	+ 116·8	+ 33·8	27	H_2O/HCl	5·0	
	—	—	—	*d*-HCl	+ 132·2	+ 34·6	27	H_2O	1·5	
	—	—	—	*d-d*-tartrate	+ 223	+ 45	27	CH_3OH–50% H_2O	2·0	515
	—	—	—	*l*-base	+ 41·5	+ 12	27	CH_3–CO–CH_3	—	
	—	—	—	*l*-base	− 109·2	− 31·6	27	H_2O/HCl	—	
	—	—	—	*d*-base	− 34·5	− 10	27	CH_3–CO–CH_3	—	
	—	—	—	*d*-base	+ 116·8	+ 33·8	27	H_2O/HCl	—	

* Unpublished data from this laboratory.

Continued from p. 13

(e) Degradation of methadols (I : R = CHOH alk) in boiling alkaline solution [36, 315].

(f) Hydrogenolysis of the carbon–sulphur bond of basic sulphones (I : R = $SO_2C_2H_5$) with Raney nickel in boiling ethanol [10].

The basis of the twenty-six known 3:3-diphenylpropylamines listed in Table IV are stable oils or low melting solids (Tables IV and VII). They are readily distilled under reduced pressure (between 110° and 180°C at 1 mm Hg) without decomposition. The chemical reactivity of these compounds is limited. They have not been used as intermediates.

The melting points of the hydrochlorides and of the methyl iodides of several of these bases have repeatedly been reported upon. Agreement among different authors is satisfactory in most cases. In Table VII the most important of these data are summarized, by listing highest melting point ranges which are in agreement with the majority of the reported figures.

Structural changes have a greater but similar influence on the melting points of the hydrochlorides than on the melting points of the methyl iodide salts. Among the unbranched dialkyl-amino derivatives the melting points of both salts decrease when the alkyl groups are lengthened ($CH_3 > C_2H_5 > C_3H_7 > C_4H_9$). Introduction of a methyl group in α-position increases and in β-position decreases the melting point of the hydrochloride salt of the resulting racemate.

Dissociation constants, refraction indices and optical rotations are listed in Table VI.

According to BECKETT the dimethylamino derivatives of type I (R = H) are stronger bases than the corresponding piperidines and much stronger than the morpholines. Methyl-branching in β-position has a relatively small inconstant effect on basic strength (Chapter 20).

The most reliable values for the reported molecular optical rotation values $[M]^{18\text{-}20}_{D}$ in various solvents are:

I : R = H; α = H; β = CH_3		Base in C_6H_{12}	Base in C_6H_5	Base in C_2H_5OH	HCl in H_2O
NAA′	Isomer				
$N(CH_3)_2$	*d**	− 168	− 127	+ 30	+ 125
$N(CH_3)_2$	*l*	—	—	—	− 125
morpholine	*d*†	+ 145	+ 123	+ 55	− 97

* The absolute configuration of this *d*-isomer is related to D-(−)-alanine (Chapter 21).
† The absolute configuration of this *d*-isomer is related to L-(+)-alanine.

TABLE VII—MELTING POINTS OF BASES, HYDROCHLORIDES AND METHYL IODIDES OF 3:3-DIPHENYLPROPYLAMINES (I : R = H)

	α	β	NAA′	Isomer	Melting point (°C)		
					Base	HCl	CH_3I
1.	H	H	$N(CH_3)_2$	—	44 ± 2 (4)*	170 ± 1 (5)	179 ± 1 (4)
2.	CH_3	H	$N(CH_3)_2$	*dl*	oil	183 ± 1 (2)	—
3.	H	CH_3	$N(CH_3)_2$	*dl*	oil	157 ± 3 (6)	199 ± 3 (2)
4.	H	CH_3	$N(CH_3)_2$	*d*	oil	183 ± 1 (2)	—
5.	H	CH_3	$N(CH_3)_2$	*l*	oil	182 ± 1 (2)	—
6.	H	H	$N(C_2H_5)_2$	—	oil	144 ± 1 (6)	161 ± 1 (3)
7.	H	H	$N(C_3H_7)_2$	—	oil	115 (2)	~145 (2)
8.	H	H	$N(iC_3H_7)_2$	—	oil	176 (1)	192 (1)
9.	H	H	$N(C_4H_9)_2$	—	oil	114 (1)	143 (1)
10.	H	H	pyrrolid.	—	oil	134 ± 1 (2)	157 (4)
11.	H	H	piperid.	—	42 ± 1 (3)	215 ± 1 (10)	175 ± 2 (3)
12.	CH_3	H	piperid.	*dl*	100 (1)	214 ± 6 (4)	—
13.	H	CH_3	piperid.	*dl*	oil	213 ± 1 (3)	—
14.	H	H	morphol.	—	oil	207 ± 2 (6)	163 (1)
15.	CH_3	H	morphol.	*dl*	oil	229 (1)	—
16.	H	CH_3	morphol.	*dl*	oil	199 (2)	—
17.	H	H	hexameth.	—	oil	196 (1)	177 (1)
18.	H	H	heptameth.	—	oil	165 (1)	173 (1)
19.	CH_3	H	heptameth.	*dl*	oil	196 (1)	—

* Number of reported melting points on which estimate is based (Table IV).

All known 3:3-diphenylpropylamines of type I (R = H) are devoid of pronounced analgesic activity in mice and rats (Table V, compounds (1.1) to (1.25)). Compound (1.4) (Table V), the degradation product of methadone, is said to be one-third as active as codeine [286]. This activity is entirely due to the laevo-isomer (two-thirds codeine), the dextro-isomer being inactive [59]. The active isomer is stereochemically related to L-(+)-alanine and the analgesically inactive dextro-isomer of methadone.

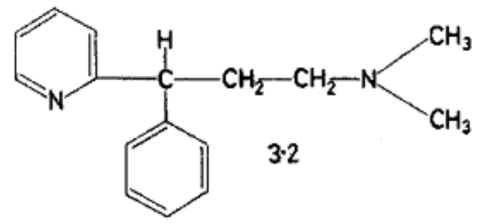
Compound (1.10) (I : R = H; $\alpha = \beta$ = H; NAA′ = piperidine; HCl), one of the ingredients of the German specialty Aspasan*, possesses weak antispasmodic, antihistaminic, parasympatholytic, antinicotinic and local anaesthetic properties.

Replacement of the piperidino group by other amino groups and branching of the side chain as a rule decreases most of these properties (JANSSEN, 1956; WHITE, 1951).

N:*N*′-di*iso*propyl-3:3-diphenylpropylamine HCl however (R 253, compound (1.20)), a constituent of Bilagol* Eupharma, is the most active

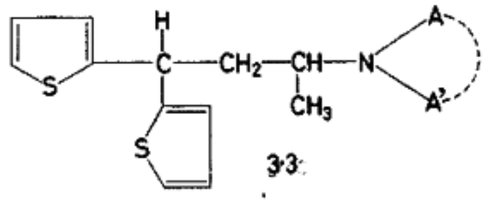
antispasmodic and antinicotinic agent of this series (JANSSEN, 1956, unpublished results).

Quaternization with methyl halides as a rule increases parasympatholytic activity, and decreases all other activities [236–240, 500]. The most active quaternary salts of this series, i.e. the methyl halides of compounds (1.16), (1.20) and (1.22), are about half as active as atropine (unpublished results).



3·2

The weak antihistaminic properties of some tertiary amines of type [3.1] become extremely pronounced among chemically related compounds (e.g. prophenpyridamine, [3.2]) in which one phenyl group is replaced by a heterocyclic ring [236–240, 273a, 293a].



3·3

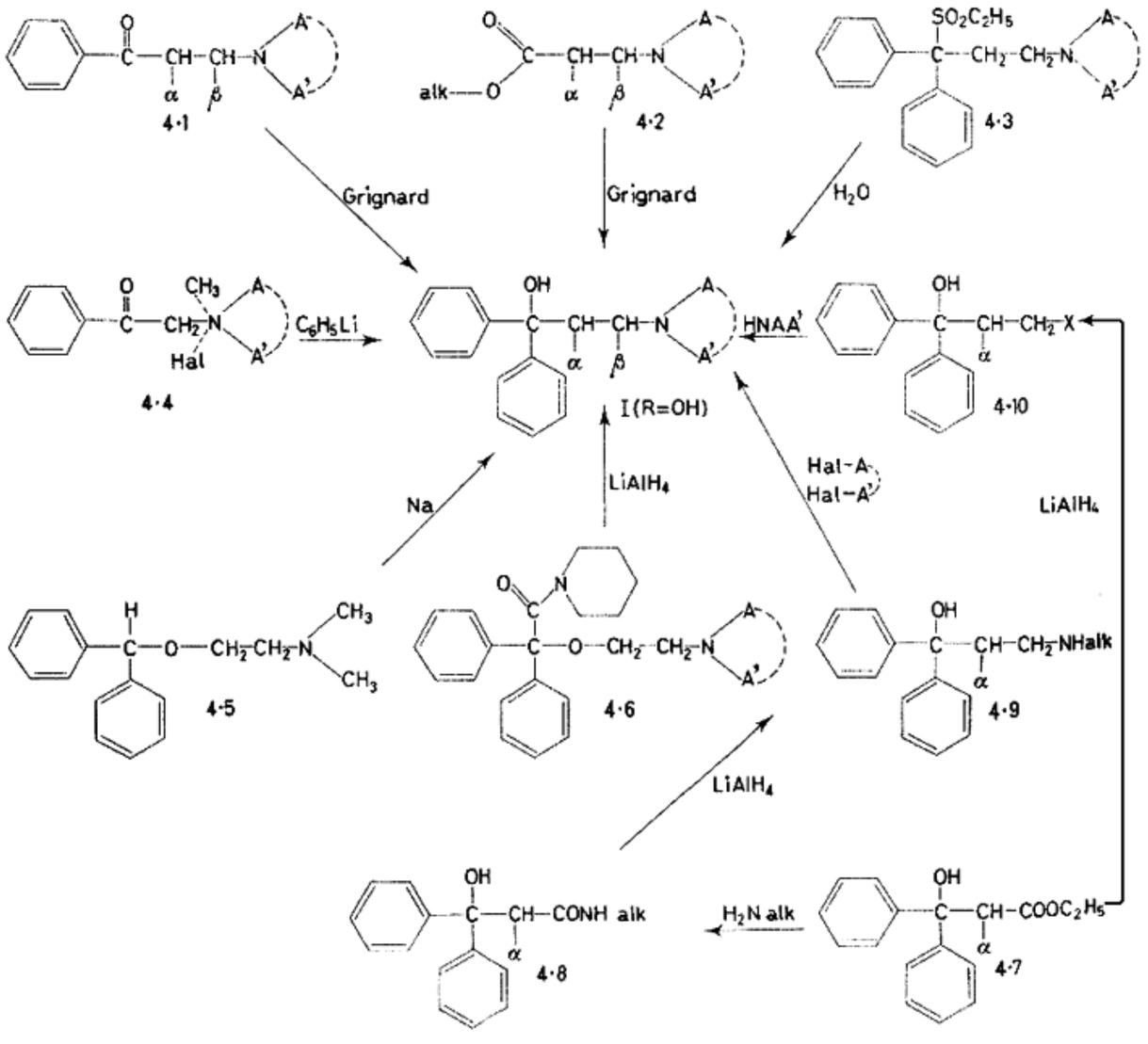
The related dithienylbutylamines are moderately active analgesics [3a, 140, 176a, 236–240].

CHAPTER IV

Tertiary Alcohols

(I: R = OH)

THE twenty-one basic tertiary alcohols I (R = OH), listed in Table IV, were prepared by one or several of the following eight methods of synthesis:



(a) *Methods 1 and 2: Grignard reactions*

All listed compounds are easily prepared by reaction of a phenylmagnesium

halide with a Mannich base [4.1] (30–50 per cent yields) or with a basic propionate [4.2] (up to 90 per cent yields) [2, 3, 52, 119–122, 236–240, 378].

(b) *Method 3*

Basic sulphones [4.3] are unstable in aqueous solution. They are slowly hydrolysed, even at room temperature, into the amino alcohols I (R = OH) (Chapter 19).

(c) *Method 4*

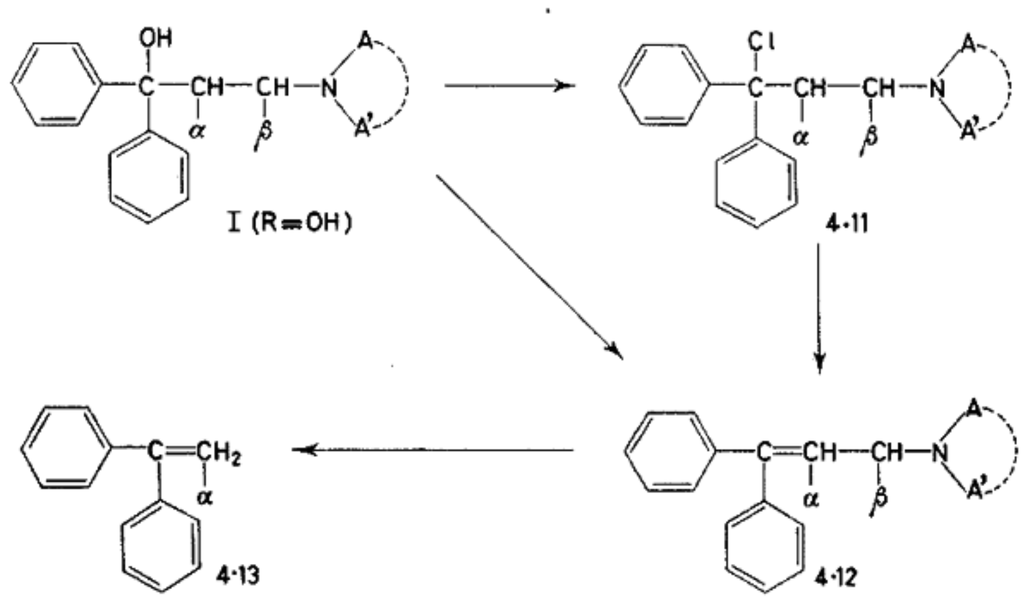
According to WITTIG [530] a quaternary salt of an aminoacetophenone [4.4] reacts with phenyl lithium to yield a tertiary alcohol I (R = OH) by Stevens–Sommelet rearrangement.

(d) *Methods 5 and 6*

Diphenhydramine [4.5] is converted to 1:1-diphenyl-3:3-dimethylaminopropanol when treated with sodium and the basic amido ethers [4.6] undergo transformation to I (R = OH) when reduced with $LiAlH_4$ [347].

(e) *Methods 7 and 8 (unpublished results)*

Method 7 involves conversion of the Reformatsky esters [4.7] via the methyl amides [4.8] and the amino alcohols [4.9], obtained by $LiAlH_4$ reduction of [4.8]. Treatment of [4.9] with alkyl halides or dihalides yields quaternary salts of I (R = OH).



Method 8 goes through $LiAlH_4$ reduction of the same Reformatsky esters [4.7] to the glycols [4.10: X = OH] and reaction of the *l*-tosylates [4.10: X = O — Ts] or the amino halides [4.10: X = halogen] with secondary or tertiary amines. These amino halides are also available from the halogenated ketones $C_6H_5COCH\ \alpha\ CH_2$.hal with phenyl magnesium halide or phenyl lithium (unpublished results). Amino alcohols related to *tricyclo*amol

were prepared by HARFENIST and MAGNIEN [183] in a similar way, starting from phenyl*cyclo*hexyl ketone. Both routes are of interest for preparing amino alcohols of type I (R = OH) containing substituents in NAA′ which react with Grignard reagents.

Most hydrochlorides of the basic tertiary alcohols I (R = OH) are stable in neutral aqueous solution, but are readily dehydrated in acid solution. ADAMSON [23] reports quantitative yields of [4.12] ($\alpha = \beta = H$) when unbranched alcohols I (R = OH; $\alpha = \beta = H$) are refluxed during 30 min in a mixture of 30 parts of concentrated HCl and 100 parts of glacial acetic acid.

The hydroxyl group in branched alcohols having a methyl group in α-position (I : R = OH; $\alpha = CH_3$; $\beta = H$) is sterically hindered. Such alcohols require very drastic treatment for dehydration. Thionyl chloride may be used for this purpose [4, 5, 258], but in some instances the isolated products were identified as the hydrochloride of an amino chloride [4.11] or as the unusual product of aniotropic degradation [4.13: $\alpha = CH_3$].

TABLE VIII—MELTING POINTS OF BASES, HYDROCHLORIDES AND METHYL IODIDES OF BASIC ALCOHOLS I (R = OH)

Structure				Base		HCl		CH_3I	
α	β	NAA′	Isomer	m.p. (°C)	n*	m.p. (°C)	n	m.p. (°C)	n
H	H	$N(CH_3)_2$	—	166 ± 2	6	204 ± 1	2	245	1
CH_3	H	$N(CH_3)_2$	*dl*	93 ± 1	5	240 ± 2	4	—	—
H	CH_3	$N(CH_3)_2$	*dl*	124 ± 2	8	207 ± 2	4	249	1
H	CH_3	$N(CH_3)_2$	*d*	150	1	—	—	—	—
H	CH_3	$N(CH_3)_2$	*l*	150 ± 2	2	—	—	—	—
H	H	$N(C_2H_5)_2$	—	52 ± 2	3	202 ± 2	3	197 ± 3	2
CH_3	H	$N(C_2H_5)_2$	*dl*	78	1	184	1	—	—
H	CH_3	$N(C_2H_5)_2$	*dl*	55	1	199	1	—	—
H	H	$N(C_3H_7)_2$	—	53 ± 1	2	161	1	183	1
H	H	$N(C_4H_9)_2$	—	42	1	109–159	2	—	—
H	H	pyrrolid.	—	172 ± 1	3	191	1	208 ± 2	2
H	H	piperid.	—	119 ± 2	7	214–238	6	218 ± 4	2
CH_3	H	piperid.	*dl*	120 ± 5	3	216–266	3	—	—
H	CH_3	piperid.	*dl*	81 ± 6	2	213–234	2	—	—
H	H	hexameth.	—	81	1	—	—	225	1
H	H	morphol.	—	106 ± 1	5	229 ± 2	3	203 ± 1	2
CH_3	H	morphol.	*dl*	122 ± 1	1	205	1	—	—

* Number of reported melting points (Table IV) on which the listed melting point ranges are based.

Tertiary alcohols derived from diphenylcarbinol (I; R = OH) are, as expected, difficult to acylate. Their esters are readily hydrolysed in aqueous solution (Chapter XIV).

According to KAWABATA [247] amino alcohols I (R = OH) are useful intermediates for the preparation of the basic nitriles I (R = CN). This author describes the conversion of the amino chlorides I (R = Cl), prepared from the alcohols with thionyl chlorides, using KCN. Attempts to repeat these experiments in this laboratory were unsuccessful (unpublished results).

Conversion of the amino alcohols I (R = OH) to the simple diphenylpropylamines I (R = H) in one or in two steps was described in Chapter III.

The bases of the amino alcohols I (R = OH) are, as a rule, crystalline solids. They form crystalline hydrochlorides and methiodides. They can be distilled only at extremely low pressures. The agreement among melting points, recorded by different authors for the same substance, is often very poor (Tables IV and VIII). Many of the described compounds must have been impure. Contamination with the products of dehydration [4.12] is very likely to have occurred in at least some cases.

Among the unbranched alcohols derived from "open" dialkylamines (I; R = OH; $\alpha = \beta = H$), lengthening of the alkyl-groups results in a progressive decrease of all melting points.

The influence of side chain branching on the melting points is irregular.

The laevo-isomer of 1:1-diphenyl-3-dimethylamino-butanol was prepared by ARCHER [10] and by BECKETT [23–27, 31, 32]. Its absolute configuration is similar to the configuration of D-(−)-alanine. The best available $[M]_D^{20} \pm 4$ values for this isomer are as follows:

base in *cyclo*hexane	$[M] = +99$
base in benzene	$[M] = +88$
base in ethanol	$[M] = -80 \pm 10$
HCl in water	$[M] = -125 \pm 15$

None of the known amino alcohols (I : R = OH) has analgesic activity in mice and rats (Table V).

Most of them, however, present some degree of atropine-like activity [101, 116–122, 236–240, 259, 280–282, 500].

This property is especially pronounced among the unbranched alcohols ($\alpha = \beta = H$) derived from cyclic amines of the type $N(CH_2)_n$ ($n \geqslant 4$). Quaternization with methyl halides as a rule increases the potency of the bases, while alkyl halides with more than two carbon atoms produce progressively less and less active quaternary salts [236–240, 500].

The most potent compounds are about as active as atropine.

It should be noted that the alcohols I (R = OH) are chemically and pharmacologically closely related to the trihexyphenidyl group of parasympatholytic and nicotinolytic compounds.

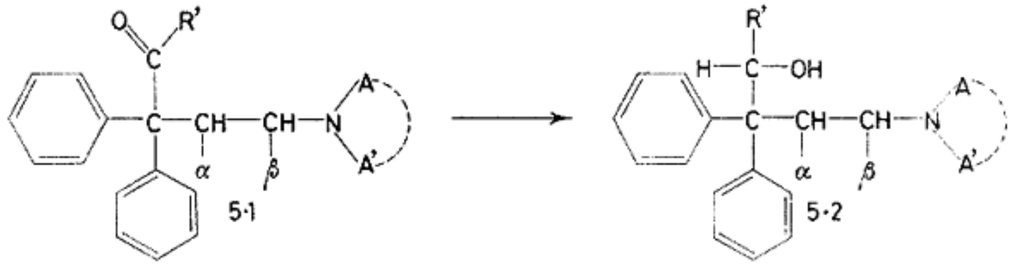
Trihexyphenidyl itself, *tricyclo*amol, tridihexethide, cycrimine and Akineton* are all obtained by substitution of one phenyl group by various *cyclo*-alkyl groups.

1:1-Diphenyl-3-piperidino-propanol HCl (Parkiphen*) has been used to some extent in the treatment of Parkinson disease.

CHAPTER V

Secondary Alcohols

(I: R = CHOH alk)



(Methadol: R′ = C_2H_5; α = H; β = CH_3; NAA′ = $N(CH_3)_2$)
(*iso*Methadol: isomer: α = CH_3)

BASIC secondary alcohols [5.2] are prepared by reduction of basic ketones of the methadone type [5.1].

According to BOCKMÜHL and EHRHART [52] unbranched ketones ($\alpha = \beta =$ H) are easily reduced with Ni–H_2 in ethanol (150°, 50–80 atm). This procedure fails to reduce the branched ketones (α or β = CH_3). Ketones with a methyl group in β-position were successfully reduced by these authors with sodium in boiling ethanol, propanol or *iso*propanol.

BECKETT and LINNELL [20, 21] reduced 4:4-diphenyl-6-morpholino-hexan-3-on in 80–90 per cent yield with aluminium *iso*propoxide in boiling toluene. The reaction required 100 hr.

According to SPEETER *et al.* [437, 438] methadone is readily reduced to methadol by the use of Adams platinum oxide catalyst at 20°C and 55 lb pressure. At 60°C reduction of one phenyl group occurs. Palladium is unsuccessful. *iso*Methadone was resistant to all attempts at catalytic hydrogenation. The morpholino analogues showed a similar behaviour. Lithium aluminium hydride, however, reduces all these compounds yielding, however, only one pure stereoisomer in nearly quantitative yield in all cases. The same isomer was also exclusively obtained by catalytic hydrogenation, as described above.

MAY and MOSETTIG [315] also obtained only one isomer of methadol (80 per cent yield) by hydrogenation of methadone with platinum oxide (CH_3OH, 20°C, 1 atm, 12–24 hr). Methadone was unaffected when subjected to hydrogenation with Raney nickel (20°C, 1 atm) or treated with aluminium *iso*propoxide and sodium amalgam. It was not attacked in the Clemmensen reduction. When subjected to the Huang–Minlon modification of the Wolff–Kirchner reaction, 1:1-diphenyl-amino-propane was formed [I : R = H; $\alpha = \beta = H$; NAA′ = $N(CH_3)_2$] by alkaline cleavage of the ethyl keto group.

The same authors [315] also studied the synthesis of *iso*methadol [5.2 : R′ = C_2H_5; $\alpha = CH_3$; $\beta = H$; NAA′ = $N(CH_3)_2$] by reduction of *iso*methadone. Unlike methadone, *iso*methadone did not absorb hydrogen in the presence of platinum oxide, but both ketones were easily reduced with $LiAlH_4$. In each instance only one stereoisomer was encountered. It was noted that alkaline cleavage of the ethyl keto group of *iso*methadone did not proceed as readily as with methadone.

The only one of the two possible diastereoisomeric methadols and *iso*-methadols obtained by catalytic reduction of methadone or *iso*methadone (*dl*, *d* and *l*) using $LiAlH_4$ are referred to as the α-isomers [361].

In order to obtain the β-isomers of methadol, EDDY *et al.* [189] reinvestigated the reduction of methadone with sodium propanol, previously described by BOCKMÜHL and EHRHART (1949). With *dl*-methadone, the predominant product, isolated in 65 per cent yield, proved to be β-*dl*-methadol, concomitantly 10 per cent of α-*dl*-methadol was produced.

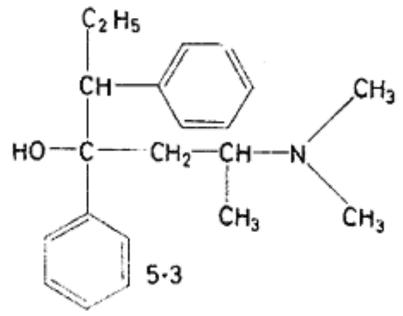
Similar reaction of *d*-methadone gave 40 per cent of β-*d*-methadol, from 5 to 10 per cent of α-*l*-methadol and 5 per cent of *l*-1:1-diphenyl-3-dimethyl-aminobutane.

Reaction of *l*-methadone gave β-*l*-methadol, α-*l*-methadol and *d*–1:1-diphenyl-3-dimethylamino-butane in approximately the same yields.

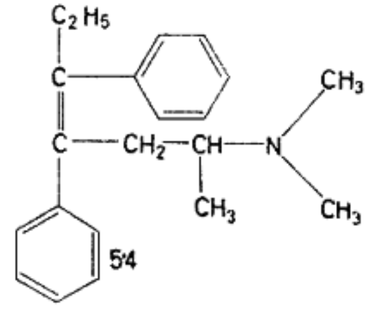
Similar studies were conducted by MAY and EDDY [316] with *dl*-, *d*-, and *l*-*iso*methadone. With $LiAlH_4$ only α-isomers were obtained. With sodium and propanol as the reducing medium, *iso*methadone gave mixtures of from 35 to 40 per cent of β-*iso*methadols and from 15 to 20 per cent of α-*iso*methadols.

Acylation of these "methadols" produces "acylmethadols", described in Chapter XV.

Attempts to prepare methadol ethers have not met with success. Methadol itself, when treated with excess dimethylsulphate in boiling ethyl acetate, rearranges to yield the tertiary alcohol [5.3] and its product of dehydration [5.4], which is also prepared from methanol with thionyl chloride under vigorous conditions [317].

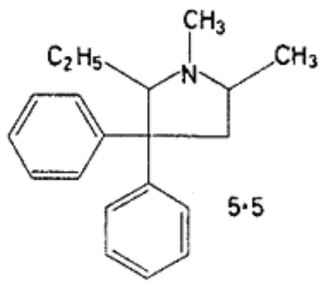


5·3

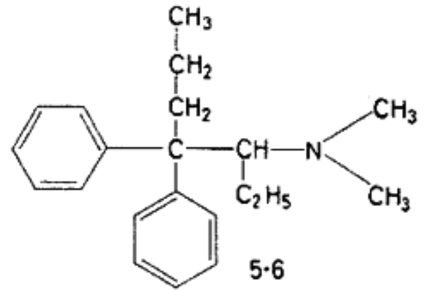


5·4

On reaction of methadol in ethyl acetate with either mesyl or tosyl chloride, a methochloride separates in 25 per cent yield, which is probably the salt of [5.5]. Hydrogenation of the olefinic material resulting from exhaustive methylation gives an isomer, which has probably structure [5.6] [317].

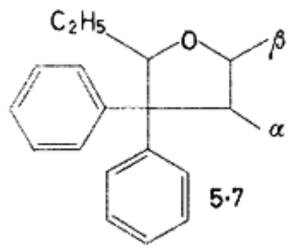


5·5



5·6

EASTON and FISH [133] investigated the pyrolitic decomposition of the methyl iodides of α-*dl*-methadol, α-*dl*-, α-*d*-, and α-*l*-*iso*methadol and of α-6-dimethylamino-4:4-diphenyl-hexanol. It was found that a stereo-specific cyclization reaction of the methadols produces the corresponding isomers of the tetrahydrofurans [5.7]:



5·7

As seen in Table IV, only eight methadols, not including the isomers, are known. All but one are derived from ethyl ketones.

Some physical properties of all possible isomers of methadol and *iso*-methadol as well as the isomeric parent ketone from which they are derived are listed in Tables IV, VI and IX.

EDDY and collaborators (Table V) investigated the analgesic activity of these isomers in mice (s.c.) with the following surprising results:

methadone
- *d* (0·39)* → *α,l*-methadol (2·8)*
- *d* (0·39)* → *β,d*-methadol (0·19)
- *l* (12) → *α,d*-methadol (0·40)
- *l* (12) → *β-l*-methadol (1·3)

*iso*methadone
- *d* (0·20) → *α,d-iso*methadol (0·16)
- *d* (0·20) → *β,l-iso*methadol (0·17)
- *l* (8·4) → *α-l-iso*methadol (0·11)
- *l* (8·4) → *β-d-iso*methadol (1.6)

* Pethidine = 1, see Table IX.

TABLE IX—PHYSICAL PROPERTIES AND ANALGESIC ACTIVITY OF ISOMERS OF METHADOL AND *iso*METHADOL (SEE TABLES IV, V AND VI)

Isomers		Methadols				*iso*Methadols			
		α, d	*α, l*	*β, d*	*β, l*	*α, d*	*α, l*	*β, d*	*β, l*
Parent ketone	methadone	*l*	*d*	*d*	*l*	—	—	—	—
	*iso*methadone	—	—	—	—	*d*	*l*	*l*	*d*
$[M]_D^{20-25}$	base in ethanol	—	—	+ 554	− 554	+ 60	− 61	+ 41	− 43
	HCl in water	+ 118	− 118	+ 257	− 285	+ 36	− 34	+ 47	− 42
Melting points	base	—	—	107	106	125	126	95	94
	HCl	171	171	208	208	204	204	243	243
Analgesic activity*		0·40	2·8	0·19	1·3	0·16	0·11	1·6	0·17

* In mice, s.c. injection; potency ratios:
pethidine = 1·0.

The parent ketones have the following potencies:

methadone : *l* = 12; *d* = 0·39
*iso*methadone : *l* = 8·4; *d* = 0·20
(EDDY *et al.*, see Table V).

The most active isomer, *α,l*-methadol, which is derived from the inactive *d*-isomer of methadone, is more active than *β-l*-methadol, prepared from the active *l*-methadone. These results were partly confirmed by POHLAND [361] and in this laboratory [241] (Table V; potency ratios: *dl*-methadone = 1·0):

	EDDY	POHLAND	JANSSEN
α-dl-methadol	0·08	0·20	0·14
α-d-methadol	0·06	0·03	—
α-l-methadol	0·46	0·40	—
β-dl-methadol	0·22	—	0·13

In the *iso*-series, only the *β,d*-isomer of *iso*methadol, derived from the active *l*-isomer of *iso*methadone, shows significant activity.

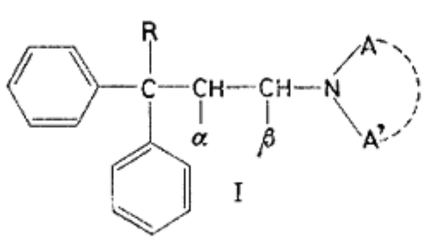
These results are obviously not in agreement with the hypothesis that all active analgesics have the same absolute configuration as D-(−)-alanine [25–27, 31, 32].

Further studies in this field are obviously desirable. Other than analgesic properties of the existing methadols are unknown. The influence of structural changes in the "alk"- and "NAA'-" portions of the general molecule [5.2] on the pharmacological properties has not yet been explored. The relation between absolute configuration of the isomers and pharmacological properties is of high theoretical interest.

CHAPTER VI

Primary Alcohols

[I : R = $(CH_2)_n$ — OH; n = 1, 2, 3]



I

SEVEN basic primary alcohols of type I[R = $(CH_2)_n$ OH; n = 1, 2 and 3] are known (Table IV).

Reduction of acids [6.2], esters [6.3] and aldehydes [6.4] to the primary alcohols [6.5] proceeds in good yields with a slight molar excess of $LiAlH_4$ or $NaBH_4$ [236–240, 437, unpublished results].

Aldehydes [6.4] are also converted to alcohols [6.5] by catalytic (Pt–H_2 760 mm Hg) hydrogenation [534].

A primary alcohol of type [6.10] was prepared by SPERBER *et al.* (1953). Diphenylmethane reacted with 2-bromoethylethylether and KNH_2 in liquid ammonia (86 per cent) to yield 3:3-diphenylpropylethylether, which was similarly converted to the basic ether [6.9] with dimethylaminoethylchloride. Treatment of [6.9] with 48 per cent HBr gave 95 per cent of the hydrobromide of the basic alcohol [6.10] [$\alpha = \beta$ = H; NAA' = $N(CH_3)_2$].

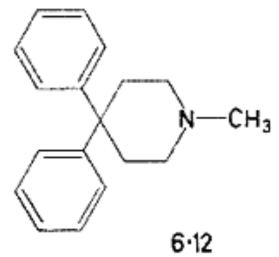
PERRINE and MAY (1954) prepared the alcohol [6.8] [α = H; $\beta = CH_3$; NAA' = $N(CH_3)_2$], starting from the aldehyde [6.8], which reacted with malononitrile to yield [6.6] (63 per cent). This nitrile was then successively

reduced (PtO–CH_3OH–H_2, 760 mm Hg) and hydrolysed with 20 per cent HCl to yield the amino acid [6.7] (35–50 per cent). The methyl ester of this acid was reduced to the alcohol [6.8] with $LiAlH_4$ (87 per cent).

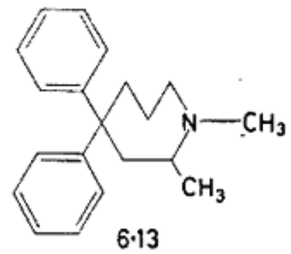
The physical properties of these primary alcohols have not been investigated in detail. Only a few melting points were reported upon (Table IV).

Esterification of the alcohols of type [6.5] will be discussed in Chapter XIX.

The alcohol [6.10] [$\alpha = \beta$ = H; NAA' = $N(CH_3)_2$] was converted by SPERBER, SHERLOCK and PAPA [439] to 1-methyl-4:4-diphenylpiperidine [6.12]. Treatment of [6.10] with thionyl chloride gave the methochloride and with a large excess of 48 per cent HBr the methobromide of [6.12]. Sublimation *in vacuo* of both quaternary salts gave the base.



6·12



6·13

With hydriodic acid the hydroxyl group of [6.8] is replaced by iodine (50 per cent). This iodide is reduced to the amine [6.11] with zinc and HCl (26 per cent), and easily cyclized to 1:2-dimethyl-4:4-diphenylhexamethylenimine methiodide [353].

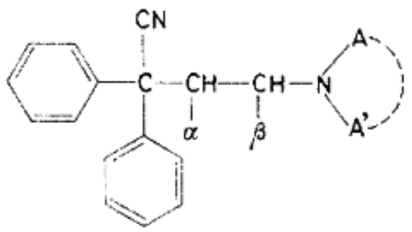
None of these primary alcohols is known to possess analgesic or other pharmacological properties (Table V).

CHAPTER VII

Nitriles

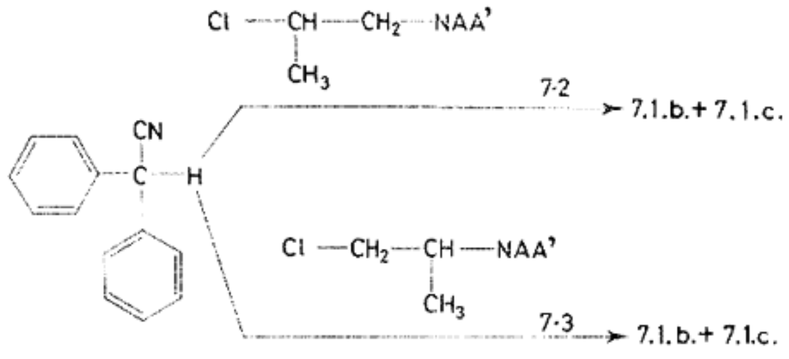
(I : R = CN)

BASIC nitriles [7.1 a, b, c] are important intermediates. Several methods of synthesis were studied in detail by many authors.

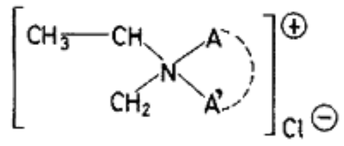


7.1(a) $\alpha = \beta = H$
7.1(b) $\alpha = CH_3$; $\beta = H$
7.1(c) $\alpha = H$; $\beta = CH_3$

The unbranched nitriles [7.1a] are conveniently prepared by condensation of diphenylacetonitrile with an aminoethylchloride $ClCH_2CH_2NAA'$ by means of condensation agents such as $NaNH_2$, KNH_2, $LiNH_2$, Na, NaOH, C_6H_5Na, t-C_4H_9ONa, etc., in boiling apolar solvents (benzene, toluene, xylene). This method, originally described by EISLEB [149], gives nearly quantitative yields in suitable experimental conditions [49, 52, 87, 92, 93, 126, 131, 132, 234–240, 340, 345, 346, 350*g*, 379, 480, 503, 504].

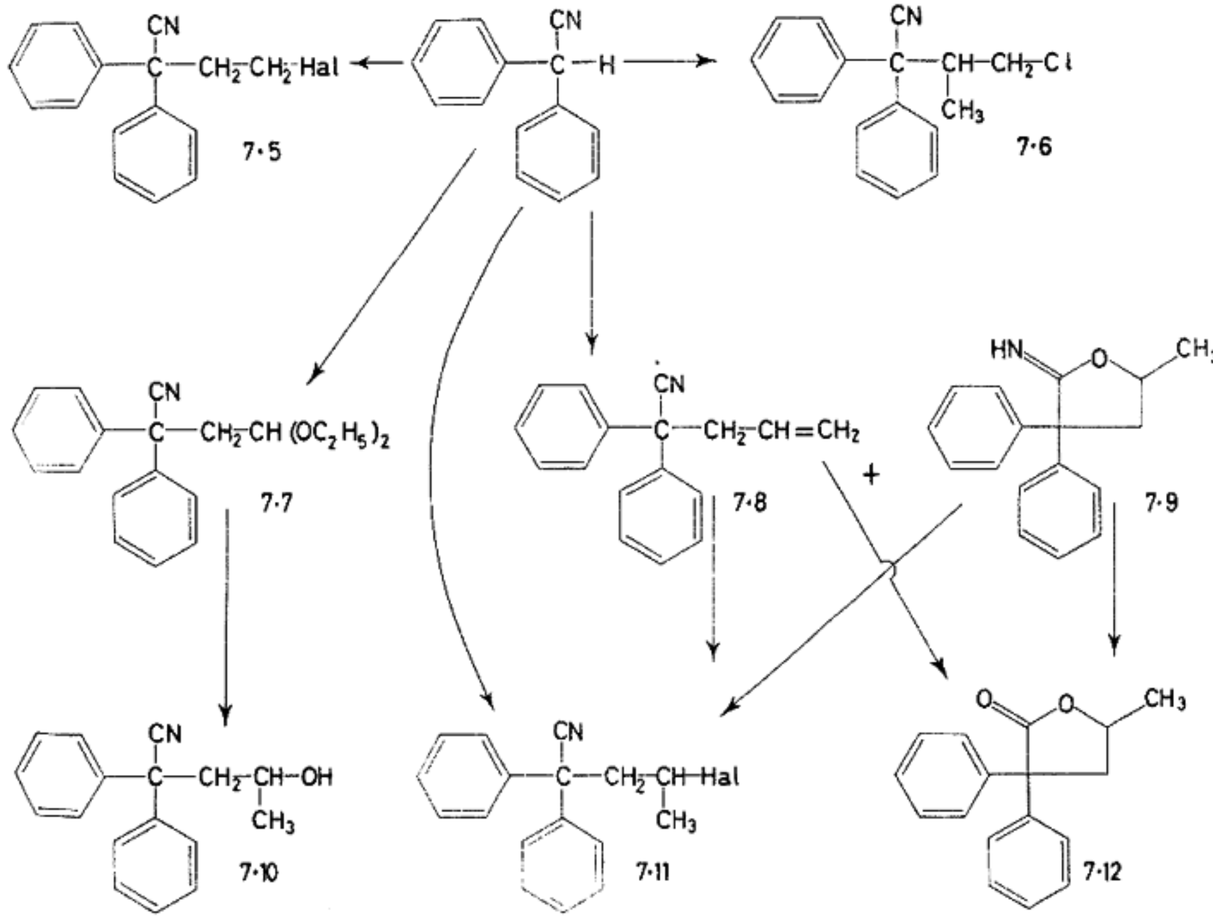


Basic propyl- and *iso*propylchlorides [7.2] and [7.3] were found to form quaternary salts [7.4]:



7·4

which react in similar conditions with diphenylacetonitrile after being rearranged to a mixture of [7.2] and [7.3]. This explains the isolation from the reaction mixture of the isomeric basic nitriles [7.1b] and [7.1c]. The ratio of the isomers obtained varies with the nature of the basic group of the chloroamine employed in the alkylation. Most methods of separation of these isomers are based on different solubilities of the bases or the hydrochlorides [12, 51, 52, 67, 87, 103, 106, 128, 129, 236–240, 350*h*, 369, 411, 456, 457, 480, 503, 504].



7·5 7·6 7·7 7·8 7·9 7·10 7·11 7·12

Halogenonitriles [7.5], [7.6] and [7.11] react with secondary amines to yield the basic nitriles [7.1a], [7.1b] and [7.1c] respectively. The bromonitriles are more reactive than the chloronitriles. The reactivity of both halogenonitriles is considerably reduced after branching with a methyl group.

Unbranched halogenonitriles [7.5] (hal = Cl, Br) are available through condensation of diphenylacetonitrile with 1:2-dibromo- or 1:2-bromochloroethane by means of $NaNH_2$ or $LiNH_2$ [52, 87, 236–240].

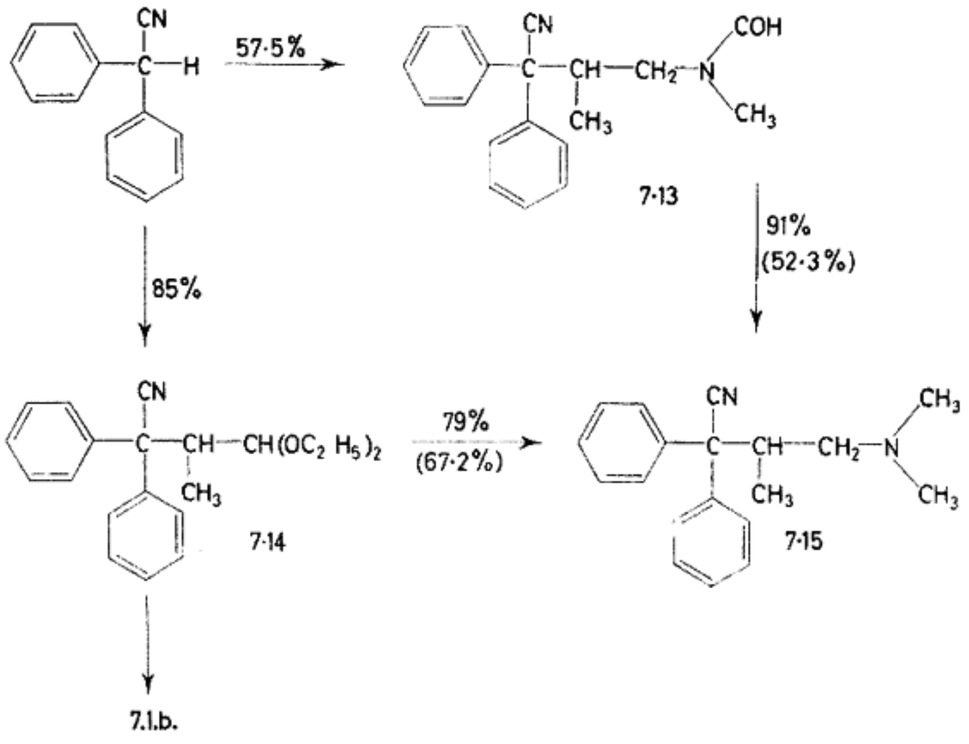
A similar condensation with the tosylate of 1-chloro-propan-2-ol or with 1-bromo-2-chloro-propane [7.11] (hal = Cl) yields the branched chloro-nitrile [7.6] (65 per cent) [12, 428].

The bromo- or iodo-nitriles [7.11] (hal = Br or I) are obtained from [7.8] through HBr or HI addition [12].

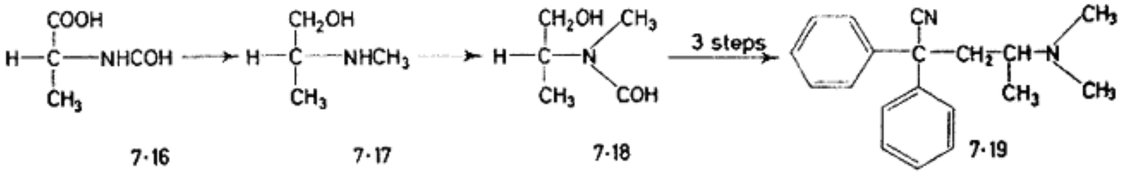
Sodamide condensation of diphenylacetonitrile with bromoacetaldehyde diethylacetal gives [7.7], which is converted to the bromonitrile [7.11] by Grignard reaction followed by bromination [345, 346].

The iminotetrahydrofuran derivative [7.9], from diphenylacetonitrile sodium and propylene oxide, is converted to [7.11] (hal = Cl or Br) on halogenation with PCl_3 or PBr_3, and on hydrolysis to the lactone [7.12], which is also obtainable from [7.8] [12, 128, 129].

Sodamide condensation of diphenylacetonitrile with *N*-methyl-2-chlor-propylformamide yields [7.13], which is reduced to *iso*methadonenitrile [7.15] [428].

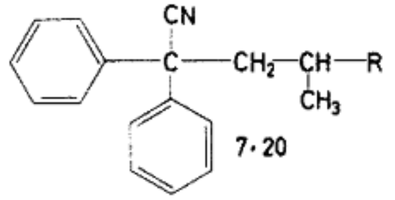


According to RUSCHIG and SCHMITT [380] this nitrile [7.15] is also available from the acetal [7.14] and methylformamide. Many other nitriles of type [7.1b] were prepared in this laboratory from [7.14] and various formylated secondary amines in 50–90 per cent yields (unpublished results).



The following elegant synthesis of *l*-methadonenitrile, starting from D-(−)-alanine was devised by BECKETT and HARPER [32]: (−)-benzoyl-D-alanine was hydrolysed with HCl to D-(−)-alanine, which was formylated to D-(+)-*N*-formylalanine [7.16]. Reduction with $LiAlH_4$ gave (−)-2-methylamino-propan-1-ol [7.17]. Sodamide condensation of the formylated derivative of the product of chlorination of the alcohol [7.18] gave an oily isomer of 2:2-diphenyl-4-*N*-methylformamido-valeronitrile, which gave *l*- or (−)-metha-done-nitrile [7.19] when reduced with formic acid. These reactions do not involve the asymmetric centre.

The Kawabata-synthesis of unbranched nitriles [7.1a], which is unsuccess-ful in our hands, is described in Chapter IV.



7·20

(a) R = COOH
(b) R = COCl
(c) R = CON3
(d) R = NCO
(e) R = $N(CH_3)_2$
(f) R = NHCHO

In a recent Austrian patent [350c], the following new synthesis of methadone nitrile is described: starting from 2-methyl-4-cyano-4:4-diphenyl-butyric acid [7.20a], the acid chloride [7.20b] and the azide [7.20c] are prepared in quantitative yields. The azide is converted to the *iso*cyanate [7.20d] when heated in boiling benzene (88 per cent) and then to methadonenitrile [7.20e] with formaldehyde and formic acid (65·5 per cent) or to the formyl-derivative [7.20f] with a formic- and acetic-anhydride mixture. On reduction with formaldehyde and formic acid [7.20e] is produced. The main objection against this elegant method is the involved synthesis of the acid [7.20a].

When heated with a large excess of thionyl chloride, primary amides of type I are dehydrated to basic nitriles [7.11] [234, 235].

The unbranched nitriles [7.1a] derived from dialkylamines are oily bases. The melting points of their hydrochloride and methiodide salts decrease when the number of carbon atoms in the unbranched alkyl groups of NAA' increases (Tables IV and X).

The other nitriles of types [7.1a, b and c] are solid bases. Introduction of a methyl group in α-position always increases the melting point. The melting points of the bases having a methyl group in β-position are as a rule inter-mediate between the unbranched and the α-CH_3-compounds.

TABLE X—MELTING POINTS OF BASIC NITRILES OF STRUCTURE [7.1]

NAA′	°C		
	$\alpha = \beta = H$	$\alpha = CH_3$	$\beta = CH_3$
$N(CH_3)_2$	< 20	*dl*: 69 ± 1 *d*: 102 ± 1 *l*: 102 ± 1	*dl*: 91 ± 1 *d*: 101 ± 1 *l*: 101 ± 1
$N(C_2H_5)_2$	< 20	*dl*: 46	*dl*: < 20
pyrrolidine	73 ± 1	*dl*: 109	—
piperidine	74 ± 4	*dl*: 106 ± 1	*dl*: 84 ± 1
hexamethyl	55	*dl*: 78	—
heptamethyl	54	*dl*: 102	—
morpholine	82 ± 1	*dl*: 138 ± 2 *d*: —	*dl*: 106 ± 3 *d*: 110
4-CH_3-piperazine	100	*dl*: 120	*dl*: 108 ± 2

Considerable disagreement exists among various authors concerning the melting points of the known salts of these nitriles (Table IV). Many of these salts are hygroscopic and decompose before melting.

Introduction of a methyl group in the side-chain of nitriles of type [7.1a] as a rule decreases their basic strength. This "base weakening" effect is most pronounced among α-CH_3-nitriles [7.1b] (Table VI, Chapter XX).

The best available estimates for the optical rotation values of the known isomeric nitriles [7.1b] and [7.1c] in various solvents are listed in Table XI.

TABLE XI—OPTICAL ROTATION OF ISOMERIC NITRILES OF TYPE [7.1A] AND [7.1B] (TABLE VI)

Structure [7.1a or b]				$[M]_D^{22} \pm 3$			
α	β	NAA′	Isomer	Base in *cyclo*hexane	In benzene	In ethanol	HCl in water
CH_3	H	$N(CH_3)_2$	*l**	—	—	− 192 ± 3	− 236
CH_3	H	$N(CH_3)_2$	*d*	—	—	+ 189 ± 6	+ 236
H	CH_3	$N(CH_3)_2$	*l*	− 171 ± 10	− 165	− 139 ± 3	+ 15 ± 5
H	CH_3	$N(CH_3)_2$	*d*†	+ 171	—	+ 136 ± 5	− 15 ± 5
H	CH_3	morphol.	*d*†	+ 211	+ 154	+ 183	− 5

* Configuration unknown.

† Configuration related to L-(+)-alanine (Chapter XXI).

Nitriles of type [7.1] have been used as intermediates in a large series of reactions.

The following reactions are discussed in detail in the chapters pertaining to the reaction products:

(a) Conversion to 3:3-diphenylpropylamines by elimination of the cyano-group (Chapter III).

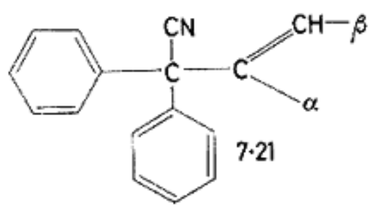
(b) Reduction of the nitrile-group to a primary amine (Chapter VIII) or to an aldehyde (Chapter XVII).

(c) Hydrolysis to primary amides (Chapter IX) or acids (Chapter X).

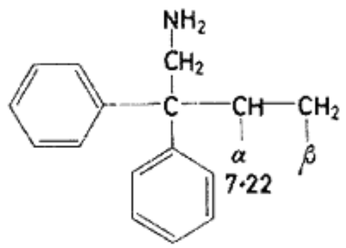
(d) Esterification (Chapter XIII).

(e) Conversion to ketimines and ketones (Chapter XVI).

Other reactions of these nitriles may be outlined as follows:

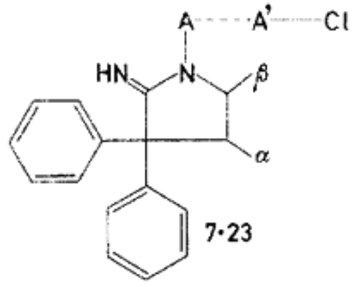


7·21



7·22

Decomposition of the methiodides of methadone- and *iso*methadonenitrile by means of silver oxide at elevated temperatures leads to the unsaturated nitriles [7.21] (α or $\beta = CH_3$), which yield saturated primary amines [7.22] on reduction with Raney nickel. These reactions constitute proof of structure, because the isomers [7.22] (α or $\beta = CH_3$) are available through unambiguous synthesis [411]. A second basic product of degradation was identified as the iminotetrohydrofuran derivative [7.9].



7·23

According to BLICKE [20, 21] iminohalides hydrohalides (I : R = CNHCl) are formed between 125 and 200°C and subsequently converted (225–350°C) to the hydrohalides of the iminopyrrolidines [7.23] when basic nitriles [7.1a, b or c] are heated with gaseous HCl or HBr. These cyclic imines [7.23] are also available from bromonitriles [7.5, 7.6 or 7.11] and ammonia or primary amines [252, unpublished results). They are furthermore formed during catalytic reduction of *N*-benzyl aminonitriles (MORRISON *et al.*, 1950) [345, 346].

Hydrolysis of the cyclic imines [7.23] yields the corresponding 2-pyrrolidones.

The low reactivity of the CN-group in nitriles [7.1] has been noted in many instances (Chapters VIII, IX, X, XIII, XVI, XVII).

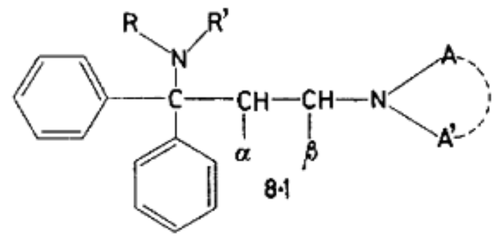
In contrast with the basic nitriles, in which one or both phenyl groups are replaced by hydrogen, compounds [7.1] fail to yield thioamides, amidines or dihydroglyoxalines, even in extreme experimental conditions ([504], unpublished results).

All known basic nitriles [7.1] are devoid of significant analgesic activity in mice or rats (Table V). Most of them, however, display atropine-like properties. The unbranched nitriles derived from piperidine and hexamethyleneimine are the most active ones in this respect. Potency is considerably increased as a rule by quaternization with methyl halides and branching of the side chain with methyl groups yields weaker compounds. The dimethylamine-derivative is, however, an exception to these rules: β-CH_3 branching increases potency and quaternization decreases it. Nitriles of type [7.1b] are less active than the isomers of type [7.1c] ([234–240, 279], unpublished results).

CHAPTER VIII

Diamines and Derivatives

(I: R Contains Amino Group or Derivative)

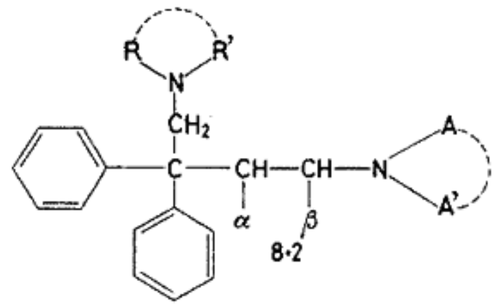


8·1

(a) $R = R' = H$
(b) $R = COR''$; $R' = H$ or SO_2 alk
(c) R = alk; $R' = H$
(d) $R = R'$ = alk

THE simplest diamines of this series [8.1a] were prepared in this laboratory ([236–240], unpublished results) by Hofmann degradation of the corresponding primary amides ($I : R = CONH_2$).

Compounds [8.1a] are also available from aminochlorides ($I : R = Cl$) and ammonia [236–240]. They react with alkyl halides, acid chlorides and anhydrides to yield derivatives of types [8.1b, c and d] in normal yields (Table IV). None of the compounds of type [8.1] listed in Table V were found to be active as analgesics or antihistaminics. Relatively weak parasympatholytic and local anaesthetic properties were detected mainly among the "reversed amides" of type [8.1b] [236–240].

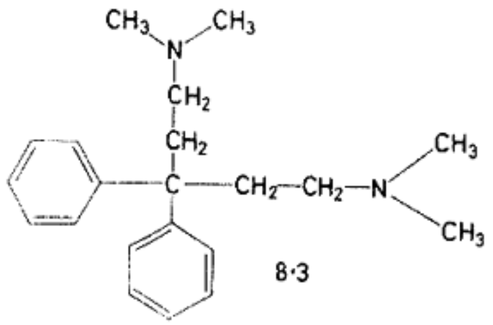


8·2

(a) $R = R' = H$
(b) $R = COR''$: $R' = H$
(c) NRR' = tertiary amine

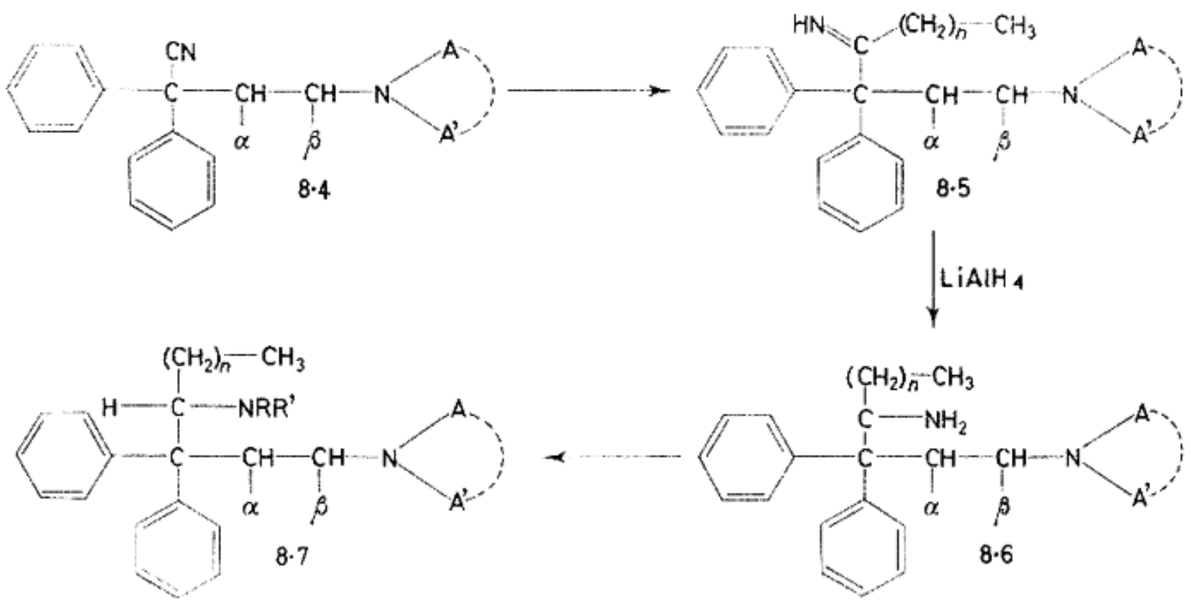
Diamines of structure [8.2a] are obtained in high yields by reduction of the corresponding nitriles (I : R = CN) with a double molar excess of $LiAlH_4$. With $\frac{1}{3}$ or 1 mole of $LiAlH_4$ the formation of aldehydes and abnormal cleavage reactions are known to occur. Raney nickel hydrogenation (20–170°C, 1–50 atm) of the same nitriles leads to the same diamines [8.2a] in low yields [63–65, 236–240, 261, 262, 318, 350g]. The derivatives [8.2b] are obtained as usual from the diamines [8.2a].

A few tertiary diamines of structure [8.2c] were prepared in this laboratory by reduction of the corresponding basic tertiary amides of the R 875-type (I : R = CONRR′) using a molar excess of $LiAlH_4$ (unpublished results). Only one of the investigated compounds of type [8.2] (Table V, compound (6.39)) was found to be active as an analgesic in mice. This compound [8.2b: $\alpha = R'' = CH_3$; $\beta = H$; NAA′ = morpholine] is about as active as codeine. Parasympatholytic activity among these compounds was not detected (unpublished results).



8·3

SPERBER *et al.* [439] prepared the diamine [8.3] from the aminochloride (I : R = CH_2CH_2Cl), described in Chapter VI (compound (6.62); Table IV).



A few ketimines related to methadone [8.5] were reduced in this laboratory with an equimolar amount of $LiAlH_4$ in ether (unpublished results).

Only one of the two possible isomers of structure [8.6] was isolated in each case. The formation of the other isomer can, however, not be excluded in view of the yields of the order of from 40 to 70 per cent which were obtained. Derivatives of structure [8.7], listed in Table IV, were obtained as usual.

Only a few of these compounds (Table V: compounds (6.19) and (6.20)) were found to be analgesically active in mice. All of them are devoid of parasympatholytic properties.

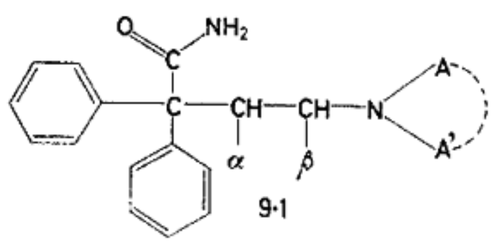
The available data on these diamines are obviously insufficient to allow for theoretically valuable conclusions concerning structure–activity relationships. Further study in this promising field is obviously desirable.

CHAPTER IX

Primary Amides

(I : R = $CONH_2$)

PRIMARY amides [9.1] are best prepared by hydrolysis of the basic nitriles (I : R = CN).



9·1

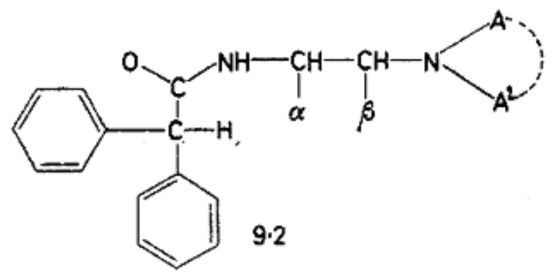
The usual procedure consists in heating the nitrile with 90 per cent sulphuric acid on a steam bath. Unbranched amides [9.1: $\alpha = \beta = H$] are formed in 80–90 per cent yields after 3 hr of heating, whereas optimal heating time of branched amides [9.1: α or $\beta = CH_3$] is prolonged due to steric hindrance of the cyano group [88, 236–240, 498, 499]. When more diluted acids are used, the nitriles are either recovered unchanged, or a mixture of acids and amides is formed [49, 236–240, 350*g*, 480].

Hydrolysis with KOH in aqueous ethanol was successfully used for preparing a few unbranched amides [52].

An alternative method of synthesis consists in treating the corresponding acid chlorides (I : R = COCl) with ammonia. This method, which is often used for preparing secondary or tertiary amides of the same type (Chapters XI, XII) is obviously of limited importance [52].

Small amounts of hydroxamamides (I : R = CONHOH) were isolated after heating nitriles (I : R = CN) with excess hydroxylamine HCl and sodium acetate in ethanol). These hydroxamamides are readily converted to primary amides [9.1] [88].

Direct synthesis of these primary amides from diphenylacetamide, dialkylaminoalkylchlorides and a condensing agent such as sodamide fails, because of the greater reactivity of the amide nitrogen. Basic amides of type [9.2] are isolated [87, unpublished results].



9·2

The large majority of the bases of amides [9.1] are crystalline solids with sharp melting points (Tables IV and XII). Among the "open" dialkylamides, the dimethylamine derivative shows the highest melting point. Branched amides of this type melt at higher temperatures. Branching in β-position has the greatest effect. The opposite effect of branching is observed among the heterocyclic amine derivatives, side chain branching lowering the melting point of the base.

The striking variation among the melting points of tertiary and quaternary salts of these amides, as reported by various authors, might be partly due to the fact that many of these salts are hygroscopic and decompose at melting temperatures. Many of them crystallize with one or more molecules of solvent.

TABLE XII — MELTING POINTS OF BASES OF PRIMARY AMIDES OF TYPE [9.1] (TABLE IV)

Base [9.1]				m.p. (°C)	*n**
α	β	NAA′	Isomer		
H	H	$N(CH_3)_2$	—	140	3
CH_3	H	$N(CH_3)_2$	*dl*	152	2
H	CH_3	$N(CH_3)_2$	*dl*	180 ± 4	5
H	CH_3	$N(CH_3)_2$	*d*	137 ± 1	2
H	CH_3	$N(CH_3)_2$	*l*	138 ± 1	2
H	H	$N(C_2H_5)_2$	—	91 ± 1	4
CH_3	H	$N(C_2H_5)_2$	*dl*	137	3
H	CH_3	$N(C_2H_5)_2$	*dl*	160 ± 3	3
H	H	$N(C_3H_7)_2$	—	103	1
H	H	$N(iC_3H_7)_2$	—	86	2
H	H	pyrrolidine	—	146 ± 1	3
H	H	piperidine	—	183 ± 5	6
CH_3	H	piperidine	*dl*	155 ± 2	3
H	CH_3	piperidine	*dl*	158 ± 2	3
H	H	hexamethyl.	—	141	1
H	H	morpholine	—	184	2
CH_3	H	morpholine	*dl*	177	1
H	CH_3	morpholine	*dl*	143 ± 1	2
H	CH_3	morpholine	*d*	82	1

* Number of published melting points, listed in Table IV, on which estimate is based.

The optical rotations of the isomers of two amides of type [9.1] ($\beta = CH_3$; NAA′ = dimethylamino and morpholino) as measured in different solvents, are listed in Table VI. The laevo-isomer of aminopentamide has the same configuration as D-(−)-alanine (Chapter XXI).

Solubility in various solvents of several unbranched amides [9.1] has been reported upon [236–240].

Primary amides [9.1] have been converted to acids by hydrolysis (Chapter X), to nitriles by dehydration with $SOCl_2$ (Chapter VII), to diamines by Hoffmann degradation (Chapter VIII) and to ketones by Grignard reaction (Chapter XVI).

The pharmacology of these basic amides [9.1] has been investigated in detail [52, 53, 72, 86, 111, 123, 194–198, 213, 215, 233–241, 253, 254, 255–257, 293–295, 321, 340, 391, 427, 471, 472].

Most of them are typical atropine-like substances. Among the tertiary bases or salts, highest activity is found among unbranched compounds [9.1: $\alpha = \beta = H$] derived from heterocyclic amines of the type $N(CH_2)_n$; 2:2-diphenyl-4-hexamethyleneimino-butyramide (R 658, Mydriamide*, compound (7.22), Table IV) is the most powerful member of this series. It is clinically used as a long-acting, non-irritating local mydriatic (JANSSEN *et al.*, in press; [253, 254, 360, 472]). As a local mydriatic agent in animals it is about as active as scopolamine. The piperidino analogue (compound (7.11); R 14) is clinically used as an antispasmodic, e.g. in combination with methadone (Polamidon-C*).

Introduction of a methyl group in the side-chain as a rule decreases atropine-like potency; aminopentamide (compound (7.3); Centrine*; *dl*-2:2-diphenyl-4-dimethylaminovaleramide HCl) is the only known exception to this rule.

This clinically used basic amide, whose laevo-isomer is twice as active as the racemate, is about half as active as atropine and about ten times more active than its unbranched analogue (compound (7.1)).

Quaternization with methyl halides as a rule increases parasympatholytic potency of the unbranched bases. The methiodide of aminopentamide is nearly inactive, however [86, 213, 214, 236]. For unbranched amides, the quantitative effect of quaternization is predictable [236–241]. Several of these methyl halides were investigated in man [255–257, 293, 294, 348, 349, 441].

The most powerful and longest acting of these compounds is *iso*propamide or 2:2-diphenyl-4-di*iso*propylamino-butyramide methiodide (R 79, Priamide*, Darbid*, Combid*, Tyrimide+) [45, 47, 56, 85, 111, 124, 178, 216, 233, 236–240, 267, 344, 348, 349, 421, 426, 441, 454, 471, 486].

Atoxic oral doses are capable of inhibiting gastric hypersecretion and gastrointestinal hypermotility for over 24 hr.

Quaternization by heavier alkyl halides decreases atropine-like activity, but tends to increase ganglion blocking and curarizing properties [194–198, 236–240, 293–295].

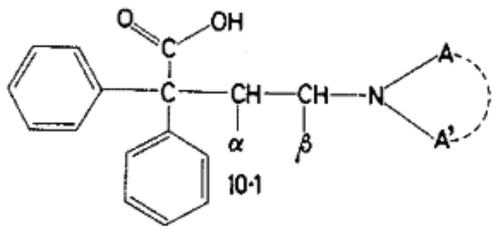
Analgesic and antihistaminic activity has not been detected among compounds of type [7.1].

Local anaesthetic activity, however, seems to be a general property of most tertiary bases and even of some quaternary salts, particularly the benzyl halides [194–198].

CHAPTER X

Acids and Acid Chlorides

(I : R = COOH or COCl)

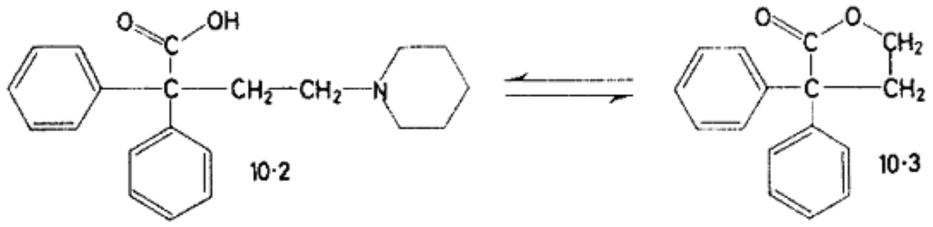


10·1

AMINO acids of type [10.1] (Table IV) are important intermediates. Most of the known examples, however, have not been purified, due to unusual technical difficulties (hygroscopic salts, separation from other reaction products). Only a few of these acids were investigated pharmacologically (Table V), but no important properties were found [236–240].

The original method of synthesis of these acids [52] consists in heating the corresponding nitrile (I : R = CN) in two parts of 80 per cent sulphuric acid at 150°C until solubility in dilute sodium hydroxide is achieved. The reaction time for the unbranched piperidino acid [10.2] is 4–5 hr. The crystalline base is obtained by pouring the hot reaction mixture in strongly basic ice water, followed by neutralization of the filtrate. Yields are low (unpublished results). Steric hindrance of the cyano group makes these nitriles very resistant to hydrolysis. Branching of the side chain increases these steric effects.

The same amino acid [10.2] was also prepared by the same authors from the corresponding ethyl ester (I : R = $COOC_2H_5$) by refluxing it for 1 hr in 5 vol of 25 per cent alcoholic potassium hydroxide.



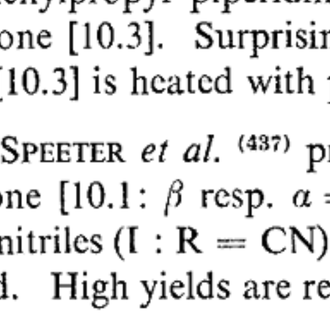
10·2 ⇌ 10·3

When heated without solvent at 230°C the acid [10.2] is partly decarboxylated to 3:3-diphenylpropyl piperidine (85 per cent) and partly converted to the butyrolactone [10.3]. Surprisingly, the acid [10.2] is again obtained when the lactone [10.3] is heated with piperidine [52, 92, 93, 480].

GARDNER *et al.* [166] and SPEETER *et al.* [437] prepared the acids related to methadone and *iso*methadone [10.1: β resp. $\alpha = CH_3$; NAA' = dimethylamine] by hydrolysis of the nitriles (I : R = CN) at 150° for 5 hr in two parts of 72 per cent sulphuric acid. High yields are reported.

WALTON *et al.* [480] obtained mixtures of acids [10.1] and primary amides (I : R = $CONH_2$) after heating under reflux unbranched and β-CH_3-branched nitriles (I : R = CN) in 4 vol of 50 per cent sulphuric acid. The α-CH_3-branched nitriles, however, are not hydrolysed in these conditions. Only the pyrrolidone [10.4] ($\alpha = A = CH_3$) was isolated when *iso*methadonenitrile was heated in a sealed tube at 180°C for 3½ hr with 48 per cent hydrobromic acid.

Pyrrolidones [10.4] are readily formed from amino acids [10.1] and thionyl chloride. At low temperatures the acid chloride is formed; above 60°C an intra-molecular reaction between acid chloride and tertiary amine starts and results in cleavage of the carbon–nitrogen bond and ring closure to pyrrolidones [10.4]. Ring formation also occurs with phosphorus trichloride, but high temperatures are required for completion of the reaction [92, 93].



10·4

According to BOCKMÜHL and EHRHART [52] the acid chloride of [10.2] is prepared by suspending the acid in 3 vol of benzene and adding ⅔ part of phosphorus pentachloride.

The temperature rapidly increases to 60–65°C, and, within 10 min, a clear supersaturated solution is obtained, from which the acid chloride hydrochloride crystallizes at room temperature. This method failed in our hands (unpublished results).

Amino acids of type [10.1] and their acid chlorides have been used as intermediates for the preparation of several compounds of type (I):

(a) Esterification (Chapter XIII).

(b) Transformation to primary, secondary and tertiary amides (Chapters IX, XI and XII).

(c) Rosemund reduction of acid chlorides to aldehydes (Chapter XVII).

(d) $LiAlH_4$-reduction to primary alcohols (Chapter IV).

(e) Decarboxylation (see above).

(f) Grignard reaction to ketones (Chapter XVI).

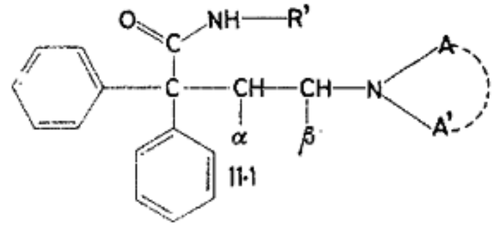
Silver salts of these acids have been obtained and used for preparing esters of these acids [166] (Chapter XIII).

CHAPTER XI

Secondary Amides

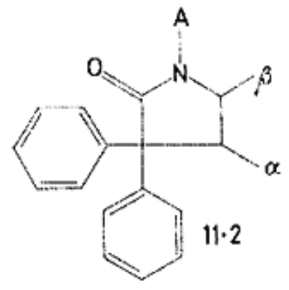
(I: R = CONHR')

IN this laboratory all basic secondary amines of type [11.1] (Table IV) were prepared from the corresponding acid chlorides (Chapter X) and the requisite primary amines, with or without solvent (benzene, chloroform) at temperatures not exceeding the cyclization temperature of the acid chloride. Optimal conditions were found to vary widely and were determined in a few cases only (unpublished results).



11·1

MOFFETT *et al.* [341], using essentially the same method, noted good results with β-CH_3-branched compounds, but with unbranched or α-CH_3-branched derivatives, the cyclization reaction of the acid chlorides to the pyrrolidones [11.2] took precedence and little if any of the desired amides [11.1] were obtained.



11·2

An alternative method of synthesis consists in the alkylation of the primary amides (I : R = $CONH_2$) with an R'-halide, using sodamide or lithium amide. The formation of quaternary salts is a side reaction which is often observed with dimethylamino derivatives (unpublished results, [341]).

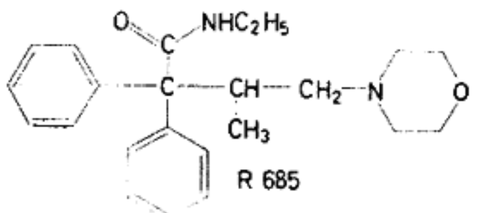
Attempts to prepare these secondary amides by heating the corresponding esters with primary amines failed, pyrrolidones [11.2] being the only isolated products [341].

The synthesis of the hydrazide (compound (9.36)) listed in Table IV has not been described in detail.

Most secondary amides [11.1] form solid bases. Melting points tend to decrease when the number of carbon atoms in substituent R′ increases.

A few selected members of series [11.1] are active analgesics. Maximal activity is observed among morpholino-derivatives structurally related to R 875 [11.1: $\alpha = CH_3$; $\beta = H$].

The optimal configuration of R′ seems to be ethyl. The most active analgesic of this series, R 685 (compound (9.20); Tables IV and V) is about as active as pethidine after subcutaneous injection in mice [241, 471].



R 685

Unbranched secondary amides [11.1] derived from piperidine as a rule parasympatholytics. Their potency is, however, much lower than the potency of the corresponding primary amides, described in Chapter IX [236–241].

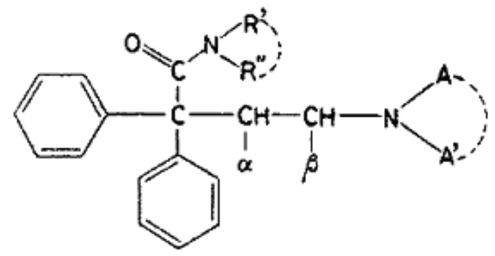
Ocytocic and diuretic activity has also been detected among secondary amides [11.1] ([341], unpublished results).

This interesting series obviously merits further study.

CHAPTER XII

R 875 and Related Basic Tertiary Amides

(I : R = CONR′R″)

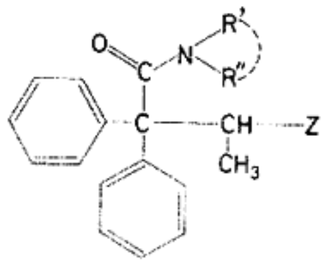


	α	β
12.1	H	H
12.2	CH_3	H
12.3	H	CH_3

THE alkali metal derivatives of *N*:*N*′-disubstituted diphenyl acetamides are readily condensed with tertiary aminoalkylchlorides. They are prepared in apolar solvents with sodamide or lithium amide.

The unbranched butyramides [12.1] are thus obtained from aminoethylchlorides ([88, 203, 204, 236–240, 342], unpublished results). Condensation with amino*iso*propylchlorides yields mixtures of isomeric branched basic amides [12.2] and [12.3] (JANSSEN, 1956, unpublished results). Separation of these isomers is achieved by taking advantage of differences in solubility. Proof of structure is afforded by unambiguous synthesis, as described below, or by ultra-violet spectrophotometry (unpublished results). As compared with the corresponding basic nitriles (Chapter VII) yields of these condensation reactions are generally lower in similar experimental conditions. Prolonged heating in high boiling solvents is generally desirable.

An unambiguous method of synthesis of all amides of type [12] consists in treating the corresponding acid chlorides (I : R = COCl) with the required secondary amine. The experimental conditions are similar to those described



12.4: $Z = CH_2 — Cl$
12.5: $Z = CH(OC_2H_5)_2$

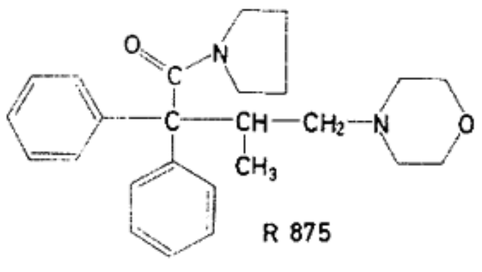
for preparing secondary amides (Chapter XI) ([236-240, 340]; MOFFETT, 1957, unpublished results). The yields depend largely on the reaction temperature. In optimal conditions very high yields may be obtained.

The synthesis of branched amides of the α-CH_3-type [12.2] was also accomplished in this laboratory by a sequence of reactions which started with a *N*:*N'*-disubstituted diphenylacetamide and went through the condensation products [12.4] or [12.5], obtained from the tosylate $TsOCHCH_3CH_2Cl$ or the bromoacetal $BrCHCH_3CH(OC_2H_5)_2$ (Chapter VII), to the desired amides [12.2] prepared from [12.4] and a suitable secondary amine, or from the acetal [12.5] and a formylated secondary amine (unpublished results).

Most tertiary amides related to R 875 [12.1, 12.2, 12.3] form crystalline bases (Table IV). Among the unbranched compounds [12.1] derived from dialkylamines (NAA' = Nalk, alk'), progressively lower melting points are observed when heavier alkyl groups are introduced. Amides of type [12.3] having a methyl group in β-position, melt at lower temperatures than their unbranched or α-CH_3-branched homologues. The influence of other structural variations on the melting points of the bases is quite irregular (Table XIII).

A few branched amides [12.2 and 12.3] have been resolved in their optical isomers. Optical rotation values are listed in Table VI.

Reduction of the tertiary amido-group with $LiAlH_4$ yields the expected diamines (Chapter VIII). Other chemical reactions with amides of type [12] have not been described.



R 875

(Dextromoramide, Palfium*)

Some of these basic tertiary amides are highly active analgesics in laboratory animals and in man [236-242, 471], (Table VI).

The relation between chemical structure and analgesic activity in mice and rats within this series can be described as follows ([236-240], unpublished results):

(a) NR'R": highest activity is found among *N*-pyrrolidino- and *N*:*N'*-dimethylamides. Compounds derived from other amides are nearly inactive.

(b) α and β: branching the side chain with a methyl group in α-position, considerably increases analgesic activity; the β-CH_3-isomers [12.3] are much less active. Branching with other alkyl groups or lengthening or shortening the side chain invariably produces inactive compounds (unpublished results).

(c) NAA': by far the most active analgesics of this type are derived from morpholine. All unbranched amides [12.1], except a few morpholino-derivatives, are completely inactive.

Analgesic activity was detected among α-CH_3-branched amides [12.2] derived from morpholine, dimethylamine, pyrrolidine and piperidine. Other structural variations produced analgesically inactive compounds.

(d) Quaternary salts are devoid of analgesic activity.

(e) In the α-CH_3 series, one of the optical isomers of each enantiomorphic pair is about twice as active as the racemic mixture; the other isomer is devoid of significant analgesic activity. The absolute configurations of these isomers is unknown.

(f) The presence of two unsubstituted phenyl groups seems to be essential. Important reduction in activity occurred when one or both phenyl rings were substituted or replaced by other groups ([236-240], unpublished results).

Dextromoramide (R 875, Palfium*), the dextro-rotatory isomer of 2:2-diphenyl-3-methyl-4-morpholino-butyryl-pyrrolidine, the most active analgesic in laboratory animals of this series, was prepared for the first time in this laboratory [236-240] and since then studied in considerable detail by many pharmacologists and clinicians [8, 11, 16, 17, 57, 74, 77, 78, 80, 83, 84, 94, 107, 108, 111, 112, 113, 125, 127, EDDY: private communication, 161, 165, 182, 236-242, 250, 272, 283, 285, 311, 320, 350, 350*b*, 350*l*, 350*j*, 351, 368, 374, 377, 383, 386, 435, 436, 440, 470, 471, 479, 536].

In eight experimental conditions, using mice and rats, R 875 was found to be from 4 to 14 times more active than methadone, from 6 to 40 times more active than morphine, from 20 to 110 times more active than pethidine, and from 80 to 385 times more active than codeine (Table V).

R 875 must be regarded as a typical morphine-like analgesic. Like morphine, it is effectively antagonized by nalorphine. It produces respiratory depression in rats, dogs and man, meiosis in man, mydriasis in mice, excitation in mice and cats, depression in rats and dogs.

There are, however, important quantitative differences between R 875 and other morphine-like analgesics:

TABLE XIII—MELTING POINTS OF BASES OF TERTIARY AMIDES OF STRUCTURE [12.1], [12.2] AND [12.3]

NAA′	α	β	isomer	CONR′R″					
				$N(CH_3)_2$	$NCH_3{\cdot}C_2H_5$	$N(C_2H_5)_2$			
$N(CH_3)_2$	H	H	—	98 ± 1	102	107	139	112	152
$N(CH_3)_2$	CH_3	H	*dl*	108	—	—	127	—	—
$N(CH_3)_2$	H	CH_3	*dl*	—	—	—	—	—	—
$N(C_2H_5)_2$	H	H	—	—	—	—	—	—	—
$N(i\text{-}C_3H_7)_2$	H	H	—	76	—	—	—	—	132
pyrrolid.	H	H	—	143 ± 1	112	—	134	—	—
pyrrolid.	CH_3	H	*dl*	—	—	—	111	—	—
pyrrolid.	H	CH_3	*dl*	—	—	—	78	—	—
piperid.	H	H	—	166 ± 3	131	105 ± 2	163	152 ± 2	171
piperid.	CH_3	H	*dl*	114	—	107	165	—	—
piperid.	H	CH_3	*dl*	—	—	—	54	—	—
morphol.	H	H	—	133	—	129	148	112	119
morphol.	CH_3	H	*dl*	129	141	108	172	162	169
morphol.	H	CH_3	*dl*	97	—	—	101	—	106

(1) In man R 875 is nearly as active by oral route as by subcutaneous injection.

(2) In all species and by all routes R 875 is characterized by a very short onset of action.

(3) Tolerance to the analgesic effect of R 875 in man and in rats develops very slowly or not at all.

(4) In man, constipation or antidiuretic effects during prolonged R 875-treatment have not been observed.

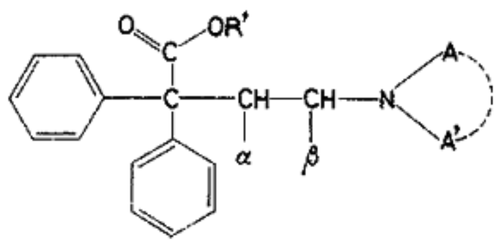
(5) The sensorium of patients, chronically treated with R 875, is not depressed or "dulled" to any significant degree. Therapeutic doses of R 875 have little or no influence on the e.e.g. in man [12].

Other pharmacological properties of selected members of this series of basic tertiary amides include diuretic, ocytocic, local anaesthetic, weak parasympatholytic and antitussive activity ([236–241, 342], unpublished results). Further study of these properties is obviously desirable.

CHAPTER XIII

Esters derived from Amino Acids of Type I

(R = COOR')



13

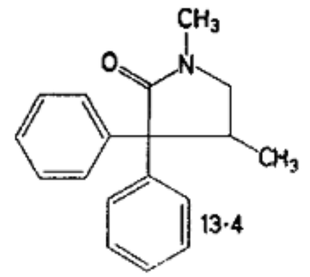
	α	β
13.1	H	H
13.2	CH_3	H
13.3	H	CH_3

THE original information on the preparation of basic esters of type (I) (R = COOR') is found in two patents applied for by BOCKMÜHL and EHRHARDT [201, 202]. The given examples are unbranched esters of structure [13.1] (R' = C_2H_5 and *i*-C_3H_7). In a subsequent publication these authors also describe β-CH_3-branched esters of type [13.3] [52]. One method of synthesis involves heating at 150°C of one part of nitrile (I: R = CN) with four parts of 70 per cent H_2SO_4 until a sample becomes soluble in dilute alkali. The mixture is then heated at 105–110°C and alcohol is added in small portions until it is collected anhydrous by distillation (50–75 per cent yields). These authors also prepared unbranched esters [13.1] from a diphenylacetic acid ester and a tertiary aminoethylchloride, using sodium phenylate as a condensing agent.

In 1948, GARDNER *et al.* [166] described a new general method of synthesis of α- and β-CH_3-branched esters [13.2] and [13.3], derived from dimethylamine. It consists in treating at room temperature and then under reflux a

suspension of the silver salt of the amino acid (I : R = COOH) in acetone with an alkyl iodide. Yields are low.

The methyl and ethyl esters related to methadone [13.3: NAA' = dimethylamine] were alternatively prepared by these authors from the acid chloride and excess alcohol at reflux temperatures. With *iso*propanol, however, no esterification occurred. The same reaction, applied to *iso*-methadone-acid (I : α = CH_3; NAA' = dimethylamine; R = COOH), fails completely, due to cyclization of the acid chloride to the substituted 2-pyrrolidone [13.4].



13·4

DUPRÉ *et al.* [126] prepared four unbranched ethyl butyrates of type [13.1] by heating the nitrile (I : R = CN) with ethanol, concentrated H_2SO_4 and NH_4Cl in a sealed tube at 160°C (40–50 per cent yield).

By allowing to react at room temperature for four days a mixture of the amino acid (I : R = COOH) and an excess of an ethereal solution of diazomethane or diazoethane, WALTON, OFNER and THORP [480] prepared several methyl- and ethyl-butyrates [13.1] and valerates [13.3].

The optical isomers of methadone nitrile were hydrolysed by POHLAND *et al.* [361] by means of 70 per cent H_2SO_4 (150°C, 18 hr) and converted without isolation to the isomeric ethyl valerates [13.3: R' = C_2H_5; NAA' = dimethylamine] by adding absolute ethanol (120°C, 10 hr) and allowing the alcohol to distill. The configuration of the analgesically active dextro-isomer is related to that of L-(−)-alanine.

Known methods of preparation were adopted by BECKETT *et al.* [31, 32], MAZONI [318], SPEETER *et al.* [437] and ourselves (unpublished results).

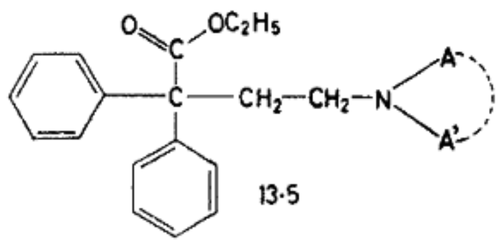
The known basic esters of structures [13.1], [13.2], and [13.3] are listed in Table IV. Only one α-CH_3-branched compound of type [13.2] is known. The bases are oils or low melting solids. The hydrochlorides are often hygroscopic or deliquescent and many of them decompose at melting temperatures.

A few p*K*-values and optical rotation values are recorded in the literature. They are listed in Table VI (Chapters XX and XXI).

Weak analgesic activity has been detected among these basic esters. Surprisingly little is known, however, about the structure–activity relationship. Published data are furthermore often contradictory:

(a) COOR′: according to EDDY *et al.* [138, 141–143] the methyl ester related to methadone [13.3 : R′ = CH_3; NAA′ = dimethylamino] is about twice as active as the ethyl-ester. WALTON *et al.* [480], however, states that both compounds are about equiactive. This author found no difference between the methyl- and the ethyl ester of 2:2-diphenyl-4-piperidino-butyric acid, whereas the former is about four times more active according to BOCKMÜHL *et al.* [52]. These authors found the benzyl-ester of this acid to be as active and the *iso*-propyl ester twice as active as the ethyl ester; butyl, *iso*butyl and phenyl esters are said to be inactive. It seems reasonable to assume, therefore, that optimal activity is to be expected among methyl esters, but further study is required to elucidate this point.

(b) NAA′: the influence of structural variations in the basic moiety NAA′ on analgesic activity was studied in some detail within the narrow framework of compounds of type [13.5] only.



13·5

The best estimate of the order of decreasing analgesic activity is: morpholine ⩾ piperidine > dimethylamine > diethylamine. The morpholino derivative of [13.5] (dioxaphetyl butyrate) is about as potent as pethidine.

(c) α and β: practically nothing is known about the effect of introduction of a methyl group in α- or β-position in esters of type [13.1] on analgesic potency. CHEN [89] and EDDY *et al.* [138] found no difference between the ethyl esters related to methadone and *iso*methadone. Other *iso*methadone-like esters ($\alpha = CH_3$) are unknown.

According to BOCKMÜHL and EHRHARDT [52] β-CH_3-branching of the ethyl ester [13.1] derived from morpholine results in total loss of activity. Further studies in this promising field are highly desirable.

(d) Optical isomers: the dextro-rotatory isomer of 2:2-diphenyl-4-dimethylamino-ethyl valerate is twice as active as the racemic mixture. It has the same absolute configuration as L-(+)-alanine and *d*-methadone. The laevo-rotatory isomer is inactive [89, 141–143, 361].

(e) Quaternary salts of these esters are analgesically inactive (unpublished results).

Some esters of type [13.1] are weak parasympatholytics. This and other

pharmacological properties have not been studied in detail [1, 52, 141–143, 236–240, 259, 281, 282].

Basic esters [13.1], [13.2], and [13.3] have been used to some extent as chemical intermediates:

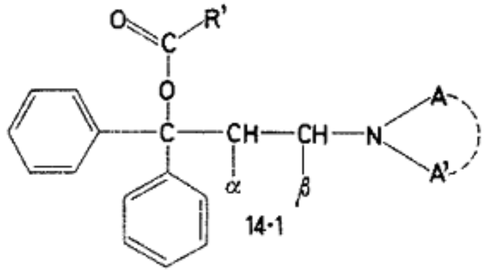
(1) Reduction to primary alcohols and aldehydes (Chapters VI and XVII).

(2) Hydrolysis to amino acids (Chapter X).

(3) Grignard reaction to ketones (Chapter XVI).

Esters derived from Tertiary Alcohols

(I : R = OCOR′)

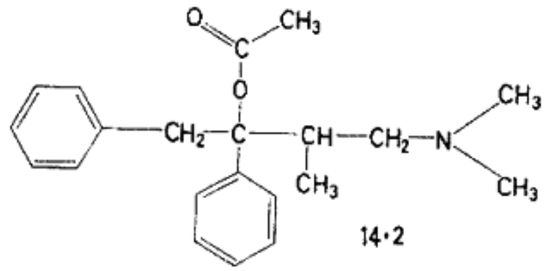


14·1

TERTIARY alcohols (I : R = OH; Chapter IV) are, as expected, difficult to acylate. BECKETT and LINNELL [20, 21] prepared aliphatic esters of structure [14.1] by the reaction of the Grignard complex of the tertiary alcohol (I : R = OH) with the appropriate acid chloride or anhydride.

Drastic conditions are necessary for accomplishing the acylation of the sterically-hindered α-CH_3-branched alcohols [352].

These esters are readily hydrolysed in aqueous solution and therefore difficult to study in pharmacological experiments. The quantitative figures, listed in Table VI and symbolizing analgesic potency of these compounds, should therefore be regarded with suspicion [20, 21, 43, 52, 89, 258, 302, 345, 346, 362, 429].

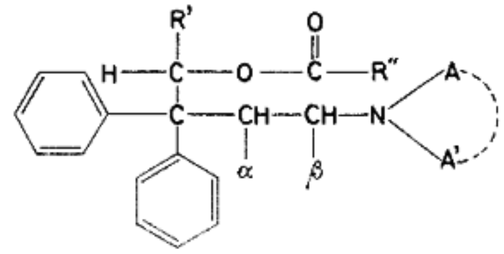


14·2

Replacement of one phenyl by a benzyl group leads to esters which are more stable in aqueous solution. The dextro-rotatory isomer of one of these compounds (propoxyphene, [14.2]) is somewhat less active as an analgesic than codeine [236–241, 362].

Esters derived from Secondary Alcohols

(I : R = CHOCOR″.R′)



15.1

ACYLATION of the secondary alcohols described in Chapter V offers no synthetic difficulties.

Acetylation, for example, may be effected with a pyridine–acetic anhydride mixture at 50–65°C [139, 316, 352, 361].

The known basic esters of type [15.1] are listed in Table IV (compounds (13.1) to (13.36)). As for the corresponding secondary alcohols, the study of the α- or β-CH_3 branched esters of this type is complicated by the existence of two asymmetric carbon atoms in the molecule, giving rise to four possible enantiomorphic isomers *α-d*, *α-l*, *β-d* and *β-l*.

Only the acetyl esters of the isomeric methadols and *iso*methadols [15.1 : R′ = C_2H_5; R″ = CH_3; α or β = CH_3; NAA′ = NMe_2] have been studied in some detail [52, 63–65, 139, 207–209, 236–241, JANSSEN: unpublished results, 315, 316, 328–332, 361, 437].

Acetylation of the isomeric methadols does not change the sign of rotation (α_D^{20} in ethanol or water), but acetylation of the *α*- and *β-iso*methadols reverses it in both instances (Tables XIV and XV).

The known bases of the acetyl methadols and acetyl *iso*methadols are solids melting around 100°C. The hydrochlorides are often hygroscopic, crystallizing with one or more molecules of water. They are therefore difficult

TABLE XIV—ACETYL METHADOLS

	Methadone		Methadol		Acetyl methadol	
Nomenclature of derived isomers	*dl* *d* *l*		*α-dl* *β-dl* *α-l* *β-d* *α-d* *β-l*		*α-dl* *β-dl* *α-l* *β-d* *α-d* *β-l*	
	base	HCl	base	HCl	base	HCl
Melting points (Table IV)	79 ± 3	232 ± 2	102 127	212 200 ± 9	— 130	213 hygrosc.
	100 ± 2	244 ± 3	— 107	171 208	— 72	202 hygrosc.
	100 ± 2	243 ± 4	— 106	171 208	— 71	203 hygrosc.
	base in ethanol	HCl in water	ethanol	water	ethanol	water
$[M]_D^{18-25}$ (Table VI)	0	0	— —	— —	— —	— —
	+ 85 ± 5	+ 436 ± 5	—	− 118	—	− 230
	− 89 ± 10	− 435 ± 4	+ 554 —	+ 257 + 118	+ 321 —	+ 188 + 222
			− 554	− 258	− 323	− 186
	ED_{50}	*dl* = 1	ED_{50}	*dl* = 1	ED_{50}	*dl* = 1
Analgesic activity in mice (s.c.) (EDDY *et al.*, Table V)	1·6	1	18·9	1	1·2	1
			7·2	1	0·7	1
	25·7	0·06	3·5	5·4	1·8	0·67
			51·1	0·14	4·6	0·15
	0·83	1·9	24·7	0·77	0·29	4·2
			7·6	0·46	0·36	1·9

to purify and identify, as shown by the different melting points reported by various authors (Table IV).

The analgesic activity in mice (s.c. and oral administration) of all possible isomeric acetyl methadols and acetyl *iso*methadols has been determined by LEIMBACH and EDDY [286]. The results are highly surprising and should be confirmed before they are used in theoretical structure–activity studies. It is indeed quite possible that the presence of small amounts of potent impurities

TABLE XV—ACETYL *iso*METHADOLS

	*iso*Methadone		*iso*Methadol		Acetyl *iso*methadol	
Nomenclature of derived isomers	*dl* *d* *l*		*α-dl* *β-dl* *α-d* *β-l* *α-l* *β-d*		*α-dl* *β-dl* *α-l* *β-d* *α-d* *β-l*	
	base	HCl	base	HCl	base	HCl
Melting points (Table IV)	oil	116–200	103 ± 1 108	200–233 254	— 79	225 ± 4 hygrosc.
	oil	232	125 94	hygrosc. 243	— 129	112 208
	oil	232	126 95	hygrosc. 243	— 129	— 209
	base in ethanol	HCl in water	ethanol	water	ethanol	water
$[M]_D^{18-25}$ (Table VI)	0	0	— —	— —	— —	— —
	+ 65	+ 228	+ 60 − 43	+ 36 − 42	— + 88	− 82 + 66
	− 62	− 242	− 61 + 41	− 34 + 47	— − 84	+ 84 − 60
	ED_{50}	*dl* = 1	ED_{50}	*dl* = 1	ED_{50}	*dl* = 1
Analgesic activity in mice (s.c.) (EDDY *et al.*, Table V)	2·5	1	66·8	1	4·8	1
			12·3	1	17·4	1
	49·8	0·05	60·7	1·1	62·7	0·08
			58·7	0·21	70·6	0·25
	1·2	2·1	91·7	0·73	2·7	1·8
			6·2	2·0	10·9	1·6

might have had considerable influence on the reported pharmacological experiments. It is furthermore not excluded that some hydrolysis might have occurred during the preparation of the aqueous solutions used for testing. One might have expected, *a priori*:

(a) To find the most active isomers of these acetyl esters among those derived from the most potent alcohols or ketones.

(b) To find one of the members of an enantiomorphic pair to be up to

twice as active as the racemic mixture, and the other isomer to be proportionally less active.

According to the available evidence, this is often not so (Tables XIV and XV), e.g.:

(a) One very active methadol (*α-l*: $ED_{50} = 3{\cdot}5$) and two active acetyl methadols (*α-l* and *β-d*: $ED_{50} = 1{\cdot}8$ and $4{\cdot}6$ respectively) are derived from the inactive *d*-methadone ($ED_{50} = 25{\cdot}7$). These findings disagree with the hypothesis that optically active analgesics have identical absolute configurations, related to D-(−)-alanine [31, 32].

(b) Resolution of the racemic mixture *α-dl*-acetylmethadol ($ED_{50} = 1{\cdot}2$) yields the approximately equipotent *α-l*-isomer ($ED_{50} = 1{\cdot}8$) and the *α-d*-isomer, which was found to be about 4·2 times more active ($ED_{50} = 0{\cdot}29$).

The available data further indicate that all isomeric acetyl methadols are more active than the methadols and methadones from which they are derived. The configuration of the ester-group of acetyl methadols has much less influence on activity than the configuration of the hydroxyl group of the methadols. All alcohols and esters derived from *d-iso*methadone are as inactive and those derived from *l-iso*methadone are less active than the parent ketone; among the latter compounds the *β*-alcohol and the *α*-ester are respectively fifteen and four times more active than their isomers.

Our present knowledge concerning the effect of other structural variations on analgesic activity of acylated secondary alcohols of type [15.1] may be summarized as follows:

(a) R′: nearly all known compounds are derived from ethyl ketones [15.1 : R′ = C_2H_5]. The two examples with R′ = CH_3 and C_3H_7 were found to be inactive. Further investigation is therefore required.

(b) R″: the acetyl-ester derived from *α-dl*-methadol is more active than the formyl-, propionyl- and butyryl-esters and *α-dl*-acetyl-*iso*methadol more active than the corresponding propionyl ester (Table V). According to SPEETER *et al.* [438] chloroacetyl methadols and *iso*methadols [15.1 : R″ = CH_2Cl] are as a rule somewhat more active than the acetyl esters. All other esters tested (R″ = C_2H_5, $CH_2C_6H_5$, NHC_6H_5, CH_2Br, C_2H_4Cl, C_6H_5, 4-NH_2-C_6H_4) were much less active [22, 438].

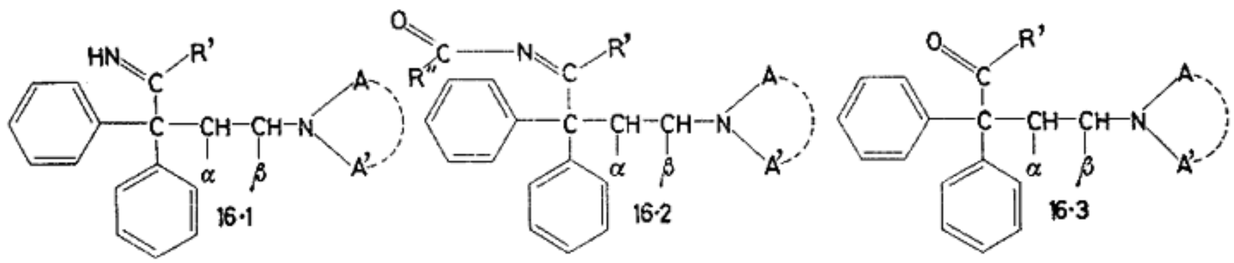
(c) NAA′: nearly all acylated methadols and *iso*methadols [15.1] which have been investigated pharmacologically are derived from dimethylamine. A few morpholino derivatives were also found to be highly active (Table V). It is safe to predict that highly potent analgesics may be prepared by acetylation of the isomeric methadols derived, e.g. from pyrrolidine and piperidine.

(d) *α* and *β*: the available data seem to indicate that the most active esters of type [15.1] are those derived from methadol. Whether this is a general rule or not is not yet known.

CHAPTER XVI

Ketimines, Acyl Ketimines and Ketones

(I : R = CNHR′, CNCOR″R′, COR′)



KETIMINES [16.1] and ketones [16.3] related to methadone are usually prepared by Grignard reaction of the corresponding nitriles (I : R = CN).

Here, as in many other reactions, the reactivity of the cyano group is considerably decreased due to steric hindrance produced by both phenyl groups, by the *α*-CH_3 group and, to a lesser extent, by the *β*-CH_3 group.

In all cases it was found necessary to heat the original ethereal mixture of nitrile and from two- to three-fold excess Grignard reagent in high boiling apolar solvents such as toluene or xylene. The conversion of the resulting ketimines [16.1] to the ketones [16.3] with hydrochloric acid often requires drastic conditions.

Methyl branching of the side chain stabilizes these ketimines. This stability is especially pronounced among ketimines of the *iso*methadone-type who require prolonged heating under pressure for conversion.

As expected, branched alkyl magnesium halides are even less reactive than unbranched Grignard reagents. *iso*Propylketones could not be obtained from the nitriles by Grignard reaction in drastic conditions, but satisfactory yields were noted when the corresponding ethyl esters (I : R = $COOC_2H_5$) were used instead. The reaction does not proceed further than the ketimine–ketone stage; no tertiary alcohols (I : R = CHOHR′R′) have been isolated.

Ketones [16.3] were also prepared by Grignard reaction from amino acids

(I : R = COOH), acid chlorides (I : R = COCl) and primary amides (I : R = $CONH_2$) [52].

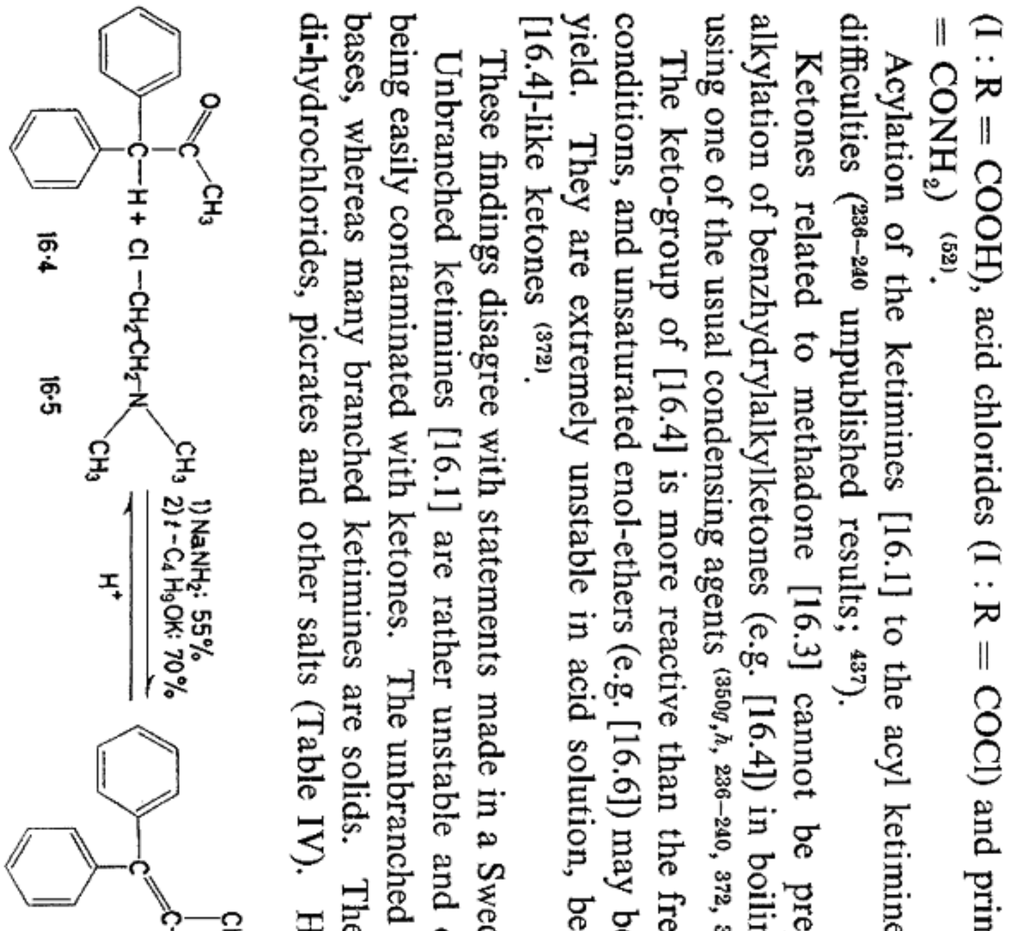
Acylation of the ketimines [16.1] to the acyl ketimines [16.2] offers no difficulties [236–240 unpublished results; 437].

Ketones related to methadone [16.3] cannot be prepared by aminoalkylation of benzhydrylalkylketones (e.g. [16.4]) in boiling apolar solvents using one of the usual condensing agents [350g,h, 236–240, 372, 385, 502].

The keto-group of [16.4] is more reactive than the free proton in these conditions, and unsaturated enol-ethers (e.g. [16.6]) may be isolated in good yield. They are extremely unstable in acid solution, being rearranged to [16.4]-like ketones [372].

These findings disagree with statements made in a Swedish patent [319].

Unbranched ketimines [16.1] are rather unstable and difficult to purify, being easily contaminated with ketones. The unbranched ketimines are oily bases, whereas many branched ketimines are solids. They form mono- or di-hydrochlorides, picrates and other salts (Table IV). Hydrolysis of these



16·4 16·5 16·6

ketimines to ketones in aqueous solution can be followed by measuring the rate of formation of the 300 ± 10 mμ absorption band ($\varepsilon = 500 \pm 150$) which is characteristic for ketones of the type $C_6H_5{\cdot}\overset{|}{C}{\cdot}CO{\cdot}$alkyl [236–240 unpublished results).

The melting points of acyl ketimines have not been studied in detail. These compounds are also hydrolysed to ketones, via the parent ketimines, under drastic conditions (unpublished results).

In spite of the extensive research conducted with ketones of type [16.3] the physical properties of these substances are not known with a desirable degree of accuracy. Most bases are oils or low melting solids. The fact that their hydrochloride salts are nearly always hygroscopic probably accounts for the large differences between the melting points as reported by various authors (Table IV). It may be assumed that many pharmacological experiments were conducted with impure ketones.

Several optical isomers of branched ketones of the [16.3]-type have been prepared. Optical rotation values are reported upon in Table VI (Chapter XXI). Relation between structure and basic strength is discussed in Chapter XX.

TABLE XVI—ANALGESIC ACTIVITY OF KETONES RELATED TO METHADONE (TABLES IV AND V)

Structure [16.3]				Relative analgesic activity† (s.c. or i.p.)	Structure [16.3]				Relative analgesic activity (s.c. or i.p.)
NAA'*	α	β	R'		NAA'	α	β	R'	
$N(CH_3)_2$	H	H	CH_3	0–2 (3)‡	NC_4H_8	H	H	C_2H_5	3 (3)
,,	,,	,,	C_2H_5	2–4 (14)	,,	CH_3	,,	C_2H_5	3 (1)
,,	,,	,,	C_3H_7	0–1 (3)	,,	H	CH_3	C_2H_5	5 (5)
,,	,,	,,	i-C_3H_7	0 (1)	NC_5H_{10}	,,	H	CH_3	0–2 (3)
,,	,,	,,	C_6H_5	0 (1)	,,	,,	,,	C_2H_5	3 (9)
,,	CH_3	,,	CH_3	2 (1)	,,	,,	,,	C_3H_7	0–2 (2)
,,	,,	,,	C_2H_5	4 (4)	,,	,,	,,	i-C_3H_7	0–3 (2)
,,	,,	,,	C_3H_7	0 (1)	,,	,,	,,	i-C_4H_9	3 (1)
,,	,,	,,	i-C_3H_7	0 (1)	,,	,,	,,	C_6H_5	0–2 (2)
,,	,,	,,	C_6H_5	0 (1)	,,	,,	,,	C_3H_5	3 (1)
,,	H	CH_3	CH_3	1–2 (3)	,,	CH_3	,,	CH_3	3 (1)
,,	,,	,,	C_2H_5	6 (34)	,,	,,	,,	C_2H_5	4 (3)
,,	,,	,,	C_3H_7	1 (1)	,,	,,	,,	C_3H_7	3 (1)
,,	,,	,,	i-C_3H_7	0 (1)	,,	H	CH_3	CH_3	3 (1)
,,	,,	,,	C_4H_9	0 (1)	,,	,,	,,	C_2H_5	4–7 (5)
,,	,,	,,	$CH_2C_6H_5$	0 (1)	,,	,,	,,	C_3H_7	0 (1)
$N(C_2H_5)_2$	,,	H	CH_3	0 (1)	NC_4H_8O	,,	H	CH_3	1 (3)
,,	,,	,,	C_2H_5	1 (3)	,,	,,	,,	C_2H_5	3–5 (6)
,,	,,	,,	C_3H_7	0 (1)	,,	,,	,,	C_3H_7	2 (1)
,,	CH_3	,,	C_2H_5	3 (1)	,,	,,	,,	C_6H_5	0 (1)
,,	H	CH_3	C_2H_5	4 (1)	,,	,,	,,	$CH_2C_6H_5$	0 (1)
$N(C_3H_7)_2$	,,	H	C_2H_5	0 (2)	,,	CH_3	,,	C_2H_5	0–3 (3)
$N(iC_3H_7)_2$	,,	,,	C_2H_5	0 (1)	,,	H	CH_3	C_2H_5	6–7 (12)

* Bases or tertiary salts were s.c. or i.p. injected.
† 6 : methadone; 4 : morphine; 2 : pethidine; 0 : $< \frac{1}{2}$ pethidine.
‡ Number of published activity data.

The relation between chemical structure and analgesic activity (s.c. or i.p. injection in mice and rats) of ketones of type [16.3] may be described as follows (Tables V and XVI):

(a) R′: highest potency is found among ketones with R′ = C_2H_5. This seems to be a quite general rule, applicable to all known examples (Table XVI). The activities of the other ketones can hardly be compared. Most of them were tested by one author only.

(b) α and β: the α-CH_3-branched ketones of the *iso*methadone type are generally somewhat more active than the unbranched ketones, with the exception of *iso*phenadoxone. The differences are, however, rather small. The majority of the known β-CH_3-branched ketones of the methadone-type on the other hand are significantly more active than the α-CH_3-branched or the unbranched homologues. The significance of the few exceptions to this rule, listed in Tables V and XVI, should be more carefully investigated.

(c) NAA′: the most active ketones of type [16.3] are derived from morpholine, piperidine, dimethylamine and pyrrolidine. Derivatives of higher dialkylamines become rapidly less active when the weight of the alkyl groups increases. Introduction of a phenyl nucleus in the NAA′-moiety of the molecule results in total loss of activity. The activity of derivatives of cyclic amines of the type $N(CH_2)_n$ reaches a maximum when n equals 5 (piperidine). Ring-substitution of cyclic amines with alkyl groups produces less active compounds. Thiomorpholine- and piperazine-derivatives are less active than morpholine-derivatives.

(d) Quaternary salts are analgesically inactive.

(e) One of the optical isomers of each enantiomorphic pair is up to twice as active as the racemic mixture; the other isomer is usually devoid of significant analgesic activity. The absolute configurations of *l*-methadone and of *l*-phenadoxone are identical and related to that of D-(−)-alanine (Chapter XXI).

(f) Replacement or substitution of one or both phenyl rings, as well as lengthening, shortening or branching with alkyl groups other than methyl of the ethylene side chain resulted in considerable loss of analgesic activity in all known examples [236–240].

There is no evidence to show that ketones of type [16.3] have other interesting pharmacological properties, although weak parasympatholytic, antihistaminic, antispasmodic and local anaesthetic activity has been noted [18, 52, 89, 176, 191, 192, 194–198, 236–241, 259].

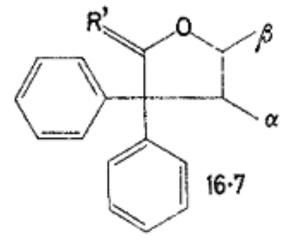
All known ketimines are less active than the corresponding ketones (Table V). It is interesting to note that the onset of action of these ketimines is a very long one, suggesting that they are metabolized *in vivo* to the ketones [236–240, unpublished results]. Some of the reported activity of these ketimines might well be due to contamination with ketones in the sample.

Among the acetyl-ketimines (Tables IV and V) a few are rather active analgesics, particularly the one related to *iso*phenadoxone (compound (14.24)) which is about ten times more active than *iso*phenadoxone itself. Further data are highly desirable.

Ketones of type [16.3] have been used as intermediates for the preparation of methadols (Chapter V).

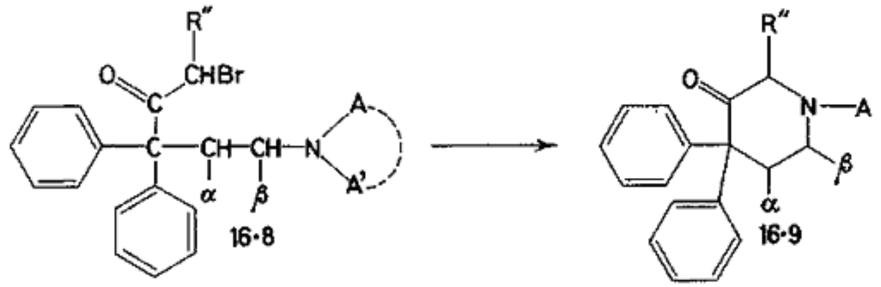
In alkaline medium the keto group may be split off (Chapter 3).

Evidence of the fact that the keto group is sterically hindered by both phenyl groups has been presented above. This point is further illustrated by the failure of these ketones to react with Grignard reagents, hydroxylamine, semi-carbazides, hydrazines, etc. [52, 236–240].



16·7

Pyrrolysis of optically active methylhalides of branched and unbranched ketones [16.3] leads to alkylidenetetrahydrofurane derivatives [16.7] with the same optical rotation [131–133, 350c].



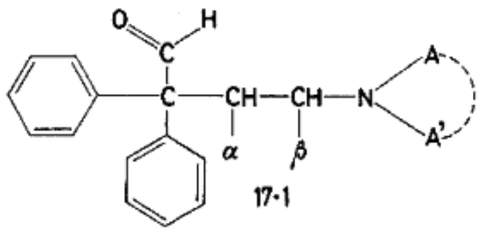
Bromination in acetic acid of ketones [16.3] leads to the hydrobromide salts of [16.8] (80–90 per cent), and to polybromo compounds when excess bromine is used.

The bases of [16.8] are instable and cyclize spontaneously to quaternary salts of [16.9], which may be converted to tertiary bases by distillation [49, 104].

CHAPTER XVII

Aldehydes

(I : R = COH)



17·1

THE five aldehydes of type [17.1], listed in Table IV, were prepared by one of the following methods:

(a) Rosemund-reduction ($Pd–H_2$) of the acid chloride (I : R = COCl) [52].

(b) Reduction of the corresponding nitriles (I : R = CN) using 0·3 moles of $LiAlH_4$ in ether [353, 534].

The known physical data are listed in Tables IV and VI.

The relation between structure and activity is unknown. Two aldehydes of type [17.1] were found to be analgesically active (Table V).

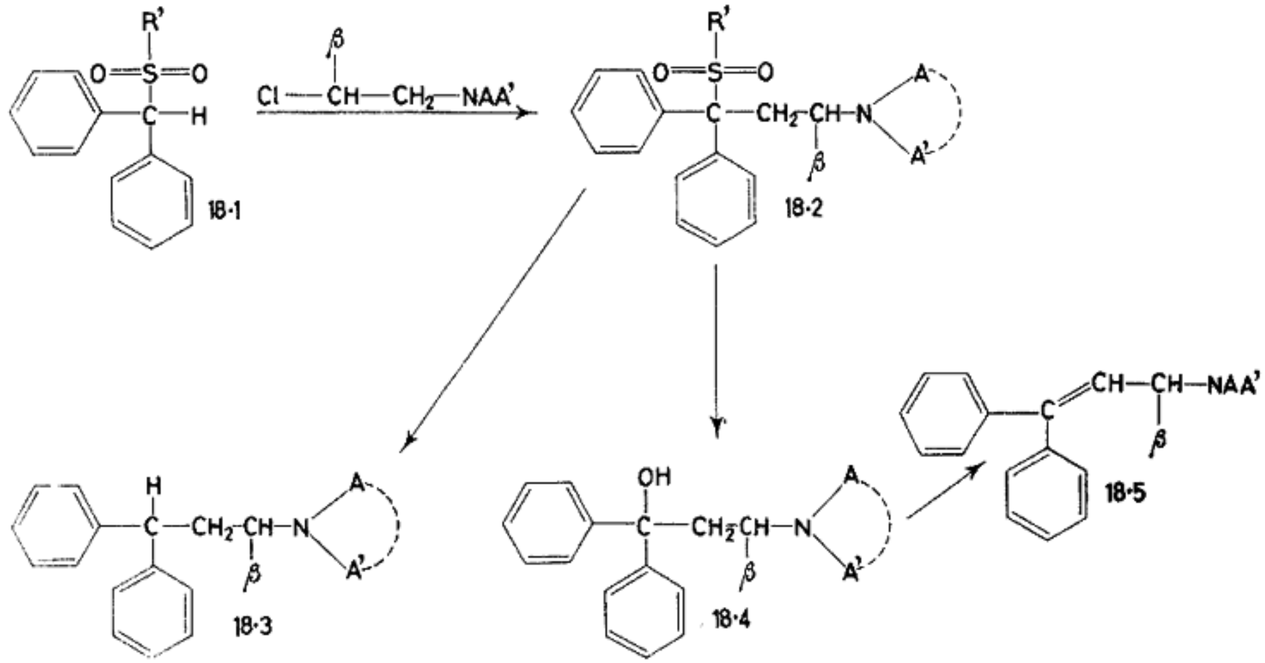
On catalytic hydrogenation (Pto–760 mm Hg) primary alcohols (I : R = CH_2OH) are formed [534].

Other reactions of these aldehydes [353] are described in Chapters VI and XIX.

CHAPTER XVIII

Sulphones

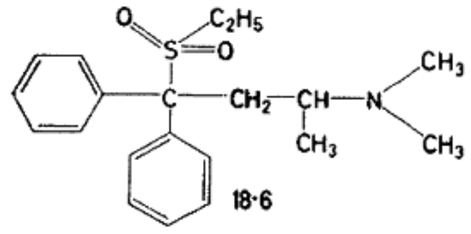
(I : R = SO_2R')



SULPHONES of type I ($R = SO_2R'$; $R' = CH_3$, C_2H_5, C_3H_7 or p-C_7H_7) were first prepared by KLENK, SUTER and ARCHER [260] by aminoalkylation of a benzhydrylsulphone [18.1] in toluene solution with sodium amide as the condensing agent.

Unbranched basic sulphones [18.2: $\beta = H$] were obtained in good yield from the reactions between [18.1] and tertiary aminoethylchlorides.

Only one crystalline basic sulphone was obtained from the reaction between ethyl benzhydryl sulphone and dimethylamino*iso*propyl chloride.



18·6

When this basic sulphone [18.6] was refluxed in ethanol with Raney nickel catalyst, hydrogenolysis occurred at the carbon–sulphur bond and a high-boiling basic oil was obtained which yielded a hydrochloride identical with the one prepared from methadone-nitrile and excess sodium amide in boiling toluene [18·3: $\beta = CH_3$; $NAA' = N(CH_3)_2$]. The configuration of the side chain of the basic sulphone was thus the same as in methadone ($\beta = CH_3$), indicating that the well known methadone rearrangement occurred in this case also.

The reaction products between other sulphones of type [18.1] and various tertiary amino *iso*propylchlorides were given the β-CH_3 structure. There is, however, no degradative evidence to support these formulations, except by analogy [260, 515, 520].

TULLAR, WETTERAN and ARCHER [462] prepared the ethylsulphone related to methadone [18.6] in 45 per cent yield as described above, but with sodium hydride as the condensing agent, and accomplished its resolution by taking advantage of the difference in solubility of the diastereomeric *d*-bitartrates in aqueous acetone [23–27]. Optical rotation figures are listed in Table VI.

The ethylsulphone related to methadone [18.6] proved to be increasingly ineffective on testing its analgesic activity in man [248–249]. Progressive decay of the drug in aqueous solution occurs during storage.

It was observed by ARCHER and AUERBACH [10] that after an aqueous solution of the hydrochloride of the laevo-isomer had been kept at 120°C for 15 min, the sign of the rotation had changed from minus to plus. A gummy mixture was thrown down with ammonium hydroxide and resolved into a laevo-rotatory crystalline solid and a dextro-rotatory viscous oil with the aid of petroleum ether. These components were shown to be isomers of the solid basic carbinol [18.4] and the oily unsaturated amine [18.5] ($\beta = CH_3$ and $NAA' = N(CH_3)_2$). Similar results were obtained with ethyl-3-piperidino-1:1-diphenylpropylsulphone.

The seven known methyl- and ethylsulphones of type [18.2], listed in Table IV, are solid crystalline bases.

The pronounced morphine-like analgesic activity of the ethyl sulphone related to methadone [18.6] was detected by KLENK *et al.* [260] and further studied in animals by BECKETT *et al.* [23–27], EDDY *et al.* [138] and LEWIS [291]. The racemate is about as active as morphine or methadone. The laevo-rotatory isomer, which is about twice as active, has the same configuration as *l*-methadone and D-(—)-alanine [23, 24]. Analgesic properties in man are described by KEATS and BEECHER [248, 249].

Very little is known about the pharmacology of related basic sulphones of type [18.2].

According to KLENK *et al.* [260] highest analgesic activity is found when $R' = C_2H_5$ ($C_2H_5 > CH_3 > C_3H_7 > p$-$C_7H_7$). The presence of the methyl group is a favourable factor.

No significant differences in activity were detected among related sulphones of type [18.2] derived from dimethylamine, diethylamine or piperidine, but this point needs further investigation.

CHAPTER XIX

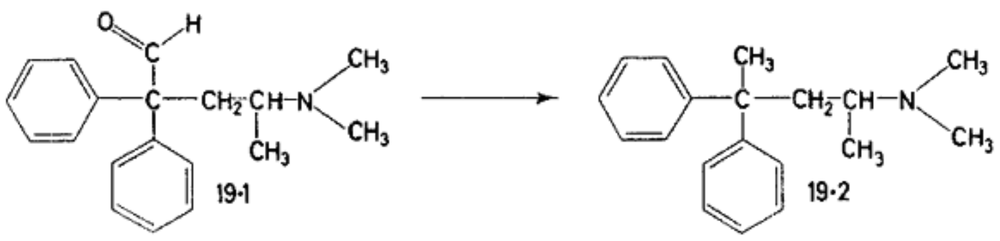
Other Compounds of Structure (I)

A FEW esters of primary alcohols (I : R = CH_2—O—COR′ and also R = —$(CH_2)_3$—O—COR′) are briefly mentioned in papers by CHEN [89], PERRINE [352] and SPEETER *et al.* [437]. They were prepared as usual from the alcohols and seem to be devoid of analgesic activity (Tables V and VI).

The two basic ethers of type I (R = O—CH_2COCH_3 and $CH_2CH_2OCH_2CH_3$), described by KJAER *et al.* [258] and SPERBER *et al.* [439] are quite interesting compounds. Practically nothing is known about them, although the study of this type of compounds could well lead to interesting results (Chapter VI).

The known halogenated derivatives of type I (R = Cl, CH_2CH_2Br, $CH_2CH_2CH_2Cl$, $CH_2CH_2CH_2I$ and $CHClC_2H_5$), described by KAWABATA [247], KJAER *et al.* [258], MAY *et al.* [315], PERRINE *et al.* [353] and SPERBER *et al.* [439], were prepared as intermediates. They are discussed in Chapters III–VI.

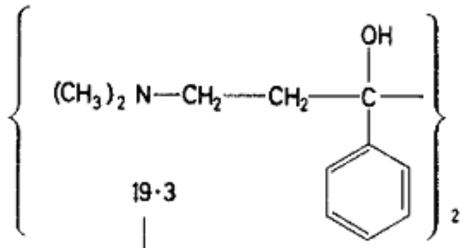
PERRINE and MAY [353] obtained the

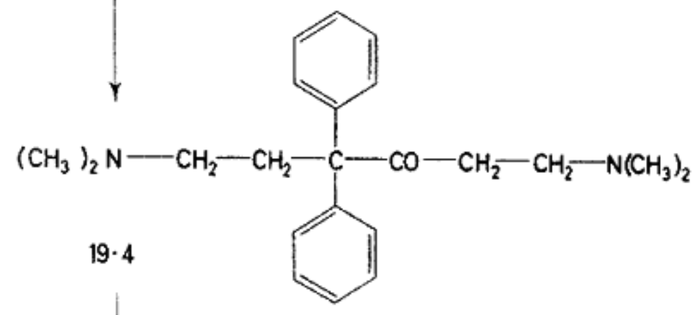


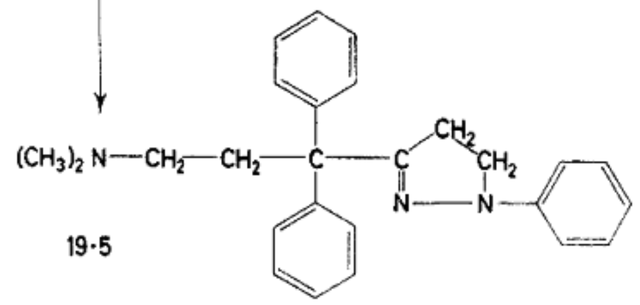
analgesically effective ($\frac{1}{30}$–$\frac{1}{40}$ morphine in mice) 4-dimethylamino-2:2-diphenylpentane by heating the basic aldehyde [19.1] for 7 hr at 175°C with hydrazine and KOH in triethylene glycol.

The inactive related aminoheptane (I : R = $CH_2CH_2CH_3$) was obtained from the methiodide of a basic iodo derivative (I : R = $CH_2CH_2CH_2I$) by means of silver oxide treatment in water [353] (Chapter VI).

ALLEN, FEARN and LEVINE [7] found the pinacol [19.3] to undergo rearrangement to the dibasic ketone [19.4] on treatment with 80 per cent







sulphuric acid. This Mannich base ketone reacted with phenylhydrazine to yield a crystalline material, for which the pyrazoline structure [19.5] was proposed. The evidence in favour of this hypothesis is, however, inconclusive.

CHAPTER XX

Dissociation Constants

BECKETT [28–30] determined pK_a values of twenty compounds of structure (I) in water at 25°C and ionic strength of approximately 0·013 M.

MARSHALL [313] using a different technique, reported on the dissociation constants of eighteen such compounds (Table VI). The results are summarised in Table XVII.

Replacement of the cyano group (I : R = CN) by a proton (I : R = H) has a base strengthening effect of 0·8 to 1·2 pK_a units.

Replacement by a ketonic group (I : R = COC_2H_5 or $COCH_3$) has a similar but smaller effect (0·7 to 0·9 pK_a units). The dissociation constants of ketones, acids and esters (I : R = COalk, COOH and COOalk) are apparently of the same order of magnitude [313].

Since cyano, ketonic, acid and ester groups are electronegative in character, the observed differences in basic strength may be attributed to the inductive effect along the chain separating these groups from the basic centre, or a field effect operating through space or solvent if the interacting groups are in close proximity, which is probably achieved by a mechanism in which the lone pair orbital of the nitrogen atom of the basic group NAA′ interacts with the electropositive carbon atom of substituent R [28–30].

The $N(C_2H_5)_2$ compounds are stronger bases than the $N(CH_3)_2$ compounds. This is attributed to the ethyl group, which has a larger + I effect than a methyl group, increasing the electron density on the nitrogen atom.

These dimethylamino compounds are stronger bases than the corresponding piperidine analogues by 0·2 to 0·7 pK_a units, and the latter are stronger bases than their morpholino analogues by 1·6 to 2·0 pK_a units [28–30]. Possible explanations of these differences have been advanced by BECKETT [28–30].

Introduction of a methyl group in the side chain has in most cases a base weakening effect. All α-CH_3 compounds are weaker bases than their β-CH_3 isomers (Table XVII).

Steric factors, favouring a neutral N atom in NAA′ rather than the larger cation are apparently more important in the majority of these compounds than the + I base strengthening contribution of the CH_3-group.

TABLE XVII—DISSOCIATION CONSTANTS pK_a OF COMPOUNDS OF TYPE (I) (TABLE VI)

NAA′	R	$\alpha = \beta = H$		$\alpha = CH_3$		$\beta = CH_3$	
		pK	Δ	pK	Δ	pK	Δ
BECKETT *et al.*, 1956 [28–30]							
$N(CH_3)_2$	CN	8·31	0	7·90	—	8·31	0
$N(CH_3)_2$	COC_2H_5	9·23	0·92	—	—	8·99	0·68
$N(CH_3)_2$	H	9·40	1·09	—	—	9·48	1·17
NC_5H_{10}	CN	8·07	0	7·54	—	7·73	0
NC_5H_{10}	COC_2H_5	8·86	0·79	—	—	8·58	0·85
NC_5H_{10}	H	8·96	0·89	—	—	8·80	1·07
NC_4H_8O	CN	6·09	0	—	—	6·10	0
NC_4H_8O	COC_2H_5	7·00	0·91	—	—	6·73	0·63
NC_4H_8O	H	7·25	1·16	—	—	6·90	0·80
MARSHALL, 1953 [313]							
$N(C_2H_5)_2$	CN	9·08	0	—	—	—	—
$N(C_2H_5)_2$	COOH	10·59	1·51	—	—	—	—
$N(C_2H_5)_2$	$COOC_2H_5$	11·59	2·51	—	—	—	—
$N(CH_3)_2$	CN	—	—	8·16	0	8·68	0
$N(CH_3)_2$	$COCH_3$	—	—	9·53	1·37	—	—
$N(CH_3)_2$	COC_2H_5	—	—	9·53	1·37	10·12	1·44
$N(CH_3)_2$	COOH	—	—	—	—	10·88	2·20
$N(CH_3)_2$	$COOC_2H_5$	9·87	—	—	—	10·12	1·44
NC_5H_{10}	CN	—	—	8·83	0	8·93	0
NC_5H_{10}	COC_2H_5	8·86	—	9·40	0·57	10·35	1·42
NC_4H_8O	COC_2H_5	—	—	7·12	—	7·70	—

CHAPTER XXI

Configurational Studies

BECKETT and collaborators [25–32] investigated the configurational relationships of several isomers of type I ($\beta = CH_3$; NAA′ = dimethylamine or morpholine).

Starting from D-(−)-alanine they synthesized the laevo-rotatory isomers of the nitrile [21.5] and the tertiary alcohol [21.8] related to methadone by a series of reactions not involving the asymmetric centre (Chapters IV and VII).

From the nitrile they obtained the laevo-isomers of methadone [21.1], amino-pentamide [21.2] and the amino ester [21.3] as well as the dextro-isomer of the amine [21.6]. This amine was also obtained from the alcohol [21.8]. Hydrolysis of the laevo-rotatory isomer of the sulphone [21.9] gave the laevo-alcohol [21.8].

All these compounds thus possess identical configurations which are related to D-(−)-alanine.

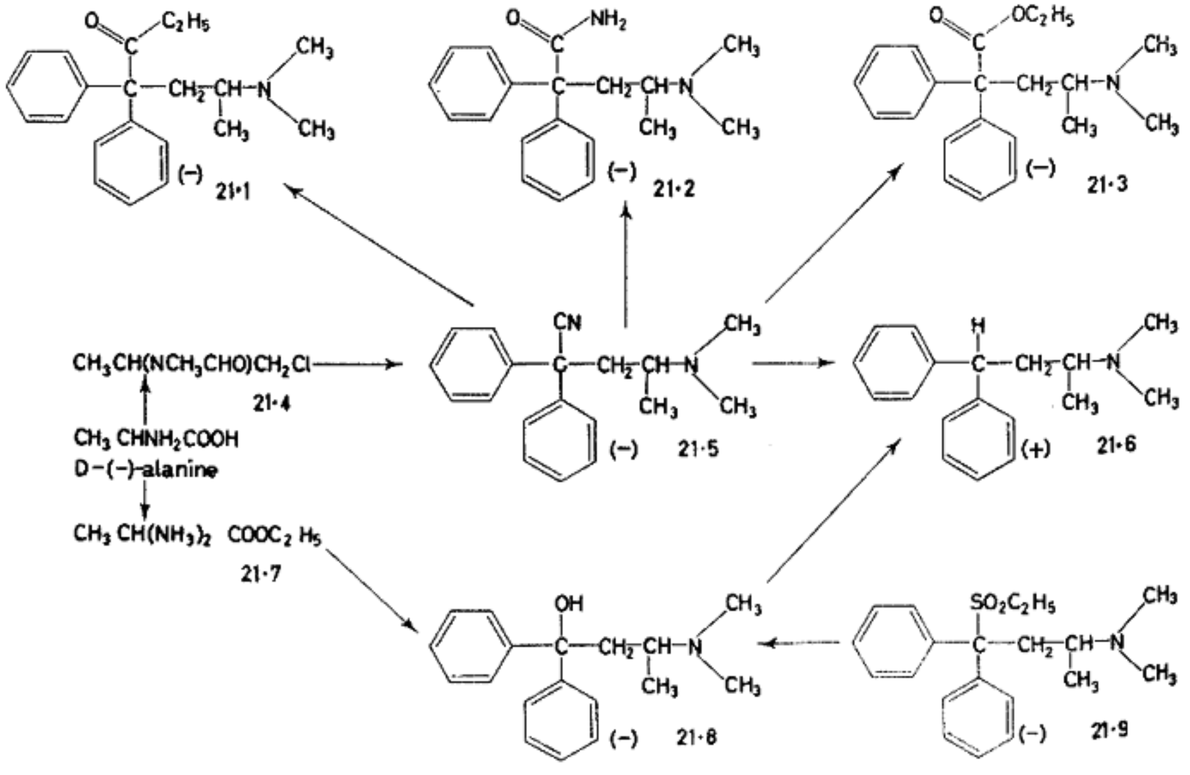


TABLE XVIII—MOLECULAR ROTATIONS $(M)_D$ OF COMPOUNDS (I) ($\alpha = H$; $\beta = CH_3$) (TABLE VI)

R	NAA′	Isomer	Base in			HCl in H_2O	Configuration*
			C_6H_{12}	C_6H_5	C_2H_5OH		
H	$N(CH_3)_2$	*d*	− 168	− 127	+ 30	+ 125	+
H	NC_2H_4O	*d*	+ 145	+ 123	+ 55	− 97	−
CN	$C(CH_3)_2$	*l*	− 170	− 165	− 139	+ 15	+
CN	NC_2H_4O	*d*	+ 183	+ 154	+ 211	− 5	−
$CONH_2$	$N(CH_3)_2$	*l*	− 497	− 536	− 332	− 249	+
$CONH_2$	NC_2H_4O	*d*	+ 420	+ 491	+ 431	+ 256	−
COC_2H_5	$N(CH_3)_2$	*l*	− 108	− 74	− 90	− 435	+
COC_2H_5	NC_2H_4O	*d*	+ 247	+ 179	+ 245	+ 345	−
OH	$N(CH_3)_2$	*l*	+ 99	+ 88	− 80	− 125	+
$CHOHC_2H_5$	$N(CH_3)_2$	*αd*	—	—	—	+ 118	+
$CHOHC_2H_5$	$N(CH_3)_2$	*βl*	—	—	− 554	− 258	+
$CHOCOCH_3C_2H_5$	$N(CH_3)_2$	*αd*	—	—	—	+ 222	+
$CHOCOCH_3C_2H_5$	$N(CH_3)_2$	*βl*	—	—	− 323	− 186	+
$COOC_2H_5$	$N(CH_3)_2$	*l*	− 278	− 240	− 163	− 135	+
$SO_2C_2H_5$	$N(CH_3)_2$	*l*	—	—	0	− 125	+
COH	$N(CH_3)_2$	*d*	—	—	+ 227	+ 91	−

* + : configuration related to D-(−)-alanine.
− : configuration related to L-(+)-alanine.

The laevo-rotatory isomers of methadone [21.1] and the corresponding ethyl sulphone [21.9] are about twice as active as analgesic agents as their racemates, the dextro-rotatory isomers being nearly inactive.

The dextro-rotatory isomer of the ester [21.3] is, however, more active in "analgesic" tests than the laevo-rotatory isomer, derived from D-(−)-alanine.

As described in Chapter XV, the *α*-methadol derived from *d*-methadone is more active as an analgesic than *α*-*d*-methadol, derived from *l*-methadone and hence also from D-(−)-alanine. Both acetylmethadols derived from *d*-methadone are finally quite active analgesics (Table XXIX).

These facts are not in agreement with the hypothesis that the absolute configurations of all analgesically-active isomers are identical and related to the configuration of D-(−)-alanine.

The laevo-isomer of aminopentamide is twice as active as a para-sympatholytic as the racemic mixture, the dextro-isomer being devoid of significant activity.

BECKETT and CASY [31, 32] used the dextro-rotatory nitrile related to phenadoxone to prepare the corresponding ethyl-ketone (phenadoxone), primary

TABLE XIX—ANALGESIC POTENCY, OPTICAL ROTATION AND ABSOLUTE CONFIGURATION OF ISOMERS RELATED TO *d*- AND *l*-METHADONE (I : $\alpha = H$; $\beta = CH_3$; $NAA' = NMe_2$)

R	Analgesic potency of racemate (*dl*-methadone = 1·0)	Optical rotation and analgesic potency (*dl*-methadone = 1·0) of isomer related to	
		D-(−)-alanine	L-(+)-alanine
β-CHOCOCH$_3$·C$_2$H$_5$	∼ 2·3	*l*: 4·2–4·4	*d*: ∼ 0·35
α-CHOCOCH$_3$·C$_2$H$_5$	1·3	*d*: 2·0–5·3	*l*: 0·3–0·9
SO$_2$C$_2$H$_5$	1·0–1·2	*l*: ∼ 1·8	*d*: ∼ 0·1
COC$_2$H$_5$	1·0	*l*: 1·5–2·3	*d*: < 0·07–0·15
COOC$_2$H$_5$	0·15–0·30	*l*: 0·03–0·07	*d*: 0·20–0·39
α-CHOH·C$_2$H$_5$	0·08–0·20	*d*: 0·03–0·06	*l*: 0·40–0·46
β-CHOH·C$_2$H$_5$	0·13–0·22	*l*: ∼ 0·2	*d*: ∼ 0·03
H	∼ 0·04	*d*: ∼ 0·07	*l*: ⩽ 0·05
CONH$_2$	inactive	*l*: inactive*	*d*: inactive
CN	inactive	*l*: inactive*	*d*: inactive
OH	inactive	*l*: inactive*	*d*: inactive

* About twice as parasympatholytically active as the racemate.

amide and denitrilated amine. All three derivatives are dextro-rotatory. Their configurational identity follows from their preparation. Dextro-phenadoxone is analgesically inactive.

The molecular rotation $[M]_D^{20}$ of dextro-phenadoxone is displaced towards increasing dextro-rotation and that of laevo-methadone towards increasing laevo-rotation as the polarity of the solvent increases from *cyclo*hexane to water, while the corresponding pairs of isomeric nitriles, amides and de-nitrilated amines (I : R = H) show opposite trends.

Unlike configurations may therefore be assigned, according to BECKETT and CASY [31, 32], to the members of each pair of both series.

The absolute configurations of the isomers of branched compounds of structure (I) in which $\alpha = CH_3$ have not yet been studied.

REFERENCES

[1] ADAMI E. and MARAZZI E. (1956) *Arch. intern. Pharmacodyn.* **107**, 322.
[2] ADAMSON D. W. (1949a) *J. Chem. Soc.* 144.S.
[3] ADAMSON D. W. (1949b) *Nature, Lond.* **164**, 500.
[3a] ADAMSON D. W.; *J. Chem. Soc.* (1950) 885.
[4] ADAMSON D. W. (1951) *Chemistry and Industry* 2.
[5] ADAMSON D. W., BARRETT P. A. and WILKINSON S. (1951) *J. Chem. Soc.* 52.
[6] ADLER T. K. and EISENBRANDT L. L. (1949) *Proc. Soc. Exp. Biol. Med.* **72**, 347.
[7] ALLEN M. J., FEARN J. E. and LEVINE H. A. (1952) *J. Chem. Soc.* 2220.
[8] ALMERSJÖ O. (1958) *Svenska Läkartidningen* **55**, 1531.
[9] ANGIBEAUD P., BUCHEL L. and LEVY J. (1956) *Anesthésie et Analgésie* **13**, 848.
[10] ARCHER S. and AUERBACH M. E. (1951) *J. Amer. Chem. Soc.* **73**, 1840.
[11] ASSAF T. (1957) *Acta Institut d'Anesthésiol.* **6**, 185.
[12] ATTENBURROW J., ELKS J., HEMS B. A. and SPEYER K. N. (1949) *J. Chem. Soc.* 510.
[13] AXELROD J. (1956) *J. Pharmacol. Exp. Therap.* **117**, 322.
[14] BAIZER M. M. (1953) *Bull. Narcotics U.N. Dep. Social Affairs* **5**, 32.
[15] BARBIZET J. (1957) *Presse Médicale* **65**, 1621.
[16] BARBIZET J. (1958) *Thérapie* **13**, 430.
[17] BARTOLOMEI G. and FRANCO G. (1957) *Attualità di Ostetricia e Ginecologia* No. 6.
[18] BASIL B., EDGE N. D. and SOMERS G. F. (1950) *Brit. J. Pharmacol.* **5**, 125.
[19] BECKER T. J., ANANENKO E., GLENWOOD C. and MILLER L. C. (1946) *Fed. Proc.* **5**, 163.
[20] BECKETT A. H. and LINNELL W. H. (1950a) *J. Pharm. Pharmacol.* **2**, 418.
[21] BECKETT A. H. and LINNELL W. H. (1950b) *J. Pharm. Pharmacol.* **2**, 427.
[22] BECKETT A. H. (1952) *J. Pharm. Pharmacol.* **4**, 425.
[23] BECKETT A. H. and CASY A. F. (1954a) *J. Pharm. Pharmacol.* **6**, 986.
[24] BECKETT A. H. and CASY A. F. (1954b) *Nature, Lond.* **173**, 1231.
[25] BECKETT A. H. and CASY A. F. (1955a) *J. Pharm. Pharmacol.* **7**, 204.
[26] BECKETT A. H. and CASY A. F. (1955b) *J. Pharm. Pharmacol.* **7**, 433.
[27] BECKETT A. H. and CASY A. F. (1955c) *J. Chem. Soc.* 900.
[28] BECKETT A. H. (1956) *J. Pharm. Pharmacol.* **8**, 848.
[29] BECKETT A. H., CASY A. F., HARPER N. J. and PHILLIPS P. M. (1956a) *J. Pharm. Pharmacol.* **8**, 860.
[30] BECKETT A. H., CASY A. F., HARPER N. J. and PHILLIPS P. M. (1956b) *J. Pharm. Pharmacol.* **8**, 874.
[31] BECKETT A. H. and CASY A. F. (1951) *J. Chem. Soc.* 3076.
[32] BECKETT A. H. and HARPER N. J. (1957) 858.
[33] BEECHER H. K. (1951) *Bull. Narcotics U.N. Dep. Social Affairs* **3**, 9.
[34] BEECHER H. K., DEFFER P. A., FINK F. E. and SULLIVAN D. H. (1951) *U.S. Armed Forces Med. J.* **2**, 1269.
[35] BEECHER H. K. (1952) *J. Pharmacol. Exp. Therap.* **106**, 372.
[36] BEECHER H. K. (1952b) *Science* **116**, 157.
[37] BEECHER H. K. (1953) *J. Pharmacol. Exp. Therap.* **108**, 158.
[38] BEECHER H. K. (1956) *J. Amer. Med. Ass.* **161**, 1609.
[39] BEECHER H. K. (1957) *Pharmacol. Revs.* **9**, 59.
[40] BENOIT G., DELAVIGNE R. and ELIOPOULO F. (1952) *Ann. Pharm. Franç.* **10**, 181.

[41] BENOIT G., JACOB J. and ELIOPOULO F. (1951) *C.R. Acad. Sci., Paris* **232**, 1262.
[42] BERGEL L. and MORRISSON A. (1948) *Quart. Revs. (London)* **2**, 349.
[43] BERTRAND J. and LESPAGNOL A. (1950) *C.R. Acad. Sci., Paris* **230**, 1480.
[44] BEZEM K. K. and SCHALY G. (1958) *Ned. Tdschr. Gen.* **102**, 1648.
[45] BHATTACHARYA K. B. (1956) *Arch. intern. Pharmacodyn.* **104**, 285.
[46] BIANCHI C. (1954) *Brit. J. Pharmacol.* **9**, 280.
[47] BLAKE A. D. (1958) *Clin. Med.* **5**, 773.
[48] BLICKE F. F. (1950) *U.S. Pat.* 2513270; *Chem. Abstr.* **45**, 5187.
[49] BLICKE F. F. and KRAPCHO J. (1952) *J. Amer. Chem. Soc.* **74**, 4001.
[50] BLICKE F. F. and TSAO E. P. (1953) *J. Amer. Chem. Soc.* **75**, 5587.
[51] BLICKE F. F. and TSAO E. P. (1954) *J. Amer. Chem. Soc.* **76**, 2203.
[52] BOCKMÜHL M. and EHRHART G. (1949) *Liebig's Ann.* **561**, 52.
[53] BOLT R. J., BRATT H. and POLLARD H. M. (1953) *Gastroenterology* **24**, 204.
[54] BONNYCASTLE D. D., COOK L. and IPSEN J. (1953) *Acta Pharmacol. Toxicol.* **9**, 331.
[55] BONNYCASTLE D. D. and LEONARD C. S. (1950) *J. Pharmacol. Exp. Therap.* **100**, 141.
[56] BOSS E. G. and BUCHANAN G. C. (1957) *Gastroenterology* **33**, 730.
[57] BOUDIN G. and BARBIZET J. (1958) *Presse Médicale* **66**, 131.
[58] BRAENDEN B. J. and WOLFF P. O. (1954) *Bull. World Health Organ.* **10**, 1003.
[59] BRAENDEN B. J., EDDY N. B. and HALBACH H. (1955) *Bull. World Health Organ.* **13**, 937.
[60] BRANDSTÄTTER M. (1953) *Arzneimittel-Forsch.* **3**, 33.
[61] BREINLICH J. (1953) *Arzneimittel-Forsch.* **3**, 93.
[62] BRISTOL (1951) *Belg. Pat.* 504085 .
[63] BRISTOL (1953a) *U.S. Pat.* 2632762.
[64] BRISTOL (1953b) *U.S. Pat.* 2647926; *Chem. Abstr.* **48**, 9405.
[65] BRISTOL (1953c) *U.S. Pat.* 2649445; *Chem. Abstr.* **48**, 9405.
[66] BRISTOL (1958) *U.S. Pat.* 2823233 .
[67] BRODE W. R. and HILL M. W. (1947) *J. Amer. Chem. Soc.* **69**, 724.
[68] BRODE W. R. and HILL M. W. (1948) *J. Org. Chem.* **13**, 191.
[69] BUCHEL L. and TANGUY O. (1956) *Anesthésie et Analgésie* **13**, 879.
[70] BUCHEL L., LÉVY J. and TANGUY O. (1957) *Anesthésie et Analgésie* **14**, 469.
[71] BURCKHALTER J. H. and JOHNSON S. H. (1951) *J. Amer. Chem. Soc.* **73**, 4830.
[72] BURTNER R. R. (1954) *Fourth National Medicinal Chemistry Symposium of the A.C.S.* pp. 1–28.
[73] CAHAL D. A. (1957) *Brit. J. Pharmacol.* **12**, 97.
[74] CAHAL D. A. (1958) *Brit. J. Pharmacol.* **13**, 30.
[75] CAHEN R. L., EPSTEIN H. J. and KREMENTZ C. S. (1948) *J. Pharmacol. Exp. Therap.* **94**, 328.
[76] CAHEN R. L., GROSKINSKY E. and PARISEK P. (1956) *Proc. Soc. Exp. Biol. Med.* **92**, 305.
[77] CALESNICK B. (1957) *Fed. Proc.* **16**, 287.
[78] CALESNICK B. (1958) *Fed. Proc.* **17**, 356.
[79] CAPRARO V. (1948) *Il Farmaco* **3**, 137.
[80] CARDENAS G. E. (1958) *Arch. Criminol., Neuro-psiquiatria y Discipl. Conexas* **6**, 200.
[81] CARNEY T. P. (1956) *Medicinal Chem.* **3**, 1.
[82] CAROL J. (1954) *J. Assoc. Offic. Agr. Chem.* **37**, 692.
[83] CAROLI J. and CHARBONNIER A. (1957) *Revue du Foie* **32**, 41.
[84] CASTEL P., ATTISSO M. and SERRE L. (1957) *Trav. Soc. Chim. Montpellier* **17**, 100.
[85] CAYER D., SOHMER M. F. and SUGG W. C. (1957) *North Carolina Med. J.* **18**(8), 311.
[86] CAZORT R. J. (1950) *J. Pharmacol. Exp. Therap.* **100**, 325.
[87] CHENEY L. C., SMITH R. R. and BINKLEY S. B. (1949) *J. Amer. Chem. Soc.* **71**, 53.
[88] CHENEY L. C., WHEATLEY W. B., SPEETER M. E., BYRD W. M., FITZGIBBON W. E., MINOR W. F. and BINKLEY S. B. (1952) *J. Org. Chem.* **17**, 770.

[89] CHEN K. K. (1948) *Ann. N.Y. Acad. Sci.* **51**, 83.
[90] CHRISTENSEN E. M. and GROSS E. G. (1948) *J. Amer. Med. Ass.* **137**, 594.
[91] *Chugai Drug Manufacturing Corporation Pat.* (Kawabata H.) (1950) *Japan* 1528; *Chem. Abstr.* **47**, 1743.
[91a] Ciba (1944) *Brit. Pat.* 565745; *Chem. Abstr.* **40**, 5534.
[92] CLARKE R. L., MOORODIAN A., LUCAS P. and SLANSON T. J. (1949) *J. Amer. Chem. Soc.* **71**, 2821.
[93] COCCHI A. (1950) *Semana Medica* **112**, 497.
[94] CLARKE R. L. and MOORODIAN A. (1949) *J. Amer. Chem. Soc.* **71**, 2825.
[95] COLEMAN D. J., LEVIN J. and JONES P. O. (1957) *Brit. Med. J.* 1092.
[96] COOK L. and BONNYCASTLE D. D. (1953) *J. Pharmacol. Exp. Therap.* **109**, 35.
[97] COOKSON R. C. and WARIYAR N. S. (1956) *J. Chem. Soc.* 2302.
[98] CRAIG P. N. (1952) *J. Amer. Chem. Soc.* **74**, 129.
[99] CRAIG P. N. and RUMP E. S. JR. (1957) *J. Org. Chem.* **22**, 510.
[100] CRONHEIM G. and WARE P. A. (1948) *J. Pharmacol. Exp. Therap.* **92**, 98.
[101] CUNNINGHAM R. W., HARNED B. K., CLARKE M. C., COSGROVE R. R., DAUGHERTY N. S., HINE C. H., VESSEY R. E. and YUDA N. N. (1949) *J. Pharmacol. Exp. Therap.* **96**, 151.
[102] CURRY A. S. and POWELL H. (1954) *Nature, Lond.* **173**, 1143.
[103] CUSIC J. (1946) *J. Amer. Chem. Soc.* **71**, 3546.
[104] CYMERMAN-CRAIG J. and GILBERT W. S. (1952) *J. Chem. Soc.* 3529.
[105] CYMERMAN-CRAIG J. and HARRISSON R. J. (1955) *Australian J. Chem.* **8**, 378.
[106] CYMERMAN-CRAIG J. and HARRISSON R. J. (1956) *Australian J. Chem.* **9**, 89.
[107] DAVID M. and DELIGNÉ P. (1957) *Presse Médicale* **65**, 731.
[108] DAVID N. A., CARTER P. and WELBORN W. S. (1957) *J. Pharmacol. Exp. Therap.* **119** 140.
[109] DAVID N. A., SEMLER H. J. and BURGNER P. R. (1956) *J. Amer. Med. Assoc.* **161**, 599.
[110] DAVIS M. E., ANDROS G. J. and KING A. G. (1952) *J. Amer. Med. Assoc.* **148**, 1193.
[111] DE JONGH D. K. and VAN PROOSDIJ-HARTZEMA E. G. (1957) *J. Pharm. Pharmacol.* **9**, 730.
[112] DELIGNÉ P. and GILLES R. M. (1957) *Anesthésie et Analgésie* **14**, 51.
[113] DELIGNÉ P. and GILLES R. M. (1958) *Anesthésie et Analgésie* **15**, 206.
[114] DEMONCEAU J. (1952) *J. Pharm. Belg.* **7**, 36.
[115] DEN OTTER G. (1958) *Ned. Tdschr. Gen.* **102**, 1637.
[116] DENTON J. E. and BEECHER H. K. (1949a) *J. Amer. Med. Assoc.* **141**, 1051.
[117] DENTON J. E. and BEECHER H. K. (1949b) *J. Amer. Med. Assoc.* **141**, 1146.
[118] DENTON J. J., STRAUSS O. H., WADDELL W. E. and BEECHER H. K. (1948) *Fed. Proc.* **7**, 214.
[119] DENTON J. J., LAWSON V. A., NEIER W. B. and TURNER R. J. (1949a) *J. Amer. Chem. Soc.* **71**, 2050.
[120] DENTON J. J., SCHEDL H. P., NEIER W. B. and LAWSON V. A. (1949b) *J. Amer. Chem. Soc.* **71**, 2054.
[121] DENTON J. J. and LAWSON V. A. (1950a) *J. Amer. Chem. Soc.* **72**, 3279.
[122] DENTON J. J., SCHEDL H. P., LAWSON V. A. and NEIER W. B. (1950b) *J. Amer. Chem. Soc.* **72**, 3795.
[123] DICKISON. Private Communication; see BURTNER 1954.
[124] DORPH M. H. (1957) *Medical Science* **2**(8), 18.
[125] DOUIN J. (1958) *Revue Méd. Liège* **13**, 332.
[126] DUPRÉ D. J., ELKS J., HEMS B. A., SPEYER K. N. and EVANS R. M. (1949) *J. Chem. Soc.* 500.
[127] DYRBERG V. and ANDERSEN E. W. (1958) *Acta Chirurgica Scandinavica* **115**, 243.

[128] EASTON N. R., GARDNER J. H. and STEVENS J. R. (1947a) *J. Amer. Chem. Soc.* **69**, 976.
[129] EASTON N. R., GARDNER J. H. and STEVENS J. R. (1947b) *J. Amer. Chem. Soc.* **69**, 2941.
[130] EASTON N. R., GARDNER J. H., EVANICK M. L. and STEVENS J. R. (1948) *J. Amer. Chem. Soc.* **70**, 76.
[131] EASTON N. R., BARTON L. R., MEINHOFER F. L. and FISH V. B. (1953a) *J. Amer. Chem. Soc.* **75**, 2086.
[132] EASTON N. R., NELSON S. J., FISH V. B. and CRAIG P. N. (1953b) *J. Amer. Chem. Soc.* **75**, 3751.
[133] EASTON N. R. and FISH V. B. (1954), *J. Amer. Chem. Soc.* **76**, 2836.
[134] EASTON N. R. and FISH V. B. (1955) *J. Amer. Chem. Soc.* **77**, 2547.
[135] EASTON N. R., LUKACH C. A., NELSON S. J. and FISH V. B. (1958) *J. Amer. Chem. Soc.* **80**, 2519.
[136] EBERMANN H. (1954) *Münch. Med. Wchschr.* **96**, 922.
[137] EDDY N. B. (1947) *J. Amer. Pharm. Ass.* **8**, 536.
[138] EDDY N. B., TOUCHBERRY C. F. and LIEBERMAN J. E. (1950) *J. Pharmacol. Exp. Therap.* **98**, 121.
[139] EDDY N. B., MAY E. L. and MOSETTIG E. (1952) *J. Org. Chem.* **17**, 321.
[140] EDDY N. B. and LEIMBACH D. (1953) *J. Pharmacol. Exp. Therap.* **107**, 385.
[141] EDDY N. B. (1956a) *J. Chronic Diseases* **4**, 59.
[142] EDDY N. B. (1956b) *J. Amer. Geriatrics Soc.* **4**, 177.
[143] EDDY N. B., HALBACH H. and BRAENDEN O. J. (1956c) *Bull. World Health Organ.* **14**, 353.
[144] EDDY N. B., HALBACH H. and BRAENDEN O. J. (1957) *Bull. World Health Organ.* **17**, 569.
[144a] EDDY N. B., Personal communication.
[145] EHRHART G. and SCHAUMANN O. (1949) *Med. Wchschr.* **8**, 605.
[146] EHRHART G. (1956) *Bull. Narcotics U.N. Dept. Social Affairs* **8**, 28.
[147] EISENBRANDT L. L., ADLER T. K., ELLIOTT W. H. and ABDON I. A. (1950) *J. Pharmacol. Exp. Therap.* **98**, 200.
[148] EISLEB O. (1941) *Ber. Deutsch. Chem. Ges.* B **74**, 1433.
[149] ELLIOTT H. W., CHANG F. N. H., ABDOU I. A. and ANDERSON H. H. (1949) *J. Pharmacol. Exp. Therap.* **95**, 494.
[150] ERLENBACH M. and SIEGLITZ A. (1953) *Brit. Pat.* 685616; *Chem. Abstr.* **48**, 3396.
[151a] ERLENBACH M. and SIEGLITZ A. (1953) *Brit. Pat.* 692931; *Chem. Abstr.* **48**, 10776.
[151b] EVERETT F. G. (1948) *Anesthesiology* **9**, 115.
[152] FABER J. S. (1950) *Pharm. Wkbl.* **85**, 719
[153] FARMILO C. G., ROSS R. J., BERRY S. and KENNETT P. M. L. (1950) *Bull. Narcotics U.N. Dept. Social Affairs* **2**(2), 21.
[154] FARMILO C. G. and LEVI L. (1953) *Bull. Narcotics U.N. Dept. Social Affairs* **5**(4), 20
[155] FELLOWS E. J. and ULLYOT G. E. (1951) *Medicinal Chem.* **1** 390.
[156] FINNEGAN J. K., HAAG H. B., LARSON P. S. and DREYFUSS M. L. (1948) *J. Pharmacol. Exp. Therap.* **92**, 269.
[157] FISCHER R. and KARAWIA M. S. (1953) *Microchim. Acta* 366.
[158] FOSTER G. E. and HALL G. F. (1952) *J. Pharm. Pharmacol.* **4**, 1088.
[159] FRAZER H. F. and ISBELL H. (1952) *J. Pharmacol. Exp. Therap.* **105**, 458.
[160] FRAZER H. F., NASH T. L., VANHORN G. D. and ISBELL H. (1954) *Arch. intern. Pharmacodyn.* **98**, 443.
[161] FREE S. M. and PEETERS F. (1958) *J. Chronic Diseases* **7**, 379.
[162] FRIEBEL H., REICHLE C. and VON GRAEVENITZ A. (1955a) *Naunyn Schmiedeberg's Arch. Exp. Pathol. Pharmakol.* **224**, 384.

[163] FRIEBEL H. and REICHLE C. (1955b) *Naunyn Schmiedeberg's Arch. Exp. Pathol. Pharmakol.* **226**, 551, 558.
[164] FRIEBEL H. and REICHLE C. (1956) *Naunyn Schmiedeberg's Arch. Exp. Pathol. Pharmakol.* **229**, 400.
[165] FRIES B. (1958) *Svenska Laekartidningen* **55**, 1479.
[166] GARDNER J. H., EASTON R. R. and STEVENS J. R. (1948) *J. Amer. Chem. Soc.* **70**, 2906.
[167] GARVEN J. D. (1956) *J. Pharm. Pharmacol.* **8**, 256.
[168] GERO A. (1954) *Science* **119**, 112.
[169] GILLHESPY R. O., COPE E. and JONES P. O. (1956) *Brit. Med. J.* **2**, 1094.
[170] GITTOS M. W. and WILSON W. (1955) *J. Chem. Soc.* 2371.
[171] GLASEBROOK A. J. (1949) *Edinburgh Med. J.* **56**, 206.
[172] GLAXO (HEMS B. A. and ELKS J.) (1949) *Brit. Pat.* 627280; *Chem. Abstr.* **44**, 3536.
[173] GLAXO (HEMS B. A. and ELKS J.) (1950) *U.S. Pat.* 2513173; *Chem. Abstr.* **44**, 9988.
[174] GOLDBAUM L. R. and KAZYAK L. (1956) *Analyt. Chem.* **28**, 1289.
[175] GRAVENSTEIN J. S., PEDERSON D. P. and BEECHER H. K. (1957) *Fed. Proc.* **16**, 302.
[176] GREEN A. F., YOUNG P. A. and GODFREY E. I. (1951) *Brit. J. Pharmacol.* **6**, 572.
[177a] GREEN A. F. and WARD N. B. (1955) *Brit. J. Pharmacol.* **10**, 418.
[177b] GREWAL R. S. (1952) *Brit. J. Pharmacol.* **7**, 433.
[178] GROSSMAN M. I. (1958) *Gastroenterology* **35**, 312.
[179] GRUBER C. JR., LEE K. S. and GRUBER C. M. (1950) *J. Pharmacol. Exp. Therap.* **99**, 317.
[180] GUNDERSEN F. O., HEIZ R. and KLEVSTRAND R. (1953) *J. Pharm. Pharmacol.* **5**, 608.
[181] HAAS H., HOHAGEN E. and KOLLMANNSPERGER G. (1953) *Arzneimittel-Forsch.* **3**, 238.
[182] HANELAND G. T. (1958) *Ned. Tdschr. Gen.* **102**, 731.
[183] HARFENIST M. and MAGNIEN (1956) *J. Amer. Chem. Soc.* **78**, 1060.
[184] HARPER N. J. (1957) *Mfg. Chemist* **28**, 213, 271, 322.
[185] HAUSER C. R., TETENBAUM M. T. and YOST R. S. (1958) *J. Org. Chem.* **23**, 916.
[186] HAÜSSLER A. (1950) *Süddeut. Apoth. Ztg.* **90**, 423.
[187] HAÜSSLER A. (1956) *Arzneimittel-Forsch.* **6**, 142.
[188] HEADLEE C. P. and EDWARDS L. D. (1955) *J. Amer. Pharm. Ass.* **44**, 743.
[189] HENDERSON F. G. and CHENN K. K. (1948) *Proc. Soc. Exp. Biol. Med.* **68**, 350.
[190] HENDERSON F. G., ROBBINS E. B. and CHENN K. K. (1949) *Arch. int. Pharmacodyn.* **79**, 282.
[191] HERR F. and PÓRSZÁSZ J. (1950a) *Naunyn Schmiedeberg's Arch. Exp. Pathol. u. Pharmakol.* **210**, 289.
[192] HERR F. and PÓRSZÁSZ J. (1950b) *Naunyn Schmiedeberg's Arch. Exp. Pathol. u. Pharmakol.* **210**, 294.
[193] HERR F., NYIRI M. and VENULET J. (1952) *Acta Physiol. Acad. Sci. Hung.* **3**, 199.
[194] HERR F., BORSI J. and PATAKY G. (1953a) *Acta Physiol. Acad. Sci. Hung.* **4**, 363.
[195] HERR F., TARDOS L. and PÓRSZÁSZ J. (1953b) *Acta Physiol. Acad. Sci. Hung.* **4**, 123.
[196] HERR F., NÁDOR K., PATAKY G. and BORSI J. (1953c) *Naunyn Schmiedeberg's Arch. Exp. Pathol. u. Pharmakol.* **217**, 447.
[197] HERR F., BORSI J. and PATAKY G. (1954a) *Naunyn Schmiedeberg's Arch. Exp. Pathol. u. Pharmakol.* **223**, 56.
[198] HERR F., BORSI I. and SZEGI J. (1954b) *Acta Sci. Hung.* **6**, 363.
[199] HILDEBRANDT F. and MATTHÄY E. (1954) *Naunyn Schmiedeberg's Arch. Exp. Pathol. u. Pharmakol.* **221**, 399.

[200] HOECHST A.G. (or I.G. FARBEN A.G.) (1941a) *D.R. Pat.* 70929; [201] (1941b) *D.R. Pat.* 710227; [202] (1941c) *D.R. Pat.* 711069; [203] (1943a) *D.R. Pat.* 731560; (1944) *Chem. Abstr.* **38**, 551; [204] (1943b) *Brevet franç.* 883539; [205] (1944) *Brevet franç.* 890633; [206] (1949) *D.B. Pat.* 858552; [207] (1952a) *D.R. Pat.* 833043, *Chem. Abstr.* **50**, 1918; [208] (1952b) *D.B. Pat.* 837849, *Chem. Abstr.* **51**, 14834; [209] (1952c) *D.B. Pat.* 849696, *Chem. Abstr.* **47**, 5453; [210] (1954) *Brit. Pat.* 708859, *Chem. Abstr.* **50**, 4235; [211] (1955a) *Dutch Pat.* 79079; [212] (1955b) *D.B. Pat.* 925468, *Chem. Abstr.* **52**, 3869.

[213] HOEKSTRA J. B. and DICKISON H. L. (1954a) **98**, 14.

[214] HOEKSTRA J. B., TISCH D. E., RAKIETEN N. and DICKISON H. L. (1954b) *J. Pharmacol. Exp. Therap.* **110**, 55.

[215] HOEKSTRA J. B., FISCHER D. S. and DICKISON H. L. (1956) *J. Pharmacol. Exp. Therap.* **116**, 29.

[216] HOFFMANN C. R. (1957) *Amer. J. Gastroenterol.* **28**, 446.

[217] HOFFMANN W. (1953) *Arzneimittel-Forsch.* **3**, 364, 440.

[218] HORN D. (1954) *Pharmazeut. Zth.* **93**, 182.

[219] HOUGS-OLSEN W. and SKOUBY A. P. (1947) *Acta Pharmacol. Toxicol.* **13**, 405.

[220] HOUGS-OLSEN W. (1949) *Acta Pharmacol. Toxicol.* **5**, 33.

[221] HOWE E. E. and SLETZINGER M. (1949) *J. Amer. Chem. Soc.* **71**, 2935.

[222] HUBACH C. E. and JONES F. T. (1950) *Analyt. Chem.* **22**, 595.

[223] I.G. FARBEN INDUSTRIE. See HOECHST.

[224] ISBELL H., WIKLER A., EDDY N. B., WILSON J. L. and MORAN C. F. (1947) *J. Amer. Med. Ass.* **135**, 888.

[225] ISBELL H., EISENMAN A. J., WIKLER A. and FRANK K. (1948a) *J. Pharmacol. Exp. Therap.* **92**, 83.

[226] ISBELL H. and EISENMAN A. J. (1948b) *J. Pharmacol. Exp. Therap.* **93**, 305.

[227] ISBELL H. and EISENMAN A. J. (1948c) *Fed. Proc.* **7**, 162.

[228] ISBELL H. and VOGEL V. H. (1949) *Amer. J. Psychiat.* **105**, 909.

[229] ISBELL H. and FRAZER H. F. (1950) *Pharmacol. Revs.* **2**, 355.

[230] ISBELL H. and FRAZER H. F. (1955) *J. Pharmacol. Exp. Therap.* **113**, 30.

[231] JACKSON H. (1952) *Brit. J. Pharmacol.* **7**, 196.

[232] JACOB J., BLOZOVSKI M. and ECHINARD-GARIN P. (1958) *Thérapie* **13**, 17.

[233] JAGENEAU A. and JANSSEN P. (1956) *Arch. int. Pharmacodyn.* **106**, 199.

[234] JANSSEN P., ZIVKOVIC D. and DEMOEN P. (1955a) *J. Amer. Chem. Soc.* **77**, 4423.

[235] JANSSEN P., ZIVKOVIC D., DEMOEN P., DE JONGH D. K. and VAN PROOSDIJ-HARTZEMA E. G. (1955b) *Arch. int. Pharmacodyn.* **103**, 82.

[236] JANSSEN P., ZIVKOVIC D. and DEMOEN P. (1956a) *J. Amer. Chem. Soc.* **78**, 3862.

[237] JANSSEN P. and JAGENEAU A. (1956b) *Experientia* **12**, 293.

[238] JANSSEN P., ZIVKOVIC D., JAGENEAU A. and DEMOEN P. (1956c) *Arch. int. Pharmacodyn.* **107**, 194.

[239] JANSSEN P. (1956d) *Verhandl. Kon. Vl. Akad. Gen. België* **18**, 136.

[240] JANSSEN P. (1956e) *Over de pharmacologie van een reeks propylaminen.* Thesis, University of Ghent.

[241] JANSSEN P. and JAGENEAU A. (1957) *J. Pharm. Pharmacol.* **9**, 381.

[242] JANSSEN P. and JAGENEAU A. (1958) *J. Pharm. Pharmacol.* **10**, 14.

[243] JATZKEWITZ H. (1953) *Z. Physiol. Chem.* **292**, 94.

[244] JILÈK J. O., BOROVICKA M. and PROTIVA M. (1952) *Chem. Listy* **46**, 292.

[245] KARCZMAR A. G. and LONG J. P. (1958) *J. Pharmacol. Exp. Therap.* **123**, 230.

[246] KASE Y., KAKU J., YAMAMOTO Y., TANAKA M., TAKASAKI Y. and NAGAO K. (1955) *Pharm. Bull. (Japan)* **3**, 394.

[247] KAWABATA H., NITTA Y. and KASAI T. (1949) *J. Pharm. Soc. Japan* **69**, 190.

[248] KEATS A. S. and BEECHER H. K. (1952a) *J. Pharmacol. Exp. Therap.* **105**, 109.

[249] KEATS A. S. and BEECHER H. K. (1952b) *J. Pharmacol. Exp. Therap.* **105**, 210.

[250] KEATS A. S. (1958) *Fed. Proc.* **17**, 383.

[251] KEELE C. A. (1952) *Analyst* **77**, 111.

[252] KING F. E., LATHAM K. G. and PARTRIDGE M. W. (1952) *J. Chem. Soc.* 4268.

[253] KING T. O. (1957a) *Arch. int. Pharmacodyn.* **110**, 71.

[254] KING T. O., POULSEN E. and ROVATI C. A. (1957b) *Arch. int. Pharmacodyn.* **110**, 77.

[255] KIRSNER J. B., PALMER W. L., LEVIN E. and KLOTZ A. P. (1951) *Ann. Int. Med.* **35**, 785.

[256] KIRSNER J. B. and PALMER W. L. (1953a) *J. Amer. Med. Ass.* **151**, 798.

[257] KIRSNER J. B., LEVIN E.. PALMER W. L., FORD H. and MAHAFFEY J. (1953) *Gastroenterology* **23**, 199.

[258] KJAER A. C. and PETERSEN P. V. (1951) *Acta Chem. Scand.* **5**, 1145.

[259] KLEIDERER E. C., RICE J. B., CONQUEST V. and WILLIAMS J. H. (1945) *Report No.* PB-981 (Office of the Publication Board, Dept. of Commerce, Washington D.C.).

[260] KLENK M. M., SUTER C. M. and ARCHER S. (1948) *J. Amer. Chem. Soc.* **70**, 3846.

[261] KLOSA J. (1953) *Chem. Techn. (Berlin)* **5**, 375.

[262] KLOSA J. (1953) *Arch. Pharm.* **286**, 104.

[263] KNOLL J., KOMLÓS E. and PÓRSZÁSZ J. (1951) *Acta Physiol. Acad. Sci. Hung.* **2**, 479.

[264] KNOLL J., KOMLÓS E. and TARDOS L. (1953) *Acta Physiol. Acad. Sci. Hung.* **4**, 131.

[265] KOMLÓS E. and KNOLL J. (1952) *Acta Physiol. Acad. Sci. Hung.* **3**, 123.

[266] KÖNIG R. and MAGYAR K. (1950) *Magyar Kém. Folyóirat* **56**, 77.

[267] KOURY J. S. (1958) *Med. Bull. Harrisburg Polyclin. Hosp.* **2**, 12.

[268] KRAPCHO J. (1951) *Univ. Microfilms, Public. No.* 2417; *Chem. Abstr.* **45**, 8205.

[269] KRAUSE D. and RUHNAN D. (1952) *Naunyn Schmiedeberg's Arch. Exp. Pathol. u. Pharmakol.* **216**, 541.

[270] KRAUSHAAR A. (1953) *Arzneimittel-Forsch.* **3**, 247.

[271] KUMLER W. D., STRAIT L. A. and ALPEN L. E. (1950) *J. Amer. Chem. Soc.* **72**, 1463.

[272] LA BARRE J. and DESMAREZ J. J. (1958a) *Arch. int. Pharmacodyn.* **114**, 480.

[273a] LA BARRE J., DESMAREZ J. J. and DUMONT J. (1958b) *Bull. Acad. Roy. Méd. Belg.* **23**, 313.

[273b] LA BELLE A. and TISLOW R. (1955) *J. Pharmacol. Exp. Therap.* **113**, 72.

[274] LABORATORIA PHARMACEUTICA DR. C. JANSSEN and NEDCHEM (1957a) *Belg. Pat.* 554757; [275] (1957b) *Belg. Pat.* 558781; [276] (1957c) *Brit. Pat.* 772921, *Chem. Abstr.* **52**, 1252.

[277] LANDS A. M. and NASH V. L. (1944) *Proc. Soc. Exp. Biol. Med.* **57**, 55.

[278] LANDS A. M., NASH V. L. and HOOPER K. Z. (1946) *J. Pharmacol. Exp. Therap.* **86**, 129.

[279] LANDS A. M., ANANENKO E., JONES G., HOPPE J. O. and BECKER T. J. (1949) *J. Pharmacol. Exp. Therap.* **96**, 1.

[280] LANDS A. M. (1951) *J. Pharmacol. Exp. Therap.* **102**, 219.

[281] LANDS A. M. and LUDUENA F. P. (1956a) *J. Pharmacol. Exp. Therap.* **116**, 177.

[282] LANDS A. M. and LUDUENA F. P. (1956b) *J. Pharmacol. Exp. Therap.* **117**, 331.

[283] LANGERON L., PAGET M. and VINCENT G. (1958) *J. Sci. Méd. Lille* 3.

[284] LARSEN A. A., TULLAR B. F., ELPERN B. and BUCK J. S. (1948) *J. Amer. Chem. Soc.* **70**, 4194.

[285] LEBOURG L., MUGNIER A. and LAUFER J. (1958) *Rev. Stomatologie* **59**, 243.

[286] LEIMBACH D. and EDDY N. B. (1954) *J. Pharmacol. Exp. Therap.* **110**, 135.

[287] LESPAGNOL A. (1951) *Actualités Pharmacol.* **3**, 27.

[288] LEVI L. and FARMILO C. G. (1952) *Canad. J. Chem.* **30**, 783, 793.

[289] LEVI L. and FARMILO C. G. (1953) *Bull. Narcotics U.N. Dept. Social Affairs* **5**(1), 15.

[290] LEVI L., HUBLEY C. E. and HINGE R. A. (1955) *Bull. Narcotics U.N. Dept. Social Affairs* **7**(1), 42.

[291] LEWIS J, R. (1949) *J. Pharmacol. Exp. Therap.* **96**, 31.

[292] LINDNER E. (1949) *Süddeut. Apoth. Ztg.* **89**, 449.
[293a] LINDNER E. (1955a) *Naunyn Schmiedeberg's Arch. Exp. Pathol. u. Pharmakol.* **224**, 357.
[293b] LINDNER E. (1955a) *Naunyn Schmiedeberg's Arch. Exp. Pathol. u. Pharmakol.* **224**, 357.
[294] LINDNER E. (1955b) *Z. Geburtshilfe* **144**, 53.
[295] LINDNER E. (1956) *Arzneimittel-Forsch.* **6**, 124.
[296] LONG J. P., LUDUENA F. P., TULLAR B. F. (1956a) *J. Pharmacol. Exp. Therap.* **116**, 39.
[297] LONG J. P., LUDUENA F. P., TULLAR B. F. and LANDS A. M. (1956b) *J. Pharmacol. Exp. Therap.* **117**, 29.
[298] LONG J. P. and LANDS A. M. (1957a) *J. Pharmacol. Exp. Therap.* **119**, 162.
[299] LONG J. P. and LANDS A. M. (1957b) *J. Pharmacol. Exp. Therap.* **120**, 46.
[300] LUDUENA F. P. and ANANENKO E. (1950) *Arch. int. Pharmacodyn.* **81**, 259.
[301] LUDUENA F. P. and LANDS A. M. (1954) *J. Pharmacol. Exp. Therap.* **110**, 282.
[302] LUNDBECK AND COMPANY (1956) *Dan. Pat.* 81034, *Chem. Abstr.* **51**, 2042.
[303] MACCOUBREY A. (1956) *J. Pharm. Pharmacol.* **8**, 800.
[304] MACDONALD A. D., WOOLFE G., BERGEL F., MORRISSON A. L. and RINDERKNECHT H. (1946) *Brit. J. Pharmacol.* **1**, 4.
[305] MACMAGNUS E. C., O'NEILL G. A., BRAUNSCHWEIG L., MCKINNEY S. E. and BEYER K. H. (1954) *Fed. Proc.* **13**, 386.
[306] MAGIDSON O. Y. and FEDOSOVA V. M. (1957) *Med. Prom. S.S.S.R.* **11**, 25.
[307] MALLINCKRODT (STOUGHTON R.) (1951) *U.S. Pat.* 2540636; *Chem. Abstr.* **45**, 6661.
[308] MALLINCKRODT (STOUGHTON R.) (1954) *U.S. Pat.* 2670375; *Chem. Abstr.* **49**, 2508.
[309] MARCH C. H., GORDAN G. S. and WAY E. L. (1950) *Arch. int. Pharmacodyn.* **83**, 270.
[310] MARCINKOWSKI T. (1949) *Polska Akad. Umiezetnöski* **11**, No. 3.
[311] MARIQUE P. and MAQUET N. (1958) *Scalpel* **111**, 515.
[312] MARQUART P., MEYER H. J. and SCHUMACHER H. (1957) *Arzneimittel-Forsch.* **7**, 457.
[313] MARSHALL P. B. (1953) *Brit. J. Pharmacol.* **10**, 270.
[314] MASSON A. H. B. (1956) *Anaesthesia* **11**, 59.
[315] MAY E. L. and MOSETTIG E. (1948) *J. Org. Chem.* **13**, 459, 663.
[316] MAY E. L. and EDDY N. B. (1952) *J. Org. Chem.* **17**, 1210.
[317] MAY E. L. and PERRINE T. D. (1953) **18**, 1572.
[318] MAZONI D. (1953) *C.R. Acad. Sci., Paris* **236**, 1898.
[319] MELANDER B. O., SUNBECK B. and WILLSTAEDT H. C. (1950) *Swed. Pat.* 128376; *Chem. Abstr.* **44**, 9481.
[320] MENDES F., DOS SANTOS J. and SOEIRO N. (1958) *Presse Médicale* **66**, 1356.
[321] MENSCH M. H. (1958) Thesis, University Utrecht.
[322] MERCK (RAHWAY) (1950a) *U.S. Pat.* 2497739, *Chem. Abstr.* **44**, 5912; [323] (1950b) *U.S. Pat.* 2508322, *Chem. Abstr.* **44**, 7356; [324] (1951a) *U.S. Pat.* 2538130, *Chem. Abstr.* **45**, 6660; [325] (1951b) *U.S. Pat.* 2565592, *Chem. Abstr.* **46**, 8677; [326] (1951c) *U.S. Pat.* 2574505, *Chem. Abstr.* **46**, 5088; [327] (1952) *U.S. Pat.* 2607794, *Chem. Abstr.* **47**, 5966; [328] (1953a) *U.S. Pat.* 2625564, *Chem. Abstr.* **47**, 11252; [329] (1953b) *U.S. Pat.* 2644010, *Chem. Abstr.* **48**, 5222; [330] (1953c) *U.S. Pat.* 2689777, *Chem. Abstr.* **47**, 7534; [331] (1954a) *U.S. Pat.* 2668814, *Chem. Abstr.* **49**, 2508; [332] (1954b) *U.S. Pat.* 2671798.
[333] MILLER J. W. and ELLIOTT H. W. (1954) *J. Pharmacol. Exp. Therap.* **110**, 106.
[334] MILLER J. W. and ELLIOTT H. W. (1955) *J. Pharmacol. Exp. Therap.* **113**, 283.
[335] MILOSEVIĆ M. P. (1955) *Arch. int. Pharmacodyn.* **104**, 50.
[336] MOFFETT R. B. and ASPERGREN B. D. (1953) *Abstracts of papers, Div. Med. Chem., Am. Chem. Soc. Meeting*, p. 8 L.
[337] MOFFETT R. B. (1956) *Abstracts of papers, Div. Med. Chem., Am. Chem. Soc. Meeting*, p. 4 N.
[338] MOFFETT R. B. and ASPERGREN B. D. (1957) *Abstracts of papers, Div. Med. Chem., Am. Chem. Soc. Meeting.*

[339] MOFFETT R. B. (1957a) *J. Amer. Chem. Soc.* **79**, 3186.
[340] MOFFETT R. B. (1957b) *J. Amer. Chem. Soc.* **79**, 4451.
[341] MOFFETT R. B. (1957c) *J. Amer. Chem. Soc.* **79**, 4457.
[342] MOFFETT R. B. (1957d) *J. Amer. Chem. Soc.* **79**, 4462.
[343] MORREN H., ZIVKOVIC D. and LEVIS S. (1957) *J. Pharm. Belg.* 128.
[345] MORRISSON A. L. and RINDERKNECHT H. (1950a) *J. Chem. Soc.* 1478.
[346] MORRISSON A. L. and RINDERKNECHT H. (1950b) *J. Chem. Soc.* 1510.
[347a] MORRISSON A. L., LONG R. F. and KÖNINGSTEIN M. (1951) *J. Chem. Soc.* 952.
[347b] MORRISSON S. (1958) *Amer. J. Gastroenterol.* **29**, 518.
[348] MULLIE A. (1956a) *Arch. intern. Pharmacodyn.* **106**, 447.
[349] MULLIE A. (1956b) *Acta Medica Scand.* **155**, 257.
[350] MURPHY E., GRIFFITH W. B., CARTER P. B. and DAVID N. (1957) *J. Pharmacol. Exp. Therap.* **119**, 172.
[350a] NACHOD F. C. and LANDS A. M. (1953) *Trans. N. Y. Acad. Sci.* **16**, 2.
[350b] NELEMANS F. A. (1958) *Ned. Tdschr. Gen.* **102**, 1661.
[350c] NELSON S. J., FISH V. B. and EASTON N. R. (1955) *J. Amer. Chem. Soc.* **77**, 1908.
[350d] NORDVALL S. (1958) *Svenska Läkartidningen* **55**, 1536.
[350e] OESTERREICHISCHE STICKSTOFFWERKE A.G. (1956) *Oesterr. Pat.* 187915; *Chem. Abstr.* **51**, 5835.
[350f] OFNER P., THORP R. H. and WALTON E. (1949) *Nature, Lond.* **163**, 479.
[350g] OFNER P., WALTON E., GREEN A. F. and WHITE A. C. (1950) *J. Chem. Soc.* 2158.
[350h] OFNER P. (1951) *J. Chem. Soc.* 1800.
[350i] OHLSSON L. (1953) *Acta Pharmacol. Toxicol.* **9**, 322.
[350j] PAROLI E. (1956) *Boll. et Atti Accad. Med. di Roma* No. 3.
[350k] PATAKY G., HERR F. and BORSI I. (1954) *Acta Physiol. Acad. Sci. Hung.* **6**, 351.
[350l] PATON W. D. M. (1957) *Brit. J. Pharmacol.* **12**, 119.
[351] PEETERS F. (1957) *Bull. Soc. Belg. Gynécol. Obstétr.* **27** (3), 265.
[352] PERRINE T. D. (1953) *J. Org. Chem.* **18**, 898.
[353] PERRINE T. D. and MAY E. L. (1954) *J. Org. Chem.* **19**, 773.
[354] PETERSEN P. V. (1951) *Acta Pharmac. Toxic. Scand.* **7**, 51.
[355] PFEIFFER C. C. (1948a) *Fed. Proc.* **7**, 255.
[356] PFEIFFER C. C., SONNENSCHEIN R. R., GLASSMAN L., JENNEY E. H. and BOGOLUB S. (1948) *Ann. N.Y. Acad. Sci.* **51**, 21.
[357] PHATAK N. M. and DAVID N. A. (1953a) *Current Researches in Anesth. and Analg.* **32**, 243.
[358] PHATAK N. M. and DAVID N. A. (1953b) *J. Pharmacol. Exp. Therap.* **109**, 139.
[359] PICCINELLI O. and TIMOSSI G. (1958) *Minerva Medica* **49**, 3.
[360] PIVONT A. and GOUGNARD L. (1958) *Soc. Belge d'Ophtalmol.* No. 117, 506.
[361] POHLAND A., MARSHALL F. J. and CARNEY T. P. (1949) *J. Amer. Chem. Soc.* **71**, 460.
[362] POHLAND A. and SULLIVAN H. R. (1953) *J. Amer. Chem. Soc.* **75**, 5898.
[363] PÓRSZÁSZ J. and HERR F. (1950) *Kisérletes Orvostud* **2**, 295.
[364] PÓRSZÁSZ J., KNOLL J. and KOMLÓS E. (1951) *Acta Physiol. Acad. Sci. Hung.* **2**, 469.
[365] PÓRSZÁSZ J., TARDOS L., HERR F. and NYIRI M. (1953) *Acta Physiol. Acad. Sci. Hung.* **4**, 107.
[366] PORTER C. C. and SILBER R. H. (1952) *J. Biol. Chem.* **182**, 109.
[367a] POWELL C. E. and CHEN K. K. (1948) *J. Amer. Pharm. Ass.* **37**, 516.
[367b] RADOUCO-THOMAS C. and NOZAL G. (1956) *Bull. Narcot.* **8**, 14.
[368] RAVINA A. and PESTEL M. (1958) *Presse Médicale* **66**, 374.
[369] REDEL J. and BOUTEVILLE A. (1955) *Bull. Soc. Chim. France* 1411.

[370] REICHLE C. and FRIEBEL H. (1955) *Naunyn Schmiedeberg's Arch. Exp. Pathol. u. Pharmakol.* **226**, 558.
[371] RICKARDS J. C., BOXER G. E. and SMITH C. C. (1950) *J. Pharmacol. Exp. Therap.* **98**, 380.
[372] RINDERKNECHT H. (1951) *J. Amer. Chem. Soc.* **73**, 5770.
[373] RINDERKNECHT H. (1952) *Science* **115**, 292.
[374] ROBA P. (1958). In press.
[375] ROSE H. A. and VAN CAMP A. (1956) *J. Amer. Pharm. Ass.* **45**, 653.
[376] ROSIÈRE C. E., WINDER C. V. and WAS J. (1956) *J. Pharmacol. Exp. Therap.* **116**, 296.
[377] ROVATI L. (1958) *Il Farmaco* **13**, 186.
[378] RUDDY A. W. and BUCKLEY J. S. JR. (1950) *J. Amer. Chem. Soc.* **72**, 718.
[379] RUDDY A. W. and BUCKLEY J. S. JR. (1951) *J. Amer. Chem. Soc.* **73**, 4096.
[380] RUSCHIG H. and SCHMITT K. (1955) *Chem. Ber.* **88**, 875.
[381] SALVESEN B. (1952) *Medd. Norsk. Farm. Selskap.* **14**, 1.
[382] SALVESEN B. and PAULSEN A. (1953) *Farm. Selskap.* **15**, 33.
[383] SANDBERG F. (1958) *Svenska Laekartidningen* **55**, 1474.
[384] SANDER M. (1952). Thesis, University of Innsbruck.
[385] SANDER M. (1954) *Arzneimittel-Forsch.* **4**, 183, 257, 375.
[386] SANTI R. To be published.
[387] SAVINI E. C. (1958) *Thérapie* **13**, 470.
[388] SCHAUMANN O. (1940) *Naunyn Schmiedeberg's Arch. Exp. Pathol. u. Pharmakol.* **196**, 109.
[389] SCHAUMANN O. (1942) *Medizin u. Chemie* **4**, 229.
[390] SCHAUMANN O. (1949) *Die Pharmazie* **4**, 364 .
[391] SCHAUMANN O. and LINDNER E. (1951a) *Naunyn Schmiedeberg's Archiv. Exp. Pathol. u. Pharmakol.* **214**, 93.
[392] SCHAUMANN O. (1951b) *Scientia Pharmazeut.* **19**, 33.
[393] SCHAUMANN O. (1952a) *Oesterr. Chem. Ztg.* **53**, 225.
[394] SCHAUMANN O. (1952b) *Naunyn Schmiedeberg's Arch. Exp. Pathol. u. Pharmakol.* **215**, 460.
[395] SCHAUMANN O. (1952c) *Naunyn Schmiedeberg's Arch. Exp. Pathol. u. Pharmakol.* **216**, 48.
[396] SCHAUMANN O. (1953a) *Naunyn Schmiedeberg's Arch. Exp. Pathol. u. Pharmakol.* **219**, 302.
[397] SCHAUMANN O. (1953b) *Scientia Pharmazeut.* **21**, 342.
[398] SCHAUMANN O. (1954a) *Naturwissensch.* **41**, 96.
[399] SCHAUMANN O. (1954b) *Deutsch. Med. Wchschr.* 1571.
[400] SCHAUMANN O. (1954c) *Arzneimittel-Forsch.* **4**, 115.
[401] SCHAUMANN O. (1956) *Brit. Med. J.* **2**, 1091.
[402] SCHAUMANN O. (1957) *Handbuch der experimentellen Pharmakologie* Vol. XII, p. 1. Springer, Berlin.
[403] SCHAUMANN W. (1954) *Naunyn Schmiedeberg's Arch. Exp. Pathol. u. Pharmakol.* **223**, 348.
[404] SCHAUMANN W. (1955) *Brit. J. Pharmacol.* **10**, 456.
[405] SCHAUMANN W. (1956a) *Naunyn Schmiedeberg's Arch. Exp. Pathol. u. Pharmakol.* **229**, 41, 432.
[406] SCHAUMANN W. (1956b) *Nature, Lond.* **178**, 1121.
[407] SCHAUMANN W. (1957) *Brit. J. Pharmacol.* **12**, 115.
[408] SCHMID J. D. (1954) *Deutsch. Med. Wchschr.* **79**, 1191.
[409] SCHMIEDT E. and ALBRECHT K. F. (1956) *Med. Klin.* **51**, 185.
[410] SCHULDINER J. A. (1949) *Analyt. Chem.* **21**, 298.

[411] SCHULTZ E. M., ROBB C. M. and SPRAGUE J. M. (1947) *J. Amer. Chem. Soc.* **69**, 188, 2454.
[412] SCHULTZ E. M. and SPRAGUE J. M. (1948) *J. Amer. Chem. Soc.* **70**, 48.
[413] SCHULTZ E. M. (1952) *J. Amer. Chem. Soc.* **74**, 5793.
[414] SCHULTZ E. M. and BICKING J. B. (1953) *J. Amer. Chem. Soc.* **75**, 1128.
[415] SCOTT C. C., ROBBINS E. B. and CHEN K. K. (1946a) *Science* **104**, 587.
[416] SCOTT C. C. and CHEN K. K. (1946b) *J. Pharmacol. Exp. Therap.* **87**, 63.
[417] SCOTT C. C. (1947a) *Anesthesia and Analgesia* **26**, 12, 18.
[418] SCOTT C. C., CHEN K. K., KOHLSTAEDT K. G., ROBBINS E. B. and ISRAEL F. W. (1947b) *J. Pharmacol. Exp. Therap.* **91**, 147.
[419] SCOTT C. C., ROBBINS E. B. and CHEN K. K. (1948) *J. Pharmacol. Exp. Therap.* **93**, 282.
[420] SEARLE G. D. (1952) *Brit. Pat.* 683236; *Chem. Abstr.* **48**, 2769.
[421] SEEHERHAM R. (1957) *Delaware State Med. J.* **29**, 265.
[422] SEREMBE M. and VISENTINI P. (1953) *Boll. Soc. Ital. Biol. Sper.* **29**, 216.
[423] SERRE L., ATTISSO M., TEMPLE J. P. and SARTRE M. (1958) *Anesthésie et Analgésie* **15**, 97.
[424] SHAPIRO D. (1949) *J. Org. Chem.* **14**, 839.
[425] SHAW W. H. C. and JEFFERIES J. P. (1951) *J. Pharm. Pharmacol.* **3**, 823.
[426] SHUTKIN M. W. (1958) *Amer. J. Gastroenterol.* **29**, 585.
[427] SIELAFF H. J. and DENGLER H. (1954) *Naunyn Schmiedeberg's Arch. Exp. Pathol. u. Pharmakol.* **222**, 413.
[428] SLETZINGER M., CHAMBERLIN E. M. and TISHLER M. (1952) *J. Amer. Chem. Soc.* **74**, 5619.
[429] SLOMKA M. B. and SCHUELER F. W. (1951) *J. Amer. Pharm. Assoc.* **41**, 618.
[430] SLOMKA M. B. and SLEETH C. K. (1953) *Proc. Soc. Exp. Biol. Med.* **84**, 532.
[431] SLOMKA M. B. and NAGLER M. (1954) *Fed. Proc.* **13**, 406.
[432] SMALL L. F. (1948) *Ann. N.Y. Acad. Sci.* **51**, 12.
[433] SMITH C. C. and LEHMAN E. G. (1953) *J. Pharmacol.* **108**, 336.
[434] SOEHRING K. and LOEHR H. JR. (1950) *Die Pharmazie* **5**, 569.
[435] SOUPAULT R., CAROLI J., RENON M., SCHOPS T. and CHARBONNIER A. (1957a) *Médicine et Hygiène* **15**, 159.
[436] SOUPAULT R., CAROLI J., RENON M., SCHOPS T. and CHARBONNIER A. (1957b) *Thérapie* **12**, 898.
[437] SPEETER M. E., BYRD W. M., CHENEY L. C. and BINKLEY S. B. (1949) *J. Amer. Chem. Soc.* **71**, 57.
[438] SPEETER M. E., CHENEY L. C. and BINKLEY S. B. (1950) *J. Amer. Chem. Soc.* **72**, 1659.
[439] SPERBER N., SHERLOCK M. and PAPA D. (1953) *J. Amer. Chem. Soc.* **75**, 1122.
[440] STARACE *et al.* (1958) *Minerva Medica* **11**, 422.
[441] STEVENS R. (1956) *Bruxelles-Médical* **36**, 814.
[442] STRAIT L. A., KUMLER W. D., SAH P. T. T., ALPEN E. L. and CHANG F. N. H. (1948) *Analyt. Chem.* **20**, 1126.
[443] SUNG CHEN YÜ and WAY E. L. (1950) *J. Pharmacol. Exp. Therap.* **98**, 72.
[444] SUNG CHEN YÜ, WAY E. L. and SCOTT K. G. (1953a) *J. Pharmacol. Exp. Therap.* **107**, 12.
[445] SUNG CHEN YÜ, WAY E. L. and SCOTT K. G. (1953b) *J. Pharmacol. Exp. Therap.* **108**, 1.
[446] SUNG CHEN YÜ and WAY E. L. (1953c) *J. Pharmacol. Exp. Therap.* **109**, 244.
[447] SUNG CHEN YÜ and WAY E. L. (1954) *J. Pharmacol. Exp. Therap.* **110**, 260.
[448] SUPNIEWSKI J. and VENULET J. (1949) *Polska Akad. Umiej. Rozpr. Wydz. Lek.* **10**, No. 8.
[449] SZIRMAI E., BAJUSZ E. and NYIRI I. (1954) *Die Pharmazie* **9**, 116.
[450] TAKAGI L., KASUYA Y. and HATTORI K. (1952) *J. Pharm. Soc. Japan* **72**, 1592.

[451] TAKAGI K., KASUYA Y. and OHTA Y. (1953) *J. Pharm. Soc. Japan.* **73**, 541, 544.
[452] TAKAGI K. (1954) *Ann. Rept. Tokamine Lab.* **6**, 110.
[453] TESHIMA K. and KIKKAWA M. (1952) *J. Osaka City Med. Center* **2**, 49.
[454] TEXTER E. C. and RUFFIN J. M. (1956) *Southern Med. J.* **49**, 910.
[455] THORPE R. H. (1946) *Brit. J. Pharmacol.* **1**, 113.
[456] THORPE R. H., WALTON E. and OFNER P. (1947a) *Nature, Lond.* **159**, 679.
[457] THORPE R. H., WALTON E. and OFNER P. (1947b) *Nature, Lond.* **160**, 605.
[458] THORPE R. H. (1949) *Brit. J. Pharmacol.* **4**, 98.
[459] TOLBERT B. M., CHRISTENSON F., CHANG F. N. H. and SAH P. T. T. (1949) *J. Org. Chem.* **14**, 525.
[460] TROXIL E. B. (1948) *J. Amer. Med. Assoc.* **136**, 920.
[461] TSAO E. P. (1954) *Univ. Microfilms (Ann Arbor) Publ. No.* 5752; *Chem. Abstr.* **48**, 2061.
[462] TULLAR B. F., WETTERAN W. and ARCHER S. (1948) *J. Amer. Chem. Soc.* **70**, 3959.
[463] TYE A. and CHRISTENSEN B. V. (1952) *J. Amer. Pharm. Assoc.* **41**, 75.
[464] YCHIYAMA J., KIRCHHOF A. C. and DAVID N. A. (1947) *Proc. Soc. Exp. Biol. Med.* **66**, 417.
[465] UPJOHN COMPANY (1952) *U.S. Pat.* 2601323, *Chem. Abstr.* **46**, 10199; [466] (1957) *U.S. Pat.* 2782206, *Chem. Abstr.* **51**, 13931; [467] (1958) *Brit. Pat.* 790102.
[468] VAN ARSDEL W. C. and DAVID N. A. (1956) *J. Amer. Pharm. Assoc.* **45**, 645.
[469] VAN DONGEN K. (1956) *Acta Physiol. Pharmacol. Neerl.* **4**, 500.
[470] VAN KEMPEN H. G. J., PINCKAERS J. A., LOKIN E. F. and VAN HOLLEBEKE F. (1958) *Ned. Tdschr. Gen.* **102**, 426.
[471] VAN PROOSDIJ-HARTZEMA E. G. and DE JONGH D. K. (1957) *Acta Physiol. et Pharmacol. Neerl.* **5**, 398.
[472] VAN PROOSDIJ-HARTZEMA E. G. (1958) *J. Amer. Pharm. Assoc.* **47**, 245.
[473] VIDIC E. (1951) *Naunyn Schmiedeberg's Arch. Exp. Pathol. u. Pharmakol.* **212**, 339.
[474] VIDIC E. (1953) *Arzneimittel-Forsch.* **3**, 34, 428.
[475] VIDIC E. (1954) *Deut. Z. ges. gerichtl. Med.* **42**, 582.
[476] VOGEL G. (1952) *Deut. Z. ges. gerichtl. Med.* **41**, 420.
[477] VON HARNACK G. A. (1957) *Arzneimittel-Forsch.* **9**, 579.
[478] VOTAVA Z. and HÓRAKÓVA Z. (1952) *Czechoslov. Farm.* **1**, 338.
[479] WALLENSTEIN S. L. and HOUDE R. W. (1958) *Pharmacology Meetings, Ann Arbor, August.*
[480] WALTON E., OFNER P. and THORP R. H. (1949) *J. Chem. Soc.* 648.
[481] WATSON R. C. and BOWMAN M. I. (1949) *J. Amer. Pharm. Assoc.* **38**, 369.
[482] WAY E. L., SUNG C. Y., MCKELWAY W. P. (1949) *J. Pharmacol. Exp. Therap.* **97**, 222.
[483] WAY E. L., SIGNOROTTI B. T., MARCH C. H. and PENG C. T. (1951) *J. Pharmacol. Exp. Therap.* **101**, 249
[484] WEBB J. P. (1954) *Fourth Nation. Medic. Chem. Symp. of A.C.S.* pp. 29–37.
[485] WEIGMANN R. and WÖHLER C. (1952) *Arzneimittel-Forsch.* **2**, 218.
[486] WEINBERG B. J. (1958) *Amer. J. Gastroenterol.* **29**, 400.
[487] WELLCOME FOUNDATION (1949a) *Brit. Pat.* 624117, *Chem. Abstr.* **44**, 3036; [488] (1949b) *Brit. Pat.* 624118, *Chem. Abstr.* **44**, 662; [489] (1949c) *Brit. Pat.* 627139, *Chem. Abstr.* **44**, 7874; [490] (1950) *Brit. Pat.* 677522, *Chem. Abstr.* **47**, 4919; [491] (1951) *Brit. Pat.* 654975; *Chem. Abstr.* **46**, 7124; [492] (1951b) *Brit. Pat.* 688481, *Chem. Abstr.* **48**, 2111; [493] (1952) *Brit. Pat.* 682161, *Chem. Abstr.* **48**, 741; [494] (1953) *U.S. Pat.* 2649444, *Chem. Abstr.* **48**, 3995; [495] (1954) *Brit. Pat.* 701803, *Chem. Abstr.* **49**, 10376; [496] (1957) *Brit. Pat.* 787279, *Chem. Abstr.* **52**, 10217.
[497] WENZEL D. G. and EMICK G. H. (1956) *J. Amer. Pharm. Assoc.* **45**, 414.
[498] WHEATLEY W. B. (1954) *J. Org. Chem.* **19**, 434.

[499] WHEATLEY W. B., MINOR W. F., BYRD W. M., FITZGIBBON W. E., SPEETER M. E., CHENEY L. C. and BINKLEY S. B. (1954) *J. Org. Chem.* **19**, 794.
[500] WHITE A. C., GREEN A. F. and HUDSON A. (1951) *Brit. J. Pharmacol.* 6, 560.
[501] WIKLER A., FRAZER H. F. and ISBELL H. (1953) *J. Pharmacol. Exp. Therap.* **109**, 8.
[502] WILSON W. (1950) *J. Chem. Soc.* 2173.
[503] WILSON W. (1952a) *J. Chem. Soc.* 6.
[504] WILSON W. (1952b) *J. Chem. Soc.* 3524.
[505] WILSON W. (1955) *Chemistry and Industry* 200.
[506] WINDER C. V. (1947) *Arch. int. Pharmacodyn.* **74**, 219.
[507] WINDER C. V. (1950) *Ann. N.Y. Acad. Sci.* **52**, 838.
[508] WINTER C. A. (1950) *J. Pharmacol.* **98**, 305.
[509] WINTER C. A. and FLATAKER L. (1952) *Proc. Soc. Exp. Biol. Med.* **81**, 463.
[510] WINTER C. A. and FLATAKER L. (1956) *Proc. Soc. Exp. Biol. Med.* **93**, 158.
[511] WINTHROP (WINTHROP-STEARNS OR STERLING-WINTHROP) (1941) *U.S. Pat.* 2230774, *Chem. Abstr.* **35**, 3391; [512] (1948) *U.S. Pat.* 2446522, *Chem. Abstr.* **43**, 1810; [513] (1951a) *U.S. Pat.* 2555353, *Chem. Abstr.* **46**, 141; [514] (1951b) *U.S. Pat.* 2566535, *Chem. Abstr.* **46**, 2584; [515] (1952a) *Brit. Pat.* 668562, *Chem. Abstr.* **47**, 5447; [516] (1952b) *Brit. Pat.* 673859, *Chem. Abstr.* **47**, 4915; [517] (1952c) *Brit. Pat.* 674246, *Chem. Abstr.* **47**, 7538; [518] (1952d) *Brit. Pat.* 676124, *Chem. Abstr.* **47**, 5963; [519] (1952e) *U.S. Pat.* 2592191, *Chem. Abstr.* **46**, 11247; [520] (1952f) *U.S. Pat.* 2618640, *Chem. Abstr.* **47**, 9342; [521] (1953) *U.S. Pat.* 2647122, *Chem. Abstr.* **47**, 10551; [522] (1954a) *D.B. Pat.* 12–0, 8. St. 6299; [523] (1954b) *U.S. Pat.* 2680115, *Chem. Abstr.* **49**, 6319; [524] (1954c) *U.S. Pat.* 2691678, *Chem. Abstr.* **49**, 14808; [525] (1955) *D.B. Pat.* 924862; [526] (1956a) *Brit. Pat.* 747866, *Chem. Abstr.* **51**, 12977; [527] (1956b) *U.S. Pat.* 2762812, *Chem. Abstr.* **51**, 7432; [528] (1956c) *U.S. Pat.* 2769812, *Chem. Abstr.* **51**, 5843; [529] (1956d) *U.S. Pat.* 2773901, *Chem. Abstr.* **51**, 7420.
[530] WITTIG G., MANZOLD R. and FELLETSCHIN G. (1948) *Liebigs Ann.* **560**, 116.
[531] WOLFF P. O. (1949) *Bull. World Health Org.* **2**, 193.
[532] WOODS L. A., WYNGAARDEN J. B. and SEEVERS M. H. (1947) *Proc. Soc. Exp. Biol. Med.* **65**, 113.
[533] YANAI A. (1955) *Folia Pharmacol. Japan* **51**, 34.
[534] YANDIK M. and LARSEN A. A. (1951) *J. Amer. Chem. Soc.* **73**, 3534.
[535] ZAUGG H. and HORROM B. W. (1948) *Analyst. Chem.* **20**, 1026.
[536] ZACCO M. (1958) *La Clinica Terapeutica* **14**, No. 2.
[537] ZAUGG H. and HORROM B. W. (1953) *J. Amer. Chem. Soc.* **75**, 292.
[538] ZAUGG H. (1955) *J. Amer. Chem. Soc.* **77**, 2910.
[539] ZAUGG H., MICHAELS R. J., GLENN H. J., SWETT L. R., FREIFELDER M., STONE G. R. and WESTON A. W. (1958a) *J. Amer. Chem. Soc.* **80**, 2763.
[540] ZAUGG H. and MICHAELS R. J. (1958b) *J. Amer. Chem. Soc.* **80**, 2768.
[541] ZAUGG H. and MICHAELS R. J. (1958c) *J. Amer. Chem. Soc.* **80**, 2770.
[542] ZAUGG H., DENET R. W. and FREIFELDER M. (1958d) *J. Amer. Chem. Soc.* **80**, 2773.
[543] ZOBOLI P. and MAGGIORE L. (1950) *Giorn. Ital. Anestesiol.* **16**, 34.