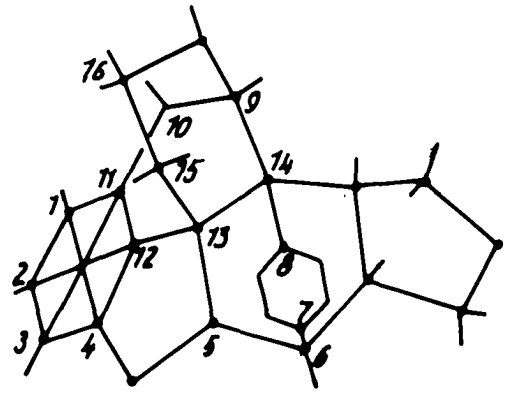
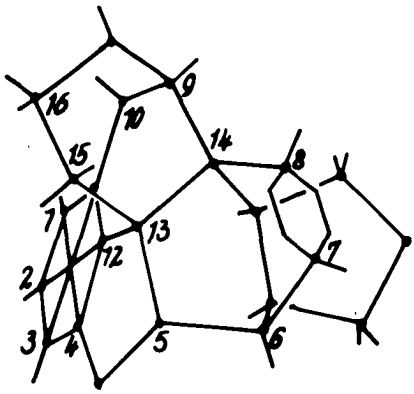
SYNTHESIS AND DIELS-ALDER REACTIONS OF NOVEL MORPHINANDIENES





J.T.M. LINDERS

SYNTHESIS AND DIELS-ALDER REACTIONS OF NOVEL MORPHINANDIENES

PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Technische Universiteit Delft
op gezag van de Rector Magnificus, prof.drs. P.A. Schenck,
in het openbaar te verdedigen ten overstaan van
een commissie aangewezen door het College van Dekanen
op maandag 12 juni 1989 te 16.00 uur

door

Joannes Theodorus Maria Linders

geboren te Roosendaal en Nispen
scheikundig ingenieur

Dit proefschrift is goedgekeurd door de promotor
Prof.dr.ir. A.P.G. Kieboom

Toegevoegd promotor Dr.ir. L. Maat

The author gratefully acknowledges Diosynth B.V., Apeldoorn, The Netherlands, for financial support of the investigations described in this thesis.

"Niemand wird als Meister geboren. Der Weg zur Meisterschaft führt über lange Jahre des Lernens, des Kämpfens, über Freude und Enttäuschungen der errungenen Resultate hinweg."

Paul Keres, "Ausgewählte Partien 1931-1956, zugleich ein Lehrbuch des praktischen Schachs."

An experiment is in progress,
but it is uncertain
if we are in control
or just observers

R. Hoffmann, "The Metamict State"

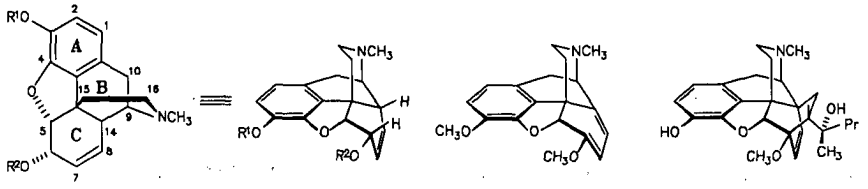
On the front cover: Two of the four possible Diels-Alder adducts of thebaine and maleic anhydride. Taken from C. Schöpf, K. von Gottberg and W. Petri, Lieb. Ann. Chem. **536**, 216 (1938).

On the back cover: X-ray structures of 7α-acetyl-6α,14α-ethenisomorphinan and 7β-acetyl-6β,14β-ethenomorphinan.

CONTENTS

CHAPTER 1 INTRODUCTION

Opium, the sun-dried latex obtained after incision of the unripe seed capsules of the poppy, *Papaver somniferum* L., has been in medicinal use since the days of ancient Egypt and Greece. During the first half of the 19th century, the major constituents of opium (Table 1) have been isolated and described[1-3]. Morphine (1, Sertürner 1805), the most abundant compound and the analgesic principle in opium, is one of the more than 40 alkaloids, isolated from the poppy[4-5].



1 $R^1 = R^2 = H$, morphine
2 $R^1 = CH_3$, $R^2 = H$, codeine
3 $R^1 = R^2 = COCH_3$, heroin

4, thebaine

5, etorphine

Table 1. Major constituents* of opium[5] (year of first isolation).

Morphine (1805)	9-14%
Codeine (1832)	0.7-2.5%
Thebaine (1835)	0.3-1.5%
Narcotine (1817)	6-11%
Papaverine (1848)	0.8-1.0%
Narceine (1832)	0.1-0.5%

*% of dry weight

In spite of its unique analgesic properties, clinical use of morphine is not without restrictions because of side-effects such as abuse liability, physical dependence, tolerance and depression of the respiration[6-7]. Therefore, since the early days of opiate research, chemists have been

searching for alternatives, based on the morphine skeleton, which would constitute "the ideal painkiller", and in which the analgesic activity would be separated from the unwanted side-effects. One of the unfortunate first trials was compound **3**, the "miracle drug", heroin, introduced as a medicine by Bayer[8-9] in 1898. Free distribution of heroin by dispensing chemists during the beginning of this century resulted in the first massive wave of drug abuse, especially in the United States (200,000 addicts in 1924)[9].

Compounds with enhanced analgesic properties were obtained upon introdution of an additional etheno bridge across the C-ring, resulting in 6α,14α-ethenoisomorphinans such as etorphine (**5**). In this chapter the history, nomenclature, and pharmacology of these bridged morphinans will be reviewed.

1.1. Diels-Alder reactions of thebaine, a historical overview

Early experiments

Thebaine (**4**), one of the many morphinan alkaloids from *Papaver somniferum* L. (Table 1), but almost the sole alkaloidal product from *P. bracteatum* Lindl.[10], is one of the few naturally occurring organic compounds that contains a conjugated diene system. In 1938, shortly after Diels and Alder had published the systematic investigations on the reaction that since then carries their names[11], the reactivity of thebaine towards dienophiles was studied by both Sandermann[12] and Schöpf *et al.*[13].

Thebaine was known to be a poisonous and, therefore, unusable natural product, in contrast to *e.g.* morphine and codeine. The diene system of thebaine (for reviews on the structure elucidations of morphine, thebaine and related compounds, see Ref. 14 and 15) was held responsible for its toxic nature. Interesting in this context is the following statement of Sandermann[12], especially when seen in the light of later research by *e.g.* Bentley and of modern structure-activity relationship studies:

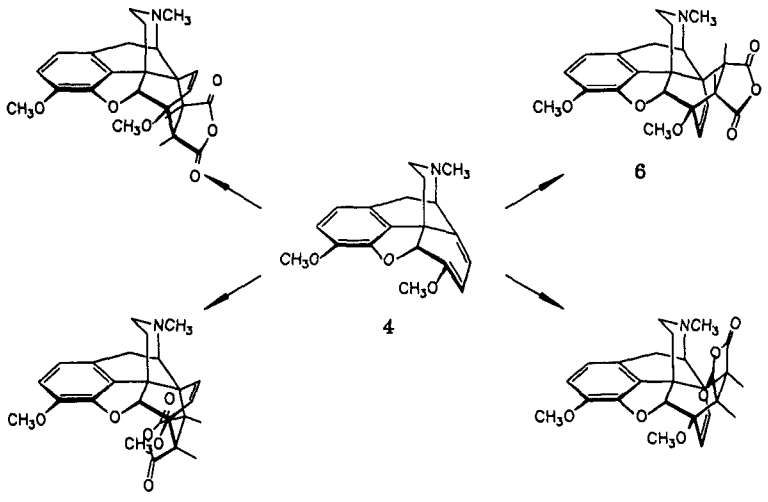
> "Die Eigenschaft des Thebains, als heftiges Krampfgift zu wirken, ist zum grossen Teil durch die stark ungesättigte Natur des Ringes II bedingt. Da dieser durch die Anlagerung der verschiedenen Dienverbindungen verändert und neue

funktionelle Gruppen eingeführt worden sind, besteht die Möglichkeit, dass diese neuen Verbindungen auch pharmakologisch von Interesse sind."

Sandermann prepared adducts of thebaine with 1,4-benzoquinone, 1,4-naphthoquinone and maleic anhydride, but he did not give any structure elucidation for the products obtained[12].

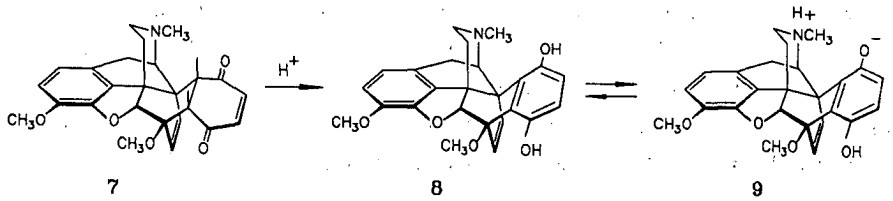
Schöpf, who claimed that his group was the first to prepare the adduct of thebaine and maleic anhydride (the elemental analysis of the adduct had already been performed in 1931), proposed the correct structure for the adducts of thebaine with both maleic anhydride and 1,4-benzoquinone[13]. He recognized the possibility of four different adducts of thebaine with these cyclic dienophiles (Scheme 1), namely the 7α,8α- and 7β,8β-substituted adducts of both the 6α,14α-ethenoisomorphinan and 6β,14β-ethenomorphinan series (for the nomenclature of these adducts, see 1.2). These compounds result from the approach of the dienophile towards the β-face and the α-face of the diene system, respectively.

α-FACE APPROACH β-FACE APPROACH



Scheme 1. The four possible adducts from the Diels-Alder reaction of thebaine (4) with maleic anhydride according to Schöpf[13].

In analogy with the reaction of thebaine with hydrogen peroxide, in which the two incoming hydroxyl groups were found to add to the exposed β-face of the diene system, yielding "oxycodeine" (14β-hydroxycodeinone), and because of the known preference of Diels-Alder reactions to give *endo*-adducts[11b], he concluded the adduct of thebaine and maleic anhydride to have structure **6**. Additional indications for this structure assignment came from acylation and methylation studies of the isomerized adduct of thebaine and 1,4-benzoquinone (**8**, Scheme 2). On the basis of these results, the adduct was concluded to have the phenol betaine structure **9**, thus excluding products resulting from the α-face approach.



Scheme 2. Adduct of thebaine and 1,4-benzoquinone (**7**): enolization to **8** and formation of phenol betaine **9**.

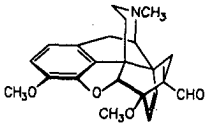
Between the first studies of Sandermann and Schöpf and the profound investigations of Bentley and coworkers in the mid-fifties and early sixties, only one other Diels-Alder reaction of thebaine was reported. Kanevskaya and Mitryagina studied the reaction of thebaine with acrolein in benzene, affording a (to them) unknown adduct in 92% yield[16]. This reaction was repeated by Bentley and coworkers[17-18] and, recently, by Kopcho and Schaeffer[19], giving the expected 7α-formyl-6α,14α-ethenoisomorphinan **10**.

The "Bentley Adducts"

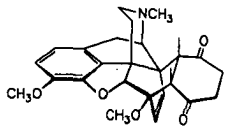
In 1950, Bentley became involved in morphinan chemistry[20]. First, together with Sir Robert Robinson, who once declared[21] "...but the star performers in the team of molecular acrobats are undoubtedly the alkaloids of the morphine group and I (shall) speak especially of thebaine.", he reinvestigated "old

reactions" of thebaine[1,14], such as its reduction with sodium in liquid ammonia[22-23] and its reaction with Grignard reagents[20,23] (see 3.1 and Chapter 6, respectively). Later, he occupied himself with structure elucidations of *e.g.* the acid-catalyzed rearrangement product of 8[24].

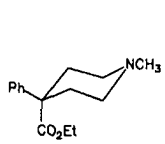
In 1956, Bentley started to publish on the Diels-Alder reaction of thebaine[25]. He not only re-examined the early work of Sandermann[12] and Schöpf[13], but also gave, for the first time, pharmacological test results. Although the adduct of thebaine and 1,4-benzoquinone 7 itself had the same toxic effect as thebaine, the partly reduced adduct 11 was shown to possess analgesic properties, comparable in strength to pethidine (meperidine, 12), its potency being 10-20% of that of morphine. Compound 13, obtained from 6 by reduction with lithium aluminium hydride, showed some analgesic activity in rats. At this point, further research into the pharmacological characteristics was temporarily stopped, because of the insufficiency of the testing methods[18,26].



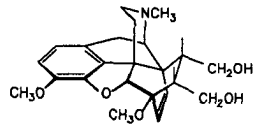
10



11



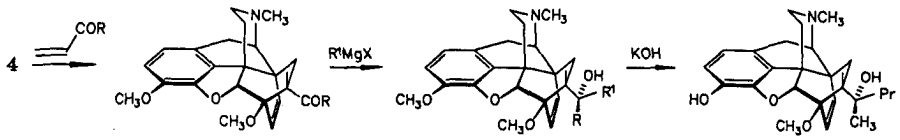
12



13

Bentley and Ball prepared the adducts of thebaine with methyl vinyl ketone and phenyl vinyl ketone[28] (14, 15) and studied their acid-[17] and base-catalyzed[29] rearrangements, which could be related to similar reactions of 7.

In 1963, the major breakthrough was reported by Bentley and Hardy in a short communication[30], in which they described a number of alcohols with the general structure 16, derived from 14 and 15 (Scheme 3). Without specification of the substituents, the bases were said to have "...analgesic activities ranging from the barely detectable to the unprecedented level of about 10,000 times that of morphine.". The compounds were fully described in a number of patents[31-33]. Lister reported[34] the first structure-activity relationships of these adducts. An example of these highly potent analgesics is etorphine (5), which is about 1000 times more active in man than morphine[35-36]. but because of serious side-effects[35], in particular respiratory depression, its use is limited to veterinary practice[37].



14 R = CH_3
15 R = Ph

16

5

Scheme 3. Preparation of etorphine (**5**) and analogues from the the Diels-Alder adducts **14** and **15**.

In a series of landmark papers[18,38-42] in 1967, as well as in his comprehensive review in "The Alkaloids" in 1971[43], Bentley disclosed his studies of the Diels-Alder reaction of thebaine and the elaboration of the adducts into strong (ant)agonists. Ideas on structure-activity relationships[34,36], on the structure of the opioid receptor[36] and a detailed study of the ^{1}H NMR spectra of 6α,14α-ethenoisomorphinans[44], were also published. The structure of the adducts was determined unambiguously by X-ray diffraction analysis of the HBr-salt of *n*-propylthevinol[45], the 3-*O*-methyl ether of etorphine (**5**).

As a result of these findings, research in this area of morphine chemistry was strongly stimulated. In two recent monographs[46-47], the progress and results are reviewed.

A pharmacological rationale

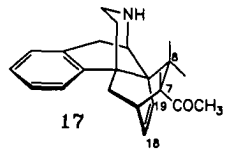
The rationale behind the study of the C-ring bridged morphinans was fairly simple. As it was postulated[48] that pharmacological effects (desired activity as well as unwanted side-effects) were caused by the fitting of the drug onto (unknown) receptor surfaces, it was expected that compounds of structures simpler than morphine, being more flexible, would fit all other receptors, thus mimicking morphine and reproducing all pharmacological effects of morphine. On the other hand, more complex compounds, such as the above-mentioned ethenoisomorphinans, which are more rigid than morphine,

would be unacceptable for some of the receptors and, thus, more selective in their activity[16,18].

1.2. Nomenclature

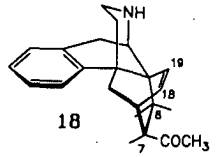
The nomenclature of the Diels-Alder adducts of thebaine has been the subject of debate and confusion. Bentley used the designation 6,7,8,14-tetrahydro-6,14-*endo*-ethenothebaine or 6,14-*endo*-ethenomorphinan for the systematic nomenclature of the adducts of type **17** (Table 2).

Table 2. Nomenclature systems of adducts of morphinan-6,8-dienes.



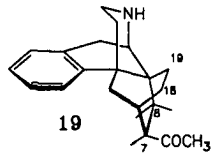
17

Bentley: 7α-acetyl-6,14-*endo*-ethenomorphinan or
7α-acetyl-6,7,8,14-tetrahydro-6,14-*endo*-ethenothebaine
Chem. Abstr.: 7α-acetyl-6,14-ethenomorphinan
Delft: 7α-acetyl-6α,14α-ethenoisomorphinan
(7α-acetyl-6,14-ethenoisomorphinan)



18

Bentley: 7β-acetyl-6,14-*exo*-ethenomorphinan (Ghosh *et al.*[49])
Chem. Abstr.: 7β-acetyl-6β,14β-ethenomorphinan
Delft: 7β-acetyl-6β,14β-ethenomorphinan
(7β-acetyl-6,14-ethenomorphinan)



19

Bentley: 7β-acetyl-6,14-*exo*-ethanomorphinan
Chem. Abstr.: 18β-acetyl-18,19-dihydro-6,14-ethenomorphinan
Delft: 7β-acetyl-6β,14β-ethanomorphinan
(7β-acetyl-6,14-ethanomorphinan)

Consequently, adducts which have the new bridge at the other side (α-face) of the C-ring (**18**) might be named 6,14-*exo*-ethenomorphinans[49]. However, the use of the prefixes "-*endo*-" and "-*exo*-" is ambiguous in this case because of the customary use of these prefixes to describe the position of the substituents (and not that of the etheno bridge) in Diels-Alder adducts of cyclic dienes[11b]. As trivial names for adducts of thebaine also thevinone, thevinol and orvinol[38,50-51] are in use.

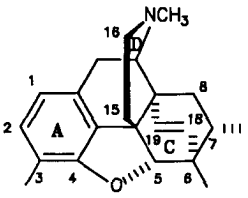
Chemical Abstracts uses a systematic nomenclature starting from **17** as parent structure, which is named a 6,14-ethenomorphinan. The stereoisomer **18** is designated by the descriptor (6β,14β): 7β-acetyl-6β,14β-ethenomorphinan. This type of nomenclature was used only once earlier, namely to describe the Diels-Alder adducts of thebaine with acetylenes[52], *e.g.* the adduct of thebaine and ethyl propiolate was named a 6,14-ethenocodeine methyl ether.

Difficulties will arise, however, when compounds such as **19** have to be named. In the Chemical Abstracts nomenclature, this compound should be named 18β-acetyl-18,19-dihydro-6,14-ethenomorphinan. The locant number of the acetyl-substituted carbon has to change from 7 to 18, through a simple hydrogenation of the double bond.

To circumvent this and other problems, an alternative nomenclature, as advocated by us[53-54], will be used throughout this thesis. When isomorphinan and morphinan, respectively, are used as parent structures, adduct **17** is named 7α-acetyl-6α,14α-ethenoisomorphinan and adduct **18** 7β-acetyl-6β,14β-ethenomorphinan. In both cases, an etheno bridge is added to a well-defined molecular structure, namely either that of an isomorphinan or a morphinan. Actually, the Greek symbols, used in the designation of the etheno bridge, are superfluous, but for the sake of clarity they will be used throughout this thesis (except in Chapter 2.2).

1.3. Pharmacology and structure-activity relationships of ethenoisomorphinans

As the above-mentioned monographs[46-47] both give a comprehensive discussion of the available pharmacological data, the subject of pharmacology and structure-activity relationships will be treated here only in brief.



20

A-ring modifications

In contrast to the simple 4,5α-epoxymorphinans, the analgesic activity of 3-deoxy compounds lies in between that of the 3-hydroxyl adducts and their 3-methoxyl ethers[55]. The phenolic compounds are 10-50 times more potent than the corresponding methyl ethers. The 3-thio-analogue of etorphine showed an analgesic potency of only 2 times of that of morphine[56].

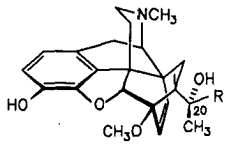
D-ring modifications

The most important feature of the D-ring is the *N*-substituent, which determines strongly whether a compound has agonist or antagonist activity. In the 3-methoxyl series, the same pattern of activity is apparent as in simple morphinans. However, in the 3-OH series, compounds remain strong agonists when the *N*-methyl group has been replaced by *e.g.* *N*-cyclopropylmethyl, stressing in this way the importance of the substituent at C-7 for high analgesic activity[39]. Introduction of substituents at C-16 and/or C-15 abolished analgesic activity almost completely[57].

C-ring modifications

The effects of the variation at C-7 and/or C-8 on the analgesic activity have been studied extensively. Although unsubstituted 6α,14α-etheno- and -ethanoisomorphinans also have considerable agonist activity (up to 80 times morphine[58]), introduction of lipophilic groups at C-7 may increase the analgesic activity dramatically. In particular the dialkyl carbinols 21 show extremely high potency (Table 3).

Table 3. Agonist activity[a] of 6α,14α-ethenoisomorphinans[39] {20-(*R*) configuration}.

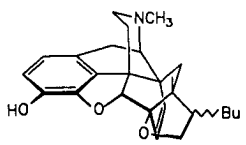


21

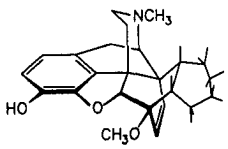
R	rel. pot.[b]
H	37
Me	63
Et	330
Pr (5)	3200
Bu	5200
Pe	4500
Hex	58
$PhCH_2CH_2$	2200
cyclohex	3400

a) Rat tail pressure test
b) Relative to morphine

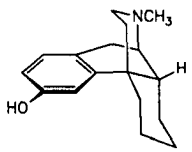
The absolute configuration of the alcoholic substituent is of paramount importance, the 20-(*S*)-diastereoisomer of etorphine being only 40 times more potent than morphine[39]. This same trend is observed in the 6-demethoxy-[50] and 6-deoxy-series[51], which led to the conclusion that intramolecular hydrogen bridge formation to the 6-methoxyl group[45,59] is not of decisive importance for high analgesic activity[50-51,60-61]. 6α,14α-Ethenoisomorphinans that lack a hydroxyl group in the lipophilic side chain showed similar characteristics, but their analgesic activity was substantially lower compared to the carbinols 21[60-61]. From the difference in activity of the constrained analogues **22**, it is clear that the lipophilic chain should be "under" the C-ring, i.e. in the α-position. This conclusion was corroborated by the high activity of **23** (1000 times morphine)[36]. The presence of a hydroxyl function in the lipophilic substituent, which fixes the alkyl chain in the desired conformation by hydrogen bridge formation with the receptor surface, is necessary for the extremely high potency of etorphine and analogues.



22



23

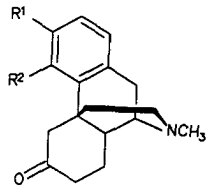


24

1.4. Scope of the thesis

The position, type and number of oxygen-containing substituents attached to the morphinan skeleton are of importance for the analgesic properties. Apart from the large differences between morphine (1) and codeine (2), this is demonstrated by the enhanced activity of levorphanol (24)[62] and by the different activities within the series of 6-ketomorphinans 25[63] (Table 4). In general, partial deoxygenation of the aromatic nucleus results in a higher analgesic activity.

Table 4. Antinociceptive activity of 6-ketomorphinans[63] (mouse hot plate test).



25

R^1	R^2	ED_{50}*	rel. pot.
H	H	0.33	2.6
H	OH	1.6	0.5
H	OCH_3	0.29	3.0
OH	H	1.9	0.5
OH	OH	5.3	0.2
OH	OCH_3	1.8	0.5
OCH_3	H	1.1	0.8
OCH_3	OH	2.4	0.4
OCH_3	OCH_3	0.35	2.5
OCH_2O		6.3	0.1
levorphanol (24)		0.17	5.9
codeine (2)		6.8	0.1
morphine (1)		0.87	1.0

*In mg/kg, subcutaneous injection

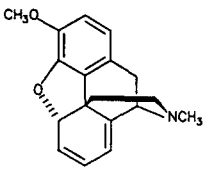
This knowledge, in combination with the much higher activity of the 6α,14α-ethenoisomorphinans has led us to the preparation of new deoxygenated ethenomorphinans, which may contribute to further understanding of structure-activity relationships.

To prepare deoxygenated ethenomorphinans, different routes can be envisaged:

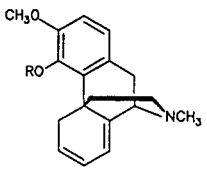
i. removal of oxygen substituents from etorphine and related compounds
ii. preparation of morphinan-6,8-dienes which have been deoxygenated in the A-ring, followed by Diels-Alder reaction with an appropiate dienophile

iii. preparation of 6-demethoxymorphinan-6,8-dienes, subsequently followed by Diels-Alder reaction and deoxygenation in the A-ring

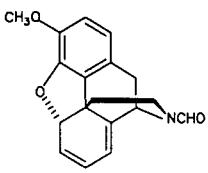
In view of the acid-sensitivity of the strained ethenoisomorphinan skeleton[17,40], route (i) may be difficult to pursue. Difficulties can also be foreseen when following route (ii). Removal of aromatic oxygen functions is usually performed under reducing conditions, *e.g.* catalytic hydrogenolysis of heterocyclic ethers[64] or diphenyl ether cleavage using sodium in liquid ammonia[65]. These reactions will be difficult to combine with the unsaturated character of the C-ring. Initial experiments[66] confirmed this view. Therefore, the work described in this thesis concentrates on route (iii). The synthesis of 6-demethoxythebaine (**26**), both from the minor opium alkaloid neopine and from codeine has been studied[67-68] (see 2.1). Investigations on the preparation of other morphinan-6,8-dienes, such as **27**, **28** and **29**, are described in Chapters 3, 5 and 6.



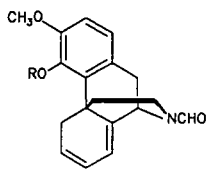
26



27



28



29

Diels-Alder reaction with methyl vinyl ketone and elaboration of the adducts into pharmacological interesting compounds is studied (Chapters 2 and 4).

Application of the exciting dienophile nitroethene[69-70] to morphinan-6,8-dienes is only possible after masking the basicity of the amino-nitrogen by converting it into a formamide. The preparation of *N*-formylmorphinan-6,8-dienes **28** and **29** has been looked at in detail (Chapters 5 and 6). Diels-Alder reaction of **28** with nitroethene exhibits a surprising loss of regioselectivity, making available in this way differently substituted etheno(iso)morphinans, which may be of use in opioid ligand studies[71] (Chapter 5). The ^{1}H and ^{13}C NMR spectra have been studied in detail, especially in relation to the *E/Z* isomerism of the *N*-CHO group (Chapter 7).

In the last chapter, force field calculations on these systems using the Allinger program MMP2(85) are discussed.

References

1. K.W. Bentley, "The Chemistry of the Alkaloids", Clarendon, Oxford, 1954.
2. G. Trier, "Die Alkaloide", 2. Aufl., Verlag von Gebrüder Borntraeger, Berlin, 1931, 479.
3. T.A. Henry, "The Plant Alkaloids", J. & A. Churchill, Ltd., London, 1939, 179.
4. R.J. Bryant, Chem. & Ind. (London) **1988**, 146.
5. "The Merck Index", 10th Ed., Merck, Rahway, 1983.
6. J.H. Jaffe and W.R. Martin, "Opioid Analgesics and Antagonists" in "The Pharmacological Basis of Therapeutics", A. Goodman Gilman, L.S. Goodman and A. Gilman (Eds.), 6th Ed., MacMillan, New York, 1980, 494.
7. P.T. White, National Geographic Magazine **167**, 143 (1985).
8. N. Evers, "The Chemistry of Drugs", E. Benn, Ltd., London, 1926, 76.

9a. A.W. McCoy, "The Politics of Heroin in Southeast Asia", Harper, New York, 1972, 1.

9b. H. Huizer, "Analytical Studies on Illicit Heroin", Thesis, University of Leiden. 1988, Chapter 1.

10. H.G. Theuns, "Constituents of *Papaver bracteatum* Lindl.", Thesis, University of Utrecht, 1984, and references cited therein.

11a. O. Diels and K. Alder, Lieb. Ann. Chem. **460**, 98 (1928).

11b. K. Alder and G. Stein, Angew. Chem. **50**, 510 (1937).

12. W. Sandermann, Ber. Dtsch. Chem. Ges. **71**, 648 (1938).
13. C. Schöpf, K. von Gottberg and W. Petri, Lieb. Ann. Chem. **536**, 216 (1938).

14a. H.L. Holmes in "The Alkaloids", Vol. II, R.H.F. Manske and H.L. Holmes (Eds.), Acadamic Press, New York 1952, 1.

14b. H.L. Holmes and (in part) G. Stork in "The Alkaloids", Vol. II, R.H.F. Manske and H.L. Holmes (Eds.), Academic Press, New York, 1952, 161.

14c. G. Stork in "The Alkaloids", Vol. VI, R.H.F. Manske (Ed.), Academic Press, New York, 1960, 219.

15. D. Ginsburg, "The Opium Alkaloids", Interscience Publishers, New York, 1962.
16. S.I. Kanevskaya and S.F. Mitryagina, J. Gen. Chem. (USSR) **17**, 1203 (1947); Chem. Abstr. **42**, 1596c (1948).
17. K.W. Bentley and J.C. Ball, J. Org. Chem. **23**, 1720 (1958).
18. K.W. Bentley and D.G. Hardy, J. Am. Chem. Soc. **89**, 3267 (1967).
19. J.J. Kopcho and J.C. Schaeffer, J. Org. Chem. **51**, 1620 (1986).
20. K.W. Bentley, Nat. Prod. Rep. **4**, 14 (1987).
21. R. Robinson, Proc. R. Soc. B**135**, v-xix (1947); R. Robinson, Nature **160**, 815 (1947).
22. K.W. Bentley and R. Robinson, Experientia **23**, 353 (1950).
23. K.W. Bentley, R. Robinson and A.E. Wain, J. Chem. Soc. 958 (1952).
24. K.W. Bentley and J. Dominguez, J. Org. Chem. **21**, 1348 (1956); K.W. Bentley, J. Dominguez and J.P. Ringe, J. Org. Chem. **22**, 409, 418 (1957).
25. K.W. Bentley and A.F. Thomas, J. Chem. Soc. 1863 (1956).
26. K.W. Bentley, Endeavour **23**, 97 (1964).
27. A.H. Beckett and A.F. Casy in "Progress in Medicinal Chemistry", Vol. 2,

G.P. Ellis and G.B. West (Eds.), Butterworths, London, 1962, 43.
28. K.W. Bentley and J.C. Ball, Chem. & Ind. (London) **1956**, 1428.
29. K.W. Bentley and J.C. Ball, J. Org. Chem. **23**, 1725 (1958).
30. K.W. Bentley and D.G. Hardy, Proc. Chem. Soc. 220 (1963).
31. J.F. Macfarlan & Co., Ltd., Brit. 902,659, Aug. 9, 1962; Chem. Abstr. **57**, 16682h (1962).
32. J.F. Macfarlan & Co., Ltd., Fr. M1378, July 30, 1962; Chem. Abstr. **58**, 14030b (1963).
33. J.F. Macfarlan & Co., Ltd., Belg. 618,392, Sept. 28, 1962; Chem. Abstr. **58**, 12614f (1963). See also: W.R. Hydro, U.S. 3,763,167, Oct 2, 1973; Chem. Abstr. **79**, 137343q (1973).
34. R.E. Lister, J. Pharm. Pharmacol. **16**, 364 (1964).
35. G.F. Blane, A.L.A. Boura, A.E. Fitzgerald and R.E. Lister, Br. J. Pharmac. Chemother. **30**, 11 (1967).
36. J.W. Lewis, K.W. Bentley and A. Cowan, Annu. Rev. Pharmacol. **11**, 241 (1971).
37a. J.D. Wallach, J. Am. Vet. Med. Assoc. **149**, 871 (1966).
37b. A.M. Harthoorn, J. Am. Vet. Med. Assoc. **149**, 875 (1966).
38. K.W. Bentley, D.G. Hardy and B. Meek, J. Am. Chem. Soc. **89**, 3273 (1967).
39. K.W. Bentley and D.G. Hardy, J. Am. Chem. Soc. **89**, 3281 (1967).
40. K.W. Bentley, D.G. Hardy and B. Meek, J. Am. Chem. Soc. **89**, 3293 (1967).
41. K.W. Bentley, D.G. Hardy, C.F. Howell, W. Fulmor, J.E. Lancaster, J.J. Brown, G.O. Morton and R.A. Hardy, J. Am. Chem. Soc. **89**, 3303 (1967).
42. K.W. Bentley, D.G. Hardy, H.P. Crocker, D.I. Haddlesey and P.A. Mayor, J. Am. Chem. Soc. **89**, 3312 (1967).
43. K.W. Bentley in "The Alkaloids", Vol. XIII, R.H.F. Manske (Ed.), Academic Press, New York, 1971, 75.
44. W. Fulmor, J.E. Lancaster, G.O. Morton, J.J. Brown, C.F. Howell, C.T. Nora, R.A. Hardy, J. Am. Chem. Soc. **89**, 3322 (1967).
45. J.H. van den Hende and N.R. Nelson, J. Am. Chem. Soc. **89**, 2901 (1967).
46. A.F. Casy and R.T. Parfitt, "Opioid Analgesics", Plenum Press, New York, 1986.
47. G.R. Lenz, S.M. Evans, D.E. Walters and A.J. Hopfinger, "Opiates", Academic Press, Orlando, 1986.
48. A.H. Beckett, Progr. Drug Res. **1**, 527 (1959).
49. A.C. Ghosh, D.E. Portlock, H.C. Dalzell, C. Malmberg, P. Herlihy, R.K. Razdan, W.L. Duax and G.D. Smith, J. Org. Chem. **48**, 4137 (1983).
50. C.W. Hutchins, G.K. Cooper, S. Pürro and H. Rapoport, J. Med. Chem. **24**, 773 (1981).
51. L.L. Knipmeyer and H. Rapoport, J. Med. Chem. **28**, 461 (1985).
52. H. Rapoport and P. Sheldrick, J. Am. Chem. Soc. **85**, 1637 (1963).
53. P.R. Crabbendam, T.S. Lie, J.T.M. Linders and L. Maat, Recl. Trav. Chim. Pays-Bas **103**, 296 (1984).
54. T.S. Lie, J.T.M. Linders and L. Maat in "The Alkaloids", Vol. 0000, A. Brossi (ed.), Academic Press, to be published.
55. J.W. Lewis and M.J. Readhead, J. Med. Chem. **13**, 525 (1970).
56. M. Hori, T.Kataoka, H. Shimizu, E. Imai, T. Iwamura, M. Nozaki, M. Niwa and H. Fujimura, Chem. Pharm. Bull. **32**, 1268 (1984).
57. J.W. Lewis, P.A. Mason and D.I. Haddlesey, J. Med. Chem. **16**, 12 (1973).
58. J.W. Lewis, M.J. Readhead and A.C.B. Smith, J. Med. Chem. **16**, 9 (1973).
59. G.H. Loew and D.S. Berkowitz, J. Med. Chem. **22**, 603 (1979).
60. C.W. Hutchins and H. Rapoport, J. Med. Chem. **27**, 521 (1984).
61. H. Rapoport in "Natural Products and Drug Development", P. Krogsgaard-Larsen, S. Brøgger Christensen and H. Kofod (Eds.), Munksgaard, Copenhagen, 1984, 429.

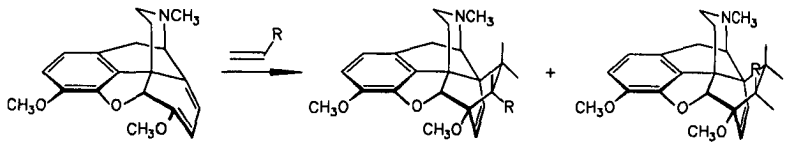
62. A. Kleemann, "Pharmazeutische Wirkstoffe", Thieme Verlag, Stuttgart, 1978, 266.
63. H. Schmidhammer, A.E. Jacobson and A. Brossi, Med. Res. Rev. 3, 1 (1983).
64. H.C. Beyerman, E. Buurman, T.S. Lie and L. Maat, Recl. Trav. Chim. Pays-Bas **95**, 43 (1976).
65. Y.K. Sawa and H. Tada, Tetrahedron **24**, 6185 (1968).
66. A. van Estrik, T.S. Lie and L. Maat, to be published.
67. P.R. Crabbendam, L. Maat and H.C. Beyerman, Recl. Trav. Chim. Pays-Bas **100**, 293 (1981).
68. H.C. Beyerman, P.R. Crabbendam, T.S. Lie and L. Maat, Recl. Trav. Chim. Pays-Bas **103**, 112 (1984).
69. D. Ranganathan, C. Bhushan Rao, S. Ranganathan, A.K. Mehrotra and R. Iyengar, J. Org. Chem. **45**, 1185 (1980).
70. L. Maat, J.A. Peters and M.A. Prazeres, Recl. Trav. Chim. Pays-Bas **104**, 205 (1985).
71. R.A. Lessor, K.C. Rice, R.A. Streaty, W.A. Klee and A.E. Jacobson, Neuropeptides (Edinburgh) **5**, 229 (1984).

CHAPTER 2 SYNTHESIS AND PHARMACOLOGY OF DEOXYGENATED ETHENOISOMORPHINANS

2.1. Introduction

Diels-Alder reaction of morphinan-6,8-dienes with mono-substituted ethenes

Thebaine (1) reacts smoothly with activated dienophiles such as acroleine[1-4], derivatives of acrylic acid[2-3,5-7], and alkyl and aryl vinyl ketones[2-3,5,8-13]. The dienophile approaches the diene system from the exposed β-side of the morphinan skeleton, i.e. from piperidine ring side (Scheme 1).



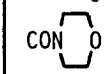
1 2 (major) 3 (minor)

Scheme 1. Diels-Alder reaction of thebaine with mono-substituted dienophiles.

The major product of the cycloaddition is in nearly all cases the 7α-substituted 6α,14α-ethenoisomorphinan 2, along with minor amounts (1-5%) of the 7β-isomer 3 (Table 1). An exception is the reaction with acrylonitrile, in which a substantial amount of the 7β-isomer is formed (7α:7β = 3:2)[3]. This phenomenon is also observed when acrylonitrile is reacted with cyclopentadiene or 1,3-cyclohexadiene. In these reactions, the epimers are formed in a ratio of 3:2 and 1:1, respectively[19-20]. The loss of selectivity can be explained[21-22] partly by the absence of advantageous secundary orbital interactions[23] and partly by the small steric demand of the nitrile group. With ethene or ethyl vinyl ether, no Diels-Alder reaction occurred[14]. Reaction of thebaine with the highly reactive

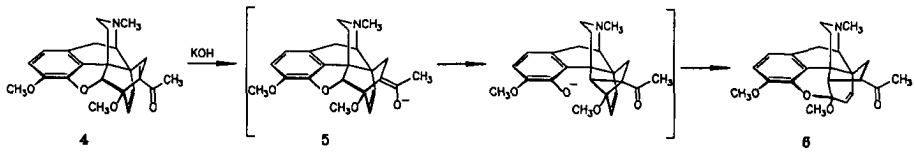
dienophile nitroethene[24] resulted in extensive polymerization of the dienophile due to the basicity (or nucleophilicity) of the tertiary amine[16,25]. When the basicity is masked by replacing the *N*-methyl by a *N*-formyl group, nitroethene cleanly adds to the morphinan, giving the expected 7α-nitro-6α,14α-ethenoisomorphinan in high yield[16].

Table 1. Thebaine and mono-substituted dienophiles (CH_2=CHR).

R	Yield	Remarks	References
H	no adduct, polymer	pressure, catalysts, rt→100 °C	14
CN	81%, 7α:7β = 3:2		2-3
CHO	92%, 7α		1-4
COMe	96.3% 7α, 1.5% 7β	1-kg scale*	2-3,8-10,15
COEt	80%, 7α		3
COnBu	no yield given, 7α		11
COtBu	90%, 7α	7α "fortement prédominant"	12-13
COPh	70%, 7α		2,8,15
CO_2Me	no yield given, 7α		3
CO_2Et	77%, 7α:7β = 94:6		3,15-16
$CONEt_2$	64%, 7α		7
	62%, 7α		7
NO_2	no adduct, polymer	pure, solution, pressure, catalysts, t -78→115 °C	16
NO_2	90%, 7α	*N*-formylnorthebaine	16
OEt	no adduct, polymer	pure, solution, pressure, $AlCl_3$	14
SO_2Me	61%, 7α		17-18
SO_2Et	no yield given, 7α		17
$SO_2CH=CH_2$	65%, 7α		17-18

*No trace of 8-substituted adducts.

Efforts to epimerize the adduct of thebaine and methyl vinyl ketone (**4**) only resulted in the rearranged product **6**, probably due to the highly nucleophilic character of the enolate intermediate **5** and the release of strain, which accompanies these rearrangements (Scheme 2).



Scheme 2. Base-catalyzed rearrangement of 7α-acetyl-6α,14α-ethenoisomorphinan **4**.

Only in the case of the adducts of thebaine and the vinylic sulfones, base-catalyzed epimerization could be effected without rearrangement[18].

From the results of the Diels-Alder reactions to thebaine analogues, it is obvious that the regioselectivity is mainly under steric control (Table 2).

Table 2. Ratio of the products of the Diels-Alder reaction of morphinan-6,8-dienes with methyl vinyl ketone yielding acetyl-6α,14α-ethenoisomorphinans.

Morphinan-6,8-diene	6-R	7α	8α	7β	Ref.
Thebaine	OMe	98	0	2	3
6-Deoxythebaine*	Me	96	3	1	11
6-Demethoxythebaine	H	88	12		26-27

*Trace amount (0.1%) of 8β-acetyl-6β,14β-ethenomorphinan isolated

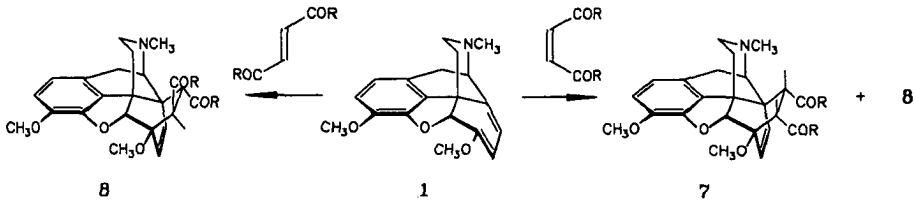
6-Demethoxythebaine, which may be considered to be a substituted 1-alkyl-1,3-cyclohexadiene, gives upon reaction with methyl vinyl ketone the 7α-acetyl-6α,14α-ethenoisomorphinan as the main product[26-27]. Probably, the steric influence of the morphinan skeleton overrides the electronic effect of the "alkyl"-substituent at C-14. This result may be compared with the reaction of methyl vinyl ketone with 1-methyl-1,3-cyclohexadiene, affording 2-acetyl-1-methylbicyclo[2.2.2]oct-5-ene as a 7:1 mixture of its epimers in 90% yield[28].

Diels-Alder reaction of thebaine with disubstituted dienophiles

Diels-Alder reaction of thebaine with cyclic dienophiles such as maleic anhydride[29-31], 1,4-benzoquinone[29-31] and maleinimides[32-33] afforded the 6α,14α-ethenoisomorphinans in high yield. However, thebaine failed to react with butenolide[34], which can be considered as a partly reduced maleic anhydride.

Reaction of thebaine with 1,1-disubstituted dienophiles proved to occur sluggishly, giving the 7-disubstituted 6α,14α-ethenoisomorphinans in low to mediocre yields, mostly after prolonged reaction time[35]. The slow reaction and the observed stereoselectivity are probably due to steric interactions in the respective transition states[21-22,36].

Analysis of the Diels-Alder reaction of thebaine with *cis*- and *trans*-disubstituted ethenes is complicated (Scheme 3, Table 3).



Scheme 3. Diels-Alder reaction of thebaine with *cis*- and *trans*-disubstituted ethenes.

Bentley[3] reported that no Diels-Alder reaction was observed between thebaine and crotonaldehyde. Reaction of thebaine with dimethyl maleate and maleonitrile, dienophiles with two, *cis*-positioned, activating groups, afforded the expected 7α,8α-disubstituted 6α,14α-ethenoisomorphinans **7** as the only products in 75% and 80% yield[32], respectively. Upon treatment of thebaine with maleic diamide, surprisingly, the ring-closed product was isolated, identical in all respects with the adduct of thebaine and maleinimide[32]. However, when thebaine was reacted with *cis*-1,2-diacetyl- or *cis*-1,2-dibenzoylethenes[37], mixtures of 7α,8α- and 7β,8α-disubstituted ethenoisomorphinans (**7**, **8**) were obtained (Table 3).

Table 3. Thebaine and acyclic 1,2-disubstituted dienophiles ($CHR^1=CHR^2$).

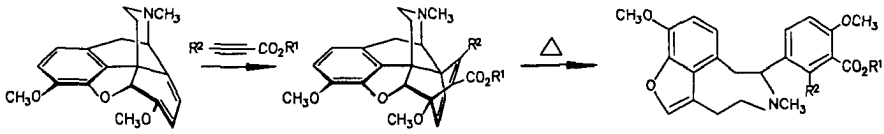
R^1	R^2	Yield	Remarks	Ref.
cis				
COMe	COMe	10% 7α,8α, 32% 7β,8α	dienophile *c:t* 2:1	37
COPh	COPh	22% 7α,8α, 37% 7β,8α		37
CO_2Me	COPh	21% 7α-COPh,8α-CO_2Me + mixture (no yield given) of 7β-COPh,8α-CO_2Me and 7β-CO_2Me,8α-COPh		37
CO_2Me	CO_2Me	75%, 7α,8α		32
$CONH_2$	$CONH_2$	76%, 7α,8α (cyclic)	see maleinimide	32
CN	CN	80%, 7α,8α		32
trans				
Me	CHO	no adduct		3
COMe	COMe	75%, 7β,8α		37
COPh	COPh	68%, 7β,8α		37
CO_2Me	COPh	47% 7β-COPh,8α-CO_2Me + 28% 7β-CO_2Me,8α-COPh		37
COCl	COCl	erratic yields	in EtOH	31

The formation of the latter product may be explained either by thermal isomerization of the dienophile during the reaction or by epimerization of the 7α,8α-adduct[37]. Efforts[37] to perform this epimerization using alkoxides resulted in deep-seated skeletal rearrangements. Reaction with the *trans*-diacylethenes afforded the 7β,8α-substituted ethenoisomorphinan 8 only without any trace of other products (Table 3). Applying asymmetrical dienophiles such as *cis*- and *trans*-methyl benzoylacrylates gave analogous results. Interestingly, the *cis*-dienophile gave, besides the isomerized products, only the adduct with the benzoyl group at C-7, but not the "reverse" one. It is noteworthy that there are no products isolated which have one of the substitutents in the 8β-orientation. The formation of these compounds seems to be hindered by the presence of the piperidine ring[37].

Diels-Alder reaction of thebaine with other dienophiles

Rapoport and Sheldrick found that ethyl propiolate reacted with thebaine only with difficulty and in low yield (benzene as solvent), yielding **9**, while dimethyl acetylenedicarboxylate (DMAD) gave adduct **10** in 90% yield[38]

(Scheme 4). The Diels-Alder adducts are thermally instable, affording benzazocine **11** upon heating in dibutyl ether[38].



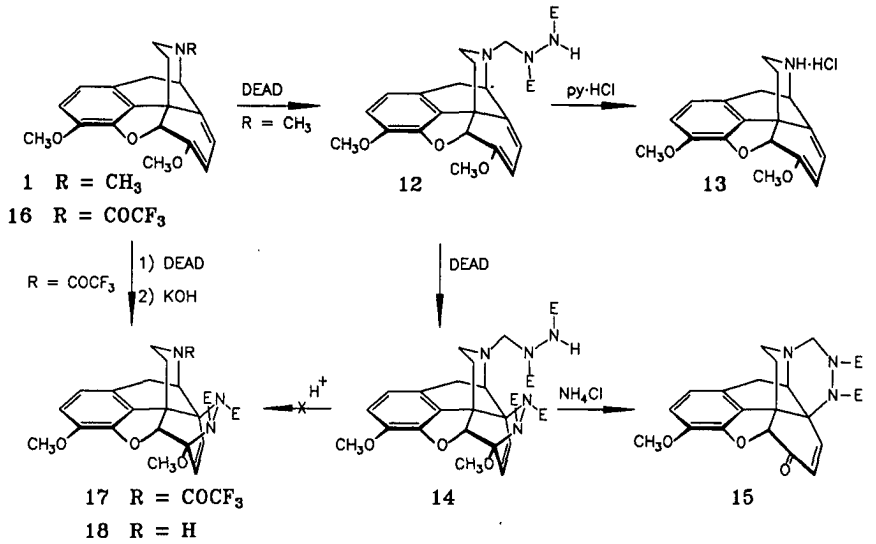
1 9 R^1 = Et, R^2 = H 11
10 R^1 = Me, R^2 = CO_2Me

Scheme 4. Diels-Alder reaction of thebaine with acetylenes.

In the early eighties, the reaction of thebaine with acetylenes was investigated in more detail by Kanematsu *et al.*[39-40] and Singh *et al.*[41-42]. The above-mentioned results were confirmed, but also an unexpected influence of the solvent was demonstrated. Depending on the properties (polarity, protic or aprotic, nucleophilicity) of the solvent used, different products were obtained, in which the C-9 - N bond was cleaved.

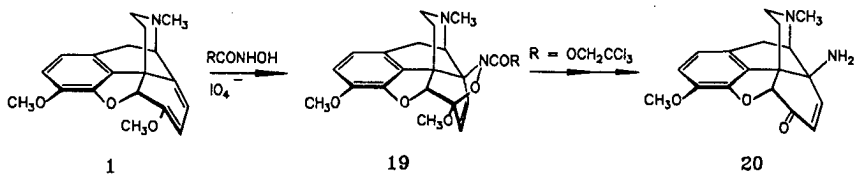
Reaction of thebaine with cyclic azo compounds occurs smoothly in high yield[43-44], giving the usual adducts (α-face attack). The reaction can be performed either by direct reaction with the dienophile or by preparing the azo compound through *in situ* oxidation ($Pb(OAc)_4$, tBuOCl) of the corresponding hydrazine derivative.

Reaction of thebaine (**1**) with diethyl azodicarboxylate (DEAD) took a different course. Addition of one equivalent of azo compound resulted in the formation of hydrazo compound **12**, which afforded *N*-northebaine (**13**) in good yield upon acid-catalyzed hydrolysis[45-47]. Excess DEAD led to subsequent Diels-Alder reaction to give **14**, which rearranged to **15** upon attempted hydrolysis. Reaction of *N*-(trifluoroacetyl)-*N*-northebaine (**16**) with DEAD gave the adduct **17** in 91% yield, which gave the *N*-demethylated adduct **18** of thebaine and DEAD after treatment with 40% potassium hydroxide (Scheme 5)[46].



Scheme 5. Reaction of thebaine (1) and *N*-(trifluoroacetyl)-*N*-northebaine (16) with DEAD.

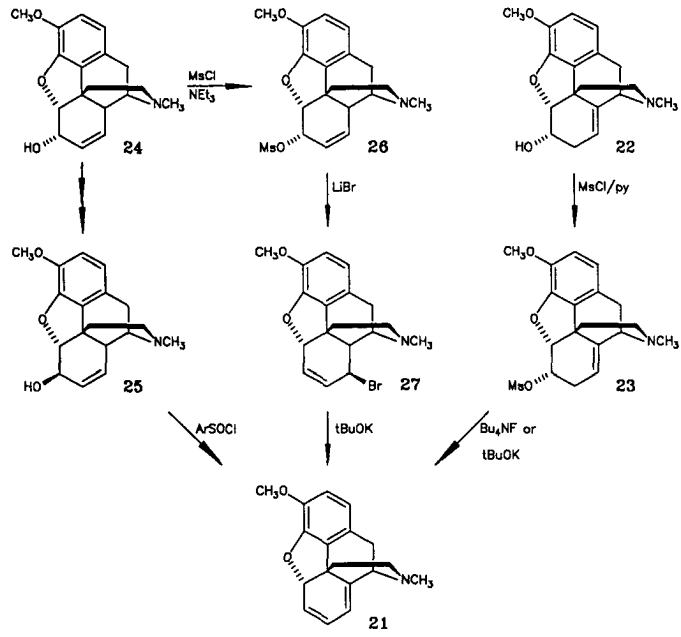
Reaction of thebaine with nitrosoarenes[47-49], nitrosyl cyanide[50-52] or transient *C*-nitrosocarbonyl compounds[53-60] afforded 1,2-oxazines **19**, providing a convenient method for the introduction of a nitrogen substituent at C-14. The investigations of Kirby *et al.* resulted in two syntheses of the pharmacologically interesting[61-62] 14β-aminocodeinone **20**, applying either 1-chloro-1-nitroso-cyclohexane[59] or, more conveniently, 2,2,2-trichloroethyl *N*-hydroxycarbamate (Scheme 6)[61] .



Scheme 6. Synthesis of 14β-aminocodeinone **20**.

Synthesis of 6-demethoxythebaine

The parent morphinan-6,8-diene 6-demethoxythebaine (**21**) could be obtained in high yield from the relatively rare opium alkaloid neopine (**22**)[63-64]. Mesylation in pyridine afforded 6-*O*-mesylneopine (**23**)[65-66], which gave **21** upon treatment with tetrabutylammonium fluoride in acetonitrile[65,67] or potassium *tert*-butanolate in methanol/ethanol[68] (Scheme 7). The same methodology was used for the preparation of 6-demethoxyoripavine from neomorphine[69].



Scheme 7. Syntheses of 6-demethoxythebaine (**21**) from neopine (**22**) and codeine (**24**).

In 1981, Hutchins *et al.*[26] reported a new synthesis of **21** starting from the more readily available codeine (**24**), which was converted to isocodeine **25** using *N,N*-dimethylformamide dineopentyl acetal and acetic acid, followed by methanolysis of the intermediate acetate (Scheme 7). Reaction of **25** with

2,4-dinitrobenzenesulfenyl chloride gave **21** (61% after chromatography), probably via rearrangement to the allylic sulfoxide[26,70]. The analogous reaction with codeine was not succesful.

A more convenient route was reported by Beyerman *et al.*[71]. Mesylation of codeine, followed by reaction with lithium bromide, afforded the nicely crystalline bromocodide (**27**), which gave **21** upon treatment with potassium *tert*-butanolate (Scheme 7). As no chromatographic purifications are required, the latter synthesis of **21** is feasible on multi-gram scale.

References

1. S.I. Kanevskaya and S.F. Mitryagina, J. Gen. Chem. (USSR), **17**, 1203 (1947); Chem. Abstr. **42**, 1596c (1948).
2. K.W. Bentley and J.C. Ball, J. Org. Chem. **23**, 1720 (1958).
3. K.W. Bentley and D.G. Hardy, J. Am. Chem. Soc. **89**, 3267 (1967).
4. J.J. Kopcho and J.C. Schaeffer, J. Org. Chem. **51**, 1620 (1986).
5. K.W. Bentley and D.G. Hardy, Proc. Chem. Soc. 220 (1963).
6. H.C. Beyerman, T.S. Lie, L. Maat and M. Noordam-Weissdorf, Recl. Trav. Chim. Pays-Bas **101**, 455 (1982).
7. O. Hromatka, M. Knollmüller and G. Sengstschmid, Monatsh. Chem. **99**, 1662 (1968).
8. K.W. Bentley and J.C. Ball, Chem. & Ind. (London) **1956**, 1428.
9. J.F. Macfarlan & Co., Ltd., Brit. 902,659, Aug. 9, 1962; Chem. Abstr. **57**, 16682h (1962).
10. J.F. Macfarlan & Co., Ltd., Fr. M1378, July 30, 1962; Chem. Abstr. **58**, 14030b (1963).
11. L.L. Knipmeyer and H. Rapoport, J. Med. Chem. **28**, 461 (1985).
12. C. Moulineau, R. Boigegrain and M. Morre, Fr. Demande. FR 2,554,816, May 17, 1985; Chem. Abstr. **104**, 110017j (1986).
13. B.C. Uff, A.S. Mallard, J.A. Davis and R. Henson, Magn. Res. Chem. **23**, 454 (1985).
14. M.A. Prazeres, T.S. Lie and L. Maat, unpublished results.
15. K.W. Bentley and J.C. Ball, J. Org. Chem. **23**, 1725 (1958).
16. L. Maat, J.A. Peters and M.A. Prazeres, Recl. Trav. Chim. Pays-Bas **104**, 205 (1985).
17. K.W. Bentley in "The Alkaloids", Vol. XIII, R.H.F. Manske (Ed.), Academic Press, New York, 1971, 75.
18. K.W. Bentley, J.W. Lewis and A.C.B. Smith, J. Chem. Soc., Perkin I, 870 (1972).
19. K. Alder, H. Krieger and H. Weiss, Ber. Dtsch. Chem. Ges. **88**, 144 (1955).
20. K. Alder, K. Heimbach and R. Reubke, Ber. Dtsch. Chem. Ges. **91**, 1516 (1958).
21. J.M. Mellor and C.F. Webb, J. Chem. Soc., Perkin II, 17 (1974).
22. B.C.C. Cantello, J.M. Mellor and C.F. Webb, J. Chem. Soc., Perkin II, 22 (1974).
23. R. Gleiter and M.C. Böhm, Pure Appl. Chem. **55**, 237 (1983).
24. D. Ranganathan, C. Bhushan Rao, S. Ranganathan, A.K. Mehrotra and R. Iyengar, J. Org. Chem. **45**, 1185 (1980).

25. D. Ranganathan, S. Ranganathan and S. Bamezai, Tetrahedron Lett. **23**, 2789 (1982).
26. C.W. Hutchins, G.K. Cooper, S. Pürro and H. Rapoport, J. Med. Chem. **24**, 773 (1981).
27. P.R. Crabbendam, T.S. Lie, J.T.M. Linders and L. Maat, Recl. Trav. Chim. Pays-Bas **103**, 296 (1984).
28. R.P. Gregson and R.N. Mirrington, Aust. J. Chem. **29**, 2049 (1976).
29. W. Sandermann, Ber. Dtsch. Chem. Ges. **71**, 648 (1938).
30. C. Schöpf, K. von Gottberg and W. Petri, Lieb. Ann. Chem. **536** , 216 (1938).
31. K.W. Bentley and A.F. Thomas, J. Chem. Soc. 1863 (1956).
32. O. Hromatka, G. Sengstschmid and K. Eichinger, Monatsh. Chem. **102**, 1015 (1971).
33. J. Lewis and W.I. Rushworth, J. Chem. Soc., (C) 560 (1970).
34. R.M. Boden, "Approaches to the Synthesis of Narcotic Antagonists and Rigid Opiates", Thesis, University of Rochester, 1979.
35. J.W. Lewis, M.J. Readhead, I.A. Selby, A.C.B. Smith and C.A. Young, J. Chem. Soc., (C) 1158 (1971).
36. B.C.C. Cantello and J.M. Mellor, Tetrahedron Lett. **9**, 5179 (1968).
37. R. Rubinstein, F. Haviv and D. Ginsburg, Tetrahedron **30**, 1201 (1974).
38. H. Rapoport and P. Sheldrick, J. Am. Chem. Soc. **85**, 1637 (1963).
39. K. Hayakawa, S. Motohiro, I. Fujii and K. Kanematsu, J. Am. Chem. Soc. **103**, 4605 (1981).
40. K. Hayakawa, I. Fujii and K. Kanematsu, J. Org. Chem. **48**, 166 (1983).
41. A. Singh, S. Archer, K. Hoogsteen and J. Hirschfield, J. Org. Chem. **47**, 752 (1982).
42. A. Singh, S. Archer, K. Hoogsteen and J. Hirschfield, J. Org. Chem. **48**, 173 (1983).
43. O. Hromatka and G. Sengstschmid, Monatsh. Chem. **102**, 1022 (1971).
44. R. Giger, R. Rubinstein and D. Ginsburg, Tetrahedron **29**, 2387 (1973).
45. Eli Lilly and Co., Neth. Appl. 6,515,815, June 8, 1966; Chem. Abstr. **65**, 15441d (1966).
46. H. Merz and K.-H. Pook, Tetrahedron **26**, 1727 (1970).
47. L.S. Schwab, J. Med. Chem. **23**, 698 (1980).
48. K.W. Bentley, P. Horsewood, G.W. Kirby and S. Singh, J. Chem. Soc., Chem. Commun. 1411 (1969).
49. G.W. Kirby, K.W. Bentley, P. Horsewood and S. Singh, J. Chem. Soc., Perkin I 3064 (1979).
50. P. Horsewood and G.W. Kirby, J. Chem. Soc., Chem. Commun. 1139 (1971).
51. P. Horsewood and G.W. Kirby, J. Chem. Soc., Perkin I 1587 (1980).
52. P. Horsewood, G.W. Kirby, R.P. Sharma and J.G. Sweeny, J. Chem. Soc., Perkin I 1802 (1981).
53. G.W. Kirby and J.G. Sweeny, J. Chem. Soc., Chem. Commun. 704 (1973).
54. G.W. Kirby and J.G. Sweeny, J. Chem. Soc., Perkin I 3250 (1981).
55. J.E.T. Corrie, G.W. Kirby and J.W.M. Mackinnon, J. Chem. Soc., Perkin I 883 (1985).
56. G.W. Kirby, J.W.M. Mackinnon and R.P. Sharma, Tetrahedron Lett. **18**, 215 (1977).
57. G.W. Kirby, H. McGuigan, J.W.M. Mackinnon, D. McLean and R.P. Sharma, J. Chem. Soc., Perkin I 1437 (1985).
57. C.C. Christie, G.W. Kirby, H. McGuigan and J.W.M. Mackinnon, J. Chem. Soc., Perkin I 2469 (1985).
58. J.E.T. Corrie, G.W. Kirby and R.P. Sharma, J. Chem. Soc., Perkin I 1571 (1982).
59. C.M. Bladon and G.W. Kirby, J. Chem. Soc., Chem. Commun. 1402 (1982).
60. P.Horsewood and G.W. Kirby, J. Chem. Res. (S) 401 (1980).

61. S. Archer, A. Seyed-Mozaffari. P. Osei-Gyimah, J.M. Bidlack and L.G. Abood, J. Med. Chem. **26**, 1775 (1983).
62. G.W. Kirby and D. McLean, J. Chem. Soc., Perkin I 1443 (1985).
63. S. Makleit, Berényi and R. Bognár, Acta Chim. (Budapest) **94**, 165 (1977).
64. R.B. Barber and H. Rapoport, J. Med. Chem. **19**, 1175 (1976).
65. S. Berényi, S. Hosztafi, S. Makleit, R.Bognár and A. Tegdes, Acta Chim. Acad. Sci. Hung. **103**, 365 (1980).
66. L. Maat, J.A. de Groot and H.C. Beyerman, Synth. Commun. **9**, 713 (1979).
67. S. Berényi, S. Hosztafi, S. Makleit and I. Szeifert, Acta Chim. Acad. Sci. Hung. **110**, 363 (1982).
68. P.R. Crabbendam, L. Maat and H.C. Beyerman, Recl. Trav. Chim. Pays-Bas **100**, 293 (1981).
69. S. Berényi, S. Hosztafi, S. Makleit and I. Molnár, Acta Chim. Hung. **113**, 51 (1983).
70. I. Fujii, M. Koreyuki and K. Kanematsu, Chem. Pharm. Bull. **36**, 1750 (1988).
71. H.C. Beyerman, P.R. Crabbendam, T.S. Lie and L. Maat, Recl. Trav. Chim. Pays-Bas **103**, 112 (1984).

2.2

Synthesis of 6,14-ethenoisomorphinans and 6,14-ethenomorphinans based on Diels-Alder adducts of 6-demethoxythebaine and 6-demethoxy-β-dihydrothebaine; pharmacology of the isomorphinans

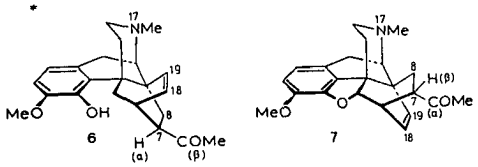
Synthesis of 6,14-ethenoisomorphinans and 6,14-ethenomorphinans* based on *Diels–Alder* adducts of 6-demethoxythebaine and 6-demethoxy-β-dihydrothebaine; pharmacology** of the isomorphinans (Chemistry of Opium Alkaloids, Part XIX***)

P. R. Crabbendam****, T. S. Lie, J. T. M. Linders and L. Maat

Laboratory of Organic Chemistry, Technische Hogeschool Delft, Julianalaan 136, 2628 BL Delft, The Netherlands
(Received May 24th, 1984)

Abstract. Two different types of *Diels–Alder* additions to morphinan-6,8-dienes have been found. 6-Demethoxythebaine (**2**) yielded ethyl 4,5α-epoxy-3-methoxy-*N*-methyl-6,14-ethenoisomorphinan-7α-carboxylate (**3**) with ethyl acrylate, in analogy to the reaction with thebaine. The ester **3** was converted into the alcohol **4**, of which the 3-methoxy ether was hydrolyzed to yield **5**. Similarly, **2** gave the 7α-acetyl-6,14-ethenoisomorphinan **7** with methyl vinyl ketone. The latter compound was converted into **4** using methylmagnesium iodide. With propylmagnesium bromide, **7** afforded four compounds; two are new etorphine analogues (**8** and **9**), to which we were able to assign the absolute configuration; the other two are the Grignard reduction products **10** and **11**.
When the 4,5α-epoxy bridge of **2** is first opened, the *Diels–Alder* reaction with methyl vinyl ketone proceeds from the other side of the diene system yielding the 7β-acetyl-6,14-ethenomorphinan **6**, which belongs to a novel class of rigid morphinans.
Preliminary pharmacological screening** of **5**, **8** and **9** showed these compounds to be potent agonists.

*



(an ethenomorphinan) (an ethenoisomorphinan)
Locant numbers 18 and 19 according to Chemical Abstracts.

The naming and numbering of morphinans is confusing because different methods are in use. Since Bentley *et al.* studied the *Diels–Alder* reaction of thebaine, a 6,7,8,14-tetradehydromorphinan, the adducts are named 7-substituted (*N*-methyl)-6,14-*endo*-ethenomorphinans (for example compound **7**). In older literature, the nitrogen of morphinan was not numbered. However, when the morphinan skeleton, as it can be found in natural morphine (depicted in IUPAC Rule F-4.12, Example 46)[19], is regarded as the parent ring system, the "Bentley-type of adducts" should be named *17-substituted* 7,8-didehydro-*N*-methyl-6,14-ethanomorphinans. If nitrogen gets locant number 17, as in Chemical Abstracts, the adducts are *18-substituted* 7,8-didehydro-17-methyl-6,14-ethanomorphinans. Consequently, the new cycloaddition products (compound **6** of this publication and compound **6b** of ref. 12) should be named *7-substituted* 18,19-didehydro-17-methyl-6,14-ethanomorphinans. This leads to much confusion when reading the older literature.
Moreover, the prefixes "*-endo-*", still *in* use for the class of compounds first mentioned, and "*-exo-*", used for the new compounds in ref. 12, are deceptive. The differences of *"endo"* and *"exo"* of the various morphinan cycloadducts are subtle and not always clear.

We therefore suggest, for the ring systems of the "*Bentley*-type of *endo*-adducts", the name 6,14-*ethenoisomorphinans*, and for the new class of compounds, the name *6,14-ethenomorphinans*. In both cases, an etheno bridge is added to a distinguishable molecule, namely isomorphinan and morphinan, respectively. This leaves the usual numbering of the ring system unaltered at the positions 7 and/or 8, together with the statements of α and β with respect to the "phenanthrene" moiety.

* Dr. *A. E. Jacobson*, National Institutes of Health, Bethesda, Maryland, U.S.A.
** Part XVIII see ref. 5.
*** Deceased September 28, 1983.

Introduction

The search for analgesics acting stereospecifically at binding sites in the central nervous system, has led to a great variety of synthetic compounds having the morphinan skeleton. *Diels–Alder* adducts of (−)-thebaine gave rise to highly potent analgesics, such as etorphine (**1**), which is about a thousand times more active than morphine[1]. In addition morphinans with fewer oxygen-containing substituents have also been developed; for instance, levorphanol [(−)-3-hydroxy-*N*-methylmorphinan]. The latter compound is an analgesic in clinical use. It is about five times more active than morphine and possesses a longer duration of action although it still has a number of drawbacks[2]. Recently, *Brossi* et al. prepared morphinans with oxygen-containing substituents at a distinctive position in the aromatic ring of the morphinan. They found striking similarities in activity between the C-4 oxygenated morphinan-6-ones and their C-3 oxygenated counterparts. In contrast, the C-2 hydroxy and methoxy analogues are practically devoid of antinociceptive activity[3]. 1-Hydroxy-*N*-methylmorphinan-6-one did not show antinociception when tested in the hot-plate assay in mice, in contrast to the methyl ether which did[4].

In the course of this laboratory's search for new analgesics, we investigated syntheses of *Diels–Alder* adducts of morphinans containing less oxygen, starting from 6-demethoxythebaine (**2**). This morphinan-6,8-diene is now readily accessible from (−)-codeine[5]. It can be used as starting material for all the 6-deoxygenated 6,14-ethenoisomorphinans* with

[1] *J. W. Lewis, K. W. Bentley* and *A. Cowan*, Annu. Rev. Pharmacol. **11**, 241 (1971).
[2] *J. Hellerbach, O. Schnider, H. Besendorf* and *B. Pellmont*, in "Synthetic Analgesics", Part II, Monograph in Organic Chemistry, Vol. **8**, Pergamon, New York, 1966, p. 16.
[3] *H. Schmidhammer, A. E. Jacobson* and *A. Brossi*, Med. Res. Rev. **3**, 1 (1983).
[4] *H. Schmidhammer* and *A. Brossi*, J. Org. Chem. **48**, 1469 (1983).
[5] *H. C. Beyerman, P. R. Crabbendam, T. S. Lie* and *L. Maat*, Recl. Trav. Chim. Pays-Bas **103**, 112 (1984).

an altered oxygen substituent pattern in the aromatic ring. Some deoxygenated 6,14-ethenoisomorphinans have been previously described in passing. In 1970, 3-deoxygenated *Diels–Alder* adducts of oripavine were prepared with allyl and cyclopropylmethyl substituents at the nitrogen atom[6]. In 1981, *Rapoport* et al.[7] described the 6-demethoxythebaine analogues of etorphine in order to study the interaction of hydrogen bonding between the 6-methoxy group and the tertiary alcohol function of etorphine. For this interaction *quantum-mechanical calculations have been performed*[8]. Conversion of **2**, using ethyl acrylate or methyl vinyl ketone, mainly yielded 7α-substituted addition products[9] (**3** and **7**, respectively), similar to the addition products of thebaine[10]. We here report on the synthesis of these adducts and their reaction products with Grignard reagents, together with some preliminary pharmacological results.

In addition, we have succeeded in opening the 4,5α-epoxy bridge of 6-demethoxythebaine **2**. This new morphinan-6,8-diene, 6-demethoxy-β-dihydrothebaine, was difficult to purify. However, treatment with methyl vinyl ketone gave the *Diels–Alder* adduct **6** with the 6,14-ethenomorphinan skeleton[11]. This is in contrast to the *Diels–Alder* addition of morphinan-6,8-dienes with the epoxy bridge closed. Thus, a novel class of potentially interesting morphinans becomes accessible. *Razdan* et al.[12] found, quite recently, a similar cycloaddition starting from β-dihydrothebaine. They called the reaction product a "7α-acetyl-6,14-*exo*-ethenomorphinan"*.

Results and discussion

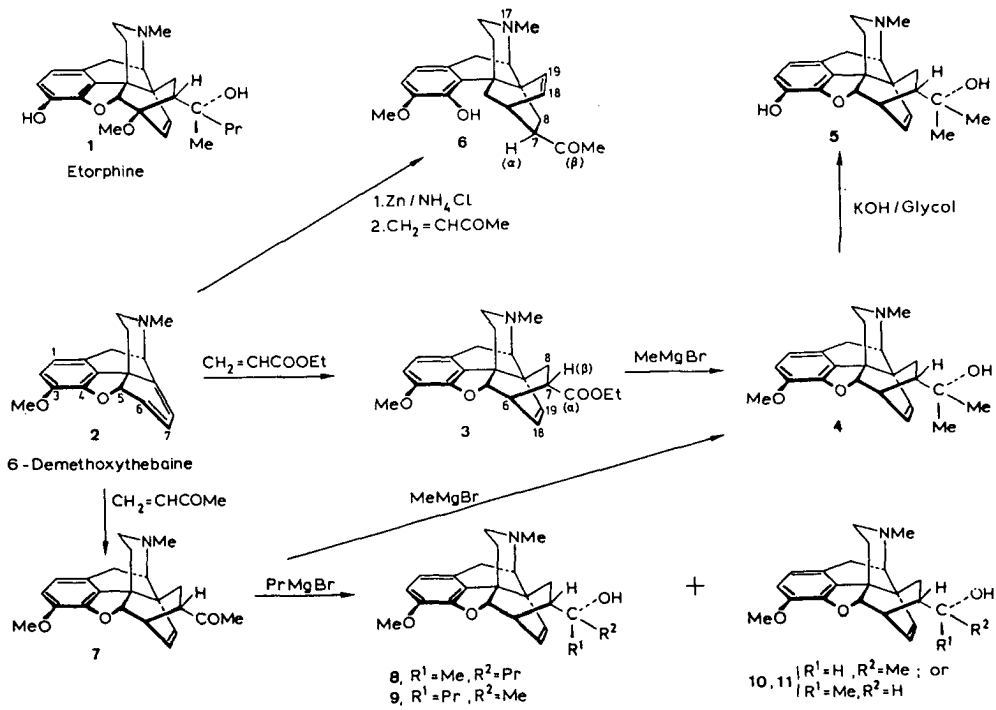
(−)-6-*Demethoxythebaine* (**2**), *prepared from natural* (−)-codeine[5], is the first morphinan-6,8-diene which has been converted into *Diels–Alder* adducts with fewer oxygen-containing substituents[7,9] as compared to the well-known "*Bentley* compounds". With ethyl acrylate it mainly gave the 7α-substituted isomer, (−)-ethyl 4,5α-epoxy-3-methoxy-*N*-methyl-6,14-ethenoisomorphinan-7α-carboxylate (**3**), in analogy to the reaction with (−)-thebaine[10] (Scheme 1).

Conversions of the 7α-ethoxycarbonyl group of **3** into a tertiary alcohol substituent gave compounds closely related to etorphine (**1**). The latter compound possesses the (*R*)-7α-methylpropylmethanol substituent.

Compound **3** *afforded exclusively the* 7α-*dimethylmethanol* **4** on treatment with an excess of methylmagnesium iodide. When one equivalent or less of the Grignard reagent was used, it was not found possible to obtain the 7α-acetyl derivative **7**; alcohol **4** was isolated together with the starting material **3**. This is in contrast to the behaviour found with analogous compounds[13]. Although the use of **3** is therefore limited, the resulting 7α-dimethylmethanol does not contain a chiral centre at the methanol group, as does etorphine (**1**)

---

[6] *J. W. Lewis* and *M. J. Readhead*, J. Med. Chem. **13**, 525 (1970).
[7] *C. W. Hutchins*, *G. K. Cooper*, *S. Pürro* and *H. Rapoport*, J. Med. Chem. **24**, 773 (1981).
[8] *G. H. Loew* and *D. S. Berkowitz*, J. Med. Chem. **22**, 603 (1979).
[9] *P. R. Crabbendam*, *L. Maat* and *H. C. Beyerman*, Recl. Trav. Chim. Pays-Bas **100**, 293 (1981).
[10] *K. W. Bentley* in "The Alkaloids", Vol. XIII (Ed. *R. H. F. Manske*), Academic Press, New York, London, 1971, p. 75.
[11] *H. van Koningsveld*, *T. S. Lie* and *L. Maat*, Acta Crystallogr., in the press.
[12] *A. C. Ghosh*, *D. E. Portlock*, *H. C. Dalzell*, *C. Malmberg*, *P. Herlihy*, *R. K. Razdan*, *W. L. Duax* and *G. D. Smith*, J. Org. Chem. **48**, 4137 (1983).
[13] *K. W. Bentley* and *D. G. Hardy*, J. Am. Chem. Soc. **89**, 3267 (1967).



Scheme 1. Diels–Alder *adducts of 6-demethoxythebaine* (**2**).

and thus no diastereomers need to be separated. In order to obtain non-symmetrical 7α-dialkylmethanols, we started from **7**, as discussed below.

For an appropriate comparison with the antinociceptive agonists, such as morphine and etorphine, the 3-methoxy group has to be converted into the 3-hydroxy substituent. We therefore studied the hydrolysis of the 3-methyl ether of **4**. Prolonged boiling of **4** with potassium hydroxide in ethylene glycol[14] gave the 3-hydroxy compound **5** in high yield. We found that the addition of a small amount of water, or alternatively starting from the hydrochloride of **4**, considerably reduced the reaction time and also minimized the corrosion of the glass reaction vessel. Product **5**,obtained by treatment of **4** with potassium *tert*-butoxide in boiling dimethyl sulfoxide, was contaminated with by-products which were difficult to remove; moreover, the yield was low. Procedures generally used to hydrolyze phenolic ethers, for example hydrogen bromide in glacial acetic acid, boron trifluoride etherate, trimethylsilyl iodide and boron tribromide, failed in the case of **4**. All these reagents gave complex mixtures of reaction products, probably contaminated with the oxygen sensitive 3,4-dihydroxy compounds.

For further alterations in the oxygen-containing substituents and, possibly, further reduction of the number of these substituents, we studied the ring opening of the 4,5α-epoxy bridge. A selective ring opening of the *Diels–Alder* adducts **4** and **7** proved impossible using the normal reagents. However, treatment of 6-demethoxythebaine (**2**) with zinc and ammonium chloride resulted in the desired ring opening. The 4-hydroxymorphinan-6,8-diene was obtained, together with a side-product which did not contain a conjugated diene system. The mixture was treated with methyl vinyl ketone and a new compound (**6**) could then be isolated. 200 MHz ^{1}H NMR of **6** confirmed the ring opening of the epoxy bridge, in that the spectrum contained the signals of the 5α and the 5β protons at 1.7 and 2.5 ppm, respectively (Table 1). NMR also indicated that the cycloaddition had taken place in a different way as compared with the 4,5α-epoxymorphinans. Obviously, opening of the epoxy bridge in **2** allows *cycloaddition from the other side of the diene system*. The structure of **6**, especially with respect to the position of the etheno bridge and that of the acetyl substituent, could not be determined unambiguously from ^{1}H NMR data. A single-crystal X-ray analysis, however, showed **6** to be (+)-7β-acetyl-4-hydroxy-3-methoxy-*N*-methyl-6,14-ethenomorphinan[11] (Fig. 1). It is clear that the acetyl substituent is again orientated to the double bond of the etheno bridge, in agreement with the "*Diels–Alder endo* rule".

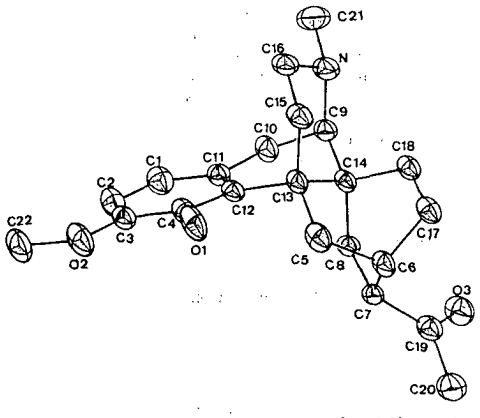


Fig. 1. ORTEP drawing of the structure of (+)-7β-*acetyl-4-hydroxy-3-methoxy*-N-*methyl-6,14-ethenomorphinan* (**6**).

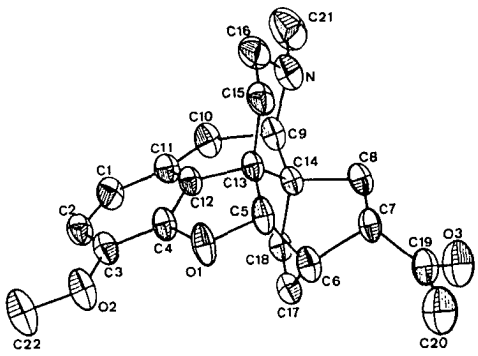


Fig. 2. ORTEP drawing of the structure of (−)-7α-*acetyl-4,5α-epoxy-3-methoxy*-N-*methyl-6,14-ethenoisomorphinan* (**7**).

Diels–Alder reaction of 6-demethoxythebaine (**2**) with methyl vinyl ketone gave the 7α-acetyl derivative **7**. The main product was again the 7α-isomer.

Evidence has been found that the 7β-, 8α- and 8β-isomers are formed in small quantities[7]; these could easily be removed by crystallization. Single-crystal X-ray analysis of **7** showed the structure to be (−)-7α-acetyl-4,5α-epoxy-3-methoxy-*N*-methyl-6,14-ethenoisomorphinan[15] (Fig. 2). This result also enabled us to assign all the ^{1}H NMR signals of **7**. Conversion of **7** with methylmagnesium iodide afforded **4**, identical with the product obtained from **3**.

In order to obtain compounds more closely related to etorphine (**1**), **7** was reacted with propylmagnesium bromide. HPLC analysis of the reaction mixture showed that four compounds were formed, in almost equal quantities. After separation, it was found that two of the compounds are the expected diastereoisomers **8** and **9**, the other two products being the so-called Grignard reduction compounds **10** and **11**.

A tentative assignment of the stereochemistry of **8** and **9** is based on the correspondence of the NMR signals of the methyl groups near the alcohol function[7,16]. The δ 0.95 ppm shift observed for **8** indicates the *R* configuration while the δ 1.08 ppm shift observed for **9** is conform the *S* configuration. The assignment of the stereochemistry of **10** and **11** on this basis failed. Similar Grignard reactions and Grignard reductions with the thebaine analogues have been described by *Bentley* et al.[17], who always found one diastereoisomer to be formed in great excess. Their explanation was based on coordination of the magnesium atom with oxygen atoms of both the C-7α carbonyl and C-6 methoxy groups. Indirect support for this mechanism may be deduced from the fact that we find almost equal amounts of diastereoisomers when using analogues not containing the C-6 methoxy group. Preliminary experiments with ethyl- and butyl-magnesium bromide confirm this. Treatment of **7** with butyllithium affords the butylmethylmethanol analogues in an *R*/*S* ratio of 1.2/1[7].

---

[14] *K. W. Bentley* and *D. G. Hardy*, J. Am. Chem. Soc. **89**, 3281 (1967).

[15] *H. van Koningsveld, L. Maat* and *T. S. Lie*, Acta Crystallogr. **C40**, 1082 (1984).

[16] *W. Fulmor, J. E. Lancaster, G. O. Morton, J. J. Brown, C. F. Howell, C. T. Nora* and *R. A. Hardy, Jr.*, J. Am. Chem. Soc. **89**, 3322 (1967).

[17] *K. W. Bentley, D. G. Hardy* and *B. Meek*, J. Am. Chem. Soc. **89**, 3273 (1967).

Pharmacology[**]

The pharmacological activity of the diastereoisomeric tertiary alcohols (*R*)-**8** and (*S*)-**9** and of compound **5** was determined using the mouse hot-plate assay (sc injection). All three compounds are potent agonists. The ratio of potenty for (*R*)-**8**/(*S*)-**9**/**5** is approximately 40/2/7 (morphine 1).
As with the etorphine series, the (*R*)-alcohol (**8**) is much more potent than the (*S*)-isomer (**9**). This also confirms the finding of *Rapoport* et al.[7] that the hydrogen bond between the methoxy group and the tertiary alcohol is not necessary for potent analgesic activity.

Experimental

Mass spectra were measured by Dr. *P. J. W. Schuyl* and Mrs. *A. H. Knol-Kalkman* using a Varian MAT 311A mass spectrometer. ^{1}H NMR spectra were measured using a Varian T-60 spectrometer. The 200 MHz spectra were obtained using a Nicolet NT-200 WB. Rotations were measured using a Perkin Elmer P141 polarimeter. Reactions were monitored by TLC on deactivated silica (0.25 mm, Merck F_{254}; eluent: dichloromethane/methanol/25% ammonia 85/15/0.5). The compounds were detected with UV (254 nm) and iodine vapour. In the case of **6**, we also used 2,6-dibromoquinone-4-chloroimide for the detection of phenols[18]. Melting points are uncorrected. Analytically, HPLC was performed using a Waters M-6000 pump on a reverse-phase column (15 cm × 0.4 cm I.D., Nucleosil C_{18}, 7 μm, 30°C), using a mixture of methanol/water/trifluoroacetic acid 50/50/0.1 as eluent, with detection on a Pye LC3 variable wave length detector at 240–250 nm.

(−)-6-Demethoxythebaine (**2**)

The starting material **2** was obtained from neopine as described in ref. 9. It is also accessible from codeine (ref. 5). M.p. 70–71°C; $[\alpha]_D^{25}$ −202° (*c* 0.5, chloroform).

(−)-Ethyl 4,5α-epoxy-3-methoxy-N-methyl-6,14-ethenoisomorphinan-7α-carboxylate (**3**)

Compound **3** was obtained as the hydrochloride as described in ref. 9. M.p. of **3** · HCl · H_2O 238°C (dec.); $[\alpha]_D^{25}$ −145° (*c* 0.5, methanol).

(−)-4,5α-Epoxy-3-methoxy-α,α,N-trimethyl-6,14-ethenoisomorphinan-7α-methanol (**4**)

a. 4 from 3. A solution of **3**, prepared from **3** · HCl · H_2O (2.5 g, 5.7 mmol) in 20 ml of diethyl ether, was slowly added to a boiling solution of methylmagnesium iodide, prepared from magnesium (240 mg) and methyl iodide (1.7 g, 12 mmol) in 15 ml of dry ether. The reaction mixture was boiled under reflux until TLC-showed complete conversion. The excess of Grignard reagent was destroyed using a saturated solution of ammonium chloride. The layers were separated and the aqueous layer extracted with ether. The combined ether layers were washed with a saturated solution of sodium chloride and dried over sodium sulfate. Evaporation of the solvent *in vacuo* afforded 2.5 g of a white foam of **4** which was crystallized as the hydrochloride from ethanol/diethyl ether. Yield 2.0 g (5.1 mmol, 89%). M.p. 247°C (dec.); $[\alpha]_D^{25}$ −145° (*c* 1.2, water). MS: M$^+$ 367. ^{1}H NMR ($CDCl_3$) of the free base: δ 1.10 (d, *J* 6 Hz, 6H, $C(CH_3)_2$), 2.38 (s, 3H, NCH_3), 3.80 (s, 3H, OCH_3), 4.47 (d, *J* 3 Hz, 1H, 5β-H), 5.57 (m, 2H, (17 + 18)-H), 6.52 (q, 2H, Ar–H).

b. 4 from 7. In a Soxhlet apparatus, compound **7** (1.0 g, 2.8 mmol) was extracted into a boiling solution of methylmagnesium iodide, prepared from magnesium (250 mg) and methyl iodide (1.4 g, 10 mmol) in 25 ml of dry ether. After the reaction was complete (TLC), the excess of Grignard reagent was destroyed using a solution of 1 M ammonium chloride and the mixture was then worked up as described above. Yield 700 mg (1.9 mmol, 67% of **4**, identical with the compound obtained from **3** by TLC, m.p. and NMR.

(−)-4,5α-Epoxy-3-hydroxy-α,α,N-trimethyl-6,14-ethenoisomorphinan-7α-methanol (**5**)

a. Starting from the base **4**. A solution of potassium hydroxide (5.0 g, 89 mmol) in 5 ml of ethylene glycol was added to compound **4** (1.0 g, 2.7 mmol) dissolved in 20 ml of ethylene glycol. The reaction mixture was refluxed for 72 h. The pH of the solution was adjusted to 7–8 using 2 *N* hydrochloric acid and, after the addition of 50 ml of water, thoroughly extracted with dichloromethane (10 portions of 45 ml). The combined organic layers were washed with a saturated solution of sodium chloride and dried over sodium sulfate. The solvent was evaporated to dryness *in vacuo*, affording 670 mg of **5** (1.9 mmol, 70%). The hydrochloride was crystallized from ethanol/ether. M.p. 230–235°C, $[\alpha]_D^{25}$ −166° (*c* 1.0, water). MS:M$^+$ 353. ^{1}H NMR ($CDCl_3$) of the free base: δ 1.10 (d, 6H, $C(CH_3)_2$), 2.40 (s, 3H, NCH_3), 4.50 (d, *J* 3 Hz, 1H, 5β-H), 5.55 (m, 2H, (17 + 18)-H), 6.45 (q, 2H, Ar–H).

b. Starting from the hydrochloride of **4**. A solution of **4** · HCl (1.0 g, 2.5 mmol) and 7 g of potassium hydroxide in 30 ml of ethylene glycol was boiled under reflux; after 6 h, the conversion was complete (TLC). The reaction mixture was poured into 100 ml of water and washed with dichloromethane. The aqueous layer was adjusted to pH 7–8 and **5** · HCl was isolated as described above (720 mg, 1.8 mmol, 75%).

(+)-7β-Acetyl-4-hydroxy-3-methoxy-N-methyl-6,14-ethenomorphinan (**6**)

a. Treatment of **2** *with zinc and ammonium chloride.* Ammonium chloride (17 g) in water (40 ml) and zinc powder (8 g) were added to a solution of **2** (10 g, 35.5 mmol) in ethanol (160 ml). The reaction mixture was refluxed for 22 h. After cooling to room temperature, 50 ml of dichloromethane was added and the solid material removed by filtration. The solvent was evaporated *in vacuo*, 250 ml of water was then added and the mixture extracted with dichloromethane. Working up in the usual manner yielded 10 g of a solid product, which was purified by crystallization from methanol/diethyl ether (1/5). TLC showed only one spot, but HPLC revealed the existence of two products in almost equal quantity. The ^{1}H NMR spectrum indicated the opening of the 4,5α-epoxy bridge with two NCH_3 signals at δ 2.31 and δ 2.35 suggesting the presence of a conjugated and an unconjugated morphinandiene.

b. Cycloaddition with methyl vinyl ketone. Without further purification, the mixture (4.0 g) was refluxed with 50 ml of freshly distilled methyl vinyl ketone. TLC showed that the reaction stopped at approximately 50% conversion, even after 72 h. Methyl vinyl ketone was removed *in vacuo* and the residue taken up in 0.5 N phosphoric acid and washed several times with dichloromethane. Some ammonia was then added to the aqueous layer which was worked up in the usual manner. Purification of the crude mixture was performed over a silica-gel column to afford (+)-7β-acetyl-4-hy-

Table 1 Chemical shifts and coupling constants observed in the 200 MHz NMR spectrum of compound **6**.

Chemical shifts (ppm) Proton	δ	Coupling constants (Hz)	
1	6.614	$J_{1,2}$	8.3
2	6.702	$J_{1,10'}$	0.9
5	2.522	$J_{5,5'}$	−13.7
5'	1.729	$J_{5,6}$	2.3
6	~2.95	$J_{5',6}$	4.8
7	2.565	$J_{6,7}$	2.3
8	~1.82	$J_{6,17}$	6.2
8'	1.483	$J_{7,8}$	9.6
9	2.913	$J_{7,8'}$	4.8
10	3.010	$J_{9,10}$	5.3
10'	2.760	$J_{10,10'}$	−17.8
15	1.925		
15'	~1.5		
16	2.300		
16'	~1.8		
17	6.081		
18	6.404		
OCH_3	3.866		
NCH_3	2.352		
$COCH_3$	2.083		

[18] *E. Nürnberg*, Dtsch. Apoth. Ztg. **101**, 268 (1961).
[19] IUPAC Nomenclature of Organic Chemistry, Sections A, B, C, D, E, F and H, 1979 Edition, Pergamon Press, Oxford 1979, pp. 506–507.

droxy-3-methoxy-*N*-methyl-6,14-ethenomorphinan (**6**). Crystallization from ethanol/diethyl ether gave 1.1 g of **6** (3.1 mmol; 22% yield starting from **2**). M.p. 204–205°C, $[\alpha]_D^{25}$ +95° (*c* 1.1, chloroform/ethanol 9/1). MS: M^+ 353; ^{1}H NMR: Table I. X-ray analysis (crystals from acetone), ref. 15: $C_{22}H_{27}NO_3$, mol. wt. 353.5. Hexagonal, $P6_1$, a = 11.899 (2) Å, c = 22.478 (6) Å, V = 2756.2 Å^3, Z = 6, D_x = 1.28 mg · m^{-3}.

(−)-7α-Acetyl-4,5α-epoxy-3-methoxy-N-methyl-6,14-ethenoisomorphinan (**7**)

A solution of **2** (15.0 g, 53 mmol) in freshly distilled methyl vinyl ketone (70 ml, 860 mmol) containing a few drops of triethylamine was refluxed for 22 h. Methyl vinyl ketone was then removed *in vacuo* and the residue taken up in 100 ml of ethanol. This solution was added to 700 ml of 1 N hydrochloric acid, while stirring, and the precipitated polymer removed by filtration over hyflo. The filtrate was rendered alkaline using ammonia and then extracted with dichloromethane (4 × 150 ml). Working up in the usual manner afforded 20.6 g of an oily product which was converted into the hydrochloride of **7** and crystallized from ethanol/diethyl ether. Yield 10.5 g of **7** · HCl (51%; ref. 7, 46%). Recrystallization as the free base from ethanol gave a product having a m.p. 161–162°C (ref. 7, m.p. 159–161°C). MS: M^+ 351. $[\alpha]_D^{25}$ −174° (*c* 1.0, chloroform/ethanol 9/1), $[\alpha]_D^{25}$ −144° (*c* < 1.9, ethanol; **7** started to crystallize). Ref. 7: $[\alpha]_D$ −143° (*c* 2.0, ethanol).
^{1}H NMR ($CDCl_3$): δ 2.08 (s, 3H, $COCH_3$), 2.35 (s, 3H, NCH_3), 3.76 (s, 3H, 3-OCH_3), 4.52 (d, *J* 3 Hz, 1H, 5β-H), 5.61 (m, 2H, (17 + 18)-H), 6.53 (q, 2H, Ar-H). X-ray analysis (crystals grown from ethyl acetate), ref. 11: $C_{22}H_{25}NO_3$, mol. wt. 351.45. Trigonal, $P3_2$, a = 10.899 (2) Å, c = 13.422 (5) Å, V = 1380.4 Å^3, Z = 3, D_x = 1.27 mg · m^{-3}.

(−)-(7α-R)-4,5α-Epoxy-3-methoxy-α,N-dimethyl-α-propyl-6,14-ethenoisomorphinan-7α-methanol (**8**) *and (−)-(7α-S)-isomer* (**9**); *(7α-R)- and (7α-S)-4,5α-epoxy-3-methoxy-α,N-dimethyl-6,14-ethenoisomorphinan-7α-methanol* (**10** *and* **11**)

In a Soxhlet apparatus compound **7** (1.5 g, 4.5 mmol) was extracted into a boiling solution of propylmagnesium bromide, prepared from magnesium (400 mg) and propyl bromide (1.23 g, 10 mmol) in 20 ml of diethyl ether. TLC showed complete conversion of the starting material and the formation of four compounds. These were isolated using HPLC.
Compound **8** (180 mg): MS: M^+ 395; ^{1}H NMR ($CDCl_3$): δ 0.95 (s, 3H, CCH_3), 2.35 (s, 3H, NCH_3), 3.76 (s, 3H, OCH_3), 4.45 (d, *J* 3 Hz, 1H, 5β-H), 5.58 (m, 2H, (17 + 18)-H), 6.56 (q, 2H, Ar–H). **8** · HCl: m.p. 172–176°C; $[\alpha]_D^{25}$ −135° (*c* 0.8, water).
Compound **9** (200 mg): MS: M^+ 395; ^{1}H NMR ($CDCl_3$): δ 1.08 (s, 3H, CCH_3), 2.35 (s, 3H, NCH_3), 3.76 (s, 3H, OCH_3), 4.45 (d, *J* 3 Hz, 1H, 5β-H), 5.58 (m, 2H, (17 + 18)-H), 6.56 (q, 2H, Ar–H). **9** · HCl: m.p. 161–164°C, $[\alpha]_D^{25}$ −135° (*c* 1.0, water).
Compounds **10** (180 mg) and **11** (130 mg) both showed the same MS (M^+ 365 and fragmentation). The main ^{1}H NMR signals of **10** and **11** were identical; only in the δ 3.3–3.5 region were some differences detectable. However, no conclusions could be drawn concerning the absolute configuration at C-7α. ^{1}H NMR ($CDCl_3$): δ 1.13 (d, *J* 6 Hz, 3H, CCH_3), 2.37 (s, 3H, NCH_3), 3.78 (s, 3H, OCH_3), 4.47 (d, *J* 3 Hz, 5β-H), 5.62 (m, 2H, (17 + 18)-H), 6.52 (q, 2H, Ar–H).

Acknowledgements

We wish to acknowledge stimulating discussions with and suggestions of Professor Dr. *H. C. Beyerman*. We thank Dr. *J. A. Peters* for recording and interpreting the 200 MHz ^{1}H NMR spectra and Mr. *P. F. C. van der Meij* for preliminary experiments. We are grateful to the Management of Diosynth, B.V., Apeldoorn, The Netherlands, for gifts of chemicals. We thank the U.S.A. Committee on Problems of Drug Dependence and Dr. *A. E. Jacobson*, Biological coordinator, for the results of the pharmacological studies. We are indebted to Dr. *A. Brossi* (National Institutes of Health, Bethesda, Maryland, U.S.A.) who acted as intermediary in the pharmacological screening.

2.3

Synthesis and preliminary pharmacology of the rigid dehydroxylated etorphine analogue 4,5α-epoxy-α,α,17-trimethyl-6α,14α-ethenoisomorphinan-7α-methanol.

SYNTHESIS AND PRELIMINARY PHARMACOLOGY* OF THE RIGID DEHYDROXYLATED ETORPHINE ANALOGUE 4,5α-EPOXY-α,α,17-TRIMETHYL-6α,14α-ETHENO-ISOMORPHINAN-7α-METHANOL (CHEMISTRY OF OPIUM ALKALOIDS, PART XXVI**)

J.T.M. Linders, T.S. Lie and L. Maat

Department of Organic Chemistry, Delft University of Technology,
Julianalaan 136, 2628 BL Delft, The Netherlands

Received : 16/05/1988 - Accepted : 20/05/1988

ABSTRACT

The synthesis of 4,5α-epoxy-α,α,17-trimethyl-6α,14α-ethenoisomorphinan-7α-methanol (6) via hydrogenolysis of the corresponding 3-(1-phenyltetrazol-5-yl) ether (5) is described. The etheno bridge was retained under the conditions used. Preliminary pharmacology of the title compound showed strong analgesic potency.

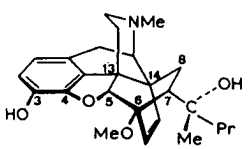
INTRODUCTION

New 6,14-etheno-bridged morphinans are important target molecules, which may contribute to a better knowledge of structure-activity relationships of analgesics[1]. Morphinan derivatives, which have the 5-13 and 8-14 bond *trans* to each other are designated isomorphinans. They are of interest since the derivatives of B/C *trans*-fused morphinans, stereochemically related to the well-known Bentley adducts[2] such as etorphine (1), have been found more potent analgesics than their B/C *cis* isomers. Extensive chemical and biological studies in the aromatic oxygenated morphinan-6-one series by Schmidhammer, Jacobson and Brossi[3] revealed that the pharmacological (i.e. analgesic) activity of morphinans is strongly dependent on the number and position of oxygen containing substituents in the aromatic nucleus as well as at C-6.
We have combined these two modifications of the morphine molecule and we found a good

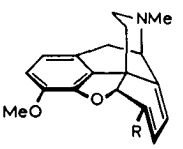
candidate in a rigid etorphine analogue lacking both the 3-*O* and 6-*O* group, namely, 4,5α-epoxy-α,α,17-trimethyl-6α,14-ethenoisomorphinan-7α-methanol (6), for which we report the preparation and preliminary pharmacological testing.

RESULTS AND DISCUSSION

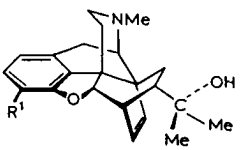
For the preparation of 6α,14α-ethenoisomorphinans without the 3- and 6-substituents containing oxygen but with the 4,5α-epoxy bridge, different routes are possible, starting from morphinan-6,8-dienes. When starting from the most common diene, namely the opium alkaloid thebaine (2), the removal of the 3- and 6-oxygen substituent is, in principle, feasible before or after the introduction of the etheno bridge by a Diels-Alder reaction. However, preliminary investigations indicated that the removal of the 6-*O* substituent in etheno-bridged morphinans is troublesome. This was circumvented by starting from 6-demethoxythebaine (3), which can be prepared conveniently from codeine. The Diels-Alder reaction of 3 with methyl vinyl ketone was followed by introduction of the dimethylcarbinol group and cleavage of the 3-methoxyl ether to give phenol 4 in 24% overall yield[4].



1 Etorphine



2 Thebaine (R=OMe)
3 6-Demethoxythebaine (R=H)



4 R^1=OH 5 R^1=OCN_4Ph
6 R^1=H 7 R^1=$OPO(OEt)_2$

The Musliner-Gates method for the dehydroxylation of phenols, used earlier by us in the total synthesis of codeine and morphine[5], was applied with some modifications. The preparation of the 3-(1-phenyltetrazol-5-yl) ether 5 was effected by treatment of 4 with 5-chloro-1-phenyl-1*H*-tetrazole in dimethylformamide. The reaction proceeded cleanly in quantitative yield by generating the phenolate anion using potassium *tert*-butanolate instead of potassium carbonate[5]. Hydrogenolysis was then performed according to the procedure described by Hussey *et al.*[6]. The ether (5) was dissolved in a mixture of benzene, ethanol and water and treated

with formic acid in the presence of 10% Pd-C, affording the title compound 6 in quantitative yield. Following this procedure, the double bond remained intact during the hydrogenolysis. This is in contrast to a similar hydrogenolysis of the phenyltetrazole ether of morphine which causes predominantly saturation of the 7,8-double bond, both by using hydrogen/palladium on charcoal[7] or catalytic hydrogen transfer methods. It is known from the 6-methoxyl series that the etheno bridge of rigid morphinans can be hydrogenated catalytically only with difficulty (Raney nickel, 160-170 °C, 200 atm). This was ascribed[8] to the hydrogen bonding between the hydroxyl and the 6-methoxyl groups, which results in a conformation in which one of the alkyl groups of the C-7 substituent points towards the etheno bridge, thus hindering the approach of the bridge to the catalyst surface. However, our results now show that the mere presence of the substituent at C-7 may be sufficient to prevent reduction of the etheno bridge.

With regard to the removal of the the 3-*O* substituent, earlier efforts to prepare 6 by hydrogenolysis of the phosphate ester 7, according to the method described for the 6-methoxyl analogues[9], were less successful. It proved to be difficult to prepare 7 from phenol 4 in pure form and on hydrogenolysis using lithium in liquid ammonia, only mixtures of 6 and the corresponding 6α,14α-ethanoisomorphinan were isolated[10].

PHARMACOLOGY*

In the mouse tail-flick assay (sc injection), etorphine analogue 6 proved to be a strong agonist. ED_{50} is 0.05 mg/kg, in comparison with 5.8 mg/kg for morphine. The compound showed no antagonist activitiy in the tail-flick assay versus morphine.

EXPERIMENTAL

Mass spectra were measured by Dr. B. van de Graaf, Mr. H. Buurmans and Mrs. A.H. Knol-Kalkman using a Varian MAT 311A mass spectrometer. ^1H NMR spectra were obtained in $CDCl_3$ as solvent and tetramethylsilane as reference using a Varian T-60 spectrometer. Rotations were measured using a Perkin-Elmer P141 polarimeter. Melting points are uncorrected.

Reactions were monitored by TLC on deactivated silica (0.25 mm, Merck F_{254}; eluent: dichloromethane/methanol/25% ammonia 85/15/0.5). The compounds were detected with UV (254 nm) and iodine vapour. Analytical HPLC was performed using a Waters M-6000 pump on a reversed phase column (8x100 mm, Nucleosil C_{18}, 10 µm, 30 °C) using mixtures of methanol/water/trifluoroacetic acid as eluent, with detection on a ERMA RI-detector ERC-7510. IR-spectra were obtained from KBr discs using a Beckman IR 4210 spectrophotometer.

(-)-4,5α-Epoxy-3-O-(1-phenyltetrazol-5-yl)-α,α,17-trimethyl-6α,14α-ethenoisomorphinan-7α-methanol (5)

Compound 2 (1.50 g, 4.25 mmol), prepared according to ref. 4, was dissolved in 40 ml of DMF, together with 1.60 g (14 mmol) of potassium *tert*-butanolate, under a nitrogen atmosphere. A solution of 5-chloro-1-phenyl-1*H*-tetrazole (0.840 g, 4.65 mmol) in 15 ml of DMF was added dropwise during 1 h. After 2 h of stirring at room temperature, a second portion of the tetrazole (0.080g, 0.44 mmol) was added and stirring was continued for 2 h (complete conversion according to TLC). The mixture was poured out into 100 ml of cold water, 150 ml of dichloromethane was added and the mixture was stirred vigourously for 0.5 h. The layers were separated and the aqueous phase was extracted with dichloromethane (3 x 50 ml). The combined organic layers were washed with water (50 ml), dried on sodium sulfate and evaporated to dryness *in vacuo*, yielding 2.10 g (4.20 mmol, 99%) of pure (TLC, HPLC) 5. An analytical sample was crystallized from ethanol/water and ethanol, subsequently. M.p. 112-113 °C; $[\alpha]_D^{25}$ -112° (c 0.9, chloroform/ethanol 9:1).
MS: m/z 497 (M+, 57), 427 (39), 353 (47), 352 (50), 294 (20), 266 (13), 230 (28), 215 (19), 174 (25), 144 (41), 132 (32), 118 (67), 91 (50), 79 (29), 59 (86), 44 (100). ^{1}H NMR: δ 1.04 (s, 3H, CH_3), 1.14 (s, 3H, CH_3), 2.39 (s, 3H, NCH_3), 4.56 (d, 1H, H-5, *J*(5,6) 5 Hz), 5.59 (dd, 1H, H-18, *J*(18,19) 8 Hz, *J*(6,18) 7 Hz), 5.81 (d, 1H, H-19), 6.61 (d, 1H, H-1, *J*(1,2) 8 Hz), 6.73 (d, 1H, H-2), 7.45-7.99 (m, 5H, Ph-). IR: ν_{max}^{KBr} 3450 (OH) cm^{-1}.

(-)-4,5α-Epoxy-α,α,17-trimethyl-6α,14α-ethenoisomorphinan-7α-methanol (6)

Water (3 ml) and 10% Pd-C (100 mg) were added to a solution of 0.5 g (1.1 mmol) 5 in a mixture of 21 ml of benzene and 9 ml of ethanol. The mixture was boiled under reflux, and formic acid (98%, 3 ml, 80 mmol) was added. Boiling was continued for 2 h. The catalyst was filtered off over Hyflo, 100 ml of 1 *N* potassium hydroxide in water was added and the organic layer was separated. The aqueous phase was extracted with dichloromethane (3 x 50 ml). The combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo*, yielding 375 mg (1.1 mmol, 100%) of crystalline 6. The compound was recrystallized from ethanol/water.
M.p. 165-167 °C; $[\alpha]_D^{25}$ -194° (c 0.8, chloroform/ethanol 9:1). MS: m/z 337 (M+, 61), 278 (38), 195 (20), 149 (27), 134 (56), 119 (36), 107 (20), 106 (27); 105 (19), 91 (57), 57 (100). ^{1}H NMR: δ 1.06 (s, 3H, CH_3), 1.16 (s, 3H, CH_3), 2.42 (s, 3H, NCH_3), 4.46 (d, 1H, H-5, *J*(5,6) 5 Hz), 5.52 (dd, 1H, H-18 *J*(18,19) 8 Hz, *J*(6,18) 7 Hz), 5.74 (d, 1H, H-19), 6.31-6.76 (m, 3H, Ar-H).
IR: ν_{max}^{KBr} 3560, 3450 (OH) cm^{-1}.

ACKNOWLEDGEMENTS

We are grateful to the Management of Diosynth, B.V., Apeldoorn, The Netherlands, for the gift of chemicals. One of us (J.T.M.L.) wishes to express his gratitude to Diosynth, B.V. for a

grant. We thank the U.S.A. Committee on Problems of Drug Dependence, Inc. and Dr. A.E. Jacobson, Chairman, Drug Testing Program, for the results of the pharmacological studies.

REFERENCES

* *Dr. A.E. Jacobson*, National Institutes of Health, Bethesda, Md, U.S.A.

** Part XXV: *J.T.M. Linders, J.P. Kokje, M. Overhand, T.S. Lie and L. Maat*, Recl. Trav. Chim. Pays-Bas, in the press.

1. *R.J. Bryant*, Chem. Ind. (London) **1988**, 146.
2. *K.W. Bentley* in "The Alkaloids", vol. XIII (ed. *R.H.F. Manske*), Academic Press, New York, London, 1971, 75.
3. *H. Schmidhammer, A.E. Jacobson and A. Brossi*, Med. Res. Rev. **3**, 1 (1983).
4. *P.R. Crabbendam, T.S. Lie, J.T.M. Linders and L. Maat*, Recl. Trav. Chim. Pays-Bas **103**, 296 (1984) and references herein.
5. *H.C. Beyerman, J. van Berkel, T.S. Lie, L. Maat, J.C.M. Wessels, H.H. Bosman, E. Buurman, E.J.M. Bijsterveld and H.J.M. Sinnige*, Recl. Trav. Chim. Pays-Bas **97**, 127 (1978).
6. *B.J. Hussey, R.A.W. Johnstone and I.D. Entwistle*, Tetrahedron **38**, 3775 (1982).
7. *V.J. Ram and J.L. Neumeyer*, J. Org. Chem. **47**, 4372 (1982).
8. *K.W. Bentley, D.G. Hardy and B. Meek*, J. Am. Chem. Soc. **89**, 3273 (1967).
9. *J.W. Lewis and M.J. Readhead*, J. Med. Chem. **13**, 525 (1970).
10. *P.F.C. van der Meij, T.S. Lie and L. Maat*, unpublished results.

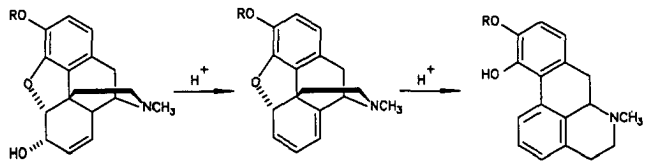
Note: The title compound has been tested *in vitro*. In the mouse vas deference test, it shows μ-agonist activity. Its potency is less than morphine (Courtesy of Dr. J.H. Woods, Dept. of Pharmacology, University of Michigan, Ann Arbor, Michigan 48109-0626).

CHAPTER 3 REDUCTIVE 4,5α-EPOXY RING SCISSION IN MORPHINANS

3.1. Introduction

Scission of the epoxy ring in 4,5α-epoxymorphinans

Attempted opening of the 4,5α-epoxy ring in morphine (1) and codeine (2) using strong acids results in the formation of aporphines (5, 6). The first step in this conversion is thought to be the elimination of water from the C-ring, yielding 6-demethoxyoripavine (3) or 6-demethoxythebaine (4)[1]. This idea was corroborated by the result of the reaction of these morphinan-6,8-dienes with methanesulfonic acid[2-4] (Scheme 1).



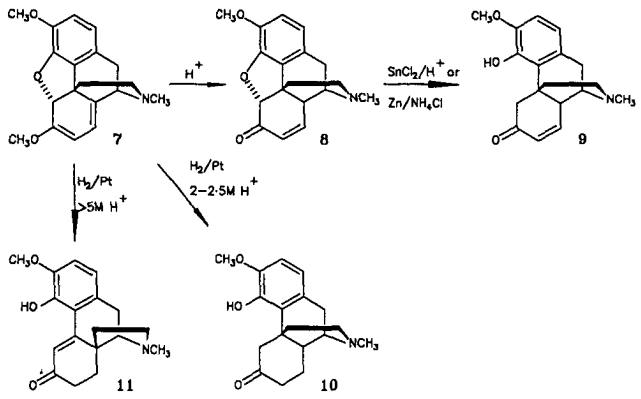
1 R = H
2 R = CH_3

3 R = H
4 R = CH_3

5 R = H
6 R = CH_3

Scheme 1. Acid-catalyzed 4,5α-epoxy ring cleavage in morphine (1) and codeine (2).

Treatment of thebaine (7) or codeinone (8), which is in the same oxidation state, with strong acids leads to aporphines or phenanthrenes, depending on the conditions used[5]. However, when reductive conditions were applied under carefully controled acidic conditions, thebainone-A (9) could be isolated in good yield[6-7]. Likewise, when thebaine is catalytically hydrogenated in acid medium (2-2.5 M), dihydrothebainone (10) is obtained[8-9a] (Scheme 2). In more concentrated acid (>5 M), metathebainone 11 is the main product[9].

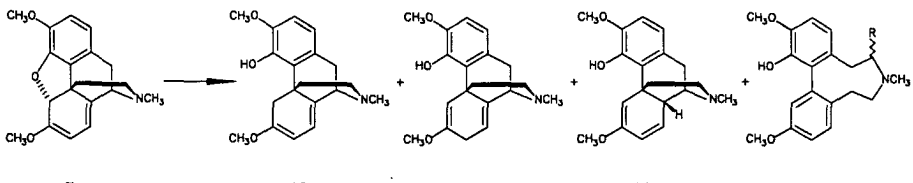


Scheme 2. Reductive epoxy ring scission in thebaine (7) and codeinone (8).

As is pointed out by Bentley[10], scission of the epoxy bridge with retainment of the morphinan skeleton is only possible when there is an activating group at C-6 (ketone or double bond). When dihydrocodeinone is reduced using zinc/ammonium chloride, the corresponding ring-opened compound is produced in good yield[11-12]. Similarly, treatment of codeinone and its 3-*O*-benzyl analogue with zinc and ammonium chloride produced the corresponding thebainone-A (9)[13]. In the latter case, careful control of the reaction conditions is necessary to prevent concomittant reduction of the double bond.

Epoxy ring scission in thebaine

Reduction of thebaine (7) gave rise to a plethora of products (Scheme 3, Table 1.). The structure elucidation and nomenclature has given rise to confusion, which was eventually clarified by Stork in the early fifties[14-15].



7 12 13 14 15

Scheme 3. Products of the reductive ring scission in thebaine

Table 1. Reductive epoxy ring cleavage of thebaine

Reagents used	Product	Yield (%)	References
PhMgBr	**15** (R=Ph)	75	16-18
MeMgBr	**15** (R=Me)	65-70	19
R-C_6H_4-CH_2MgBr	**15** (R=R-C_6H_4-CH_2)	not reported	20
Na/ethanol	**13**	50	21-23
$LiAlH_4$	**12**	42	24-26
$LiAlH_4/AlCl_3$ 1:1-4	**15** (R=H)	40-50	27,36
$LiAlH_4/AlCl_3$ 3-4:1	**14**	50	27,36
Li/NH_3[a]	**13**	60	28-29
Na/NH_3[b]	**13**	95	15,30-32
Na/NH_3	**12**:**13** = 1:3	95	28-29
K/NH_3	**12**:**13** = 1:1	34 (cryst. **12**)	28-29
$K/NH_3/FeCl_3$	**13**	100	28-29
Ca/NH_3	**13**	50	28-29
Me_2CuLi[c]	**13** (7β-Me)	95[d]	33
Zn/HOAc	**14**	47	34-35

a) Na added in 35 min, quench after 10 min
b) Na added in 80 min, quench after 60 min
c) $Fe(CO)_3$ complex of thebaine[35]
d) Overall yield after 4-*O*-methylation and oxidative deprotection

As can be seen from the results in Table 1, reductive ring cleavage of thebaine gives the non-conjugated **13**, dihydrothebaine-ϕ, in most cases. Only when thebaine is treated with potassium in liquid ammonia, a reasonable yield of crystalline β-dihydrothebaine (**12**) is obtained[28-29]. Furthermore, it was possible to isomerize dihydrothebaine-ϕ to a 1:1 mixture of **12** and **13**, using K/NH_3 and a catalytical amount of $Fe(NO_3)_3$. Thus, in principle, a complete conversion of thebaine to its ring-cleaved analogue **12** can be obtained[28-29]. Reduction of thebaine with lithium aluminium hydride was also reported to give β-dihydrothebaine[24-26], but this method proved to be

difficult to reproduce[27]. The reaction of thebaine with mixtures of lithium aluminium hydride and aluminium chloride (1:1, 1:3, or 1:4) gave neodihydrothebaine (15, R=H) as the major product (40-50%)[28]. This result may be compared with the results of the reactions of thebaine with alkyl Grignards[16-20] and the reaction of thebaine with magnesium iodide, followed by reduction with sodium borohydride[36]. With lithium aluminium hydride-aluminium chloride (4:1 or 3:1), the major product was thebainone-A enol methyl ether (14), a morphinan-5,7-diene[27].

References

1. K.W. Bentley, "The Chemistry of the Morphine Alkaloids", Clarendon Press, Oxford, 1954, 21, 61, 309 and references cited therein.
2. C.W. Hutchins, G.K. Cooper, S. Pürro and H. Rapoport, J. Med. Chem. **24**, 773 (1981).
3. S. Berényi, S. Hosztafi, S. Makleit and I. Szeifert, Acta Chim. Acad. Sci. Hung. **110**, 363 (1982).
4. S. Berényi, S. Hosztafi, S. Makleit and I. Molnár, Acta. Chim. Hung. **113**, 51 (1983).
5. Ref. 1, Chapters X, XI, XXIII and references cited therein.
6. L. Knorr, Ber. Dtsch. Chem. Ges. **38**, 3171 (1905).
7. C. Schöpf and Hirsch, Lieb. Ann. Chem. **489**, 224 (1931).
8. C. Schöpf and Winterhalder, Lieb. Ann. Chem, **452**, 232 (1927).

9a. K. Goto and H. Shishido, Bull. Chem. Soc. Japan **10**, 597 (1935).

9b. R.S. Cahn, J. Chem. Soc. 1038 (1933).

10. K.W. Bentley, "The Isoquinoline Alkaloids", Pergamom Press, London, 1965, 141.
11. C. Schöpf and T. Pfeifer, Lieb. Ann. Chem. **483**, 157 (1930).
12. C. Olieman, L. Maat and H.C. Beyerman, Recl. Trav. Chim. Pays-Bas **95**, 189 (1976).
13. K.M.J. Brands, T.S. Lie and L. Maat, Recl. Trav. Chim. Pays-Bas **105**, 544 (1986).
14. G. Stork, J. Am. Chem. Soc. **73**, 504 (1951).
15. G. Stork, J. Am. Chem. Soc. **74**, 768 (1952).
16. M. Freund, Ber. Dtsch. Chem. Ges. **38**, 3234 (1905).
17. Ref. 1, Ch. XX and references therein.

18a. R. Robinson, Proc. R. Soc. London, B **135**, v-xix (1947); R.Robinson, Nature **160**, 815 (1947). See also: K.W. Bentley, Nat. Prod. Rep. **4**, 13 (1985).

18b. L. Small, L.J. Sargent and J.A. Bralley, J. Org. Chem. **12**, 847 (1947).

19. L. Small and E.M. Fry, J. Org. Chem. **3**, 509 (1939).
20. G. Satzinger, M. Herrmann, E. Fritschi, H. Bahrmann, V. Gamser, B. Wagner and W. Steinbrecher, Ger. Patent Ger. Offen DE 3,007,710, sep. 10 1981; Chem. Abstr. **96**, 35125d (1982).
21. M. Freund and C. Holtoff, Ber. Dtsch. Chem. Ges. **32**, 168 (1899).
22. M. Freund and E. Speyer, Ber. Dtsch. Chem. Ges. **49**, 1287 (1916).
23. L. Small and G.L. Browning, J. Org. Chem. **3**, 618 (1939).
24. H. Schmid and P. Karrer, Helv. Chim. Acta **33**, 863 (1950).
25. H. Schmid and P. Karrer, Helv. Chim. Acta **34**, 1948 (1951).

26. K. Hayakawa, I. Fujii and K. Kanematsu, J. Org. Chem. **48**, 166 (1983).
27. K.W. Bentley, J.W. Lewis and J.B. Taylor, J. Chem. Soc., (C) 1945 (1969).
28. D.E. Portlock, US Patent 4,025,521, May 24, 1977; Chem. Abstr. **87**, 102508k (1977). See also: D.E. Portlock, US Patent 4,075,132, Feb. 21, 1978.
29. R.K. Razdan, D.E. Portlock, H.C. Dalzell and C. Malmberg, J. Org. Chem. **43**, 3604 (1978).
30. K.W. Bentley and R. Robinson, Experientia **6**, 353 (19500.
31. K.W. Bentley, R. Robinson and A.E. Wain, J. Chem. Soc. 958 (1952).
32. K.W. Bentley and H.M.E. Cardwell, J. Chem. Soc. 3252 (1955). See also: G. Stork and F. Clarke, J. Am. Chem. Soc. **78**, 4619 (1956).
33. D.L. Leland, J.O. Polazzi and M.P. Kotick, J. Org. Chem. **45**, 4026 (1980).
34. I. Fujii, K. Ryu, K. Hayakawa and K. Kanematsu, J. Chem. Soc., Chem. *Commun.* 844 (1984).
35. A.J. Birch and M. Fitton, Aust. J. Chem. **22**, 971 (1969).
36. K.W. Bentley, J. Am. Chem. Soc. **89**, 2464 (1967).

3.2

Scission of the epoxy ring in 4,5α-epoxymorphinans: a convenient synthesis of β-dihydrothebaine, 6-demethoxy-β-dihydrothebaine and desoxycodeine-A

Scission of the epoxy ring in 4,5α-epoxymorphinans: A convenient synthesis of β-dihydrothebaine, 6-demethoxy-β-dihydrothebaine and desoxycodeine-A (Chemistry of opium alkaloids, Part XXI*)**

J. T. M. Linders, R. J. O. Adriaansens, T. S. Lie and L. Maat

Laboratory of Organic Chemistry, Technische Hogeschool Delft, Julianalaan 136, 2628 BL Delft, The Netherlands
(Received May 20th, 1985)

Abstract. The use of zinc and aqueous potassium hydroxide for the reductive epoxy ring opening of thebaine (**1**) and 6-demethoxythebaine (**2**) is described. The reaction affords exclusively β-dihydrothebaine (**3**) and 6-demethoxy-β-dihydrothebaine (**4**), respectively. The synthesis of desoxycodeine-A (**9**) has been improved and evidence for its configuration is discussed.

Introduction

A key step in the preparation of analgesics with a rigid structure and fewer oxygen-containing substituents than morphine is the scission of the epoxy ring in 4,5α-epoxymorphinan-6,8-dienes, which are intermediates for *Diels–Alder* derivatives[1–3]. Investigations of morphinans having an alkyl bridge over ring C have been mainly concerned with 6,14-etheno(iso)morphinans. The activity of 5,8-ethenomorphinans, for which morphinan-5,7-dienes may be starting materials, can also contribute to a better understanding of drug–receptor interactions. An attempted total synthesis of this type of compound failed[4].

Scission of the epoxy ring with retention of the conjugated 6,8-diene function is difficult[2,5]. Reaction products of the reductive ring scission are depicted in Scheme 1.

* Part XX, *L. Maat, J. A. Peters* and *M. A. Prazeres*, Recl. Trav. Chim. Pays-Bas **104**, 205 (1985).

** Partly presented at the SON meeting, Organic Synthesis, Lunteren, The Netherlands, October 29–30, 1984.

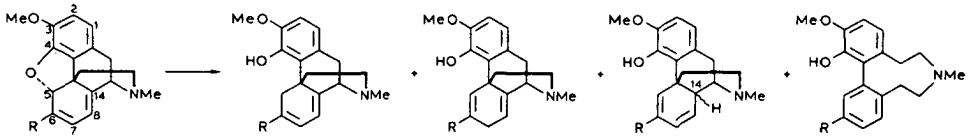
[1] *K. W. Bentley* in "The Alkaloids", Vol. XIII, *R. H. F. Manske*, Ed., Academic Press, New York, 1971, p. 75.

[2] *P. R. Crabbendam, T. S. Lie, J. T. M. Linders* and *L. Maat*, Recl. Trav. Chim. Pays-Bas **103**, 296 (1984).

[3] *A. C. Ghosh, D. E. Portlock, H. C. Dalzell, C. Malmberg, P. Herlihy, R. K. Razdan, W. L. Duax* and *G. D. Smith*, J. Org. Chem. **48**, 4137 (1983).

[4] *V. F. Roche, E. B. Roche, D. L. Nagel* and *A. T. McPhail*, J. Org. Chem. **49**, 3881 (1984).

[5] *R. K. Razdan, D. E. Portlock, H. C. Dalzell* and *C. Malmberg*, J. Org. Chem. **43**, 3604 (1978) and references cited therein.



1, R = OMe
2, R = H

3, R = OMe
4, R = H

5, R = OMe
6, R = H

7, R = OMe (14α H)
8, R = OMe (14β H)
9, R = H (14β H)

10, R = OMe

Scheme 1. Products formed from the epoxy ring opening of thebaine (1) and 6-demethoxythebaine (2), respectively.

Reduction of (−)-thebaine (**1**) with potassium in liquid ammonia[5,6] afforded a 1/1 mixture (95%) of β-dihydrothebaine (**3**) and dihydrothebaine-ϕ (**5**), from which **3** was crystallized selectively (34%). From the mother liquor, **5** was isolated and isomerized to a 1/1 mixture (79%) of **3** and **5** using potassium in liquid ammonia in the presence of iron(III) nitrate. Recently, *Fujii* et al.[7] reported the preparation of the 4-methyl ether of **3** in 47% yield using zinc/acetic acid reduction of the iron tricarbonyl complex of thebaine[8], followed by etherification of the hydroxyl group and removal of the iron complex, respectively.

We now wish to report a convenient method for the preparation of (+)-β-dihydrothebaine (**3**) and (+)-6-demethoxy-β-dihydrothebaine (**4**) from (−)-thebaine (**1**) and (−)-6-demethoxythebaine[9] (**2**), respectively, in almost quantitative yield using zinc and aqueous potassium hydroxide. Furthermore, we have improved the synthesis[10,11] of desoxycodeine-A (**9**), a morphinan-5,7-diene (Scheme 2), and we provide further evidence for its configuration.

Results and discussion

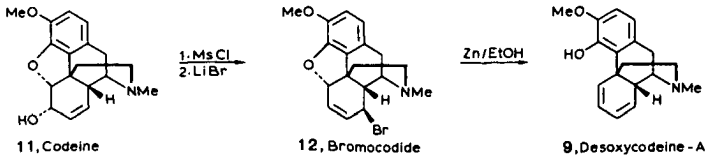
Our earlier investigations[2] of the reductive epoxy ring opening of 6-demethoxythebaine (**2**) were carried out using zinc and ammonium chloride. The reaction in ethanol/water 4/1 yielded two products, one of which was active in the *Diels–Alder* reaction with methyl vinyl ketone and proved to be the 6,8-diene **4**. By changing the ethanol/water ratio, the yield of **4** increased only slightly. NMR and mass spectral data showed the second product, isolated by semi-preparative HPLC, to be 6-demethoxydihydrothebaine-ϕ (**6**). The splitting pattern of H-5 in the ^{1}H NMR spectrum of **6** shows the double bond between C-5 and C-6, with the methylene group at C-7[12]. IR absorption at 1650 and 1610 cm^{-1} also indicates the non-conjugated diene system of **6**.

We have investigated other methods of cleaving the epoxy ring and found that simple treatment of an emulsion of **2** in boiling aqueous potassium hydroxide with zinc[13] afforded almost exclusively **4**. In order to prevent early precipitation of **4**, it was necessary to add some ethanol. 6-Demethoxy-β-dihydrothebaine (**4**) gave a positive *Gibbs* reaction for phenols[14]. The NMR spectrum showed one broad signal for the vinylic protons at δ 5.73 ppm. The disappearance of the IR bands attributed to the epoxy ring[15] is also indicative of the epoxy ring opening.

When 6-demethoxythebaine was treated with lithium aluminium hydride in benzene and diethyl ether, according to a method described for the epoxy ring opening of thebaine[16], a mixture containing three major compounds was obtained. Separation by silica column chromatography afforded desoxycodeine-A (**9**, (+)-5,6,7,8-tetradehydro-3--methoxy-17-methylmorphinan-4-ol) and a 1/1 mixture of **4** and **6**. The identity of **9** was proven by comparison with the authentic compound, prepared by treatment of bromocodide (**12**,(+)-8 β-bromo-6,7-didehydro-4,5α-epoxy-3-methoxy-17--methylmorphinan)[9] with zinc in absolute ethanol (Scheme 2). Conversion was complete within one hour and is more convenient than the method starting from the 8 β-chloro analogue[10,11]. The structure of **9** has never been characterized by spectral data. The mass spectrum of **9** showed a peak at *m/z* 59 of very low abundance, which is quite unusual for B/C *cis*-fused *N*-methylmorphinans[17]. In view of the structure of the starting material, a B/C *trans*-morphinan is not to be expected. Therefore, a single-crystal X-ray analysis (Fig. 1) was carried out[18] which confirmed the *cis*-fused structure; the MS fragmentation pattern is, indeed, anomalous. Peaks at *m/z* 146, 178 and 255 in the mass spectrum of **9** may be explained by fragmentations, leading to aromatization of the C ring, which seems to be the preferred pathway for this compound, in contrast to other B/C *cis*-fused morphinans.

The procedure worked out for the epoxy ring opening of 6-demethoxythebaine was then applied successfully to thebaine. The reaction yielded almost quantitatively β-dihydrothebaine (**3**) with only 2% (HPLC) of the non-conjugated

[6] *D. E. Portlock*, US Patent 4,075,132 (1978).
[7] *I. Fujii, K. Ryu, K. Hayakawa* and *K. Kunematsu*, J. Chem. Soc., Chem. Commun. 844 (1984).
[8] *A. J. Birch* and *H. Fitton*, Aust. J. Chem. **22**, 971 (1969).
[9] *H. C. Beyerman, P. R. Crabbendam, T. S. Lie* and *L. Maat*, Recl. Trav. Chim. Pays-Bas **103**, 112 (1984).
[10] *L. F. Small* and *F. L. Cohen*, J. Am. Chem. Soc. **53**, 2214 (1931).
[11] *L. Knorr* and *R. Wäntig*, Ber. Dtsch. Chem. Ges. **40**, 3860 (1907).
[12] *H. G. Theuns, R. H. A. M. Janssen, A. V. E. George* and *H. W. A. Biessels*, J. Chem. Res. (S) 122 (1985); J. Chem. Res. (M) 1461 (1985).
[13] *M. Iwao, K. K. Mahanalabis, M. Watanabe, S. O. de Silva* and *V. Snieckus*, Tetrahedron **39**, 1955 (1983).
[14] *E. Nürnberg*, Dtsch. Apoth. Ztg. **101**, 268 (1961).
[15] *Z. Dinya, S. Makleit, S. Szabó, T. Mile* and *R. Bognár*, Acta Chim. Acad. Sci. Hung. **75**, 393 (1973).
[16a] *H. Schmid* and *P. Karrer*, Helv. Chim. Acta **33**, 863 (1950).
[16b] *H. Schmid* and *P. Karrer*, Helv. Chim. Acta **34**, 1948 (1951).
[17] *A. Mandelbaum* and *D. Ginsburg*, Tetrahedron Lett. 2479 (1965).
[18] *H. van Koningsveld, J. C. Jansen, T. S. Lie* and *L. Maat*, Acta Crystallogr., in the press.



11, Codeine

12, Bromocodide

9, Desoxycodeine-A

Scheme 2. Synthesis of desoxycodeine-A (9) from codeine via bromocodide.

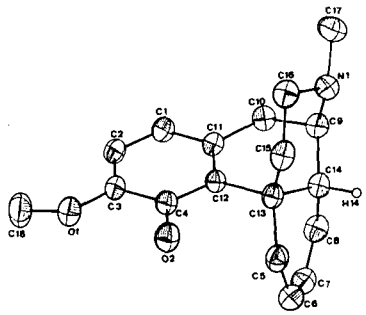


Fig. 1. ORTEP drawing of the structure of (+)-5,6,7,8-tetradehydro-3-methoxy-17-methylmorphinan-4-ol (9).

isomer (**5**)[5]. Acetone was the preferred cosolvent; the use of other solvent mixtures, such as water with methanol, ethanol or dioxane, resulted in more side-products. β-Dihydrothebaine was characterized by its IR spectrum[19]. The pattern in the 1600–1700 cm^{-1} region is typical for the position of the double bonds. The disappearance of the bands attributed to the epoxy ring[15] and a positive *Gibbs* reaction[14] confirmed the scission of the epoxy ring. NMR spectroscopy showed two doublets for the vinylic protons at δ 5.80 and δ 4.87 ppm[5]. Thus, β-dihydrothebaine (**3**), 6-demethoxy-β-dihydrothebaine (**4**) and desoxycodeine-A (**9**), starting materials for the preparation of C-ring-bridged morphinans, can now be prepared easily in high yield from thebaine or codeine.

Experimental

Mass spectra were measured by Dr. *B. van de Graaf* and Mrs. *A. H. Knol-Kalkman* using a Varian MAT 311A mass spectrometer. ^{1}H NMR spectra were recorded using a Varian T-60 spectrometer in deuteriochloroform as solvent and with tetramethylsilane as internal standard. The rotations were determined using a Perkin Elmer P141 polarimeter. Reactions were monitored by TLC on deactivated silica (0.25 mm, Merck F_{254}; eluent: dichloromethane/methanol/25% ammonia 85/15/0.5). The compounds were detected with UV (254 nm), iodine vapour and *Gibbs* reagent (0.5% *solution of 2,6-dibromoquinone 4-chloroimide in methanol*)[14]. IR spectra were recorded on a Beckman IR 4210 spectrometer using KBr discs. Melting points are uncorrected. Analytical HPLC was performed using a Waters M-6000 pump on a reversed-phase column (10 × 0.8 cm I.D., Nucleosil C_{18}, 10 μm, 30°C), using a mixture of methanol/water/trifluoroacetic acid 50/50/0.1 as eluent, with detection on a ERMA RI detector ERC-7510. Semi-preparative HPLC (reversed-phase column 20 × 1 cm I.D., polygosil C_{18}, 10 μm, 22°C, methanol/water/trifluoroacetic acid 50/50/0.1, UV detection at 280 nm) was performed with the assistance of Mr. *E. P. Sedlick*. For the preparation of **3**, **5** and **9**, we used zinc of different qualities (electrolytically precipitated zinc and zinc of UCB, N ≤ 0.002%).

(+)-6,7,8,14-Tetradehydro-3,6-dimethoxy-17-methylmorphinan-4-ol (3) from (−)-thebaine (1)

Zinc (15.0 g, 230 mmol) was added to a boiling solution of thebaine (10.0 g, 32.3 mmol) in 250 ml of acetone and 250 ml of water containing 7.5 g of potassium hydroxide. At intervals of 10 h, two other portions of zinc (5 g) were added. After 25 h of boiling, the reaction was complete (TLC), the excess zinc was filtered off over hyflo and the precipitate washed with 100 ml of dichloromethane. The aqueous layer was extracted with dichloromethane (100 ml and 3 × 50 ml). The combined organic layers were washed with saturated brine (100 ml), dried (Na_2SO_4) and evaporated *in vacuo*, yielding 20 g of an oily residue. Upon trituration with 100 ml of *hexane, the morphinan solidified (9.5 g, 95%). An analytical sample* was crystallized twice from ethyl acetate, m.p. 168-169°C, $[\alpha]_D^{25}$ 260° (*c* 0.9, ethanol) [ref.5: 167–168°C (dec), ref. 16a: 171–172°C, $[\alpha]_D^{18}$ 307° (*c* 0.6 ethanol)]. MS: M^+ 313, ^{1}H NMR ($CDCl_3$): δ 2.35 (s, 3H, N-CH_3), 3.63 (s, 3H, 6-OCH_3), 3.86 (s, 3H, 3-OCH_3), 4.87 (d, *J* 6 Hz, 1H, 8-H), 5.43 (bs, 1H, OH exchangeable with CD_3OD), 5.80 (d, *J* 6 Hz, 1H, 7-H), 6.67 (d, *J* 2 Hz, 2H, Ar-H).

[19] *G. Stork*, J. Am. Chem. Soc. **74**, 768 (1952).

(+)-6,7,8,14-Tetradehydro-3-methoxy-17-methylmorphinan-4-ol (4) from (−)-6-demethoxythebaine (2)

Zinc (10 g, 155 mmol) was added to a boiling and stirred emulsion of **2** (14.5 g, 51.6 mmol) in 50 ml of ethanol and 250 ml of 2 *N* potassium hydroxide. After 15 min, 25 ml of ethanol was added to the boiling reaction mixture in order to keep the compounds in solution. At intervals of 15 min, two portions of 5 g of zinc and 25 ml of ethanol were added. The reaction was complete in 1 h (TLC). Ethanol (50 ml) was added, the excess zinc was filtered off over hyflo and the filter was washed with warm ethanol. The volume of the *filtrate was reduced by evaporation in vacuo*. Ammonium chloride (20 g) was added and the mixture was extracted with dichloromethane. The organic layer was evaporated *in vacuo* and the residue taken up in 600 ml of ether. A brownish precipitate was removed. Evaporation of the solvents afforded 13.5 g of **4** (47.7 mmol, 92%, pure according to TLC). An analytical sample was crystallized from ethyl acetate. M.p. 115–117°C; $[\alpha]_D^{25}$ 264° (*c* 1, chloroform/ethanol 9/1). MS: M^+ 283, ^{1}H NMR ($CDCl_3$): δ 2.38 (s, 3H, NCH_3), 3.80 (s, 3H, OCH_3), 5.73 (m, 3H), 6.47 (s, 1H, OH), 6.61 (d, *J* 2 Hz, 2H, Ar-H).

(+)-5,6,7,8-Tetradehydro-3-methoxy-17-methylmorphinan-4-ol (9, desoxycodeine-A) from (+)-8β-bromo-6,7-didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan (12, bromocodide)

Zinc (20 g, 310 mmol) was added to a solution of bromocodide (10.0 g, 27.6 mmol)[9] in 150 ml of absolute ethanol. The mixture was boiled for 1 h after which the zinc was filtered off over hyflo and the filtrate was dried (Na_2SO_4) and evaporated *in vacuo*. The white residue was dissolved in 50 ml of dichloromethane and 50 ml of an aqueous potassium hydroxide solution (pH 10). The aqueous layer was extracted with dichloromethane (2 × 50 ml). The combined organic layers were dried and evaporated *in vacuo* to give a red foam containing 91% of **9** (HPLC). Crystallization from methanol/water 5/1 afforded 4.6 g (59%) of desoxycodeine-A (**9**). M.p. 122-123°C (ref. 10: 121-122°C) and $[\alpha]_D^{25}$ 117° (*c* 0.9, 96% ethanol) [ref. 10: $[\alpha]_D$ 118° (*c* 3.6, 96% ethanol)]. High-resolution mass determination 283.156; calcd. for $C_{18}H_{21}NO_2$: 283.157. A very low abundance at 59 in the mass spectrum was observed. ^{1}H NMR ($CDCl_3$): δ 2.4 (s, 3H, NCH_3), 3.8 (s, 3H, OCH_3), 5.7 (m, 3H, 6-H, 7-H, 8-H), 6.4 (bs, 1H, 5-H), 6.6. (dd, 2H, Ar-H). X-Ray analysis[18] (crystals grown from 96% ethanol): $C_{18}H_{21}NO_2 \cdot \frac{1}{2}H_2O$; mol. wt. 292.4. Orthorhombic, $P2_12_12_1$, a = 10.480 (4) Å, b = 14.336 (3) Å, c = 21.274 (3) Å, V = 3196.2 Å^3, Z = 8, D_x = 1.22 Mg · m^{-3}. The hydrogen at 14-C is in the β-position. The two independent molecules are linked together by one water molecule via hydrogen bonds.

Reduction of 6-demethoxythebaine (2) with lithium aluminium hydride to give 9, 4 and 6

Lithium aluminium hydride (60 mg, 1.6 mmol) in 4 ml of anhydrous diethyl ether was added to **2** (400 mg, 1.4 mmol) in 6 ml of anhydrous benzene and 4 ml of anhydrous ether. The mixture was boiled under reflux for 1 h. Ethyl acetate (5 ml) and water (20 ml) were added and a precipitate was filtered off over hyflo. The filtrate was adjusted to pH 8 with 2 *N* hydrogen chloride, the organic layer was separated and the aqueous layer extracted with dichloromethane (2 × 50 ml). The combined organic layers were dried (Na_2SO_4) and the solvents were evaporated *in vacuo* to yield 0.4 g of foam. HPLC analysis showed three major products which could be separated over silica (CH_2Cl_2/CH_3OH 80/20) to yield desoxycodeine-A (**9**) and a mixture of **4** and **6**. Compound **9** crystallized from methanol/water and proved to be identical to the compound preparated from bromocodide (TLC, NMR, IR, HPLC and m.p.).

Isolation of 5,6,8,14-tetradehydro-3-methoxy-17-methylmorphinan-4-ol (6)

A mixture of **4** and **6** (1/1) was treated with methyl vinyl ketone. After removal of the *Diels–Alder* adduct by column chromatography[2], an enriched mixture (1/4) was obtained. Separation with the aid of semi-preparative HPLC of this mixture (150 mg) yielded 80 mg of **6**. MS: M^+ 283, ^{1}H NMR ($CDCl_3$): δ 2.42 (s, 3H, N-CH_3), 3.42 (d, *J* 5.6 Hz, 1H, H-9), 3.83 (s, 3H, O-CH_3), 5.67–5.95 (m, 2H, H-6 + H-8), 6.58 (d, *J* 8.3 Hz, H-1), 6.68 (d, *J* 8.3 Hz, H-2), 6.95 (dt, 1H, H-5).

Acknowledgements

We wish to acknowledge stimulating discussions with Professor Dr. *H. C. Beyerman*. We are grateful to Mrs. *Lucie Havlová Jirů*, Czechoslovakia, for technical assistance and we wish to thank the Management of Diosynth B.V., Apeldoorn, The Netherlands, for gifts of chemicals.

CHAPTER 4 SYNTHESIS AND PHARMACOLOGY OF 3-HYDROXY-α,α,17-TRIMETHYL-6β,14β-ETHENOMORPHINAN-7β-METHANOL

4.1

Diels-Alder reaction of 6-demethoxy-β-dihydrothebaine with methyl vinyl ketone using microwave heating; preparation and pharmacology of 3-hydroxy-α,α,17-trimethyl-6β,14β-ethenomorphinan-7β-methanol, a novel deoxygenated diprenorphine analogue

Diels–Alder reaction of 6-demethoxy-β-dihydrothebaine with methyl vinyl ketone using microwave heating; preparation and pharmacology* of 3-hydroxy-α,α,17-trimethyl-6β,14β-ethenomorphinan-7β-methanol, a novel deoxygenated diprenorphine analogue (chemistry of opium alkaloids, part XXV**)

J. T. M. Linders, J. P. Kokje, M. Overhand, T. S. Lie and L. Maat

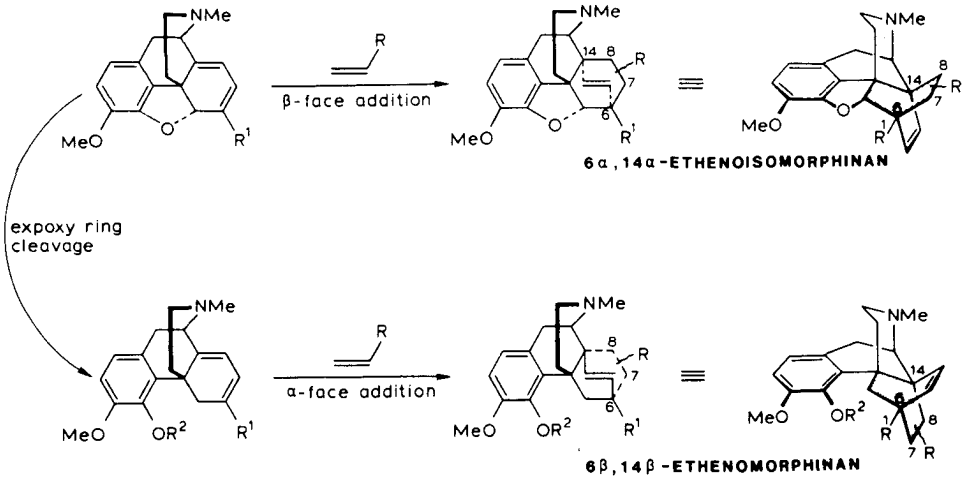
Laboratory of Organic Chemistry, Delft University of Technology, Julianalaan 136, 2628 BL Delft, The Netherlands
(Received February 4th, 1988)

Abstract. *Diels–Alder* reaction of 6-demethoxy-β-dihydrothebaine **6** with methyl vinyl ketone (3-buten-2-one) yielded, in a 3:2 ratio, (+)-7β-acetyl-3-methoxy-17-methyl-6β,14β-ethenomorphinan-4-ol (**7**) and the novel (+)-8β-acetyl-3-methoxy-17-methyl-6β,14β-ethenomorphinan-4-ol (**8**). Performing the reaction in a microwave oven resulted in a faster and cleaner reaction. ^{1}H NMR and mass spectra of **8** were studied and the structure was finally established by single-crystal X-ray analysis of its 4-*O*-phenyl ether **13**. In contrast to thebaine and 6-demethoxythebaine, the cycloaddition reaction of 6-demethoxy-β-dihydrothebaine with methyl vinyl ketone occurred at the α-face of the diene system.
Ullmann reaction of **7** with bromobenzene, followed by Grignard reaction with methylmagnesium bromide and removal of the phenoxyl group using sodium in liquid ammonia, afforded the tertiary alcohol **11**. *O*-Demethylation of **11** by potassium hydroxide in boiling glycol, using microwave heating, afforded (+)-3-hydroxy-α,α,17-trimethyl-6β,14β-ethenomorphinan-7β-methanol **12**. The structure of **12** was confirmed by ^{1}H NMR and single-crystal X-ray analysis. Compound **12** showed morphine-like activity in the PPQ assay.

Introduction

Diels–Alder reaction of 4,5α-epoxymorphinan-6,8-dienes with mono-substituted ethenes may afford, in principle, eight isomeric adducts. This was first observed by *Schöpf* in 1938[1]. A major breakthrough came in the early sixties when *Bentley* and *Hardy*[2-3] reported analgesics of extraordinary potency derived from 6α,14α-ethenoisomorphinans[4] (Scheme 1). The 7α-substituted isomer was the major product of the *Diels–Alder* reaction of thebaine (**1**) with unsymmetrical dienophiles such as acrylates or methyl vinyl ketone. Usually, a small amount of the 7β-substituted isomer accompanied the main product.
Only recently, 4,5α-epoxymorphinan-6,8-dienes other than thebaine have become available. The *Diels-Alder* reaction of 6-demethoxythebaine (**2**) gave the 7α-substituted 6α,14α-ethenoisomorphinan as the main product[5-7], together with 12% of the 8α-substituted derivative, whereas 6-deoxythebaine (**3**) gave a 96:3:1 ratio of the 7α-, 8α- and 7β-substituted 6α,14α-ethenoisomorphinans, together with a trace (0.1%) of the 8β-substituted 6β,14β-ethenomorphinan[8] (Scheme 1).
With a decreasing electronic influence at C-6, obviously the effect of the two alkyl substituents (C-9 and C-13) attached to C-14 becomes more important; this results in an increasing ratio of the 8α/7α isomers. The fact that the 7α-isomer remains the major product, even in the case of 6-demethoxythebaine, strongly indicates that stereochemical control dominates over electronic effects.
In contrast to the above mentioned *Diels–Alder* reaction of 4,5α-epóxymorphinan-6,8-dienes, the cycloaddition of dienophiles to morphinan-6,8-dienes *lacking the epoxy bridge* occurs exclusively from the other side, *i.e.* at the α-face of the diene system, yielding the 6β,14β-ethenomorphinans (Scheme 1). *Ghosh* et al.[9] reported on the *Diels-Alder* reaction of the 4-*O*-phenyl ether of β-dihydrothebaine (**5**) with methyl vinyl ketone and obtained the 7β-acetyl-6β,14β-ethenomorphinan. Simultaneously, we independently obtained similar results in preliminary experiments using a mixture of 6-demethoxy-β-dihydrothebaine (**6**) and its 5,8-diene isomer as starting material[7].
We now report on the *Diels–Alder* reaction of methyl vinyl

* Dr. *A. E. Jacobson*, National Institutes of Health, Bethesda, Md, U.S.A.
** Part XXIV: *R. A. van Gurp, T. S. Lie, C. Mense* and *L. Maat*, Bull. Soc. Chim. Belg. **96**, 325 (1987).



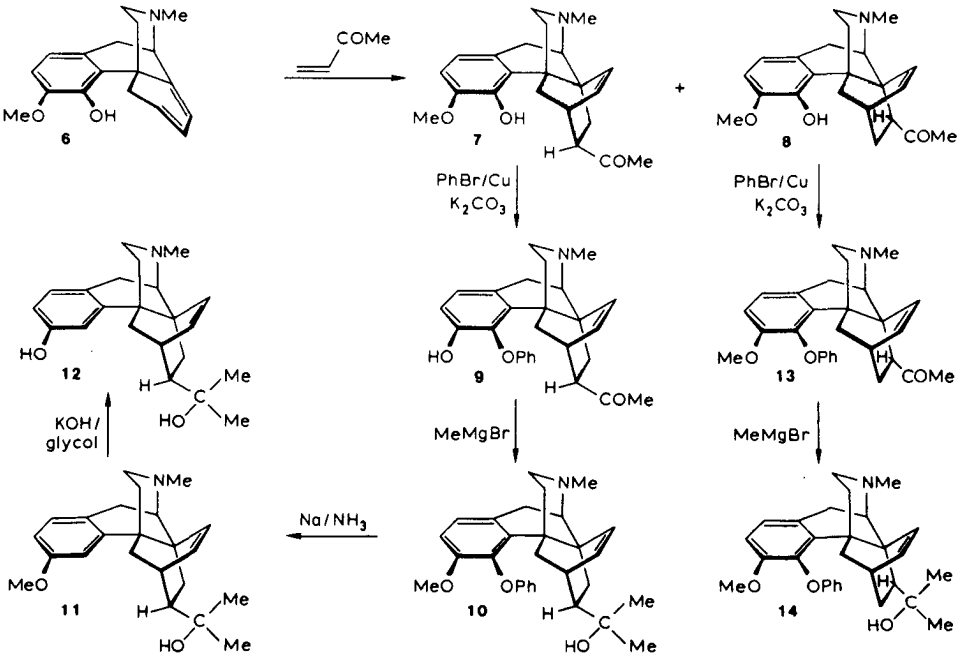
Scheme 1. Two ways of cycloaddition to morphinan-6,8-dienes.

ketone (3-buten-2-one) with 6-demethoxy-β-dihydrothebaine, for which we have developed a convenient synthesis[10]. The 7β-substituted adduct **7** thus obtained was converted into 3-hydroxy-α,α,17-trimethyl-6β,14β-ethenomorphinan-7β-methanol (**12**), a novel diprenorphine analogue, for which we here present the first pharmacological results.

Results and discussion

Diels–Alder *reaction of 6-demethoxy-β-dihydrothebaine*

Heating 6-demethoxy-β-dihydrothebaine (**6**)[10] in an excess of methyl vinyl ketone under reflux for 60 h yielded two adducts, in a ratio of 3:2, according to HPLC (Scheme 2).



Scheme 2. Diels–Alder *reaction of 6-demethoxy-β-dihydrothebaine* (**6**) *with methyl vinyl ketone; conversion of adducts* **7** *and* **8** *into carbinols* **12** *and* **14**, *respectively.*

Table I Chemical shifts (ppm, $CDCl_3$) of the vinylic protons of some 6α,14α-ethenoisomorphinans and 6β,14β-ethenomorphinans.

Substitution pattern						Shifts		
4,5α	6,14	4	6	7	8	H-18	H-19	Ref.
-O-	α		OMe	α-NO_2		5.88–5.22		16
-O-	α		OMe	α-COMe		5.85	5.54	15
-O-	α		Me	α-COMe		5.36	5.60	8
-O-	α		H	α-COMe		5.60	5.54	6
-O-	β		H		β-NO_2	6.32	6.46	14
-O-	β		Me		β-COMe	6.75	5.62	8
	β	OPh	OMe	β-COMe		6.36	6.00	9
	β	OH	H	β-COMe		6.08	6.40	7
	β	OH	H		β-COMe	6.26	6.50	[a]
	β	OPh	H	β-COMe		6.00	6.40	[a]
	β	OPh	H		β-COMe	6.20	6.50	[a]

[a] This work.

In preliminary experiments[7], where **6** was only available as a mixture with its non-conjugated 5,8-diene isomer[7,10], the main product (**7**) could be isolated by column chromatography. The structure of the compound was elucidated by single-crystal X-ray analysis[11] and was proved to be the 7β-acetyl-6β,14β-ethenomorphinan **7**. This implies that the cycloaddition takes place at the α-side of the diene system. The *Diels–Alder* reaction performed under conventional conditions caused extensive polymerization of the dienophile, which made the work-up and the isolation of the adducts cumbersome. A dramatic improvement was achieved when the cycloaddition was carried out using a modified microwave oven. Recently, the use of microwave heating in organic synthesis has been reported[12,13]. The reactions described were carried out in closed vessels which resulted in high reaction pressure and temperature. In our set-up, we work under atmospheric conditions. Surprisingly, the reaction was complete within 24 h with substantially less formation of polymeric material, although the reaction temperature must have been similar to that in our earlier experiments[7]. The usual work-up procedure involving acid–base extraction gave the pure adducts **7** and **8** after selective crystallization.

Structure elucidation of the new addition product **8** met with difficulties. In the ^{1}H NMR spectrum, most of the signals could be assigned. From the shifts of the vinylic protons H-18 and H-19 at δ 6.26 and δ 6.50, respectively, it may be concluded that the etheno bridge is at the β-face of the molecule, as in adduct **7**. In the ^{1}H NMR spectra of other 6β,14β-ethenomorphinans[7,9,14], the vinylic protons are also found in this region, whereas these protons in the 6α,14α-ethenoisomorphinans are found below δ 6 (Table I). For a series of 22 compounds of the 6-methoxy-6α,14α-ethenoisomorphinan type, the signals of H-18 and H-19 are to be found at δ 5.91 (± 0.08) and δ 5.48 (± 0.06)[15], respectively. The downfield shift of the vinylic protons can be attributed to the deshielding effect of the aromatic nucleus. However, detailed ^{1}H NMR experiments, including solvent-induced shift, 2D-COSY and irradiation techniques, as well as ^{13}C NMR, did not result in an unequivocal assignment of the acetyl group. The signals of the protons at C-7 and C-8 coincide with those of the acetyl and *N*-methyl groups.

Mass spectrometry showed the expected molecular ion at *m/z* 353. The presence of a fragment *m/z* 57 (C_3H_5O) can be explained by a McLafferty rearrangement of the acetyl group. Molecular models show that this rearrangement can only occur in two 6β,14β-ethenomorphinans, *viz.* 7α- and 8β-acetyl, and in two 6α,14α-ethenoisomorphinans. However, the latter two can be ruled out on the basis of the NMR data.

From these spectral data, together with the application of the *Diels–Alder "endo"* rule[17], we tentatively assigned the 8β-acetyl-6β,14β-ethenomorphinan structure to amorphous **8**.

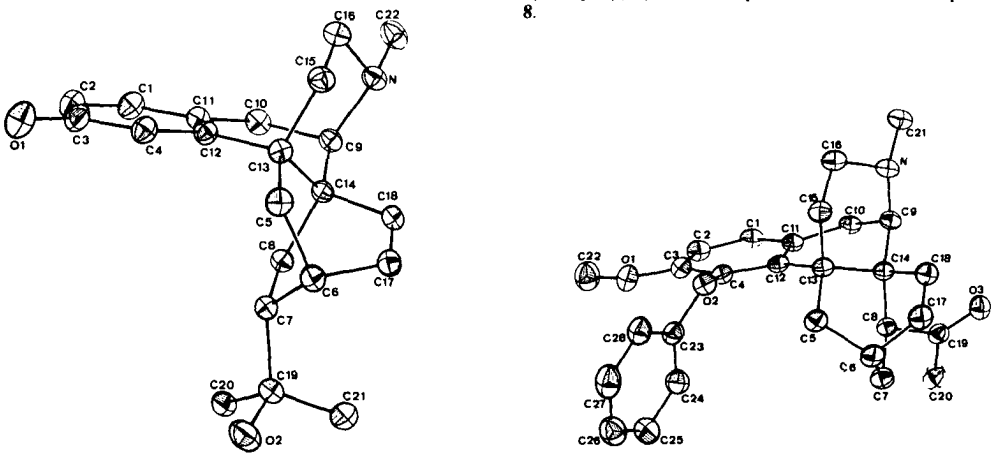


Fig. 1. Orientation of the 7β- and 8β-substituents of the ethenomorphinans **12** *(l) and* **13** *(r) from ORTEP drawings.*

In order to obtain final proof by single-crystal X-ray analysis, a crystalline derivative of **8** was required. Therefore, **8** was converted by an Ullmann reaction with bromobenzene into the 4-*O*-phenyl ether derivative **13** which readily crystallized from diethyl ether. The X-ray analysis[18] showed the compound to be the expected 8β-acetyl-3-methoxy-17-methyl-4-phenoxy-6β,14β-ethenomorphinan **13**, as depicted in Fig. 1. We may conclude that the *Diels–Alder* reaction of **6** with methyl vinyl ketone affords the 7β- and 8β-acetyl substituted 6β,14β-ethenomorphinans in a 3:2 ratio. Protection of the 4-hydroxyl group and *Diels–Alder* silica catalysis, as applied to β-dihydrothebaine (**4**)[9], are not required in this particular case in order to obtain satisfactory yields of the cycloadducts.

With respect to the site selectivity of the *Diels–Alder* reaction of 6-demethoxymorphinan-6,8-dienes, we may compare the cycloaddition with that of methyl vinyl ketone to 1-methyl-1,3-cyclohexadiene, which gave 2-acetyl-1-methylbicyclo[2.2.2]oct-5-ene as a 7:1 mixture of its epimers (90%)[19] (Scheme 3). Apparently, the methyl group has a strong directing effect on the *Diels–Alder* reaction. Both 6-demethoxythebaine and 6-demethoxy-β-dihydrothebaine can also be considered as substituted 1-alkyl-1,3-cyclohexadienes. Based on the above mentioned results, the cycloaddition reaction with monosubstituted dienophiles is expected to give the 8-substituted etheno(iso)morphinan as the main product.

However, in the case of 6-demethoxythebaine (**2**), there is a preference for the formation of 7-substituted 6α,14α-ethenoisomorphinans (88%)[20]. The influence on the course of the cycloaddition, caused by the morphinan skeleton, must be mainly of steric origin, since electronic effects of substituents connected via a C atom (σ bond) to a diene system (*e.g.* the epoxy bridge) are negligible.

In the case of 6-demethoxy-β-dihydrothebaine (**6**), which lacks the epoxy bridge, the 7- and 8-substituted adducts are formed in a ratio of 3:2, indicating that steric factors also govern the cycloaddition in this compound. Remarkably, opening of the epoxy ring results in *Diels–Alder* reaction from the other side of the diene system, compared with 4,5α-epoxymorphinan-6,8-dienes. With the information at hand it is only possible to speculate as to the course of the cycloaddition; this reaction will be the subject of further study.

Preparation of 3-hydroxy-α,α,17-trimethyl-6β,14β-ethenomorphinan-7β-methanol (**12**)

The target molecule **12**, reminiscent both of diprenorphine and of compounds previously prepared by us[7,21], was chosen for pharmacological testing. To prepare this compound, we followed the reaction pathway depicted in Scheme 2. Dehydroxylation of **7** was achieved using the procedure of *Sawa* et al.[22]. Reaction of the 4-hydroxyl group of **7** with bromobenzene in boiling pyridine in the presence of potassium carbonate and copper powder gave the crystalline 4-phenyl ether derivative **9**. At this stage, the acetyl group was converted into the desired tertiary alcohol by means of a Grignard reaction with methylmagnesium bromide because of its expected susceptibility in liquid ammonia. The phenoxyl group was then easily removed by sodium in liquid ammonia, affording **11**.

Finally, *O*-demethylation of **11**, using potassium hydroxide in glycol[2] with a small amount of water[7] and applying microwave heating, gave the desired phenolic compound **12**. First attempts at this demethylation using boron tribromide resulted in a complex mixture, as previously experienced in the case of the 4,5α-epoxy adducts[7].

The structure of **12** was definitively proven by single-crystal X-ray analysis[23] to be 3-hydroxy-α,α,17-trimethyl-6β,14β-ethenomorphinan-7β-methanol (Fig. 1), excluding a possible epimerization of the acetyl side-chain during the Ullmann and Grignard reactions.

Initial attempts to dehydroxylate **7** involving heterogeneously catalyzed hydrogenolysis were unsuccessful. Hydrogenolysis of the 5-phenyl-1-tetrazolyl ether using hydrogen and palladium on charcoal[24] or hydrogen transfer methods[25] resulted in reduction of the etheno bridge, while forcing conditions[26] under high pressure only led to decomposition. An attempt to hydrogenolyze the mesyl ester[27] of **7** also resulted in reduction of the double bond.

The Grignard reaction of the 8β-acetyl compound **13** with methylmagnesium bromide was laborious. A competitive side-reaction[8] seems to be the deprotonation of the acetyl group by the Grignard reagent. Hydrolysis of the reaction product gives a mixture of the starting material and some alcohol **14**. Repeating this procedure six times, finally, gave an acceptable yield (64%) of alcohol **14**.

Pharmacology*

Compound **12** appears to show activity in only one of the biological assays (sc injection in mice). In the PPQ (paraphenylquinone stretching) assay it is morphine-like. In the tail-flick test at 1.0, 10.0 and 30.0 mg/kg the compound is inactive as it is in the mouse hot-plate assay.

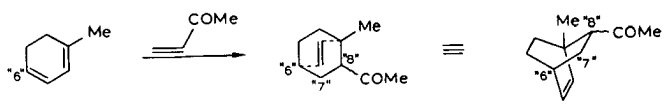
Since it has been previously noted that the PPQ assay is less discriminating with respect to the opioid-like activity, the compound will be examined further at the receptor level.

Experimental

Mass spectra were measured by Dr. *B. van de Graaf*, Mr. *H. Buurmans* and Mrs. *A. H. Knol-Kalkman* using a Varian MAT 311A mass spectrometer. ^{1}H NMR spectra were measured using a Varian T-60 spectrometer. The 200-MHz spectra were obtained using a Nicolet NT-200 WB, operated by Dr. *J. A. Peters* and Dr. *A. Sinnema*. All spectra were recorded in $CDCl_3$ as solvent with tetramethylsilane as reference. Rotations were measured using a Perkin-Elmer P141 polarimeter in chloroform/ethanol 9:1 as solvent.

Reactions were monitored by TLC on deactivated silica (0.25 mm, Merck F_{254}; eluent: dichloromethane/methanol/25% ammonia 85/15/0.5). The compounds were detected with UV (254 nm), iodine vapour and, in the case of phenolic compounds, with 2,6-dibromoquinone 4-chloroimide[28]. Melting points are uncorrected. Analytical HPLC was performed using a Waters

* Dr. *A. E. Jacobson*, National Institutes of Health, Bethesda, Md, U.S.A.



Scheme 3. Diels–Alder *reaction of 1-methyl-1,3-cyclohexadiene with methyl vinyl ketone.*

M-6000 pump on a reversed-phase column (8 × 100 mm, Nucleosil C_{18} or NovaPak, 10 µm, 30°C), using mixtures of methanol/water/trifluoroacetic acid as eluent, with detection on an ERMA RI-detector ERC-7510 or a Pye LC3 variable wave length detector at 240–250 nm. IR spectra were obtained from KBr discs using a Beckman IR 4210 spectrophotometer.

For microwave heating, we used a Sharp R-4060(w), 400 W, 2450 MHz microwave oven in the back wall of which a hole was bored for connection with a reflux condensor which was wrapped in copper wire gauze. After every 15 min of heating, the oven was switched off for 15 min to prevent overheating.

(+)-7β-Acetyl-3-methoxy-17-methyl-6β,14β-ethenomorphinan-4-ol (**7**) *and (+)-8β-acetyl-3-methoxy-17-methyl-6β,14β-ethenomorphinan-4-ol* (**8**)

6-Demethoxy-β-dihydrothebaine (**6**)[10] (10.2 g, 35 mmol) was boiled under reflux in 125 ml of freshly distilled methyl vinyl ketone using microwave heating (see introduction, experimental section). After 24 h, the mixture was evaporated *in vacuo*. The residue was dissolved in methanol and evaporated to dryness. The solid material (29.3 g) was dissolved in 300 ml of 0.5 *N* sulfuric acid and extracted with chloroform (5 × 75 ml). The organic layers were washed with 0.5 *N* sulfuric acid. The combined aqueous fractions were rendered alkaline with 4 *N* ammonia (pH 9–10) and extracted with chloroform (3 × 100 ml). The chloroform extract was washed with water (2 × 50 ml) and dried (Na_2SO_4) and the solvent was removed *in vacuo* (coevaporation with methanol), giving 9.25 g of solid material. Crystallization from methanol/diethyl ether gave 2.71 g (7.7 mmol, 22%) of the 7β-acetyl adduct **7** as white needles. M.p. 202°C (ref. 7: m.p. 204–205°C); $[\alpha]_D^{25}$ 100° (*c* 1) [ref. 7: $[\alpha]_D^{25}$ 95° (*c* 1.1)]. MS: *m/z* 353 (M^+, 100), 310 (31), 282 (15), 190 (24), 44 (47). ^1H NMR: ref. 7. IR: ν_{max}^{KBr} 3350 (OH), 1700 (C=O) cm^{-1}.

Evaporation of the mother liquor and repeated crystallization from methanol/diethyl ether gave 1.27 g (3.6 mmol, 10%) of the 8β-acetyl adduct **8** as a white amorphous material. M.p. 172–173°C; $[\alpha]_D^{25}$ 102° (*c* 1.2). MS: *m/z* 353 (M^+, 100), 310 (33), 282 (47), 190 (33), 110 (45), 57 (69). ^1H NMR: δ 1.20 (m, 1H, H-15'), 1.68 (dd, 1H, H-5, *J*(5,6) 2.3 Hz, *J*(5,5') − 13.7 Hz), 1.80 (m, 1H, H-16'), 1.90 (m, 2H, H-8 + H-15), 1.97 (s, 3H, $COCH_3$), 2.00 (m, 1H, H-5), 2.30 (m, 1H, H-7'), 2.35 (s, 3H, NCH_3), 2.56 (dd, 1H, H-10', *J*(1,10') 1 Hz, *J*(10,10') − 19.0 Hz), 2.60 (m, 1H, H-6), 2.97 (dd, 1H, H-10, *J*(9,10) 5.0 Hz), 3.00 (m, 1H, H-7), 3.19 (d, 1H, H-9), 3.87 (s, 3H, OCH_3), 5.87 (bs, 1H, OH), 6.26 (dd, 1H, H-18, *J*(18,19) 8.2 Hz, *J*(6,18) 6.5 Hz), 6.50 (d, 1H, H-19), 6.62 (d, 1H, H-1, *J*(1,2) 8.3 Hz), 6.71 (d, 1H, H-2). IR: ν_{max}^{KBr} 3360 (OH), 1700 (C=O) cm^{-1}.

(+)-7β-Acetyl-3-methoxy-17-methyl-4-phenoxy-6β,14β-ethenomorphinan (**9**)

The 7β-acetyl compound **7** (7.01 g, 19.9 mmol) was dissolved in 100 ml of pyridine (dried over KOH). Bromobenzene (4.0 g, 25.6 mmol), copper powder (4 g, 63 mmol) and solid anhydrous potassium carbonate (4 g, 29 mmol) were added and the mixture was boiled under reflux in a nitrogen atmosphere for 100 h.

The mixture was filtered over hyflo and the residue was washed with warm pyridine (3 × 15 ml). The filtrate was evaporated *in vacuo* and the oily residue was dissolved in 300 ml of toluene. This solution was washed with ammonia (3 × 75 ml) and water (2 × 50 ml). After drying (Na_2SO_4), the solvent was removed *in vacuo* and the residue was dissolved in 300 ml of diethyl ether. A fine precipitate was removed by filtration. After evaporation of the ether, the residue was taken up in 750 ml of hexane. Filtration and removal of the solvent gave 7.79 g of an off-white foam. Crystallization from 400 ml of hexane gave 4.15 g (9.7 mmol, 49%) of *compound* **9**. M.p. 158°C; $[\alpha]_D^{25}$ 93° (*c* 1). MS: *m/z* 429 (M^+, 100), 386 (25), 358 (10), 266 (20). ^1H NMR: δ 2.05 (s, 3H, $COCH_3$), 2.35 (s, 3H, NCH_3), 3.62 (s, 3H, OCH_3), 6.00 (dd, 1H, H-18, *J*(18,19) 8 Hz), *J*(6,18) 6 Hz), 6.40 (d, 1H, H-19), 6.70–7.40 (m, 7H, Ar−H). IR: ν_{max}^{KBr} 1705 (C=O) cm^{-1}.

(+)-3-Methoxy-α,α,17-trimethyl-4-phenoxy-6β,14β-ethenomorphinan-7β-methanol (**10**)

To a boiling mixture of 150 ml of anhydrous diethyl ether and 4 ml of a 3-M solution of methylmagnesium bromide in diethyl ether (12 mmol), a solution of the 7β adduct **9** (3.82 g, 8.9 mmol) in 150 ml of diethyl ether was added dropwise (20 min). After completion of the addition, an additional amount of 3 M methylmagnesium bromide solution (0.4 ml, 1.2 mmol) was added to the mixture. After 10 min, all starting material had disappeared (TLC), the oil bath was removed and a solution of ammonium chloride (12 g) in 200 ml of water was added cautiously. The layers were separated and the aqueous phase was extracted with diethyl ether (3 × 50 ml). The combined organic fractions were washed with water (2 × 50 ml), dried (Na_2SO_4) and evaporated to dryness, yielding 3.82 g (8.6 mmol, 96%) of the title compound **10** as a white foam, pure according to TLC and HPLC. $[\alpha]_D^{25}$ 72° (*c* 0.7). MS: *m/z* 445 (M^+, 100), 386 (32), 358 (20), 266 (35). ^1H NMR: δ 0.97 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 2.32 (s, 3H, NCH_3), 6.20 (dd, 1H, H-18, *J*(18,19) 8 Hz, *J*(6,18) 6 Hz), 6.50 (d, 1H, H-19), 6.70–7.40 (m, 7H, Ar−H). IR: ν_{max}^{KBr} 3560 (OH) cm^{-1}.

(+)-3-Methoxy-α,α,17-trimethyl-6β,14β-ethenomorphinan-7β-methanol (**11**)

A solution of **10** (3.72 g, 8.4 mmol) in 150 ml of diethyl ether (dried over molecular sieve 4 Å) was added over 30 min to a solution of 1 g (44 mmol) of sodium in 200 ml of liquid ammonia at −58°C[29]. After 10 min, the reaction was complete (TLC), solid ammonium chloride and ethanol were added and the mixture was warmed to room temperature. The solvents were evaporated *in vacuo*. The residue was taken up into 100 ml of water and rendered alkaline with 2 *N* KOH solution (100 ml) to pH 9–10. This solution was extracted with dichloromethane (75 ml and 2 × 30 ml). The combined organic layers were washed with 2 *N* KOH (2 × 50 ml) and water (2 × 50 ml) and dried (Na_2SO_4). Evaporation of the solvent *in vacuo* gave 3.00 g (8.4 mmol, 100%) of pure (TLC, HPLC) **11** as a white foam. $[\alpha]_D^{25}$ 54° (*c* 1). MS: *m/z* 353 (M^+, 100), 338 (19), 336 (14), 294 (28), 266 (12), 221 (15), 209 (20), 195 (11), 174 (14). ^1H NMR: δ 0.97 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 2.38 (s, 3H, NCH_3), 3.79 (s, 3H, OCH_3), 6.21 (dd, 1H, H-18, *J*(18,19) 8 Hz, *J*(6,18) 6 Hz), 6.50 (d, 1H, H-19), 6.74–7.08 (m, 3H, Ar−H). IR: ν_{max}^{KBr} 3450 (OH) cm^{-1}.

(+)-3-Hydroxy-α,α,17-trimethyl-6β,14β-ethenomorphinan-7β-methanol (**12**)

A solution of compound **11** (2.32 g, 6.6 mmol) and potassium hydroxide (15 g) in a mixture of glycol (75 ml) and water (1 ml) was refluxed using microwave heating. After 5 h heating, 15 g of potassium hydroxide and 1 ml of water were added. The heating was continued for a further 5 h (complete conversion on TLC). After cooling to room temperature, the reaction mixture was diluted with 100 ml of water and extracted with dichloromethane (50 ml) to remove non-phenolic material. The aqueous layer was adjusted with concentrated hydrochloric acid to pH 7–8 and thoroughly extracted with dichloromethane (14 × 60 ml) and diethyl ether (5 × 70 ml). The combined organic layers where washed with water, dried (Na_2SO_4) and evaporated *in vacuo*, yielding 1.40 g (4.1 mmol, 63%) of pure (TLC) **12** as a white foam. Crystallization from hexane/diethyl ether gave 270 mg of the 3-hydroxy adduct **12** as white crystals, suitable for X-ray analysis. M.p. 184–186°C (dec.); $[\alpha]_D^{25}$ 55° (*c* 0.7). MS: *m/z* 339 (M^+, 100), 324 (18), 280 (29), 252 (12), 195 (19), 160 (14). ^1H NMR: δ 0.99 (s, 3H, CH_3), 1.11 (s, 3H, CH_3), 2.38 (s, 3H, NCH_3), 2.72 (dd, 1H, H-10, *J*(9,10) 5.5 Hz, *J*(10,10') − 18 Hz), 2.77 (m, 1H, H-6), 2.92 (d, 1H, H-9), 3.06 (d, 1H, H-10'), 6.19 (dd, 1H, H-18, *J*(18,19) 8.1 Hz, *J*(6,18) 6.3 Hz), 6.50 (d, 1H, H-19), 6.58–6.94 (m, 3H, Ar−H). IR: ν_{max}^{KBr} 3300 (OH) cm^{-1}. X-ray analysis, ref. 23: $C_{22}H_{29}NO_2$, mol. wt. 339.5. Orthorhombic, $P2_12_12_1$, a = 7.810 (2), b = 14.152 (2), c = 16.705 (4) Å, V = 1846.4 Å^3, Z = 4, D_x = 1.23 g·cm^{-3}.

(+)-8β-Acetyl-3-methoxy-17-methyl-4-phenoxy-6β,14β-ethenomorphinan (**13**)

Bromobenzene (1.75 g, 11.2 mmol), copper powder (1.75, 27.8 mmol) and anhydrous, powdered potassium carbonate (1.75 g, 12.8 mmol) were added to a solution of the 8β-acetyl adduct **8** (2.88 g, 8.2 mmol) in pyridine (45 ml). After 50 h boiling, the reaction was complete. The mixture was cooled to room temperature, filtered and worked up as described for the 7β-acetyl adduct **9**. The treatment with hexane was repeated three times, yielding 1.97 g (4.6 mmol, 56%) of pure **13** after evaporation of the solvent. Crystalli-

zation from diethyl ether gave suitable crystals for X-ray analysis. M.p. 130–131 °C; $[\alpha]_D^{25}$ 90° (*c* 1). MS: *m/z* 429 (M^+, 100), 386 (20), 358 (28), 266 C24). ^{1}H NMR: δ 1.96 (s, 3H, $COCH_3$), 2.33 (s, 3H, NCH_3), 3.62 (s, 3H, OCH_3), 6.20 (dd, 1H, H-18, *J*(18,19) 8 Hz, *J*(6,18) 6 Hz), 6.50 (d, 1H, H-19), 6.70–7.40 (m, 7H, Ar–H). IR: ν_{max}^{KBr} 1705 (C=O) cm^{-1}. X-ray analysis, ref. 18: $C_{28}H_{31}NO_3$, mol. wt. 429.6. Orthorhombic, $P2_12_12_1$, a = 11.899 (2), b = 15.511 (3), c = 20.543 (4) Å, V = 2292.3 Å^3, Z = 4, D_x = 1.25 g·cm^{-3}.

(+)-3-Methoxy-α,α,17-trimethyl-4-phenoxy-6β,14β-ethenomorphinan-8β-methanol (**14**)

A solution of **13** (1.65 g, 3.8 mmol) in 50 ml of anhydrous diethyl ether was added over 30 min to a boiling mixture of diethyl ether (100 ml) and a 3-M solution (2 ml, 6 mmol) of methylmagnesium bromide in diethyl ether. After the addition was complete, the excess of the Grignard reagent was destroyed with a saturated ammonium chloride solution, the layers were separated and the aqueous fraction was extracted with diethyl ether (2 × 25 ml). The combined ether fractions were dried (Na_2SO_4) and evaporated *in vacuo*. The residue, which consisted of a mixture of carbinol **14** and unreacted **13**, was redissolved in 50 ml of diethyl ether and again treated with methylmagnesium bromide solution (2 ml, 6 mmol). This procedure was repeated five times, finally giving 1.08 g (2.4 mmol, 64%) of **14**. M.p. 199–202°C (dec.); $[\alpha]_D^{25}$ 53° (*c* 1). MS: *m/z* 445 (M^+, 100), 430 (10), 386 (23), 358 (27),281 (12), 266 (19). ^{1}H NMR: δ 0.90 (m, 2H, H-15, H-15′), 1.04 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 1.11 (m, 1H, H-8), 1.60 (m, 2H, H-5 + H-5′), 1.90 (m, 1H, H-7), 2.00 (m, 2H, H-16 + H-16′), 2.20 (m, 1H, H-7′), 2.33 (s, 3H, NCH_3), 2.40 (m, 1H, H-6), 2.92 (dd, 1H, H-10, *J*(9,10) 5.8 Hz, *J*(10,10′) – 18.6 Hz), 3.38 (d, 1H, H-9), 3.64 (s, 3H, OCH_3), 3.66 (d, 1H, H-10′), 6.06 (dd, 1H, H-18, *J*(18,19) 8.1 Hz, *J*(6,18) 6.1 Hz), 6.34 (d, 1H, H-19), 6.68 (d, 1H, H-1, *J*(1,2) 8.6 Hz), 6.72 (d, 1H, H-2), 6.80–7.25 (m, 5H, PhO–). IR: ν_{max}^{KBr} 3400 (OH) cm^{-1}.

Acknowledgements

We are grateful to the Management of Diosynth, B.V., Apeldoorn, The Netherlands for the gift of chemicals. One of us (J.T.M.L.) wishes to express his gratitude for financial support from Diosynth, B.V. We thank the U.S.A. Committee on Problems of Drug Dependence, Inc. and Dr. *A. E. Jacobson*, Chairman, Drug Testing Program, for the results of the pharmacological studies. We thank Dr. *J. A. Peters* and Dr. *A. Sinnema* for interpretation of the 200-MHz ^{1}H NMR spectra and Dr. *B. van de Graaf* for interpretation of the mass spectra.

References

[1] *C. Schöpf, K. von Gottberg* and *W. Petri*, Lieb. Ann. Chem. **536**, 216 (1938).

[2] *K. W. Bentley* and *D. G. Hardy*, Proc. Chem. Soc. 220 (1963).

[3] *K. W. Bentley* in "The Alkaloids", Vol. XIII, Ed. *R. H. F. Manske*, Academic Press, New York, London, 1971, p. 75.

[4] See foot-note on nomenclature of ethano(iso)morphinans in Ref. 7.

[5] *P. R. Crabbendam, L. Maat* and *H. C. Beyerman*, Recl. Trav. Chim. Pays-Bas **100**, 293 (1981).

[6] *C. W. Hutchins, G. K. Cooper, S. Pürro* and *H. Rapoport*, J. Med. Chem. **24**, 773 (1981).

[7] *P. R. Crabbendam, T. S. Lie, J. T. M. Linders* and *L. Maat*, Recl. Trav. Chim. Pays-Bas **103**, 296 (1984).

[8] *L. C. Knipmeyer* and *H. Rapoport*, J. Med. Chem. **28**, 461 (1985).

[9] *A. C. Ghosh, D. E. Portlock, H. C. Dalzell, C. Malmberg, P. Herlihy, R. K. Razdan, W. L. Duax* and *D. G. Smith*, J. Org. Chem. **48**, 4137 (1983).

[10] *J. T. M. Linders, R. J. O. Adriaansens, T. S. Lie* and *L. Maat*, Recl. Trav. Chim. Pays-Bas **105**, 27 (1986).

[11] *H. van Koningsveld, L. Maat* and *T. S. Lie*, Acta Crystallogr. C**40**, 1082 (1984).

[12] *R. Gedye, F. Smith, K. Westaway, H. Ali, L. Baldisera, L. Laberge* and *J. Rousell*, Tetrahedron Lett. **27**, 279 (1986).

[13] *R. J. Giguere, T. L. Bray, S. M. Duncan* and *G. Majetich*, Tetrahedron Lett. **27**, 4945 (1986).

[14] *M. A. Prazeres, J. A. Peters, J. T. M. Linders* and *L. Maat*, Recl. Trav. Chim. Pays-Bas **105**, 554 (1986).

[15] *W. Fulmor, J. E. Lancaster, G. O. Morton, J. J. Brown, C. F. Howell, C. T. Nora* and *R. A. Hardy*, J. Am. Chem. Soc. **89**, 3322 (1967).

[16] *L. Maat, J. A. Peters* and *M. A. Prazeres*, Recl. Trav. Chim. Pays-Bas **104**, 205 (1985).

[17] *R. Gleiter* and *M. C. Böhm*, Pure Appl. Chem. **55**, 237 (1983).

[18] *H. van Koningsveld, J. C. Jansen, M. Overhand, L. Maat* and *T. S. Lie*, Acta Crystallogr. C**43**, 1773 (1987).

[19] *R. P. Gregson* and *R. N. Mirrington*, Aust. J. Chem. **29**, 2049 (1976).

[20] 8α-Acetyl-4,5α-epoxy-3-methoxy-6α,14α-ethenoisomorphinan could be isolated from the reaction mixture obtained from the *Diels–Alder* reaction of 6-demethoxythebaine with methyl vinyl ketone, after crystallization of the major 7α-acetyl adduct[7], by column chromatography followed by preparative TLC (multiple elution). The ^{1}H NMR spectrum was in accordance with the published, calculated spectrum[6]; *J. T. M. Linders, T. S. Lie* and *L. Maat*, to be published.

[21] 4,5α-Epoxy-α,α,17-trimethyl-6α,14α-ethenoisomorphinan-7α-methanol, *J. T. M. Linders, T. S. Lie* and *L. Maat*, to be published.

[22] *Y. K. Sawa, N. Tsuji* and *S. Maeda*, Tetrahedron **15**, 144 (1961).

[23] *H. van Koningsveld, J. C. Jansen, M. Overhand, T. S. Lie* and *L. Maat*, Acta Crystallogr. C**43**, 2384 (1987).

[24] *H. C. Beyerman, E. Buurman, T. S. Lie* and *L. Maat*, Recl. Trav. Chim. Pays-Bas **95**, 43 (1976).

[25] *B. J. Hussey, R. A. W. Johnstone* and *I. D. Entwistle*, Tetrahedron **38**, 3775 (1982).

[26] *J. Reden, M. F. Reich, K. C. Rice, A. E. Jacobson* and *A. Brossi*, J. Med. Chem. **22**, 256 (1979).

[27] *K. Clausz* and *H. Jensen*, Angew. Chem. **85**, 981 (1971).

[28] *E. Nürnberg*, Dtsch. Apoth. Ztg. **101**, 268 (1961).

[29] *H. C. Beyerman, F. F. van Leeuwen, T. S. Lie, L. Maat* and *C. Olieman*, Recl. Trav. Chim. Pays-Bas **95**, 238 (1976).

4.2. Comment on the use of microwave ovens in chemistry[1-3]

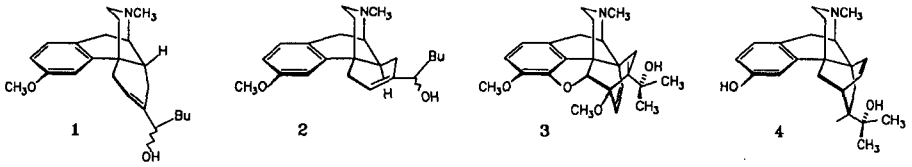
Although already during the 1950s attention has been given to the effects of microwave radiation on biosystems[3], the use of this source of energy and means of heating for chemical purposes has not been documented until recently. Only in the fields of analytical and polymer chemistry, biochemistry and geology, application of microwave heating has been described[4-6].

In the last years, a number of reports appeared in which the use of microwave heating for chemical reactions was described ("The Chemist's Quick Cookbook")[4]. Gedye *et al.*[5] and Giguere *et al.*[6-7] performed reactions in closed teflon vessels. Hwang *et al.*[8] used this technology to prepare short-lived radiopharmaceuticals.

In 1988, Gedye *et al.*[9] reported that no significant accelleration of a test reaction was observed using microwave heating, when compared to conventional oil bath heating. This is contrast to our findings as reported in 4.1. Simultaneously with our paper, Isobe *et al.*[10] presented results of a comparative study on transesterifications and ester hydrolyses using conventional oil bath and microwave heating, using a set-up similar to ours. The hydrolysis of methyl benzoate in 2% HCl in dioxane/water was shown to be 50% faster when microwave heating was applied. Even more dramatical were results obtained by Sun *et al.*[11] on the hydrolysis of ATP. Samples irradiated for 4 min showed 90.9% hydrolysis, while on conventional (dry block) heating only 6.9% of the starting material was hydrolyzed. They explain this phenomena by invoking the term 'spectroscopic heating'. The energy transferred is specifically used to heat up solvent molecules, which use this additional energy both to perform chemical reactions and to heat up the vessel. This is in contrast to conventional heating, in which the energy is first used to heat up the reaction flask, and subsequently the contents. In a recent study of Straathof *et al.*[12] on the thermolysis of (1→4)-D-glucans in an open beaker put in a commercial microwave oven, this phenomenon has been decribed as well. The reaction was found to start in the centre of the sample after a few minutes of heating.

4.3. Molecular matching of 6β,14β-ethenomorphinans with 6α,14α-ethenoisomorphinans and simple (iso)morphinans.

Recently, Quick *et al.*[13] reported on the preparation and pharmacological activity of morphinan **1** and isomorphinan **2**.



Whereas **2** surprisingly showed very strong analgesic properties, its isomer **1** was essentially inactive. Superposition[14] of **1** (7-hydroxymethyl instead of 7-hydroxypentyl) and 6β,14β-ethenomorphinan **4**[15] (See 4.1) shows a striking spatial resemblance, either when aromatic carbons or the carbon atoms in the piperidine ring are matched (Fig. 1). Compound **4** can be considered as an etheno bridged analogue of **1**. Apparently, there is no important positive effect of this additional bridge on the analgesic activity.

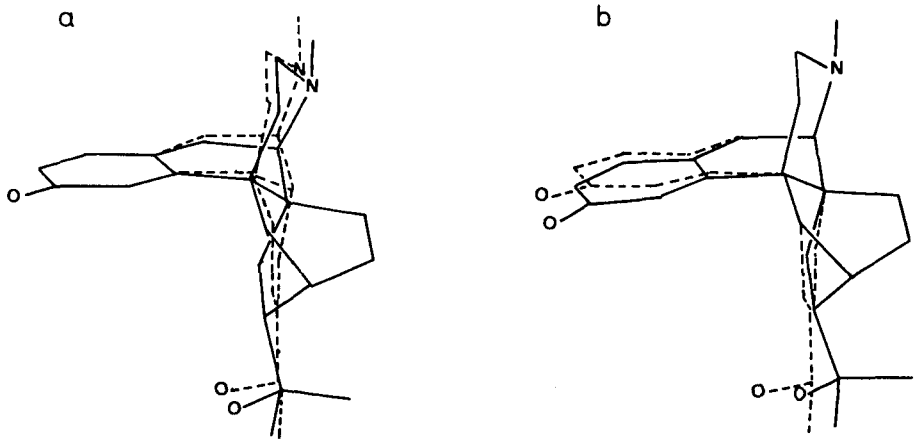


Fig. 1. Superposition of morphinan **1** (---) and 6β,14β-ethenomorphinan **4** (——).
a. Aromatic carbons matched
b. Piperidine ring matched

Superposition of the active compound **2** (7-hydroxymethyl instead of 7-hydroxypentyl) with 6α,14α-ethenoisomorphinan **3**[16], an etorphine analogue, is shown in Fig. 2. Here the structural resemblance is less, especially when the orientation of the lipophilic part is considered. The position of the 7-substituent relative to the piperidine ring is largely the same, but relative to the aromatic moiety, there are significant differences.

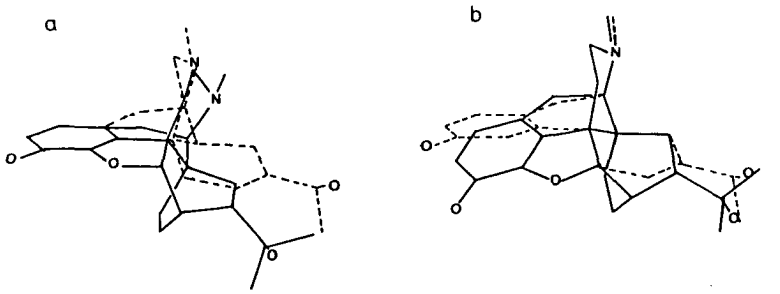


Fig. 2. Superposition of isomorphinan **2** (- - -) and 6α,14α-ethenoisomorphinan **3** (——).
a. Aromatic carbons matched
b. Piperidine ring matched

When **3** and **4** are superimposed (Fig. 3), the complete different orientation of the lipophilic tail is obvious, either when the aromatic carbons or the piperidine ring are matched.

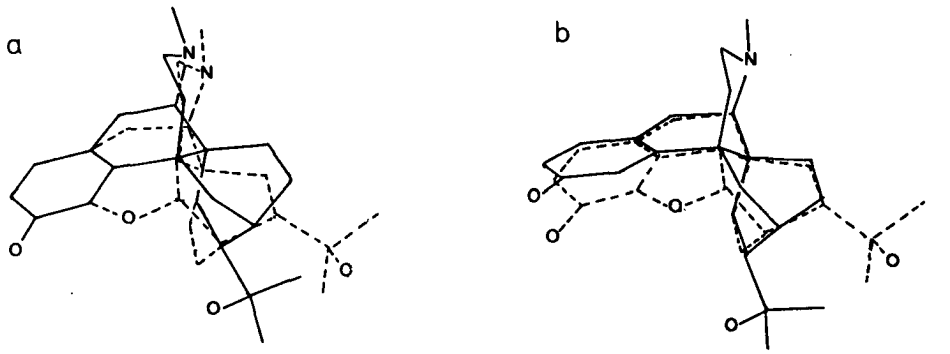
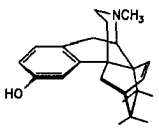
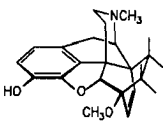


Fig 3. Superposition of 6α,14α-ethenoisomorphinan **3** (- - -) and 6β,14β-ethenomorphinan **4** (——).
a. Aromatic carbons matched
b. Piperidine ring matched

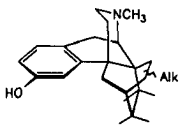
Rapoport and coworkers[17-20] have shown the importance of the orientation of the carbon substituent at the 7-position of the Diels-Alder adducts for high analgesic activity. It is clear that the picture of the spatial and conformational requirements of this lipophilic substituent is far from complete. Therefore, it would be useful to prepare and test the unsubstituted 6β,14β-ethenomorphinan **5**, keeping in mind that the 6α,14α-analogue **6** is a moderately active analgesic[21]. Pharmacological testing of compounds **7** and **8**, which should be accessible from **5** and **6** by derivatization of the etheno bridge, and of 7α-substituted 6β,14β-ethenomorphinans, which probably can be obtained by epimerization of the 7β-analogue, could enlarge the knowledge about structure-activity relationships.



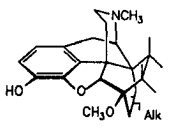
5



6



7



8

Acknowledgements

Use of the services and facilities of the Dutch CAOS/CAMM Center, under grant numbers SON - 11-20-700 and STW - NCH-44.0703, is gratefully acknowledged. I am grateful to Ir. K.M.J. Brands for putting Ref. 13 to my attention.

References

1. D.A. Copson, "Microwave Heating in Freeze-Drying, Electronic Ovens, and Other Applications", The AVI Publishing Co., Westport, CT, 1975, Chapter 1.
2. J. Walker, Sci. Am. **256**, 98 (1987).
3. K.R. Foster and A.W. Guy, Sci. Am. **255**, 28 (1986).
4. J. Emsley, New Scientist, November 12 1988, 56.
5. R. Gedye, F. Smith, K. Westaway, H. Ali, L. Baldisera, L. Laberge and J. Rousell, Tetrahedron Lett. **27**, 279 (1986) and references cited therein.
6. R.J. Giguere, T.L. Bray, S.M. Duncan and G. Majetich, Tetrahedron Lett. **27**, 4945 (1986) and references cited therein.
7. R.J. Giguere, A.M. Namen, B.O. Lopez, A. Arepally, D.E. Ramos, G. Majetich and J. Defauw, Tetrahedron Lett. **28**, 6553 (1987).

8. D.-R. Hwang, S.M. Moerlein, L. Lang and M.J. Welch, J. Chem. Soc., Chem. Commun. 1799 (1987).
9. R. Gedye, F.E. Smith and K.C. Westaway, Can. J. Chem. **66**, 17 (1988).
10. K. Isobe, T. Kawada, K. Mohri and Y. Tsuda, Poster presented at the Japan-United States Congress of Pharmaceutical Sciences, Honolulu, december 2-7, 1987; See J. Pharm. Sci. **76**, S237 (1987).
11. W.-C. Sun, P.M. Guy, J.H. Jahngen, E.F. Rossomando and E.G.E. Jahngen, J. Org. Chem. **53**, 4414 (1988).
12. A.J.J. Straathof, H. van Bekkum and A.P.G. Kieboom, Recl. Trav. Chim. Pays-Bas **107**, 647 (1988).
13. J. Quick, P. Herlihy and J.F. Howes, J. Med. Chem. **27**, 632 (1984).
14. Structures were minimized with MMP2(85) using X-ray data as starting geometry. Superpositions were performed within the MODEL and CHEM-X suites (See also Chapter 8).
15. H. van Koningsveld, J.C. Jansen, M. Overhand, T.S. Lie and L. Maat, Acta Cryst. C**43**, 2384 (1987).
16. J.H. van den Hende and N.R. Nelson, J. Am. Chem. Soc. **89**, 2901 (1967).
17. C.W. Hutchins, G.K. Cooper, S. Pürro and H. Rapoport, J. Med. Chem. **24**, 773 (1981).
18. C.W. Hutchins and H. Rapoport, J. Med. Chem. **27**, 521 (1984).
19. L.L. Knipmeyer and H. Rapoport, J. Med. Chem. **28**, 461 (1985).
20. H. Rapoport in "Natural Products and Drug Development", P. Krogsgaard-Larsen, S. Brøgger Christensen and H. Kofod (Eds.), Munksgaard, Copenhagen, 1984, 429.
21. J.W. Lewis, M.J. Readhead and A.C.B. Smith, J. Med. Chem. **16**, 9 (1973).

CHAPTER 5 SYNTHESIS AND DIELS-ALDER REACTIONS OF *N*-FORMYLMORPHINAN-6,8-DIENES

5.1. Introduction

During more than 180 years of morphine chemistry, surprisingly little attention has been paid to the preparation, properties[1] and synthetic potential of *N*-formylmorphinans. It is illustrative that a simple compound as *N*-formyl-*N*-norcodeine has not been described. 6-*O*-Acetyl-*N*-formyl-dihydro-*N*-norcodeine was prepared accidentally through direct oxidation (chromium(VI) oxide in the presence of pyridine) of the *N*-methyl group of the corresponding dihydrocodeine[2].

Replacement of the *N*-methyl by an *N*-formyl group leads to some distinct changes in the nature of the nitrogen atom. Its basicity and nucleophilicity are masked, allowing reactions possible using acid catalysis or base-sensitive reagents. The flat formamide moiety results in two rotamers, which can often be observed separately on TLC[3] or HPLC[4,5] and in some instances may be separated by selective crystallization[6]. In the Delft total synthesis of morphinans, 1-benzyl-*N*-formylisoquinolines were used as starting material for the acid-catalyzed ring closure to the morphinan skeleton[4,7]. The geometrical constraints imposed by the amide bring the reacting groups in a closer proximity than in the corresponding *N*-methyl analogue. Bosch *et al.*[8] made also use of this effect in the synthesis of B-norbenzomorphans. Recently, Lukanov *et al.* used *N*-formylated phenethylamines as starting material for the preparation of 1-benzyl-*N*-formylisoquinolines[9].

The introduction and subsequent removal of the formyl group can be performed in high yield under mild conditions, making the formyl group a suitable protecting group for secondary amines. Moreover, the *N*-formyl group can be reduced directly to *N*-methyl using diborane in THF[3,10] or catalytic hydrogenation[7,10].

References

1. A comprehensive review on the conformation of acyl groups in heterocyclic compounds has been published recently: R. Benassi, U. Folli, L. Schenetti and F. Taddei, Adv. Heteroc. Chem. **41**, 75 (1987).
2. T.D. Perrine and L.F. Small, J. Org. Chem. **21**, 111 (1956).
3. K.C. Rice and A. Brossi, J. Org. Chem. **45**, 592 (1980).
4. C. Olieman, "Synthetic Investigations on Morphinans", Thesis, Delft University of Technology, Delft, 1980.
5. C. Olieman, L. Maat, K. Waliszewski and H.C. Beyerman, J. Chromatogr. **133**, 382 (1977).
6. C. Szántay, G. Blaskó, M. Bárczai-Beke, G. Dörnyei and L. Radics, Heterocycles **14**, 1127 (1980).
7. H.C. Beyerman, E. Buurman, L. Maat and C. Olieman, Recl. Trav. Chim. Pays-Bas **95**, 184 (1976).
8. J. Bosch, M. Rubiralta, M. Moral and J. Bolós, J. Chem. Soc., Perkin I 1459 (1984).
9. L.K. Lukanov, A.P. Venkov and N.M. Mollov, Synthesis 1031 (1987).
10. H.C. Beyerman, L. van Bommel, L. Maat and C. Olieman, Recl. Trav. Chim. Pays-Bas **95**, 312 (1976).

5.2

4,5α-Epoxy-3-methoxy-8β-nitro-6β,14β-ethenomorphinan, a novel type Diels-Alder adduct from 6-demethoxy-17-formylnorthebaine

4,5α-EPOXY-3-METHOXY-8β-NITRO-6β,14β-ETHENOMORPHINAN, A NOVEL TYPE DIELS-ALDER ADDUCT FROM 6-DEMETHOXY-17-FORMYLNORTHEBAINE AND NITROETHENE

(Chemistry of Opium Alkaloids, Part XXIII)*

M.A. Prazeres, J.A. Peters, J.T.M. Linders and L. Maat

Laboratory of Organic Chemistry, Delft University of Technology, Julianalaan 136, 2628 BL Delft, The Netherlands

(Received: *November 4th, 1986*)

Abstract: 4,5α-Epoxy-3-methoxy-8β-nitro-6β,14β-ethenomorphinan (**5**) was isolated as one of two major cycloaddition products of 6-demethoxy-17-formylnorthebaine (**3**) and nitroethene. Structure elucidation was mainly based on ^{1}H NMR data.

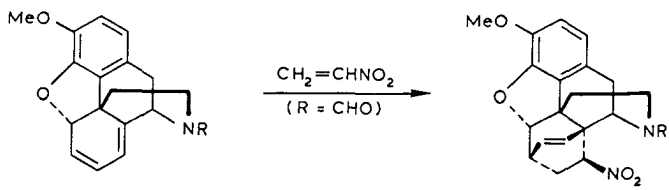
Thebaine readily forms Diels-Alder adducts with a great variety of dienophiles. Mono-substituted ethenes give predominantly 7α-substituted 6α,14α-ethenoisomorphinans, sometimes along with a minor amount of the 7β-isomer[1]. Several of these compounds exhibit, after further modification, extremely high analgesic potency.

When other morphinan-6,8-dienes are subjected to Diels-Alder reaction, a greater diversity in isomeric bicyclic analogues of morphine is produced. The cycloaddition of morphinan-6,8-dienes without the 4,5α-epoxy bridge proceeds from the opposite side of the diene system compared to thebaine, affording a novel class of 7β-substituted 6β,14β-ethenomorphinans[2,3].

Only recently, the formation of an 8β-substituted 6β,14β-ethenomorphinan was described as a minor reaction product (0.1%) from 6-deoxythebaine, a 4,5α-epoxy bridge containing 6-methylmorphinan-6,8-diene, with methyl vinyl ketone. The major isomer isolated was again the 7α-substituted 6α,14α-ethenoisomorphinan (71%) along with the 7β- and 8α-substituted isomers[4].

This prompts us to report on the synthesis of a new 8β-substituted 6β,14β-ethenomorphinan **5** (Scheme 1) starting from a 4,5α-epoxymorphinan **3**, now as one of two major adducts.

6-Demethoxy-17-formylnorthebaine (**3**) was prepared from 6-demethoxythebaine (**1**) according to procedures described earlier for thebaine[5]. *N*-Demethylation with diethyl azodicarboxylate yielded **2** {63%; m.p. HCl-salt 258-261 °C (dec); ^{1}H NMR ($CDCl_3$): δ 3.8 (s, 3H, OCH_3), 5.3-6 (m, 4H, H-5 - H-8), 6.6 (m, 2H, H-1 and H-2); M.S: *m/z* 267 (M^+)}. *N*-Formylation of **2** with ethyl formate in DMF gave **3** {96%; m.p. 120-122 °C; ^{1}H NMR ($CDCl_3$): δ 3.85 (s, 3H, OCH_3), 5.3-6 (m, 4H, H-5 ~ H-8), 6.7 (m, 2H, H-1 and H-2); 8.1 (d, 1H, *E*- and *Z*-CHO); MS: *m/z* 295 (M^+)}. Compound **3** (0.96 g, 3.2 mmol) was boiled under reflux in 20 ml of benzene with an excess of nitroethene (2.3 eq) freshly prepared from nitroethanol and phthalic anhydride[6]. After 60 h (75% conversion) the reaction mixture was evaporated to dryness *in vacuo*. The



1, R = Me, 6-Demethoxythebaine
2, R = H, 6-Demethoxynorthebaine
3, R = CHO, 6-Demethoxy-17-formylnorthebaine
4, R = CHO
5, R = H

mixture was more complex than the similar reaction product starting from *N*-formylnorthebaine[5]. The Diels-Alder adducts were separated from starting material and polymers by preparative TLC (silicagel plates, 1 mm, Merck Art. 13895, dichloromethane/methanol 9:1). In order to avoid difficulties in the interpretation of the ^{1}H NMR spectra due to the presence of (*E*)- and (*Z*)-formyl isomers, the product was hydrolyzed in 0.8 M hydrochloric acid in methanol. HPLC analysis of the mixture obtained showed the presence of five new compounds in a ratio of 1:1:0.4:0.1:0.05 (Waters M-6000 pump, RCM 100, reversed-phase column Novapack C_{18}, 5µm, methanol/water/trifluoroacetic acid 50:50:0.1, RI detection). Using preparative TLC (silicagel plates, 1 mm, Merck Art. 13895, dichloromethane/methanol 9:1) only one of the two major compounds could be isolated in a pure but amorphous state {20%; ^{1}H NMR (C_6D_6): δ 1.52 (m, 1H, H-7α), 1.66 (m, 1H, H-7β), 3.44 (m, 1H, H-8), 3.58 (s, 3H, OCH_3), 3.84 (d, 1H, H-5), 5.72 (m, 1H, H-18), 6.23 (d, 1H, H-19), 6.52 (d, 1H, H-2) and 6.66 (d, 1H, H-1); MS: *m/z* 340 (M^+)}.

The signals in the 200 MHz ^{1}H NMR spectrum of 5 were assigned with the use of a homonuclear 2D correlation (COSY). From the magnitude of the vicinal couplings between H-7α and H-7β and H-8 ($J_{7\alpha,8}$ 8.5 Hz and $J_{7\beta,8}$ 4.0 Hz) it can be concluded that the nitro group is at the 8β-position. The 6β,14β orientation of the etheno bridge with respect to the isomorphinan skeleton was established by the long range coupling between H-5 and H-7β (1.3 Hz), which is in agreement with the W-arrangement of the respective protons in that structure. Moreover, long range couplings between H-5 and H-18, and between H-7β and H-18, as present in the case of 6α,14α-etheno bridged adducts, were not observed in this compound. In addition, it is to be noted that proton H-8α is shielded (1.2 ppm) with respect to the corresponding H-7β in the 7α-nitro-6α,14α-ethenoisomorphinan[5], which might be explained by the shielding effect as a result of the proximity of the benzene ring in the 6β,14β-etheno adduct. A downfield shift in the resonance of the vinyl protons H-18 and H-19 of 0.4 and 0.8 ppm, respectively, was also observed. In conclusion, the structure of the new compound is 4,5α-epoxy-3-methoxy-8β-nitro-6β,14β-ethenomorphinan.

The regioselectivity of the Diels-Alder reaction of morphinan-6,8-dienes has been explained as a combination of steric and electronic effects[1]. The release of the strain of the 4,5α-epoxy bridge of thebaine allows, obviously, the approach of the dienophile with some ease from the α-side of the C-ring. Flattening at the nitrogen by replacing the *N*-methyl group by a *N*-formyl group alone does not change the accessibility of the diene system compared to thebaine[5]. However, this in combination with the removal of the methoxyl group in position 6 gives an entry to 8β-substituted 6β,14β-ethenomorphinans.

Acknowledgements: We thank the Management of Diosynth B.V., Apeldoorn, The Netherlands, for the gift of chemicals.

REFERENCES

* Part XXII: K.M.J. Brands, T.S. Lie, and L. Maat, Recl. Trav. Chim. Pays-Bas **105**, 544 (1986).

1. K.W. Bentley and D.G. Hardy, J. Am. Chem. Soc. **89**, 3267 (1967).
2. A.C. Ghosh, D.E. Portlock, H.G. Dalzell, C. Malmberg, P. Herlihy, and R.K. Razdan, J. Org. Chem. **48**, 4137 (1983).
3. P.R. Crabbendam, T.S. Lie, J.T.M. Linders, and L. Maat, Recl. Trav. Chim. Pays-Bas **103**, 296 (1984).
4. L.C. Knipmeyer and H. Rapoport, J. Med. Chem. **28**, 461 (1985).
5. L. Maat, J.A. Peters, and M.A. Prazeres, Recl. Trav. Chim. Pays-Bas **104**, 205 (1985).
6. D. Ranganathan, C. Bushan Rao, S. Ranganathan, A.K. Mehrotra, and R. Iyengar, J. Org. Chem. **45**, 1185 (1980).

5.3

Preparation of 6-demethoxy-*N*-formyl-*N*-northebaine and its Diels-Alder reactions with methyl vinyl ketone and nitroethene; novel 8-nitro-substituted 6α,14α-ethenoisomorphinans and 6β,14β-ethenomorphinans

Preparation of 6-demethoxy-*N*-formyl-*N*-northebaine and its Diels-Alder reactions with methyl vinyl ketone and nitroethene; novel 8-nitro-substituted 6α,14α-ethenoisomorphinans and 6β,14β-ethenomorphinans (Chemistry of opium alkaloids, Part XXVIII)*

J.T.M. Linders, P. Briel, E. Fog, T.S. Lie and L. Maat

Department of Organic Chemistry, Delft University of Technology,
Julianalaan 136, 2628 BL Delft, The Netherlands

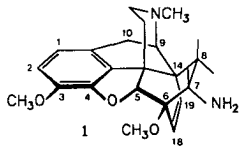
Abstract

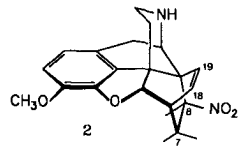
The synthesis of 6-demethoxy-*N*-formyl-*N*-northebaine (**5**) and its Diels-Alder reactions with methyl vinyl ketone and nitroethene are described.
N-Demethylation of 6-demethoxythebaine (**3**) with diethyl azodicarboxylate, followed by hydrolysis, gave 6-demethoxy-*N*-northebaine (**4**) which was *N*-formylated with ethyl formate in DMF to give **5**, using "Ketjencat LA-LPV Steamed" as a catalyst.
Reaction of **5** with methyl vinyl ketone using microwave heating gave the expected 7α-acetyl-6α,14α-ethenoisomorphinan **9** by direct crystallization from the reaction mixture. On the other hand, Diels-Alder reaction of **5** with nitroethene afforded the 7α-nitro-6α,14α-ethenoisomorphinan **12** as a minor product (10%). The major products were 8α-nitro-6α,14α-ethenoisomorphinan **10** (50%) and 8β-nitro-6β,14β-ethenomorphinan **11** (30%). The structure of the new adducts was elucidated by ^{1}H NMR.
Factors which may influence the course of the Diels-Alder reaction of morphinan-6,8-dienes are discussed. The surprising change in selectivity seems to be governed mainly by steric effects.

Introduction

Diels-Alder reactions of thebaine or other morphinan-6,8-dienes with monosubstituted alkenes are known to yield predominantly 7α-substituted

6α,14α-ethenoisomorphinans[1-4], which can be converted into narcotic analgesics of extraordinary potency, such as etorphine, and into medicinally used agonist-antagonists such as buprenorphine. 7α-Amino-6α,14α-ethenoisomorphinan **1**, which has been prepared from the adduct of thebaine and ethyl acrylate[5], is an important starting material of opioid ligands which bind irreversibly to the opiate receptor[6]. In 1985, we reported on an improved preparation of **1** via a Diels-Alder reaction of *N*-formyl-*N*-northebaine and nitroethene[7]. The use of the *N*-formylmorphinandiene was premeditated to avoid the base-catalyzed polymerization of the dienophile[8] and it affords furthermore flexibility in this synthesis in the choice of the substituent on the nitrogen.





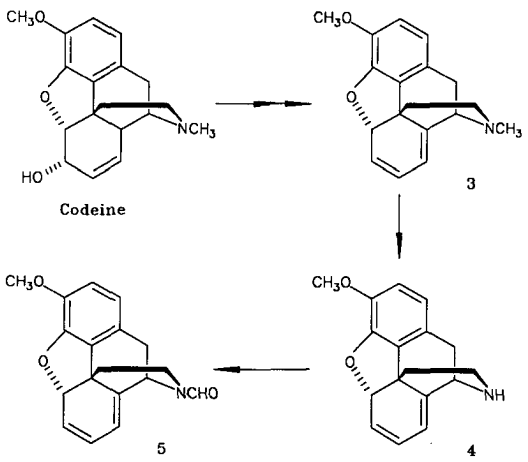
Depending on the substitution pattern of the diene system, other adducts are formed in minor amounts[2-4]. In the case of 6-deoxythebaine with methyl vinyl ketone a mixture of four products was obtained, consisting of 7α-acetyl-, 8α-acetyl- and 7β-acetyl-6α,14α-ethenoisomorphinan in a 96:3:1 ratio and a trace (0.1%) of 8β-acetyl-6β,14β-ethenomorphinan[4]. Recently, we reported in a preliminary communication[9] on the isolation of 8β-nitro-6β,14β-ethenomorphinan **2**, one of two major products of the Diels-Alder reaction of 6-demethoxy-*N*-formyl-*N*-northebaine (**5**) with nitroethene. The structure of **2** was elucidated by ^{1}H NMR after hydrolysis of the *N*-formyl group.

We now report on the detailed synthesis of 6-demethoxy-*N*-formyl-N-northebaine (**5**) and its Diels-Alder reactions with both nitroethene and methyl vinyl ketone. The former dienophile exhibited a striking reversal of selectivity in the Diels-Alder reaction of **5**, giving for the first time both 8α-nitro-6α,14α-ethenoisomorphinan **10** and 8β-nitro-6β,14β-ethenomorphinan **11** in preparative amounts. These compounds will only be accessible, if at all, with difficulty by other routes.

Results

Preparation of 6-demethoxy-N-formyl-N-northebaine

For the preparation of 6-demethoxy-*N*-formyl-*N*-northebaine (**5**) (Scheme 1) we started with the *N*-demethylation of 6-demethoxythebaine (**3**), which can be obtained in high overall yield from codeine[10].



Scheme 1. Preparation of 6-demethoxy-*N*-formyl-*N*-northebaine (**5**) from 6-demethoxythebaine (**3**).

Reaction of **3** with diethyl azodicarboxylate in benzene[7,11], followed by hydrolysis of the intermediate hydrazo compound with pyridinium hydrochloride in aqueous ethanol, afforded crystalline 6-demethoxy-*N*-northebaine hydrochloride (**4**) (55% on 30-mmol scale). When the reaction was performed on a larger scale, the yield dropped to 35-40%. When acetonitrile was used as solvent[12] the reaction was faster, but the yield was lower. Under other conditions for the hydrolysis (ammonium chloride, 2*N* HCl), lower yields of **4** were found. On TLC several side-products were visible. In the case of hydrolysis with 2*N* HCl the formation of a second, more polar reaction product was observed. Although we were not able to purify the

compound completely, mass spectral and ^{1}H NMR data showed it to have the characteristics of the Diels-Alder adduct of diethyl azodicarboxylate and 6-demethoxy-*N*-northebaine in which one of the ethoxycarbonyl groups had been eliminated.

Formylation of **4** with ethyl formate in DMF proved to be unexpectedly cumbersome, taking 24-48 h to reach completion. The long time needed had a negative influence on the purity of the product. A major improvement was obtained when the reaction was performed in the presence of silica-alumina catalysts. We found "Ketjencat LA-LPV Steamed" (Low Alumina, Low Pore Volume)[13], a macroporous cracking catalyst consisting of 13% alumina on silica, to be the most suitable. The reaction was now complete within 4 h with only few side-products. Zeolites of the 4A type also catalyzed this reaction, but proved to be less effective, suggesting predominantly outer-surface catalysis. Probably both types of catalysts, which contain strong acidic sites, catalyze the reaction by activating the carbonyl group of ethyl formate[13a], thus making it more susceptible for nucleophilic attack of the secondary amine. Activation of the catalyst by heating it at 400 °C for 16 h before use proved to be beneficial. Acid catalysis for the *N*-formylation of simple amines *by DMF* has been described previously[14]. However, when **4** was heated in DMF without ethyl formate in the presence of the above-mentioned catalyst, no reaction occurred, proving that DMF is not the formylating agent in the system we use.

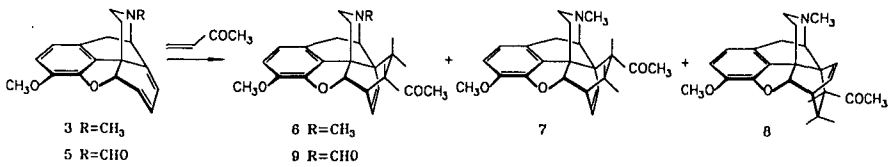
Alternatively, the formylation of **4** to give **5** could also be performed by reaction of **4** in the form of its hydrochloride with triethyl orthoformate[15].

To remove traces of alkaline contaminants, which may induce polymerization of nitroethene, the crude product **5** was purified using Vacuum Liquid Chromatography (VLC)[16], a simple chromatographic technique, eminently suited to perform rapid separations. This technique can also be used advantageously to remove traces of high-boiling solvents such as DMF and DMSO.

*Diels-Alder reactions of 6-demethoxy-*N*-formyl-*N*-northebaine*

In order to determine the influence of the nitrogen substituent on the course of the cycloaddition we compared the results of the Diels-Alder reactions of *N*-formylmorphinandienes with those of their *N*-methyl counterparts. We therefore studied the Diels-Alder reactions of **3** and **5** with

methyl vinyl ketone (Scheme 2). The reaction of 6-demethoxythebaine (3) with methyl vinyl ketone has been described by Rapoport *et al.*[2] and by our group[3]. The main isomer obtained was the 7α-acetyl-6α,14α-ethenoisomorphinan **6**. According to HPLC, a second product was formed (about 10%), the structure of which was proposed to be the 8α-isomer **7** on the basis of an ^{1}H NMR spectrum[2] obtained by subtraction.



Scheme 2. Diels-Alder reaction of **3** and **5** with methyl vinyl ketone.

Using preparative, multiple elution TLC, we succeeded in isolating a small amount of this adduct from the mother liquor after removing the 7α-adduct **6** by crystallization. Analysis of the ^{1}H NMR-spectrum of compound **7** showed the compound indeed to be the 8α-acetyl-6α,14α-ethenoisomorphinan. The vinylic protons were found in the expected positions. The position of the substitituent was secured by 2D-COSY analysis and inspection of the coupling constants (Table 1). Furthermore, it was essentially identical to the calculated spectrum[2].

A third product was isolated in 0.4% yield by column chromatography. The structure of this adduct was elucidated by ^{1}H NMR (**8**, Table 1). From the shift of the vinylic protons (H-18 δ 5.99 and H-19 δ 6.79), it can be concluded that the etheno bridge is in 6β,14β-orientation[17]. This assignment was confirmed by the presence of a small long range coupling of H-5 to H-7β (W-arrangement). The shift of H-19 to low field, compared to other 6β,14β-ethenomorphinans is caused by the anisotropy of the nitrogen atom and the acetyl group. The same effect is observed for H-8β in compound **7**, which is found at δ 3.90. The position of the acetyl group is ascertained by the size of the different coupling constants and the position of H-9 which is at rather low field (δ 3.47), compared to that of compound **6**. In conclusion, this compound is 8β-acetyl-6β,14β-ethenomorphinan **8**.

A fourth, minor, product (<0.5%) –possibly the isomeric 7β-substituted 6α,14α-ethenoisomorphinan– could not be obtained in a pure form.

Table 1. Some selected values from the ^{1}H NMR spectrum of compounds **2** and **6-12**. ($CDCl_3$, δ, *J* (Hz)). Values for the minor rotamer are given in parentheses.

	NH	NCH_3			NCHO			
Compound	**2**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Proton								
6	3.17	3.25	2.97	3.03	3.33	3.21	3.21	3.77
7α	1.97		1.58	1.54		2.46	1.99	
7β	1.97	2.68	1.81	1.15	2.70	1.96	2.06	4.63 (4.69)
8α	3.64	1.36		2.40	1.50		3.67	2.04 (1.97)
8β		2.86	3.90		2.16	5.12 (5.05)		2.56 (2.63)
9	3.83	3.20	3.49	3.47	4.09 (5.09)	4.68 (5.62)	4.53 (5.44)	5.18 (4.19)
18	6.32	5.75	5.86	5.99	5.82 (5.85)	6.15 (6.05)	6.35 (6.32)	5.85 (5.86)
19	6.46	5.51	5.47	6.79	5.53 (5.54)	5.34 (5.56)	6.18 (6.22)	5.70 (5.68)
Coupling constants								
J(7α,7β)	-14.8		-13.4	-12.5		-15.3	-15.0	
J(7α,8α)	8.5			8.0			8.5	
J(7α,8β)			4.4			4.7		
J(7β,8α)	4.0	6.6		2.6	4.2		3.0	5.1
J(7β,8β)		9.3	9.9		9.4	8.4		9.0
J(8α,8β)		-12.7			-12.6			-13.3

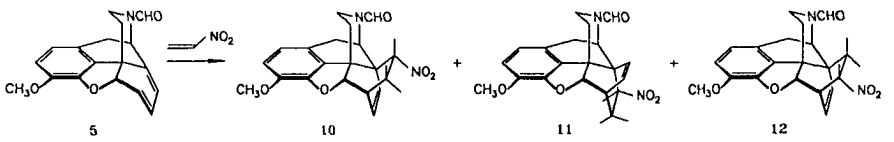
The Diels-Alder reaction of 6-demethoxy-*N*-formyl-*N*-northebaine (**5**) with methyl vinyl ketone, performed inside a modified microwave oven[17], gave similar results (Scheme 2). From the two products formed in a ratio of 9:1), the major isomer crystallized directly from the reaction mixture as a pure compound. ^{1}H NMR data and decoupling experiments showed the structure of this adduct to be the 7α-acetyl-6α,14α-ethenoisomorphinan **9** (Table 1).

Independent synthesis of **9** via *N*-demethylation of the *N*-methyl adduct **6** followed by formylation confirmed this structure assignment.

As experienced earlier with 6-demethoxy-β-dihydrothebaine[17], the reaction time for the Diels-Alder reaction with microwave heating was considerably shorter than when conventional oil bath heating was applied.

Initial experiments showed that the Diels-Alder reaction of **5** with methyl vinyl ketone could be catalyzed by $AlCl_3$, providing the possibility to perform the reaction at room temperature. In the *N*-methyl series, the use of Lewis acids for the catalysis of the Diels-Alder reaction is precluded, due to the basicity of the nitrogen. Furthermore, thebaine itself suffers from rearrangement in the presence of Lewis acids[18].

Cycloaddition of nitroethene to 6-demethoxy-*N*-formyl-*N*-northebaine afforded a complex mixture. After hydrolysis (0.8*N* HCl in methanol) of a sample of the mixture, HPLC showed four compounds in a ratio of 50:30:10:3 (Scheme 3). In order to take advantage of the favourable crystallizing properties of *N*-formylmorphinans, we separated the products in the formyl stage in contrast to our preliminary experiments[9]. In this way we could isolate the three major products by column chromatography, followed by selective crystallization. Using HPLC, the relative amounts in the original mixture were determined by comparison of samples of the separately hydrolyzed, pure adducts with the hydrolyzed reaction mixture.



Scheme 3. Diels-Alder reaction of **5** with nitroethene.

The major product (50%) proved to be 8α-nitro-6α,14α-ethenoisomorphinan **10**. In the ^1H NMR spectrum, H-19 is found at δ 5.34, indicative for the 6α,14α-orientation of the etheno bridge. H-18 is at somewhat lower field than expected for 6α,14α-ethenoisomorphinans[17] (Table 1). The position of

the nitro group was established by analysis of the spin system and of the coupling constants ($J(7\alpha,8\beta)$, $J(7\beta,8\beta)$). H-8β is found at remarkably low field (δ 5.12) due both to the fact that it is on the same carbon as the nitro group and its proximity to the amide nitrogen.

The structure of the second product (30%) was elucidated also by ^{1}H NMR (11, Table 1). The small long-range couplings of H-7α with H-5 and of H-8α with H-9 together with the shift of the vinylic protons to δ 6.32 and 6.18 are conclusive for the 6β,14β-orientation of the vinylic part. A long-range coupling between H-8α and H-19, which are in W-arrangement, corroborates the assignment. Deformylation of **11** gave a crystalline product, which was identical in all respects to **2**, which has been described earlier[9].

The ^{1}H NMR spectrum of the third product **12** (10%), especially its COSY-plot, showed strong resemblance to that of the 7α-nitro adduct obtained from the Diels-Alder reaction of *N*-formyl-*N*-northebaine and nitroethene[7]. Analysis of the ^{1}H NMR spectrum (Table 1) confirmed the structure assignment.

The use of microwave heating did not give a significant increase in the rate of this reaction, which is carried out in benzene. This solvent is assumed to be a poor absorber for microwave radiation[19]. Consequently, only the reactants **5** and nitroethene efficiently absorb microwave energy. Sun *et al.*[20] introduced the term 'spectroscopic heating' for this type of selective microwave heating.

Discussion

Nitroethene showed two striking differences in the Diels-Alder reaction to morphinan-6,8-dienes, when compared to methyl vinyl ketone or other dienophiles. Firstly, in the reaction of 6-demethoxy-*N*-formyl-*N*-northebaine with nitroethene the 7α-substituted 6α,14α-ethenoisomorphinan is only a minor product, the major products being two 8-substituted isomers. Secondly, a considerable amount of 8β-nitro-6β,14β-ethenomorphinan **11** is formed, the cycloadduct arising from the attack of the dienophile at the more hindered α-face of the diene system. To explain the different behaviour of nitroethene, several factors have to be taken into account.

It seems that the replacement of the *N*-methyl by an *N*-formyl group neither alters the geometry of the diene system significantly nor its accessibility.

Diels-Alder reaction of methyl vinyl ketone to both 6-demethoxythebaine and its *N*-formyl analogue yielded the 7α-acetyl-6α,14α-ethenoisomorphinan as major product, along with only minor amounts of other adducts. Therefore, it must be concluded that the observed change in selectivity is predominantly due to differences between the two dienophiles. Nitroethene has a planar geometry, as has been proven by microwave spectroscopy[21-22]. Methyl vinyl ketone, although having the carbon and oxygen atoms in one plane, has the methyl hydrogens projecting out of the plane[23-24]. Moreover, when dimensions of the molecules are compared[22,24], it is clear that nitroethene is the smaller of the two dienophiles. These geometrical factors may furnish an explanation for the formation of 30% of the 6β,14β-ethenomorphinan in the case of nitroethene.

The remarkable selectivity for the 8-substituted isomers can be explained by (i) the strong regio-directing properties of the nitro group on cycloadditions[25-26] and (ii) the smaller size of nitroethene compared to that of methyl vinyl ketone, which causes less steric interaction with the morphinan skeleton (especially with H-15)[27], in combination with (iii) the tendency of 6-demethoxythebaine to give the 8α-substituted adduct as a significant side-product, as described above.

Recently, Hehre and Kahn[28-30] proposed a rationale to explain face selectivity in the Diels-Alder reaction to chiral dienes that have a lone pair bearing substitutent in an allylic position. By *ab initio* calculations (3-21G split valence basis set), these substituents are shown to induce a higher electron density on the face of the diene system that is *syn*-positioned to the lone pair, making this face more reactive in the Diels-Alder reaction with electron-deficient dienophiles.

Morphinan **5** has two substituents in an allylic position, namely the *N*-formyl group at the β-face and the 4,5α-epoxy bridge at the α-face of the diene system. Based on the "Hehre-Kahn rationale", they are expected to induce a higher electron density on either one of the faces of the diene system. However, the electronic influence of the nitrogen lone pair will be small, because of the spatial arrangement of the nitrogen atom, making the lone pair point away from the diene system. The presence of the electron-withdrawing formyl group will diminish a possible electronic influence even more. The position of the epoxy bridge, being almost perpendicular to the α-face of the diene system, makes the approach of the dienophile to that side difficult[30-31]. The formation of the 8β-substituted 6β,14β-ethenomorphinans

in the case of the 6-demethoxy-systems may be the result of some activation of the α-face by one of the lone pairs of the oxygen. With an important activating effect of the epoxy bridge on the Diels-Alder reaction applied to morphinan-6,8-dienes, the 7β-substituted 6β,14β-ethenomorphinans should have been formed upon cycloaddition of monosubstituted alkenes to thebaine. In particular, this should occur in the reaction of nitroethene to *N*-formyl-*N*-northebaine because of the geometrical factors and the regio-directing effect mentioned above. By experiment, the latter reaction is shown to give the 7α-nitro-6α,14α-ethenoisomorphinan as the only product[7]. In this case, the approach of the dienophile is expected to meet with severe steric hindrance from the epoxy bridge.

In summary, the face selectivity in the systems we have studied is more likely to be caused by steric interactions than by major electronic influences.

Experimental

Mass spectra were measured by Dr. J.M.A. Baas, Dr. B. van de Graaf and Mrs. A.H. Knol-Kalkman using a VG 70-SE mass spectrometer. ^{1}H and ^{13}C NMR spectra were measured using a Nicolet NT-200 WB and a Varian VXR-400S, operated by Dr. J.A. Peters, Dr. A. Sinnema and Mr. J. van den Toorn. All spectra were recorded in $CDCl_3$ as solvent with tetramethylsilane as reference unless otherwise stated. For the *N*-formyl compounds, the shift values for the minor rotamer are given in parentheses. Rotations were measured using a Perkin-Elmer P141 polarimeter in chloroform/ethanol 9:1 as solvent unless otherwise stated. IR spectra were obtained from KBr discs using a Beckman IR 4210 spectrophotometer.

Reactions were monitored by TLC on deactivated silica (0.25 mm, Merck F_{254}; eluent: dichloromethane/methanol/25% ammonia 85:15:0.5 and 95:5:0.5). The compounds were detected with UV (254 nm) and iodine vapour. Melting points are uncorrected. Analytic HPLC was performed using a Waters M-6000 pump on a reversed-phase column (8x100 mm, Nucleosil C_{18} or Novapak, 10 μm, 30 °C) using mixtures of methanol/water/trifluoroacetic acid or acetonitrile/water as eluent, with detection on an ERMA RI-detector ERC-7510 or a Pye LC3 variable wave length detector at 240-250 nm. The microwave oven (Sharp R-4060 (W), 2.45 GHz, 400 W) was modified as described earlier[17].

(-)-6-Demethoxy-N-northebaine (4)

6-Demethoxythebaine (3, 7.50 g, 27 mmol) was dissolved in 75 ml of anhydrous benzene and heated till reflux. A solution of diethyl azodicarboxylate (5.50 g, 31 mmol) in 17 ml of anhydrous benzene was added in 0.5 h and the resulting mixture was boiled for 5 h. More azo compound was added (0.50 g, 3.1 mmol) and boiling was continued for 1 h (complete conversion on TLC) The solvents were evaporated *in vacuo* and the oily residue was dissolved in 35 ml of ethanol. To this solution pyridinium hydrochloride (5.00 g, 43 mmol) dissolved in 17 ml of water was added. After standing overnight, the crystals were filtered off, and washed with cold ethanol and diethyl ether, yielding 3.00 g (11 mmol, 43%) of pure (TLC) 6-demethoxy-*N*-northebaine hydrochloride (4.HCl). Upon cooling of the mother liquor a second crop (0.80 g, 3 mmol) of 4.HCl crystallized. Total yield 55%. M.p. 258-260 °C (dec); $[\alpha]_D^{25}$ -210° (c 1, water) (Ref. 32: m.p. 253-255 °C; $[\alpha]_D^{20}$ -176° (c 0.5, water)). ^{1}H NMR (DMSO-d6): δ 1.89 (m, 1H, H-15), 2.22 (m, 1H, H-15'), 3.15 (d, 1H, H-10β, J(10α,10β) -17.8 Hz), 3.35 (m, 3H, H-10α + H-16 + H-16'), 3.76 (s, 3H, OCH_3), 4.56 (d, 1H, H-9, J(9,10α) 6.9 Hz), 5.60 (dd, 1H, H-5, J(5,6) 3.5 Hz, J(5,7) 1.5 Hz), 5.78 (dd, 1H, H-6, J(6,7) 10 Hz), 5.90 (d, 1H, H-8, J(7,8) 5.5 Hz), 6.02 (ddd, 1H, H-7), 6.67 (d, 1H, H-1, J(1,2) 8.2 Hz), 6.80 (d, 1H, H-2) IR: ν_{max}^{KBr} 3000-2400 (NH_2^+) cm^{-1}.

The hydrochloride was dissolved in a mixture of 2*N* KOH (50 ml) and dichloromethane (50 ml) and the aqueous layer was extracted with dichloromethane (2 x 50 ml). After drying on Na_2SO_4, the combined organic extracts were evaporated, giving 3.16 g of 6-demethoxy-*N*-northebaine (4) as amorphous solid. An analytical sample was crystallized from methanol, giving 4 as methanol solvate. M.p. 98-98.4 °C (Ref. 32: oil); $[\alpha]_D^{25}$ -230° (c 1). MS: m/z 267 (M^+, 100), 238 (8), 223 (14), 206 (15), 165 (11), 152 (15). IR: ν_{max}^{KBr} 3300, 3180 (NH) cm^{-1}.

*(-)-6-Demethoxy-*N*-formyl-*N*-northebaine* (**5**)

A. With ethyl formate from **4**

6-Demethoxy-*N*-northebaine (**4**, 3.16 g; 12 mmol) was dissolved in a mixture of 75 ml of DMF and 20 ml of ethyl formate. Activated "Ketjencat LA-LPV Steamed" cracking catalyst (2.1 g) was added and the mixture was heated while stirring for 4 h (oil bath temperature 115 °C). After filtering off the solids, the filtrate was evaporated *in vacuo*. The oily residue was dissolved in 100 ml of dichloromethane and washed with 2 x 50 ml of 2*N* KOH and 2 x 50 ml 2*N* H_2SO_4. The aqueous extracts were washed with 50 ml of dichloromethane. The combined organic layers were washed with 2 x 50 ml of water, dried on Na_2SO_4 and evaporated *in vacuo*. With the aid of methanol, last traces of DMF were removed. Yield 2.78 g (9.4 mmol, 80%) of the *N*-formyl compound **5**, pure according to TLC and HPLC. An analytical sample was crystallized from ethyl acetate. M.p. 156-157 °C, [α] -190° (c 1). MS: m/z 295 (M^+, 60), 250 (15), 237 (100). ^{1}H NMR (DMSO-d6): δ 1.81 (m, 1H, H-15), 2.03 (m, 1H, H-15′), 2.84 (dd, 1H, H-16, *J*(15,16′) 4.6 Hz, *J*(16,16′) -13.2 Hz), 2.89 (3.15) (d, 1H, H-10β, *J*(10α,10β) -18 Hz), 3.10 (3.34) (dd, 1H, H-10α, *J*(9,10α) 6.5 Hz), 3.75 (s, 3H, OCH_3), 4.18 (3.66) (dd, 1H, H-16′, *J*(15,16′) 5.1 Hz), 4.76 (5.26) (d, 1H, H-9), 5.50 (m, 1H, H-5), 5.68 (dd, 1H, *J*(5,6) 3.5 Hz, *J*(6,7) 10 Hz), 5.71 (5.65) (d, 1H, H-8, *J*(7,8) 5.0 Hz), 5.96 (m, 1H, H-7), 6.60 (d, 1H, H-1, *J*(1,2) 8.2 Hz), 6.75 (d, 1H, H-2), 8.00 (8.14) (s, 1H, CHO). IR: ν_{max}^{KBr} 1660 (C=O) cm^{-1}.

B. With triethyl orthoformate from **4**.HCl

A suspension of **4**.HCl (300 mg, 0.99 mmol) in 5 ml of triethyl orthoformate was boiled until dissolution (0.5 h). TLC showed complete conversion of the starting material. After cooling to room temperature, the solution was diluted with 20 ml 0.1*N* HCl. After stirring for 0.5 h, the resulting aqueous solution was extracted with dichloromethane (3 x 10 ml). The combined organic layers were dried on Na_2SO_4 and evaporated *in vacuo*, giving **5** (280 mg, 96%) identical in all respects to the compound described under A.

Isolation of (-)-8α-acetyl-4,5α-epoxy-3-methoxy-N-methyl-6α,14α-ethenoisomorphinan (7) *and (-)-8β-acetyl-4,5α-epoxy-3-methoxy-N-methyl-6β,14β-ethenomorphinan* (8)

The Diels-Alder reaction of 6-demethoxythebaine (3) was performed as described earlier[3]. After crystallization of the 7α-acetyl adduct, the mother liquor was evaporated till dryness (1.6 g). A part (200 mg) of the oily residue was put on two thick-layer plates (silicagel, 1 mm, Merck Art. 13895). Five developments in dichloromethane/methanol 98:2 gave 50 mg of 8α-acetyl-6β,14β-ethenoisomorphinan 7 as an amorphous solid. M.p. 145-146 °C, $[\alpha]_D^{25}$ -130° (c 1). MS: m/z 351 ($M^{+\cdot}$, 55), 308 (12), 281 (36), 280 (29), 238 (11), 225 (28), 144 (56), 132 (28), 91 (22), 43 (100). ^{1}H NMR: δ 1.25 (m, 1H, H-15), 1.58 (ddd, 1H, H-7α, J(7α,7β) -13.4 Hz, J(7α,8β) 4.4 Hz, J(6,7α) 4.4 Hz), 1.81 (dd, ^{1}H, H-7β, J(7β,8β) 9.9 Hz), 1.90 (m, 1H, H-15′), 2.05 (m, 1H, H-16), 2.16 (s, 3H, $COCH_3$), 2.36 (s, 3H, NCH_3), 2.45 (dd, 1H, 10-Hα, J(9,10α) 7 Hz), 2.50 (m, 1H, H-16′), 2.97 (m, 1H, H-6), 3.20 (d, 1H, H-10β, J(10α,10β) -18.6 Hz), 3.49 (d, 1H, H-9), 3.81 (s, 3H, OCH_3), 3.90 (dd, 1H, H-8β), 4.48 (d, 1H, H-5, J(5,6) 3.2 Hz), 5.47 (d, 1H, H-19, J(18,19) 8.3 Hz), 5.86 (dd, 1H, H-18, J(6,18) 6.4 Hz), 6.53 (d, 1H, H-1, J(1,2) 8.2 Hz), 6.62 (d, 1H, H-1). IR: ν_{max}^{KBr} 1720 (C=O) cm^{-1}.

The residue (1.25 g) was put to a silica column (200 g) and eluted with 2% methanol in dichloromethane. The first fractions consisted of a mixture of 6 and 7 (200 mg), followed by fractions of pure 6 (400 mg). Evaporation of the last fractions and crystallization from methanol gave 50 mg of 8β-acetyl-6β,14β-ethenomorphinan 8. M.p. 160-162 °C, [α] -140° (c 1). MS: m/z 351 ($M^{+\cdot}$, 75), 308 (60), 280 (41), 149 (43), 132 (100), 91 (23). ^{1}H NMR: δ 1.15 (m, 1H, H-7β, J(7α,7β) -12.5 Hz, J(6,7β) 2.6 Hz, J(7β,8α) 2.6 Hz, J(5,7β) 1.4 Hz), 1.54 (m, 1H, H-7α, J(7α,8α) 8.0 Hz), 1.75 (dd, 1H, H-15, J(15,15′) -11.0 Hz, J(15,16) 2.6 Hz), 1.82 (s, 3H, OCH_3), 1.95 (m, 1H, H-15′), 2.26 (dd, 1H, H-10α, J(10α,10β) -18.5 Hz, J(9,10α) 6.5 Hz), 2.35 (m, 1H, H-16), 2.39 (s, 3H, OCH_3), 2.40 (dd, 1H, H-8α), 3.03 (m, 1H, H-6), 3.20 (d, 1H, H-10β), 3.20 (m, 1H, H-16′), 3.47 (d, 1H, H-9), 3.90 (s, 3H, OCH_3), 4.33 (dd, 1H, H-5, J(5,6) 4.1 Hz), 5.99 (dd, H-18, J(18,19) 8.2 Hz, J(6,18) 5.9 Hz), 6.63 (d, 1H, H-1, J(1,2) 8.1 Hz), 6.70 (d, 1H, H-2), 6.79 (d, 1H, H-19). IR: ν_{max}^{KBr} 1720 (C=O) cm^{-1}.

(-)-7α-Acetyl-4,5α-epoxy-N-formyl-3-methoxy-6α,14α-ethenoisomorphinan (9) *from* **5**

6-Demethoxy-*N*-formyl-*N*-northebaine (**5**, 5.03 g, 17.1 mmol) was heated in 75 ml of freshly destilled methyl vinyl ketone in a modified microwave oven. After 1 h, the solids were filtered off, the filtrate was evaporated till dryness, redissolved in 75 ml of methyl vinyl ketone and boiled under reflux for 1 h in the microwave oven. The solid material was filtered off again, and the procedure was repeated another 3 times. The solid material proved to be pure (HPLC) 7α-acetyl adduct **9**. The total yield was 4.88 g (13.4 mmol, 78%). An analytical sample was crystallized from benzene/acetone 1:1. M.p. 258-258.5 °C (dec), [α] -212° (c 1.5). HRMS: m/z = 365.1633; Calculated for $C_{22}H_{23}NO_4$ 365.1627; MS: m/z 365 (M^+, 100), 322 (20), 277 (30), 243 (40), 230 (25), 91 (20).^{1}H NMR: δ 1.50 (dd, 1H, H-8α, *J*(8α,8β) -14.7 Hz, *J*(7β,8α) 6.6 Hz), ~1.9 (m, 2H, H-15 + H-15'), 2.16 (dd, 1H, H-8β, *J*(7β,8β) 9.3 Hz), 2.19 (s, 3H, $COCH_3$), 2.70 (m, 1H, H-7β), 2.95 (3.50) (ddd, 1H, H-16, *J*(15,16) 4.8 Hz, *J*(16,16') -12.6 Hz, *J*(15',16) 11.0 Hz), 3.00 (d, 1H, H-10β, *J*(10α,10β) -18.5 Hz, *J*(1,10α) 0.9 Hz), 3.20 (dd, 1H, H-10α, *J*(9,10α) 7.0 Hz), 3.33 (m, 1H, H-6), 3.83 (s, 3H, OCH_3), 4.09 (5.09) (d, 1H, H-9), 4.41 (3.07) (dd, 1H, H-16', *J*(15,16') 6.5 Hz), 4.59 (dd, 1H, H-5, *J*(5,6) 3.6 Hz, *J*(5,18) 1.7 Hz), 5.53 (5.54) (d, 1H, H-19, *J*(18,19) 8.3 Hz), 5.82 (5.85) (dd, 1H, H-18, J(6,18) 6.1 Hz), 6.57 (d, 1H, H-1, *J*(1,2) 8.1 Hz), 6.68 (d, 1H, H-2), 8.17 (s, 1H, CHO). IR: ν_{max}^{KBr} 1710 (C=O), 1660, 1650 (NC=O).

(-)-7α-Acetyl-4,5α-epoxy-N-formyl-3-methoxy-6α,14α-ethenoisomorphinan (9) *from* **6**

N-Methyl adduct **6**[3] (1.19 g, 3.4 mmol) was dissolved in 15 ml of dry benzene, diethyl azodicarboxylate (1.1 g, 6.3 mmol) was added and the mixture was heated till reflux. After 122 h of boiling, another portion (0.5 ml) of azo compound was added and boiling was continued for 24 h (complete conversion on TLC). The reaction mixture was evaporated till dryness, the residue was dissolved in 50 ml of ethanol and 10 ml of saturated ammonium chloride lution was added. After standing overnight, the aqueous solution was washed with ether (3 x 10 ml) and the ethanol was removed by evaporation. After

adjusting the pH to 9.5 with ammonia, the aqueous solution was extracted with dichloromethane (3 x 25 ml). The combined organic layers were washed with water (25 ml), dried (Na_2SO_4) and evaporated till dryness, giving 1.07 g of solid off-white material. TLC showed one major product and several minor impurities. ^1H NMR showed the disappearance of the *N*-methyl protons.

The crude material (1.01 g) was dissolved in a mixture of 25 ml of DMF and 10 ml of ethyl formate. Activated cracking catalyst (1 g) was added and the resulting mixture was boiled for 7 h. The catalyst was filtered off and washed with 5 ml of DMF. The reaction mixture was evaporated till dryness. The residue was dissolved in 10 ml of dichloromethane, washed with 2*N* KOH (2 x 25 ml) and 2*N* H_2SO_4 (2 x 25 ml). The aqueous layers were washed with 25 ml of dichloromethane. The combined organic extracts were washed with water (2 x 25 ml), dried (Na_2SO_4) and evaporated till dryness. Crystallization of the residue from benzene gave 0.17 g (0.47 mmol, 16%) of **9**, identical in all respects to the product obtained from the Diels-Alder reaction described above.

Diels-Alder reaction of 6-demethoxy-N-formyl-N-northebaine (**5**) *with nitroethene*

6-Demethoxy-*N*-formyl-*N*-northebaine (**5**, 4.00 g, 13.6 mmol), purified by VLC[16] over silicagel (eluent: 2% methanol in dichloromethane), was dissolved in 50 ml of a 10% solution of nitroethene[33] in benzene. The solution was boiled during 50 h (95% conversion according to HPLC). After filtration of solid, polymeric material, the filtrate was evaporated *in vacuo*. The dry residue (5.0 g) was put onto 200 g of silica and eluted with 2% methanol in dichloromethane. Fractions with about the same composition were pooled and chromatographed again over silica using 0.5-2% methanol in dichloromethane. The first fraction gave after evaporation of the solvents and crystallization from methanol 0.40 g (0.11 mmol, 8%) of **11**. The second fraction afforded 0.82 g (0.25 mmol, 17%) of **10** (needles from methanol). Evaporation and crystallization from ethyl acetate of the most polar fraction gave 0.10 g (0.3 mmol, 2%) of **12**.

(-)-4,5α-Epoxy-N-*formyl-3-methoxy-8α-nitro-6α,14α-ethenoisomorphinan* (10) M.p. 294-296 °C; $[\alpha]_D^{25}$ -90 (c 1). MS: m/z 368 (M^+, 100), 277 (27), 256 (13), 186 (17), 174 (95), 148 (59), 115 (16), 91 (35). ^{1}H NMR: δ 1.75 (m, 1H, H-15), 1.96 (dd, 1H, H-7β, *J*(7α,7β) -15.3 Hz, *J*(7β,8β) 4.7 Hz), 2.04 (dd, 1H, H-15′, *J*(15,15′) -16.3 Hz, *J*(15′,16) 4.1 Hz), 2.46 (ddd, 1H, H-7α, *J*(7α,8β) 8.4 Hz, *J*(6,7α) 2.3 Hz), 3.01 (3.48) (ddd, 1H, H-16, *J*(16,16′) -13.5 Hz, *J*(15,16) 4.1 Hz, *J*(15′,16) 12.7 Hz), 3.07 (d, 1H, H-10β, *J*(10α,10β) -18.9 Hz), 3.20 (dd, 1H, H-10α, *J*(9,10α) 6.9 Hz), 3.21 (m, 1H, H-6), 3.84 (s, 3H, OCH_3), 4.47 (d, 1H, H-5, *J*(5,6) 3.7 Hz), 4.49 (3.57) (dd, 1H, H-16′, *J*(15,16′) 6.2 Hz), 4.68 (5.62) (d, 1H, H-9), 5.12 (5.05) (dd, 1H, H-8β), 5.34 (5.56) (d, 1H, H-19, *J*(18,19) 8.4 Hz), 6.15 (6.05) (dd, 1H, H-18, *J*(6,18) 6.4 Hz), 6.60 (d, 1H, H-1, *J*(1,2) 8.2 Hz), 6.70 (d, 1H, H-2), 8.36 (8.19) (s, 1H, CHO). IR: ν_{max}^{KBr} 1670 (NC=O), 1555, 1340 (N-O).

(-)-4,5α-Epoxy-N-*formyl-3-methoxy-8β-nitro-6β,14β-ethenomorphinan* (11) M.p. 239-241 °C; $[\alpha]_D^{25}$ -72 (c 1). MS: m/z 368 (M^+, 100), 277 (25), 256 (200, 186 (22), 174 (7), 115 (12), 91 (24). ^{1}H NMR: δ 1.85 (m, 2H, H-15 + H-15′), 1.99 (m, 1H, H-7α, *J*(7α,7β) -15.0 Hz), 2.06 (m, 1H, H-7β), 3.10 (2.99) (d, 1H, H-10β, *J*(10α,10β) -18.7 Hz), 3.21 (m, 1H, H-6), 3.43 (2.99) (m, 1H, H-16), 3.48 (ddd, 1H, H-10α, *J*(9,10α) 7.0 Hz, *J*(1,10α) 0.9 Hz), 3.67 (ddd, 1H, H-8α, *J*(7α,8α) 8.5 Hz, *J*(7β,8α) 3.0 Hz, *J*(8α,9) 0.7 Hz), 3.90 (s, 3H, OCH_3), 4.28 (3.45) (dd, 1H, H-16′, *J*(16,16′) -13.6 Hz, *J*(15,16′) 5.4 Hz), 4.34 (dd, 1H, H-5, *J*(5,6) 4.2 Hz, *J*(5,7β) 1.3 Hz), 4.54 (5.43) (d, 1H, H-9), 6.18 (6.22) (d, 1H, H-19, *J*(18,19) 8.4 Hz), 6.35 (6.32) (dd, 1H, H-18, *J*(6,18) 6.7 Hz), 6.77 (6.75) (ddd, 1H, H-1, *J*(1,2) 8.2 Hz, *J*(1, 10β) 0.9 Hz), 6.85 (6.86) (d, 1H, H-1), 8.24 (8.12) (s, 1H, CHO). IR: ν_{max}^{KBr} 1662 (NC=O), 1542, 1375 (N-O) cm^{-1}.

(-)-4,5α-Epoxy-N-*formyl-3-methoxy-8β-nitro-6α,14α-ethenoisomorphinan* (12) M.p. 200-202 °C; $[\alpha]_D^{25}$ -95 (c 1). MS: m/z 368 (M^+, 100), 277 (45), 230 (12), 186 (23), 115 (13), 91 (38). ^{1}H NMR: δ 1.40 (m, 1H, H-15), 1.70 (m, 1H, H-15′), 2.04 (1.97) (dd, 1H, H-8α, *J*(7β,8α) 5.1 Hz, *J*(8α,8β) -13.3 Hz), 2.56 (2.63) (dd, 1H, H-8β, *J*(7β,8β) 9.0 Hz), 2.90 (3.50) (m, 1H, H-16), 2.92 (3.02) (d, 1H, H-10β, *J*(10α,10β) -18.9 Hz), 3.10 (3.20) (dd, 1H, H-10α, *J*(9, 10α) 7.0 Hz), 3.77 (m, 1H, H-6), 3.84 (s, 3H, OCH_3), 4.42 (3.45) (dd, 1H, H-16′, *J*(16,16′) -13.5 Hz, *J*(15, 16′) 4.1 Hz), 4.58 (dd, 1H, H-5, *J*(5,6) 3.2

Hz, J(5,18) 0.7 Hz), 4.63 (4.69) (m, 1H, H-7), 5.18 (4.19) (d, 1H, H-9), 5.85 (5.86) (d, 1H, H-19, J(18,19) 6.0 Hz), 5.70 (5.68) (dd, 1H, H-18, J(6,18) 8.2 Hz), 6.60 (dd, 1H, H-1, J(1,2) 8.2 Hz, J(1,10β) 0.9 Hz), 6.70 (d, 1H, H-2), 8.17 (8.19) (s, 1H, CHO). IR: ν_{max}^{KBr} 1660 (NC=O), 1550, 1340 (N-O) cm^{-1}.

Hydrolysis of the N-formyl compounds. General procedure

A small amount (50 mg) of the pure amide or the reaction mixture was boiled in 10 ml of 0.8*N* HCl in methanol. After cooling to room temperature, the solution was evaporated till dryness. The residue was redissolved in 5 ml of 2*N* HCl, the solution was made alkaline with ammonia (pH 8-9) and extracted with dichloromethane (3 x 10 ml). The combined organic fractions were dried (Na_2SO_4), evaporated and analyzed with HPLC.

(-)-4,5α-Epoxy-3-methoxy-8β-nitro-6β,14β-ethenomorphinan (2)

Adduct 11 was hydrolyzed as described above, giving 40 mg of crystalline 2 identical to the compound described in Ref. 9 on ^1H NMR, HPLC and TLC. M.p. 99-100 ^0C; $[\alpha]_D^{25}$ -100^0 (c 1).

Acknowledgements

We are grateful to the management of Diosynth, B.V., Apeldoorn, The Netherlands for the gift of chemicals. One of us (J.T.M.L.) wishes to express his gratitude for financial support from Diosynth, B.V.. Stimulating discussions with Dr. M.A. Prazeres are gratefully acknowledged. We thank Dr. J.A. Peters and Dr. A. Sinnema for their help in the interpretation of the ^1H and ^{13}C NMR spectra and Dr. J.M.A. Baas and Dr. B. van de Graaf for the interpretation of the mass spectra.

References

*Part XXVII: J.T.M. Linders, R.J. Booth, T.S. Lie and L. Maat, epted for publication in Recl. Trav. Chim. Pays-Bas.

1. K.W. Bentley in "The Alkaloids", R.H.F. Manske (Ed.), Vol XIII, Acad. Press, New York, London, 1971, 75.
2. C.W. Hutchins, G.K. Cooper, S. Pürro and H. Rapoport, J. Med. Chem. 24, 773 (1981).
3. P.R. Crabbendam, T.S.Lie, J.T.M. Linders and L. Maat, Recl. Trav. Chim. Pays-Bas 103, 296 (1984).
4. L.L. Knipmeyer and H. Rapoport, J. Med. Chem. 28, 461 (1985).
5. K.W. Bentley, D.G. Hardy and A.C.B. Smith, J. Chem. Soc. (C) 2235 (1969).
6. R.A. Lessor, K.C. Rice, R.A. Streaty, W.A. Klee and A.E. Jacobson, Neuropeptides (Edinburgh) 5, 229 (1984).
7. L. Maat, J.A. Peters and M.A. Prazeres, Recl. Trav. Chim. Pays-Bas 104, 205 (1985).
8. D. Ranganathan, S. Ranganathan and S. Bamezai, Tetrahedron Lett. 23, 2789 (1982).
9. M.A. Prazeres, J.A. Peters, J.T.M. Linders and L. Maat, Recl. Trav. Chim. Pays-Bas 105, 554 (1986).
10. H.C. Beyerman, P.R. Crabbendam, T.S. Lie and L. Maat, Recl. Trav. Chim. Pays-Bas 103, 112 (1984).
11. Eli Lilly and Co., Neth. Appl. 6,515,815, June 8, 1966; Chem. Abstr. 65, 15441d (1966).
12. L.S. Schwab, J. Med. Chem. 23, 698 (1980).
13a. Th.M. Wortel, W.H. Esser, G. van Minnen-Pathuis, R. Taal, D.P. Roelofsen and H. van Bekkum, Recl. Trav. Chim. Pays-Bas 96, 44 (1977); See also Th. M. Wortel, "Some Applications of Zeolites in Organic Chemistry", Thesis, Delft University of Technology, 1979, Chapter 3.
13b. LA-LPV was treated with 1 atm. steam at 750 ^{0}C.
14. M.A. Kraus, Synthesis 361 (1973).
15. S.V. Rogozhin, Yu.A. Davidovich and V.V. Korshak, Izv. Akad. Nauk SSSR, Ser. Khim. 772 (1970); Chem. Abstr. 73, 15212b (1970).
16. J.C. Coll, S.J. Mitchell and G.J. Stokie, Aust. J. Chem. 30, 1862 (1977); B.F. Bowden, J.C. Coll, S.J. Mitchell and G.J. Stokie, Aust. J. Chem. 31, 1310 (1978); See also S.W. Pelletier, B.S. Joshi and H.K. Desai in "Advances in Medicinal Plant Research", A.J. Vlietinck and R.A. Dommisse (Eds.), Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart, 1985, 153.
17. J.T.M. Linders, J.P. Kokje, M. Overhand, T.S. Lie and L. Maat, Recl. Trav. Chim. Pays-Bas 107, 449 (1988).
18. K.W. Bentley, J. Am. Chem. Soc. 89, 2464 (1967).
19a. R.N. Gedye, F.E. Smith and K.C. Westaway, Can. J. Chem. 66, 17 (1988).
19b. Gedye *et al.*[19a] found a correlation between the the dielectric constant of a solvent and its heating rate on microwave radiation. Although benzene is not included in their studies, it can be considered to be a poor absorber of microwave radiation with its ϵ=2, comparable to heptane and similar hydrocarbons.
20. W.-C. Sun, P.M. Guy, J.H. Jahngen, E.F. Rossomando and E.G.E. Jahngen, J. Org. Chem. 53, 4414 (1988).
21. H.D. Hess, A. Bauder and Hs.H. Günthard, J. Mol. Spectry. 22, 208 (1967).
22. P. Nösberger, A. Bauder and Hs.H. Günthard, Chem. Phys. 1, 426 (1973).
23. P.D. Foster, V.M. Rao and R.F. Curl, J. Chem. Phys. 43, 1064 (1965).
24. A.C. Fantoni, W. Caminati and R. Meyer, Chem. Phys. Lett. 133, 27 (1987).
25. N. Ono, H. Miyaki and A. Kaji, J. Chem. Soc., Chem. Commun. 33 (1982).
26. N. Ono, H. Miyaki, A. Kamimura and A. Kaji, J. Chem. Soc. Perkin I 1929 (1987) and references cited therein.

27. R. Rubinstein, F. Haviv and D. Ginsburg, Tetrahedron **30**, 1201 (1974).
28. S.D. Kahn, C.F. Pau, L.E. Overman and W.J. Hehre, J. Am. Chem. Soc. **108**, 7381 (1986).
29. S.D. Kahn and W.J. Hehre, J. Am. Chem. Soc. **109**, 663 (1987).
30. M.J. Fisher, W.J. Hehre, S.D. Kahn and L.E. Overman, J. Am. Chem. Soc. **110**, 4625 (1988).
31. The conformation of the epoxydiene system in morphinan-6,8-dienes is comparable to that of the systems discussed in Ref. 30.
32. S. Berényi, S. Hosztafi, S. Makleit and I. Szeifert, Acta. Chim. Acad. Sci. Hung. **110**, 363 (1982).
33. D. Ranganathan, C. Bushan Rao, S. Ranganathan, A.K. Mehrotra and R. Iyengar, J. Org. Chem. **45**, 1185 (1980).

5.4

Diels-Alder adducts from 4-*O*-acetyl-6-demethoxy-*N*-formyl-β-dihydro-*N*-northebaine with methyl vinyl ketone and nitroethene

Diels-Alder adducts from 4-*O*-acetyl-6-demethoxy-*N*-formyl-β-dihydro-*N*-northebaine with methyl vinyl ketone and nitroethene (Chemistry of opium alkaloids, Part XXIX)*

J.T.M. Linders, P.J.L. Lipman, E. Saly, T.S. Lie and L. Maat

Department of Organic Chemistry, Delft University of Technology,
Julianalaan 136, 2628 BL Delft, The Netherlands

Abstract

Reductive epoxy ring scission of 6-demethoxy-*N*-northebaine (**5**) with zinc and potassium hydroxide gave a 85:15 mixture of **6a** and its non-conjugated isomer. Formylation with triethyl orthoformate, followed by acetylation with acetic anhydride in the presence of 4-(dimethylamino)pyridine gave a 4:1 mixture of the title compound **6c** and its non-conjugated isomer in 80% overall yield.
Diels-Alder reaction of **6c** with methyl vinyl ketone afforded a 2:1 mixture of 7β-acetyl- and 8β-acetyl-6β,14β-ethenomorphinan **7** and **8a**. Cycloaddition of nitroethene yielded the 8β-nitro-6β,14β-ethenomorphinan **8b** as major product.
N-Demethylation of **2b**, the 4-*O*-phenyl ether of 6-demethoxy-β-dihydrothebaine (**2a**), with diethyl azodicarboxylate failed to give the *N*-norcompound.

Introduction

Thebaine is known to undergo Diels-Alder reactions easily with mono-substituted ethenes yielding 7α-substituted 6α,14α-ethenoisomorphinans[1], which give access to pharmacologically interesting compounds. β-dihydrothebaine, obtained from thebaine by reductive 4,5α-epoxy ring scission, reacted with methyl vinyl ketone to give the 7β-acetyl-6β,14β-ethenomorphinan as the only product[2]. In this case, the dienophile has

approached the diene system from the α-face. Recently, we have shown that 6-demethoxy analogues of thebaine and β-dihydrothebaine give rise to a greater variety of Diels-Alder adducts[3-4]. Reaction of 6-demethoxy-*N*-formyl-*N*-northebaine with nitroethene afforded, in comparable amounts, four isomeric nitro-substituted etheno(iso)morphinans[3]. We have also reported[4] on the Diels-Alder reaction of 6-demethoxy-β-dihydrothebaine (**2a**) with methyl vinyl ketone yielding 7β- and 8β-acetyl-6β,14β-ethenomorphinan **3a** and **4a** in a 2:1 ratio (Scheme 1).

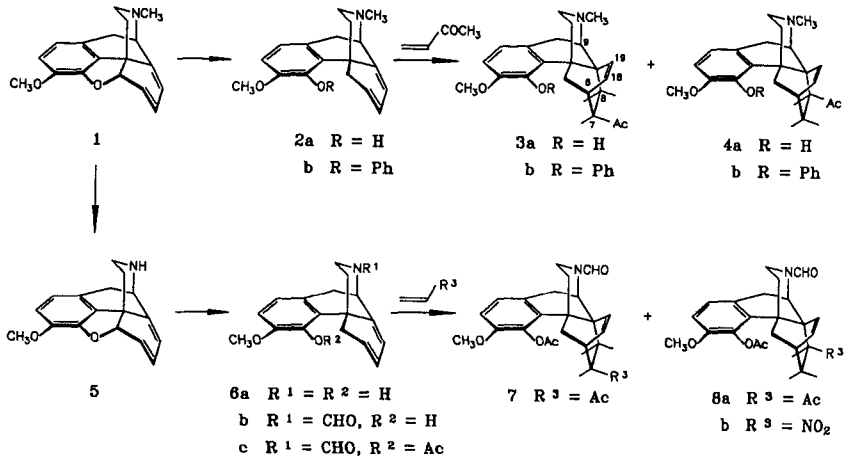
We have now combined these features in the preparation of the *N*-formyl analogue of 6-demethoxy-β-dihydrothebaine **6c** and its Diels-Alder reaction with methyl vinyl ketone as well as with nitroethene.

Results and discussion

For the preparation of the appropriate *N*-formylmorphinandiene, we firstly envisaged a route involving the *N*-demethylation of 6-demethoxy-β-dihydrothebaine (**2a**) with diethyl azodicarboxylate (Scheme 1). Because this reagent is known to cause oxidation of alcoholic functions[5], we protected the 4-hydroxyl group of **2a** as the phenyl ether, which eventually can be cleaved reductively to give the 4-deoxygenated compounds[4,6]. Reaction of **2a** with bromobenzene under the usual Ullmann conditions[2,4,6] gave the 4-phenyl ether **2b** in 45% yield after 5 days of boiling. A major improvement was obtained when cesium carbonate was used instead of potassium carbonate, giving **2b** in 80% yield after only 45 h of reaction. We observed a similar increase in rate in a test reaction with phenol. We ascribe the rate enhancement to the higher solubility of cesium carbonate in pyridine[7], rather than to the so-called "cesium effect"[8], which has been invoked to explain the different behaviour of cesium salts compared with other alkali metal salts in the formation of macrocyclic ethers and esters.

N-Demethylation of **2b** with diethyl azodicarboxylate failed to give the desired *N*-norcompound. When **2b** was mixed with the azo compound in anhydrous chloroform, we observed the slow precipitation of crystalline diethyl hydrazine-1,2-dicarboxylate from the reaction mixture, suggesting aromatization[9]. Two equivalents of the azo compound were needed for a complete conversion of the starting material as evidenced by the disappearance of the *N*-methyl signal in the ^{1}H NMR spectrum. On attempted

isolation using either acid-base extraction or chromatography over silicagel, the reaction product decomposed into several new products, none of which could be obtained in a pure state. We therefore left this route and decided to perform the 4,5α-epoxy ring scission after the *N*-demethylation.



Scheme 1. Synthesis and Diels-Alder reactions of morphinan-6,8-dienes **2b** and **6c**.

The hydrochloride of 6-demethoxy-*N*-northebaine (**5**) was prepared from 6-demethoxythebaine (**1**) in 55% yield[3]. Treatment of **5**.HCl with zinc and 1*N* potassium hydroxide in ethanol/water 1:1 gave a 85:15 mixture of the desired **6a** and its non-conjugated 5,8-isomer. Efforts to improve on this result were not successful. Upon increasing the hydroxide concentration to 2*N*, the amount of **6a** dropped to 40%, while that of the undesired isomer rose to 60%. When DMSO was used instead of ethanol, the starting material rapidly decomposed. Using DMF as cosolvent, no reaction occurred.

The 85:15 mixture of dienes thus obtained was converted into the hydrochlorides with ethanolic HCl and treated with triethyl orthoformate[3,10] to give the *N*-formyl compound **6b**. Because of its sensitivity to oxygen, the phenolic hydroxyl group was protected as the acetate by reaction with acetic anhydride in the presence of 4-(dimethylamino)pyridine[11]. HPLC and ^{1}H NMR analysis showed a 4:1 mixture of the 6,8-diene **6c** and its non-conjugated 5,8-isomer.

When this mixture was boiled in methyl vinyl ketone in the presence of 1% of hydroquinone, only the 6,8-diene reacted and two adducts were formed in a 2:1 ratio (HPLC). For the cycloaddition microwave heating was applied[4]. After removal of polymeric material by Vacuum Liquid Chromatography (VLC)[12], the adducts were separated with the aid of preparative HPLC. The structure of the two products was elucidated using ^{1}H NMR and ^{13}C NMR (Table 1). The signals in the ^{13}C NMR spectra were assigned with the use of APT (Attached Proton Test)[13] spectra and comparison with literature values[14-15].

Table 1. Some selected NMR data of the Diels-Alder adducts **3a**, **4a**, **7**, **8a**, and **8b**. Values for the minor rotamer are given in parentheses.

	3a	**4a**	**7** (R^3=$COCH_3$)	**8a** (R^3=$COCH_3$)	**8b** (R^3=NO_2)
#H					
6	~3.00	~2.60	3.00	2.60	2.70
7α	2.57	1.68	2.60	a	1.88
7β		1.90		a	2.10
8α	}1.82	~2.30	}1.75	a	4.12
8β					
9	2.91	3.19	4.87 (3.85)	4.42 (5.15)	4.96 (3.96)
18	6.08	6.26	6.15 (3.85)	6.27	6.51 (6.48)
19	6.40	6.50	6.03	6.13	5.93 (5.94)
#C					
6	33.95	30.81	33.86 (33.66)	30.62 (30.77)	30.03 (30.16)
7	53.45	33.84	53.50 (53.16)	b	b
8	27.64	49.72	26.96 (26.61)	49.26 (48.34)	84.25 (83.99)
9	59.16	56.37	55.05 (47.60)	52.27 (45.30)	52.21 (44.79)
18	127.61	129.79	129.72 (129.60)	134.06 (134.39)	133.04 (133.39)
19	138.67	136.41	136.23 (135.78)	131.68 (131.25)	130.34 (130.99)

a) H-7 and H-8 could not be assigned because of strongly overlapping signals.
b) C-7 could not be assigned unambiguously.

The position of the vinylic protons is conclusive for the 6β,14β-orientation of the etheno bridge[4]. The position of the acetyl substituent could not be established by analysis of the coupling constants, because of strongly overlapping signals, but the shifts of H-9 and H-6 have proved to give reliable information for an unequivocal assignment[3]. In addition, the shifts of C-9 and C-6 afforded further proof for the proposed structures. Comparison with the NMR-spectra of the *N*-methyl analogues **3a** and **4a**

confirmed the structure assignment. In preliminary experiments, **6c** was also reacted with nitroethene, giving a mixture of two adducts in a 6:1 ratio. Although the adducts could not be separated, ^{1}H and ^{13}C data (Table 1) showed the major compound to be the 8β-nitro adduct **8b** ($R^3=NO_2$).

One may expect some influence from the substituent at the 4-position on the course of the Diels-Alder reaction. However, reaction of the 4-phenyl ether **2b** with methyl vinyl ketone gave a mixture of the two adducts **3b** and **4b** in a 2:1 ratio according to HPLC, implying that there is no steric effect of the bulky phenyl group on the course of the Diels-Alder reaction. The adducts were identified by comparison with authentic samples[4] using HPLC.

In conclusion, the results show that replacement of the *N*-methyl by an *N*-formyl group in 6-demethoxy-β-dihydrothebaine (**2a**) does not change the course of the Diels-Alder reaction[3]. In both cases methyl vinyl ketone gave the 7β-acetyl- and 8β-acetyl-6β,14β-ethenomorphinans in a 2:1 ratio. The cycloaddition of nitroethene to morphinan-6,8-dienes yielded the 8-substituted 6β,14β-ethenomorphinan as major product, as in the 4,5α-epoxy series[3].

Experimental

Mass spectra were measured by Dr. J.M.A. Baas, Dr. B. van de Graaf and Mrs. A.H. Knol-Kalkman using a VG 70-SE mass spectrometer. ^{1}H and ^{13}C NMR spectra were measured using a Nicolet NT-200 WB and a Varian VXR-400S, operated by Dr. J.A. Peters, Dr. A. Sinnema and Mr. J. van der Toorn. All spectra were recorded in $CDCl_3$ as solvent and tetramethylsilane as reference. For the *N*-formyl compounds, the shift values for the minor rotamer are given in parentheses. In the ^{13}C NMR spectra p, d, t, q denote primary, secondary, tertiary and quaternary carbons, respectively. Rotations were measured using a Perkin-Elmer P141 polarimeter in chloroform/ethanol 9:1 as solvent. IR spectra were obtained from KBr discs using a Beckman IR 4210 spectrophotometer.

Reactions were monitored by TLC on deactivated silica (0.25 mm, Merck F_{254}; eluent: dichloromethane/methanol/25% ammonia 85:15:0.5 or 95:5:0.5). The compounds were detected with UV (254 nm) and iodine vapour. Melting points are uncorrected. Analytical HPLC was performed using a Waters M-6000

pump on a reversed-phase column (8x100 mm, Nucleosil C_{18} or Novapak, 10 μm, 30 °C) using mixtures of methanol/water/trifluoroacetic acid or acetonitrile/water as eluent, with detection on an ERMA RI-detector ERC-7510 or a Pye LC3 variable wave length detector at 240-250 nm. Preparative HPLC was performed using a Waters PrepLC/System 500 on a reversed-phase column PrepPak-500/C18 using methanol/water 50:50 as eluent, with RI detection. The microwave oven (Sharp R-4060 (W), 2.45 GHz, 400 W) was modified and operated as described earlier[4].

(+)-6-Demethoxy-4-O-phenyl-β-dihydrothebaine (**2b**)

To a solution of 6-demethoxy-β-dihydrothebaine (**2a**)[16] (5.6 g, 20 mmol) in 60 ml of pyridine (dried on KOH) were added Cs_2CO_3 (7.3 g, 22 mmol), copper powder (2.4 g, 38 mmol), and bromobenzene (3.9 g, 23 mmol) and the resulting mixture was refluxed under nitrogen for 45 h. The reaction mixture was filtered over Hyflo and the residue was washed with 3 x 20 ml of warm pyridine. The filtrate and washings were combined and evaporated *in vacuo*. The residue was taken up in 280 ml of toluene and washed with 150 ml of 4*N* ammonia. The aqueous phase was extracted with dichloromethane (3 x 50 ml) and the combined organic layers were evaporated *in vacuo*. The residue was dissolved in 100 ml of toluene, washed with 25 ml of 4*N* ammonia and 25 ml of water, dried on Na_2SO_4, and evaporated to dryness, yielding 5.8 g of **2b** (16 mmol, 80%) as slightly yellow foam, pure according to TLC and HPLC. $[\alpha]_D^{25}$ +200° (c 1). MS: m/z 359 (M^+, 100), 318 (20), 105 (15), 91 (30), 57 (90), 43 (95). ^{1}H NMR: δ 2.40 (s, 3H, NCH_3), 3.60 (s, 3H, OCH_3), 5.50-5.80 (m, 3H, H-6 + H-7 + H-8), 6.60-7.30 (m, 7H, Ar-H).

4-O-Acetyl-6-demethoxy-N-*formyl-β-dihydro*-N-*northebaine* (**6c**)

A solution of 6-demethoxy-*N*-northebaine.HCl[3] (**5**.HCl, 3.7 g, 12 mmol) in a mixture of 50 ml of 2*N* KOH and 50 ml of ethanol was heated to boiling and zinc dust (2.6 g, 40 mmol) was added. The suspension was boiled for 45 min under vigorous stirring[16] (complete conversion on TLC). The mixture was filtered over Hyflo and the residue was washed with 50 ml of warm ethanol and 50 ml of dichloromethane. The filtrate and washings were combined and

the organic solvents were evaporated *in vacuo*. Ammonium chloride (5.3 g, 99 mmol) was added and the resulting solution was extracted with dichloromethane (3 x 50 ml). The combined organic layers were washed with water (20 ml), dried on Na_2SO_4 and evaporated to dryness to give **6a**. MS: m/z 269 ($M^{+\cdot}$, 100), 254 (15), 228 (15), 165 (15). ^1H NMR: δ 3.80 (s, 3H, OCH_3), 5.75 (m, 3H, H-6 + H-7 + H-8), 6.65 (m, 2H, H-1 + H-2). IR: ν_{max}^{KBr} 3400, 3300 (OH, NH) cm^{-1}.

The residue was dissolved in 20 ml of absolute ethanol and ethanolic HCl was added (pH 4). This solution was evaporated to dryness, yielding 3.6 g (12 mmol, 97%) of a 85:15 mixture of **6a**.HCl and its non-conjugated isomer.

The mixture of hydrochlorides (3.6 g, 12 mmol) was suspended in 60 ml of triethyl orthoformate and boiled under reflux for 12 h. After cooling to room temperature, the reaction mixture was diluted with 40 ml of water and 3 ml of 2*N* HCl. After stirring for 30 min, the mixture was extracted with dichloromethane (3 x 20 ml). The combined organic layers were washed with 2N KOH (3 x 100 ml), dried (Na_2SO_4) and evaporated *in vacuo*, yielding 3.2 g (11 mmol, 90%) of **6b** and its non-conjugated isomer (85:15). MS: m/z 297 ($M^{+\cdot}$, 15), 295 (16), 237 (20), 225 (75), 193 (100), 181 (15), 165 (35), 152 (15), 73 (53). ^1H NMR: δ 3.80 (s, 3H, OCH_3), 5.60-5.90 (m, 3H, H-6 + H-7 + H-8), 6.60 (m, 2H, H-1 + H-2), 8.10 (7.95) (s, 1H, CHO). IR: ν_{max}^{KBr} 3450 (OH), 1660 (NCHO) cm^{-1}.

The *N*-formylated dienes (3.2 g, 11 mmol) were dissolved in 70 ml of dichloromethane, together with 1.8 g (15 mmol) of 4-(dimethylamino)pyridine. To this solution, acetic anhydride (1.6 g, 16 mmol) in 30 ml of dichloromethane was added. After stirring overnight an additional 0.5 ml of acetic anhydride was added and stirring was continued for 1 h. Water (50 ml) was added and the pH was adjusted to 4 with acetic acid. The aqueous phase was extracted with dichloromethane (2 x 20 ml). The combined organic layers were washed with water (20 ml), dried on Na_2SO_4 and evaporated *in vacuo*. Chromatography of the solid residue over silicagel (eluent 0.5% methanol in dichloromethane) gave 3.2 g (9.5 mmol, 80% overall yield from **5**) of a 4:1 (HPLC) mixture of **6c** and its non-conjugated 5,8-isomer as a white foam. MS: m/z 340 ($M^{+\cdot}$+1, 5), 339 ($M^{+\cdot}$, 3), 297 (17), 280 (10), 268 (55), 226 (65), 225 (65), 193 (100), 181 (25), 165 (55), 152 (30), 73 (75). ^1H NMR: δ 2.22 (s, 3H, $COCH_3$), 3.79 (s, 3H, OCH_3), 5.60-5.85 (m, 3H, H-6 + H-7 + H-8), 6.80 (m, 2H, H-1 + H-2), 7.95 (8.05) (s, 1H, CHO). IR: ν_{max}^{KBr} 1775 ($COCH_3$), 1675 (NCHO) cm^{-1}.

Diels-Alder reaction of **6c** *with methyl vinyl ketone*

A mixture of **6c** and its non-conjugated isomer (4:1, 4.2 g, 12 mmol) was dissolved in 90 ml of freshly distilled methyl vinyl ketone containing 0.1 g of hydroquinone. The resulting mixture was boiled using microwave heating for 20 h (complete conversion of **6c** according to HPLC). The solvent was evaporated *in vacuo*. VLC[12] over silicagel (eluent: 2% methanol in dichloromethane) gave 2.5 g of two adducts, which were separated by preparative HPLC.

(-)-4-Acetoxy-7β-acetyl-N-formyl-3-methoxy-6β,14β-ethenomorphinan (7)

Yield 0.80 g (2.0 mmol, 17%). $[\alpha]_D^{25}$ -15° (c 1). HRMS: m/z 409.1882, calculated for $C_{24}H_{27}NO_5$ 409.1889; MS: m/z 409 (35, $M^{+\cdot}$), 367 (52), 295 (15), 225 (100), 193 (75), 165 (20), 71 (55). ^{13}C NMR: δ 207.73 (q, $CCOCH_3$), 168.80 (q, $OCOCH_3$), 161.22 (161.62) (t, NCHO), 150.15 (150.26) (q, C-3), 138.79 (q, C-4), 136.23 (135.78) (t, C-19), 135.044 (134.99) (q, C-12), 129.72 (129.60) (t, C-18), 127.54 (128.24) (q, C-11), 125.63 (125.74) (t, C-1), 110.83 (110.88) (t, C-1), 56.05 (p, OCH_3), 55.05 (47.60) (t, C-9), 53.50 (53.16) (t, C-7), 41.22 (36.26) (d, C-16), 40.76, 41.00, 40.44, 40.30 (q, C-13, C-14), 35.22 (35.07) (d, C-5), 33.86 (33.66) (t, C-6), 32.91 (31.49) (d, C-10), 28.12 (28.04) (p, $CCOCH_3$), 26.96 (26.61) (d, C-8), 21.13 (p, $OCOCH_3$). ^1H NMR: Table 1. Other signals: δ 2.06 (2.09) (s, 3H, $CCOCH_3$), 2.30 (s, 3H, $OCOCH_3$), 2.77 (2.71) (d, 1H, H-10β, J(10α,10β) -18.6 Hz), 3.20 (4.08) (dd, 1H, H-16, J(16,16′) -13.6 Hz, J(16,15) 4.4 Hz), 3.44 (3.35) (dd, 1H, H-10α, J(9,10α) 5.6 Hz), 6.86 (d, 1H, H-2, J(1,2) 8.5 Hz), 6.97 (6.99) (d, 1H, H-1), 8.06 (8.18) (s, 1H, CHO). IR: ν_{max}^{KBr} 1760 ($OCOCH_3$), 1710 ($CCOCH_3$), 1670 (NCHO) cm^{-1}.

(-)-4-Acetoxy-8β-acetyl-N-formyl-3-methoxy-6β,14β-ethenomorphinan (8a)

Yield 0.15 g (0.4 mmol, 3%). $[\alpha]_D^{25}$ -10° (c 1). HRMS: m/z 409.1819, calculated for $C_{24}H_{27}NO_5$ 409.1889; MS: m/z 409 ($M^{+\cdot}$, 45), 367 (35), 297 (22), 268 (25), 237 (40), 226 (70), 225 (100), 193 (100), 181 (25), 165 (20), 73 (60). ^{13}C NMR: δ 209.49 (q, $CCOCH_3$), 168.72 (q, $OCOCH_3$), 162.44 (161.73) (t, NCHO), 150.21 (150.39) (q, C-3), 138.80 (q, C-4), 135.06 (134.86) (q, C-12),

134.06 (134.34) (t, C-18), 131.68 (131.25) (t, C-19), 127.56 (128.28) (q, C-11), 125.71 (t, C-1), 110.86 (t, C-2), 56.04 (p, OCH_3), 52.27 (45.38) (t, C-9), 49.26 (48.34) (t, C-8), 41.88, 41.73, 41.65, 41.31 (q, C-13, C-14), 36.44 (41.86) (s, C-16), 35.45, 35.28, 34.77, 33.90, 32.71, 31.13, 31.42 (d, C-15, C-10, C-7, C-5), 30.62 (30.77) (d, C-6), 28.72 (29.31) (p, $CCOCH_3$), 21.13 (p, $OCOCH_3$). ^1H NMR: Table 1. Other signals: δ 1.99 (2.00) (s, 3H, $CCOCH_3$), 2.29 (s, 3H, $OCOCH_3$), 3.82 (s, 3H, OCH_3), 6.88 (d, 1H, H-2, J(1,2) 8.5 Hz), 6.98 (6.99) 9d, 1H, H-1), 8.22 (8.05) (s, 1H, CHO). IR: ν_{max}^{KBr} 1760 ($OCOCH_3$), 1705 ($CCOCH_3$), 1670 (NCHO) cm^{-1}.

Diels-Alder reaction of **6c** *with nitroethene*

The 4:1 mixture of 6c and its non-conjugated isomer (1.1 g, 3.2 mmol) was dissolved in 10 ml of a 10% solution of nitroethene[17] in benzene and the resulting solution was boiled for 50 h. After cooling to room temperature the mixture was filtered and the solvents were evaporated *in vacuo*. With VLC, using 5% methanol in dichloromethane as eluent, some polymeric material was removed. The residue was chromatographed over silicagel using 1% methanol in dichloromethane as eluent, yielding 0.50 g (1.2 mmol, 27%) of solid material, consisting of 85% of 8β-nitro-6β,14β-ethenomorphinan 8b and 15% of an unknown nitro-substituted 6β,14β-ethenomorphinan. MS: m/z 413 (M^+ +1, 17), 412 (M^+, 10), 370 (10), 337 (10), 295 (23), 266 (22), 237 (20), 225 (70), 224 (100), 209 (35), 193 (47), 181 (30), 165 (35), 152 (25), 91 (27), 73 (35). ^{13}C NMR: δ 168.73 (168.68) (q, $OCOCH_3$), 161.55 (161.32) (t, NCHO), 150.55 (150.41) (q, C-3), 138.65 (q, C-4), 133.39 (133.04) (t, C-18), 133.14 (q, C-12), 130.99 (130.33) (t, C-19), 127.59 (127.06) (q, C-11), 126.04 (125.92) (t, C-1), 111.64 (111.54) (t, C-2), 84.25 (84.99) (t, C-8), 56.14 (p, OCH_3), 52.21 (44.79) (t, C-9), 44.14 (q, C-13), 41.47 (41.25) (q, C-14), 36.22 (40.93) (s, C-16), 36.22, 34.99, 32.26 30.87 (s, C-15, C-7, C-10, C-5), 30.03 (30.16) (t, C-6), 21.07 (p, $OCOCH_3$). ^1H NMR: Table 1. Other signals: δ 2.28 (s, 3H, $OCOCH_3$), 3.82 (s, 3H, OCH_3), 6.92 (d, 1H, H-2, J(1,2) 8.4 Hz), 7.03 (7.05) (d, 1H, H-1), 8.17 (8.05) (s, 1H, NCHO).

Aknowledgements

We thank the Management of Diosynth B.V., Apeldoorn, The Netherlands, for the gift of chemicals. One of us (J.T.M.L.) wishes to express his gratitude to Diosynth B.V. for financial support.

References

*Part XXVIII: See Ref. 3.

1. K.W. Bentley in "The Alkaloids", R.H.F. Manske (Ed.), Vol XIII, Academic Press, 1971, 75.
2. A.C. Ghosh, D.E. Portlock, H.C. Dalzell, C. Malmberg, P. Herlihy, R.K. Razdan, W.L. Duax and G.D. Smith, J. Org. Chem. **48**, 4137 (1983).
3. J.T.M. Linders, P. Briel, E. Fog, T.S. Lie and L. Maat, submitted for publication.
4. J.T.M. Linders, J.P. Kokje, M. Overhand, T.S. Lie and L. Maat, Recl. Trav. Chim. Pays-Bas **107**, 442 (1988).
5. F. Yomada, H. Suzuki and Y. Nitta, J. Am. Chem. Soc. **88**, 2328 (1966).
6. Y.K. Sawa, N. Tsuji and S. Maeda, Tetrahedron **14**, 144 (1961).
7. G. Dijkstra, W.H. Kruizinga and R.M. Kellogg, J. Org. Chem. **52**, 4230 (1987).
8. B. Klieser, L. Rossa and F. Vögtle, Kontakte (Darmstadt) **1984**(1), 3.
9. G. Mehta and S.K. Kapoor, Org. Prep. Proc. Int. **4**, 257 (1972).
10. S.V. Rogozhin, Yu. Davidovich and V.V. Korshak, Izv. Akad. Nauk SSSR, Ser. Khim. 772 (1970); Chem. Abstr. **73**, 15212b (1970).
11. K. Hayakawa, I. Fujii and K. Kanematsu, J. Org. Chem. **48**, 166 (1983).
12. J.C. Coll, S.J. Mitchell and G.J. Stokie, Aust. J. Chem. **30**, 1862 (1977); B.F. Bowden, J.C. Coll, S.J. Mitchell and G.J. Stokie, Aust. J. Chem. **31**, 1310 (1978); See also S.W. Pelletier, B.S. Joshi and H.K. Desai in "Advances in Medicinal Plant Research", A.J. Vlietinck and R.A. Dommisse (Eds.), Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart, 1985, 153.
13. S.L. Patt and J.N. Shoolery, J. Magn. Res. **46**, 535 (1982).
14. F.I. Carroll, C.A. Moreland, G.A. Brine and J.A. Kepler, J. Org. Chem. **41**, 996 (1976).
15. A. Brossi, F.-L. Hsu, K.C. Rice, M.D. Rozwadowska, H. Schmidhammer, C.D. Hufford, C.C. Chiang and I.L. Karle, Helv. Chim. Acta **64**, 1672 (1981).
16. J.T.M. Linders, R.J.O. Adriaansens, T.S. Lie and L. Maat, Recl. Trav. Chim. Pays-Bas **105**, 27 (1986).
17. D. Ranganathan, C. Bushan Rao, S. Ranganathan, A.K. Mehrotra and R. Iyengar, J. Org. Chem. **45**, 1185 (1980).

CHAPTER 6 A NEW SYNTHESIS OF 6-DEMETHOXY-*N*-FORMYL-*N*-NORTHEBAINE AND ITS REARRANGEMENT TO A DIBENZ[*d*,*f*]AZONINE

6.1

Diene systems in *N*-formylmorphinans; formation of a dibenz[*d*,*f*]azonine: a new example of molecular acrobatics in morphinans

Diene systems in *N*-formylmorphinans: formation of a dibenz[*d*,*f*]azonine: a new example of molecular acrobatics in morphinans[1] (Chemistry of opium alkaloids, Part XXVII)*

J.T.M. Linders, R.J. Booth, T.S. Lie, A.P.G. Kieboom and L. Maat

Department of Organic Chemistry, Delft University of Technology,
Julianalaan 136, 2628 BL Delft, The Netherlands

Abstract

A new synthesis of 6-demethoxy-*N*-formyl-*N*-northebaine (1) and its spectacular rearrangement to dibenzazonine 8 are described.
N-Demethylation of codeine (2) gave *N*-norcodeine (3) which was converted into mesyl compound 5 by *N*-formylation with ethyl formate followed by reaction with mesyl chloride in pyridine. A short treatment of 5 with lithium bromide afforded 7 which, upon reaction with potassium *tert*-butanolate, yielded 1. Reaction of 7 with zinc in ethanol gave morphinan-5,7-diene 9.
Prolonged treatment of morphinan 5 with lithium bromide gave dibenzazonine 8, which could be obtained also by reaction of 1 with hydrogen bromide. A mechanism for this rearrangement is proposed.
The ^{1}H and ^{13}C NMR spectra of the new compounds are discussed.

Introduction

In studies of new morphine-based rigid opiates[2] with an altered oxygen substitution pattern, we focused our attention until now on Diels-Alder adducts of *N*-methylated morphinan-6,8-dienes[3-4]. However, for the cycloaddition of nitroethene, which polymerizes rapidly in the presence of a base[5], we needed the *N*-formylated morphinandienes[6-7], in which the basicity of the amine is masked. They are obtained via *N*-demethylation of *N*-methylmorphinans with diethyl azodicarboxylate in benzene, which proceeds in

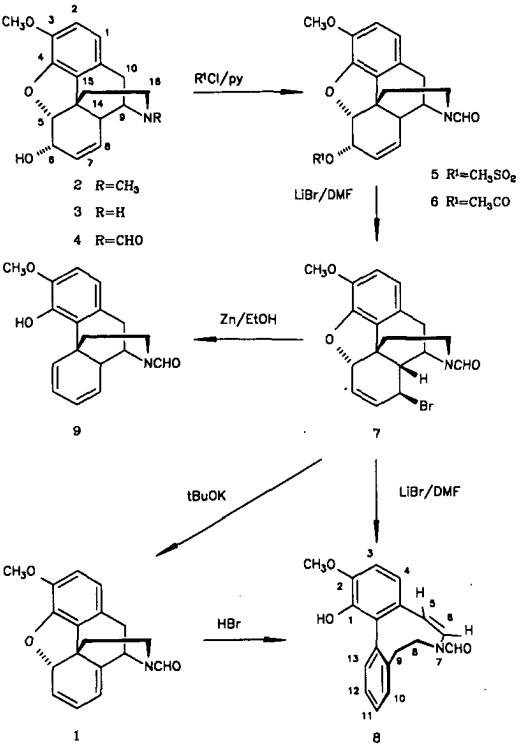
low to moderate yields[6-7], followed by *N*-formylation of the norcompound. Additional advantages of the *N*-formylmorphinans compared to the *N*-methyl analogues are their better crystallizing properties, which facilitates work-up procedures, and their easy conversion into other *N*-alkylated morphinans.

For the synthesis of 6-demethoxy-*N*-formyl-*N*-northebaine (1), we developed an alternative route along the lines of the synthesis of 6-demethoxythebaine from codeine[8], using *N*-formyl-*N*-norcodeine as starting material. Unexpectedly, we found that 1 underwent a spectacular rearrangement to dibenzazonine 8 in the presence of acid, reminiscent of the molecular acrobatism of thebaine, first mentioned by Bentley[1]. The latter compound is a member of a class of new drugs, such as asocainol (11, R = phenethyl)[9], which show important antiarrhythmic and local anaesthetic properties.

Results and discussion

In order to obtain *N*-formylmorphinandienes we started with the *N*-demethylation of codeine (2), which was effected applying a modification of the two-step procedure of DeGraw *et al.*[10]. *In the presence of potassium hydrogen carbonate*[11], codeine was treated with 2,2,2-trichloroethyl chloroformate, giving now a complete conversion of the starting material. The intermediate carbamate[12] was reduced using zinc dust in buffered aqueous THF, affording *N*-norcodeine (3) in high yield. Formylation of 3 with ethyl formate in DMF gave quantitatively *N*-formyl-*N*-norcodeine (4), which had not been described previously.

Treatment of a solution of 4 in pyridine with methanesulfonyl chloride at 0 °C, gave the mesyl ester 5 in almost quantitative yield. Likewise, the 6-*O*-acetyl compound 6 was obtained upon reaction of 4 with acetic anhydride in pyridine. Earlier attempts to prepare 5 according to the procedure used for codeine, namely mesylation in dichloromethane in the presence of triethylamine[8], failed due to the insolubility of 4. Treatment of 5 with lithium bromide in boiling toluene/DMF for 20 min gave *N*-formyl-*N*-norbromocodide (7) in 93% yield.



Scheme 1. Synthesis of 6-demethoxy-*N*-formyl-*N*-northebaine (**1**) and (*R*)-(*Z*)-7-formyl-8,9-dihydro-2-methoxy-7*H*-dibenz[*d*,*f*]azonine-1-ol (**8**).

The structures of the compounds **3-7** were confirmed by means of ^{13}C and ^{1}H NMR spectra and by comparison of their spectra with those of the *N*-methyl counterparts. Replacing the *N*-methyl by the *N*-formyl group leads to characteristic changes in the NMR-spectra (Table 1). The ^{13}C NMR spectra of the *N*-formyl compounds show the characteristic doubling of signals[6], due to *E/Z* isomerism. This is particularly clear for C-9 and C-16, for which the signals of both rotamers differ by 7 and 4 ppm, respectively. This observation has been made also by Llinares *et al.*[13] for simple monocyclic *N*-formyl compounds. A similar doubling of signals is observed in the ^{1}H NMR spectra for CHO, H-9, H-14, H-10 and H-16. In the ^{13}C NMR spectra of codeine (**2**) and *N*-norcodeine (**3**), there is a significant difference in the shift of C-10. The same effect is observed for C-9 and C-16, however *in the opposite*

direction, suggesting it may be caused by the position of the lone pair on nitrogen.

Table 1. Selected signals (value for the minor rotamer in parentheses) in the ^{13}C NMR spectra ($CDCl_3$, relative to TMS) of compounds **2**-**7** and of bromocodide (**7**, *N*-Me instead of *N*-CHO).

Carbon no.	9	10	14	16
Compound				
2[a]	58.76	20.38	40.33	46.28
3	51.92	31.40	41.27	38.48
4	46.34 (53.68)	28.98 (30.25)	40.72 (39.27)	40.13 (35.96)
5	46.37 (53.70)	28.85 (30.19)	39.15 (40.56)	35.51 (40.20)
6	46.58 (53.92)	28.85 (30.25)	40.65 (39.22)	40.44 (35.47)
7	52.08 (44.78)	29.37 (28.18)	47.82 (49.33)	35.18 (40.14)
7 (*N*-Me)	57.01	19.54	49.19	46.66

a) Values taken from Lit. 17.

A striking solvent effect on the position of the signals of H-1 and H-2 was observed for *N*-formyl-*N*-norcodeine (**4**). The ^1H NMR spectrum taken in $CDCl_3$/DMSO-d6 (1:1) showed H-1 and H-2 at δ 6.53 and 6.67, respectively. In pure $CDCl_3$, these protons are found in the reverse order. A similar observation was made by Glasel and Reiher for morphine, on changing the solvent from $CDCl_3$ to CD_3OD[14].

When the bromo compound **7** was treated with an excess of potassium *tert*-butanolate[8] at 0 °C and the reaction was quenched on ice after 1 min, 70% of the desired **1** could be isolated. Due to the instability of **1** in the strong alkaline solution, fast work-up of the reaction mixture was essential. Scaling-up of this reaction proved to be difficult. Treatment of **7** with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), as well as with $LiBr/Li_2CO_3$ failed to give **1**.

Other routes involving thermolysis of the esters **5** or **6** to obtain the desired 6,8-diene system were also explored. Heating acetate **6** in THF in the

presence of triethylamine and $Pd(PPh_3)_4$[15] only led to decomposition of the starting material. When the mesyl ester **5** was used as starting material, up to 50% of **1** was formed (HPLC). Similar results were obtained when a solution of **5** in DMF was heated in a microwave oven using K_2CO_3 as acid scavenger. For the analogous thermolysis of codeine xanthates, Kanematsu et al.[16] pointed out that these reactions occur via a [3,3]-sigmatropic rearrangement, giving the 6,8-diene in low yield via the 8α-substituted morphinan. Because the transition state will be located at the crowded α-face of the morphinan, high reaction temperatures and/or long reaction times are required, which lead to side reactions.

When 6-*O*-mesyl-*N*-formyl-*N*-norcodeine (**5**) was heated with lithium bromide in toluene/DMF over a longer period (5 h), the initially formed *N*-formyl-*N*-norbromocodide, surprisingly, was converted for about 80% (HPLC) into a new compound. When **7** was heated *in the absence* of lithium bromide, it was recovered unchanged. The molecular mass of the unknown compound was 295.1207 ($C_{18}H_{17}NO_3$). The ^1H NMR showed the presence of a *cis*-vinyl system (*J* 10.2 Hz). Selective irradiation at δ 5.5 removed the coupling to the aromatic nucleus, showing that the double bond formed part of a styrene system. The absence of peaks for H-9 and H-10, the absence of a quaternary carbon at about 45 ppm (characteristic for C-13 in morphinans[17]), together with additional absorptions in the aromatic area in both the ^1H and the ^{13}C NMR spectra, suggested that the morphinan skeleton had rearranged completely. The IR spectrum showed the presence of a hydroxyl and a carbonyl function. The UV spectrum exhibited two maxima at 220 (ε = 25000) and 270 nm (ε=15000), indicating high aromaticity. The spectral data did not lead to elucidation of the structure, therefore a single crystal X-ray analysis was performed showing the compound to be (*Z*)-7-formyl-8,9-dihydro-2-methoxy-7*H*-dibenz[*d*,*f*]azonine-1-ol (**8**) (Fig. 1)[18].

With the structure at hand it was now possible to assign the signals in both the ^1H and ^{13}C NMR spectra, using APT (Attached Proton Test)[19], ^1H-^{13}C correlation and INAPT (Insensitive Nuclei Assigned by Polarization Transfer)[20] techniques (Table 2). Although compound **8** contains an *N*-formyl group, there is no doubling of the signals due to restricted rotation around the amide bond. Apparently, the conjugation of the nitrogen atom with the vinylic system decreases the rotational barrier of the *N*-CHO bond.

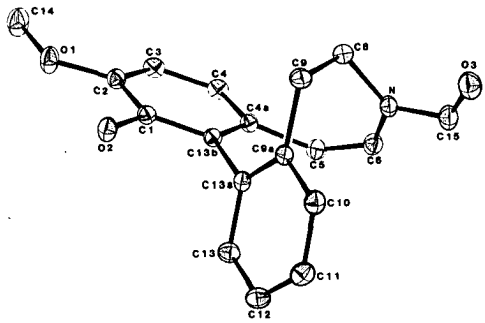


Fig. 1. ORTEP drawing of the structure of (+)-(*R*)-(*Z*)-7-formyl-8,9-dihydro-2-methoxy-7*H*-dibenz[*d*,*f*]azonine-1-ol (**8**).

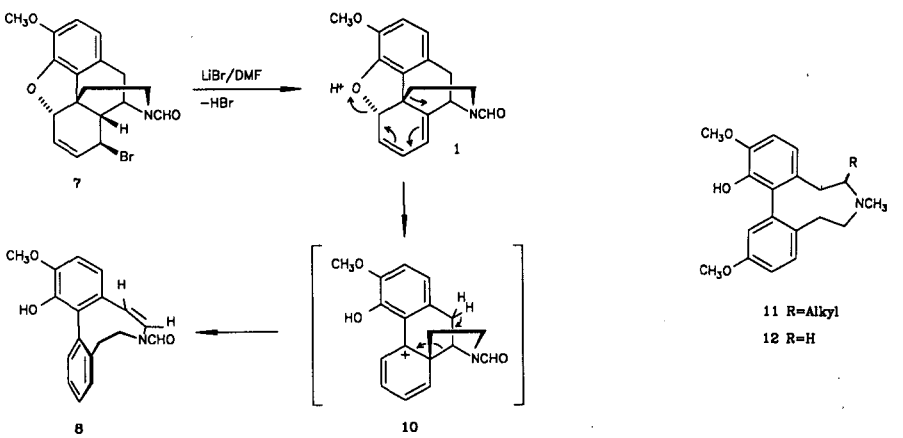
Table 2. Assignment of ^{1}H and ^{13}C NMR signals of **8** ($CDCl_3$, δ(ppm), J(Hz)).

Carbon or proton	^{13}C NMR	^{1}H NMR
1	142.57 (s)	-
2	145.55 (s)	-
3	109.82 (d)	6.88 (d, J(3,4) 8.4)
4	119.75 (d)	6.74 (dd, J(4,5) 1.1)
5	108.08 (d)	5.49 (dd, J(5,6) 10.2)
6	127.76 (d)	6.05 (d)
8	41.28 (t)	3.44[a] (ddd, J(8,8′) -13.8, J(8,9) 8.4)
		3.85[b] (dd, J(8′,9) 10.9, J(8′,9′) 7.3)
9	31.74 (t)	2.88[b] (dd, J(9,9′) -13.8)
		3.10 (ddd)
10	131.18 (d)	7.15 (m)
11	127.76 (d)	7.22 (m)
12	127.00 (d)	7.22 (m)
13	128.94 (d)	6.98 (m)
CH_3O	56.02 (q)	3.95 (s)
CHO	162.81 (d)	8.02 (s)
4a	129.26 (s)	-
9a	136.84 (s)	-
13a	136.71 (s)	-
13b	127.14 (s)	-
OH	-	5.49 (bs)

a) Small long range coupling (~0.5 Hz) to CHO.
b) Line broadening due to J(8′,9′).

The formation of the dibenzazonine **8** from **7** can be explained by the mechanism depicted in Scheme 2. The elimination of HBr by lithium bromide in

the presence of DMF, a known reaction from steroid chemistry[21-22], produces diene **1**, together with an equimolar amount of HBr, which induces a Wagner-Meerwein rearrangement by protonation of the 4,5α-epoxy bridge to give carbocation **10**. Deprotonation at C-10, followed by fragmentation, ultimately affords the dibenzazonine. In order to find support for this mechanism, 6-demethoxy-*N*-formyl-*N*-northebaine (**1**) was treated with HBr giving dibenzazonine **8** as the only product. This is in contrast to the analogous *N*-methyl series, where elimination of HBr during the lithium bromide treatment leads to the formation of 6-demethoxythebaine. In that case, the liberated acid is effectively neutralized by the tertiary amino group present. Given the mechanism as shown in Scheme 2, compound **8** will have the *R*-configuration.



Scheme 2. Mechanism of the formation of dibenzazonine **8** from *N*-formyl-*N*-norbromocodide (**7**) and 6-demethoxy-*N*-formyl-*N*-northebaine (**1**).

A similar mechanism has been proposed for the formation of dibenz[*d*,*f*]azonines **11** and **12**. Compound **11** has been obtained by reaction of alkyl Grignards with thebaine[1,23-24], while treatment of thebaine with Lewis acids, followed by metal hydride reduction[25-27] afforded **12**. In these

reactions, the initially formed cation (6-methoxy analogue of 10) is neutralized by the lone pair of the nitrogen. The resulting iminium species is either alkylated to give 11 or reduced to unsubstituted 12, neodihydrothebaine.

Treatment of morphine or codeine with strong acids is known to give aporphines[28] via a mechanism involving 6-demethoxyoripavine[29] and 6-demethoxythebaine[30-31], respectively. Protonation of the oxygen bridge again yields carbocation 10 (*N*-CH_3 instead of *N*-CHO), in which the aminoethano link subsequently moves to C-8[28]. Apparently, in the compound studied by us, the *N*-formyl group exerts influence on this reaction path by stabilizing the carbocation and facilitating the fragmentation of the C-9/C-14 bond, thereby preventing the formation of aporphines.

Morphinan-5,7-diene 9 is an interesting starting material for the preparation of 5,8-ethenomorphinans. Recently, we reported[32] on an improved synthesis of the *N*-methyl analogue of 9, desoxycodeine-A. We have now found that a simple treatment of bromo compound 7 with zinc in absolute ethanol afforded in quantitative yield 17-formyl-3-methoxy-5,6,7,8-tetradehydromorphinan-4-ol (9), which will be difficult to prepare by other procedures.

Experimental

Mass spectra were measured by Dr. J.M.A. Baas, Dr. B. van de Graaf and Mrs. A.H. Knol-Kalkman using a VG 70-SE mass spectrometer. ^1H and ^{13}C NMR spectra were measured using a Nicolet NT-200 WB, operated by Dr. J.A. Peters and Dr. A. Sinnema. All spectra were recorded in $CDCl_3$ as solvent unless otherwise stated, and tetramethylsilane as reference. Shift values for the minor isomer are given in parentheses. Rotations were measured using a Perkin-Elmer P141 polarimeter in chloroform/ethanol 9:1 as solvent. IR spectra were obtained from KBr discs using a Beckman IR 4210 spectrophotometer. UV spectra were measured using a Pye Unicam SP8-250 UV/VIS spectrophotometer. Reactions were monitored by TLC on deactivated silica (0.25 mm, Merck F_{254}; eluent: dichloromethane/methanol/25% ammonia 95:5:0.5). The compounds were detected with UV (254 nm) and iodine vapour. Melting points are uncorrected. Analytical HPLC was performed using a Waters M-6000 pump on a reversed-phase column (8x100 mm, Nucleosil C_{18} or Novapak, 10 μm, 30 ^{0}C) using mixtures of

methanol/water/trifluoroacetic acid or acetonitrile/water as eluent, with detection on an ERMA RI-detector ERC-7510 or a Pye LC3 variable wave length detector at 240-250 nm.

(-)-N-*Norcodeine* (3) *from (-)-codeine* (2)

Codeine.H_2O (31.50 g, 100 mmol) was dried azeotropically with toluene (400 ml) in a Dean-Stark apparatus. After removal of the solvent, the white residue was dissolved in 250 ml of 1,1,2,2-tetrachloroethane, $KHCO_3$ (15.00 g, 130 mmol) and 2,2,2-trichloroethyl chloroformate (38.10 g, 194 mmol) were added and the mixture was boiled under reflux for 2.5 h (complete conversion *on TLC*).
After cooling to room temperature, the mixture was filtered and the solvents were evaporated *in vacuo*. The residue was redissolved in 250 ml of THF, zinc powder (60 g) and 1*N* solution of NaH_2PO_4 (100 ml) were added, and the resulting mixture was boiled under reflux with vigourous stirring for 1 h. After cooling to room temperature, diethyl ether (100 ml), 2-propanol (250 ml), chloroform (450 ml) and 25% ammonia (20 ml) were added. The heterogeneous mixture was vigorously stirred for 30 min. After filtration, the layers were separated and the extraction procedure was repeated on the aqueous layer and the filtered-off residue. The organic extracts were combined, washed with 100 ml of brine and 100 ml of water, dried (Na_2SO_4) and evaporated *in vacuo* giving 24.2 g of solid material. Crystallization from ethyl acetate gave 21.0 g (74 mmol, 74%) of pure *N*-norcodeine (3), m.p. 186-187 °C. (Ref. 10: m.p. 186-187 °C). Evaporation of the mother liquor and crystallization from ethyl acetate afforded an additional 1.9 g of *N*-norcodeine (Total yield 80%).

(-)-N-*Formyl*-N-*norcodeine* (4) *from (-)*-N-*norcodeine* (3)

N-Norcodeine (13.95 g, 48.6 mmol) was dissolved in DMF (46 ml) by heating. Ethyl formate (30 ml, 370 mmol) was added to this solution and the mixture was boiled under reflux for 24 h (bath temperature 100 °C). After cooling to room temperature, the solvents were removed by evaporation in vacuo, giving pure *N*-formyl-*N*-norcodeine (4). The crystalline residue was recrystallized

from 1-propanol, yielding 13.25 g (42.3 mmol, 86%) of *N*-formyl-*N*-norcodeine (**4**).
M.p. 242-244 °C; $[\alpha]_D^{27}$ -192° (c 1). MS: m/z 313 (M^+, 100), 241 (81), 223 (31), 209 (67), 181 (38), 115 (15), 73 (35), 58 (15). ^{1}H NMR ($CDCl_3$/DMSO-d6 1:1): δ 1.87 (m, 2H, H-15 + H-15′), 2.44 (2.53) (m, 1H, H-14, J(9,14) 3.4 Hz, J(8,14) 3.0 Hz, J(7,14) 3.0 Hz), 2.65 (2.74) (d, 1H, H-10, J(10,10′) -18.4 Hz), 2.77 (3.32) (m, 1H, H-16), 2.82 (2.96) (m, 1H, H-10′), 3.81 (s, 3H, OCH_3), 4.17 (bs, 1H, OH), 4.27 (3.45) (m, 1H, H-16′), 4.63 (m, 1H, H-6), 4.85 (d, 1H, H-5, J(5,6) 5.9 Hz), 5.09 (4.32) (dd, 1H, H-9, J(9,10′) 6.0 Hz), 5.31 (m, 1H, H-8, J(7,8) 9.9 Hz), 5.72 (m, 1H, H-7, J(6,7) 2.0 Hz), 6.53 (d, 1H, H-2, J(1,2) 8.2 Hz), 6.67 (d, 1H, H-1), 8.03 (8.19) (s, 1H, CHO). IR: ν_{max}^{KBr} 3400 (OH), 1645 (C=O) cm^{-1}

(-)-N-*Formyl-6*-O-*mesyl*-N-*norcodeine* (**5**) *from (-)*-N-*formyl*-N-*norcodeine* (**4**)

N-Formyl-*N*-norcodeine (5.07 g, 16.1 mmol) was dissolved in pyridine (50 ml) by heating. After cooling to 0 °C in an ice bath, methanesulfonyl chloride (5 ml, 65 mmol), dissolved in pyridine (5 ml), was added dropwise to this solution. The reaction mixture was stirred for 3 h at 0 °C (complete conversion on TLC). The resulting solution was diluted with 200 ml of ice-cold saturated $NaHCO_3$ solution and extracted with dichloromethane (3x100 ml). After drying on Na_2SO_4, the solvent was removed, leaving behind 6.28 g of crude crystalline product, which proved to be pure enough for further use. For analysis and characterization, the crude product was crystallized, with some difficulty, from dichloromethane/ethyl acetate, followed by chloroform, yielding 5.26 g (13.5 mmol, 83%) of a slightly coloured **5**, pure according to TLC and HPLC.
M.p. 145-146 °C; $[\alpha]_D^{27}$ -219° (c 1). MS: m/z 391 (M^+, 8), 295 (70), 267 (22), 237 (45), 223 (20), 62 (45), 45 (100). ^{1}H NMR: δ 1.98 (m, 2H, H-15 + H-15′), 2.52 (2.60) (m, 1H, H-14, J(8,14) 3.0 Hz, J(9,14) 3.4 Hz), 2.71 (2.75) (d, 1H, H-10, J(10,10′) -18.6 Hz), 3.05 (2.90) (m, 1H, H-10′), 3.24 (s, 3H, SCH_3), 3.35 (3.29) (dd, 1H, H-16, J(16,16′) -14 Hz, J(15,16) 4.5 Hz), 3.86 (s, 3H, OCH_3), 4.38 (3.52) (m, 1H, H-16′), 5.08 (d, 1H, H-5, J(5,6) 6.6 Hz), 5.20 (4.27) (m, 1H, H-9, J(9,10′) 6.0 Hz), 5.20 (m, 1H, H-6), 5.50 (m, 1H, H-8, J(7,8) 10 Hz, J(6,8) 1.1 Hz), 5.81 (m, 1H, H-7), 6.60 (d, 1H, H-1, J(1,2) 8.2 Hz), 6.73 (d, 1H, H-2), 8.06 (8.23) (s, 1H, CHO). IR: ν_{max}^{KBr} 1660 (C=O) cm^{-1}.

(-)-6-O-Acetyl-N-formyl-N-norcodeine (6) *from (-)-N-formyl-N-norcodeine* (4)

N-Formyl-*N*-norcodeine (3.00 g, 9.5 mmol) was dissolved in pyridine (30 ml) by heating. After cooling to 0 °C in an ice bath, a mixture of acetic anhydride (3.5 ml, 37 mmol) and pyridine (3.5 ml) was added dropwise. After 0.5 h, the ice bath was removed and the reaction mixture was boiled under reflux for 0.5 h. After cooling to room temperature, the mixture was diluted with 50 ml of saturated $NaHCO_3$ solution and extracted with dichloromethane (1x100 ml, 5x50 ml). Drying (Na_2SO_4) and evaporation of the solvents gave a semi-crystalline residue, which was recrystallized from dichloromethane/ethyl acetate, giving 2.84 g (8.0 mmol, 84%) of 6, pure according to TLC and HPLC.
M.p. 206-207 °C; $[\alpha]_D^{27}$ -241° (c 1). MS: m/z 355 (M^+, 100), 313 (9), 250 (18), 241 (15), 223 (61), 209 (43), 105 (100), 97 (20), 77 (54), 69 (30), 57 (55). ^1H NMR: δ 1.94 (m, 2H, H-15 + H-15'), 2.16 (s, 3H, $COCH_3$), 2.55 (2.63) (m, 1H, H-14, J(8,14) 3.0 Hz, J(9,14) 3.4 Hz), 2.69 (2.77) (d, 1H, H-10, J(10,10') -18.7 Hz), 2.99 (2.86) (m, 1H, H-10'), 3.34 (3.28) (dd, 1H, H-16, J(16,16') -14 Hz, J(15,16) 4.5 Hz), 3.87 (s, 3H, OCH_3), 4.37 (3.52) (m, 1H, H-16'), 5.09 (d, 1H, H-5, J(5,6) 6.8 Hz), 5.17 (4.25) (dd, 1H, H-9, J(9,10') 6.0 Hz), 5.18 (m, 1H, H-6), 5.47 (m, 1H, H-8, J(7,8) 10 Hz, J(6,8) 1.1 Hz), 5.73 (m, 1H, H-7, J(6,7) 6.0 Hz), 6.57 (d, 1H, H-1, J(1,2) 8.2 Hz), 6.71 (d, 1H, H-2), 8.06 (8.23) (s, 1H, CHO). IR: ν_{max}^{KBr} 1780 (C=O), 1660 (C=O) cm^{-1}.

(-)-N-Formyl-N-norbromocodide (7) *from (-)-N-formyl-6-O-mesyl-N-norcodeine* (5)

N-Formyl-6-*O*-mesyl-*N*-norcodeine (4.50 g, 11.5 mmol) was dissolved in a mixture of toluene (80 ml) and DMF (20 ml), by heating. To this solution, lithium bromide (2.00 g, 23 mmol), dissolved in 35 ml of a 1/1 mixture of toluene and DMF, was added and the resulting mixture was boiled for 20 min (complete conversion on TLC). After cooling to room temperature, the mixture was washed with 50 ml 2*N* potassium hydroxide. The aqueous layer was extracted with 20 ml of toluene, the organic layers were combined and dried (Na_2SO_4). The volume was reduced to 20 ml. After standing overnight,

crystals (3.00 g) of pure **7** could be isolated. Upon further evaporation of the mother liquor, a second crop of pure **7** was obtained (Total 4.02 g, 10.6 mmol, 93%).
M.p. 166-167 °C; $[\alpha]_D^{27}$ -60° (c 1). MS: m/z 377 (M^+, 5), 375 (M^+, 5), 296 (23), 225 (10), 193 (10), 62 (60), 45 (100). ^{1}H NMR: δ 1.85 (m, 2H, H-15 + H-15'), 2.52 (2.58) (dd, 1H, H-14, *J*(8,14) 8.7 Hz, *J*(9,14) 3.2 Hz), 2.73 (2.81) (d, 1H, H-10, *J*(10,10') -18.8 Hz), 3.16 (3.09) (m, 1H, H-10'), 3.23 (2.67) (dd, 1H, H-16, *J*(16,16') -14 Hz, *J*(15,16) 4.5 Hz), 3.45 (4.32) (m, 1H, H-16', *J*(15,16') 4.1 Hz), 3.86 (s, 3H, OCH_3), 5.05 (dd, 1H, H-5, *J*(5,6) 3.5 Hz, *J*(5.7) 1.2 Hz), 5.38 (4.45) (dd, 1H, H-9, *J*(9,10') 6.4 Hz), 5.71 (m, 1H, H-6, *J*(6,7) 10.4 Hz), 6.05 (m, 1H, H-7), 6.67 (d, 1H, H-1, *J*(1,2) 8.2 Hz), 6.77 (d, 1H, H-2), 8.04 (8.24) (s, 1H, CHO). IR: ν_{max}^{KBr} 1650 (C=O) cm^{-1}.

*(-)-6-Demethoxy-*N*-formyl-*N*-northebaine* (**1**) *from (-)-*N*-formyl-*N*-norbromocodide* (**7**)

Bromo compound **7** (0.50 g, 1.33 mmol) was dissolved in 5 ml of DMF by heating. The solution was cooled to 0 °C and added *at once* to a well-stirred solution of potassium *tert*-butanolate (0.40 g, 2.69 mmol) in 10 ml of DMF, kept at 0 °C in an ice-bath. After one minute, the deep-red solution was poured onto 100 g of crushed ice. Extraction with dichloromethane (3x10 ml), washing of the organic layers with saturated brine (5 ml) and water (5 ml), drying and evaporation *in vacuo* gave a solid residue, from which 0.28 g (0.90 mmol, 70%) of **1** was isolated by vacuum liquid chromatography (VLC)[33] using 2% methanol in dichloromethane as eluent. The product obtained was identical in all respects (TLC, HPLC, ^{1}H NMR, IR, m.p. and $[\alpha]_D^{25}$) to the material prepared by *N*-demethylation of 6-demethoxythebaine, followed by formylation[7].

*(+)-*N*-Formyl-*N*-nordesoxycodeine-A* (**9**) *from (-)-*N*-formyl-*N*-norbromocodide* (**7**)

To a boiling solution of **7** (0.15 g, 0.40 mmol) in 5 ml of absolute ethanol, 0.15 g (2.3 mmol) of zinc powder was added, and the mixture was boiled for 2 h.
After cooling to room temperature, 5 ml of 1M HCl was added and the mixture was filtrated over Hyflo. Extraction with dichloromethane (3x5 ml), drying

(Na_2SO_4) and evaporation *in vacuo* gave 100 mg (0.33 mmol, 85%) of 9 as a light-yellow oil, which crystallized on standing.
M.p. 125-126 °C; $[\alpha]_D^{25}$ 121°. MS: m/z 297 (M^+, 18), 296 (36), 268 (15), 225 (95), 200 (53), 181 (35), 165 (50), 152 (32), 73 (100). ^1H NMR: δ 1.90 (m, 2H, H-15+H-15'), 3.80 (s, 3H, OCH_3), 3.10 (4.10) (m, 1H, H-16), 5.20 (4.05) (m, 1 H, H-9), 5.4-6.0 (m, 4H, H-5 + H-6 + H-7 + H-8), 6.4 (bs, 1H, OH), 6.55 (d, 1H, H-1, J(1,2) 8 Hz), 6.60 (d, 1H, H-2), 8.20 (8.05) (s, 1H, CHO). IR: ν_{max}^{KBr} 3400 (OH), 1660 (C=O) cm^{-1}.

(+)-(R)-(Z)-7-Formyl-8,9-dihydro-2-methoxy-7H-dibenz[d,f]*azonine-1-ol* (8)

A.

N-Formyl-6-*O*-mesyl-*N*-norcodeine (5, 90 mg, 0.23 mmol) was dissolved in a mixture of 4 ml of toluene and 1 ml of DMF, by heating. To this solution lithium bromide (40 mg, 0.46 mmol), dissolved in 1 ml of a 1/1 mixture of toluene and DMF, was added and the resulting mixture was heated to reflux. Aliquots (50 µl) were taken from this mixture, evaporated *in vacuo*, redissolved in 100 µl of acetonitrile/water 40/60 and analyzed with HPLC. After 20 minutes, the starting material had disappeared and bromo compound 7 was the only product observed. On continued heating, 7 was slowly converted into a new substance (80% conversion after 5 h), which proved to be 8 on comparison with an authentic sample (see B).

B.

N-Formyl-*N*-norbromocodide (2.24 g), containing 35% of 8, was dissolved by heating in DMF (15 ml). The hot solution was poured into a cold, well-stirred solution of potassium *tert*-butanolate (1.80 g, 16 mmol) in 4 ml of DMF. After one hour, the reaction mixture was poured onto ice (20 g) and 20 ml of 2*N* potassium hydroxide solution was added. Extraction with dichloromethane (3x50 ml), drying (Na_2SO_4) and evaporation *in vacuo* afforded a crystalline residue. Crystallization from ethanol afforded 0.50 g (1.7 mmol, 28%) of 8, pure according to TLC and HPLC.
M.p. 226-227.5 °C; $[\alpha]_D^{27}$ 369° (c 1). HRMS: m/z = 295.1207; Calculated for $C_{18}H_{17}NO_3$ 295.1208; MS: m/z 295 (M^+, 100), 267 (27), 252 (18), 237 (21), 211 (15), 165 (13). ^1H and ^{13}C NMR: see Table 2. IR: ν_{max}^{KBr} 3400 (OH), 1680, 1640, 1600 cm^{-1}. UV (ethanol): λ_{max} 270 (ϵ = 15000), 220 (ϵ = 25000) nm.

C.

6-Demethoxy-*N*-formyl-*N*-northebaine (50 mg, 0.16 mmol) was dissolved in 2 ml of toluene and 0.5 ml of DMF by heating untill reflux. Concentrated hydrobromic acid (48%, 10 μl) was added and the solution was refluxed for 5 min. After cooling to room temperature, saturated $NaHCO_3$ (1 ml) was added, the layers were separated and the organic fraction was dried on Na_2SO_4. Evaporation of the solvents and crystallization of the residue from ethanol afforded 45 mg (90%) of pure **8**, identical to the material described under B.

Acknowledgements

We are indebted to the management of Diosynth, B.V., Apeldoorn, The Netherlands for the gift of chemicals. One of us (J.T.M.L.) wishes to express his gratitude to Diosynth, B.V. for financial support. Stimulating discussions with Prof. H.J.T. Bos (Utrecht) are gratefully acknowledged. We thank Dr. J.A. Peters and Dr. A. Sinnema for their help in the interpretation of the ^1H and ^{13}C NMR spectra and Dr. J.M.A. Baas for the interpretation of the mass spectra.

References

*Part XXVI: J.T.M. Linders, T.S. Lie and L. Maat, Bull. Soc. Chim. Belg. **97**, 463 (1988).

1a. R. Robinson, Proc. R. Soc. London, B **135** v-xix (1947).
1b. R. Robinson, Nature (London) **160**, 815 (1947).
1c. K.W. Bentley, Nat. Prod. Rep. **4**, 13 (1985).
2. K.W. Bentley in "The Alkaloids", R.H.F. Manske (Ed.), Vol. XIII, Academic Press, New York, 1971, 75.
3. P.R. Crabbendam, J.T.M. Linders, T.S. Lie and L. Maat, Recl. Trav. Chim. Pays-Bas **103**, 296 (1984).
4. J.T.M. Linders, J.P. Kokje, M. Overhand, T.S. Lie and L. Maat, Recl. Trav. Chim. Pays-Bas **107**, 449 (1988).
5. D. Ranganathan, S. Ranganathan and S. Bamezai, Tetrahedron Lett. **23**, 2789 (1982).
6. L. Maat, J.A. Peters and M.A. Prazeres, Recl. Trav. Chim. Pays-Bas **104**, 205 (1985).
7. M.A. Prazeres, J.A. Peters, J.T.M. Linders and L. Maat, Recl. Trav. Chim. Pays-Bas **105**, 554 (1986).
8. H.C. Beyerman, P.R. Crabbendam, T.S. Lie and L. Maat, Recl. Trav. Chim. Pays-Bas **103**, 112 (1984).
9. F. Späh, New Cardiovasc. Drugs 129 (1986).

10. J.I. DeGraw, J.A. Lawson, J.L. Crase, H.L. Johnson, M. Ellis, E.T. Uyeno, G.H. Loew and D.S. Berkowitz, J. Med. Chem. **21**, 415 (1978).
11a. M.M. Abdel-Monem and P.S. Portoghese, J. Med. Chem. **15**, 208 (1972).
11b. T.A. Montzka, J.D. Matiskella and R.A. Partyka, Tetrahedron Lett. 1325 (1974).
12. Possibly, the 6-hydroxyl function is esterified during the reaction with 2,2,2-trichloroethyl chloroformate[11a]. However, this formyl ester will be hydrolyzed under the conditions of the zinc reduction.
13. J. Llinares, R. Faure, E.J. Vincent and J. Elguero, Spectrosc. Lett. **14**, 423 (1981).
14. J.A. Glasel and M.W. Reiher, Magn. Res. Chem. **23**, 236 (1985).
15. B.M. Trost, T.R. Verhoeven and J.M. Fortunak, Tetrahedron Lett. 2301 (1979).
16. I. Fujii, M. Koreyuki and K. Kanematsu, Chem. Pharm. Bull. **36**, 1750 (1988).
17. F.I. Carroll, C.G. Moreland, G.A. Brine and J.A. Kepler, J. Org. Chem. **41**, 996 (1976).
18. H. van Koningsveld, J.C. Jansen, J.T.M. Linders, R.J. Booth, L. Maat and T.S. Lie, submitted for publication to Acta Cryst.
19. S.L. Patt and J.N. Shoolery, J. Magn. Reson. **46**, 535 (1982).
20. A. Bax, J.A. Feretti, N. Nashed, D.M. Jerina, J. Org. Chem. **50**, 3029 (1985).
21. R.P. Holysz, J. Am. Chem. Soc. **75**, 4432 (1953).
22. N.L. Wendler, D. Taub and H. Kuo, J. Am. Chem. Soc. **82**, 5701 (1960).
23a. M. Freund, Ber. Dtsch. Chem. Ges. **38**, 3234 (1905).
23b. M. Freund and E. Speyer, Ber. Dtsch. Chem. Ges. **49**, 1287 (1916).
24. G. Satzinger, M. Herrmann, E. Fritschi, H. Bahrmann, V. Ganser, B. Wagner and W. Steinbrecher, Ger. Patent Ger. Offen DE 3,007,710 (1982); Chem. Abstr. **96**, 35125d (1982).
25. K.W. Bentley, J. Am. Chem. Soc. **89**, 2464 (1967).
26. D.M. Hall and W.W.T. Manser, J. Chem. Soc., Chem. Commun. 112 (1967).
27. K.W. Bentley, J.W. Lewis and J.B. Taylor, J. Chem. Soc. (C) 1945 (1969).
28. K.W. Bentley, "The Chemistry of Morphine Alkaloids", Clarendon Press, Oxford, 1954, 309 and references cited therein.
29. S. Berényi, S. Hosztafi, S. Makleit and I. Molnár, Acta Chim. Hung. **113**, 51 (1983).
30. C.W. Hutchins, G.K. Cooper, S. Pürro and H. Rapoport, J. Med. Chem. **24**, 773 (1981).
31. S. Berényi, S. Hosztafi, S. Makleit and I. Szeifert, Acta Chim. Acad. Sci. Hung. **110**, 363 (1982).
32. J.T.M. Linders, R.J.O. Adriaansens, T.S. Lie and L. Maat, Recl. Trav. Chim. Pays-Bas **105**, 27 (1986).
33. J.C. Coll, S.J. Mitchell and G.J. Stokie, Aust. J. Chem. **30**, 1859 (1977); B.F. Bowden, J.C. Coll, S.J. Mitchell and G.J. Stokie, Aust. J. Chem. **31**, 1303 (1978); See also S.W. Pelletier, B.S. Joshi and H.K. Desai in "Advances in Medicinal Plant Research, A.J. Vlietinck and R.A. Dommisse (Eds.), Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart, 1985, 153.

6.2

Structure of an unexpected dibenz[*d*,*f*]azonine from the HBr elimination of *N*-formyl-*N*-norbromocodide

Structure of an unexpected dibenz[*d*,*f*]azonine from the HBr elimination of *N*-formyl-*N*-norbromocodide.

By H. van Koningsveld

Laboratory of Applied Physics, Delft University of Technology, Lorentzweg 1, 2628 CJ Delft, The Netherlands

and J.T.M. Linders, R.J. Booth, T.S. Lie and L. Maat

Department of Organic Chemistry, Delft University of Technology, Julianalaan 136, 2628 BL Delft, The Netherlands.

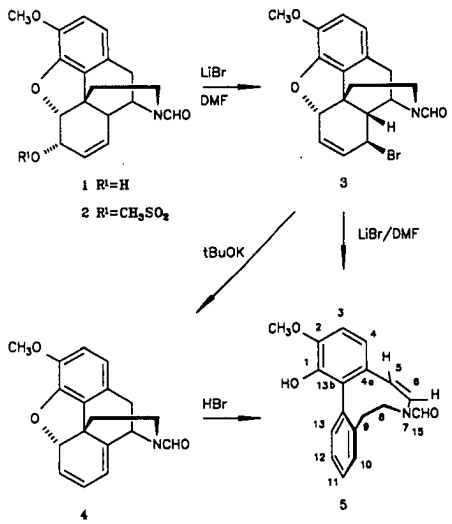
Abstract

(+)-(*R*)-(*Z*)-7-Formyl-8,9-dihydro-2-methoxy-7*H*-dibenz[*d*,*f*]azonine-1-ol, $C_{18}H_{17}NO_3$, M_r = 295.34, orthorhombic, $P2_12_12_1$, a = 9.966(2), b = 14.025(3), c = 10.595(2) Å, V = 1480.9 Å^3, Z = 4, D_x = 1.33 g cm^{-3}, $\lambda(CuK_\alpha)$ = 1.54180 Å, μ = 7.44 cm^{-1}, $F(000)$ = 608, T = 293 K, R = 0.036 for 1773 reflections. The title compound is formed via an acid-catalyzed rearrangement of 6-demethoxy-*N*-formyl-*N*-northebaine, the HBr elimination product from *N*-formyl-*N*-norbromocodide.

Introduction

Amino-substituted ethenomorphinans are valuable starting materials for the preparation of probes for narcotic receptor mediated phenomena (Lessor, Rice, Streaty, Klee & Jacobson, 1984). A first synthesis of 7α-amino-6α,14α-ethenoisomorphinan started from the Diels-Alder adduct of thebaine and ethyl acrylate (Bentley, Hardy & Smith, 1969). Recently, a new route using the cycloaddition of thebaine derivatives with nitroethene was found. Because nitroethene polymerizes in the presence of base, it was necessary to convert thebaine into the neutral *N*-formyl-*N*-northebaine (Maat, Peters & Prazeres, 1985). In order to obtain novel ethenomorphinans with less oxygen containing substituents, 6-demethoxy-*N*-formyl-*N*-northebaine (4) was synthesized

starting from *N*-formyl-*N*-norcodeine (1) (Scheme 1), analogously to the preparation of 6-demethoxythebaine from codeine (Beyerman, Crabbendam, Lie & Maat, 1984). However, during the reaction of 6-*O*-mesyl-*N*-formyl-*N*-norcodeine (2) with lithium bromide, the slow formation of an unknown product was observed. The same product was obtained when 6-demethoxy-*N*-formyl-*N*-northebaine (4) was boiled with a catalytic amount of HBr. Neither the mass spectrum nor the ^{1}H or ^{13}C NMR spectra could give an unambiguous proof of the structure. Therefore, a single-crystal X-ray analysis was undertaken which proved the structure of the new compound to be (+)-(*R*)-(*Z*)-7-formyl-8,9-dihydro-2-methoxy-7*H*-dibenz[*d*,*f*]azonine-1-ol (5). To our knowledge, this is the first time a single-crystal X-ray study of such a dibenzazonine is reported.



Scheme 1. Synthesis of **4** and **5** from *N*-formyl-*N*-norcodeine (1).

Experimental

Title compound **5** was prepared in the Department of Organic Chemistry (Linders, Booth, Lie, Kieboom & Maat, 1988). Crystals grown from ethanol, m.p. 499-500.5 K, $[\alpha]_D^{27\ ^0C}$ +369° [chloroform/ethanol 9:1, 1.0 g dm^{-3}]. Crystal of dimensions 0.35 × 0.18 × 0.18 mm selected for data collection. Cell parameters from least-squares refinement of the setting angles of 25 reflections with $28 < \theta < 71$; Enraf-Nonius CAD-4 diffractometer. Intensity

data collected for 1788 reflections in range $0 \leq h \leq 12$, $0 \leq k \leq 17$, $0 \leq l \leq 13$ using graphite monochromated CuK_α radiation and $\omega/2\theta$ scan mode, width = $(0.85 + 0.15 \tan \theta)°$, $\theta_{max} = 76.0°$. Max. recording time 90 s., $\sigma_{count}(I)/I < 0.02$ requested in a scan. Three reference reflections showed no decay. No correction was made for absorption effects. Structure solved by direct methods (*MULTAN*; Germain, Main & Woolfson, 1971). Full-matrix least-squares refinement on F of anisotropic non-hydrogen atoms (H atoms from ΔF with fixed isotropic thermal parameters) carried out using *XRAY72* (Stewart, Kruger, Ammon, Dickinson & Hall, 1972). Model converged with 1773 observations [1719 with $I > 1.0\ \sigma(I)$ plus those for which $F_c > F_o$], 251 variables to $R = 0.036$, $wR = 0.036$, $w = 1$, $S = 1.77$, max. shift/error = 0.6 and average shift/error = 0.04. Final ΔF synthesis has $|\rho| < 0.15$ e A^{-3}. All calculations performed on the Delft University Amdahl 470 /V7B computer. Atomic scattering factors from *XRAY72*.

Discussion

The final atomic parameters are listed in Table 1.* Figure 1 shows the conformation and atom numbering. Bond distances and angles are given in Table 2. As can be seen from Figure 1, dibenzazonine **5** consists of two

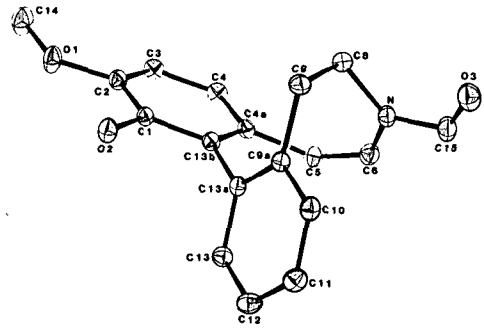


Fig. 1. *ORTEP* plot (Johnson, 1965) of the title compound. Boundary surfaces are drawn to enclose 50% probability.

Table 1. *Fractional atomic coordinates (× 10^4) and U_{eq} ($Å^2$) values. U_{eq} = 1/3 (U_{11} + U_{22} + U_{33})*

	x	y	z	U_{eq}
C(1)	0.3772(2)	0.5107(2)	0.3348(2)	0.034(1)
C(2)	0.4387(2)	0.6003(2)	0.3231(2)	0.039(1)
C(3)	0.3712(3)	0.6811(2)	0.3584(3)	0.047(1)
C(4)	0.2417(3)	0.6737(2)	0.4041(3)	0.042(1)
C(4a)	0.1777(2)	0.5861(2)	0.4161(2)	0.036(1)
C(5)	0.0429(3)	0.5831(2)	0.4754(3)	0.043(1)
C(6)	-0.0727(3)	0.5448(2)	0.4404(3)	0.044(1)
N(7)	-0.1069(2)	0.4992(1)	0.3261(2)	0.038(1)
C(8)	-0.0203(2)	0.5030(2)	0.2142(2)	0.039(1)
C(9)	0.0616(3)	0.4114(2)	0.1950(2)	0.039(1)
C(9a)	0.1007(2)	0.3633(2)	0.3174(2)	0.031(1)
C(10)	0.0433(2)	0.2754(2)	0.3477(3)	0.039(1)
C(11)	0.0743(3)	0.2298(2)	0.4600(3)	0.043(1)
C(12)	0.1646(3)	0.2702(2)	0.5429(3)	0.043(1)
C(13)	0.2206(3)	0.3585(2)	0.5147(2)	0.039(1)
C(13a)	0.1887(2)	0.4059(2)	0.4030(2)	0.031(1)
C(13b)	0.2474(3)	0.5026(2)	0.3812(2)	0.032(1)
C(14)	0.6360(4)	0.6837(2)	0.2542(4)	0.070(2)
C(15)	-0.2262(3)	0.4534(2)	0.3191(3)	0.048(1)
O(1)	0.5674(2)	0.5963(1)	0.2764(2)	0.055(1)
O(2)	0.4449(2)	0.4292(1)	0.3029(2)	0.044(1)
O(3)	-0.2687(2)	0.4136(1)	0.2242(2)	0.057(1)

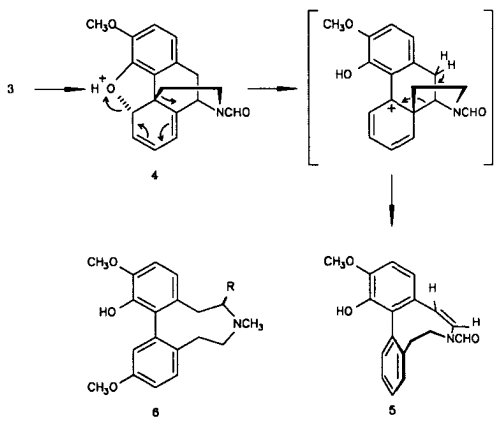
Table 2. *Bond lengths (Å) and bond angles (°)*

C(1)-C(2)	1.404(3)	C(8)-C(9)	1.535(4)
C(1)-O(2)	1.369(3)	C(9)-C(9a)	1.513(3)
C(1)-C(13b)	1.389(3)	C(9a)-C(10)	1.397(3)
C(2)-O(1)	1.376(3)	C(9a)-C(13a)	1.396(3)
C(2)-C(3)	1.370(4)	C(10)-C(11)	1.385(4)
C(3)-C(4)	1.383(4)	C(11)-C(12)	1.379(4)
C(4)-C(4a)	1.390(4)	C(12)-C(13)	1.391(4)
C(4a)-C(5)	1.483(4)	C(13)-C(13a)	1.394(3)
C(4a)-C(13b)	1.411(4)	C(13a)-C(13b)	1.495(3)
C(5)-C(6)	1.324(4)	C(14)-O(1)	1.423(4)
C(6)-N(7)	1.411(3)	C(15)-O(3)	1.226(4)
C(8)-N(7)	1.468(3)	C(15)-N(7)	1.353(3)
C(2)-C(1)-C(13b)	120.7(2)	C(8)-C(9)-C(9a)	113.3(2)
O(2)-C(1)-C(13b)	118.6(2)	C(9)-C(9a)-C(10)	119.1(2)
O(2)-C(1)-C(2)	120.7(2)	C(13a)-C(9a)-C(10)	119.0(2)
C(1)-C(2)-C(3)	120.2(2)	C(9)-C(9a)-C(13a)	121.9(2)
O(1)-C(2)-C(3)	126.1(2)	C(9a)-C(10)-C(11)	120.9(2)
O(1)-C(2)-C(1)	113.7(2)	C(10)-C(11)-C(12)	120.2(2)
C(2)-C(3)-C(4)	119.5(2)	C(11)-C(12)-C(13)	119.4(2)
C(3)-C(4)-C(4a)	121.8(2)	C(12)-C(13)-C(13a)	121.1(2)
C(4)-C(4a)-C(5)	118.6(2)	C(13)-C(13a)-C(13b)	118.3(2)
C(13b)-C(4a)-C(5)	122.2(2)	C(9a)-C(13a)-C(13b)	122.2(2)
C(4)-C(4a)-C(13b)	118.9(2)	C(13)-C(13a)-C(9a)	119.4(2)
C(4a)-C(5)-C(6)	132.9(3)	C(13a)-C(13b)-C(1)	119.5(2)
C(5)-C(6)-N(7)	129.4(3)	C(4a)-C(13b)-C(1)	118.9(2)
C(6)-N(7)-C(15)	118.3(2)	C(13a)-C(13b)-C(4a)	121.4(2)
C(8)-N(7)-C(15)	119.3(2)	C(2)-O(1)-C(14)	118.2(2)
C(6)-N(7)-C(8)	122.3(2)	N(7)-C(15)-O(3)	124.4(3)
N(7)-C(8)-C(9)	112.9(2)		

phenyl rings, which are almost perpendicular to each other [The angle between the two phenyl rings is 83.6(4)°]. The nine-membered ring is in a boat-like conformation. The *N*-formyl amide moiety is practically planar: the maximum deviation of the plane through C(6), C(8), N(7), C(15) & O(3) is 0.15 Å [N(7)]. The hydrogen atoms in the saturated part of the ring are in a gauche position. The olefinic bond has the *cis*-configuration and is rotated out of the plane of the aromatic ring over an angle of approximately 55^0. The rotation of the C-C bond of the biphenyl moiety is restricted because of the ring system.

Similar compounds have been obtained under completely different conditions. When thebaine was treated with alkyl Grignards (Freund, 1905; Small & Fry 1939; Small, Sargent & Bralley, 1947), the 6-alkyl substituted dibenz[*d*,*f*]azonines were obtained in good yields. This reaction has been used recently (Herrmann & Satzinger, 1985) for the preparation of asocainol (**6**, R=CH_2-CH_2-Ph), a new antiarrhythmic drug (Späh, 1986). Reduction of thebaine with metal hydrides in the presence of Lewis acids (Bentley, 1967; Bentley, Lewis & Taylor, 1969) gave the unsubstituted parent compound, neodihydrothebaine (**6**, R=H).

The mechanism, we propose for this rearrangement, is depicted in Scheme 2. Given this mechanism, the chirality around the central phenyl-phenyl bond has the *R* configuration.



Scheme 2. Mechanism for the formation of **5** from **3**.

*Lists of structure factors, anisotropic thermal parameters, H atom coordinates and bond lengths to H atoms have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP xxxxx (xxx pp.) Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

References

Bentley, K.W. (1967). *J. Am. Chem. Soc.* **89**, 2464-2469.
Bentley, K.W., Hardy, D.G. & Smith, A.C.B. (1969). *J. Chem. Soc. (C)* 2235-2236.
Bentley, K.W., Lewis, J.W. & Taylor, J.B. (1969). *J. Chem. Soc. (C)* 1945-1946.
Beyerman, H.C., Crabbendam, P.R., Lie, T.S. & Maat, L. (1984). *Recl. Trav. Chim. Pays-Bas*, **103**, 112-114.
Freund, M. (1905). *Ber. Dtsch. Chem. Ges.* **38**, 3234-3256.
Germain, G., Main, P. & Woolfson, M.M. (1971). *Acta Cryst.* A27, 368-376.
Hermann, W. & Satzinger, G. (1985). *Ger. Offen. DE* 3,419,099; *Chem. Abstr.* (1986) **105**, 43135b.
Johnson, C.K. (1965). *ORTEP*. Report ORNL-3794, revised June 1970. Oak Ridge National Laboratory, Tennessee, USA.
Lessor, R.A., Rice, K.C., Streaty, R.A., Klee, W.A. & Jacobson, A.E. (1984). *Neuropeptides (Edinburgh)*, **5**, 229-232.
Linders, J.T.M., Booth, R.J., Lie, T.S., Kieboom, A.P.G. & Maat, L. (1989). *Recl. Trav. Chim. Pays-Bas*, accepted.
Maat, L., Peters, J.A. & Prazeres, M.A. (1985). *Recl. Trav. Chim. Pays-Bas*, **104**, 205-208.
Small, L. & Fry, E.M. (1939). *J. Org. Chem.* **3**, 509-540.
Small, L., Sargent, L.J. & Bralley, J.A. (1947). *J. Org. Chem.* **12**, 839-868.
Späh, F. (1986). *New Cardiovascular Drugs*, pp. 129-139.
Stewart, J.M., Kruger, G.J., Ammon, H.L., Dickenson, C.W. & Hall, S.R. (1972). The *XRAY72* system-version of June 1972. Tech. Rep. TR-192. Computer Science Center, Univ. of Maryland, College Park, Maryland, USA.

CHAPTER 7 A ^{1}H AND ^{13}C NMR STUDY OF *N*-FORMYLMORPHINANS AND THEIR 6,14-BRIDGED DERIVATIVES; COMPARISON WITH *N*-ME AND *N*-H ANALOGUES

A ^{1}H and ^{13}C NMR study of *N*-formylmorphinans and their 6,14-bridged derivatives; comparison with *N*-Me and *N*-H analogues (Chemistry of opium alkaloids, Part XXX)*

J.T.M. Linders, M.A. Prazeres, T.S. Lie, and L. Maat

Laboratory of Organic Chemistry, Delft University of Technology, Julianalaan 136, 2628 BL Delft, The Netherlands

Abstract

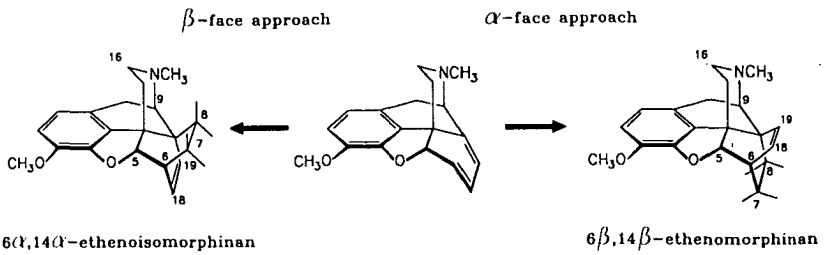
The ^{1}H NMR and ^{13}C NMR spectra of *N*-formylated morphinans were compared with those of the *N*-methyl and *N*-demethyl analogues. The magnitude of the changes in chemical shift of C-9, C-16 and C-10 depended crucially on the nature of the substituent at nitrogen.

For the 6α,14α-ethenoisomorphinans and 6β,14β-ethenomorphinans the proton chemical shifts of the protons of the 6,14-etheno bridge across ring C are differently affected by the nitrogen atom. In the 6α,14α-ethenoisomorphinans, the vinylic protons are found between δ 5.3 and δ 5.9, while in the 6β,14β-ethenomorphinans these protons are found downfield from δ 6.0. A similar, but opposite, anisotropy effect of the nitrogen is observed for the 8β-proton. These results are important for the elucidation of the structures of these types of compounds.

Introduction

Diels-Alder reaction of thebaine[1] or other 4,5α-epoxymorphinan-6,8-dienes[2-5] with mono-substituted ethenes provides good access to compounds of importance as potential analgesics such as buprenorphine and etorphine[1]. The major cycloadduct is the 7α-substituted derivative, in which the dienophile has approached the diene system from the exposed β-face (Scheme 1). The ^{1}H NMR spectra of these 7α-substituted 6α,14α-ethenoisomorphinans[6] have been studied by Fulmor *et al.*[7]. In a series of 21 adducts derived from thebaine, they found the vinylic protons to be at δ 5.91 ± 0.08 (H-18) and δ 5.48 ±

0.06 (H-19), while H-9 was found at δ 3.13 ± 0.04. Carroll *et al.*[8] and Uff *et al.*[9] published a detailed overview of the ^{13}C NMR spectra of these adducts.



Scheme 1. Diels-Alder reactions of a morphinan-6,8-diene

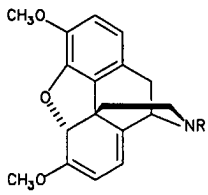
We have extended these studies with a wide variety of new compounds prepared in our laboratory, which include *N*-formylmorphinans[5,10-12,14] and 6β,14β-ethenomorphinans[3,5,13-14], the latter being products of the Diels-Alder reaction at the α-face of the diene system (Scheme 1). The spectra of the *N*-formyl derivatives are complicated by the appearance of double signals due to the restricted rotation around the amide bond. In this paper we focus our attention on the changes in the ^{1}H and ^{13}C NMR spectra caused by the different substituents on the nitrogen atom. Furthermore, the effect of the anisotropy of the nitrogen atom on the shift of the hydrogen atoms of the 6,14-bridged ring C will be discussed.

Results and discussion

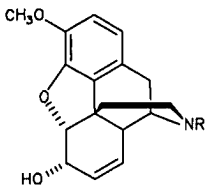
^{13}C NMR

In Tables 1 and 2, ^{13}C NMR chemical shifts are shown for thebaine (**1a**), codeine (**2a**), and their respective *N*-demethylated and *N*-formylated analogues. The signal assignment of **1b-c** and **2b-c** is based on APT (Attached Proton Test)[15] studies and comparison with *N*-methyl compounds[8]. In Table 3 data for bromocodide (**3c**) and its *N*-formyl derivative **3d** are given, together with literature data for the 8β-methoxyl and 8β-chloro derivatives[16]. The relative differences in shift values between **3a**, **3b** and **3c** are in accordance

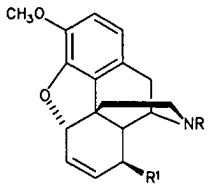
with the expected substituent effects[17]. ^{13}C NMR Data for a series of 7α-acetyl-6α,14α-ethenoisomorphinans are given in Table 4. The spectrum of the 6-demethoxy compound **4c** has been published earlier by Hutchins *et al.*[2], but no assignment was reported by them.



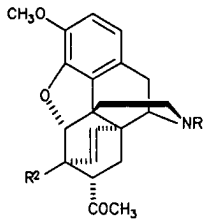
1a R = CH_3, thebaine
b R = H
c R = CHO



2a R = CH_3, codeine
b R = H
c R = CHO



3a R = CH_3, R^1 = OCH_3
b R = CH_3, R^1 = Cl
c R = CH_3, R^1 = Br
d R = CHO, R^1 = Br



4a R = CH_3, R^2 = CH_3O
b R = CH_3, R^2 = CH_3
c R = CH_3, R^2 = H
d R = CHO, R^2 = H

Table 1. ^{13}C NMR Chemical shifts (ppm) of thebaines **1a-c**.

#C	*N*-CH_3[a]	*N*-H	*N*-CHO major	*N*-CHO minor
1	118.85	119.17	119.57	119.44
2	112.26	112.82	113.50	113.37
3	142.45	142.80	143.14	143.19
4	144.40	144.82	144.95	144.95
5	88.81	89.26	88.69	88.57
6	152.15	152.45	153.19	152.86
7	95.59	95.83	95.62	95.23
8	111.19	109.88	112.58	111.81
9	60.47	53.95	48.50	55.54
10	29.17	40.95	39.99	37.94
11	127.33	127.94	126.07	125.57
12	131.96	133.47	132.02	132.23
13	45.70	46.78	46.96	46.96
14	132.94	134.30	128.76	129.42
15	36.73	38.60	37.17	37.00
16	45.70	37.94	38.35	33.96
3-OMe	56.09	56.39	56.39	56.44
6-OMe	54.58	54.91	55.03	55.05
NMe	42.09			
NCHO			159.74	159.90

a) Ref. 8
b) E/Z = 55:45

Table 2. ^{13}C NMR Chemical shifts (ppm) of codeines **2a-c**.

#C	*N*-CH_3[a]	*N*-H	N_bCHO major	N_bCHO minor
1	119.39	119.48	120.14	120.02
2	112.81	112.81	113.57	113.43
3	142.12	142.10	142.64	142.72
4	146.17	146.33	146.43	146.43
5	91.15	91.95	90.96	90.86
6	66.18	66.30	65.87	65.31
7	133.39	133.59	134.55	135.06
8	127.39	128.11	126.27	125.72
9	58.76	51.92	46.34	53.68
10	20.38	31.39	28.98	30.25
11	126.71	127.37	125.32	124.79
12	131.10	131.10	129.62	129.48
13	42.90	43.86	44.08	44.20
14	40.33	41.27	39.27	40.72
15	35.40	36.63	33.97	34.72
16	46.28	38.49	40.13	35.96
3-OMe	56.18	56.29	56.27	56.33
NMe	42.76			
NCHO			160.24	160.38

a) Ref. 8
b) E/Z = 55:45

Table 3. ^{13}C NMR Chemical shifts (ppm) of 8β-substituted codides **3a-d**.

#C	R^1 *N*-R	OCH_3[a] *N*-CH_3	Cl[a] *N*-CH_3	Br *N*-CH_3	Br *N*-CHO[b]	
1		118.0	119.0	119.17	119.67	119.80
2		112.0	113.7	113.42	114.19	114.33
3		142.3	143.2	143.31	143.88	143.80
4		143.5	144.1	143.96	144.37	144.37
5		86.2	86.3	86.36	86.01	86.12
6		132.7	134.6	135.29	134.59	135.13
7		124.2	125.5	125.61	125.19	125.70
8		73.4	56.1	47.08	45.54	44.89
9		54.9	54.8	57.01	52.08	44.74
10		19.5	19.6	19.53	29.37	28.18
11		126.6	126.8	126.75	124.98	124.38
12		129.0	128.4	128.35	126.95	127.04
13		39.8	42.0	42.75	43.97	43.84
14		44.6	48.7	49.19	47.82	49.33
15		34.5	35.0	35.23	33.99	34.32
16		45.0	46.5	46.67	40.41	35.18
3-OMe		55.6	56.3	56.32	56.37	56.40
8-OMe		55.3				
NMe		42.3	42.9	43.12		
NCHO					160.23	160.61

a) Ref. 16
b) E/Z = 50:50

Table 4. ^{13}C NMR Chemical shifts (ppm) of 7α-acetyl-6α,14α-etheno-isomorphinans 4a-d.

#C	R^2 *N*-R	OCH_3[a] *N*-CH_3	CH_3[b] *N*-CH_3	H[c] *N*-CH_3	H *N*HCH_3^+	H *N*-CHO major[d]	H *N*-CHO minor
1		119.15	118.9	119.22	119.93	119.81	119.84
2		113.39	112.7	112.67	114.18	113.34	113.43
3		141.59	141.6	141.83	142.96	142.33	142.67
4		147.76	147.6	148.27	148.49	148.44	148.51
5		95.00	97.7	94.16	92.62	93.82	93.82
6		81.02	40.8	37.60	37.44	37.40	37.60
7		50.47	52.4	47.73	47.09	47.28	47.47
8		29.74	29.9	28.50	26.39	25.66	26.30
9		59.76	59.7	60.48	62.43	55.38	48.01
10		22.21	21.9	22.47	25.38	31.31	32.81
11		127.96	127.9	128.35	126.21	125.72	126.21
12		133.78	133.9	134.38	132.15	132.87	132.99
13		47.24	45.7	45.76	44.42	47.14	47.10
14		43.01	42.8	43.60	43.13	42.65	42.07
15		33.26	32.8	33.26	30.06	32.30	33.10
16		45.24	45.1	45.71	47.22	33.28	39.35
18		135.66	135.8	137.69	134.66	135.74	135.69
19		125.73	129.4	124.83	123.41	125.85	126.04
3-OMe		56.46	56.0	56.36	56.48	56.35	56.35
6-OMe		53.24					
6-Me			17.8				
NMe		43.31	43.1	43.28	42.94		
COMe		208.68	208.6	207.44	206.17	206.13	206.21
COMe		30.23	29.8	26.81	28.66	28.52	28.42
NCHO						160.74	160.66

a) Ref. 8
b) Ref. 4
c) Identical to unassigned spectrum in Ref. 2.
d) E/Z = 60:40

In general, the assignment of ^{13}C NMR spectra is performed using tabulated shift values of model compounds and comparisons with structurally related compounds. The ^{13}C NMR spectra of the *N*-formyl derivatives contain an additional dimension which can be used for the assigment. Due to the restricted rotation around the amide bond, virtually all resonances are double. The separation of the peaks which belong to the same carbon atom correlates roughly with the distance of that atom to the formyl group. The fact that the ratio of the intensities is fairly constant for all carbon atoms except for those next to the nitrogen[18], also provides information which is of use in the assignment of the signals.

C-10, C-9 And C-16 are most affected when the nature of the nitrogen substituent is changed. *N*-Demethylation causes a shift of C-9 and C-16 to

higher field by about 7 ppm. The signal for C-10 undergoes a downfield shift of about 11 ppm. Its relatively high position in the *N*-methyl compounds is due to steric compression exerted by the *N*-methyl group which is in γ-gauche position. The relative changes are in accordance with observations made in a series of simple piperidines[19].

Upon introduction of the formyl group, C-9 and C-16 again experience the strongest effect. The shift of C-10 is also noteworthy. In comparison with the *N*-methyl derivatives it undergoes a downfield shift of about 10 ppm, which is accounted for by the absence of the γ gauche effect of the *N*-methyl group. The effect of the replacement of the *N*-methyl by an *N*-formyl group on the shifts of the different carbon atoms can be divided into two parts. There is a through-bond effect, caused by the electronic properties of the carbonyl group, which leads to a decreased electron density on the nitrogen atom. This will have an equal effect on both the neighbouring carbon atoms. On the other hand, there is a clear influence from the position of the carbonyl group which is different for each of the two α-carbons. The resonance for the carbon atom that is in *anti*-position relative to the carbonyl group is found at lower field[20-21]. From the data in Tables 1-4, it can be concluded that in *N*-formyl-*N*-northebaine and *N*-formyl-*N*-norcodeine the formyl group is *anti*-positioned relative to C-16, while in the Diels-Alder adduct **4d** the *syn*-orientation is most prominent. For *N*-formyl-*N*-norbromocodide there is no preference for either one of the orientations.

The importance of the electron density on the nitrogen atom for the shift of the different carbon atoms can be shown by comparison of the spectrum of the free base with that of the hydrochloride salt. The results for the Diels-Alder adduct **4c** are shown in Table 4. The change of the shifts upon protonation is in accordance with data for the conformer of 2,5-dimethyl-*N*-methylpiperidine which has the *N*-methyl group in equatorial position[19]. In the case of **4c**.HCl there are no indications for the presence of the conformer with the methyl group in axial position. In monocyclic piperidines[19], and also in morphine and nalorphine[22], these conformers were both observed. Obviously, the presence of the additional etheno bridge across ring C makes the skeleton more rigid and causes the equilibrium *N*-$Me_{eq} \rightleftharpoons$ *N*-Me_{ax} to be towards the "left" side. The salts of oxymorphone and naloxone, morphinans which both have a hydroxyl substituent at C-14, are also shown to exist mainly (>95%) in the configuration with the alkyl group in equatorial position[23].

Table 5. ^{1}H NMR Chemical shifts (ppm) of 7α-acetyl-6α,14α-ethenoisomorphinans 4a-d.

#H	R[2] *N*-R	OCH_3[a,b] *N*-CH_3	CH_3[c] *N*-CH_3	H[d] *N*-CH_3	H *N*HCH_3^+	H[d] *N*-CHO	H[e] *N*-CHO major	H[e] *N*-CHO minor	H[f] *N*-CHO major	H[f] *N*-CHO minor
1		6.54 ± 0.03	6.53	6.52	6.62	6.57	6.43	6.43	6.51	6.51
2		not given	6.63	6.62	6.69	6.68	6.61	5.99	6.66	6.66
5		4.53	4.09	4.54	4.67	4.59	5.34	5.30	4.59	4.59
6				3.25	~3.3	3.33	3.12	3.12	3.19	3.19
7β		2.90	2.56	2.68	2.91	2.70	2.40	2.40	2.85	2.85
8α		1.34 (1.68)	1.19	1.36	1.65	1.50	1.39	1.32	1.36	1.26
8β		2.91	2.95	2.86	2.99	2.19	1.95	1.95	2.19	2.19
9		3.13 ± 0.04 (4.23)	3.19	3.20	4.06	4.09	5.00	3.74	4.86	4.25
10α		~2.4	2.42	2.41	3.08	3.20	2.90	2.88	2.75	2.85
10β		3.15 ± 0.05	3.23	3.23	3.32	3.00	2.64	2.61	3.11	3.21
15		not given	1.94	1.97	2.54	}1.9	}1.5	}1.5	}1.8	}1.8
15′		not given	1.83	1.84	2.06					
16		not given	2.54	2.55	}3.52	4.41	3.12		4.15	3.59
16′		not given	2.40	2.45		2.95	2.62		2.76	3.27
18		5.85	5.60	5.75	5.81	5.82	5.61	5.98	5.67	5.67
19		5.54	5.54	5.51	5.52	5.53	5.34	5.31	5.54	5.50
3-OMe		3.81 ± 0.02	3.84	3.82	3.83	3.83	3.64	3.63	3.69	3.69
6-OMe		3.65 ± 0.1								
6-Me			1.33							
NMe		2.43 ± 0.02 (3.13)	2.38	2.40	3.06					
COMe		not given	2.09	2.14	2.18	2.16				
NH					~2.5					
NCHO						8.17	8.04	8.00	8.14	8.01

a) Ref. 7
b) Values for protonated compound in parentheses
c) Ref. 5
d) Ref. 5, in $CDCl_3$
e) In C_6D_6/acetone-d6 1:1, C_6H_6 as reference (δ 7.24)
f) In DMSO-d6 at 60 °C

^1H NMR

The doubling of the signals can also be observed in the ^1H NMR spectrum of the *N*-formylmorphinans. The protons at C-9 and C-16 are most affected. The signals shift to lower field as in the protonated compound (Table 5). Using $CDCl_3$ as the solvent the spectrum of **4d** shows the ratio of the two rotamers to be 9:1, making the assigment of the minor rotamer difficult. In DMSO-*d6* or C_6D_6/acetone-d6 the ratio is close to 1:1. Under these conditions both rotamers can be observed, showing large differences for H-9 and H-16 (Table 5).

The influence of the nitrogen on the position of the signals for the protons of the bridged ring C can be demonstrated when a series of structurally related 6α,14α-ethenoisomorphinans is compared with their 6β,14β counterparts (Table 6). In 7- and 8-substituted 6α,14α-ethenoisomorphinans, the vinylic protons are characteristically found between δ 5.3 and δ 5.9 (Entries 1-13). On the other hand, for the 6β,14β-ethenomorphinans, in which the nitrogen atom is much closer to the vinylic moiety, the signals for H-18 and H-19 are found downfield from δ 6.0 (Entries 14-25). Also, the relative positions of H-18 and H-19 are influenced by the proximity of the nitrogen atom. In the *N*-methyl-6β,14β-ethenomorphinans H-19 is found downfield from H-18, while in the corresponding ethenoisomorphinan series the signal for H-19 is always at higher field: *e.g.* the two 8β-acetyl-6β,14β-ethenomorphinans (Entries 14 and 15) exhibit H-19 at about δ 6.7. In contrast, the 6α,14α-ethenoisomorphinans show this proton in its usual position at δ 5.5 (Entries 5 and 8). In the 6β,14β-ethenomorphinans there is a notable effect on the position of H-19 when the amino nitrogen is converted into an amide. In the *N*-formyl-6β,14β-ethenomorphinans H-19 is at its normal place, upfield from H-18 (Compare the entry pairs 16-17, 20-21, and 23-24).

In the 6α,14α-ethenoisomorphinans the anisotropy of the nitrogen causes the 8β-proton to shift to anomalously low field. In particular, the 8α-acetyl- and 8α–nitro-substituted 6α,14α-ethenoisomorphinans show this proton at about δ 3.90 and δ 5.12, respectively (Entries 5, 8 and 13), lower than can be expected by the presence of the substituent alone (compare with 7-substituted 6α,14α-ethenoisomorphinans). The difference in the shift of H-8α

Table 6. ^{1}H NMR Chemical shifts (ppm) of acetyl- and nitro-substituted 6α,14α-ethenoisomorphinans and 6β,14β-ethenomorphinans.

Entry	Substitution Pattern							Shifts									
	4,5α	6,14	4	6	7	8	*N*	5	6	7α	7β	8α	8β	9	18	19	Ref.
1	-O-	α		OMe	αCOMe		Me	4.53			2.90	1.34	2.91	3.13	5.85	5.54	7
2	-O-	α		OMe	βCOMe		Me	4.95		2.69		1.40	3.04	3.13	6.04	5.48	7
3	-O-	α		Me	αCOMe		Me	4.09			2.56	1.19	2.95	3.19	5.60	5.54	4
4	-O-	α		Me	βCOMe		Me	5.1		2.4		1.2	3.2	3.16	5.5	5.45	4
5	-O-	α		Me		αCOMe	Me	4.12		1.40	1.66		3.95	3.49	5.60	5.48	4
6	-O-	α		H	αCOMe		Me	4.54	3.25		2.68	1.36	2.86	3.20	5.75	5.51	2,5
7	-O-	α		H	αCOMe		CHO	4.59	3.33		2.70	1.50	2.16	4.09(5.09)	5.82	5.53	5
8	-O-	α		H		αCOMe	Me	4.48	2.97	1.58	1.81		3.90	3.49	5.86	5.47	2,5
9	-O-	α		OMe	αNO_2		Me	4.56			a	a	a	a	5.80	5.60	10
10	-O-	α		OMe	αNO_2		H	4.60			a	a	a	a	5.91	5.65	10
11	-O-	α		OMe	αNO_2		CHO	4.60			4.88	1.94	2.74	5.16(4.18)	5.90	5.70	10
12	-O-	α		H	αNO_2		CHO	4.59	3.77		4.63	2.04	2.56	5.18(4.19)	5.85	5.70	5
13	-O-	α		H		αNO_2	CHO	4.47	3.21	2.46	1.96		5.12	4.68(5.62)	6.15	5.34	5
14	-O-	β		Me		βCOMe	Me	4.05		1.35	0.90	1.82		3.45	5.62	6.75	3
15	-O-	β		H		βCOMe	Me	4.33	3.03	1.54	1.15	2.40		3.47	5.99	6.79	5
16	-O-	β		H		βNO_2	H	4.30	3.17	1.97	1.97	3.64		3.83	6.32	6.46	11
17	-O-	β		H		βNO_2	CHO	4.33	3.21	1.99	2.06	3.67		4.53(5.44)	6.35	6.18	5
18		β	OPh	OMe	βCOMe		Me	a	a	a		a	a	a	6.00[c]	6.36[c]	24
19		β	OH	H	βCOMe		Me	1.73 2.52	2.95	2.57		1.82	1.48	2.91	6.08	6.40	4
20		β	OPh	H	βCOMe		Me	a	a	a		a	a	a	6.00	6.40	13
21		β	OAc	H	βCOMe		CHO	a	3.00	2.60		1.75	1.75	4.87(3.85)	6.15	6.03	14
22		β	OH	H		βCOMe	Me	1.68 2.00	2.60	1.68	1.90	2.30		3.19	6.26	6.50	13
23		β	OPh	H		βCOMe	Me	a	a	a	a	a		a	6.20	6.50	13
24		β	OAc	H		βCOMe	CHO	a	2.60	a	a	a		4.42(5.15)	6.27	6.13	14
25		β	OAc	H		βNO_2	CHO	a	2.70	1.88	2.20	4.12		4.96(3.96)	6.51	5.93	14

a) Not reported
b) Shift value for minor rotamer in parentheses
c) Our assignment, not assigned in Ref. 24

and H-8β is caused also by the nitrogen anisotropy. In the 6β,14β-ethenomorphinans the signals for these protons almost coincide.

The observations described here provide a suitable diagnostic for the recognition of 6α,14α-ethenoisomorphinans or 6β,14β-ethenomorphinans, respectively.

In a recent study[5] we have analyzed the stereo- and regioselectivity of the Diels-Alder reaction of morphinan-6,8-dienes in the context of the "Hehre-Kahn rationale"[25-26]. We concluded that the course of the cycloaddition is largely determined by steric effects and by the substituent at C-6, rather than by the lone pair bearing substituents which are in an allylic position relative to the diene system (*viz.* the nitrogen atom and the 4,5α-epoxy bridge)[26]. This NMR study shows that the nitrogen atom does indeed have a demonstrable electronic influence in the direction of ring C. This influence is diminished, as expected[5], when the amino nitrogen is converted into an amide. However, the electronic effect of the nitrogen is not determinant for the selectivity of the Diels-Alder reaction. When morphinan-6,8-dienes without the 4,5α-epoxy bridge are reacted with methyl vinyl ketone, 6β,14β-ethenoisomorphinans are the only cycloaddition products found[13-14,24]. In spite of the short distance of the nitrogen atom to the β-face of the diene system, the Diels-Alder reaction occurs at the other face.

Experimental

The ^{1}H and ^{13}C NMR spectra were recorded on a Nicolet NT-200 WB and a Varian VXR-400S. All spectra were taken in $CDCl_3$ using TMS as reference unless otherwise stated. The samples were spun in 5 mm o.d. tubes at ambient temperature, at concentrations of 5-10% w/v. Typical pulse widths were 3 μs (Nicolet) and 7 μs (Varian). The chemical shifts were measured on 8000 Hz (Nicolet) or 25000 Hz (Varian) sweep width spectra.

Acknowledgements

Stimulating discussions with Dr. J.A. Peters and Dr. A. Sinnema are gratefully acknowledged. We thank Diosynth B.V., Apeldoorn, The Netherlands

for the gift of chemicals. One of us (J.T.M.L.) wishes to express his gratitude to Diosynth B.V. for financial support.

References

*Part XXIX: See Ref. 14.

1. K.W. Bentley in "The Alkaloids", R.H.F. Manske (Ed.), Vol. XIII, Academic Press, London, New York, 1971, 75.
2. C.W. Hutchins, G.K. Cooper, S. Pürro and H. Rapoport, J. Med. Chem. **24**, 773 (1981).
3. P.R. Crabbendam, T.S. Lie, J.T.M. Linders and L. Maat, Recl. Trav. Chim. Pays-Bas **103**, 296 (1984).
4. L.L. Knipmeyer and H. Rapoport, J. Med. Chem. **28**, 461 (1985).
5. J.T.M. Linders, P. Briel, E. Fog, T.S. Lie and L. Maat, Accepted for publication in Recl. Trav. Chim. Pays-Bas.
6. For a discussion on the nomenclature of these adducts, see the foot-note in Ref. 3.
7. W. Fulmor, J.E. Lancaster, G.O. Morton, J.J. Brown, C.F. Howell, C.T. Nora and R.A. Hardy, J. Am. Chem. Soc. **89**, 3322 (1967).
8. F.I. Carroll, C.G. Moreland, G.A. Brine and J.A. Kepler, J. Org. Chem. **41**, 996 (1976).
9. B.C. Uff, A.S. Mallard, J.A. Davis and R. Henson, Magn. Res. Chem. **23**, 454 (1985).
10. L. Maat, J.A. Peters and M.A. Prazeres, Recl. Trav. Chim. Pays-Bas **104**, 208 (1985).
11. M.A. Prazeres, J.A. Peters, J.T.M. Linders and L. Maat, Recl. Trav. Chim. Pays-Bas **105**, 554 (1986).
12. J.T.M. Linders, R.J. Booth, T.S. Lie and L. Maat, Recl. Trav. Chim. Pays-Bas, in the press.
13. J.T.M. Linders, J.P. Kokje, M. Overhand, T.S. Lie and L. Maat, Recl. Trav. Chim. Pays-Bas **107**, 449 (1988).
14. J.T.M. Linders, P.J.L. Lipman, E. Saly, T.S. Lie and L. Maat, Bull. Soc. Chim. Belg., in the press.
15. S.L. Patt and J.N. Shoolery, J. Magn. Res. **46**, 535 (1982).
16. H.G. Theuns, R.H.A.M. Janssen, A.V.E. George, H.W.A. Biessels, J. Chem. Res (S) 122 (1985), J. Chem. Res. (M) 1461 (1985).
17. G.N. Maciel and H.C. Dorn, J. Am. Chem. Soc. **93**, 1268 (1971).
18. G.C. Levy and G.L. Nelson, J. Am. Chem. Soc. **94**, 4897 (1972).
19. E.L. Eliel, D. Kandasamy, C.-Y. Yen and K.D. Hargrave, J. Am. Chem. Soc. **102**, 3698 (1980).
20. H. Fritz and T. Winkler, Helv. Chim. Acta **59**, 903 (1976).
21. J. Llinares, R. Faure, E.J. Vincent and J. Elguero, Spectrosc. Lett. **14**, 423 (1981).
22. J.A. Glasel and H.W. Reiher, Magn. Res. Chem. **23**, 236 (1985).
23. E.L. Eliel, S. Morris-Natschke and V.M. Kolb, Org. Magn. Res. **22**, 258 (1984).
24. A.C. Ghosh, D.E. Portlock, H.C. Dalzell, C. Malmberg, P. Herlihy, R.K. Razdan, W.L. Duax and D.S. Smith, J. Org. Chem. **48**, 4137 (1983).
25. S.D. Kahn, C.F. Pau, L.E. Overman and W.J. Hehre, J. Am. Chem. Soc. **108**, 7381 (1986).
26. S.D. Kahn and W.J. Hehre, J. Am. Chem. Soc. **109**, 663 (1987).

CHAPTER 8 FACE SELECTIVITY OF THE DIELS-ALDER REACTION OF THEBAINE-LIKE MORPHINANDIENES, A COMPUTATIONAL APPROACH

Face selectivity of the Diels-Alder reaction of thebaine-like morphinandienes, a computational approach (Chemistry of opium alkaloids, Part XXXI)*

J.T.M. Linders and L. Maat

Laboratory of Organic Chemistry, Delft University of Technology, Julianalaan 136, 2628 BL, Delft, The Netherlands.

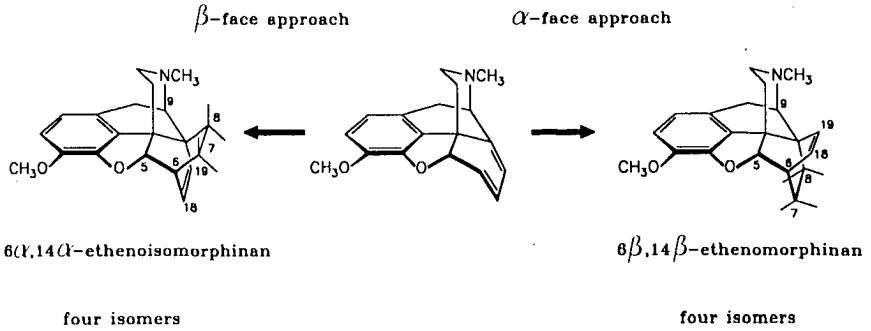
Abstract

Molecular mechanics (MMP2(85)) have been employed for the calculation of the geometry of morphinan-6,8-dienes.
The X-ray structure of desoxycodeine-A, a morphinan-5,7-diene, and of other morphinans were well-reproduced by the minimization program. The conformations of 4,5α-epoxymorphinan-6,8-dienes and their 4-hydroxy analogues show considerable differences, which account for the observed face selectivity in the Diels-Alder cycloaddition.

Introduction

About ten years ago, Duchamp wrote[1]: "Although most medicinal chemists use structure-activity relationships of various sorts in drug design, very few use quantitative three-dimensional structural information in designing potentially active molecules.". Nowadays, the picture has changed radically and computer graphics have become an indispensible tool in the search for new drugs[2-7]. The use of molecular calculations[6,8], in a more or less sophisticated fashion depending on the size of the systems studied, forms an important part of computer-aided drug design. With respect to molecules of the size of morphinans, application of molecular mechanics (MM)[9] is well-suited to obtain a reliable picture of the geometry. There are only a few examples of the application of molecular modelling techniques in the study of the course of chemical reactions[9].

Diels-Alder reaction of morphinan-6,8-dienes with mono-substituted ethenes can afford, in principle, eight isomeric adducts, namely four 6α,14α-ethenoisomorphinans and four 6β,14β-ethenomorphinans (Scheme 1). Reaction of thebaine or other 4,5α-epoxymorphinan-6,8-dienes with methyl vinyl ketone yields the 7α-acetyl 6α,14α-ethenoisomorphinan as almost the only product. When the epoxy bridge is opened, Diels-Alder reaction occurs at the other side, the α-face, to give the 7β-substituted 6β,14β-ethenomorphinans[10-12].



Scheme 1. The Diels-Alder reaction of morphinan-6,8-dienes, yielding 6α,14α-ethenoisomorphinans and 6β,14β-ethenomorphinans.

We discuss here these observations in a 'computational' way. First, we compare structures of some selected morphinans obtained by minimization using molecular mechanics {MMP2(85)} to X-ray structures, in order to get confidence in the procedures used. Then, minimized structures of different morphinan-6,8-dienes are studied and compared to each other, resulting in an explanation for the reversal of the stereoselectivity of the Diels-Alder reaction after opening of the 4,5α-epoxy bridge in thebaine and analogues[10,12].

Methodology

X-Ray structures were obtained either directly from the Cambridge Crystallographic Database[13] or by manual input of atomic coordinates via the keyboard. The starting geometries for the MM calculations were prepared

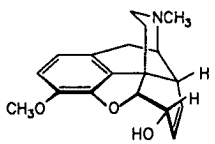
starting from the X-ray data, if necessary manipulated using the MODEL (version KS 2.92)[14] or CHEM-X[15] software. Minimizations were performed using the Allinger molecular mechanics program MMP2(85)[16], an improved version of MMP2, which treats conjugated π-systems by self-consistent field (SCF) calculation[16]. Molecular fittings were performed within the MODEL or CHEM-X suites, making use of the available least-square methods[17]. Structures were made visible on a Digital VT-100 Video Terminal with a Visual 550 keyboard. Hard copies were produced on a Anadex Silent Scribe DP-9500B Printer.
All calculations were performed on a VAX 11/785 computer, located at Nijmegen University.

Torsion angles τ(ABCD) are defined as the clockwise rotation of atom A to eclipse atom D while looking along the BC bond from B to C[18].

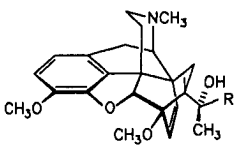
Results and discussion

Comparison with X-Ray Structures

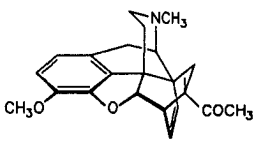
The structures of compounds **1-6** were minimized by MMP2(85) and, subsequently, compared to the published X-ray structures. For compound **2b** no X-ray data were available. Therefore, the structure of **2a**[19] was used, in which the propyl group is replaced by a methyl group.



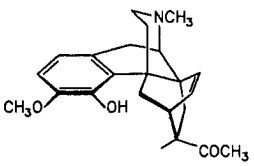
1 codeine



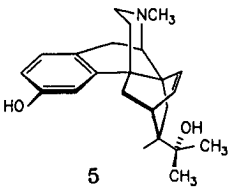
2a R = Pr
b R = Me



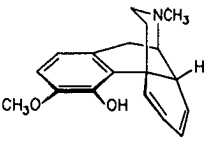
3



4



5



6

Average differences in bond lengths, valence and torsion angles are given in Table 1. Using the fit-option in MODEL, the calculated structures were matched with the X-ray structures. Average distances between matching atoms are given in Table 1. It is clear that the X-ray structures are well reproduced by the MM optimization. Although molecular mechanics generally consider isolated molecules (gas phase) only, comparison of the calculated structures with X-ray data, especially when limited to the skeleton atoms, seems to be justified. Only for the geometry of the pending groups, such as methoxyl, acetyl and dimethyl carbinol, are relatively large deviations found, especially in the torsion angles. These groups are rather sensitive to intermolecular interactions within the crystal.

Table 1. Comparison[a,b] of calculated and X-ray structures of the compounds 1-6. Values in parentheses are without pending acetyl or dimethyl carbinol group.

					all atoms		heavy atoms[c]		skeleton[d]	
Comp.	Ref.	rms Δl (Å)	rms $\Delta\theta$ (°)	rms $\Delta\tau$ (°)	δ (Å)	rms δ (Å)	δ (Å)	rms δ (Å)	δ (Å)	rms δ (Å)
1	20	0.020	1.6	1.8	0.15	0.21	0.15	0.17	0.03	0.04
2b	19	0.021	2.2	3.9 (3.3)	0.17	0.21	0.11	0.14	0.06	0.07
3	21	0.014	1.7	3.4 (2.7)	0.13	0.16	0.10	0.11	0.08	0.12
4	22	0.015	1.3	3.0 (2.0)	0.12	0.15	0.08	0.11	0.04	0.05
5	23	0.011	1.3	4.8 (4.3)	0.32	0.47	0.22	0.28	0.16	0.19
6	24	0.014	1.3	2.1	0.12	0.16	0.05	0.06	0.04	0.04

a) rms $\Delta x = [\sum_i (x_i^{X\text{-ray}} - x_i^{cal})^2/n]^{0.5}$, rms $\delta = [\sum_i \delta_i^2/n]^{0.5}$.

b) l = bond length, θ = valence angle, τ = torsion angle, δ = distance between matching atoms.

c) All atoms except hydrogen.

d) No pending groups taken into consideration.

In Fig. 1, the rotation around the C7 - C20 bond is given as a function of the torsion angle. The local minima for the three compounds are given in Table 2.

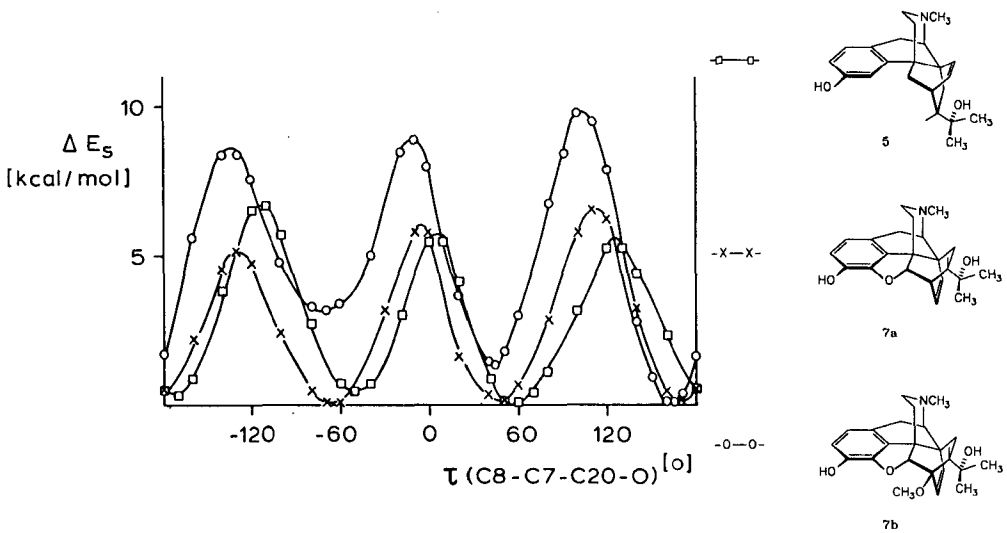


Fig. 1. Steric energy differences as a function of the rotation around the C7 - C20 bond ($\Delta E_s^{\tau} = E_s^{\tau} - E_s^{min}$).

Table 2. Local minima (τ(C8-C7-C20-O), °) and corresponding steric energy (E_s, kcal/mol) for the rotation of the dimethyl carbinol group in compounds **5**, **7a** and **7b**.

Compound	5		7a		7b	
Minimum	τ	E_s	τ	E_s	τ	E_s
1	59.2	41.53	48.6	50.28	41.4	58.81
2	-171.3	41.88	170.8	50.19	162.5	57.37
3	-49.7	41.98	-68.4	50.11	-69.8	60.44
X-ray	-54.5[a]		----		167.8[b]	

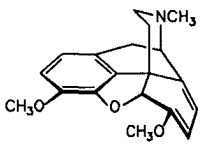
a) Ref. 23.
b) 3-*O*-Methyletorphine[19]

To perform the pertinent calculations, the dihedral driver option[25] was used. The torsion angle τ(C8-C7-C20-O) was set at a certain value and then the structure was minimized. As expected, the graphs show the presence of

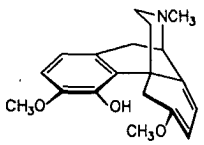
three minima. There are distinct barriers for the rotation around the C7 - C20 bond. The curve of the etorphine analogue **7b** is somewhat different from those of the 6-demethoxy compounds **5** and **7a**. Due to the steric hindrance exerted by the methoxyl group, the height of the rotational barriers is increased. Because of the formation of a hydrogen bond between the alcohol function in the lipophilic 'tail' and the 6-methoxyl group, there is additional stabilization at τ(C8-C7-C20-O) = 162.5°. This is in agreement with the value of 162° found by Loew and Berkowitz[26], who made use of PCILO calculations.

MM Calculations on morphinan-6,8-dienes

The conformation of the morphinan-6,8-dienes **8** and **9** has been calculated with MMP2(85). Some characteristic geometrical features are given in Table 3. For comparison, calculated structural data for the morphinan-5,7-diene **11** are also given, together with the corresponding values of desoxycodeine-A (**6**), taken from X-ray analysis[24]. It is clear that the geometry of the diene system in **6** is well-reproduced by the MM-calculations. The structures **8** and **9** are model systems for thebaine (**12**) and its 4-hydroxy analogue, β-dihydrothebaine (**13**). The 3-methoxyl group has been left out of the

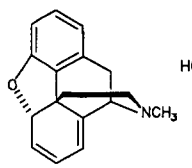


12

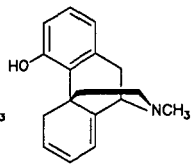


13

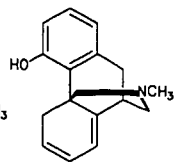
calculations, because it is expected that the effect on the overall structure and, consequently, the effect on the course of the Diels-Alder reaction will be small. The 6-methoxyl group has not been taken into consideration either. This group has a great influence on the course of the Diels-Alder reaction as has been shown earlier[11]. However, this influence is only important for the position of the substituent in the adduct, being 7 or 8, but is not critical for the choice between α-face or β-face approach.



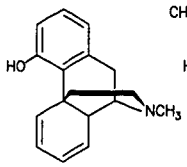
8



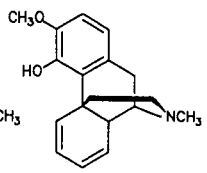
9



10



11



6

Table 3. Some selected geometrical features of morphinandienes 8-11, calculated with MMP2(85).

	8	9	10	11	6[a]
	bond lengths				
5- 6	1.510	1.502	1.503	1.348	1.313
6- 7	1.348	1.345	1.345	1.461	1.438
7- 8	1.461	1.459	1.459	1.347	1.334
8-14	1.345	1.351	1.349	1.510	1.504
14-13	1.496	1.514	1.511	1.540	1.533
13 -5	1.539	1.545	1.545	1.516	1.527
	valence angles				
5- 6- 7	124.1	120.3	121.2	119.6	119.8
6- 7- 8	122.2	119.1	119.6	118.5	120.3
7- 8-14	119.8	121.0	120.8	121.0	118.9
8-14-13	121.8	122.3	122.8	110.9	110.8
14-13- 5	119.6	107.6	109.5	106.2	106.1
13- 5- 6	111.8	113.5	113.9	121.7	121.6
	torsion angles				
5- 6- 7- 8	2.8	5.6	5.9	17.6	18.8
6- 7- 8-14	1.2	10.8	9.2	1.8	0.5
7- 8-14-13	0.4	4.8	4.4	-34.3	-37.4
8-14-13- 5	5.7	32.2	28.5	51.3	51.9
14-13- 5- 6	-8.6	-45.1	-39.3	40.3	37.2
13- 5- 6- 7	7.5	35.1	30.4	6.1	2.3
5αH- 5- 6- 7	-114.3	-87.7	88.9		
5βH- 5- 6- 7		165.0	158.8		
0- 5- 6- 7	128.2				
H15-15-13-14	71.5	68.0	66.3		
H15'-15-13-14	-171.5	-174.8	-177.0		
15-13-14- 8	-138.0	-149.5	-147.7		
12-13-14- 8	102.0	94.9	97.2		

a) X-ray, Ref. 24

This is evidenced by the fact that both β-dihydrothebaine (**13**) and its 6-demethoxy analogue afford only 6β,14β-ethenomorphinans when reacted with methyl vinyl ketone[10], while the two 4,5α-epoxy congeners yield the 6α,14α-etheno isomers as the major adduct[11].

It is noteworthy that the shape of the C-ring of the different morphinan-6,8-dienes changes rather dramatically upon opening of the 4,5α-epoxy bridge. In 4,5α-epoxy structure **8** the C-ring is essentially planar, all torsion angles being less than 10^0. When the epoxy bridge is opened, C-5 moves in upward direction, towards the piperidine ring. Consequently, H-5β undergoes also a significant displacement, becoming perpendicular to the diene system in compound **9** (Fig. 2). These changes in geometry may furnish the explanation for the observed reversal in the stereochemical course of the Diels-Alder reaction of methyl vinyl ketone with these two morphinan-6,8-diene systems.

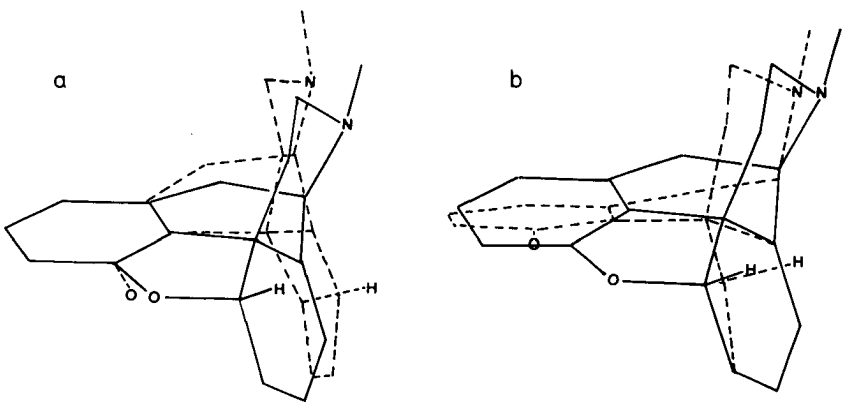
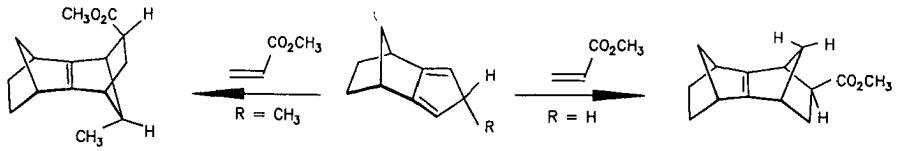


Fig. 2. Matching (H-5β indicated) of morphinan-6,8-dienes **8** (——) and **9** (---).
a. Aromatic carbons superimposed
b. Diene systems superimposed

The Diels-Alder reaction of morphinan-6,8-dienes can be compared with those of isodicyclopentadiene[27-28] (Scheme 2) and 5-alkyl-substituted cyclopentadienes[28]. Introduction of a methyl group on the 4-position in



Scheme 2. Diels-Alder reaction of isodicyclopentadienes with methyl acrylate.

isodicyclopentadiene reverses the course of the Diels-Alder reaction with methyl acrylate completely. Although several explanations[27-29] based on electronic factors have been proposed, Houk and coworkers have shown the cause being mainly steric in nature[27-28]. When these isodicyclopentadienes are matched with structure **9**, some similarity in spatial arrangement is apparent (Fig. 3).

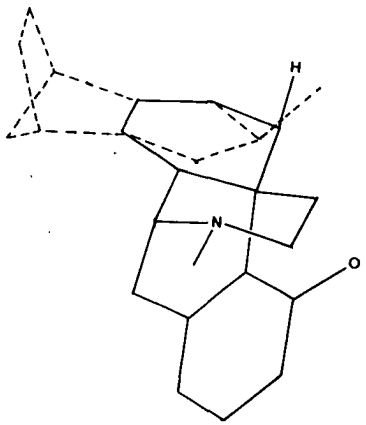


Fig. 3. Alignment of 4-methyl-isodicyclopentadiene with morphinan-6,8-diene **9** (H-5β indicated).

From this point of view it would be interesting to investigate the Diels-Alder reactions of the recently described 5β-alkylthebaines[30]. Possibly, the presence of the alkyl substituent at the β-face of the diene system will cause the Diels-Alder reaction to occur at the other face, giving access to 4,5α-epoxy-6β,14β-ethenomorphinans.

Recently, Hehre and Kahn proposed an explanation for the face selectivity in the Diels-Alder reaction which was based on electronic factors[31]. Lone pair bearing allylic substituents were shown to induce a higher electron density on the face of the diene system which is *syn*-positioned to the lone pair, and to make this face more reactive to Diels-Alder reactions with electron-deficient dienophiles. In structure **9**, the nitrogen atom could play such a role, being close to the β-face of the diene system. However, no 6α,14α-ethenoisomorphinans are formed upon reaction with methyl vinyl ketone[10,12], indicating that there is no activating effect from the nitrogen atom. The experimental results obtained with morphinan-6,8-dienes without the epoxy-bridge[12] support the idea that steric effects are crucial for the face selectivity of the Diels-Alder reactions of morphinan-6,8-dienes[11].

The Diels-Alder reactions of *N*-formylmorphinan-6,8-dienes and their *N*-methyl analogues with methyl vinyl ketone occur with the same face selectivity[11-12]. Therefore, we conclude that replacement of the *N*-methyl group by an *N*-formyl group does not change the conformation of the morphinandiene significantly. In Fig. 4. the structures of **8** and **9** are matched with their respective *N*-formyl analogues[32], showing that there is neither a notable change in the geometry of the diene system nor in the accessiblity for the dienophile.

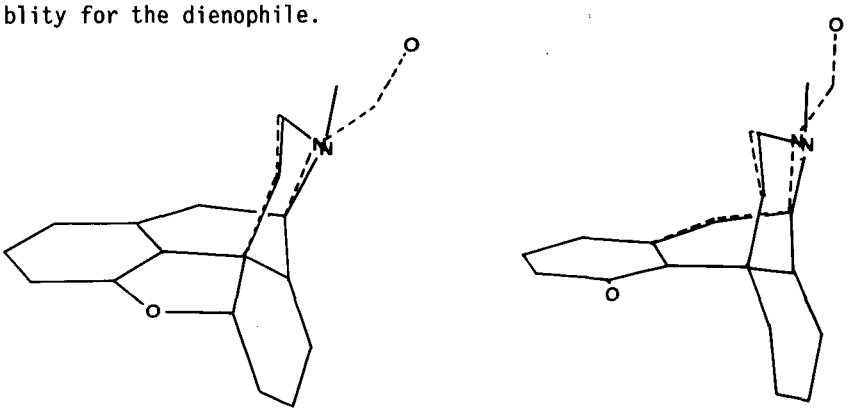


Fig. 4. Matching of morphinan-6,8-dienes **8** and **9** (——) with their *N*-formyl analogues (- - -).

In Table 3, the structural data of 16-aza-17-carbamorphinan-6,8-diene **10** are also given. This compound (with a 6-methoxyl group), synthesized by Wiesner and coworkers[33] in order to prepare etorphine analogues that have

the nitrogen atom in a different position, is reported to undergo Diels-Alder reaction with methyl vinyl ketone analogously to thebaine, giving the 6α,14α-etheno isomer. Based on the structural similarity of this diene **10** with morphinandiene **9** (Table 3, Fig.5), it is unlikely that the Diels-Alder reaction takes place at the β-face. This is supported by the fact that the vinylic protons are found at δ 6.24, *i.e.* in a position which is typical for 6β,14β-ethenomorphinans[10,34]. Thus, the structure assignment of the adduct seems to be incorrect.

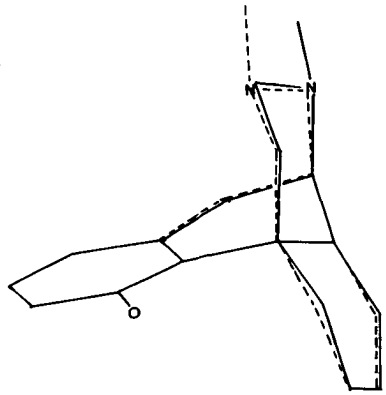


Fig. 5. Matching (aromatic carbons superimposed) of dienes **9** (——) and **10** (– – –).

Conclusions

Molecular mechanics have proven to be well-suited to reproduce X-ray structures of morphinans and, therefore, can be considered to give reliable structural information of compounds for which no X-ray data are available. Apart from its applications in drug design, molecular mechanics can give more insight into the course of chemical reactions.

The conformations of 4,5α-epoxymorphinan-6,8-dienes and their 4-hydroxy analogues, calculated by molecular mechanics, show considerable differences. The observed change in face selectivity in the Diels-Alder reaction of morphinan-6,8-dienes is caused primarily by the conformational differences.

Acknowledgements

Use of the services and facilities of the Dutch CAOS/CAMM Center, under grant numbers SON - 11-20-700 and STW - NC-44.0703, is gratefully acknowledged. We thank Dr. H. Borkent, Dr. H. Bruins-Slot and Dr. J.H. Noordik (CAOS/CAMM Center, University Nijmegen) for providing valuable information and advice in the calculations and the operation of the minimization programs. We are indebted to Dr. B. van de Graaf and Dr. J.M.A. Baas for stimulating discussions. One of us (J.T.M.L.) wishes to express his gratitude to Diosynth B.V., Apeldoorn, the Netherlands for financial support.

References

*Part XXX: see Ref. 34.

1. D.J. Duchamp in "Computer Assisted Drug Design", E.C. Olson and R.E. Christoffersen (Eds.), ACS Symp. Ser. 118, American Chemical Society, Washington DC, 1979, 79.
2. B.V. Cheney, D.J. Duchamp and R.E. Christoffersen in " Quantitative Structure-Activity Relationships of Analgesics, Narcotic Antagonists and Hallucinogens", G. Barnett, M. Trsic and R.E. Willette (Eds.), NIDA Research Monograph 22, National Institute on Drug Abuse, Washington DC, 1978, 218.
3. J.P. Tollenaere, H. Moereels and M. van Loon, Prog. Drug. Res. 30, 92 (1986).
4. J. Martin and P. Andrews, J. Comput.-Aided Mol. Design 1, 53 (1987).
5. R.P. Sheridan and R. Venkataraghavan, Acc. Chem. Res. 20, 322 (1987).
6. H. Frühbeis, R. Klein and H. Wallmeier, Angew. Chem. 99, 413 (1987).
7. K. Müller, H.J. Ammann, P.R. Gerber, K. Gubernator and G. Schrepfer, Bull. Soc. Chim. Belg. 97, 655 (1988).
8. R.W. Counts, J. Comput.-Aided Mol. Design 1, 177 (1987).
9. U. Burkert and N.L. Allinger, "Molecular Mechanics", ACS Monograph 177, American Chemical Society, Washington DC, 1982.
10a. J.T.M. Linders, J.P. Kokje, M. Overhand, T.S. Lie and L. Maat, Recl. Trav. Chim. Pays-Bas 107, 449 (1988).
10b. A.C. Ghosh, D.E. Portlock, H.C. Dalzell, C. Malmberg, P. Herlihy, R.K. Razdan, W.L. Duax and G.D. Smith, J. Org. Chem. 48, 4137 (1983).
11. J.T.M. Linders, P. Briel, E. Fog, T.S. Lie and L. Maat, accepted for publication in Recl. Trav. Chim. Pays-Bas.
12. J.T.M. Linders, P.J.L. Lipman, E. Saly, T.S. Lie and L. Maat, Bull. Soc. Chim. Belg., in the press.
13. F.H. Allen, S. Bellard, M.D. Brice, B.A. Cartwright, A. Doubleday, H. Higgs, T. Hummelink, B.G. Hummelink-Peters, O. Kennard, W.D.S. Motherwell, J.R. Rodgers and D.G. Watson, Acta Cryst. B35, 2331 (1979).
14. MODEL (Version KS 2.92) is a rewritten and improved version of the MODEL-software, as originally designed by W.C. Still.

15. Chem-X, developed and distributed by Chemical Design Ltd, Oxford, England.
16. MMP2(85) is an improved and enlarged version of MMP2; See J.T. Sprague, J.C. Tai, Y. Yuh and N.L. Allinger, J. Comput. Chem. **8**, 581 (1987) and references cited therein.
17. The algorithm used in MODEL and CHEM-X is based upon A.D. MacLachlan, Acta Cryst. **A28**, 656 (1972), W. Kabsch, Acta Cryst. **A32**, 922 (1976) and W. Kabsch, Acta Cryst. **A34**, 827 (1978). Similar methods are described by S.C. Nyburg, Acta Cryst. **B30**, 251 (1974) and E. Gavuzzo, S. Pagliuca, V. Pavel and C. Quagliata, Acta Cryst. **B28**, 1968 (1972).
18. W. Klyne and V. Prelog, Experientia **16**, 521 (1960).
19. J.H. van den Hende and N.R. Nelson, J. Am. Chem. Soc. **89**, 2910 (1967).
20. G. Kharta, F.R. Ahmed and W.H. Barnes, Acta Cryst. **15**, 326 (1962).
21. H. van Koningsveld, L. Maat and T.S. Lie, Acta Cryst. **C40**, 1082 (1984).
22. H. van Koningsveld, T.S. Lie and L. Maat, Acta Cryst. **C40**, 1963 (1984).
23. H. van Koningsveld, J.C. Jansen, M. Overhand, T.S. Lie and L. Maat, Acta Cryst. **C43**, 2384 (1987).
24. H. van Koningsveld, J.C. Jansen, T.S. Lie and L. Maat, Acta Cryst. C42, 103 (1986).
25. U. Burkert and N.L. Allinger, J. Comput. Chem. **3**, 40 (1982).
26. G.H. Loew and D.S. Berkowitz, J. Med. Chem. **22**, 603 (1979).
27. F.K. Brown and K.N. Houk, J. Am. Chem. Soc. **107**, 1971 (1985) and references cited therein.
28. F.K. Brown, K.N. Houk, D.J. Burnell and Z. Valenta, J. Org. Chem. **52**, 3050 (1987) and references cited therein.
29. W.H. Watson, "Stereochemistry and Reactivity of Systems Containing π Electrons", Verlag Chemie International, Deerfield Beach, FL, 1983.
30a. R.M. Boden, M. Gates, S.P. Ho and P. Sundararaman, J. Org. Chem. **47**, 1347 (1982).
30b. M. Gates, R.M. Boden and P. Sundararaman, J. Org. Chem. **54**, 972 (1989).
31. S.D. Kahn and W.J. Hehre, J. Am. Chem. Soc. **109**, 663 (1987).
32. Missing parameters for the calculations on the *N*-formyl systems were obtained from the work of J.P. Snyder: E.D. Thorsett, E.E. Harris, S.D. Aster, E.R. Peterson, J.P. Snyder, J.P. Springer, J. Hirshfield, E.W. Tristram, A.A. Patchett, E.H. Ulm and T.C. Vassil, J. Med. Chem. **29**, 251 (1986); J.P. Snyder, personal communication.
33a. K. Wiesner, J.G. McCluskey, J.K. Chung and V. Småla, Can. J. Chem. **49**, 1072 (1971).
33b. K. Wiesner, U.S. Pat. 3,819,636, June 25, 1969; Chem. Abstr. **81**, 120506p (1974).
34. J.T.M. Linders, M.A. Prazeres, T.S. Lie and L. Maat, submitted to Magn. Res. Chem.

CONCLUDING REMARKS

Morphine and related compounds have been the subject of intensive study and research for many years. The morphinan skeleton has been considered to be a constant. To a large extent the same can be said for the 7α-substituted 6α,14α-ethenoisomorphinans. The chemistry and pharmacological aspects of these adducts have been studied for over 50 years. However, the choice to study the 7α-adducts was premeditated by their availability, being the sole product of the Diels-Alder reaction of thebaine. There is no reason why 6,14-bridged morphinans with substituents in other positions would not show activity. Furthermore, it is unlikely that xenobiotic substances such as morphinans will have the ideal spatial arrangement of aromatic nucleus, nitrogen atom and (substituents on) ring C to fit onto some "pain-receptor" in the human body.

In the first chapter of this thesis, a goal was presented, namely the preparation of Diels-Alder adducts with an altered oxygen substituent pattern compared to etorphine. What has come out eventually is much broader. Apart from the possibility to prepare deoxygenated etorphine analogues, the Diels-Alder reactions of thebaine analogues with less oxygen substituents and the application of nitroethene gave an entry to 8-substituted 6α,14α-ethenoisomorphinans and to the novel series of 6β,14β-ethenomorphinans. Although the first pharmacological test results of the latter compounds may seem disappointing with respect to their analgesic potency, further research in this area seems to be appropriate. Replacement of the *N*-methyl group by an *N*-formyl had an unexpected large influence on the chemical reactivity of the morphinans, indicating that in a well-studied system as the morphinan skeleton, new reactions and reactivities still can be found. Finally, the use of molecular modeling techniques, not only for the study of structure-activity relationships and drug design but also as a tool in the study of the course of reactions, is important to mention.

SUMMARY

In this thesis the synthesis of new deoxygenated thebaine analogues, and their Diels-Alder reactions with methyl vinyl ketone and nitroethene are described.

In *Chapter 1*, a historical overview of the research on the Diels-Alder adducts of thebaine is given. Nomenclature systems and structure-activity relationships of etheno(iso)morphinans are discussed. The scope of this thesis is presented.

Chapter 2 starts with a systematic description of the Diels-Alder reaction of thebaine with different dienophiles. Cycloaddition of mono-substituted ethenes yields predominantly 7α-substituted 6α,14α-ethenoisomorphinans, together with small amounts of the 7β-isomer.

The Diels-Alder reaction of 6-demethoxythebaine with methyl vinyl ketone is studied and the major 7α-acetyl-6α,14α-ethenoisomorphinan has been converted into some deoxygenated etorphine analogues, which proved to be rather potent morphine-like analgesics. Removal of the 3-hydroxyl group led to a compound which was an active analgesic (180 x morphine) *in vivo*, but which proved to have only little *in vitro* activity.

In *Chapter 3* the zinc-mediated epoxy ring scission in thebaine and 6-demethoxythebaine is studied. Performing this reaction in aqueous alkali afforded the desired 4-hydroxy-morphinan-6,8-dienes in almost quantitative yield.

Diels-Alder reaction of 6-demethoxy-β-dihydrothebaine with methyl vinyl ketone gave a 2:1 mixture of the 7β-acetyl- and 8β-acetyl-6β,14β-ethenomorphinan (*Chapter 4*). The 7β-adduct was converted into a diprenorphine analogue, which surprisingly was found to be inactive. On the basis of molecular modelling some ideas for future research are forwarded.

In *Chapter 5* the application of nitroethene as dienophile is described. Because of the base-catalyzed polymerization of the dienophile, the morphinandienes had to be converted into the neutral *N*-formyl derivatives. Diels-Alder reaction of 6-demethoxy-*N*-formyl-*N*-northebaine yielded a 5:1:3

mixture of 8α-nitro-6α,14α–ethenoisomorphinan, its 7α-isomer and 8β-nitro-6β,14β-ethenomorphinan. The change in the course of the Diels-Alder reaction is due to the characteristic properties of nitroethene and steric effects. The results of the Diels-Alder reactions of 4-*O*-acetyl-6-demethoxy-*N*-formyl-β-dihydro-*N*-northebaine supported these conclusions.

In *Chapter 6* an alternative route for the preparation of 6-demethoxy-*N*-formyl-*N*-northebaine is presented. The formation of an unexpected [*d,f*]-dibenzazonine was observed, the structure of which was elucidated by single-crystal X-ray analysis. A mechanism for its formation by acid catalyzed rearrangement of the morphinan-6,8-diene is proposed.

The ^{1}H and ^{13}C NMR spectra of *N*-formylmorphinans are studied in *Chapter 7*. Emphasis is put on the comparison with *N*-methyl and *N*-H analogues. A detailed study of the ^{1}H NMR spectra of 6α,14α-ethenoisomorphinans and 6β,14β-ethenomorphinans disclosed an important anisotropy effect of the nitrogen atom on the position of the vinylic protons, providing the possibility of a convenient structure elucidation of the adducts.

In the final chapter the results of molecular mechanics calculations are presented. Comparison of the molecular structure of morphinandienes with and without the 4,5α-epoxy bridge showed important conformational differences, which may be the cause of the changed course of the Diels-Alder reaction.

SAMENVATTING

In dit proefschrift worden de synthese en de Diels-Alder-reacties van nieuwe thebaine-analogen met minder zuurstofhoudende substituenten beschreven.

In *Hoofdstuk 1* wordt een historisch overzicht van het onderzoek van de Diels-Alder-adducten van thebaine gegeven. Nomenclatuursystemen en structuur-activiteits-relaties van etheno(iso)morfinanen worden beschouwd. Een overzicht van de inhoud van dit proefschrift wordt gegeven.

Hoofdstuk 2 begint met een systematische beschrijving van de Diels-Alder-reactie van thebaine met verschillende dienofielen. Cycloadditie van monogesubstitueerde ethenen geeft voornamelijk 7α-gesubstitueerde 6α,14α-ethenoisomorfinanen, samen met kleine hoeveelheden van het 7β-isomer. De Diels-Alder-reactie van 6-demethoxythebaine met methylvinylketon is onderzocht en het hoofdproduct, het 7α-acetyl-6α,14α-ethenoisomorfinan, werd omgezet in een aantal gedeoxygeneerde etorfine-analoga, die sterke, morfine-achtige, analgetische activiteit bleken te hebben. Verwijdering van de 3-hydroxylgroep gaf een verbinding die *in vivo* sterke analgetische activiteit bleek te hebben (180x morfine), maar slechts geringe *in vitro*-activiteit.

In *Hoofdstuk 3* wordt de opening van de 4,5α-epoxyring onder invloed van zink behandeld. Wanneer deze reactie werd uitgevoerd in waterige loog, konden de gewenste 4-hydroxy-morfinan-6,8-diënen in bijna kwantitatieve opbrengst worden verkregen.

Diels-Alder-reactie van 6-demethoxy-β-dihydrothebaine met methylvinylketon gaf een 2:1 mengsel van het 7β-acetyl- en het 8β-acetyl-6β,14β-ethenomorfinan (*Hoofdstuk 4*). Het 7β-adduct werd omgezet in een diprenorfine-analoog, dat echter inactief bleek te zijn. Op basis van "molecular modeling"-resultaten worden enkele ideeën voor toekomstig onderzoek geopperd.

In *Hoofdstuk 5* wordt de toepassing van nitroetheen als dienofiel beschreven. Vanwege de eigenschap van het dienofiel om te polymeriseren in de aanwezigheid van base, moesten de morfinandienen worden omgezet in de

neutrale *N*-formylderivaten. Diels-Alder-reactie van 6-demethoxy-*N*-formyl-*N*-northebaine gaf een 5:3:1 mengsel van het 8α-nitro-6α,14α-ethenoisomorfinan, het 7α-isomeer en het 8β-nitro-6β,14β-ethenomorfinan. De verandering in het verloop van Diels-Alder-reactie kan worden verklaard aan de hand van de eigenschappen van nitroetheen en sterische effecten. De resultaten van Diels-Alder-reacties van 4-*O*-acetyl-6-demethoxy-*N*-formyl-β-dihydro-*N*-northebaine ondersteunden deze conclusies.

In *Hoofdstuk 6* wordt een alternatieve route voor de bereiding van 6-demethoxy-*N*-formyl-*N*-northebaine gepresenteerd. De vorming van een onverwacht [*d,f*]-dibenzazonine werd waargenomen. De structuur werd bewezen met röntgendiffractie. Een mechanisme voor de vorming door zuur-gekatalyseerde omlegging van het morfinan-6,8-dieen wordt voorgesteld.

De ^{1}H en ^{13}C NMR-spectra van *N*-formylmorfinanen worden beschreven in *Hoofdstuk 7*. De nadruk wordt gelegd op de vergelijking met de *N*-Me en *N*-H-derivaten. Een uitgebreide studie van de ^{1}H NMR-spectra van 6α,14α-ethenoisomorfinan en 6β,14β-ethenomorfinanen toonde een belangrijke anisotropie-effect van het stikstofatoom op de vinylprotonen, wat een handige mogelijkheid gaf voor de structuuropheldering van de adducten.

In het laatste hoofdstuk worden de resulaten van moleculaire mechanica berekeningen gepresenteerd. Vergelijking van de moleculaire structuur van morfinandiënen met en zonder 4,5α-epoxyring toonde belangrijke conformationele verschillen, die verantwoordelijk kunnen zijn voor het andere verloop van de Diels-Alder-reactie.

DANKWOORD

Aan het eind van dit proefschrift zou ik van de gelegenheid gebruik willen maken om enkele woorden van dank uit te spreken. Hoewel op het titelblad slechts mijn naam staat, zou het werk, beschreven in de daarop volgende pagina's, niet tot stand zijn gekomen zonder de steun van een groot aantal collega's, vrienden en bekenden. Deels was die hulp direct tastbaar en heeft zijn neerslag gevonden in de verschillende publicaties. Een ander deel kan niet nauwkeurig omschreven worden. Het was de steun die veelal onbewust werd gegeven: een gewillig oor, soms tot diep in de nacht, adviezen, discussies, kortom het waren de praatpalen die iedereen af en toe wel nodig heeft.

Een aantal mensen zou ik apart willen noemen. Op de eerste plaats zijn daar Leen Maat en Tom Kieboom, die als toegevoegd promotor en promotor het werk hebben begeleid. Leen Maat nam de dagelijkse begeleiding op zich en sleepte mij door elk dieptepunt heen naar de afronding van een volgende publicatie. Tom Kieboom kwam pas de laatste anderhalf jaar als promotor in mijn gezichtsveld, maar hij heeft in die korte tijd een niet te onderschatten katalytisch effect gehad op het gereedkomen van dit proefschrift. Joop Lie ben ik dankbaar voor zijn aanwijzingen op preparatief gebied én voor het omdraaien van de zinsvolgorde in vele publicaties, zodat alles de nadruk kreeg die het verdiende. In dit verband zou ik ook Dr. Jim P. Ward willen bedanken, die alle publicaties en hoofdstuk 1 heeft doorgelezen en waar nodig de hollandicismes heeft "verengelst". Dr. H.A.P de Jongh, Dr. P. Vrijhof en Dr. A. Sanders (Diosynth, AKZO) ben ik zeer erkentelijk voor hun inspanningen op het organisatorische vlak.

Vele HLO- en IAESTE-stagiair(e)s ben ik tegengekomen in deze tijd; twee van hen wil ik noemen: Mark Overhand, die voor zijn bijdrage (hoofdstuk 4.1) de Gouden Spatel kreeg en John Booth, die grotendeels verantwoordelijk was voor het ontstaan van hoofdstuk 6, hoewel hij jammer genoeg al weer terug in Engeland was toen ik de laatste cruciale experimenten uitvoerde. Met veel plezier denk ik terug aan de discussies met Joop Peters en Anton Sinnema over de vele NMR-spectra en die met Bas van de Graaf en Jan Baas op MS-gebied. Hun inspanningen zouden echter veel van hun waarde hebben

verloren, als ik niet eerst de zuiverheid van de verbindingen had kunnen bepalen met HPLC, daarbij gebruik makend van een min of meer exotisch eluens, uitgedacht door Fred van Rantwijk of Eckhard Sedlick.

De drie steunpilaren van de afdeling mogen natuurlijk niet ontbreken in deze opsomming: Mieke van der Kooij voor het type-werk, Wim Jongeleen voor de tekeningen én voor zijn adviezen toen ik met "whimsical" WIMP aan de slag ging en Ernst Wurtz, zonder wie de kabouters echt alles zouden moeten opknappen.

Chris van Drongelen en Bert van der Hulst ben ik dankbaar voor hun vriendschap en voor de ondersteuning in de vorm van liters koffie en de ochtendkrant. Tenslotte zou ik Maria Prazeres willen bedanken voor haar steun en voortdurende interesse in het verloop van mijn onderzoek en voor de inspirerende discussies, zowel per brief als per telefoon.

CURRICULUM VITAE

Joannes (Jan) Theodorus Maria Linders werd op 19 oktober 1960 geboren te Roosendaal. Na het eindexamen gymnasium-β aan het Gertrudis lyceum te Roosendaal, begon hij in september 1979 met de studie Scheikundige Technologie aan de Technische Hogeschool Delft. Het ingenieursexamen werd afgelegd op 29 januari 1985. Het afstudeeronderzoek, onder leiding van dr. L. Maat, werd begonnen onder Prof. H.C. Beyerman en werd formeel afgesloten bij Prof. H. van Bekkum. Het was de grondslag voor het promotie-onderzoek, waarvan het resultaat nu voor u ligt.

STELLINGEN

1. Tolstikov *et al.* zien over het hoofd dat de door hen beschreven retro-Diels-Alder-reacties gevolgd moeten worden door dehydrogenering (oxidatief of door disproportionering) om tot de gevonden eindproducten te komen.

   G.A. Tolstikov *et al.*, J. Org. Chem. USSR 20, 313 (1984).
   G.A. Tolstikov *et al.*, Tetrahedron 42, 591 (1986).

2. Het aantal mogelijke isomere Diels-Alder-adducten van thebaine met *cis*- of *trans*-1,2-digesubstitueerde ethenen is vier en niet twee zoals Rubinstein *et al.* beweren.

   R. Rubinstein *et al.*, Tetrahedron 30, 1201 (1974).

3. Michel *et al.* nemen ten onrechte aan dat in de farmacologisch actieve conformatie van etorfine en analoge verbindingen de hydroxylgroep in het lipofiele stuk een intramoleculaire waterstofbrug vormt naar de 6-methoxylgroep.

   J. DiMaio *et al.*, J. Med. Chem. 29, 1658 (1986).
   A. Michel *et al.*, Can. J. Chem. 66, 2498 (1988).

4. Er is weinig reden om aan te nemen dat de conformatie van leucine-enkefaline in kristal iets gemeen heeft met de conformatie in oplossing, laat staan met de farmacologisch actieve conformatie op de receptor.

   A. Aubry *et al.*, J. Chem. Soc., Chem. Commun. 963 (1988).

5. De methode van Donaldson om de geschiktheid van MMX voor het verkrijgen van betrouwbare geometrische informatie van colchicine te testen aan de hand van berekeningen aan de farmacologisch inactieve, maar even ingewikkelde, verbinding isocolchicine is weinig overtuigend.

   W.A. Donaldson, Tetrahedron 44, 7409 (1988).

6. Hehre en Kahn houden bij het toepassen van hun "Reactivity Model" op ingewikkelde verbindingen onvoldoende rekening met sterische effecten.

   S.D. Kahn and W.J. Hehre, J. Am. Chem. Soc. 109, 663 (1987).
   Dit proefschrift, hoofdstuk 5.

7. Dat etorfine na ozonolyse van de aromaatkern nog ongeveer de activiteit van morfine bezit, kan veroorzaakt worden door een geringe hoeveelheid onomgezet etorfine (activiteit 1000 x morfine) in het eindproduct.

   K.W. Bentley *et al.*, J. Chem. Soc. (C) 2385 (1969).

8. Het is onwaarschijnlijk dat de Diels-Alder-reactie van een 16-aza-17-carbamorphinan-6,8-dieen zonder 4,5α-epoxybrug een 6α,14α-ethenoverbinding zou opleveren.

K. Wiesner *et al.*, Can. J. Chem. 49, 1092 (1971).

Dit proefschrift, hoofdstuk 8.

9. Het organiseren van damesschaaktoernooien is een vorm van positieve discriminatie met negatieve gevolgen. Correspondentieschaaktoernooien alleen voor dames zijn het toppunt van rolbevestiging.

10. Als Carl Djerassi gelijk heeft met zijn stelling "Chemists are never poets", wat moet de wetenschappelijke wereld dan denken van zijn gedichten en die van Roald Hoffmann. Hopelijk is van toepassing: "Violations. There are some!", en niet: "Violations. There are none!".

C. Djerassi in "Natural Products and Drug Development", P. Krogsgaard-Larsen, S. Brøgger Christensen and H. Kofod (Eds.), Munksgaard, Copenhagen, 1984, p. 548

R. Hoffmann, "The Metamict State", University of Central Florida Press, Orlando, 1987.

R.B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry", Verlag Chemie, Weinheim, 1970.

11. Gezien recente publicaties over de aantoonbaarheid van opiaten in urine na de consumptie van maanzaadproducten, zullen sportlieden voortaan ook voorzichtig moeten zijn met het gebruik van dit soort voedsel.

R. Struempfler, J. Anal. Toxicol. 11, 97 (1987).

A.M. Zebelman *et al.*, J. Anal. Toxicol. 11, 131 (1987).

L.W. Hayes *et al.*, Clin. Chem. 33, 806 (1987).

B.C. Pettitt *et al.*, Clin. Chem. 33, 1251 (1987).

12. Het gebruik van de aanduidingen $^{32}O_2$ en $^{36}O_2$ voor de moleculen dizuurstof-16 en -18 is onzinnig. Het gebruik van deze aanduidingen naast $^{16}O_2$ en $^{18}O_2$ in één publicatie is op zijn minst niet consequent.

N.A. Porter and J.S. Wujek, J. Am. Chem. Soc. 52, 5085 (1987).

13. De kans dat U deze laatste stelling als eerste leest is minstens (100/13)%, en waarschijnlijk groter dan 50%.

J.T.M. Linders, 12 juni 1989