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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***)

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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.

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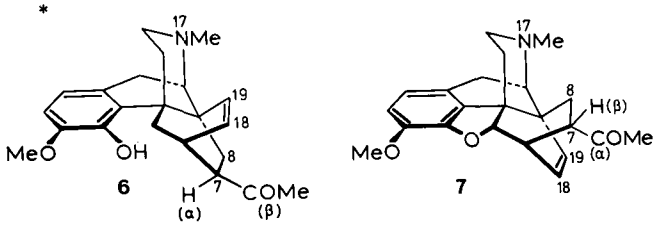

(an ethenomorphinan) (an ethenoisomorphinan)
Locant numbers 18 and 19 according to Chemical Abstracts.

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.

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*** 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"*.

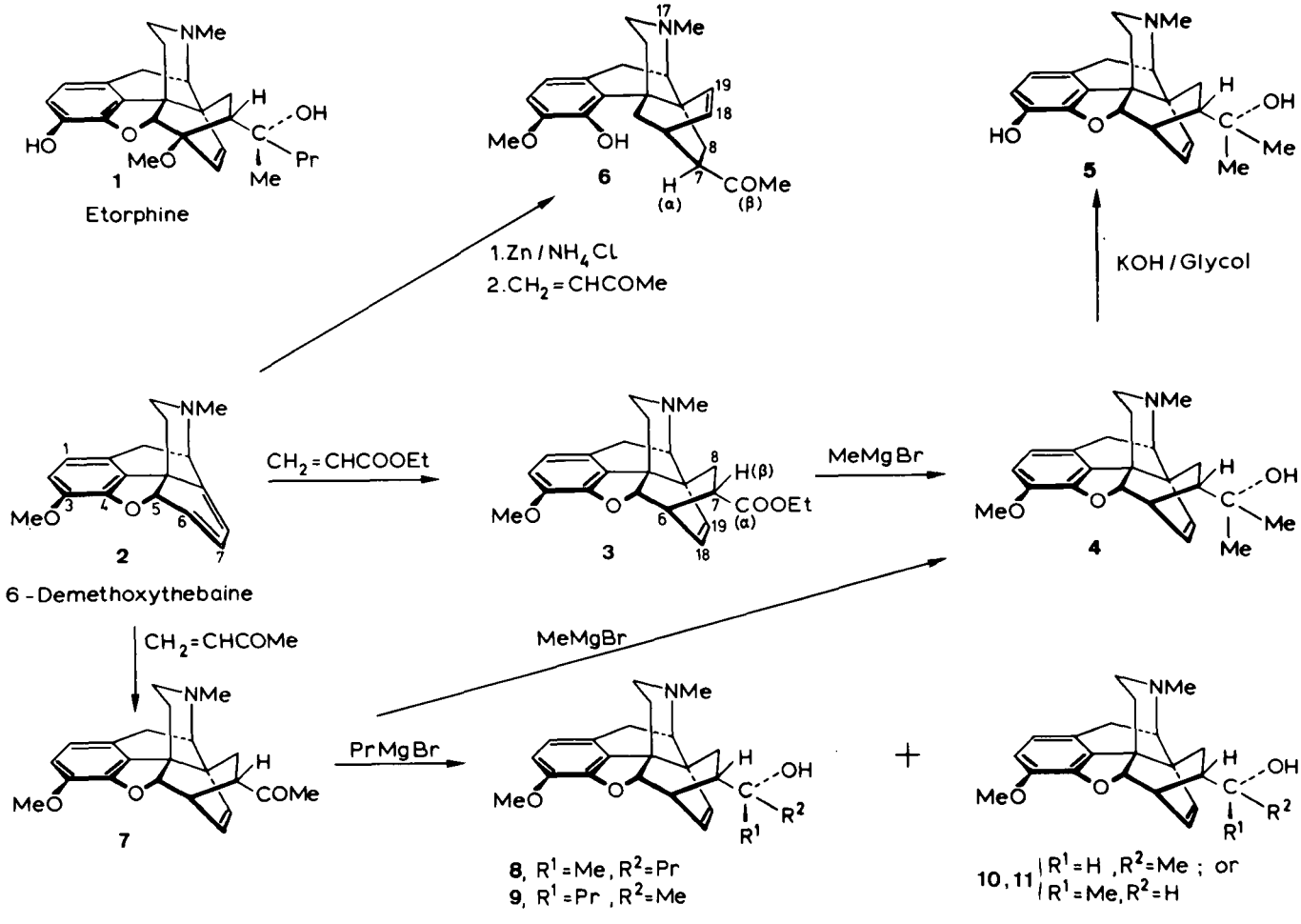
Results and discussion

(−)-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 I). 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".

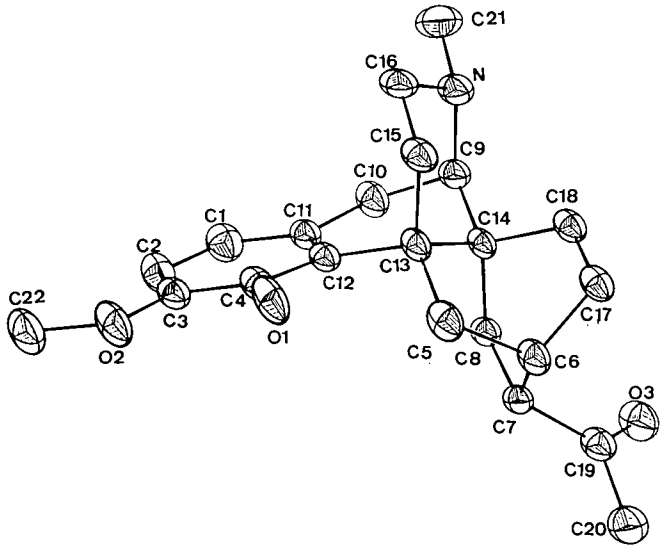


Fig. 1. ORTEP drawing of the structure of (+)-7β-*acetyl-4-hydroxy-3-methoxy*-N-*methyl-6,14-ethenomorphinan* (**6**).

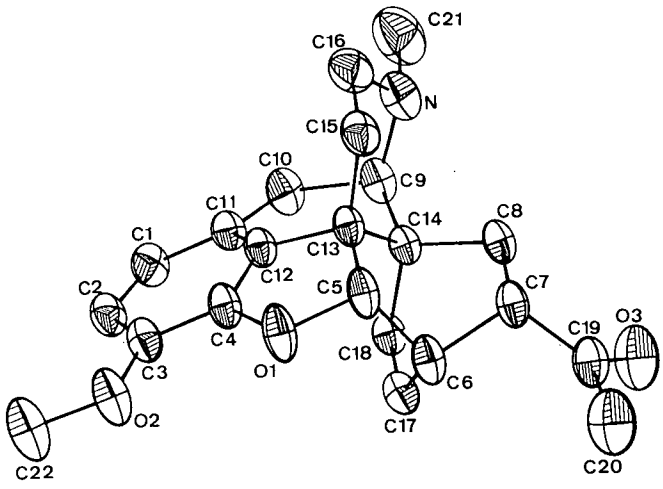


Fig. 2. ORTEP drawing of the structure of (−)-7α-*acetyl-4,5α-epoxy-3-methoxy*-N-*methyl-6,14-ethenoisomorphinan* (**7**).

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].

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[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 I 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).

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Dutch Ph. D. Theses

copies of the theses may be available at the supervisor's address

REDUCTIONS WITH A REGENERABLE POLYMER-BOUND NADH MODEL. September 7, 1984

Berend Eling

Supervisors: Prof.Dr. G. Challa, Laboratory of Polymer Chemistry, State University Groningen, and Prof.Dr. U.K. Pandit, Organic Chemistry Laboratory, University of Amsterdam.

This thesis describes the development of a polymer-bound nicotinamide reagent which can be used several times in the reduction of different activated substrates. Because both the reaction between the substrate and the dihydropyridine and the regeneration step proceed adequately in polar solvents, polar gel-type resins or macroreticular resins had to be chosen. For practical reasons, a macroreticular polystyrene network was selected. Since the stability of the nicotinamide system is sensitive to species of electrophilic and nucleophilic origin, the reutilization of the polymer-bound reagent was strongly dependent on the reaction conditions (e.g. medium, substrate and temperature). The highest recovery per cycle (98%) was observed for the pyridine-2-carbaldehyde/immobilized dihydronicotinamide system. A valuable spin-off of this study was the insight gained in the mechanism of metal ion catalysis in non-enzymatic reductions by 1,4-dihydronicotinamides. The concepts developed are applicable to the mechanism of action of those NADH-mediated dehydrogenases which have an essential metal ion requirement.

Thesis written in English.

DETECTION AND SIGNAL EVALUATION IN CAPILLARY ISOTACHOPHORESIS, 18 September 1984.

J.C. REIJENGA.

Supervisors: Prof.Dr.Ir. F.M. Everaerts and Prof. Dr.Ir. C.A. Cramers, Laboratory of Instrumental Analysis, University of Technology, Eindhoven.

Capillary isotachophoresis (ITP) is now regarded as a useful analytical technique for the determination of all kinds of ionic species, ranging from heavy metals and halogenides to carboxylic acids, nucleotides and proteins.
A general introduction is followed by chapters summarizing steady-state properties, detection methods and signal evaluation.
The last chapter consists of a number of publications on aspects of detection; the effect of electro-osmosis on detection; closed systems for buffer preparation and analysis; domain transform technique for processing the conductivity detector signal; UV-absorption detection at 206 nm; the introduction of dual-wavelength UV-absorption detection and fluorescence emission and fluorescence quenching as detection methods in ITP.
Applications of ITP presented include: the determination of anions in wines, bile acid conjugates in human bile, the binding of theophylline to human serum proteins and quinine in beverages, pharmaceuticals and human urine, after the consumption of tonic.

Thesis written in English.