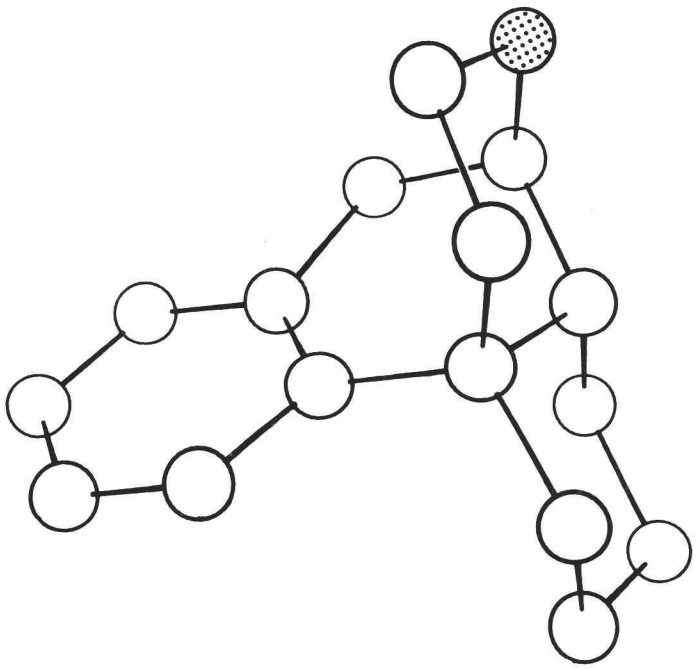
Synthetic Investigations on Morphinans

C. Olieman



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PROEFSCHRIFT ter verkrijging van
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en Dr. Ir. L. MAAT.

On the front cover an ORTEP drawing
of the morphinan molecule.

I am most grateful to the Delfts Hogeschool Fonds
for a fellowship in 1974 and 1975.

Drawings: Mr. J.M. Dijksman
Typing : Mrs. M.A.A. van der Kooij-van Leeuwen

Contents

1. Introduction

Morphinan is the name of a tetracyclic system, containing one nitrogen atom (Fig. 1). Compounds derived from the morphinan enantiomer, depicted in Fig. 1, occur in alkaloids of *Papaver* species. Alkaloids containing the derivatives of the optical antipode of morphinan are also found, *e.g.* in *Sinomenium acutum* Rehd. and Wils..

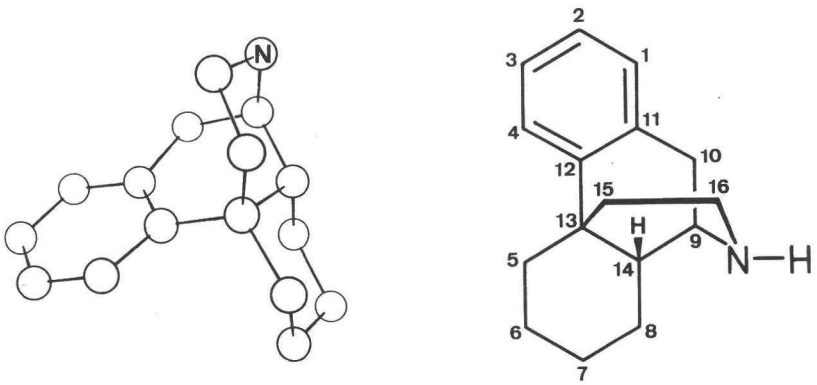


Fig. 1. Morphinan

The sun-dried latex of the unripe capsules of *Papaver somniferum* L. is opium. It contains morphine (3-25%), codeine (0.5-4%), and thebaine as the major morphinan alkaloids (Fig. 2). Morphine is used in medicinal practice as a strong, narcotic analgesic (centrally acting). Codeine, which is mostly obtained by methylation

of the 3-hydroxyl substituent present in morphine, is used as an anti-tussive. However, part of the opium is sold illegally. Morphine is extracted from this opium and most of it is acetylated to give heroin. Morphine and the more strongly addictive heroin are sold to addicts.

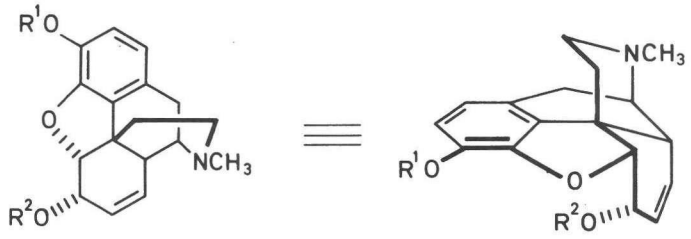
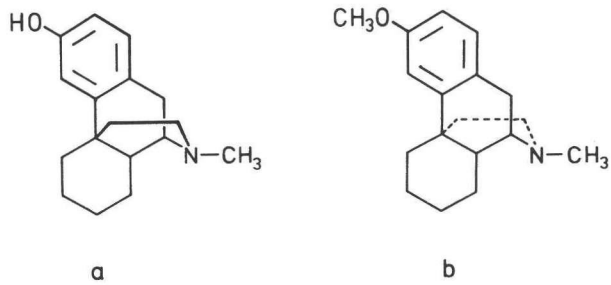


Fig. 2. Morphine ($R^1 = R^2 = H$), Codeine ($R^1 = CH_3$, $R^2 = H$), Heroin ($R^1 = R^2 = CH_3CO$).

Prohibition of the cultivation of *Papaver somniferum* L. prevents illegal use of opium, but deprives patients of morphine, codeine and derivatives. Alternative medicines, *e.g.* the synthetic morphinans levorphanol and dextrometorphan (Fig. 3), are used on a limited scale only. Therefore a synthesis of morphine and codeine, feasible on an industrial scale, should be available. Moreover, the availability of an industrial synthesis sets an upper limit for the price of the raw material, from which morphine and codeine are extracted. In addition to the production of codeine and morphine, a total synthesis might give access to analogues, which are difficult or impossible to obtain from natural sources and which might possess interesting pharmacological properties.

Several total syntheses of codeine and morphine are known[1-5], but the number of reaction steps is too great or the reactions for producing codeine and morphine industrially proceed with too low yields.



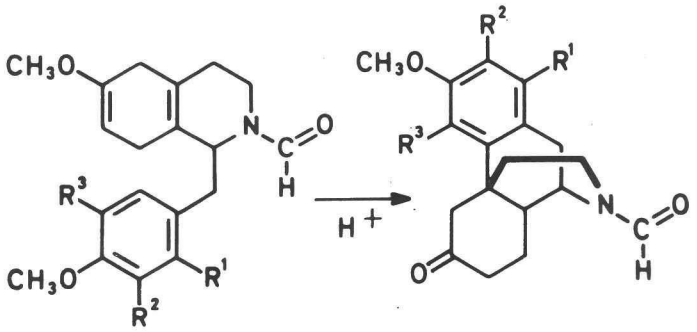
a b

Fig. 3. Synthetic Morphinans: a, Levorphanol; b, Dextrometorphan.

The acid-catalysed ring closure of various 1-benzyl-1,2,3,4,5,8--hexahydroisoquinolines has been investigated at the Laboratory of Organic Chemistry of the Delft University of Technology, leading to a rational synthesis of codeine and morphine.

The ring closure of (-)-2-formyl-1,2,3,4,5,8-hexahydro-1-(5--hydroxy-4-methoxy-2-methylbenzyl)-6-methoxyisoquinoline (**1**, Fig. 4) gave a high yield of (-)-*N*-formyl-1-methylnordihydrothebainone (**2**)[6]. The methyl group in **1** blocked the reactive 2'-position, so that morphinan **2** was formed, which had the hydroxyl group in the desired 4-position. The use of a removable bromine atom as a protecting group has been suggested in a patent of Merck Inc.[7]. The Delft group and others[8] could not repeat the procedure described in this patent.

Another strategy was developed in Delft[4] and independently, but unsuccessfully, by *DeGraw et al.*[8]. The starting material was a 1-benzylhexahydroisoquinoline, which was substituted symmetrically in the benzyl radical, in consequence the 2'- and the 6'-positions are identical. Ring closure of (-)-1-(3,5-dihydroxy-4-methoxy-benzyl)-2-formyl-1,2,3,4,5,8-hexahydro-6-methoxyisoquinoline (**3**) gave exclusively (-)-*N*-formyl-2-hydroxynordihydrothebainone (**4**). The corresponding *N*-methyl compound of **3** could also be cyclized in an analogous way[5]. In both morphinans the hydroxyl group in the 2-position could be removed selectively[9].



1, 3 **2, 4**

Fig. 4. **1, 2**: $R^1 = CH_3$, $R^2 = H$, $R^3 = OH$
3, 4: $R^1 = H$, $R^2 = R^3 = OH$

In this thesis synthetic and related analytical investigations are discussed, which are connected with the total synthesis of codeine and other substituted morphinans *via* the acid-catalysed cyclization of substituted 1-benzylisoquinolines. No details of the different objectives are given here. All the investigations, described in this thesis, have been published or are being printed. These publications are the Chapters 2 up to and inclusive 9, each with an introduction and an objective.

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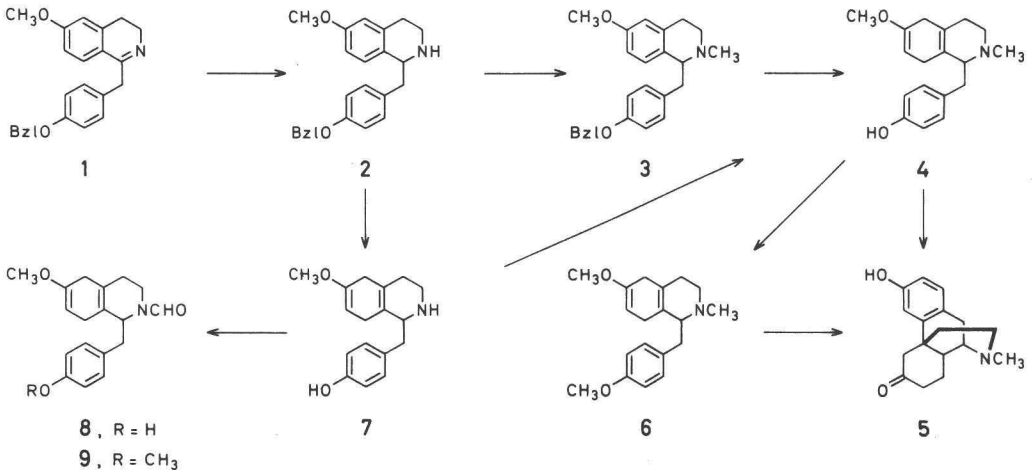
2. Synthesis of 3-Hydroxy-*N*-methyl-6-oxomorphinan*

Introduction

3-Hydroxy-*N*-methyl-6-oxomorphinan (Scheme, **5**) may be of use as an intermediate in syntheses of narcotic analgesics. Elimination of the 6-oxo substituent of (-)-**5** yields levorphanol[1], which is used as a synthetic analgesic. Introduction of an oxygen bridge between C4 and C5 in (-)-**5** should give access to morphine and derivatives. An unsuccessful attempt was made to form the oxygen bridge *via* introduction of an hydroxyl group at C4, with C2 protected by bromine substitution. In this case an unexpected 2,4-shift of the bromine atom was observed[2].

(-)-3-Hydroxy-*N*-methyl-6-oxomorphinan (**5**) was initially obtained from (-)-dihydrothebainone[2], which in turn had been prepared from natural material. A total synthesis of **5** has been described by Maeda *et al.*[3]; the octahydroisoquinoline obtained from 3-hydroxymethyl-4-methylpyridine was cyclised using phosphoric acid. The overall yield of this seventeen-step synthesis was low. We report herein a much shorter synthesis of racemic **4** *via* a Bischler-Napieralski cyclization of *N*-(3-methoxyphenylethyl)-4-benzyloxyphenylacetamide to **1**. Racemic **5** was obtained from **4** by cyclisation using Maeda's method[3].

* C. Olieman, Ph. Nagelhout, A.D. de Groot, L. Maat, and H.C. Beyerman, Recl. Trav. Chim. Pays-Bas 99 (1980), in the press.



Scheme 1. Synthesis of 3-hydroxy-*N*-methyl-6-oxomorphinan (**4**).

Results and Discussions

The syntheses of the 1,2,3,4,5,8-hexahydroisoquinolines **4** and **8** are similar to those described for other 1-benzylhexahydroisoquinolines[4,5]. Compound **4** was also prepared *via* **7** by reductive *N*--methylation using formaldehyde and sodium cyanoborohydride. As the experiment of Maeda shows that the 4-methoxybenzyl compounds give reasonable results, **4** and **8** were methylated to **6** and **9**, respectively. The cyclization of the *N*-methylisoquinolines **4** and **6**, and of the *N*-formylisoquinolines **8** and **9**, was attempted using orthophosphoric acid (85% and 100%), polyphosphoric acid, and sulfuric acid (80% and 96%) in the range of 20-140 ^{o}C.

The reaction mixtures were analysed by HPLC for **5** and/or its *O*-methylated derivative; **5** was detected only for cyclization of **4** and **6** in orthophosphoric acid (85%) at 140 ^{o}C. It is noteworthy that formation of the morphinan skeleton is dependent on the substitution pattern. *N*-Acyl-1-(4-hydroxybenzyl)-1,2,3,4,5,6,7,8--octahydroisoquinoline can be converted smoothly into levorphanol[6]. The corresponding 6-methoxy compound needs drastic conditions and gives **5** in a moderate yield. Activation of the benzylic moiety at position 3 by an hydroxyl group gives smoothly the morphinan derivative.

In acidic solution the enol ether in **6** is hydrolyzed to the compound used by Maeda *et al.* for acid-catalysed ring closure. In this case concomitant demethylation of the aromatic methoxy group of **6** occurs. Cyclization of **4** gave fewer by-products than cyclization of **6**. Racemic 3-hydroxy-*N*-methyl-6-oxomorphinan (**5**) was obtained and found to be identical with (-)-**5** prepared from (-)-dihydrothebainone according to TLC, HPLC, MS, and ^{1}H and ^{13}C NMR spectroscopy.

The IR spectra (KBr disc) of racemic and (-)-**5** were markedly different. Racemic **5** crystallizes as an internal salt and consequently the hydroxyl peak was absent from the IR spectrum, whereas ammonium peaks were present. The high melting point of racemic **5** is also consistent with salt formation.

Experimental part

Mass spectra were measured by Dr. *P.J.W. Schuyl* and Mrs. *A.H. Knol-Kalkman* with a Varian-Mat SM-1 mass spectrometer. ^{13}C NMR spectra were obtained with a Varian CFT-20 spectrometer [spectral

width 5000 Hz, pulse width 5 μs, 8 K, acquisition time 0.8 s, pulse delay = acquisition time]. The ^{13}C-chemical shifts were measured in ppm from internal tetramethylsilane (TMS). ^{1}H NMR spectra were measured with a Varian T-60 spectrometer. The compounds were dissolved (10% w/v) in deuteriochloroform and/or hexadeuteriodimethyl sulfoxide. TMS was used as internal reference. Infrared spectra were obtained from KBr discs with a Beckman IR 4210 spectrophotometer. Analytical HPLC was performed on a reverse-phase column (15 cm x 0.4 cm I.D., Nucleosil C_{18}, 7 μm or 30 cm x 0.4 cm I.D., Polygosil 60, 10 μm, C_{18}) with mixtures of methanol and water, containing 5 mmol/l of heptanesulfonate and 2% of acetic acid (ion-pair method)[7] with detection at 280 nm. TLC was performed on deactivated silicagel (Merck F-254) with dichloromethane/methanol/2 *N* ammonia 85:15:2 as the mobile phase. the compounds were detected with UV (254 nm) and iodine vapour. Combustion analyses were performed by Mr. *H.M.A. Buurmans*. Organic layers of extractions were dried on sodium sulfate.

N-*(3-Methoxyphenylethyl)-4-benzyloxyphenylacetamide*

A solution of 4-benzyloxyphenylacetic acid[8] (117 g, 0.48 mol) and 2-(3-methoxyphenyl)ethylamine[9] (77 g, 0.51 mol) in *p*-xylene (600 ml) containing molecular sieve (3A) was boiled under reflux for 8 h. After cooling the amide crystallized and was washed with petroleum ether (b.p. 40-60 °C, 300 ml). More amide (3 g) was recovered from the mother liquor, affording a total of 172.5 g (0.46 mol, 95%). A small sample was recrystallized twice from ethanol: m.p. 95-96 °C, calcd. for $C_{24}H_{25}NO_3$ (375.47): C 76.77; H 6.71; N 3.73, found C 76.9; H 6.8; N 3.9. ^{1}H NMR ($CDCl_3$): δ 2.67 (t, J 6Hz, 2H, CH_2); δ 3.42 (q, J 6Hz, 2H, CH_2); δ 3.42 (s, 2H, CH_2CO); δ 5.01 (s, 2H, CH_2O); δ 6.50-7.10 (m, 7H, H(Ar)); δ 7.35 (s, 5H, H(Ar)).

*1-(4-Benzyloxybenzyl)-1,2,3,4-tetrahydro-6-methoxyisoquinoline (***2***)* via **1**

A suspension of *N*-(3-methoxyphenylethyl)-4-benzyloxyphenylacetamide (56.6 g, 151 mmol) in benzene (400 ml) was treated with phosphoryl chloride (72 g, 42.5 ml, 260 mmol) and boiled for 1 h. The mixture was evaporated, the residue dissolved in warm ethanol (150 ml) and the solution again evaporated yielding **1**.

To a cool, well-stirred solution of crude **1** in ethanol (850 ml), sodium tetrahydroborate (15.1 g, 380 mmol) was added in four equal portions during 2 h. After 1 h of stirring at 0 °C and 3 h at room temperature, 2 *N* hydrochloric acid (180 ml) was added until pH 2. The mixture was diluted with ethanol (370 ml) and boric acid was filtered off. The filtrate was evaporated at reduced pressure. The residue was dissolved in water (400 ml) and made alkaline (pH 8-9) by addition of ammonia (50 ml). Chloroform extraction (1 x 250 ml and 2 x 100 ml), drying ($MgSO_4$), evaporation to dryness, and crystallization from ethanol afforded **2** (41.1 g, 115 mmol, 76%).

A small sample was recrystallized from ethanol: m.p. 126-127 °C, calcd. for $C_{24}H_{25}NO_2$ (359.47): C 80.19; H 7.01; N 3.90, found C 80.2; H 7.1; N 3.8. ^{1}H NMR ($CDCl_3$): δ 1.70 (s, 1H, NH); δ 3.75 (s, 3H, CH_3O); δ 4.09 (dd, J 9Hz, J 3.5Hz, H(1)); δ 5.03 (s, 2H, $ArCH_2O$); δ 6.63-7.30 (m, 7H, H(Ar)); δ 7.40 (s, 5H, H(Ar)).

*1-(4-Benzyloxybenzyl)-1,2,3,4-tetrahydro-6-methoxy-2-methyl-isoquinoline (**3**)*

In a nitrogen atmosphere platinum-on-carbon (5%, 1 g) and formaldehyde (37-40%, 16.5 ml) were added to **2** (4.7 g, 13.1 mmol) in methanol (200 ml). The solution was hydrogenated at 45 °C for 10 h. Then the catalyst was filtered over hyflo and the filtrate evaporated under reduced pressure. The residue was taken up in some warm methanol and evaporated again. This was repeated once more and, finally, the residue was crystallized from ethanol (20 ml) yielding **3** (4.5 g, 12.0 mmol, 92%).

A small sample was recrystallized twice from ethanol: m.p. 75-76 °C, calcd. for $C_{25}H_{27}NO_2$ (373.50): C 80.40; H 7.29; N 3.75, found C 80.3; H 7.4; N 3.9. ^{1}H NMR ($CDCl_3$): δ 2.46 (s, 3H, CH_3N); δ 3.66 (m, 1H, H(1)); δ 3.72 (s, 3H, CH_3O); δ 5.00 (s, 2H, $ArCH_2O$); δ 6.52-7.30 (m, 7H, H(Ar)); δ 7.38 (s, 5H, H(Ar)).

*1,2,3,4,5,8-Hexahydro-1-(4-hydroxybenzyl)-6-methoxy-2-methyl-isoquinoline (**4**) from* **3**

A solution of **3** (3.0 g, 8.04 mmol) in *tert*-butanol/tetrahydrofuran (40 ml, 1:1) was added dropwise during 15 min under nitrogen and at –60–65 °C to lithium (1.2 g, 170 mmol) in liquid ammonia (150 ml) and *tert*-butanol/tetrahydrofuran (90 ml, 1:1) in an apparatus as described in reference 10. After 2 h TLC analysis

showed a complete conversion. The excess of lithium was destroyed with methanol at -50 °C. Ammonia and the other solvents were carefully distilled off, the latter at reduced pressure. The residue was dissolved in water, ammonium chloride (22.5 g) was added (pH 8). The solution was extracted with chloroform (3 x 100 ml). The chloroform extract was washed with water (50 ml), dried, and evaporated affording **4** (2.2 g, 7.7 mmol, 96%, purity > 98% (HPLC)).

A small sample was crystallized twice from ethanol: m.p. 156-157 °C, calcd. for $C_{18}H_{23}NO_2$ (285.39): C 75.76; H 8.12; N 4.91, found C 76.0; H 8.2; N 4.8. ^1H NMR ($CDCl_3$): δ 2.37 (s, 3H, CH_3N); δ 3.50 (s, 3H, CH_3O); δ 4.55 (b, 1H, H(7)); δ 6.06 (s, 1H, OH); δ 6.48 (d, $J_{2',3'}$ 8Hz, 2H, H(3') and H(5')); δ 6.95 (d, $J_{2',3'}$ 8Hz, 2H, H(2' and 6')).

*1,2,3,4,5,8-Hexahydro-1-(4-hydroxybenzyl)-6-methoxy-2-methyl-isoquinoline (**4**) from **7***

Formaldehyde (37-40%, 1.7 ml) and sodium cyanoborohydride (0.44 g, 7.0 mmol) were added at 20 °C to a suspension of **7** (1.20 g, 4.4 mmol) in acetonitrile (150 ml). After 30 min the *N*-methylation was complete (TLC). The solvent was evaporated *in vacuo*. The residue was dissolved in water and made alkaline with sodium carbonate (pH 9). Extraction with dichloromethane afforded (1.18 g, 4.1 mmol, 94%, purity > 99% (HPLC)).

*3-Hydroxy-N-methyl-6-oxomorphinan (**5**)*

A solution of **4** (1.00 g, 3.5 mmol) in orthophosphoric acid (85%, 50 ml) was heated for 24 h at 135-140 °C. The cooled mixture was diluted with water (75 ml) and heated for 2 h at 100 °C. The cooled, dark-brown solution was added to a mixture of water (100 ml), chloroform (100 ml) and 2-propanol (30 ml), the mixture was made alkaline (pH 9) with concentrated ammonia. The organic layer was separated and the aqueous layer was extracted four times with chloroform/2-propanol (4:1). Evaporation of the combined organic layers yielded a product (0.96 g) which was purified by preparative liquid chromatography on a column (30 x 0.4 cm I.D.) packed with deactivated silicagel (Woelm) with dichloromethane/methanol/4 *N* ammonia (90:12:1) as the eluent. The fraction containing **5** was collected, evaporated (136 mg, 0.5 mmol, 14%) and crystallized from

methanol: m.p. 240-241 °C. ^{1}H NMR, ^{13}C NMR, HPLC, and TLC of (±)-**5** were identical with the data of (-)-**5** prepared from natural starting material[2]. The IR spectrum of racemic **5** differs from that of (-)-**5**; (±)-**5** crystallizes as an internal salt, no O-H stretching at about 3600 cm^{-1} is observed, but absorption at 2680 and 2585 cm^{-1} indicates the presence of NH_2^+. ^{13}C NMR ($CDCl_3$ + 5% CD_3OD): δ 23.3 (10); δ 26.8 (8); δ 40.9, and δ 41.3 (7, 13, and 15); δ 42.5 (NCH_3); δ 43.2 (14); δ 46.2 (16); δ 51.3 (5); δ 57.4 (9); δ 112.6, and δ 114.6 (2, and 4); δ 126.7 (11); δ 129.1 (1); δ 138.3 (12); δ 155.9 (3); δ 211.0 (6).

1,2,3,4,5,8-Hexahydro-6-methoxy-1-(4-methoxybenzyl)-2-methyl-isoquinoline (**6**)

Phenyltrimethylammonium chloride (855 mg, 5.0 mmol) and sodium methoxide (540 mg, 10.0 mmol) were added to a solution of **4** (710 mg, 2.5 mmol) in dioxane (8 ml). After heating at 70 °C for 2 h, sodium hydride (100 mg, 4.2 mmol) was added. The methylation was complete according to TLC after 2 h. The solvent was evaporated *in vacuo*. The residue was taken up in water and evaporated *in vacuo* (5 x) in order to remove dimethylaniline. Extraction with dichloromethane afforded **6** (m.p. 79-81 °C, 744 mg, 2.5 mmol, 99%). ^{1}H NMR ($CDCl_3$): δ 2.39 (s, 3H, CH_3N); δ 3.54 (s, 3H, CH_3O(6)); δ 3.75 (s, 3H, CH_3O(4')); δ 4.60 (b, 1H, H(7)); δ 6.76 (d, $J_{2',3'}$, 9Hz, 2H, H(3' and 5')); δ 7.15 (d, $J_{2',3'}$, 9Hz, 2H, H(2' and 6')), IR (KBr: 1665 and 1692 cm^{-1} (C=C).

1,2,3,4,5,8-Hexahydro-1-(4-hydroxybenzyl)-6-methoxyisoquinoline (**7**)

In the same way as described for compound **4**, **2** (3.0 g, 8.3 mmol) was converted into **7** (2.2 g, 8.1 mmol, 97.7%). The latter compound crystallized from the final aqueous reaction mixture at 0 °C. A small sample was recrystallized twice from ethanol: m.p. 194-195 °C, calcd. for $C_{17}H_{21}NO_2$ (271.36): C 75.25; H 7.80; N 5.16, found C 75.2; H 7.8; N 5.4. ^{1}H NMR ($CDCl_3$/DMSO-d_6): δ 3.53 (s, 3H, CH_3O); δ 4.67 (b, 1H, H(7)); δ 6.71 (d, $J_{2',3'}$, 8Hz, 2H, H(3' and 5')); δ 7.02 (d, $J_{2',3'}$, 8Hz, 2H, H(2' and 6')).

2-Formyl-1,2,3,4,5,8-hexahydro-1-(4-hydroxybenzyl)-6-methoxy-isoquinoline (**8**)

A mixture of ethyl formate (30 ml, 440 mmol) and **7** (1.0 g, 3.7

mmol) in warm dioxane (40 ml) were boiled under reflux for 10 h. The product (0.8 g) crystallized after 2 days at 4 °C. More product was recovered from the mother liquor, affording a total of 1.1 g (3.68 mmol, 99.7%, purity > 99% (HPLC)). A small sample was recrystallized from ethanol: m.p. 190-191 °C, calcd. for $C_{18}H_{21}NO_3$ (299.37): C 72.22; H 7.07; N 4.68, found C 72.3; H 7.2; N 4.5. ^{1}H NMR (DMSO-d_6): δ 3.50 (s, 3H, CH_3O); δ 4.70 (b, 1H, H(7)); δ 6.75 (m, 4H, H(Ar)); δ 7.34 and δ 7.87 (2 x s, 1H, CHO, *syn/anti*).

*2-Formyl-1,2,3,4,5,8-hexahydro-1-(4-methoxybenzyl)-6-methoxy-isoquinoline (***9***)**

Methyl iodide (0.09 ml, 1.4 mmol) and sodium hydride (60% in oil, 80 mg, 2.0 mmol) were added to **8** (600 mg, 2.0 mmol) dissolved in a mixture of tetrahydrofuran (20 ml) and *N*,*N*-dimethylformamide (4 ml). After 6 h of stirring another portion of methyl iodide (0.06 ml, 0.8 mmol) and sodium hydride (40 mg, 1.0 mmol) were added. The conversion was complete after 16 h (TLC). The solvents were evaporated *in vacuo*, the residue was taken up in water. Extraction with dichloromethane afforded **9** (m.p. 112-115 °C, 445 mg, 1.4 mmol, 71%). ^{1}H NMR ($CDCl_3$): δ 3.56 (s, 3H, $CH_3O(6)$); δ 3.76 (s, 3H, $CH_3O(4')$); δ 4.21 (m, 1H, H(1)); δ 4.59 (m, 1H, H(7)); δ 6.90 (m, 4H, H(Ar)); δ 7.40 and δ 7.93 (two signals due to *syn-anti* isomers, s, 1H, NCHO). High-resolution MS: 313.170 ± 6, calculated for $C_{19}H_{23}NO_3$: 313.167, IR (KBr): 1662 cm^{-1} (NCHO), 1700 cm^{-1} (C=C).

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* The *N*-formyl *syn-anti* isomers of **8** and **9** could be separated by high-performance liquid chromatography (HPLC), using a reverse-phase octadecyl-silica column, see reference 7, p. 384. Semi-preparative HPLC yielded the pure rotamers. With Dr. H. van Koningsveld, we are at present engaged in assigning the *syn-anti* configuration to these rotamers by single-crystal X-ray crystallography.

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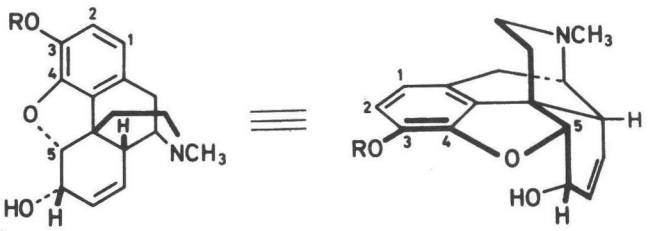
3a. Oxidation of 2-Bromo-3-hydroxy-*N*-methyl-6--oxomorphinan by Fremy's Salt. An Unprecedented 2,4-Shift of the Bromo Substituent*

Introduction

We have investigated the acid-catalysed ring closure, important in our synthesis of morphine and codeine[1,2] (Fig. 1), of various 1-benzyl-1,2,3,4,5,8-hexahydroisoquinolines[3]. A strategy which was developed here[1], made use of a 1-benzylhexahydroisoquinoline, substituted symmetrically in the benzyl radical.



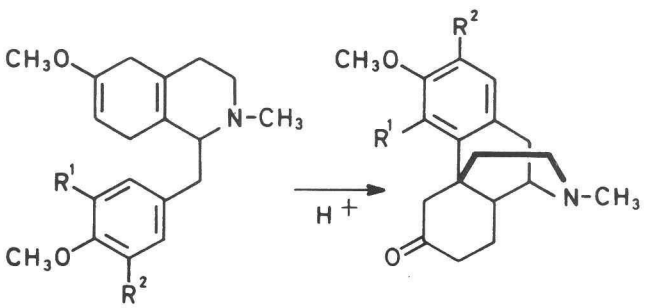
R = H, Morphine
R = CH_3, Codeine

Fig. 1

Ring closure of (−)-1-(3,5-dihydroxy-4-methoxybenzyl)-1,2,3,4,5,8-hexahydro-6-methoxy-2-methylisoquinoline (**1**, Fig. 2) gave exclusively (−)-2-hydroxydihydrothebainone

* A reprint of C. Olieman, L. Maat, and H.C. Beyerman, Recl. Trav. Chim. Pays-Bas *99*, 169 (1980).

(**2**)[2]. The hydroxyl group in the 2-position could be removed selectively[4] to give dihydrothebainone (**5**). The preparation of codeine from **5** is known[5] and we have studied it in detail[6], as have also *Weller* and *Rapoport*[7,**]. A problem in the synthesis is the availability of methyl 3,5-dihydroxy-4-methoxybenzoate, a synthon for the benzyl radical in **1**, which could be synthesized only in low yield[8]. This problem can be avoided by starting from a benzyl group which is also symmetrically substituted but in a simpler way, such as the 4-methoxybenzyl group in **3**. This compound is synthetically readily accessible[9].



1: $R^1 = R^2 = OH$
3: $R^1 = R^2 = H$

2: $R^1 = R^2 = OH$
4: $R^1 = R^2 = H$
5: $R^1 = OH$, $R^2 = H$

Fig. 2

Cyclization of **3** will yield 3-hydroxy-*N*-methyl-6-oxomorphinan (**6a**). Into this compound must be introduced a substituent which can be converted into the 4,5-oxygen bridge, such as is present in morphine and codeine. Formally, two approaches are possible, *viz.* substitution in position 4 and in position 5 of the morphinan (Fig. 1). We decided to introduce a hydroxyl group in the – sterically unfavourable – 4-position of **4**. We chose the oxidation of a phenol to an *ortho*-quinone, followed by reduction. Fremy's salt $\{K_2(SO_3)_2NO\cdot\}$[10] oxidizes phenols to *ortho*-quinones in good yields if an alkyl or an alkoxy group is present in the *para*-position, which is the case with **6**. Diphenylseleninic anhydride[11] oxidizes phenols with an unprotected *para*-position selectively to *ortho*-quinones. Initial experiments with this reagent and morphinans **6a** and **6b** (Fig. 3) were discouraging and were abandoned.

Results and discussion

(−)-3-Hydroxy-*N*-methyl-6-oxomorphinan (**6a**, Fig. 3) can be readily obtained from (−)-dihydrothebainone (**5**). The oxidation of **6a** with Fremy's salt occurred in the 2-position, which is less sterically hindered than the 4-position. Quinone **7a** was, without isolation, reduced to (−)-2,3-dihydroxy-*N*-methyl-6-oxomorphinan (**8a**). Methylation of **8a** afforded (−)-2,3-dimethoxy-*N*-methyl-6-oxomorphinan (**9a**). The structure of **9a** follows from comparison (MS, ^{1}H- and ^{13}C-NMR) with totally synthetic **9a** obtained from racemic *N*-formyl-2-hydroxy-3-methoxymorphinan which was methylated to the 2-methoxy compound, deformylated, and *N*-methylated. In order to arrive at the desired oxidation in the 4-position, we envisaged blocking of the 2-position of **6a** with a bromine atom to be removed afterwards. Oxidation of (−)-2-bromo-3-hydroxy-*N*-methyl-6-oxomorphinan (**6b**) under the same conditions as for **6a** resulted in the formation of *two* products, as shown by liquid chromatography. One of the products (~40%), according to HPLC, was identical with quinone **7a**; obviously the bromine atom was split off. The other product had a longer retention time, and it was expected to be the desired *ortho*-quinone. To enhance the selective formation of this compound, different reaction conditions were examined. Lowering of the temperature and addition of an organic solvent enhanced the selectivity, but reduced the reaction rate***. No attempt was made to isolate the quinones, because they are too unstable. The *in situ* reduction of *ortho*-quinone **7a** proceeded satisfactorily with iron powder as well as with sodium cyanotrihydridoborate. The latter is usually the more convenient reagent but for **7b** reduction with sodium cyanotrihydridoborate was slow, whereas the reaction proceeded satisfactorily with iron powder. Methylation of the reduced products afforded compounds which could be readily purified and characterized. Catalytic hydrogenolysis of the reaction product of **6b** gave a debrominated product which, however, was not identical with the expected (−)-3,4-dihydroxy-*N*-methyl-6-oxomorphinan (**10a**), prepared by demethylation of dihydrothebainone (**5**), but was found to be identical (HPLC, MS, and ^{1}H-NMR) with (−)-2,3-dihydroxy-*N*-methyl-6-oxomorphinan (**8a**). The same result was obtained with the methylated product. In this case (−)-2,3-dimethoxy-*N*-methyl-6-oxomorphinan (**9a**) was formed, and not the expected (−)-3,4-dimethoxy-*N*-methyl-6-oxomorphinan (**11a**), which was prepared by methylation of dihydrothebainone (**5**). This means that the pyrocatechol formed did not have the desired structure **10b**, but structure **8b**, in which the *bromine atom has shifted from the 2- to the 4-position,* assuming that no shift has taken place during the hydrogenolysis. With ^{1}H- and ^{13}C-NMR it was not possible

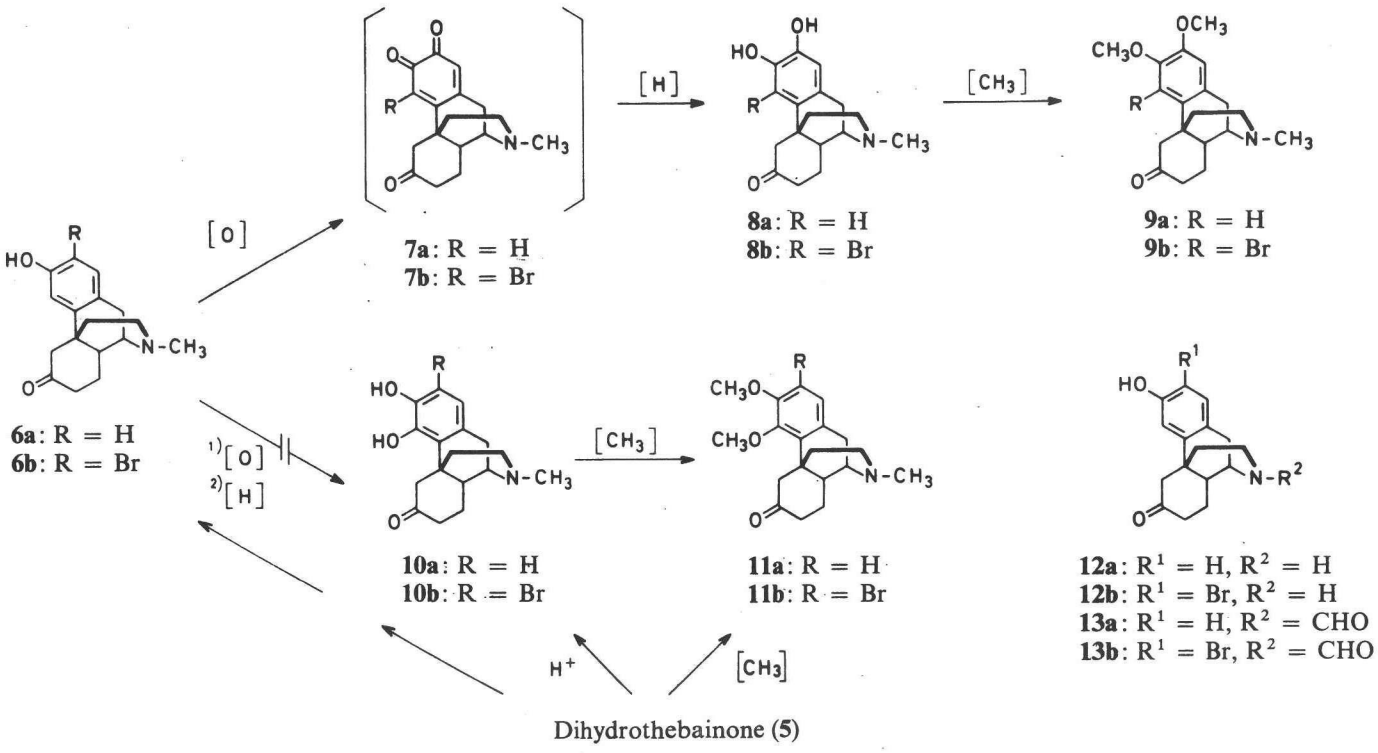


Fig. 3. Conversions of the 3-hydroxy-6-oxomorphinans.

to discern structure **9b** or **11b** in the methylated product of **8b**. The chemical shift of the 5α-proton (^{1}H-NMR) indicated the presence of a substituent in the 4-position. A single-crystal X-ray analysis proved that the methylated product of **8b** was (−)-4-bromo-2,3-dimethoxy-*N*-methyl-6-oxomorphinan (**9b**), (Fig. 5)[12]. During the oxidation of **6b** therefore a shift of the 2-bromine atom to the sterically hindered 4-position has taken place. Catalytic hydrogenolysis of the bromo substituent in the 4-position proceeded at a higher temperature than for 1-bromo-substituted morphinans[6]. In **9a** both methoxy groups are in the aromatic ring plane, because it appeared from experiments with tris[1,1,1,2,2,3,3-heptafluoro-7,7-dimethyloctanedionato-(4,6)]-europium [Eu(FOD)$_3$] in ^{1}H-NMR that bidentate complex formation with the methoxy groups[13] takes place. In the case of **9b** this was not observed, because, probably owing to steric interaction of the 3-methoxy group with the 2-methoxy and the 4-bromo substituent, the 3-methoxy group is out of the plane of the aromatic ring. This is confirmed by the X-ray analysis of **9b**; the 3-methoxy group has a dihedral angle $CH_3OC(3)C(2)$ of 80° [71°]****, while the 2-methoxy group has a dihedral angle $CH_3OC(2)C(1)$ of 9° [5°]****. One synthesis only is known of a morphinan dienone with a pattern of aromatic substitution similar to that of **9b**; *viz. via* anodic coupling of 1-(3-bromo-4,5-dimethoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline[14].

The oxidation was also investigated for other derivatives of **6a**, in order to obtain more stable *ortho*-quinones and to decrease the loss of the protective group. Morphinans **12a** and **13a** gave, upon oxidation, similar results to **6a**. Oxidation of 2-bromo-3-hydroxy-6-oxomorphinan (**12b**) and its *N*-formyl derivative (**13b**) both showed increased formation of the undesirable **7a** derivative; for the oxidation of **13b** this was even 50% (HPLC). 3-Methoxy-*N*-methyl-6-oxomorphinan (**4**) was prepared from dihydrothebainone (**5**), and **6a** was prepared from **4**. In both syntheses we used a modified procedure of *Sawa* et al.[15,16]. Compound **6b** was prepared from **6a** by bromination in acetic acid. *N*-Demethylation of **4**, followed by *O*-demethylation and bromination in acetic acid, gave **12b**. *N*-Formylation of **12b** gave **13b**.

In order to find out whether the reaction path in the oxidation of **6b** has general validity, we investigated a model compound, 2-bromo-4,5-dimethylphenol (**15**, Fig. 4). Oxidation with Fremy's salt, followed by reduction with iron powder, gave a crystalline product. Reduction of this product with lithium tetrahydridoaluminate yielded 4,5-dimethylpyrocatechol (**17**), which was identical with that prepared from

with Fremy's salt, followed by reduction with iron powder, gave a crystalline product. Reduction of this product with lithium tetrahydridoaluminate yielded 4,5-dimethylpyrocatechol (**17**), which was identical with that prepared from 3,4-dimethylphenol (**14**) by oxidation with Fremy's salt[17] followed by reduction with sodium tetrahydridoborate. Bromination of **17** gave 3-bromo-4,5-dimethylpyrocatechol (**16**), which was identical with the reaction product of **15**.

Here too, the bromine atom has shifted, although owing to the presence of the two methyl groups it is not possible to tell whether this is a shift from the 2- to the 3- or to the 6-position in **15**. Oxidation of 2-chloro- and 2-iodo-4,5-dimethylphenol gave increased formation of the 4,5-

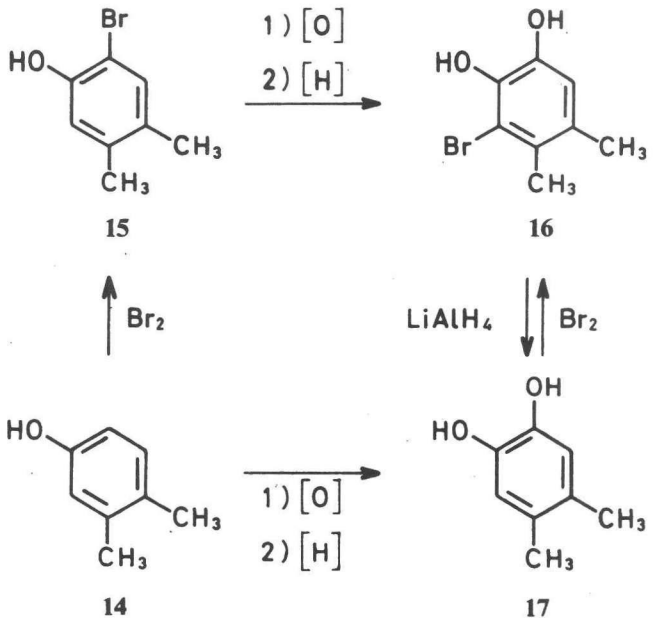


Fig. 4. Synthesis and reduction of 3-bromo-4,5-dimethylpyrocatechol.

dimethyl-1,2-benzoquinone. We are not aware of a comparable rearrangement. However, it is known that the oxidation of phenols with a bromine or chlorine atom in the *para*-position does not yield the expected *ortho*-quinones[18-20], but *para*-quinones, the halogen being expelled.

In summary, the proposed simplification of the synthesis of morphine and codeine *via* the direct introduction of the hydroxyl group in position 4 was thwarted by the occurrence

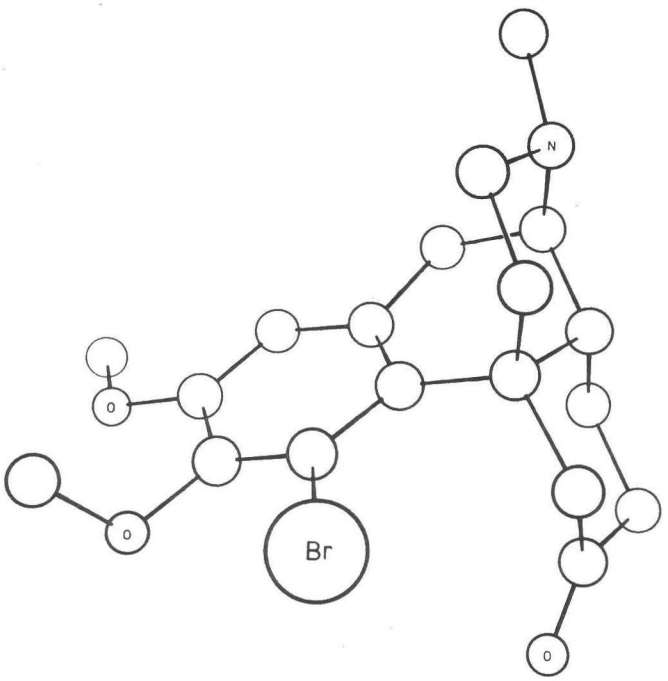


*Fig. 5. ORTEP drawing of the structure of (−)-4-bromo--2,3-dimethoxy-*N*-methyl-6-oxomorphinan* (**9b**).

of an unexpected bromine atom migration. With the information to hand it is possible only to speculate about the mechanism of the migration; this reaction will be subject of further study. Introduction of the hydroxyl group in position 2 proceeds smoothly by means of the method described.

Experimental part

Combustion analyses were performed under the supervision of Mr. *W. J. Buis* (Analytical Section of the Institute of Organic Chemistry TNO, Utrecht, The Netherlands) and by Mr. *H. M. A. Buurmans* (Delft). Melting points are uncorrected. Mass spectra were measured by Dr. *P. J. W. Schuyl* and Mrs. *A. H. Knol–Kalkman* with a Varian-Mat 311 A mass spectrometer. ^{13}C NMR analyses were obtained with a Varian CFT-20 spectrometer [spectral width 5000 Hz, pulse width 8 μs (α 45°), 8 K, acquisition time 0.8 s, pulse delay = acquisition time]. The compounds were dissolved in deuteriochloroform. The ^{13}C-chemical shifts (Table I) were measured in ppm from internal tetramethylsilane (TMS). The ^{1}H NMR spectra were measured with a Varian T-60 spectrometer. The compounds were dissolved (10% w/v) in deuteriochloroform and/or hexadeuteriodimethyl sulfoxide. TMS was used

as internal reference. Rotations were measured with a Perkin-Elmer P-141 polarimeter. Infrared spectra were obtained from KBr with a Beckman IR 4210 spectrophotometer. Analytical HPLC was performed on a reverse-phase column (15 cm × 0.4 cm I.D., Nucleosil C18, 5 μm) with mixtures of methanol and water, containing 0.005 *M*-heptanesulfonate and 2% of acetic acid (ion-pair method)[21] with detection at 280 nm (Table II). Preparative separations were performed on a reverse-phase column (20 cm × 0.8 cm I.D., Merck RP-18, 10 μm) with mixtures of methanol and water, containing trifluoroacetic acid (TFA). TLC was performed on deactivated silicagel (Merck F-254) with dichloromethane/methanol/2 *N* ammonia 85 : 15 : 2 as the mobile phase, the compounds were detected with UV (254 nm) and iodine vapour. Fremy's salt was prepared as described in ref. 10. Organic layers of extractions were dried over Na_2SO_4.

Table I ^{13}*C-Chemical shifts* (δ) *of some representative morphinans,* δ_c *in deuteriochloroform.*

C atom	Compound			
	9a	**9b**	**11a**	**4**
1	109.4[a]	111.3	122.9	128.7
2	147.7[b]	152.3[a]	111.6	111.3[a]
3	147.8[b]	151.9[a]	149.1[a]	158.3
4	110.8[a]	119.5	151.5[a]	112.4[a]
5	51.8	50.0*	51.4*	51.6
6	209.0	209.5	210.3	208.8
7	40.8[c]	40.8	41.3[b]	41.1
8	26.9	26.7	27.2	26.8
9	57.3	56.5	57.1	57.2
10	23.8	25.9	24.2	23.2
11	128.8	135.3	130.4[c]	128.4
12	129.5	128.6	130.6[c]	138.8
13	41.9	42.8	41.6[b]	42.0
14	44.2	46.1	45.9	44.1
15	41.1[c]	37.9	40.2	41.1
16	46.1	46.5	46.7	46.1
$N-CH_3$	42.8	42.5	42.7	42.8
$-O^3-CH_3$	55.8[d]	60.4	55.8	55.2
$-O-CH_3$	56.1[d]	55.8	60.4	

[a,b,c,d] These assignments may be interchanged in each column.

* Double doublet in the off-resonance spectrum, due to a large difference in chemical shift for H(5α) and H(5β).

(−)-*3-Methoxy*-N-*methyl-6-oxomorphinan* (**4**)

(−)-O^4-Phenyldihydrothebainone (58.5 g, 155 mmol), prepared from (−)-dihydrothebainone (**5**) as described by *Sawa* et al.[15], was dissolved in 250 ml of dioxane and 50 ml of glycol (0.89 mmol), and 35 g (184 mmol) of *p*-toluenesulfonic acid hydrate were added.

Table II Capacity factors (k') of substituted morphinans, column: Nucleosil C_{18} (5 μm); eluent: methanol/H_2O 40:60 containing 0.005 M-sodium heptanesulfonate and 2% of acetic acid; flow: 1.0 ml/min.

Compound	*k'*	Compound	*k'*
6a	3.53	**10a**	3.03
6b	5.54	**11a**	7.01
8a	2.50	**12a**	4.34
8b	1.89	**12b**	8.45
9a	4.23	**13a**	2.66; 2.86*
9b	7.22	**13b**	7.49, 8.35*

* Two values, due to *syn-anti* isomerization of the *N*-formyl group, interconversion is relatively slow at 30°C.

The mixture was boiled in a continuous extractor containing 100 g of activated molecular sieve (3 A). After 5 h the solvent was removed *in vacuo*, 100 ml of 2 *N*-KOH was added and the product was extracted with dichloromethane. Yield 63.9 g (152 mmol, 98%) of the amorphous ethylene acetal of **4**. This acetal {20.0 g (47.5 mmol)} in 50 ml of THF, was added to a solution of 1.54 g (220 mmol) of lithium in 400 ml of liquid ammonia and 50 ml of THF at −60°C in an apparatus as described in ref. 22. After 1 h, benzoic acid was added until the blue colour of the reaction mixture disappeared, the solvents were evaporated *in vacuo*, and the residue was acidified (pH 2) with 2 *N*-HCl, heated for 1 h on a steam bath and made alkaline (pH 13) with 4 *N*-KOH. Extraction with dichloromethane afforded, after evaporation, 13.2 g (46.3 mmol, 97.5%) of **4**. This was recrystallized from ethanol, m.p. 190–192°C, $[\alpha]_D^{25}$ −99° (*c* 1.87, ethanol) (ref. 15: m.p. 187–189°C, $[\alpha]_D^{25}$ −97°, *c* 2.09, ethanol).

(−)-*3-Hydroxy*-N-*methyl-6-oxomorphinan* (**6a**)

A solution of 3.01 g (10.6 mmol) of **4** in 20 ml of 48% hydrobromic acid was heated at 100°C during 4 h and then poured into 200 ml of water. The pH was then adjusted to 13 with solid NaOH and the solution was extracted three times, each with 50 ml of ether to remove **4**. The pH was then adjusted to 9 with acetic acid and the solution extracted four times, each with 50 ml of chloroform. After evaporation the residue was dissolved in 3 ml of acetone and **6a**·½acetone (2.40 g, 8.0 mmol, 76%) crystallized, m.p. 214–215°C, $[\alpha]_D^{25}$ −114° (*c* 0.83, ethanol), [ref. 16: m.p. 226–227, $[\alpha]_D^{25}$ −109° (*c* 1.08, ethanol)]. The acetone was removed *in vacuo* at 80°C.

(−)-*2-Bromo-3-hydroxy*-N-*methyl-6-oxomorphinan* (**6b**)

A solution of bromine in acetic acid (53 ml, 0.11 M; 1 eq) was added during 2 h to 1.60 g (5.90 mmol) of **6a** in 100 ml of acetic acid. The solvent was removed *in vacuo* and the residue was taken up in a mixture of 50 ml of water and 20 ml of chloroform. 2 *N*-Ammonia

was added with stirring to pH 9, the chloroform layer was separated and the aqueous layer was extracted three times each with 30 ml of chloroform. Evaporation of the combined chloroform extracts afforded 1.90 g (5.41 mmol, 92%) of **6b**. This was crystallized from 5 ml of water as the (+)-tartrate, m.p. >250°C (dec.), $[\alpha]_D^{25}$ −43°, $[\alpha]_{365}^{25}$ −258° (*c* 0.52, 0.2 *M*-phosphoric acid in water). $C_{17}H_{20}BrNO_2 \cdot \frac{1}{2}(C_4H_6O_6)$ (425.30), calc. C 53.66; H 5.45; N 3.29, found C 53.1; H 5.6; N 3.4. ^{1}H NMR of the free base in DMSO: δ 2.46 (s, 3H, CH_3N); δ 6.74 (s, 1H, H(4)); δ 7.20 (s, 1H, H(1)), IR 1708 cm^{-1} (C=O).

(−)-3-Hydroxy-6-oxomorphinan (**12a**)

2,2,2-Trichloroethyl chloroformate (4.0 ml) was added to a solution of 4.00 g (14.0 mmol) of **4** and 1.0 g of $NaHCO_3$ in 75 ml of chloroform (ethanol free). After 5 h boiling, the reaction was complete (TLC). Water (30 ml) was added and the mixture was stirred during 1 h. The chloroform layer was separated and the aqueous layer was extracted twice with chloroform. Evaporation of the combined chloroform extracts afforded (−)-3-methoxy-6-oxo-*N*-(2,2,2-trichloroethoxycarbonyl)morphinan as an oil. This product was dissolved in 40 ml of acetic acid and 9.0 g of powdered zinc were added. After 2 h' stirring at room temperature, the excess zinc was filtered off. The filtrate was evaporated *in vacuo*, the residue was dissolved in 100 ml of a mixture of methanol/water (4 : 1) and was made alkaline with concentrated ammonia. The solid was filtered off and the methanol in the filtrate was evaporated *in vacuo*. The aqueous residue was extracted three times each with 20 ml of chloroform. The chloroform was evaporated, the residue was dissolved in 20 ml of ethanol, and concentrated hydrobromic acid was added (pH 3). The ethanol was evaporated *in vacuo* and the residue was dissolved in 10 ml of a mixture of chloroform/methanol (85 : 15). (−)-3-Methoxy-6-oxomorphinan hydrobromide (4.79 g, 13.6 mmol, 97%) crystallized, m.p. 227–229°C, $[\alpha]_D^{25}$ −52°, $[\alpha]_{365}^{25}$ −309°, (*c* 0.48, chloroform/methanol 9 : 1). ^{1}H NMR in $CDCl_3$/DMSO (2 : 1): δ 3.76 (s, 3H, CH_3O); δ 6.65–6.90 (m, 2H, H(2) and H(4)); δ 7.10 (d, $J_{1,2}$ 8 Hz, 1H, H(1)), IR 1716 cm^{-1} (C=O).

A solution of 5.63 g (16.0 mmol) of (−)-3-methoxy-6-oxomorphinan hydrobromide in 90 ml of hydrobromic acid (48%) was heated at 90–95°C. After 5 h the solution was cooled and 90 ml of water were added. The solvent was evaporated *in vacuo*, the residue was dissolved in ethanol and evaporated *in vacuo* several times to remove excess of hydrogen bromide. Amorphous **12a**·HBr was isolated. ^{1}H NMR in $CDCl_3$/DMSO (1 : 1): δ 6.55–6.83 (m, 2H, H(2) and H(4)); δ 6.95 (d, $J_{1,2}$ 8 Hz, 1H, H(1)), IR 1704 cm^{-1} (C=O).

(−)-2-Bromo-3-hydroxy-6-oxomorphinan (**12b**)

To a solution of 1.38 g (4.08 mmol) of **12a**·HBr in 100 ml of acetic acid (90%) 83.2 ml (3.92 mmol, 0.047 *M*) of bromine in acetic acid were added during 3 h. The solvent was removed *in vacuo*, the residue was taken up in dilute ammonia (pH 9) and the solution was extracted four times with a mixture of chloroform/isopropanol (3 : 1). Evaporation of the solvent gave 1.16 g (3.42 mmol, 84%) of amorphous **12b**. ^{1}H NMR in $CDCl_3$/DMSO (9 : 1): δ 6.94 (s, 1H,

H(4)); δ 7.25 (s, 1H, H(1)), IR 1708 cm^{-1} (C=O).

(−)-N-*Formyl-3-hydroxy-6-oxomorphinan* (**13a**)

A solution of 0.94 g (2.78 mmol) of **12a**·HBr in a mixture of 3 ml of ethanol, 10 ml of dioxane, 2 ml of ethyl formate, and 0.5 g of K_2CO_3 was heated during 48 h at 50°C. The solvent was evaporated *in vacuo* and the residue was taken up in 20 ml of water, acidified with dilute hydrochloric acid and extracted with a mixture of chloroform/isopropanol (5 : 1). Evaporation afforded 0.32 g (0.88 mmol, 32%) of amorphous **13a**. ^1H NMR in DMSO: δ 6.53 (dd, $J_{1,2}$ 8 Hz, $J_{2,4}$ 2 Hz, 1H, H(2)); δ 6.66 (d, $J_{2,4}$ 2 Hz, 1H, H(4)); δ 6.85 (d, $J_{1,2}$ 8 Hz, 1H, H(1)); δ 7.90 and δ 8.08 (s, 1H, HCO, syn-anti), IR 1652 cm^{-1} (HC=O); 1709 cm^{-1} (C=O).

(−)-2-*Bromo*-N-*formyl-3-hydroxy-6-oxomorphinan* (**13b**)

A solution of 1.00 g (2.97 mmol) of **12b** in a mixture of 20 ml of dioxane and 5 ml of ethyl formate was boiled during 24 h. The solvent was evaporated *in vacuo*, the residue was taken up in 20 ml of 0.01 *M*-HCl and extracted three times each with 15 ml of chloroform. After evaporation, 410 mg (1.12 mmol, 38%) of amorphous **13b** were isolated. The product crystallized from 3 ml of ethanol (90%), m.p. 272–275°C, $[\alpha]_D^{25}$ −171°, $[\alpha]_{365}^{25}$ −760° (*c* 0.47, chloroform/methanol 9 : 1). $C_{17}H_{18}BrNO_3$ (364.24), calc. C 56.06; H 4.98; N 3.85, found C 56.1; H 5.2; N 3.8. ^1H NMR in $CDCl_3$/DMSO (1 : 1): δ 6.88 (s, 1H, H(4)); δ 7.14 (s, 1H, H(1)); δ 7.92 and δ 8.08 (s, 1H, HCO, *syn-anti*), IR 1642 cm^{-1} (HC=O); 1713 cm^{-1} (C=O).

(−)-*2,3-Dihydroxy*-N-*methyl-6-oxomorphinan* (**8a**)

To a solution of 0.57 g (2.11 mmol) of **6a** in a mixture of 37 ml of 1/6 *M*-H_3PO_4, 72 ml of 1/6 *M*-NaH_2PO_4, and 150 ml of water, 1.1 g (4.1 mmol) of Fremy's salt was added at 0°C. After 10 min another 1.1 g of Fremy's salt was added. The reaction mixture became red and after 30 min HPLC indicated a conversion of 92% of **6a**; 0.12 g (1.90 mmol) of sodium cyanotrihydridoborate was then added. The reaction mixture became colourless after a few minutes. After 15 min, 10 ml of acetone was added and the solution was stirred 45 min. The solvents were then evaporated *in vacuo*. The product was desalted and purified by preparative HPLC, eluent: methanol/ water 1 : 4, containing 0.5% of TFA, injection 1.0 ml (20 mg), flow: programmed (9 min) from 2 ml/min to 6 ml/min. The fraction containing the product was collected and evaporated *in vacuo*. In this way 0.56 g (1.40 mmol, 66%) of pure, amorphous **8a**·TFA was obtained, $[\alpha]_D^{25}$ −42°, $[\alpha]_{365}^{25}$ −185° (*c* 0.50, water). ^1H NMR in $CDCl_3$/DMSO (1 : 1): δ 3.95 (s, 3H, CH_3N); δ 6.56 and δ 6.65 (2 × s, 2 × 1H, H(1) and H(4)).

(−)-*2,3-Dimethoxy*-N-*methyl-6-oxomorphinan* (**9a**)

A suspension of 500 mg (1.25 mmol) of **8a**·TFA in 50 ml of dioxane was heated under nitrogen at 80°C. Phenyltrimethylammonium chloride 0.86 g (5.0 mmol) and 1.08 g (20 mmol) of sodium methoxide were added. After 2 h the same amount of these reagents was added. After 5 h the solvent was evaporated and the residue was evaporated four times with water to remove *N,N*-dimethylaniline.

The residue was taken up in water and extracted three times with dichloromethane. Evaporation afforded 277 mg (0.88 mmol, 73%) of crude **9a**. This product was purified by preparative HPLC, (eluent methanol/water 30 : 70 containing 0.5% of TFA). The methanol of the combined fractions was removed *in vacuo*, the aqueous solution was made alkaline (pH 9) with ammonia, and extracted with dichloromethane. Evaporation afforded 160 mg (0.51 mmol) of pure, amorphous **9a**, $[\alpha]_D^{25}$ −81°, $[\alpha]_{436}^{25}$ −196° (*c* 0.83, chloroform/ethanol 9 : 1), $C_{19}H_{25}NO_3$ (315.1834), found by high-resolution MS 315.1844. ^{1}H NMR in $CDCl_3$: δ 2.43 (s, 3H, CH_3N); δ 3.80 and δ 3.82 (2 × s, 2 × 3H, $CH_3O(2)$ and $CH_3O(3)$); δ 6.55 and δ 6.65 (2 × s, 2 × 1H, H(1) and H(4)), IR 1708 cm^{-1} (C=O).

(−)-*4-Bromo-2,3-dihydroxy*-N-*methyl-6-oxomorphinan* (**8b**)

A solution of 300 mg (0.86 mmol) of **6b** in a mixture of 60 ml of methanol, 15 ml of 1/6 *M*-phosphoric acid, and 170 ml of water was cooled at −10°C. Fremy's salt (0.90 g) dissolved in 30 ml of 1/6 *M*-NaH_2PO_4 was added and, after 15 min, the same quantity was extracted four times with a mixture of chloroform/isopropanol (3 : 1). Evaporation of the solvent gave 1.16 g (3.42 mmol, 84%) of amorphous **12b**. ^{1}H NMR in $CDCl_3$/DMSO (9 : 1): δ 6.94 (s, 1H, H(4)); δ 7.25 (s, 1H, H(1)), IR 1708 cm^{-1} (C=O).

(−)-N-*Formyl-3-hydroxy-6-oxomorphinan* (**13a**)

A solution of 0.94 g (2.78 mmol) of **12a**·HBr in a mixture of 3 ml of ethanol, 10 ml of dioxane, 2 ml of ethyl formate, and 0.5 g of K_2CO_3 was heated during 48 h at 50°C. The solvent was evaporated *in vacuo* and the residue was taken up in 20 ml of water, acidified with dilute hydrochloric acid and extracted with a mixture of chloroform/isopropanol (5 : 1). Evaporation afforded 0.32 g (0.88 mmol, 32%) of amorphous **13a**. ^{1}H NMR in DMSO: δ 6.53 (dd, $J_{1,2}$ 8 Hz, $J_{2,4}$ 2 Hz, 1H, H(2)); δ 6.66 (d, $J_{2,4}$ 2 Hz, 1H, H(4)); δ 6.85 (d, $J_{1,2}$ 8 Hz, 1H, H(1)); δ 7.90 and δ 8.08 (s, 1H, HCO, syn-anti), IR 1652 cm^{-1} (HC=O); 1709 cm^{-1} (C=O).

(−)-2-*Bromo*-N-*formyl-3-hydroxy-6-oxomorphinan* (**13b**)

A solution of 1.00 g (2.97 mmol) of **12b** in a mixture of 20 ml of dioxane and 5 ml of ethyl formate was boiled during 24 h. The solvent was evaporated *in vacuo*, the residue was taken up in 20 ml of 0.01 *M*-HCl and extracted three times each with 15 ml of chloroform. After evaporation, 410 mg (1.12 mmol, 38%) of amorphous **13b** were isolated. The product crystallized from 3 ml of ethanol (90%), m.p. 272–275°C, $[\alpha]_D^{25}$ −171°, $[\alpha]_{365}^{25}$ −760° (*c* 0.47, chloroform/methanol 9 : 1). $C_{17}H_{18}BrNO_3$ (364.24), calc. C 56.06; H 4.98; N 3.85, found C 56.1; H 5.2; N 3.8. ^{1}H NMR in $CDCl_3$/DMSO (1 : 1): δ 6.88 (s, 1H, H(4)); δ 7.14 (s, 1H, H(1)); δ 7.92 and δ 8.08 (s, 1H, HCO, *syn-anti*), IR 1642 cm^{-1} (HC=O); 1713 cm^{-1} (C=O).

(−)-*2,3-Dihydroxy*-N-*methyl-6-oxomorphinan* (**8a**)

To a solution of 0.57 g (2.11 mmol) of **6a** in a mixture of 37 ml of 1/6 *M*-H_3PO_4, 72 ml of 1/6 *M*-NaH_2PO_4, and 150 ml of water, 1.1 g (4.1 mmol) of Fremy's salt was added at 0°C. After 10 min

25 mg (0.069 mmol) of 2-bromo-3-methoxy-*N*-methyl-6-oxomorphinan, k' 14.1, TLC R_f 0.46, ^{1}H NMR in $CDCl_3$: δ 2.47 (s, 3H, CH_3N); δ 3.88 (s, 3H, CH_3O); δ 6.78 (s, 1H, H(4)); δ 7.27 (s, 1H, H(1)).

Catalytic hydrogenolysis

115 mg (0.29 mmol) of **8b**·HCl were dissolved in 20 ml of 2 *M*-acetic acid, containing 3.6 g of sodium acetate, and 70 mg of palladium (10%) on carbon were added. After 24 h at 20°C, HPLC indicated that one product had been formed, identical with **8a**.
In 5 ml of 2 *M*-acetic acid, containing 0.7 g of sodium acetate, 25 mg (0.063 mmol) of **9b** were dissolved and 10 mg of palladium (10%) on carbon added. After 1 h at 80°C, HPLC and TLC indicated that one product had been formed, identical with **9a**. The catalyst was filtered off, the filtrate was made alkaline, and extracted with dichloromethane. ^{1}H NMR and IR showed that this product was identical with **9a**.

(−)-*3,4-Dihydroxy*-N-*methyl-6-oxomorphinan* (**10a**)

A solution of 1.20 g (3.56 mmol) of **5**·HCl in 80 ml of 48% HBr was heated during 14 h at 90°C. The solvent was evaporated *in vacuo*, the residue was taken up in water (3×) and ethanol (3×), and evaporated each time. The amorphous product was triturated four times with ether to remove hydrobromide and dried *in vacuo* over KOH. ^{1}H NMR in $CDCl_3$/DMSO (9 : 1): δ 2.90 (s, 3H, CH_3N); δ 4.30 (d, J 14 Hz, 1H, H(5α); δ 6.48 and 6.77 (2 × d, J 8 Hz, 2 × 1H, H(1) and H(2)), IR 1706 cm^{-1} (C=O).

(−)-*3,4-Dimethoxy*-N-*methyl-6-oxomorphinan* (**11a**)

Phenyltrimethylammonium chloride (0.86 g; 5.01 mmol) and 0.54 g (10.0 mmol) of sodium methoxide were added to 1.00 g (3.32 mmol) of **5** in 30 ml of dioxane. The solution was boiled under nitrogen. After 8 h, 0.4 g (2.33 mmol) of phenyltrimethylammonium chloride was added. After 16 h the solvent was evaporated *in vacuo*, the residue was evaporated four times with water to remove *N,N*-dimethylaniline, the residue was taken up in water, and extracted with dichloromethane. After evaporation of the dichloromethane, the residue was dissolved in 2 ml of ethanol. On standing, 0.76 g (2.41 mmol; 73%) of **11a** crystallized, m.p. 149–150°C, $[\alpha]_D^{25}$ −82°, $[\alpha]_{365}^{25}$ −520° (*c* 1.08, chloroform/ethanol 9 : 1), $C_{19}H_{25}NO_3$ (315.1834), found by high-resolution MS 315.1829. ^{1}H NMR in $CDCl_3$: δ 2.38 (s, 3H, CH_3N), δ 3.77 (s, 3H, CH_3O(3)); δ 3.93 (s, 3H, CH_3O(4)); δ 3.98 (d, J 14 Hz, 1H, H(5α)); δ 6.75 (s, 2H, H(1) and H(2)), IR 1696 cm^{-1} (C=O).

Racemic N-*formyl-2,3-dimethoxy-6-oxomorphinan*

Trimethylphenylammonium chloride (0.50 g, 2.91 mmol) and 0.34 g (6.30 mmol) of sodium methoxide were added to a solution of 0.66 g (2.01 mmol) of rac.*N*-formyl-2-hydroxy-3-methoxy-6-oxomorphinan in a mixture of 20 ml of dioxane and 5 ml of DMF. The mixture was heated at 80°C. After 3 h and after 8 h similar amounts of the reagents were added. After 12 h the solvent was evaporated *in vacuo*, the residue was taken up in water several times and the solvents were evaporated. Extraction with dichloromethane and evaporation of the solvent afforded 0.65 g (1.90 mmol, 93%) of

rac. *N*-formyl-2,3-dimethoxy-6-oxomorphinan, m.p. 166–169°C (ethanol)), ^{1}H NMR in $CDCl_3$: δ 3.77 and δ 3.81 (2 × s, 2 × 3H, $CH_3O(2)$ and $CH_3O(3)$); δ 6.53 and δ 6.72 (2 × s, 2 × 1H, H(1) and H(4)); δ 7.98 and δ 8.16 (s, 1H, HCO, *syn-anti*), IR 1663 cm^{-1} (HC=O); 1710 cm^{-1} (C=O).

Racemic 2,3-dimethoxy-6-oxomorphinan

A solution of 0.653 g (1.97 mmol) of rac. *N*-formyl-2,3-dimethoxy-6-oxomorphinan in 50 ml of 1 *N*-HCl in methanol was boiled during 6 h. The solvent was evaporated *in vacuo*, the residue taken up in water, the solution made alkaline (pH 9) with ammonia and extracted with dichloromethane. Evaporation afforded 0.570 g (1.89 mmol, 96%) of rac.2,3-dimethoxy-6-oxomorphinan, m.p. 198°C (decomp., ethanol), ^{1}H NMR in $CDCl_3$: δ 3.80 and δ 3.83 (2 × s, 2 × 3H, $CH_3O(2)$ and $CH_3O(3)$); δ 6.56 and δ 6.70 (2 × s, 2 × 1H, H(1) and H(4)), IR 1710 cm^{-1} (C=O).

Racemic 2,3-dimethoxy-N-*methyl-6-oxomorphinan* (**9a**)

Aqueous formaldehyde (0.6 ml, 37%) and 0.150 g (2.38 mmol) of sodium cyanotrihydridoborate were added to a solution of 0.445 g (1.48 mmol) of rac. 2,3-dimethoxy-6-oxomorphinan in 15 ml of acetonitrile. After 15 min at room temperature the conversion to the *N*-methyl compound was complete according to TLC, and the solvent was evaporated *in vacuo*. The residue was taken up in water, made alkaline (pH 10) with ammonia and extracted with dichloromethane. Evaporation afforded 0.454 g (1.44 mmol, 97%) of amorphous **9a**.

4,5-Dimethylpyrocatechol (**17**)

3,4-Dimethylphenol (**14**, 0.50 g, 4.1 mmol) was oxidised with Fremy's salt as described in ref. 17. After 30 min the 4,5-dimethyl-1,2-quinone was reduced *in situ* with 0.31 g (8.2 mmol) of sodium tetrahydridoborate. The solution was decolourised immediately and was then acidified with dilute aqueous HCl. Extraction with chloroform afforded, after evaporation, 0.41 g (3.0 mmol, 73%) of crystalline **17**. ^{1}H NMR in CCl_4: δ 1.97 (s, 6H, CH_3); δ 6.00 (s, 2H, OH); δ 6.45 (s, 2H, H–Ar).

3-Bromo-4,5-dimethylpyrocatechol (**16**) *from* **15** *and from* **17**, *respectively*

A solution of 0.50 g (2.5 mmol) of **15** {^{1}H-NMR ($CDCl_3$): δ 2.11 (s, 6H, 2 × CH_3); 5.28 (s, 1H, OH); 6.78 (s, 1H, H(6)); 7.15 (s, 1H, H(3)} in 80 ml of methanol was added at 0°C to a solution of 3.0 g (11.2 mmol, 2.3 equiv.) of Fremy's salt in a mixture of 300 ml of water and 20 ml of 1/6 M-NaH_2PO_4. After 2½ h, 1 g of iron powder suspended in 10 ml of 1/6 *M*-phosphoric acid was added and the mixture was stirred for 20 min. The excess of iron was removed with the aid of a magnet and phosphoric acid was added until the precipitate had been completely dissolved. The solution was extracted four times each with 30 ml of chloroform. The combined extracts were washed with 1/6 *M*-H_3PO_4, dried, and evaporated. The residue (0.40 g, 1.84 mmol, 77%) was chromatographed on a column of deactivated silica with chloroform as the eluent. The product, **16**, was crystallized from cyclohexane, m.p. 101°C

(decomp.), ^{1}H NMR in $CDCl_3/CCl_4$ (1 : 1): δ 2.17 and δ 2.20 (2 × s, 2 × 3H, CH_3(3) and CH_3(4)); δ 5.37 (s, 2H, OH); δ 6.62 (s, 1H, H(5)).

A solution of 0.141 g of bromine in 5 ml of acetic acid was added during 30 min to a solution of 0.121 g (0.87 mmol) of **17** in a mixture of 5 ml of acetic acid and 0.1 ml of 48% HBr. The solvent was evaporated *in vacuo* and the residue was chromatographed on a column of deactivated silica with chloroform as the eluent. Evaporation of the main fraction gave **16**, identical (^{1}H NMR, IR, HPLC) to that prepared by oxidation and reduction of **15**.

Reduction of **16**

Lithium tetrahydridoaluminate (150 mg, 3.95 mmol) was added to a solution of 100 mg (0.46 mmol) of **16** in 10 ml of THF. The solution was boiled during 48 h, the excess of the reagent was destroyed with ethyl acetate, and dilute aqueous acetic acid, respectively. The solution was extracted with ether several times. Evaporation gave 35 mg (0.25 mmol, 55%) of crystalline **17**, identical (^{1}H-NMR, IR, HPLC) to that prepared by oxidation and reduction of **14**.

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** We mentioned[6] that *Weller* and *Rapoport*[7] found 65% of the brominated material to be 1,5α,7β-tribromodihydrothebainone. This must be 1,5β,7α-tribromodihydrothebainone, as can be seen also from our Figure 4[6].

*** In 20% aqueous methanol, Fremy's salt still dissolves reasonably, so that it was found possible to carry out the reaction at −10°C; in that case ~ 15% of **7a** was formed. The pH did not have much influence on the selectivity, but it did affect the stability of the *ortho*-quinone formed; the optimal pH was found to be 2–4.

**** Results of two independent molecules in the unit cell.

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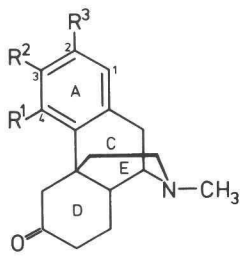
3b. X-Ray Analysis of 4-Bromo-2,3-dimethoxy-*N*-methyl--6-oxomorphinan*

Preliminary information. The introduction of a hydroxyl group at position 4 in (-)-2-bromo-3-hydroxy-*N*-methyl-6-oxomorphinan (1, Fig. I) gives a potential precursor for the synthesis of morphine and codeine†. Oxidation of 1 with Fremy's Salt, followed by reduction and methylation was expected to give 2-bromo-3,4-dimethoxy-*N*-methyl-6-oxomorphinan (2). However, removal of the bromo atom by catalytic hydrogenolysis afforded (-)-2,3-dimethoxy-*N*--methyl-6-oxomorphinan (3, Olieman *et al.*, 1979). Therefore, the structure of the reaction product of 1 should be 4-bromo-2,3-dimethoxy-*N*-methyl-6--oxomorphinan (4), instead of 2, supposing no rearrangement has taken place during the hydrogenolysis. No evidence in favour of one of the structures 2 or 4 could be obtained from ^{1}H and ^{13}C NMR and therefore a single-crystal X-ray analysis was started. This analysis confirmed structure 4 for the reaction product of 1.

Crystal data. From single-crystal diffractometry, Cu-K_{α_1} = 1.54051 Å. a = 10.893(3), b = 13.690(4), c = 11.836(3) Å, β = 91.13(4)°, space group $P2_1$, D_m = 1.47 g/cm^3, D_c = 1.482 g/cm^3, for Z = 4.

* A reprint of H. van Koningsveld and C. Olieman, Cryst. Struct. Comm. *9*, 11 (1980).



1: R^1 = H, R^2 = OH, R^3 = Br
2: R^1 = R^2 = OCH_3, R^3 = Br
3: R^1 = H, R^2 = R^3 = OCH_3
4: R^1 = Br, R^2 = R^3 = OCH_3

Fig. I

Intensity data, structure determination and refinement. Intensities of 2650 independent reflections above background (I > 2.85 σ(I)) were measured from an orange-red crystal with the shape of a triangular plate of dimensions *ca.* 0.5, 0.6, 0.6, 0.15 mm using a computer controlled NONIUS single-crystal diffractometer. The structure was solved by Patterson and Fourier techniques and refined by full-matrix least-squares calculations, using programs of the XRAY system (1972). The form factors for Br, C, N, and O were taken from Cromer and Mann (1968). No absorption correction has been applied ($\mu_{Cu\text{-}K_\alpha}$ = 36.4 cm^{-1}). All heavy atoms were refined anisotropically. No hydrogen atoms were placed, although some peaks in a difference map were located on places where hydrogen atoms could be expected. Calculation of structure factors indicated that the intensities of 26 reflections (*e.g.* 13 h 0 1, 7 h 1 1 reflections) were apparently strongly attenuated by absorption and secondary extinction. These reflections were omitted in the final refinements. The final conventional *R*-value is 8.1%. The final atomic coordinates for both independent molecules I and II are listed in Table I. The absolute configuration has not been established by the effect of anomalous dispersion because of the strong absorption encountered. However, calculation of structure factors for the antipode resulted in a higher *R*-value.

Table I. *Final atomic fractional coordinates (× 10^4 for Br, × 10^3 for the other atoms) and their estimated standard deviations in parenthesis for molecules I and II.*

Atom	*x/a*		*y/b*		*z/c*	
	I	II	I	II	I	II
C1	85(1)	472(1)	245(1)	35(1)	-6(1)	544(1)
C2	13(1)	506(1)	162(1)	-44(1)	-1(1)	474(1)
C3	53(1)	427(2)	89(1)	-119(1)	80(1)	463(1)
C4	156(1)	320(1)	101(1)	-119(1)	142(1)	509(1)
C5	441(2)	110(2)	105(1)	-137(1)	215(1)	703(2)
C6	484(2)	193(2)	69(1)	-177(2)	97(2)	794(2)
C7	555(2)	217(2)	144(1)	-113(2)	27(2)	891(2)
C8	476(1)	260(2)	237(1)	-12(1)	17(1)	848(1)
C9	365(1)	213(2)	368(1)	132(1)	122(1)	715(1)
C10	258(1)	338(1)	353(1)	125(1)	47(1)	670(1)
C11	192(1)	361(1)	254(1)	33(1)	59(1)	599(1)
C12	236(1)	278(1)	181(1)	-42(1)	133(1)	592(1)
C13	354(1)	160(1)	197(1)	-39(1)	197(1)	655(1)
C14	439(1)	172(1)	274(1)	28(1)	135(1)	758(1)
C15	330(1)	57(1)	239(1)	6(1)	316(1)	579(1)
C16	264(1)	89(2)	335(1)	112(1)	307(1)	542(1)
C17	286(2)	139(2)	504(1)	275(1)	238(1)	617(2)
C18	-127(1)	698(2)	215(1)	27(2)	-148(1)	422(2)
C19	-126(1)	455(2)	22(1)	-183(2)	158(1)	277(2)
Br	1803(2)	2051(2)	0*	-2176(2)	2515(2)	4604(2)
N	340(1)	116(1)	403(1)	170(1)	241(1)	652(1)
O1	-93(1)	617(1)	145(1)	-49(1)	-56(1)	418(1)
O2	-23(1)	457(1)	7(1)	-200(1)	89(1)	396(1)
O3	467(2)	237(2)	-15(1)	-257(1)	69(1)	782(1)

* Parameter was held fixed.

Table II. *Bond distances* (Å)

	I	II		I	II		I	II
1	1.39(2)	1.38(2)	10	1.46(2)	1.47(2)	19	1.59(2)	1.53(2)
2	1.38(2)	1.41(2)	11	1.53(2)	1.54(2)	20	1.59(2)	1.56(2)
3	1.44(2)	1.34(2)	12	1.42(2)	1.38(2)	21	1.51(2)	1.52(2)
4	1.34(2)	1.30(2)	13	1.49(2)	1.50(2)	22	1.22(2)	1.21(2)
5	1.41(2)	1.51(2)	14	1.56(2)	1.55(2)	23	1.33(2)	1.39(2)
6	1.55(2)	1.49(3)	15	1.49(2)	1.56(3)	24	1.49(2)	1.38(3)
7	1.54(3)	1.47(3)	16	1.49(2)	1.55(2)	25	1.40(2)	1.40(2)
8	1.54(3)	1.56(3)	17	1.52(2)	1.38(2)	26	1.41(2)	1.42(2)
9	1.54(2)	1.52(2)	18	1.53(2)	1.58(2)	27	1.91(1)	1.92(1)

Bond angles (°)

	I	II		I	II		I	II
1,2	122(1)	120(1)	6,7	116(2)	116(2)	13,19	112(1)	110(1)
1,11	115(1)	113(1)	6,20	109(1)	112(1)	13,20	117(1)	118(1)
1,12	123(1)	125(1)	6,22	120(2)	119(2)	14,15	111(1)	112(1)
2,3	116(1)	118(1)	7,8	108(2)	109(2)	14,19	106(1)	106(1)
2,23	127(1)	124(2)	7,22	124(2)	125(2)	14,20	107(1)	108(1)
3,4	121(1)	122(2)	8,9	111(1)	111(1)	15,16	109(1)	106(1)
3,23	117(1)	118(2)	9,18	109(1)	112(1)	16,17	114(1)	113(1)
3,25	116(1)	120(1)	9,19	111(1)	113(1)	16,21	112(1)	107(1)
4,5	125(1)	124(1)	10,11	117(1)	114(1)	17,18	106(1)	107(1)
4,25	123(1)	118(1)	10,17	117(1)	122(1)	17,21	110(1)	112(1)
4,27	113(1)	117(1)	10,18	110(1)	109(1)	18,19	107(1)	108(1)
5,12	113(1)	110(1)	11,12	121(1)	122(1)	19,20	104(1)	105(1)
5,13	128(1)	128(1)	12,13	119(1)	121(1)	23,24	117(1)	121(1)
5,27	122(1)	119(1)	13,14	111(1)	110(1)	25,26	114(1)	115(1)

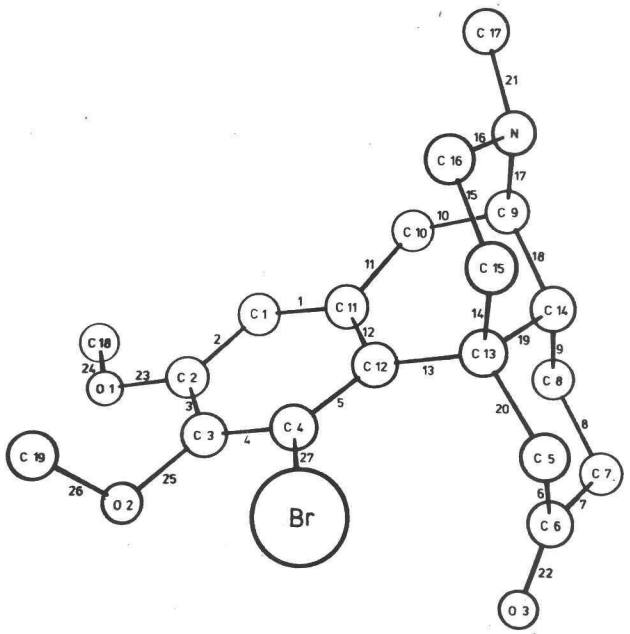


Fig. II

Comments. The structure of the molecule is shown in Fig. II. Bond distances and angles are listed in Table II. Features of molecule I are given below. The analogous results for molecule II are given between square brackets.

a) The bromo atom is 0.23 Å [0.38 Å] from the aromatic ring plane A (σ = 0.02 [0.02]).

b) In both molecules O1 and O2 are nearly in the ring plane A; the maximum deviation is 0.07 Å for O2 in molecule II.

c) The dihedral angle C18O1C2C1 is 9° [5°]. The C18 and Br atoms are at different [the same] side of plane A.

d) The dihedral angle C19O2C3C2 is 80° [71°], undoubtedly caused by the methoxy and bromo substituents in ortho positions. In both molecules the C19 and Br atoms are on the same side of plane A.

e) The angle between the least-square plane through the atoms of the ring D and E (σ = 0.27 [0.26]) and plane A is 90° [88°], close to the angle found in other morphinans (81.9°-90.9°, Gylbert *et al.*, 1977).

f) The distance between the bromo atoms in molecule I and II is 3.877(3) Å. This distance is approximately equal to twice the Van der Waals radius of the bromo atom (3.90 Å, Pauling, 1960).

g) The nitrogen-carbon bond distance 17 in molecule II is significantly shorter than the corresponding distance in I and in other morphinans (1.48-1.53 Å, Gylbert *et al.*, 1977; Hardy *et al.*, 1975). Repetition of molecule II along a twofold screw axis results in a distance of 4.02(1) Å between the nitrogen atom in the original molecule II and the bromo atom in the repeated molecule II. This is only 0.57 Å more than the sum of the Van der Waals radii (3.45 Å, Pauling, 1960). There are no other non-bonded contacts smaller than 5 Å between nitrogen and bromo atoms.

References

* The present paper is related to synthetic investigations in this Laboratory; see Beyerman, H.C. *et al.*, The Chemistry of Opium Alkaloids, Part X, (1978), *Recl. Trav. Chim. Pays-Bas* 97, 127 and preceding publications.

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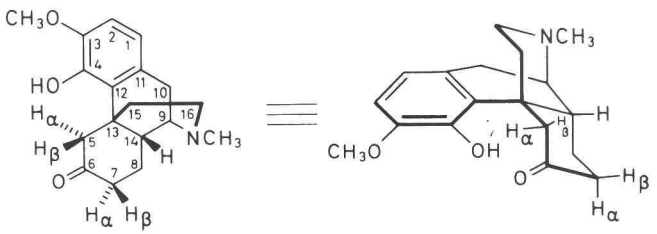
4. On the Closure of the 4,5-Oxygen Bridge in Morphinans. ^{1}H and ^{13}C NMR Spectroscopy of Brominated Intermediates*

Introduction

In our synthesis of morphine and its derivatives[1,2] it was especially the formation of the complex carbon skeleton of (−)-dihydrothebainone (**1**) from 1-benzylisoquinolines which received attention. For the conversion of **1** into codeine the closure of the 4,5-oxygen bridge is needed. This conversion has already been carried out[3,4]. For this purpose dihydrothebainone is treated with bromine, in the course of which initially substitution at position 1 of the aromatic nucleus occurs. Next, mono- and di-α-bromination with respect to the carbonyl group takes place. The oxygen bridge is formed with separation of hydrogen bromide. This reaction was first studied by *Schöpf* et al.[3], who assumed that one bromide atom in position 5 is needed for the ring closure, and from the fact that 1-bromosinomeninone was isolated, concluded that a subsequent (third) bromine atom was present in position 7. Later, evidence was obtained along several lines that the third equivalent of bromine leads directly to 1,7-dibromodihydrocodeinone[4]; there were too few data to define the initially formed tribrominated product.

* A reprint of C. Olieman, L. Maat, and H.C. Beyerman, Recl. Trav. Chim. Pays-Bas *97*, 31 (1978).



(−)-Dihydrothebainone (**1**)

In order to achieve optimum yield of the 4,5-oxygen bridge closure[1,5] we studied brominated intermediates by ^{1}H and ^{13}C NMR spectroscopy.

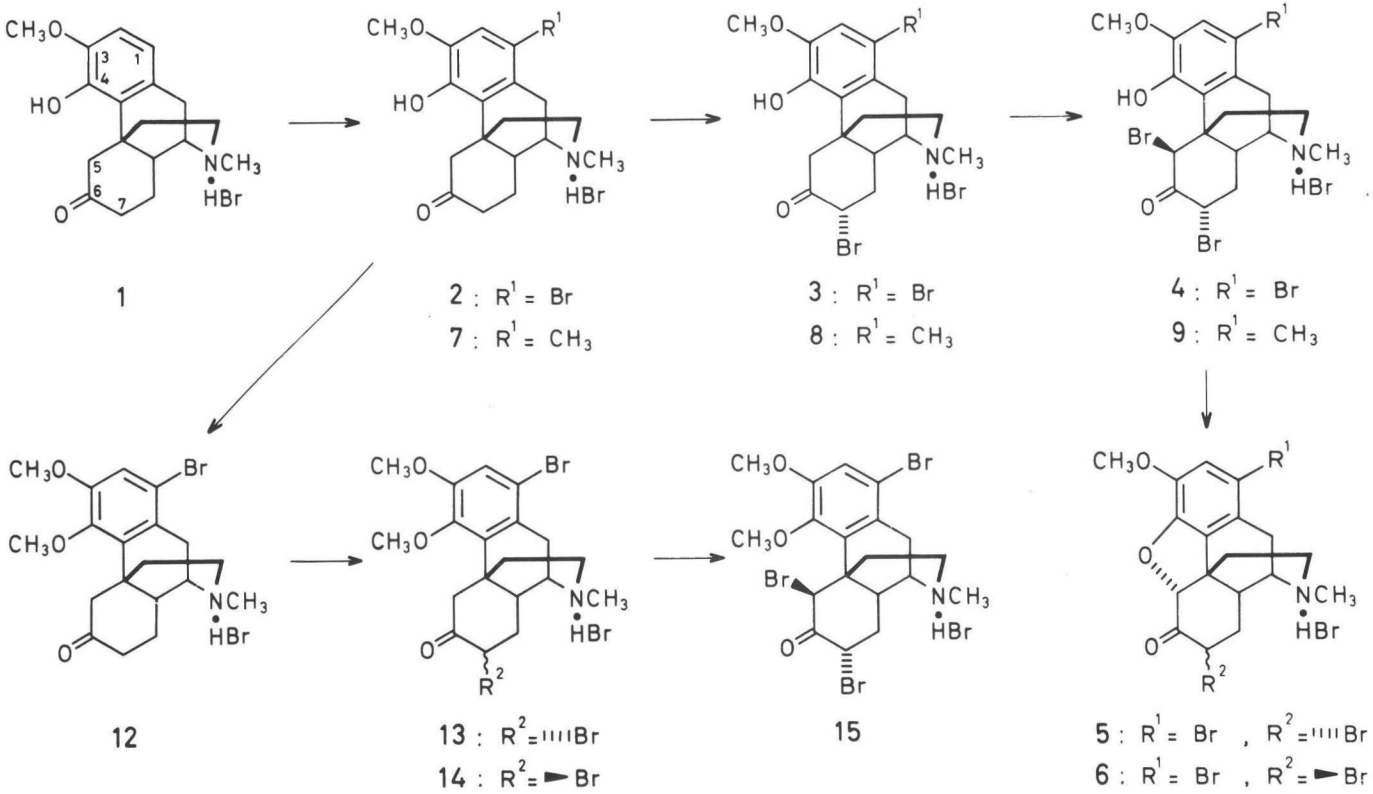
In a recent publication some brominated dihydrothebainones were studied by ^{1}H NMR[6]. 1,7α-Dibromodihydrothebainone (**3**) showed no distinguishing absorption in the region δ 4–7 for C(7) hydrogen of **3**.
Also the presence of 1,7,7-tribromodihydrothebainone after tribromination of dihydrothebainone could not be excluded, since only 65% of the material comprised 1,5β,7α-tribromodihydrothebainone (**4**).

We found ^{13}C NMR pre-eminently suited for characterizing the reactive tribrominated dihydrothebainones **4** and **9** (Scheme). The compounds were prepared in acetic acid in which they are reasonably stable and, after careful evaporation of the solvent, dissolved in trideuterioacetic acid. From our ^{13}C NMR data it appears that by tribromination of **1** only 1,5β,7α-tribromodihydrothebainone (**4**) is formed.

The O^4-methyl group in 1-bromo-O^4-methyldihydrothebainone (**12**) prevents the closure of the oxygen bridge. Consequently, bromination leads to stable products. Here again, on bromination only the 1,5β,7α-tribromo derivative (**15**) is formed. A bromine atom in position 1 – *para* with respect to the phenolic hydroxyl group involved in the oxygen bridge formation – is not essential for ring closure, as can be inferred from the fact that this reaction is also possible with 1-methyldihydrothebainone (**7**).

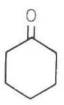
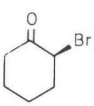
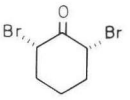
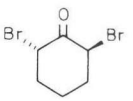
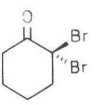
Results and discussion

The steric structure of dihydrothebainone (**1**) shows that of the four possible positions of the bromine atoms introduced



Scheme. *Bromination of* (−)*-dihydrothebainone* (**1**) *and derivatives.*

Table I ^{13}C *Chemical shifts* (δ) *of* α*-brominated cyclohexanones in trideuterioacetic acid (and between brackets in deuteriochloroform).*

C atom	Compound				
					
1	214.3 (211.6)	204.8 (203.4)	194.9 (193.2)	196.4 (195.3)	196.1 (195.1)
2	42.1 (42.1)	54.6 (53.6)	54.2 (52.7)	51.9 (50.8)	70.6 (69.6)
3	27.6 (27.1)	37.7 (37.0)	40.0 (39.1)	37.6 (37.3)	50.8 (50.3)
4	25.4 (25.1)	23.1 (22.2)	26.8 (26.0)	22.2 (21.8)	24.5[a] (24.0)
5	27.6 (27.1)	27.3 (26.8)	40.0 (39.1)	37.6 (37.3)	26.6[a] (26.3)
6	42.1 (42.1)	38.7 (38.0)	54.2 (52.7)	51.9 (50.8)	36.0 (35.5)

[a] May be interchanged.

adjacent to the carbonyl group position 5α is less accessible. The other positions which the bromine atoms may occupy will affect the reaction mechanism and the circumstances of the closure of the oxygen bridge. The position of the bromine atom in position 7, remaining after the ring closure, is important for the introduction of the double bond between C(7) and C(8) present in codeine and morphine.

We were able to characterize the whole series of compounds by ^{1}H and ^{13}C NMR spectroscopy. The assignments for the carbonyl and adjacent carbon atoms C(5) and C(7) in the ^{13}C NMR spectra were made by comparison with data from suitably substituted cyclohexanones (Table I).

It should be borne in mind in evaluating the data from Table I, that 2-bromocyclohexanone exists as an equilibrium between two conformers, one with an axial and one with an equatorial bromine atom[7], while for *trans*-2,6-dibromocyclohexanone two equivalent conformers, each with an axial and an equatorial bromine atom, are in equilibrium. Both equilibria are rapid on the NMR time-scale. Comparison of the data from *cis*- and *trans*-2,6-dibromocyclohexanone for C(4) and C(2)/C(6) reveals that the so-called γ-effect[8] of an axial bromine atom is an up-field shift of about 4.5 ppm. This effect is also operative

Table II ^{13}C *Chemical shifts* (δ) *of brominated dihydrothebainones,* δ_c *in trideuterioacetic acid.*

C atom	Compound 1	2	3	4	7	8	9	12	13	14	15[a]
1	120.2	114.0	114.2	115.0	121.5	120.7	122.0	118.9	119.1	119.0	119.4
2	111.7	115.5	115.7	116.0	113.4	113.6	113.7	117.6	117.9	117.9	118.8
3	147.1	148.0	148.1	148.2	146.9	146.8	147.1	149.2	149.1	149.4	148.1
4	145.9	145.8	145.8	145.5	144.0	143.9	144.1	153.7	153.7	153.9	153.5
5	49.5	49.2	47.5	55.8	49.5	46.4	55.7	49.9	48.7	49.7	56.0
6	214.1	213.1	201.1	195.1	214.6	201.2	195.5	212.1	200.5	203.2	195.6
7	41.7	41.7	54.7	52.2	41.4	54.8	52.9	41.7	54.9	54.7	54.8
8	26.9	26.7	39.2	38.7	26.4	38.0	38.8	26.6[b]	39.0	38.1	38.3[b]
9	60.7	60.3	59.5	58.8	60.6	59.9	59.2	60.1	59.3	59.3	58.5
10	24.2	26.7	26.3	26.9	27.7	27.0	26.9	26.9[b]	26.8	27.1	26.7
11	127.3	126.0	125.6	125.9	127.9	128.1	128.9	126.0	125.6	126.0	125.8
12	121.6	123.7	122.8	120.3	125.1	125.0	124.8	131.0	129.9	130.3	127.1
13	40.5	40.5	41.4	49.9	40.6	41.2	50.1	40.5	41.0	42.0	49.5
14	42.8	42.4	43.2	43.9	42.5	42.9	43.5	42.5	43.9	43.8	43.9
15	36.8	36.4	35.5	36.5	36.7	35.6	35.5	37.6	37.0	37.0	37.6[b]
16	48.5	48.2	48.2	48.1	48.5	48.4	49.0	48.1	48.1	48.1	47.4
$N-CH_3$	41.7	41.0	41.7	42.1	40.7	42.1	42.2	41.2	41.7	41.5	41.5
$-O-CH_3$	56.8	57.0	57.0	57.4	56.8	56.8	56.8	56.6	56.7	56.6	56.8
$-CH_3$					25.4	26.2	26.2				
$-O^4-CH_3$								61.1	61.3	61.2	61.6

[a] Because of poor solubility in trideuterioacetic acid, 100 mg of **15** were dissolved in 2.5 ml of a mixture of trideuterioacetic acid, octadeuteriodioxane, and water (45 : 45 : 10).

[b] These assignments may be interchanged in each column.

1 Dihydrothebainone hydrochloride.

in 2-bromocyclohexanone, and clearly visible in the chemical shifts of C(4) and C(6).
The signals of the ^{13}C NMR spectrum of 1-bromodihydrothebainone hydrobromide (**2**) in trideuterioacetic acid could be assigned with the aid of an off-resonance proton decoupled spectrum and data from the literature[9] (Table II). Bromination of **2** yielded 1,7α-dibromodihydrothebainone hydrobromide (**3**). The equatorial position of the bromine atom on carbon 7 appeared from ^{1}H NMR, a double doublet centred at δ 5.02 (J_{aa} 12 Hz, J_{ae} 6 Hz). The ^{13}C NMR spectrum of **3** is consistent with those of the model compounds (Table I). The small variations can be attributed to the preferentially axial position of the bromine atom in 2-bromocyclohexanone[7,10] [see also 1,7α- and 1,7β-dibromo-O^4-methyldihydrothebainone hydrobromide (**13** and **14**)]. The ^{13}C NMR spectrum of the reaction mixture of the monobromination of 1-methyldihydrothebainone also showed the presence of the 7α-substituted compound (**8**), while in addition two other compounds were present, possibly the 7β- [C(6) δ 204.1] and 5α-substituted compound [C(6) δ 205.1]. Dibromination of 1-bromodihydrothebainone hydrobromide gave only 1,5β,7α-tribromodihydrothebainone hydrobromide (**4**), as appeared from the ^{13}C NMR spectrum of the reaction product. The values are consistent with those of *trans*-2,6-dibromocyclohexanone in a fixed conformation. The presence of 1,7,7-tribromodihydrothebainone hydrobromide was excluded because no signals were present at ~ δ 70 (2,2-dibromocyclohexanone). The dibromination of 1-bromodihydrothebainone hydrobromide (**2**) in glacial acetic acid therefore proceeds analogously to that of cyclohexanone, where *trans*-2,6-dibromocyclohexanone is the main product after equilibration[10]. Bromine in the equatorial position on C(5) is unlikely for steric reasons.

The dibromination of 1-methyldihydrothebainone[2] (**7**) was carried out as described for that of 1-bromodihydrothebainone hydrobromide (**2**), but in the dark to prevent radical bromination. The ^{13}C NMR spectrum showed that the main product was 5β,7α-dibromo-1-methyldihydrothebainone hydrobromide (**9**), while a small amount of products with a closed oxygen bridge was present (**10** and **11**).

Methylation of the 4-hydroxyl group of 1-bromodihydrothebainone (**2**) yielded 1-bromo-O^4-methyldihydrothebainone hydrobromide (**12**). This protection of the 4-hydroxyl group prevents the closure of the oxygen bridge. In the ^{13}C NMR spectrum C(4) has undergone a downfield shift of Δδ 7.9 in relation to 1-bromodihydrothebainone hydrobromide (**2**), which is in agreement with the literature[11].

Bromination of **12** yielded 1,7α-dibromo-O^4-methyldihydrothebainone hydrobromide (**13**). The ^{1}H NMR spectrum showed a double doublet, centred at δ 4.95 (J_{aa} 13 Hz, J_{ae} 6 Hz), which confirmed the equatorial position of the bro-

mine atom on C(7). The ^{13}C NMR spectrum of **13** was similar to that of **3**. After 15 h at 35° compound **13** epimerized in acetic acid to a mixture of 1,7α- and 1,7β-dibromo-O^4-methyldihydrothebainone hydrobromide [**13** (60%) and **14** (40%)]. Dibromination of **12** yielded 1,5β,7α-tribromo-O^4-methyldihydrothebainone hydrobromide (**15**), which was found to be a stable, crystalline compound. In the ^1H NMR spectrum at δ 6.20 a singlet of the 5α-proton was present, which had undergone a downfield shift of Δδ 1.98, which was due to the 5β-bromine atom. A double doublet centred at δ 5.90 (J_{aa} 13 Hz, J_{ae} 6 Hz) confirmed the presence of the 7α-bromine atom. The ^{13}C NMR spectrum was completely consistent with that of 1,5β,7α-tribromodihydrothebainone hydrobromide (**4**) which supports the correctness of the structure of **4**.

Table III ^{13}C *Chemical shifts* (δ) *of dihydrocodeinones,* δ_c *in trideuterioacetic acid.*

C atom	Compound			
	5	**6**	**16**	**17**
1	114.6	114.6	114.2	122.0
2	120.2	120.2	119.6	118.1
3	145.6	145.6	145.3	144.0
4	146.1	146.1	146.2	144.5
5	88.8	92.0	91.6	91.3
6	200.3	199.6	209.3	210.3
7	52.9	52.9	39.9	40.0
8	36.0	37.0	25.3	25.4
9	61.7	61.5	62.1	62.3
10	–	–	23.1	–
11	123.5	123.4	123.5	126.9
12	128.0	128.2	128.6	130.9
13	46.9	45.7	46.5	46.2
14	39.8	39.8	39.9	39.9
15	33.1	33.1	33.4	33.6
16	49.7	48.7	48.7	48.9
$N-CH_3$	42.2	42.2	42.2	42.1
$-O-CH_3$	58.0	58.0	57.7	57.6

16 1-Bromodihydrocodeinone hydrobromide.
17 1-Methyldihydrocodeinone hydrobromide.

The next step in our synthesis is the closure of the oxygen bridge.

Boiling of 1,5β,7α-tribromodihydrothebainone hydrobromide (**4**) in ethanol yielded almost quantitatively a mixture of 1,7α- and 1,7β-dibromodihydrocodeinone hydrobromides (**5** and **6**). The ^{13}C NMR spectrum of the equilibrium mixture of **5** (35%) and **6** (65%) showed the largest shifts in relation to 1-bromodihydrocodeinone hydrobromide (**16**) for carbons 5, 6 and 7 (Table III). Further, it is found that

the shift of the bromine-substituted carbon 7 is independent of the position of the bromine atom.

Starting with 5β,7α-dibromo-1-methyldihydrothebainone hydrobromide (**9**), the ring closure proceeded also readily by boiling with ethanol and yielded a mixture of 7α- and 7β-bromo-1-methyldihydrocodeinone hydrobromides (**10** and **11**). After a catalytic hydrogenolysis of bromine at C(7), the 1-methyldihydrocodeinone thus formed was found to be identical with that prepared by methylation of dihydrocodeinone[12]. As regards the oxygen bridge closure, bromine in position 1 has no more perceptible influence on the result of the reaction than the methyl group, as appears from the conversion of 1-methyldihydrothebainone (**7**) into 1-methyldihydrocodeinone.
The oxygen bridge formation that follows the removal of the 5β-bromine substituent is now possible *via* an S_{N^2} mechanism.

Experimental part

Combustion analyses were performed by Mr *H. M. A. Buurmans*. ^{13}C NMR spectra were obtained with a Varian CFT-20 spectrometer [spectral width 5000 Hz, pulse width 8 μs (α 45°), 8 K, acquisition time 0.8 s, pulse delay = acquisition time]. The compounds were dissolved in trideuterioacetic acid (0.4 M). The ^{13}C-chemical shifts were measured in ppm from internal tetramethylsilane (TMS). The ^1H NMR spectra were measured with a Varian T-60 spectrometer. The compounds were dissolved (10% w/v) in deuteriochloroform and/or hexadeuteriodimethyl sulfoxide. TMS was used as internal reference. Rotations were measured with a Perkin-Elmer P-141 polarimeter. The purity of the compounds was checked by HPLC on a reversed-phase column (1 ft, 4 mm, Merck RP-18) with mixtures of methanol and water, containing 0.005 *M* heptanesulfonic acid (ion-pair method)[13].

1,7α-Dibromodihydrothebainone hydrobromide (**3**)

To a solution of 1.80 g (3.9 mmol) of **2** in 40 ml of acetic acid 31.8 ml of 0.123 *M* bromine in acetic acid (1 eq) was added over 2 h. The solvent was evaporated *in vacuo*. The residue was triturated four times with ether to remove the excess of hydrogen bromide. The solid was mixed with 20 ml of water and methanol was added to dissolve the product. Compound **3** (1.15 g; 2.1 mmol; 55%) crystallized; m.p. 210° (dec.). ^1H NMR ($CDCl_3$ and DMSO-d_6): δ 2.90 (s, 3H, CH_3N); δ 3.85 (s, 3H, CH_3O); δ 4.55 (d, *J* 13 Hz, 1H, 5α-*H*); δ 5.02 (dd, J_{aa} 12 Hz, J_{ae} 6 Hz, 1H, 7β-*H*); δ 6.97 (s, 1H, *H*Ar), IR (KBr): 1727 cm^{-1} (C=O), $[\alpha]_D^{25}$ −64°; $[\alpha]_{365}^{25}$ −375° (*c* 1.46, water).

1,5β,7α-Tribromodihydrothebainone hydrobromide (**4**)

To a solution of 0.462 g (1.0 mmol) of **2** in 25 ml of acetic acid, 10.6 ml of 0.188 M bromine in acetic acid (2 eq) was added over 2½ h. The solvent was carefully evaporated *in vacuo* and the residue (**4**) was dissolved in trideuterioacetic acid for recording a ^{13}C NMR spectrum.

Dihydrocodeinone

1,5β,7α-Tribromodihydrothebainone hydrobromide (**4**) (0.61 g, 1.0 mmol) was boiled in 5 ml of ethanol for ½ h. Evaporation of the solvent *in vacuo* afforded an equilibrium mixture of 1,7α- and 1,7β-dibromodihydrocodeinone hydrobromides (**5** and **6**) as indicated by HPLC; methanol/water (60 : 40), 0.005 M heptanesulfonic acid, **5** (35 %) K′ 1.0 and **6** (65 %) K′ 2.9. The solid was hydrogenated in 10 ml of a buffer of 2 *N* acetic acid and 1.8 g anhydrous sodium acetate in the presence of 30 mg 10 %-Pd/C as a catalyst at 45° and 1 atm. After 2 h the catalyst was filtered off, the filtrate was made alkaline and extracted with chloroform. The chloroform was dried with Na_2SO_4 and evaporated *in vacuo*. Dihydrocodeinone (0.23 g, 0.77 mmol, 77 %), identical with an authentic sample, crystallized from 1 ml of ethanol.

1-Methyldihydrocodeinone (**17**)

To a solution of 0.200 g (0.63 mmol) of 1-methyldihydrothebainone (**7**) in 10 ml of acetic acid, 0.11 ml (0.96 mmol) of a 47 % solution of hydrogen bromide was added. Bromine (2.78 ml, 0.456 M) in acetic acid was added in the dark over 2 h. The solvent was evaporated *in vacuo*. The residue was boiled in 10 ml of ethanol during ½ h. The ethanol was evaporated *in vacuo*. The residue was dissolved in 8 ml of a buffer of 2 *N* acetic acid and 1.5 g of anhydrous sodium acetate and hydrogenated in the presence of 30 mg of 10 %-Pd/C as a catalyst at 45° and 1 atm. After 2 h the catalyst was filtered off; the filtrate was made alkaline and extracted with chloroform. The chloroform was dried with Na_2SO_4 and evaporated *in vacuo*. 1-Methyldihydrocodeinone (**17**) (0.128 g, 0.41 mmol, 65 %) crystallized from 1 ml of ethanol. The IR spectrum was identical with that of 1-methyldihydrocodeinone prepared from dihydrocodeinone[12]. The ^{13}C NMR spectra of 7α-bromo-1-methyldihydrothebainone hydrobromide (**8**) and 5β,7α-dibromo-1-methyldihydrothebainone hydrobromide (**9**) were recorded of the crude products after bromination with one and two equivalents of bromine, respectively.

1-Bromo-O⁴-methyldihydrothebainone hydrobromide (**12**)

Phenyltrimethylammonium chloride (1.72 g, 10.0 mmol) and 1.09 g (20.2 mmol) of sodium methoxide were added to a solution of 1-bromodihydrothebainone (**2**, 2.57 g, 6.75 mmol) in 40 ml of dioxane. The suspension was boiled for 1½ h and the solvent was evaporated *in vacuo*. The residue was taken up in 40 ml of water and the pH was ajusted to 5 with acetic acid. Extraction with cyclohexane removed the by-product dimethylaniline. The aqueous layer was made alkaline and extracted with chloroform. The chloroform extract was dried with Na_2SO_4 and evaporated *in vacuo*. The residue was mixed with 5 ml of water, and one equivalent of concentrated hydrogen bromide was added. We obtained 2.59 g (5.45 mmol, 81 %) of 1-bromo-*O*⁴-methyldihydrothebainone hydrobromide (**12**), m.p. 155° (dec.). $C_{19}H_{24}BrNO_3 \cdot HBr$ (475.22): calcd. C 48.02; H 5.30; N 2.95, found C 47.9; H 5.5; N 3.0, ^1H NMR ($CDCl_3$): δ 2.90 (s, 3H, CH_3N); δ 3.81 (s, 3H, $CH_3OC(3)$); δ 3.97 (s, 3H, $CH_3OC(4)$); δ 7.10 (s, 1H, *H*Ar), IR (KBr): 1711 cm^{-1} (C=O), $[\alpha]_D^{25}$ −32°, $[\alpha]_{365}^{25}$ −248° (*c* 1.02, chloroform/ethanol 9 : 1).

1,7α-Dibromo-O⁴-methyldihydrothebainone hydrobromide (**13**)

To a solution of 1.10 g (2.31 mmol) of **12** in 25 ml of acetic acid, 12.6 ml of 0.183 M bromine in acetic acid (1 eq) was added over 1 h. The solvent was evaporated *in vacuo*. The residue was taken up in 4 ml of water, and methanol was added to dissolve the product on heating. Compound **13** (0.85 g, 1.51 mmol, 65% crystallized, m.p. 188° (dec.). $C_{19}H_{23}Br_2NO_3 \cdot HBr \cdot \frac{1}{2}H_2O$ (563.12): calcd. C 40.53; H 4.48; N 2.49, found C 40.4; H 4.6; N 2.5. The presence of water was also indicated by ^{1}H NMR and IR. ^{1}H NMR ($CDCl_3$): δ 2.90 (s, 3H, CH_3N); δ 3.84 (s, 3H, $CH_3OC(3)$); δ 4.01 (s, 3H, $CH_3OC(4)$); δ 4.22 (d, J 11 Hz, 1H, 5α-*H*); δ 4.96 (dd, J_{aa} 13 Hz, J_{ae} 6 Hz, 1H, 7β-*H*), δ 7.10 (s, 1H, *H*Ar), IR (KBr): 1731 cm^{-1} (C=O), $[\alpha]_D^{25}$ −40°, $[\alpha]_{365}^{25}$ −335° (*c* 1.01, chloroform/ethanol 9 : 1).

1,5β,7α-Tribromo-O⁴-methyldihydrothebainone hydrobromide (**15**)

Bromine in acetic acid (13.0 ml of 0.183 M, 2 eq) was added over $1\frac{1}{2}$ h to a solution of 0.560 (1.18 mmol) of **12** in 20 ml of acetic acid. The solvent was evaporated *in vacuo*. The residue was triturated with ether, dried, and mixed with 3 ml of water. The solid was filtered off and yielded 0.555 g (0.87 mmol, 74%) of **15**. The product was crystallized from dioxane/water 1 : 1, m.p. 222° (dec.). $C_{19}H_{22}Br_3NO_3 \cdot HBr$ (633.01): calcd. C 36.05; H 3.66; N 2.21, found C 35.9; H 3.9; N 2.1, ^{1}H NMR ($CDCl_3$ and DMSO-d_6): δ 2.90 (s, 3H, CH_3N); δ 3.86 (s, 3H, $CH_3OC(3)$); δ 3.94 (s, 3H, $CH_3OC(4)$); δ 5.90 (dd, J_{aa} 13 Hz, J_{ae} 6 Hz, 1H, 7β-*H*); δ 6.20 (s, 1H, 5α-*H*); δ 7.30 (s, 1H, *H*Ar), IR (KBr): 1720 cm^{-1} (C=O), $[\alpha]_D^{25}$ +33°; $[\alpha]_{365}^{25}$ +247° (*c* 1.00, chloroform/ethanol 9 : 1).

Acknowledgement

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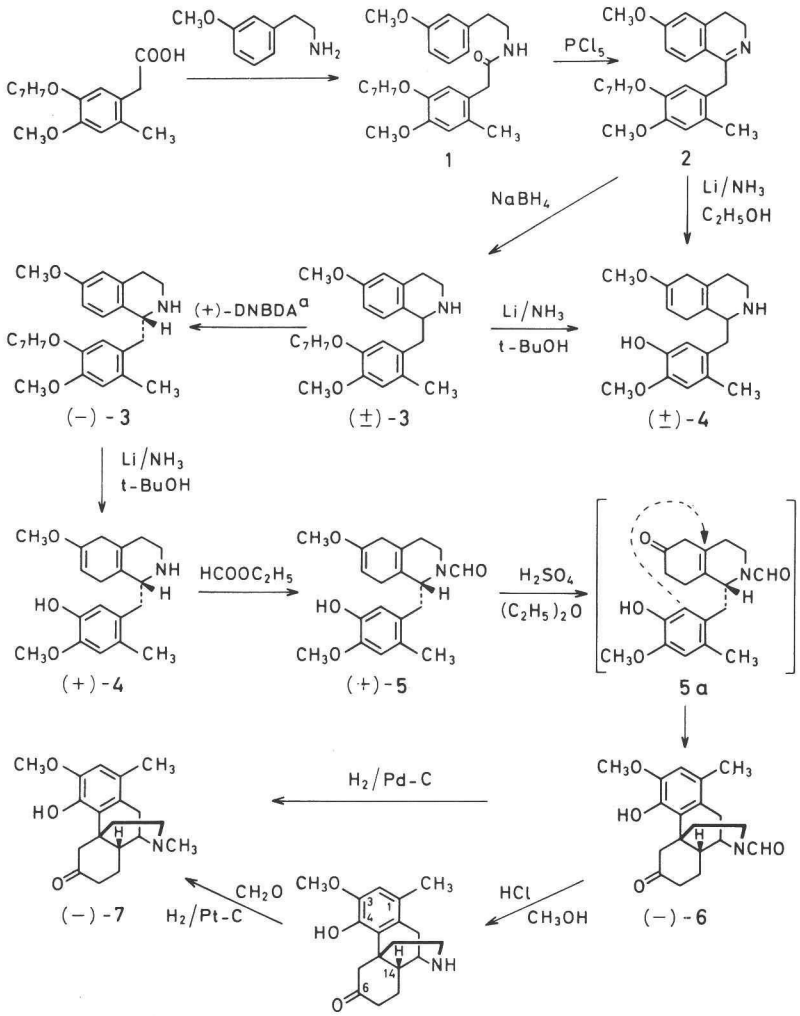
5. Synthesis of Racemic and of (+)- and (−)-1--Methyldihydrothebainone*

Introduction

In a preliminary communication[1] some of us reported the synthesis in a high yield of racemic *N*-formyl-1-methylnordihydrothebainone (Scheme 1, **6**). We now give the details. Moreover, we report the resolution of 1-(5-benzyloxy-4-methoxy-2-methylbenzyl)-1,2,3,4-tetrahydro-6-methoxyisoquinoline (**3**) with the aid of the optically active 6,6′-dinitrobiphenyl-2,2′-dicarboxylic acids. Each of the enantiomers of **3** was subjected to a Birch reduction, followed by a *N*-formylation and an acid-catalysed cyclization according to *Grewe*[2], as a result of which a high yield of (+)- and (−)-*N*-formyl-1-methylnordihydrothebainone (**6**) was formed. By reductive methylation we obtained (+)- and (−)-1-methyldihydrothebainone (**7**), respectively. The (−)-isomer of **7** was found to be identical with (−)-1-methyldihydrothebainone obtained from natural material[3].

In 1967 *Grewe* et al.[4] and *Morrison* et al.[5] independently published the cyclization of 1,2,3,4,5,8-hexahydro-1-(3-hydroxy-4-methoxybenzyl)-6-methoxy-2-methylisoquinoline (Scheme 2, **8**). Although they worked with different acids, *viz.* 85% phosphoric acid and 10% hydrochloric acid, respectively, both groups of workers obtained the 4-hydroxymorphinan **9** in a 3% yield and the isomeric 2-hydroxy compound **10** in a 37% yield. In order to obtain codeine and

* A reprint of H.C. Beyerman, E. Buurman, L. Maat, and C. Olieman, Recl. Trav. Chim. Pays-Bas 95, 184 (1976).

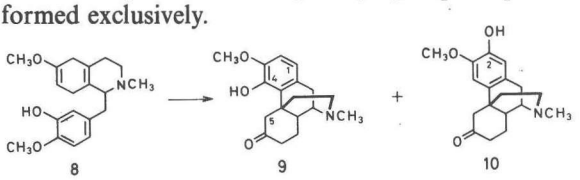


Scheme 1. Synthesis of racemic and of (+)- and (−)-1-methyldihydrothebainone, the synthesis depicted is that of (−)-1-methyldihydrothebainone (7) *with the natural configuration.*

[a] DNBA = 6,6′-dinitrobiphenyl-2,2′-dicarboxylic acid.

morphine, a hydroxyl group in position 4 is required; with this the oxygen bridge between the C atoms 4 and 5 can be closed[6]. The isomer **10** (37% yield) is unsuitable for this purpose.

We reasoned that a blocking group in position 2 of the benzyl radical would prevent formation of **10**, and we hoped that **9** might be the exclusive product. The choice of the blocking group is determined in the first instance by the reaction conditions during the preparation of **4**. For this we chose the methyl group, a stable substituent in a readily accessible starting material, but in a later stage it could not be removed. We proposed to repeat the synthesis with a removable substituent (*e.g.* halogen)[1]. A recent patent of Merck Inc.[7] mentions a bromine substituent in position 2 of the benzyl group. We found it impossible to repeat the procedure. Similar experiments by *DeGraw* et al.[8] were also unsuccessful. We had already applied a modified approach in the synthesis of morphine and codeine[9]. We used the symmetrically substituted 3,5-dibenzyloxy-4-methoxybenzyl radical, in consequence of which, after cyclization one morphinan derivative with the essential hydroxyl group in position 4 and a selectively removable hydroxyl group in position 2 is formed exclusively.



Scheme 2. Acid-catalysed cyclization of 1,2,3,4,5,8-hexahydro-1-(3-hydroxy-4-methoxybenzyl)-6-methoxy-2-methylisoquinoline (**8**).

2-Formyl-1,2,3,4,5,8-hexahydro-1-(5-hydroxy-4-methoxy-2-methylbenzyl)-6-methoxyisoquinoline (**5**) was prepared and subjected to the acid-catalysed cyclization. The cyclization of racemic **5** and of the enantiomers of **5** indeed results in high yields and exclusively in racemic and (+)- and (−)-*N*-formyl-1-methylnordihydrothebainone (**6**), respectively.

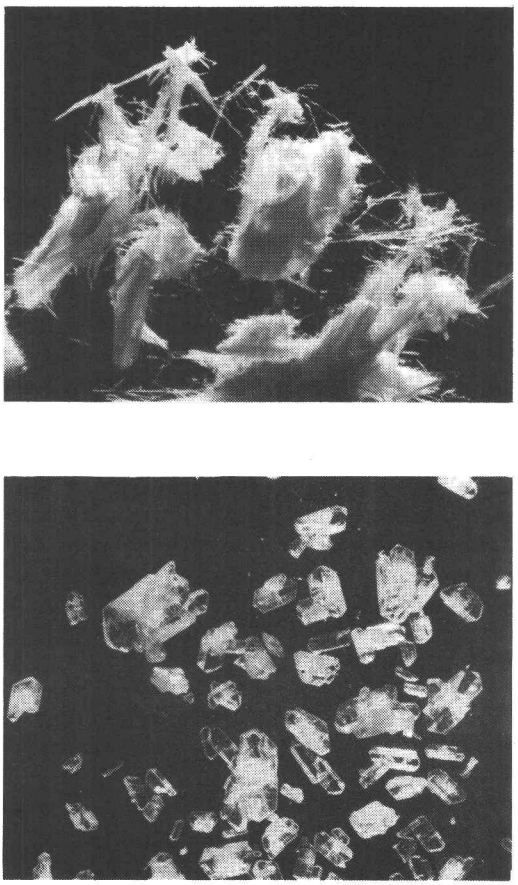
Results and discussion

For the synthesis of the title compounds we started from 3,4-dimethoxytoluene. By means of a Vilsmeier reaction a formyl group was introduced exclusively in position 2. The benzaldehyde thus obtained could be partially demethylated, in position 3. Successive treatment with potassium cyanide and tin(II) chloride afforded (5-hydroxy-4-methoxy-2-methylphenyl)acetic acid. This was benzylated in position 5 and condensed with 3-methoxyphenethylamine[10] (Scheme 1).

The amide **1** thus formed was converted into 3,4-dihydroisoquinoline **2** by means of a Bischler-Napieralski reaction. Subsequently, **2** was subjected to a Birch reduction[11]. The 1,2 double bond was reduced, the benzyloxy group removed, and the isoquinoline part reduced to 1,2,3,4,5,8-hexahydro-1-(5-hydroxy-4-methoxy-2-methylbenzyl)-6-methoxyisoquinoline (**4**). 1,2,3,4-Tetrahydro-1-(5-hydroxy-4-methoxy-2-methylbenzyl)-6-methoxyisoquinoline was isolated as a by-product if the correct quantities of co-solvent had not been used. In analogous reactions *Grewe* et al.[12] also found a by-product, which they called starting material without offering any evidence. Upon repeating *Grewe*'s experiment we could show that a 1,2,3,4-tetrahydroisoquinoline is indeed formed as a by-product. After the hydrogenolysis of the benzyl ether the remaining phenol is, as phenolate anion, unsusceptible to a Birch reduction.

The 1,2 double bond can first be reduced also with sodium tetrahydridoborate. Compound **3** can thus be obtained in almost quantitative yield. This compound (**3**) is the first in the synthesis with a chiral centre. Resolution was found possible with the aid of the 6,6′-dinitrobiphenyl-2,2′-dicarboxylic acids. After this, a Birch reduction afforded the enantiomers of **4**. Studies showed us that it may be preferable to carry out the cyclization with *N*-formyl compounds. The morphinan ring closure of **5** took place in high yield. The removable formyl group offers protection against oxidation, against ring closure towards the nitrogen, and favourably affects the desired ring closure, probably owing to steric and possibly inductive effects. An advantage of the *N*-formyl group is that it can be reduced to the *N*-methyl group. The formylation proceeds quantitatively by boiling with ethyl formate. The solubility of the optical antipodes differs considerably from that of the racemic mixture. The heterogeneous formylation of the racemate thus proceeded more rapidly than that of the enantiomers. There is a striking difference in appearance between the crystals of the hydrochlorides of racemic and optically active **3** (Plate).

The cyclization of **5** in a mixture of 80% sulfuric acid and ether (10 : 8) afforded *N*-formyl-1-methylnordihydrothebainone (**6**) in a yield of 85%. We presume that first **5** (enol ether) is converted into the intermediate **5a**. The spectroscopic data (NMR, MS, ORD) of the reaction product were in conformity with structure **6**. Formally, there is another possibility in the cyclization between the *ortho* position of the benzyl group with C-4a of the isoquinoline part. This gives the undesirable addition in which the hydrogen on C-14 of the morphinan does not get into the β position, but into the α position (Figure 1). An important peak in the mass spectrum for the ion (*m/e* 73) corresponding to the loss of the *N*-formyliminoethano bridge, pointed to the desired structure[13].

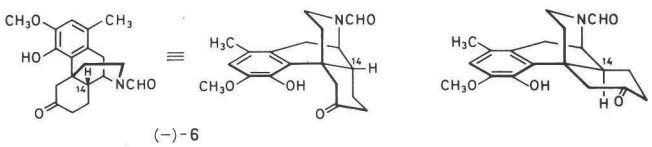


2.5 mm

Plate. Crystals of racemic and optically active 1-(5-benzyloxy-4-methoxy-2-methylbenzyl)-1,2,3,4-tetrahydro-6-methoxyisoquinoline hydrochloride.

Definitive proof of the structure gave the conversion of **6** into **7**. The *N*-formyl group could be removed by acidolysis with methanolic hydrochloric acid. Reductive *N*-methylation with formaldehyde, catalysed by platinum on carbon, yielded (+)- and (−)-1-methyldihydrothebainone (**7**). The *N*-formyl group could also be converted directly into the *N*-methyl group by palladium on carbon catalysed hydrogenation in an acid medium. In both conversions the 6-oxo function remained intact. The (−)-isomer of **7** was found to be identical with the (−)-1-methyldihydrothebainone we had obtained by partial synthesis from natural material[3].

The laevo-rotatory **3** obtained with the aid of (+)-6,6′-dinitrobiphenyl-2,2′-dicarboxylic acid shows an optical rotatory dispersion (ORD) spectrum which corresponds to that of related 1-benzylisoquinolines[14]. A negative Cotton effect at approximately 240 nm points to the *R* configuration. After the Birch reduction, in which the benzene chromophore is converted into a diene chromophore, the sign of the Cotton effect is changed. The compounds **4** and **5** obtained from (−)-**3** show a positive Cotton effect at approximately



(−)-6

Fig. 1. Two isomers of N-*formyl-1-methylnordihydrothebainone* (**6**) *after cyclization, "natural" structure with 14-H in* β *position (left) and structure with 14-H in* α *position (right).*

285 nm (Fig. 2). Continuing in this series, finally (−)-*N*-formyl-1-methylnordihydrothebainone (**6**) and (−)-1-methyldihydrothebainone (**7**) are obtained. The ORD spectra of **6** and **7** correspond to those of the natural morphinans such as (−)-dihydrothebainone and (−)-codeine[15] with a negative Cotton effect at 285 nm. The (−)-1-methyldihydrothebainone obtained from natural (−)-dihydrocodeinone has the same chiroptical properties. For the optical antipodes mirror image ORD curves were obtained.

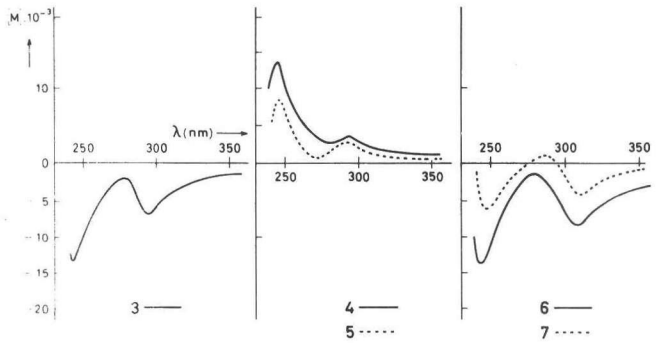


Fig. 2. ORD spectra in 96% ethanol of (−)-*1-(5-benzyloxy-4-methoxy-2-methylbenzyl)-1,2,3,4-tetrahydro-6-methoxyisoquinoline* (**3**), (+)-*1,2,3,4,5,8-hexahydro-1-(5-hydroxy-4-methoxy-2-methylbenzyl)-6-methoxyisoquinoline* (**4**), (+)-*2-formyl-1,2,3,4,5,8-hexahydro-1-(5-hydroxy-4-methoxy-2-methylbenzyl)-6-methoxyisoquinoline* (**5**), (−)-N-*formyl-1-methylnordihydrothebainone* (**6**), *and* (−)-*1-methyldihydrothebainone* (**7**).

Experimental part

Combustion analyses were performed by Messrs. *M. van Leeuwen* and *H. M. A. Buurmans*. Proton magnetic resonance spectra were measured with a Varian XL-100 or a Varian T-60 spectrometer by Messrs. *A. Sinnema* and *J. M. van der Toorn*. The compounds were dissolved (10% w/v) in deuteriochloroform and/or hexadeuteriodimethyl sulfoxide. TMS was used as internal reference. The mass spectra were obtained with a Varian MAT SM-1 or a Varian 311 A spectrometer by Messrs. *B. van de Graaf, J. A. Peters* and Dr. *P. J. W. Schuyl*. Optical rotatory dispersion curves were measured with a Spectropol I spectropolarimeter (FICA, France).

6-Methylveratraldehyde

To a mixture of 192 g (1.25 mol) of freshly distilled phosphoryl chloride and 168 g (1.25 mol) of *N*-methylformanilide, after 45 min, 190 g (1.25 mol) of 3,4-dimethoxytoluene was added with stirring at room temperature. After stirring for 65 hr at room temperature the viscous mixture was poured into 750 g of water and 750 g of crushed ice. Crystalline 6-methylveratraldehyde was obtained by extraction with benzene. Crystallization from isopropyl alcohol yielded 181.5 g (1.01 mol; 82%; m.p. 73–74°).

6-Methylisovanilline

6-Methylisovanilline (m.p. 152–153°) was obtained as described in Ref. 16.

5-Hydroxy-4-methoxy-2-methylmandelonitrile

6-Methylisovanilline (60 g; 0.36 mol) was dissolved at 50° in 270 ml of water and 45 g of sodium hydrogen sulfite. The solution was cooled rapidly to 0°, treated for 45 min with 35.0 g (0.72 mol) of sodium cyanide in 75 ml of water, and, after 30 minutes stirring, acidified with ~180 ml of 4 *N* sulfuric acid to pH 6. After another 30 minutes stirring the cyanohydrin was extracted with ether. The residue, obtained after drying the solution and evaporation of the solvent, was treated with hot methylene chloride in order to crystallize the nitrile (43 g; 0.22 mol; 61%; m.p. 83–86°).

(5-Hydroxy-4-methoxy-2-methylphenyl)acetic acid

A solution of 84.5 g of tin(II) chloride dihydrate in 75 ml of concentrated hydrochloric acid was added to 43.0 g (0.22 mol) of 5-hydroxy-4-methoxy-2-methylmandelonitrile in 10 ml of glacial acetic acid. After boiling for 5 hr, 90 ml of warm water were added. The clear solution was transferred to a percolator, as described in Ref. 17, and extracted with chloroform during 6 hr. The residue was crystallized from chloroform and benzene respectively (34.8 g; 0.18 mol; 81%; m.p. 160–161°). $C_{10}H_{12}O_4$ (196.20), calc. C 61.21; H 6.17, found C 61.2; H 6.2.

(5-Benzyloxy-4-methoxy-2-methylphenyl)acetic acid

To a solution of 15.1 g (77 mmol) of (5-hydroxy-4-methoxy-2-methylphenyl)acetic acid and 7.2 g (180 mmol) of sodium hydroxide in 25 ml of methanol, 23.0 g (180 mmol) of benzyl chloride was added at the boiling point over one hr. After boiling for 1.5 hr, another 3.6 g of sodium hydroxide dissolved in 3.6 g of water were added. The reaction mixture was boiled for another 2 hr, the methanol removed *in vacuo*, and 400 ml of water added. After standing overnight, the solution was washed with chloroform. Addition of 4 *N* sulfuric acid to pH 3 yielded 20.0 g (70 mmol; 91%, m.p. 121–122°) of (5-benzyloxy-4-methoxy-2-methylphenyl)acetic acid. $C_{17}H_{18}O_4$ (286.31), calc. C 71.31; H 6.34, found C 71.4; H 6.3.

N-*(3-Methoxyphenethyl)-(5-benzyloxy-4-methoxy-2-methylphenyl)acetamide* (**1**)

(5-Benzyloxy-4-methoxy-2-methylphenyl)acetic acid (9.4 g; 33 mmol) and 5.0 g (33 mmol) of (3-methoxyphenethyl)amine were heated in 25 ml of boiling xylene during 4.5 hr. Water was separated continuously. On cooling, the amide **1** crystallized (13.2 g; 31.5 mmol; 95%; m.p. 109–112°). M.p. 112–113° after recrystallization from ethanol. $C_{26}H_{29}NO_4$ (419.50), calc. C 74.44; H 6.97; N 3.34, found C 74.3; H 7.0; N 3.2.

1-(5-Benzyloxy-4-methoxy-2-methylbenzyl)-3,4-dihydro-6-methoxyisoquinoline hydrochloride (**2**)

Compound **1** (4.20 g; 10 mmol) was added at 0° to a suspension of 3.12 g (15 mmol) of phosphorus pentachloride in 10 ml of chloroform. Crystals separated almost immediately from the brownish-red solution. After 24 hr at room temperature, 7.5 ml of absolute methanol was added at 0° and the crystals were dissolved. The solvent was removed *in vacuo* below 50°. The residue was dissolved in 4 ml of absolute ethanol and 0.5 ml of concentrated hydrochloric acid. After 5 days 3.66 g (8.4 mmol; 83%) of the crystalline product was

collected. It was recrystallized from ethanol containing a trace of hydrochloric acid (m.p. 180–181°). $C_{26}H_{27}NO_3 \cdot HCl$ (437.97), calc. C 71.30; H 6.44; N 3.13, found C 70.8; H 6.6; N 3.3.

Racemic 1,2,3,4,5,8-hexahydro-1-(5-hydroxy-4-methoxy-2-methylbenzyl)-6-methoxyisoquinoline (**4**)

Liquid ammonia (160 ml) was added at −65° to 20 ml of ether in a nitrogen atmosphere[11]. Then 5.6 g (0.8 mol) of small pieces of lithium and 11.6 g (26.5 mmol) of powdered 1-(5-benzyloxy-4-methoxy-2-methylbenzyl)-3,4-dihydro-6-methoxyisoquinoline hydrochloride (**2**) were added with stirring. After 3.5 hr at ~ −60° the temperature was raised to ~ −50° and during 45 min 65 ml of absolute ethanol were added until the blue colour had disappeared. The ammonia was evaporated, the remaining ammonia and the ether were distilled off under reduced pressure. Water (250 ml) was added, followed by 45 g of ammonium chloride with stirring. After 15 min the product was filtered off, and washed with 200 ml of water and 20 ml of cold methanol. Recrystallization from ethanol gave 6.8 g of **4** (21.6 mmol; 82%; m.p. 163–165°). A sample, after chromatography, melted at 163–164°. $C_{19}H_{25}NO_3$ (315.40), calc. C 72.35; H 7.99; N 4.44, found C 72.3; H 8.0; N 4.4.

Racemic 1-(5-benzyloxy-4-methoxy-2-methylbenzyl)-1,2,3,4-tetrahydro-6-methoxyisoquinoline (**3**)

Sodium tetrahydridoborate (1.22 g; 32 mmol) was added in portions at 20° to a solution of 7.00 g (16 mmol) of the hydrochloride of **2** in 400 ml of ethanol. After stirring, for 1 hr, 20 ml of 2 *N* hydrochloric acid were added to pH 3, followed, after 15 min, by 4 *N* ammonia to pH 7. The solvent was evaporated *in vacuo* and the residue was dissolved in a mixture of 130 ml of chloroform and 200 ml of 1 *N* ammonia. After stirring for 15 min, the mixture was separated and the aqueous layer was extracted twice, each time with 20-ml portions of chloroform. The combined chloroform extracts were washed with 50 ml of 1 *N* ammonia, dried over magnesium sulfate, and evaporated *in vacuo*. The oily residue (6.7 g) was dissolved in 150 ml of hot ethanol, and concentrated hydrochloric acid was added to pH 3. Upon cooling, the hydrochloride of **3** crystallized; from the mother liquor again some **3** was collected: total 6.32 g (14.4 mmol; 90%). The melting range of a sample, prepared for analysis by four crystallizations from ethanol, varied with the size of the crystals: 180° to 195° within 0.8°. $C_{26}H_{29}NO_3 \cdot HCl$ (439.98), calc. C 70.98; H 6.87; N 3.18, found C 70.8; H 7.1; N 3.1. NMR: δ 2.02 (s, 3H, CH_3–Ar); δ 3.69 (s, 3H, CH_3–O–C_9H_9N); δ 3.82 (s, 3H, CH_3–O–Ar); δ 4.66 (m, 1H, CH–N); δ 5.02 (s, 2H, $-CH_2-$O).

Resolution of 1-(5-benzyloxy-4-methoxy-2-methylbenzyl)-1,2,3,4-tetrahydro-6-methoxyisoquinoline (**3**)

(+)- *and* (−)-*6,6'-Dinitrobiphenyl-2,2'-dicarboxylate of* **3**

A hot solution of 3.20 g (9.60 mmol) of (−)-6,6'-dinitrobiphenyl-2,2'-dicarboxylic acid ($[\alpha]_D^{27}$ −117.8°, *c* 2, CH_3OH) in 6 ml of acetone and 6 ml of ethanol was added to a solution of 6.45 g (16.0 mmol) of rac. **3** in 6 ml of acetone with 6 ml of ethanol. The (−)-salt (4.34 g; 73%) crystallized and was recrystallized from 70 ml of a mixture of acetone, ethanol, and water (3 : 1 : 1): m.p. 230–231°; $[\alpha]_D^{25}$ −15°, $[\alpha]_{436}^{25}$ −128° (*c* 0.34, 95% acetic acid).

The filtrate was evaporated *in vacuo*, treated with 50 ml of 1 *N* ammonia and 50 ml of chloroform, and separated after 15 min of stirring. The aqueous layer was extracted twice, each time with 15 ml of chloroform, and the chloroform extract was dried and evaporated. The residue was treated with 3.20 g (9.60 mmol) of (+)-6,6′-dinitrobiphenyl-2,2′-dicarboxylic acid ($[\alpha]_D^{27}$ +119.3°, *c* 2, CH_3OH) in the same way as described above which gave the (+)-salt: m.p. 230–231°, $[\alpha]_D^{25}$ +15°, $[\alpha]_{436}^{25}$ +130° (*c* 0.34, 95% acetic acid). $C_{40}H_{37}N_3O_{11}$ (735.75), calc. C 65.30; H 5.07; N 5.71, found C 65.2; H 5.3; N 5.5.

(+)-1-(5-Benzyloxy-4-methoxy-2-methylbenzyl)-1,2,3,4-tetrahydro-6-methoxyisoquinoline [(+)-**3**]

The laevo-rotatory 6,6′-dinitrobiphenyl-2,2′-dicarboxylate of (+)-**3** (9.9 g; 13.5 mmol) was suspended in a mixture of 125 ml of 0.5 *N* ammonia with 125 ml of chloroform. After stirring for 15 min the chloroform solution was separated and the aqueous layer was extracted twice, each time with 30 ml of 0.5 *N* ammonia. After drying over magnesium sulfate and evaporation, the oily residue (5.44 g; 100%), dissolved in ethanol, was treated with 2 *N* hydrochloric acid, which yielded the (+)-hydrochloride of **3**: m.p. 215–216°, $[\alpha]_D^{25}$ +43°, $[\alpha]_{365}^{25}$ +190° (*c* 0.5, 95% acetic acid). $C_{26}H_{29}NO_3 \cdot HCl$ (439.98), calc. C 70.98; H 6.87; N 3.18, found C 70.9; H 7.1; N 3.2.

From the dextro-rotatory salt the (−)-base was isolated as the (−)-hydrochloride: m.p. 215–217°, $[\alpha]_D^{25}$ −42°, $[\alpha]_{365}^{25}$ −189° (*c* 0.5, 95% acetic acid).

(+)- and (−)-1,2,3,4,5,8-Hexahydro-1-(5-hydroxy-4-methoxy-2-methylbenzyl)-6-methoxyisoquinoline (**4**)

The Birch reduction of (+)- and (−)-**3** was performed in an apparatus as described in Ref. 11. The reaction mixture remained at −60° up to and inclusive the decomposition with methanol and was kept in a nitrogen atmosphere until the product was filtered off.

Ammonia (140 ml) was distilled from sodium into a glass filter containing 1.0 g (143 mmol, washed in ether) of small pieces of lithium. Subsequently, 60 ml of *tert*-butanol and 60 ml of tetrahydrofuran were added during 15 min. Then 4.85 g (12.0 mmol) of (−)-**3** in 10 ml of *tert*-butanol and 10 ml of tetrahydrofuran were added over a period of 25 min, in such a way that the temperature remained at −60 ± 3°. The progress of the reaction was followed by thin-layer chromatography (R_f 0.5, Silicagel, Merck F-254; methylene chloride/methanol/2 *N* ammonia 85 : 15 : 2) by putting a drop of the reaction mixture directly on the thin layer. After 30 min, 10 ml of methanol were added during 5 min; about 20 min later the blue colour had disappeared. The solvents were removed *in vacuo* and the residue was dissolved in 130 ml of water. Ammonium chloride (33 g) was added and the mixture was stirred for 15 min at 20° and for 15 min at 0°. The precipitate was collected by filtration, and washed with 130 ml of water and 10 ml of cold ethanol. After recrystallization from 100 ml of ethanol, 2.95 g (9.36 mmol; 78%) of the dextro-rotatory **4** was obtained: m.p. 189–190°, $[\alpha]_D^{25}$ +96°, $[\alpha]_{365}^{25}$ +407° (*c* 0.5, chloroform/ethanol 9 : 1) $C_{19}H_{25}NO_3$ (315.41), calc. C 72.35; H 7.99; N 4.44, found C 72.1; H 8.1; N 4.4. NMR in DMSO: δ 2.20 (s, 3H, CH_3); δ 3.57 (s, 3H, CH_3O); δ 3.79 (s, 3H, CH_3O); δ 4.75 (m, 1H, −CH=C); δ 6.70 and

6.78 (s, 2H, C_6H_2). IR: 1665 and 1691 cm^{-1} (C=C) and 3290 cm^{-1} (NH).
Similarly 5.1 g (12.7 mmol) of (+)-**3** were converted into 2.87 g (9.10 mmol; 72%) of (−)-**4**; m.p. 191–192°, $[\alpha]_D^{25}$ −91°, $[\alpha]_{365}^{25}$ −396° (*c* 0.5, chloroform/ethanol 9 : 1).

(+)- and (−)-2-Formyl-1,2,3,4,5,8-hexahydro-1-(5-hydroxy-4-methoxy-2-methylbenzyl)-6-methoxyisoquinoline (**5**)

Compound (+)-**3** (2.83 g; 8.98 mmol) was suspended under nitrogen in 70 ml of toluene and 30 ml of freshly distilled ethyl formate. Tlc (R_f 0.7, Silicagel, Merck F-254, methylene chloride/methanol/2 *N* ammonia 85 : 15 : 2) showed that the reaction was complete after 50 hr of boiling; the product had been dissolved. The solvents were evaporated *in vacuo* and the residue was crystallized from 40 ml of 96% ethanol, yielding 1.65 g of crystals. A second and a third crop of crystals were obtained from the mother liquor, total yield 2.73 g (7.95 mmol; 89%) of (−)-**5** {m.p. 161–162°; $[\alpha]_D^{25}$ −43°, $[\alpha]_{365}^{25}$ −114° (*c* 0.45, chloroform/ethanol 9 : 1)}.
In the same way, (−)-**3** (2.68 g; 8.51 mmol) was formylated to yield (+)-**5** (2.24 g; 6.53 mmol; 77%). A sample, after two recrystallizations from ethanol, possessed the following data: m.p. 158–159°, $[\alpha]_D^{25}$ +39°, $[\alpha]_{365}^{25}$ +97° (*c* 0.45 chloroform/ethanol 9 : 1), $C_{20}H_{25}NO_4$ (343.178347), found by high-resolution MS 343.17835, $C_{20}H_{25}NO_4$ (343.41), calc. C 69.95; H 7.33; N 4.08, found C 70.0; H 7.4; N 4.1, NMR in DMSO: δ 2.15 (two signals due to different conformations of the 1-benzyl group, 3H, CH_3−Ar); δ 3.45 (s, 3H, CH_3OC_9); δ 3.68 (s, 3H, CH_3OAr); δ 4.70 (m, 1H, −CH=C); δ 6.43 and 6.64 (d, *J* 3 Hz, 2H, C_6H_2); δ 7.52 (two signals, syn/anti NCHO), δ 8.56 (s, 1H, HOAr), IR 1698 cm^{-1} (C=C); 1648 cm^{-1} (CH=O).

Racemic 2-formyl-1,2,3,4,5,8-hexahydro-1-(5-hydroxy-4-methoxy-2-methylbenzyl)-6-methoxyisoquinoline (**5**)

Racemic **5** (1.40 g; 4.08 mmol; 99%) was obtained, in the same way as described for the optical antipodes, from 1.30 g (4.12 mmol) of rac. **4**. An analytical sample from methanol/water and methanol (2×) melted at 179–180°, $C_{20}H_{25}NO_4$ (343.41), calc. C 69.95; H 7.33; N 4.08, found C 70.0; H 7.3; N 4.1.

(+)- and (−)-N-Formyl-1-methylnordihydrothebainone (**6**)

Sulfuric acid (107 ml; 80%) was added over a period of 2 hr in an atmosphere of nitrogen at 0° to a suspension of 1.47 g (4.28 mmol) of (+)-**5** in 80 ml of ether. After 20 hr at room temperature the yellow mixture was poured into 400 g of ice and the solution was extracted with chloroform. The chloroform extract was washed with water, dried over magnesium sulfate, and evaporated *in vacuo*. The residue crystallized from 10 ml of ethanol: 1.13 g (3.43 mmol; 80%). An analytical sample was recrystallized twice from ethanol: m.p. 226–227°, $C_{19}H_{23}NO_4$ (329.38), calc. C 69.28; H 7.04; N 4.25, found C 69.0; H 7.3; N 4.2, $[\alpha]_D^{25}$ +237°, $[\alpha]_{365}^{25}$ +1008° (*c* 0.45, chloroform/ethanol 9 : 1), NMR in DMSO: δ 2.05 (s, 3H, CH_3−Ar); δ 3.72 (s, 3H, CH_3O); δ 4.68 (m, 1H, CH−N); δ 6.72 (s, 1H, H−Ar); δ 8.05 (two signals, *syn/anti* NCHO); δ 8.23 (s, 1H, HO−), IR 1650 cm^{-1} (NCHO); 1705 cm^{-1} (C=O); 3440 cm^{-1} (OH).

The laevo-rotatory compound (−)-**6** (1.89 g; 5.74 mmol; 73%) was obtained from 2.70 g (7.86 mmol) of (−)-**5**. M.p. 227–228°, after one recrystallization from ethanol, $[\alpha]_D^{25}$ −228°, $[\alpha]_{365}^{25}$ −1000° (*c* 0.45, chloroform/ethanol 9 : 1).

Racemic N-*formyl-1-methylnordihydrothebainone* (**6**)

By the same procedure 5.1 g (14.9 mmol) of racemic **5** could be converted into 4.1 g (12.5 mmol; 84%) of (±)-**6**: m.p. 223–225°; $C_{19}H_{23}NO_4$ (329.38), calc. C 69.28; H 7.04; N 4.25, found C 69.3; H 7.0; N 4.2.

(−)-*1-Methyldihydrothebainone* (**7**) *from* (−)-N-*formyl-1-methylnordihydrothebainone*

(−)-*N*-Formyl-1-methylnordihydrothebainone (566 mg; 1.72 mmol) was dissolved at the boiling point in 50 ml of 1 *N* hydrochloric acid in methanol. After 6 hr the acidolysis was complete, according to tlc. The solvent was evaporated *in vacuo*, the residue was treated with 25 ml of ammonia and with 20 ml of chloroform, and extracted with chloroform. The organic solvent was evaporated after drying over magnesium sulfate, which yielded 526 mg of an oily residue (100%).

Platinum on carbon (5%; 90 mg) in 20 ml of methanol was saturated with hydrogen at 45°. Subsequently 1.4 ml of formaldehyde (40% wt; 18.7 mmol; 11 eq), and the oily residue (526 mg) in 1 ml of methanol were added. According to tlc analysis the reductive methylation was complete after 17 hr and 35 ml of hydrogen consumed (1.58 mmol; 92%). The catalyst was filtered off and the solvent evaporated *in vacuo*. The residue was treated with ammonia to pH 9 and extracted with chloroform. After drying over magnesium sulfate the solvent was evaporated *in vacuo*. The residue was dissolved in 1 ml of 96% ethanol and acidified with hydrochloric acid in ethanol to pH 3. (−)-**7** crystallized, 305 mg (0.87 mmol; 50% overall yield), m.p. 198–199°, R_f 0.3 (Silicagel, Merck F-254, methylene chloride/methanol/2 *N* ammonia 85 : 15 : 2) NMR in $CDCl_3$ and DMSO: δ 2.25 (s, 3H, CH_3Ar); δ 2.85 (s, 3H, CH_3N); δ 3.80 (s, 3H, CH_3O); δ 4.30 (d, *J* 3 Hz, 2H, $COCH_2$); δ 6.63 (s, 1H, HAr); δ 7.80 (s, 1H, HOAr), IR 1703 cm^{-1} (C=O); 3400 cm^{-1} (OH). An analytical sample, obtained after three crystallizations from ethanol, melted at 197–198°, $[\alpha]_D^{25}$ −43°, $[\alpha]_{365}^{25}$ −255° (*c* 0.49, chloroform/ethanol 9 : 1).

The IR spectrum and m.p. of (−)-**7** were identical with those of compound **7** prepared from natural material[3]. A mixture melting point determination showed no depression.

The dextro-rotatory compound, (+)-**7**, showed m.p. 196–197° and $[\alpha]_D^{25}$ +46°, $[\alpha]_{365}^{25}$ +262° (*c* 0.51, chloroform/ethanol 9 : 1).

Racemic 1-methyldihydrothebainone (**7**)

Palladium on carbon (10%; 50 mg) was added to a solution of 130 mg (0.684 mmol) of *p*-toluenesulfonic acid monohydrate in 12 ml of ethanol and was saturated with hydrogen during 30 min at 50°. Rac. *N*-formyl-1-methylnordihydrothebainone (102 mg; 0.310 mmol) was added. After 120 hr of hydrogenation at 50°, the catalyst was filtered off and the solvent was evaporated *in vacuo*. The

residue was treated with ammonia until pH 9 and extracted with chloroform. The solution was dried and evaporated. The residue was dissolved in 1 ml of ethanol and some 2 *N* hydrochloric acid to pH 3. We obtained 33 mg (0.094 mmol; 30%) of rac. 1-methyl-nordihydrothebainone hydrochloride.

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6. Conversion of (−)-Dihydrocodeinone into (−)-1-Methyldihydrocodeinone, (−)-1-Methyldihydrocodeine and (−)-1-Methyldihydrothebainone*

Introduction

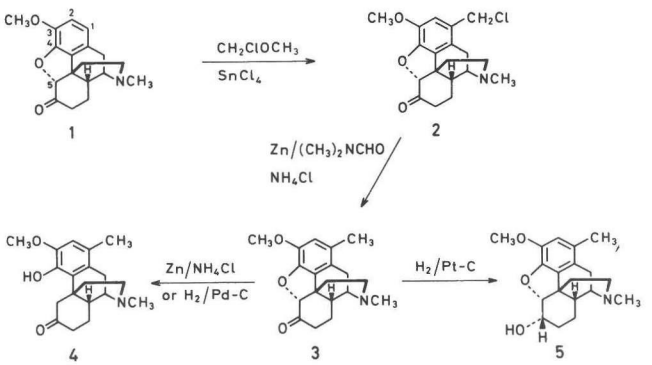
In model experiments for our synthesis of codeine and morphine[1,2] we obtained the enantiomers of 1-methyldihydrothebainone (**4**) starting from substituted 1-benzylisoquinolines[3]. In order to complete the proof of the structure of **4** it appeared desirable to prepare the laevo-rotatory 1-methyl derivative also from a natural morphinan. For this we chose (−)-dihydrocodeinone (**1**) and we now report the results.

Alkylation of the aromatic nucleus of morphinans has received hardly any attention. We have introduced a methyl group *via* a chloromethylation reaction followed by reduction with zinc. Satisfactory results were obtained starting from (−)-dihydrocodeinone (**1**). It appears, however, that the chloromethylation has a wider scope, in consequence of which new derivatives of codeine and morphine will become accessible for pharmacological investigation.
The dihydrothebainone desired derivative **4** was obtained by a reductive opening of the oxygen bridge of (−)-1-methyldihydrocodeinone (**3**).

Results and discussion

Many derivatives of codeine and morphine have been obtained by aromatic substitution, but of the alkylated derivatives only 1-ethyldihydrocodeine has been described. It was

* A reprint of C. Olieman, L. Maat, and H.C. Beyerman, Recl. Trav. Chim. Pays-Bas *95*, 189 (1976).



obtained in small yield by acetylating codeine by the Friedel-Crafts method, followed by reduction, *via* 1-(1-hydroxyethyl)codeine[4]. Electrophilic substitution of codeine takes place in position 1[5], but morphine, when nitrated, yields a product substituted in position 2[6].

We have examined a number of reactions in order to obtain a product methylated in position 1. Thus we found that chloromethylation with the aid of chloromethyl methyl ether in nitromethane in the presence of tin(IV) chloride proceeds smoothly. This reaction can be stopped by the addition of dimethylformamide, which deactivates the catalyst. The reactive 1-chloromethyl product **2** could be reduced with zinc to the 1-methyl compound **3**. When we carried out this reaction in dimethylformamide with ammonium chloride as proton donor, it was unnecessary first to isolate the reaction product from the mixture of tin chlorides. In a medium containing acetic acid the 1-(acetoxymethyl) compound was readily formed and with phenol the 1-(phenoxymethyl) compound; these compounds, however, could not be converted into the 1-methyl compound by catalytic hydrogenolysis.

Other potential methods appeared to be methylation *via* the phenylthiomethyl compound[7] and that *via* the 1-(1,3-dithiolan-2-yl) compound[8]. However, these methods gave no conversion or yielded complex mixtures.

In order to obtain a compound which could be directly compared with the compound obtained by total synthesis[3], the codeinone derivative **3** had to be converted into the thebainone derivative **4**. On analogy[9] the 4,5-oxygen bridge was reductively opened with zinc and ammonium chloride. A catalytic ring opening also was found possible with palladium on carbon in a strongly alkaline medium. With platinum on carbon, on the other hand, the 6-oxo group of **3** was stereospecifically reduced to the 6α-hydroxyl group, as a result of which (−)-1-methyldihydrocodeine (**5**) was formed.

The (−)-1-methyldihydrothebainone (**4**) described above was identical with the synthetic laevo-rotatory product **4**, obtained starting from (−)-1-(5-benzyloxy-4-methoxy-2-methylbenzyl)-1,2,3,4-tetrahydro-6-methoxyisoquinoline[3]. Since this gives the 1-methyl compound, it has thus been proved that the chloromethylation described takes place exclusively in position 1.

Experimental part

Combustion analyses were performed by Mr. *H. M. A. Buurmans.* Proton magnetic resonance spectra were measured with a Varian T-60 spectrometer; the compounds were dissolved in deuteriochloroform and/or hexadeuteriodimethyl sulfoxide and TMS was used as internal reference. The mass spectra were obtained by Dr. *P. J. W. Schuyl* and Mr. *B. van de Graaf.* Rotations were measured with a Perkin-Elmer P-141 polarimeter.

1-(Chloromethyl)dihydrocodeinone (**2**)

Approximately 1.35 ml of tin(IV) chloride (the exact quantity was determined by weighing) was mixed with 60 ml of nitromethane, dried over a 3A molecular sieve. (−)-Dihydrocodeinone {0.90 equivalents, approximately 3 g; $[\alpha]_D^{25}$ of the hydrochloride −126° (*c* 1.08, chloroform/ethanol 9 : 1)} was dissolved in this mixture, which was then cooled to 0°. Dry chloromethyl methyl ether (2.1 ml, 2.5 eqs) was added to the reaction mixture. The mixture was allowed to reach room temperature in 1 hr. After 3 hr the conversion was complete, according to tlc (R_f 0.55, methylene chloride/methanol/2 *N* ammonia 85 : 15 : 2). Dimethylformamide (1.5 ml) was added. The solvents were evaporated *in vacuo.* (The excess of carcinogenic chloromethyl methyl ether was destroyed.) The residue was treated twice, each time with 20 ml of toluene, to remove traces of nitromethane. The amorphous chloromethyl compound **2** was kept *in vacuo* in a desiccator over phosphorus pentoxide, potassium hydroxide and charcoal.

(−)-*1-Methyldihydrocodeinone* (**3**)

A solution of 2.62 g (7.5 mmol) of **2** in 60 ml of freshly distilled dimethylformamide was added slowly to a well-stirred suspension of 4.9 g (91.6 mmol; 12 equivs.) of ammonium chloride and 2.46 g (37 mmol; 5 equivs.) of powdered zinc in 80 ml of freshly distilled dimethylformamide. After 1 hr, 20 ml of water was added; after stirring for 15 min the solvents were evaporated *in vacuo.* After 20 hr *in vacuo* over phosphorus pentoxide, potassium hydroxide, and charcoal, the residue was treated with 50 ml of water and 50 ml of concentrated ammonia. After stirring for 15 min the suspension was extracted with ether. The ethereal solution was washed with two portions of 50 ml of 0.4 *N* potassium hydroxide and with 50 ml of 0.1 *N* ammonia and evaporated on a water bath. After standing overnight *in vacuo*, the residue was dissolved in 2 ml of 90% ethanol and the pH adjusted to 4 with hydrochloric acid in ethanol. 1-

Methyldihydrocodeinone hydrochloride (0.63 g; 1.8 mmol; 24%; m.p. 241–243°) crystallized $[\alpha]_D^{25}$ −134°, $[\alpha]_{365}^{25}$ −1089° (*c* 0.93, chloroform/ethanol 9 : 1). IR and NMR both showed the presence of some water. $C_{19}H_{23}NO_3 \cdot HCl \cdot 1/3\ H_2O$ (355.86), calc. C 64.13; H 6.99; N 3.94, found C 64.1; H 7.3; N 3.8. NMR in deuteriochloroform and dimethyl sulfoxide-d_6: δ 2.20 (s, 3H, CH_3–Ar); δ 2.83 (s, 3H, CH_3–N); δ 3.82 (s, 3H, CH_3O); δ 4.82 (s, 1H, H–CO); δ 6.55 (s, 1H, H–Ar), IR (KBr) 1730 cm^{-1} (C=O). M.p. of the base 190–191.5°. MS: 313, 298, 255, 199, 57.

(−)-1-Methyldihydrothebainone (**4**)

Zinc powder (0.398 g; 6.08 mmol) and 0.68 g (12.7 mmol) of ammonium chloride in 2.5 ml of water were added to a solution of 0.554 g (1.56 mmol) of (−)-1-methyldihydrocodeinone hydrochloride in 25 ml of ethanol. After boiling for 3 h the reaction was complete, according to tlc. The solvent was evaporated *in vacuo* and the residue was treated with 20 ml of dilute ammonia (pH 9) and 15 ml of chloroform. The aqueous layer was repeatedly extracted with chloroform, the combined extracts were dried, and the solvent was evaporated *in vacuo*. The residue was dissolved in 96% ethanol and treated with alcoholic hydrochloric acid to pH 3, yielding 0.37 g (1.04 mmol; 66%) of (−)-1-methyldihydrothebainone hydrochloride, m.p. 194–197°. Recrystallization from ethanol gave m.p. 197–198°; $[\alpha]_D^{25}$ −55°, $[\alpha]_{365}^{25}$ −351° (*c* 0.47, chloroform/ethanol 9 : 1). $C_{19}H_{25}NO_3 \cdot HCl \cdot H_2O$ (369.90), calc. C 61.70; H 7.36; N 3.79, found C 62.2; H 7.8; N 3.8. The identity with the product obtained by total synthesis was proven[3].

(−)-1-Methyldihydrocodeine (**5**)

Platinum on carbon (5%; 40 mg) was saturated with hydrogen at 45° in a mixture of 30 ml of ethanol and 2.28 ml of 2 *N* potassium hydroxide (4.56 mmol; 2.1 equivs.). After 15 min, 0.67 g (2.13 mmol) of **3**, dissolved in 5 ml of ethanol, was added. The reduction was complete after 4 hr and the solution was neutralized with hydrochloric acid. The catalyst was filtered off and the solvents were removed *in vacuo*. The residue was taken up in 0.1 *N* ammonia and extracted three times with chloroform. The chloroform, after drying, was removed *in vacuo* and the residue was dissolved in 5 ml of 50% ethanol, containing 0.33 g (2.2 mmol) of (+)-tartaric acid. (−)-1-Methyldihydrocodeine tartrate (0.86 g; 1.85 mmol; 87%; m.p. 127–128°) crystallized: $[\alpha]_D^{25}$ −41°, $[\alpha]_{365}^{25}$ −202° (*c* 0.724, chloroform/ethanol 9 : 1), $C_{19}H_{25}NO_3 \cdot C_4H_6O_6$ (465.51), calc. C 59.34; H 6.71; N 3.01, found C 58.9; H 7.0; N 3.0. NMR in dimethyl sulfoxide-d_6: δ 2.22 (s, 3H, CH_3–Ar); δ 2.70 (s, 3H, CH_3N); δ 3.85 (s, 3H, CH_3O); δ 4.55 (d, *J* 5 Hz, 1H, H–CO); δ 6.65 (s, 1H, H–Ar). MS: 315 (M^+), 257, 164, 57.

Acknowledgements

We thank Messrs. *A. van Estrik* and *J. Muys* for preliminary experiments and Mr. *J. Vos* for technical assistance. We are indebted to Mr. *E. Buurman* of the Verenigde Pharmaceutische Fabrieken B.V. (V.P.F.), Apeldoorn, for discussions and thank the Management of V.P.F. for gifts of chemicals.

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7. Conversion of (−)-*N*-Formylnordihydrothebainone into (−)-Dihydrothebainone and *vice versa**

Introduction

In the total synthesis of morphine and codeine by some of us[1] *N*-formylnordihydrothebainone (**1**) had to be converted into dihydrothebainone (**3**). The catalytic (10% Pd/C or 5% Pt/C) reduction of *N*-formylnordihydrothebainone proceeded slowly and was discontinued. Still, in the first instance we required the *N*-formyl group, since the latter appeared important for the acid-catalysed cyclization of the starting material as well as for the selective removal of the 2-hydroxyl group in, *e.g.*, 2-hydroxy-*N*-formylnordihydrothebainone[2].

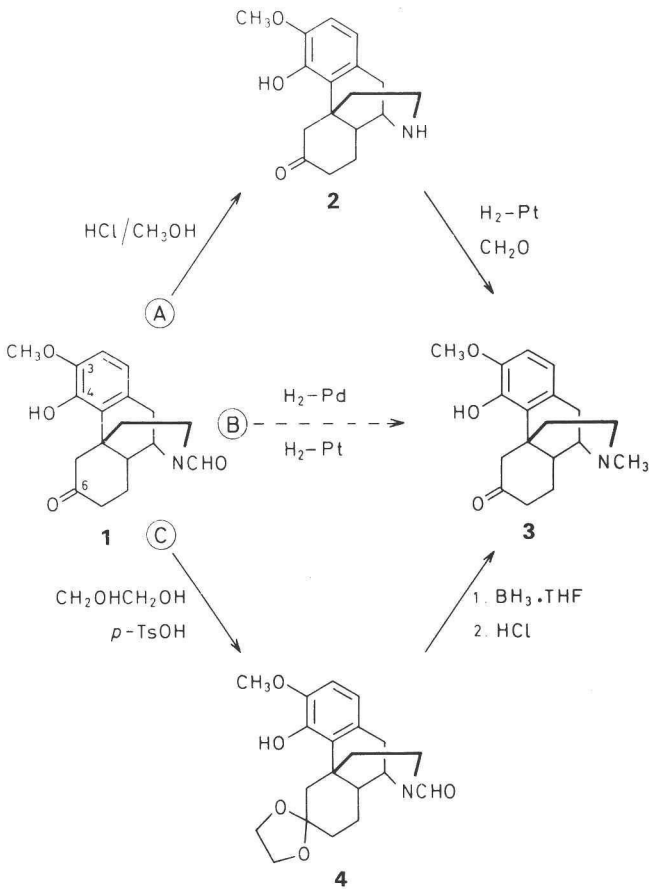
We examined two routes: removal of the *N*-formyl group followed by *N*-methylation (Scheme 1, route A) and direct reduction of the *N*-formyl group (Scheme 1, routes B and C). For our model experiments we used (−)-**1** made from semi-synthetic (−)-**3**.

Results and discussion

Only a small number of *N*-acylated morphinans are known. These derivatives have been described mainly as intermediates in the *N*-demethylation, such as the *N*-(2,2,2-trichloroethyl)oxycarbonyl compounds[3,4]. No attention has so far been given to (−)-*N*-formylnordihydrothebainone (**1**) and other *N*-formylmorphinans.

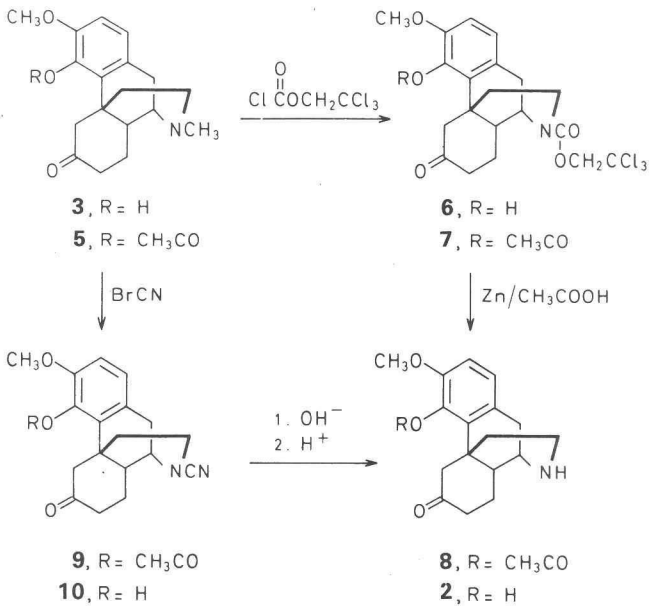
* A reprint of H.C. Beyerman, L. van Bommel, L. Maat, and C. Olieman, Recl. Trav. Chim. Pays-Bas 95, 312 (1976).

By treatment of (−)-*N*-formylnordihydrothebainone (**1**) with methanolic hydrochloric acid the formyl group was removed. The (−)-nordihydrothebainone (**2**) thus formed could be converted subsequently with formaldehyde and hydrogen, with platinum on carbon as a catalyst, into (−)-dihydrothebainone (**3**). Both conversions proceeded quantitatively, according to thin-layer chromatography (tlc) (Scheme 1, route A).



Scheme 1. Conversion of (−)-N-*formylnordihydrothebainone* (**1**) *into* (−)-*dihydrothebainone* (**3**).

For a direct hydride reduction of the *N*-formyl group it was first necessary to protect the 6-oxo group in the form of an acetal. A reducing agent which is sufficiently active to reduce tertiary amides but which leaves the acetal intact was found in a solution of diborane in tetrahydrofuran[5]. The 6,6-(ethylenedioxy)-*N*-formylnordihydrothebainone (**4**) formed from **1** and an excess of glycol with *p*-toluenesulfonic acid as a catalyst with a molecular sieve 3A as a dehydrating agent[6], was thus reduced in a high yield. Too small a quantity of diborane (less than 7.5 moles) and a temperature above 5° caused removal of the *N*-formyl group and should therefore be avoided. Aqueous hydrochloric acid decomposed the boron complexes and at the same time hydrolyzed the acetal group, as a result of which (−)-dihydrothebainone (**3**) was formed (Scheme 1, route C).



Scheme 2. Demethylation of (−)-dihydrothebainone (3, R = H).

The required (−)-*N*-formylnordihydrothebainone (**1**) was obtained by boiling (−)-nordihydrothebainone (**2**) with ethyl formate. (−)-Nordihydrothebainone (**2**) was prepared by two methods from (−)-dihydrothebainone (**3**) of natural origin[7].

(i) Demethylation as described by *von Braun* has already been applied to morphine[4] and a number of structurally

related compounds[8]. To this end, (−)-dihydrothebainone (**3**) was acetylated, yielding **5**, which was subsequently treated with cyanogen bromide, yielding **9**. By the use of alkali and acid successively the acetyl group and the cyano group respectively were removed, yielding (−)-nordihydrothebainone (**2**) (Scheme 2).

(ii) Recently demethylation was carried out with the aid of 2,2,2-trichloroethyl chloroformate and good results obtained with this method for morphine[3] induced us to apply it to (−)-dihydrothebainone (**3**). Treatment of **3** with 2,2,2-trichloroethyl chloroformate, followed by removal of the *N*-(2,2,2-trichloroethyl)oxycarbonyl group with zinc and acetic acid yielded (−)-nordihydrothebainone (**2**). Protection of the phenolic hydroxyl group by acetylation was found to be unnecessary, but it did enhance the yield.

Experimental part

Combustion analyses were performed by Mr. *H. M. A. Buurmans.* Melting points were determined with a Mettler FP-2 instrument. The infrared spectra were measured with a Hilger and Watts Infrascan spectrometer. The proton magnetic resonance spectra were obtained with a Varian T-60 spectrometer. The compounds were dissolved in deuteriochloroform or in hexadeuteriodimethyl sulfoxide (10% w/v), and tetramethylsilane was used as internal standard. The rotations were measured with a Perkin-Elmer P-141 polarimeter.

(−)-*Dihydrothebainone* (**3**) *from* (−)-N-*formylnordihydrothebainone* (**1**) via *route A (Scheme 1)*

(−)-*N*-Formylnordihydrothebainone (**1**, 618 mg, 1.96 mmol) was boiled under reflux in 50 ml of 0.8 *M* hydrochloric acid in methanol. After 16 h the solvent was removed *in vacuo* and the residue crystallized from acetone; it yielded the hydrochloride of (−)-nordihydrothebainone (**2**) with one molecule of acetone (672 mg, 1.77 mmol, 90%). This product was converted into (−)-nordihydrothebainone (**3**) by extraction of the ammoniacal solution (pH 9) with a mixture of chloroform and isopropanol (3 : 1). An analytical sample crystallized from ethanol, m.p. 190–191°, $[\alpha]_D^{25}$ −82°, $[\alpha]_{365}^{25}$ −495° (*c* 1.07, chloroform/ethanol 9 : 1). $C_{17}H_{21}NO_3$ (287.36), calcd. C 71.06, H 7.37, N 4.87; found C 71.0, H 7.4, N 4.8. NMR ($CDCl_3$): δ 3.80 (s, 3H, OCH_3), δ 4.27 (d, *J* 13 Hz, 1H, CH_2CO), δ 6.65 (s, 2H, aromatic).

(−)-Nordihydrothebainone (**2**, 300 mg, 1.05 mmol) was dissolved in 15 ml of methanol and 0.75 ml of formalin (40%), and hydrogenated during 24 h at 1 atmosphere and 45° in the presence of 58 mg of platinum on carbon (10%). The catalyst and the solvents were removed. The residue crystallized from ethanol in the form of (−)-dihydrothebainone (**3**) hydrochloride (m.p. 295°, dec., 289 mg, 0.86 mmol, 82%). The IR spectrum and the m.p. of this product were identical with those of the compound prepared from natural material[7].

(−)-*Dihydrothebainone* (**3**) *from* (−)-N-*formylnordihydrothebainone* (**1**) via *route C (Scheme 1)*

(−)-*N*-Formylnordihydrothebainone (**1**, 1.00 g, 3.18 mmol) was added to a mixture of 4 ml of glycol (71 mmol), 1.87 g (9.84 mmol) of *p*-toluenesulfonic acid hydrate, and 10 g of molecular sieve (3A). After 1 h the molecular sieve was filtered and washed with 100 ml of chloroform, and the filtrate was extracted with three portions of 100 ml of aqueous ammonia (pH 9). The aqueous layer was extracted once more with 100 ml of chloroform, and the combined chloroform layers were dried (magnesium sulfate) and evaporated *in vacuo*, yielding about 1 g of crude 6,6-(ethylenedioxy)-*N*-formyldihydrothebainone. This product (0.4 g, 1.1 mmol) was dissolved in 80 ml of tetrahydrofuran. A 1 *M* solution of diborane in tetrahydrofuran (20 ml, 20 mmol) was added at −10°. After 1 h at −10° the reaction was stopped by adding water. The solvent was removed *in vacuo* and the residue was treated at room temperature with 200 ml of 2 *N* hydrochloric acid. After 18 h the solvent was removed and the residue crystallized from ethanol. This gave 250 mg (0.74 mmol, 58 %) of (−)-dihydrothebainone (**3**) hydrochloride (m.p. 295°, dec.).

(−)-N-*Formylnordihydrothebainone* (**1**)

(−)-Nordihydrothebainone (**2**, 2.5 g, 8.7 mmol) was dissolved in 50 ml of ethyl formate. The mixture was boiled under reflux during 4 h. The solvent was removed and the residue crystallized from chloroform/ethanol yielding 2.4 g (7.6 mmol, 87 %) of (−)-*N*-formylnordihydrothebainone (**1**). An analytical sample melted at 265° dec., $[\alpha]_D^{25}$ −191°, $[\alpha]_{365}^{25}$ −858° (*c* 0.47, chloroform/ethanol 9 : 1). $C_{18}H_{21}NO_4$ (315.37), calcd. C 68.55, H 6.71, N 4.44; found C 68.3, H 6.8, N 4.6. NMR (DMSO-d_6): δ 3.80 (s, 3H, OCH_3), δ 4.13 (d, *J* 13 Hz, 1H, CH_2CO), δ 6.65 and 6.75 (2 × d, *J* 8 Hz, 2 × H, aromatic), δ 8.10 (two signals, *syn*/*anti* NCHO), and δ 8.50 (s, H, OH).

O-*Acetyldihydrothebainone* (**5**)

A solution of (−)-dihydrothebainone[7] (**3**, 18.8 g, 62.5 mmol, m.p. 128–129°, $[\alpha]_D^{25}$ −75°, c 0.77 in ethanol, $[\alpha]_D^{25}$ −77°, $[\alpha]_{365}^{25}$ −417°, *c* 0.74 in chloroform/ethanol 9 : 1) in 100 ml of anhydrous pyridine was treated with 20 ml of acetic anhydride at room temperature and in a nitrogen atmosphere. After seven days the pyridine was evaporated and the excess of the anhydride was decomposed with sodium bicarbonate in water. The mixture was extracted with chloroform. The chloroform solution was dried (magnesium sulfate) and evaporated. The dark red residue crystallized from a mixture of ethanol and ethyl acetate (1 : 4) and hydrochloric acid. Recrystallization from ethanol/ethyl acetate (3 : 1) gave 21.1 g (55.6 mmol, 89 %) of *O*-acetyldihydrothebainone (**5**) hydrochloride (m.p. 244–245°, $[\alpha]_D^{25}$ +0.8°, $[\alpha]_{365}^{25}$ −147°, *c* 0.94, chloroform/ethanol 9 : 1. NMR ($CDCl_3$): δ 2.35 (s, 3H, $COCH_3$), δ 2.80 (s, 3H, NCH_3), δ 3.80 (s, 3H, CH_3O), δ 6.90 and 7.05 (2 × d, *J* 6.5 Hz, 2 × H, aromatic).

(−)-*Nordihydrothebainone* (**2**) *from* (−)-**5** *with the aid of cyanogen bromide*

A solution of the hydrochloride of **5** (6.23 g, 16.4 mmol) in 150 ml of water was treated with concentrated ammonia (pH 9) and extracted

with 100 ml of chloroform. The chloroform solution was dried (magnesium sulfate) and evaporated. The residue was dissolved in 20 ml of chloroform and boiled with 2.79 g (26.3 mmol) of cyanogen bromide during 26 h. The mixture was then treated with 100 ml of water. A chloroform extract yielded, after drying (magnesium sulfate) and evaporation, the oily *O*-acetyl-N-cyanonordihydrothebainone (**9**). This was dissolved in 20 ml of ethanol and boiled with 1 g potassium hydroxide in 20 ml of water during 10 min. The hot solution was poured onto 400 g of ice and neutralized with acetic acid. The precipitate (*N*-cyanonordihydrothebainone, **10**) was boiled with 2 *N* hydrochloric acid during 55 h. This mixture was made alkaline with ammonia (pH 9) and extracted with a mixture of chloroform and isopropanol (3 : 1). The combined organic layers were dried and evaporated. The residue crystallized on treatment with concentrated hydrochloric acid and acetone (pH 2) in the form of (−)-nordihydrothebainone hydrochloride acetonate (2.4 g, 0.63 mmol, 38 %).

(−)-*Nordihydrothebainone* (**2**) *from* (−)-**5** *with the aid of 2,2,2-trichloroethyl chloroformate*

A solution of the hydrochloride of **5** (18.4 g, 48.5 mmol) in 500 ml of chloroform was mixed with 39 g (184 mmol) of 2,2,2-trichloroethyl chloroformate and 10 g of sodium bicarbonate. The solution was boiled for 7 h and, after cooling, extracted with 150 ml and 100 ml of water, respectively. The aqueous layer was extracted again with chloroform and the combined chloroform layers were dried and evaporated. The residue, *O*-acetyl-*N*-(2,2,2-trichloroethoxycarbonyl)nordihydrothebainone (**7**), was dissolved in 500 ml of acetic acid (90 %) and treated with 30 g of zinc powder. After 75 min stirring at room temperature, the zinc was filtered off. The filtrate was diluted with 400 ml of water and treated with 100 ml of 2 *N* hydrochloric acid. An ether extraction removed starting material **7**. The aqueous layer was partly evaporated and treated with concentrated ammonia (pH 8–9). The precipitate was removed by filtration and the filtrate was extracted 4 times each with 100 ml of a mixture of chloroform and isopropanol (3 : 1). The organic layer was dried and evaporated. The residue (*O*-acetylnordihydrothebainone, **8**) was hydrolyzed with potassium hydroxide in a similar way as described above, yielding (−)-nordihydrothebainone (**2**) which was purified in the form of the hydrochloride of **2**: 9.6 g (29.6 mmol, 61 %).

Acknowledgements

We are indebted to Mr. *E. Buurman* of the Verenigde Pharmaceutische Fabrieken B.V. (V.P.F.), Apeldoorn for discussions and thank the Management of V.P.F. for gifts of chemicals.

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8. A Practical Technique for Laboratory Birch Reductions*

Introduction

For our syntheses of codeine and morphine[1] and 1-methylmorphinans[2,3] from substituted 1-benzylisoquinolines it was necessary to carry out Birch reductions[4,5] under reproducible circumstances. It was essential to control the choice and the sequence of the addition of the reactants, the temperature, and the mixing. Furthermore, any catalytic influence of transition metals (*e.g.* the iron present in crude ammonia[6]) and oxygen had to be excluded. In our experiments the apparatus described[7] was not satisfactory. For that reason an apparatus was developed (Fig. 1) which makes possible various ways of carrying out Birch reductions[1-3].

Apparatus

For the construction of the apparatus (Fig. 1) use was made of glass (Pyrex), of high-pressure polyethylene, and of screw-fit couplings. Perfluoropolyethylene (Teflon) was avoided, since this is attacked by mixtures of alkali metal and ammonia.

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

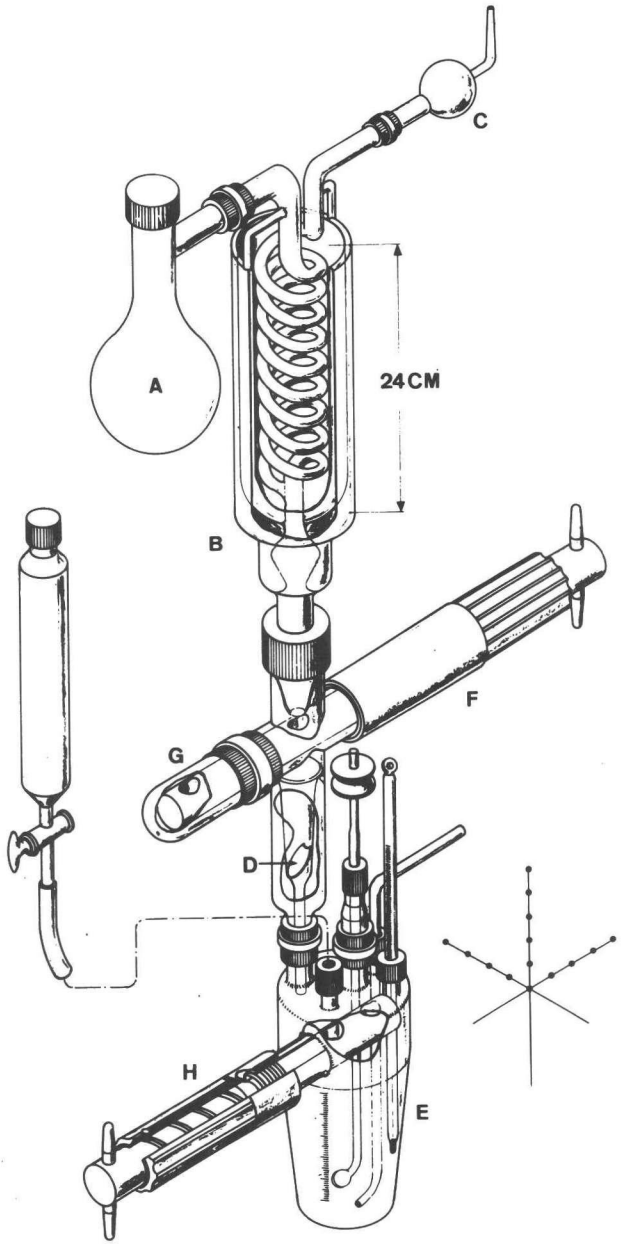


Fig. 1. Schematic view of apparatus for laboratory Birch reductions. Isomeric projection, scale (X-Y-Z-axis) 1 : 1.25. A, flask containing ammonia; B, acetone-cooled condensor; C, drying tube; D, glass filter (type O) with overflow; E, glass reaction vessel; F, dispensing device (analogous to H); G, metal-containing compartment; H, dispensing device (analogous to F).
(Axonometric drawing by G. S. C. Fiedler *and* W. J. de Haas*)*

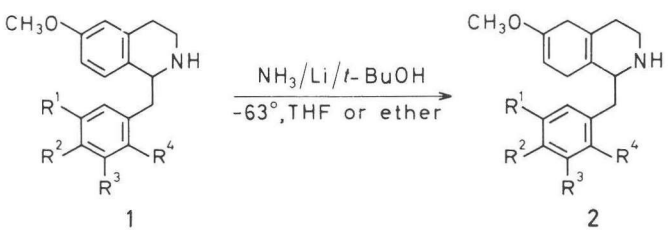
From flask A ammonia is distilled, which condenses in a carbon dioxide/acetone-cooled double spiral B. The condenser is provided with a drying tube C containing potassium hydroxide pellets. *Via* glass filter D (type 0, large pores) the ammonia enters the carbon dioxide/acetone-cooled reaction vessel E. The funnel with glass filter can be filled with pieces of sodium or lithium with the aid of the dispensing device F. This consists of a polyethylene tube with a closely fitting polyethylene rod, which is partly provided with coarse screw-thread similar to H (see Fig. 1). Tube and rod both have a bore such that in the position shown in Fig. 1 the ammonia can drip freely from the condenser into the funnel, while at the end of the rod, compartment G can be filled with the alkali metal. After the screw cap has been mounted, the rod can be turned, so that the metal is conveyed to the funnel. The filter D placed at a slant

Table I Results of Birch reductions of 1-(X-benzyl)-1,2,3,4-tetrahydro-6-methoxyisoquinolines.

No.	R^1	R^2	R^3	R^4
1a	OBzl	OMe	H	CH_3
1b	OBzl	OMe	OBzl	H
1c	H	OBzl	H	H
1d	OBzl	OMe	H	H

No.	R^1	R^2	R^3	R^4	Yield	M.p., °C
2a[2]	OH	OMe	H	CH_3	85%	163–164
2b[1]	OH	OMe	OH	H	85%	214–215
2c	H	OH	H	H	90%	178 (dec.)
2d[8]	OH	OMe	H	H	75%	185–186

* **1d** has been used exclusively as 3,4-dihydroisoquinoline.



1 2

in the funnel has an overflow, because, when lithium is used, the concentrated $Li(NH_3)_4$ solution formed at first has a high surface tension and consequently cannot pass through the filter. The amount of the material left on the filter after the experiment can be determined by weighing. The reaction flask has a side connection with a dispensing device H for solids similar to F. Furthermore there are connections for a dropping funnel, a thermometer, a nitrogen-inlet tube, and a mechanical stirrer. Two connections, for drawing samples and for transferring the contents of the reaction vessel to a round-bottomed flask by means of a vacuum pump, are not shown in Fig. 1.

Reductions have been carried out in this apparatus with amounts of 0.1 to 10 g of starting material.

Experimental procedure

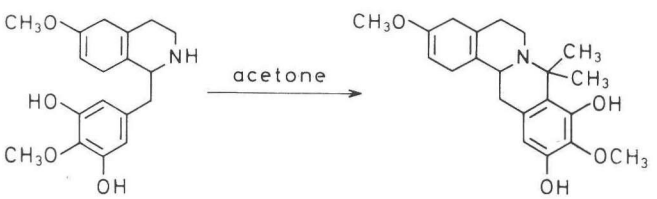
The apparatus is freed from moisture and oxygen by passing through purified nitrogen. Subsequently, the condenser and the reaction flask are cooled with a mixture of carbon dioxide and acetone. The crude ammonia in flask A is first dried with sodium or lithium before the flask is connected to the apparatus. The rate of distillation can be increased by warming flask A. The choice and the sequence of the additions of the reactants depend on the substance to be reduced and on the desired result. Usually tetrahydrofuran or ether is suitable as co-solvent, and *tert*-butanol as a proton donor, to which some co-solvent has been added to prevent solidification in the dropping funnel. At the end of the reaction the excess of alkali metal can be destroyed with methanol or, if the desired product is susceptible to further reduction, with ammonium chloride or benzoic acid. The reaction mixture is siphoned with suction into a round-bottomed flask and the ammonia is carefully evaporated with a rotatory vacuum evaporator, after which the product is worked up.

Examples and results

1-Benzylisoquinolines

The starting materials for morphinan derivatives were 1-(X-benzyl)-3,4-dihydro-6-methoxyisoquinolines, which were converted into the 1-(Y-benzyl)-1,2,3,4,5,8-hexahydro-6-methoxyisoquinolines. The compounds all had one or two benzyloxy substituents in the 1-benzyl radical. In the alkaline medium the benzyl ether cleaved during the Birch reduction yields a phenolate anion, which prevents further reduction of the 1-benzyl group on the isoquinoline moiety. The 1,2 double bond of the latter is also reduced. This double bond can also be reduced first with sodium tetrahydridoborate yielding a product with a chiral centre suitable for optical resolution. During the Birch reduction of the enantiomers the optical activity is maintained[1,3]. Table I gives the results.

Suitably substituted 1-benzyl-1,2,3,4,5,8-hexahydroisoquinolines (**2**) can react with acetone. After treatment with acetone in ethanol or water, compound **2b** gave a high yield (>90%) of the hexahydrodimethyl protoberberine derivative **3**, m.p. 221° (dec.), $C_{21}H_{27}NO_4$ (357.43), calc. C 70.56; H 7.61; N 3.92; found C 70.7; H 7.6; N 4.0.



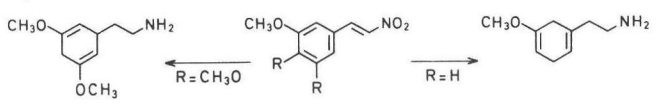
2 b 3

Benzene derivatives

Another approach to obtain the 1-(Y-benzyl)-1,2,3,4,5,8-hexahydroisoquinolines (**2**) starts from 2,5-dihydrophenethylamines (**5**) which can be condensed with phenylacetic acid. To this end two methoxy-β-nitrostyrenes (**4**) were reduced under the conditions used for the 1-benzylisoquinolines. 3-Methoxy-β-nitrostyrene yielded 2-(2,5-dihydro-3-methoxyphenyl)ethylamine (**5**, 91%) and 3,4,5-trimethoxy-β-nitrostyrene yielded 2-(1,4-dihydro-3,5-dimethoxyphenyl)ethylamine (**6**, 96%). Neither of the two reactive compounds was purified and they were characterized as follows:

5: ^{1}H NMR (CCl_4) δ 1.22 (2H, s, NH_2), δ 2.07 (2H, t, *J* 7 Hz, $CH_2CH_2NH_2$), δ 2.63 (4H, s, CH_2 at C(2) and C(5)), δ 2.73 (2H, m, *J* 7 Hz, CH_2NH_2), δ 3.48 (3H, s, CH_3O), δ 4.56 (1H, m, C(4)), δ 5.43 (1H, m, C(6)); IR (CCl_4) 3380 cm^{-1} (NH), 1696 and 1666 cm^{-1} (dihydroanisole).
6: ^{1}H NMR (CCl_4) δ 1.15 (2H, s, NH_2), δ 1.52 (2H, t, *J* 7 Hz, $CH_2CH_2NH_2$), δ 2.7 (2H, m, *J* 7 Hz, CH_2NH_2), δ 2.7 (2H, s, CH_2 at C(4)), δ 3.0 (1H, m, CH at C(1)), δ 3.50 (6H, s, CH_3O), δ 4.52 (2H, m, C(2) and C(6)); IR (CCl_4) 3370 cm^{-1} (NH), 1696 and 1664 cm^{-1} (dihydroanisole).

Reduction of 2-(3,4,5-trimethoxyphenyl)ethylamine (mescaline) also afforded **6**. In the case of the corresponding benzaldehyde and phenylethanol, too, the 4-methoxy substituent is cleaved under the circumstances of the Birch reduction.



6 4 5

If during the reduction of mescaline no proton donor is added, the 4-methoxy group is not cleaved, but a 3,5-dihydroxy-4-methoxy derivative is formed. This is in agreement with what was found in the reduction of 2-(3,4-dimethoxyphenyl)ethylamine[9].

Acknowledgements

We are indebted to Mr. *E. Buurman* of the Verenigde Pharmaceutische Fabrieken B.V. (V.P.F.), Apeldoorn, for discussions and thank the Management of V.P.F. for gifts of chemicals. We are grateful to Mr. *Ph. Nagelhout*, who prepared the new compound **1c**.

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9. Separation of Opium Alkaloids and Related Compounds by Ion-Pair High-Performance Liquid Chromatography*

INTRODUCTION

In our synthetic investigations of the medicinally useful alkaloids morphine (1) and codeine (2) (Fig. 1) and related compounds[1–3,6] (Fig. 2), it was necessary also to separate closely related derivatives. The application of high-performance liquid chromatography (HPLC) to the analysis of morphinans has already been described[4,5], mainly with natural compounds. These methods were found to be unsuitable for the separation of non-substituted morphinans from, *e.g.*, synthetic[2,6] 1-methyl-substituted morphinans.

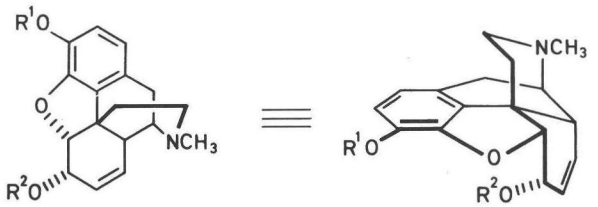


Fig. 1. Structure of alkaloids: $R^1 = R^2 = H$, morphine (1); $R^1 = CH_3$, $R^2 = H$, codeine (2); $R^1 = R^2 = CH_3CO$, heroin (3).

When use is made of ion-pair chromatography[7] with *n*-heptanesulphonate as the counter ion over a reversed-phase column, these analyses can be carried out satisfactorily. The analysis of natural morphinans has also been considerably improved by this means.

EXPERIMENTAL

Materials

Compounds 1–6, 11, 20 and 21 were obtained from the Verenigde Pharmaceutische Fabrieken, B.V., Apeldoorn, The Netherlands, while compounds 7, 8, 15

* A reprint of C. Olieman, L. Maat, K. Waliszewski, and H.C. Beyerman, J. Chromatogr. *133*, 382 (1977).

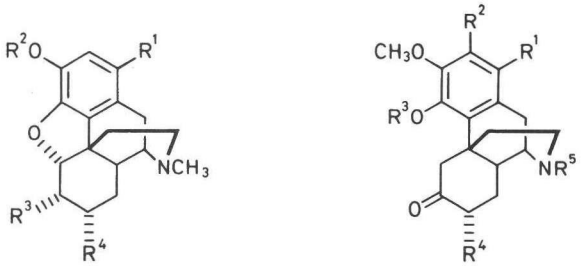


Fig. 2. Structures of morphinan derivatives analysed by HPLC:

No.	R^1	R^2	R^3	R^4	*No.*	R^1	R^2	R^3	R^4	R^5
4	H	H	OH	H	11	H	H	H	H	CH_3
5	H	CH_3	OH	H	12	H	H	$COCH_3$	H	CH_3
6	H	CH_3	=O	H	13	H	H	H	H	H
7	CH_3	CH_3	OH	H	14	H	H	H	H	CHO
8	CH_3	CH_3	=O	H	15	CH_3	H	H	H	CH_3
9	Br	CH_3	=O	H	16	CH_3	H	H	H	CHO
10	Br	CH_3	=O	Br	17	Br	H	H	H	CH_3
20	Thebaine				18	Br	H	H	Br	CH_3
21	Oripavine				19	H	OH	H	H	CH_3

and 16; 9, 10, 17 and 18; 12, 13 and 14; and 19 were synthesized according to refs. 2, 6, 8, 3 and 1, respectively.

Apparatus

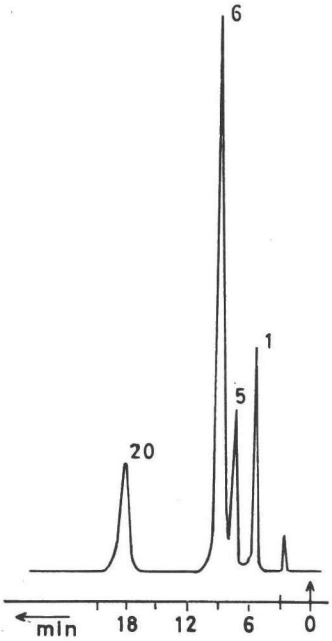
A Waters Assoc. Model 6000 A pump with a Model U6K injector was used in combination with a Varian Aerograph UV detector at 254 nm. The column was a μBondapak C_{18} from Waters Assoc. The flow-rate was set at 1.2 ml/min and the column was maintained at room temperature. The mobile phase contained 0.005 *M* *n*-heptanesulphonic acid (PIC reagent B-7) obtained from Waters Assoc. (Milford, Mass., U.S.A.).

RESULTS AND DISCUSSION

The analysis of morphinans on a silica gel column has already been described[4,5]. The most important opium alkaloids that have been separated by this method are morphine, codeine, heroin, thebain, 6-(O-acetyl)morphine, dihydromorphine, dihydrocodeine and nalorphine, the structures and basicity of which are closely related.

We have repeated the analysis of a number of these alkaloids on μPorasil, with chloroform–methanol–diethylamine, diethyl ether–methanol–diethylamine and methanol–2 *N* ammonia–1 *N* ammonium nitrate in water. For alkaloids with high retention times the results were not satisfactory, especially owing to tailing of the peaks. Application of this technique to a number of closely related morphinans and to the derivatives of dihydrothebainone did not yield good separations, while some of them were retained on the column. The use of a reversed-phase column (μBondapak C_{18}) in combination with methanol–0.1 *N* ammonium hydrogen carbonate also resulted in bad separations and much tailing of the peaks.

Ion-pair chromatography on a reversed-phase column gave very good separations of some important morphinan alkaloids (Fig. 3). From Fig. 4, it can be seen that this technique gives good results for the separation of closely related morphinans, *e.g.*, 1-methyldihydrocodeine from dihydrocodeine.



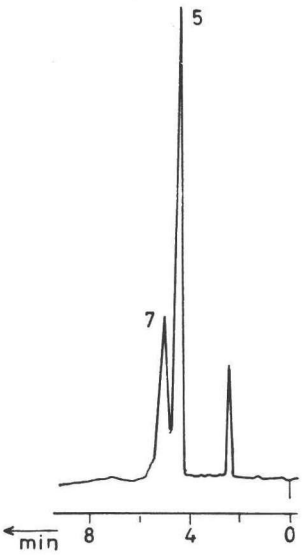


Fig. 3. Separation of some important morphine alkaloids. Morphine (1), dihydrocodeine (5), dihydrocodeinone (6), and thebaine (20) were separated on μBondapak C_{18} using methanol–water (40:60) containing 0.005 *M* *n*-heptanesulphonic acid. Flow-rate, 1.2 ml/min; UV detection at 254 nm.

Fig. 4. Chromatogram of dihydrocodeine (5) and 1-methyldihydrocodeine (7) on μBondapak C_{18} using methanol–water (50:50) containing 0.005 *M* *n*-heptanesulphonic acid. Flow-rate, 1.2 ml/min; UV detection at 254 nm.

The retention times increase as the polarity of the molecule decreases (Table I). By varying the methanol (or acetonitrile) to water ratio in the mobile phase, the retention times can be varied, an increase in the water content resulting in an increase in the retention time. With the aid of gradient elution (increase in methanol concentration), various alkaloids can be separated in a reasonably short time. The compounds can be injected in the form of a salt (*e.g.*, hydrochloride) or as the free base, with no change in the retention times. Non-basic compounds, such as the N-formyl compounds, can also be separated under these circumstances. It is striking that the N-formyl compounds give two partially overlapping peaks (14 and 16), which is attributed to the *syn–anti* isomerism of the N-formyl group. Rotation around the formyl nitrogen–carbon bond is sufficiently slow for this purpose at room temperature.

For the separation of many other alkaloids and basic compounds, the reversed-phase, ion-pair mode of HPLC appears to offer good prospects.

TABLE I

RETENTION TIMES (min) OF MORPHINANS FOR DIFFERENT SOLVENT SYSTEMS (CONTAINING 0.005 *M* *n*-HEPTANESULPHONIC ACID)

Dashes indicate no elution within a reasonable time (> 30 min).

Compound	*Solvent system*		
	Methanol–water (50:50)	*Methanol–water (40:60)*	*Acetonitrile–water (25:75)*
1	4.0	5.6	4.5
2	4.6	7.5	6.1
3	7.3	19.4	16.2
4	4.1	6.0	4.9
5	4.5	7.7	5.7
6	5.1	8.8	8.0
7	5.4	9.6	7.6
8	5.9	12.7	11.5
9	8.0	18.7	17.6
10	14.5	—	—
11	5.2	9.0	7.5
12	5.5	10.1	8.7
13	5.1	9.5	6.7
14	5.1, 5.3	9.2, 9.8	10.0
15	6.0	12.6	10.1
16	6.5, 7.0	13.3, 14.7	14.4
17	8.0	21.4	14.0
18	11.7	—	—
19	4.0	5.7	5.6
20	7.5	17.9	17.5
21	4.8	8.7	7.5

ACKNOWLEDGEMENT

We are indebted to the management of Verenigde Pharmaceutische Fabrieken B.V., Apeldoorn, for gifts of alkaloids.

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Summary

In the introduction the occurrence of alkaloids with a morphinan skeleton is briefly explained, as well as the drug problem that is connected with the use of some of these compounds. A short review is given of the Delft synthesis of morphine and codeine.

Chapter 2[1]. A synthesis is described of racemic 3-hydroxy-*N*-methyl--6-oxomorphinan by acid-catalysed cyclization of 1-(4-hydroxybenzyl)-1,2,3,4,5,8-hexahydro-6-methoxy-2-methylisoquinoline (**4**, Scheme 1, p. 7) and its 4'-methyl ether. The corresponding *N*-formyl derivatives did not give the desired cyclization.

Chapter 3[2,3]. (-)-3-Hydroxy-*N*-methyl-6-oxomorphinan and its (-)-2-bromo derivative were converted into (-)-2,3-dihydroxy-*N*--methyl-6-oxomorphinan and its (-)-4-bromo derivative (**8b**, Fig. 3, p. 18) respectively, by oxidation with Fremy's salt to the *o*-quinones, followed by reduction. Methylation of the compounds obtained in this way gave the corresponding methyl esters. Catalytic hydrogenolysis of (-)-4-bromo-2,3-dihydroxy-*N*-methyl-6-oxomorphinan and the corresponding 2,3-dimethoxy compound gave (-)-2,3-dihydroxy-, and (-)-2,3-dimethoxy-*N*-methyl-6-oxomorphinan, respectively. The structure of (-)-2,3-dimethoxy-*N*-methyl-6-oxomorphinan was confirmed by total synthesis, and that of (-)-4-bromo-2,3-dimethoxy--*N*-methyl-6-oxomorphinan (**4**, Fig. 2, p. 34) by single-crystal X-ray analysis.

The model compound 2-bromo-4,5-dimethylphenol gave, analogously, 3-bromo-4,5-dimethylpyrocatechol.

Chapter 4[4]. ^{1}H And ^{13}C nuclear magnetic resonance (NMR) spectra of brominated dihydrothebainones, intermediates in the closure of the oxygen bridge of morphinans to form morphine derivatives, were studied. Bromination of (-)-dihydrothebainone yielded successively 1-bromo-, 1,7α-dibromo-, and 1,5β,7α-tribromodihydrothebainone (**4**, Scheme 1, p. 39). 1-Bromo-*O*[4]-methyldihydrothebainone gave, after bromination, a stable, crystalline 1,5β,7α-tribromo derivative. A 5β,7α-dibromo derivative was formed also, starting with 1-methyldihydrothebainone.

Closure of the oxygen bridge in 1,5β,7α-tribromodihydrothebainone in boiling ethanol, yields an equilibrium mixture of 1,7α- and 1,7β-dibromodihydrocodeinone (35:65). 5β,7α-Dibromo-1--methyldihydrothebainone gave a similar result.

^{13}C NMR spectra of the model compounds cyclohexanone, 2-bromo-, 2,2-dibromo-, *cis*- and *trans*-2,6-dibromocyclohexanone were studied.

Chapter 5[5]. Racemic 1-(5-benzyloxy-4-methoxy-2-methylbenzyl)--1,2,3,4-tetrahydro-6-methoxyisoquinoline (**3**, Scheme 1, p. 49) was synthesized. Resolution with (+)- and with (-)-6,6'-dinitrobiphenyl-2,2'-dicarboxylic acid yielded the enantiomers. By a Birch reduction, followed by *N*-formylation, and by acid-catalysed cyclization racemic, (-)-, and (+)-*N*-formyl-1-methylnordihydrothebainone were obtained in high yield. In two ways, by direct reduction and by deformylation followed by reductive methylation, racemic, (-)-, and (+)-*N*-formyl-1-methylnordihydrothebainone could be converted selectively into racemic, and (-)-, and (+)-1--methyldihydrothebainone.

Synthetic (-)-1-methyldihydrothebainone was found to be identical with the product prepared from natural material. This completed the proof of the structure.

The optical rotatory dispersion (ORD) spectra are discussed.

Chapter 6[6]. Chloromethylation of (-)-dihydrocodeinone (**1**, Scheme 1, p. 62) followed by reduction with zinc yielded 1-methyldihydrocodeinone. Further reduction afforded (-)-1-methyldihydrothebainone. The latter compound proved to be identical with (-)-1-methyldihydrothebainone prepared by total synthesis. This proves position 1 of the chloromethylation and, in consequence, of the methyl group. (-)-1-Methyldihydrocodeinone could also be reduced catalytically to (-)-1-methyl-

dihydrocodeine.

Chapter 7[7]. (-)-*N*-Formylnordihydrothebainone (**1**, Scheme 1, p. 67) was converted into (-)-dihydrothebainone by two routes: removal of the formyl group followed by reductive methylation, and direct hydride reduction (diborane in tetrahydrofuran) after protection of the 6-oxo substituent in the form of an acetal.

The starting material (-)-*N*-formylnordihydrothebainone was obtained by *N*-demethylation of (-)-dihydrothebainone, which was prepared from natural material.

Chapter 8[8]. A practical technique and an apparatus are described, which makes possible various ways of carrying out Birch reductions reproducibly on a 0.1-10 g scale. Examples of reductions of 1-benzylisoquinolines and β-nitrostyrenes are discussed. Reaction of 1,2,3,4,5,9-hexahydro-(3,5-dihydroxy-4-methoxybenzyl)-6-methoxyisoquinoline with acetone yielded a hexahydrodimethylprotoberberine (**3**, Scheme 1, p. 77).

Chapter 9[9]. Opium alkaloids and related compounds can be analysed with the technique of ion-pair chromatography with *n*-heptanesulfonate as the counter ion on a reverse-phase column; eluents are mixtures of an organic solvent, water, acetic acid (2%), and sodium *n*-heptanesulfonate (0.005 M). Non-basic compounds, such as the *N*-formyl compounds, can also be analysed under these circumstances. The *N*-formyl compounds give two peaks, due to the *syn-anti* isomerism of the *N*-formyl group.

Samenvatting

In de introduktie wordt het voorkomen van alkaloïden met een morfinanskelet beknopt uiteengezet, evenals het drugsprobleem, dat met het gebruik van sommige van deze verbindingen samenhangt. Een kort overzicht van de Delftse synthese van morfine en codeïne wordt gegeven.

Hoofdstuk 2[1]. Een synthese van racemisch 3-hydroxy-*N*-methyl-6-oxomorfinan door zuur-gekatalyseerde cyclisatie van 1-(4-hydroxybenzyl)-1,2,3,4,5,8-hexahydro-6-methoxy-2-methylisochinoline (**4**, Schema 1, p. 7) en zijn 4'-methylether wordt beschreven. De korresponderende *N*-formylderivaten gaven niet de gewenste cyclisatie.

Hoofdstuk 3[2,3]. (-)-3-Hydroxy-*N*-methyl-6-oxomorfinan en zijn (-)-2--broomderivaat werden door middel van oxidatie met Fremy's zout tot de *o*-chinonen, gevolgd door reduktie omgezet tot respektievelijk (-)-2,3-dihydroxy-*N*-methyl-6-oxomorfinan en zijn (-)-4-broomderivaat (**8b**, Fig. 3, p. 18). Methylering van de aldus verkregen verbindingen gaf de overeenkomstige methylethers. Katalytische hydrogenolyse van (-)-4-broom-2,3-dihydroxy-*N*-methyl-6-oxomorfinan en de overeenkomstige 2,3-dimethoxyverbinding gaf respektievelijk (-)--2,3-dihydroxy- en (-)-2,3-dimethoxy-*N*-methyl-6-oxomorphinan. De struktuur van (-)-2,3-dimethoxy-*N*-methyl-6-oxomorfinan werd door totale synthese bevestigd en die van (-)-4-broom-2,3-dimethoxy-*N*--methyl-6-oxomorfinan (**4**, Fig. 2, p. 34) door röntgenanalyse van een éénkristal.

De modelverbinding 2-broom-4,5-dimethylfenol gaf op analoge wijze 3-broom-4,5-dimethylpyrocatechol.

Hoofdstuk 4[4]. ^{1}H en ^{13}C kernspinresonantie (NMR) spektra van gebromeerde dihydrothebaïnonen, die door sluiting van de zuurstofbrug morfinederivaten geven, werden bestudeerd. Bromering van (-)-dihydrothebaïnon leverde achtereenvolgens 1-broom-, 1,7α-dibroom- en 1,5β,7α-tribroomdihydrothebaïnon (**4**, Schema, p. 39). 1-Broom-*O*[4]-methyldihydrothebaïnon gaf, na bromering, een stabiel, kristallijn 1,5β,7α-tribroomderivaat. Een 5β,7α-dibroomderivaat werd eveneens gevormd, uitgaande van 1-methyldihydrothebaïnon.

Sluiting van de zuurstofbrug in 1,5β,7α-tribroomdihydrothebaïnon in kokende ethanol gaf een evenwichtsmengsel van 1,7α- en 1,7β-dibroomdihydrocodeïnon (35:65). 5β,7α-Dibroom-1-methyldihydrocodeïnon gaf een soortgelijk resultaat.

^{13}C NMR spektra van de modelverbindingen cyclohexanon, 2-broom-, 2,2-dibroom-, *cis*- en *trans*-2,6-dibroomcyclohexanon werden bestudeerd.

Hoofdstuk 5[5]. Racemisch 1-(5-benzyloxy-4-methoxy-2-methylbenzyl)-1,2,3,4-tetrahydro-6-methoxyisochinoline (**3**, Schema 1, p. 49) werd gesynthetiseerd. Splitsing met behulp van (+)- en (-)-6,6'-dinitrobifenyl-2,2'-dicarbonzuur leverde de enantiomeren.

Door een Birch reduktie, gevolgd door *N*-formylering en door zuur-gekatalyseerde cyclisatie werd in hoge opbrengst racemisch *N*-formyl-1-methylnordihydrothebaïnon verkregen. Op analoge wijze werden de (+)- en de (-)-verbinding verkregen. Deze verbindingen konden op twee manieren selektief worden omgezet tot racemisch en (-)- en (+)-1-methyldihydrothebaïnon, namelijk door reduktie en door deformylering gevolgd door een reduktieve methylering.

Synthetisch (-)-1-methyldihydrothebaïnon was identiek met het produkt bereid uit natuurlijk materiaal. Dit maakte het bewijs van de struktuur volledig.

De optische rotatie dispersie (ORD) spektra worden besproken.

Hoofdstuk 6[6]. Chloormethylering van (-)-dihydrocodeïnon (**1**, Schema, p. 62) gevolgd door reduktie met zink gaf (-)-1-methyldihydrocodeïnon. Verdere reduktie gaf (-)-1-methyldihydrothebaïnon. Laatstgenoemde verbinding bleek identiek te zijn met (-)-1-methyldihydrothebaïnon bereid door totaalsynthese. Dit bewijst dat de chloormethylering op positie 1 plaats vindt. (-)-1-Methyldihydrocodeïnon kon eveneens katalytisch tot (-)-1-methyldihydrocodeïne

worden gereduceerd.

Hoofdstuk 7[7]. (-)-*N*-Formylnordihydrothebaïnon (**1**, Schema 1, p. 67) werd tot (-)-dihydrothebaïnon *via* twee routes omgezet: verwijdering van de formylgroep gevolgd door reduktieve methylering en direkte hydride-reduktie (diboraan in tetrahydrofuran) na bescherming van de 6-oxosubstituent in de vorm van een acetaal.

De uitgangsstof (-)-*N*-formylnordihydrothebaïnon werd door *N*-demethylering verkregen uit (-)-dihydrothebaïnon, dat bereid was uit natuurlijk materiaal.

Hoofdstuk 8[8]. Een praktische techniek en een apparaat worden beschreven, waarmee het mogelijk is om Birch redukties op verschillende manieren reproduceerbaar uit te voeren op een schaal van 0,1-10 g. Voorbeelden van redukties van 1-benzylisochinolinen en β-nitrostyrenen worden besproken. Reaktie van 1,2,3,4,5,8-hexahydro--1-(3,5-dihydroxy-4-methoxybenzyl)-6-methoxyisochinoline met aceton leverde een hexahydrodimethylprotoberberine (**3**, Schema, p. 77).

Hoofdstuk 9[9]. Opiumalkaloïden en verwante verbindingen kunnen met de techniek van ionpaar chromatografie worden geanalyseerd met *n*-heptaansulfonaat als tegenion op een 'reverse-phase' kolom; eluentia zijn mengsels van een organisch oplosmiddel, water, azijnzuur (2%) en natrium-*n*-heptaansulfonaat (0,005 M). Ook niet-basische verbindingen, zoals de *N*-formylverbindingen, kunnen onder deze omstandigheden worden geanalyseerd. De *N*-formylverbindingen geven twee pieken ten gevolge van de *syn-anti* isomerie van de *N*-formylgroep.

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STELLINGEN

1. Het voorschrift van *Heicken* betreffende de bereiding van 4,5-dimethyl-2--joodfenol en andere monojoodxylenolen is onjuist.

   K. Heicken, Angew. Chemie 52 (1939) 263.

2. Het verdient aanbeveling om het stikstofatoom van morfinan nummer 17 te geven.

   IUPAC Nomenclature of Organic Chemistry, Section F, General principles for the naming of natural products and related compounds, Regel F-4.13, Pergamon Press, Oxford, 1979 edition, p. 507.

3. Het toepassen van gradiëntelutie bij de kontrole van de zuiverheid van peptiden met hoge druk vloeistofchromatografie geeft geen informatie over de aanwezigheid van nauw met het hoofdprodukt verwante bijprodukten.

   W.A.A.J. Bijl, J.W. van Nispen en *H.M. Greven,* Recl. Trav. Chim. Pays-Bas 98 (1979) 571; 99 (1980) 57 en 63.

4. De analyse met hoge druk vloeistofchromatografie van het Vasoactive Intestinal Peptide (VIP), gesynthetiseerd door *Coy* en *Gardner*, is weinig zeggend als de kapaciteitsfaktor van het hoofdprodukt 1,8 is.

   D.H. Coy en *J. Gardner*, Int. J. Pept. Protein Res. 15 (1980) 73.

5. Een belangrijke tijdsbesparing in het organisch praktikum kan worden bereikt door het capillair bij vakuümdestillaties te vervangen door een geschikt roersysteem, bijv. een magneetroerder.

6. De redakties van chemische tijdschriften dienen, alvorens een publikatie te accepteren, van de auteurs gegevens te eisen, waaruit blijkt dat het gebruik van benzeen-bevattende eluentia voor bijvoorbeeld dunnelaag- en kolomchromatografie niet vervangen kan worden door het gebruik van minder toxische oplosmiddelen.

7. De piekhoogte is een betere maat voor de hoeveelheid dan het piekoppervlak, als men gebruik maakt van 'flow'-programmering bij hoge druk vloeistofchromatografie.

   A.H. Lewin, S.R. Parker en *F.J. Carrol*, J. Chromatogr. 193 (1980) 371.

8. De verklaring die *Hancock* e.a. geven voor de dubbele pieken van sommige tripeptiden bij het gebruik van tetrapropylammoniumionen in de 'reverse--phase' vloeistofchromatografie, is aan twijfel onderhevig.

   W.S. Hancock, C.A. Bishop, J.E. Battersby, D.R.K. Harding en *M.T.W. Hearn*, J. Chromatogr. 168 (1979) 377.

9. De zorg van politici voor het milieu staat in schril kontrast tot het milieu waarin zij veelal vergaderen.

10. Het verdient aanbeveling om in de 'Aanwijzingen voor de promotor en de promovendus' van het Promotiereglement van de Technische Hogeschool Delft de aanwijzingen, met betrekking tot de kleding van de promovendus, voor mannen en vrouwen een gelijke nauwkeurigheid te geven.

    College van Dekanen, Promotiereglement Technische Hogeschool Delft, vastgesteld bij besluit College van Dekanen d.d. 6 juni 1977, laatste wijzigingen d.d. januari 1980.

C. Olieman

30 oktober 1980