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Synthetic Morphinans and Hasubanans. Part IV.[1] Total Synthesis of 3,14-Dihydroxyisomorphinans, 3-Methoxy-$\Delta^{8,14}$-morphinans, and 9α-Hydroxy-3-methoxyhasubanan

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IVO MONKOVIĆ, HENRY WONG, BERNARD BELLEAU, IRWIN J. PACHTER, and YVON G. PERRON. Can. J. Chem. **53**, 2515 (1975).

The synthesis of a versatile intermediate 4a-(2-aminoethyl)-1,2,3,4,4a,9-hexahydro-6-methoxyphenanthrene (**3***a*) and its utilization in the synthesis of 9α-hydroxy-3-methoxy-17-methylhasubanan (**10**), 3,14-dimethoxy-17-methylisomorphinan (**9***l*), various 14-hydroxyisomorphinans (**9**), and 3-methoxy-$\Delta^{8,14}$-morphinan (**11***b*) is described. A number of 17-alkyl-3,14-dihydroxyisomorphinans were prepared and tested for narcotic antagonist and analgesic activities in laboratory animals. Some of these new compounds have exhibited significant activities.

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On décrit la synthèse de l'intermédiaire versatile (aminoéthyl-2)-4a hexahydro-1,2,3,4,4a,9 méthoxy-6 phénanthrène (**3***a*) de même que son usage dans la préparation de l'hydroxy-9α méthoxy-3 méthyl-17 hasubanane (**10**), du diméthoxy-3,14 méthyl-17 isomorphinane **9***l*, de divers hydroxy-14 isomorphinanes (**9**) ainsi que du méthoxy-3 $\Delta^{8,14}$-morphinane (**11***b*). On a préparé un certain nombre d'alkyl-17 dihydroxy-3,14 isomorphinanes dont on a examiné l'activité sur des animaux de laboratoire comme antagoniste de narcotiques et comme analgésique. Quelques-uns de ces composés ont démontré des activités importantes.

[Traduit par le journal]

Introduction

At the outset of our studies on narcotic antagonists some years ago, the most exciting agent in this field was naloxone **I** (Scheme 1). Cumulative reports on its powerful antagonist activity not only against morphine but also against side effects (analgesia, psychotomimetic disorders) of other narcotic antagonists such as levalorphan (**II***a*), cyclorphan (**II***b*), cyclazocine (**III**), and others (see ref. 3 for a review) have placed naloxone in a class of its own *i.e.* a 'pure' or 'total' narcotic antagonist.

However, a more critical examination of the pharmacological properties of naloxone revealed that it suffers from a number of drawbacks: although parenterally highly potent, it is short acting, it is very poorly absorbed by the oral route, and from the chemical standpoint it is derived from thebaine which is only a minor constituent of opium. On the other hand, some totally synthetic analogs such as cyclazocine are known to be long acting and orally effective,

[1]Reference 1 is regarded as part III. For part II see ref. 2.

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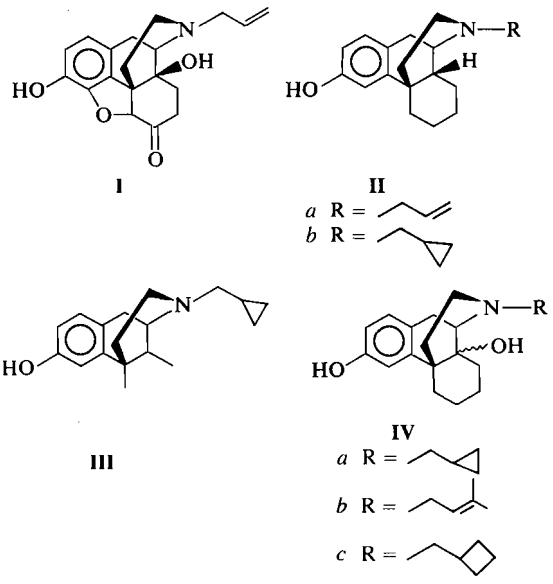
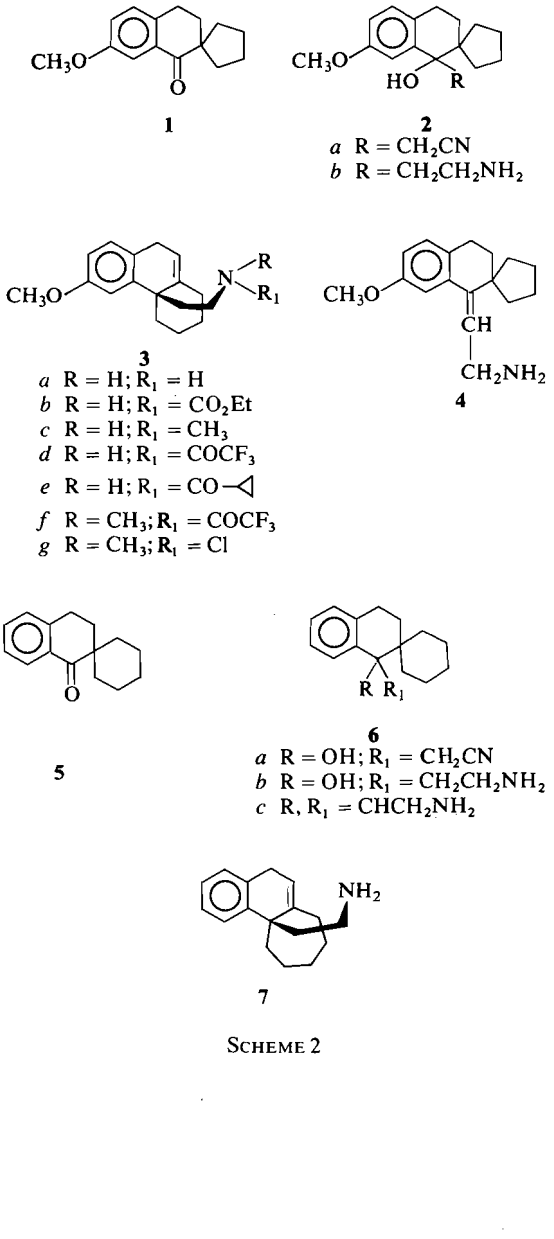


SCHEME 1

even though adverse psychomomimetic side effects have been observed with them. It seemed desirable then to prepare by total synthesis (so as to avoid opium-based starting materials) some representative 3,14-dihydroxymorphinans (**IV***a–c*) which by definition incorporate the carbon skeleton and the 14-hydroxyl substituent of naloxone as well as the nitrogen substituents of cyclazocine and pentazocine. In addition, a flexible synthetic method was desirable, which would allow for the preparation of both, 14β- and 14α-hydroxymorphinans. The latter have not been reported in the tetracyclic morphine-related structures, even though certain 14-unsubstituted isomorphinans have shown potent analgesic (4) and narcotic antagonist activities (5).

The choice of practical synthetic approaches to this end appeared to be between a classical Grewe synthesis (6, 7) which did not appear attractive to us[4] and that of a modification of thebaine, which we rejected for the already stated reasons.[5]

Consequently, we decided to utilize a synthetic approach which was initiated by one of us some years ago (10) and recently developed in our laboratories toward a successful total synthesis of D-normorphinan systems (11, 12). This approach proved to be fruitful and flexible, allowing for the preparation of various 3,14-dihydroxymorphinans (13), 3,14-dihydroxyisomorphinans (1), and a number of hasubanan derivatives (1, 2). It is the purpose of this communication to describe in full the synthesis of the common key intermediate 4a-(2-aminoethyl)-1,2,3,4,4a,9-hexahydro-6-methoxyphenanthrene **3***a* (Scheme 2), our initial studies on the intramolecular oxidative cyclization of **3***a* to morphinan and hasubanan systems, and the synthesis of a number of 3,14-dihydroxyisomorphinans, some of which exhibited moderate narcotic antagonist and analgesic activities.



SCHEME 2

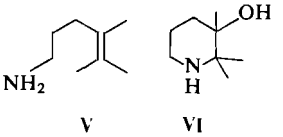
[4]Attempt along these lines has been published recently by Onda *et al.* (8).

[5]Successful conversion of thebaine to 3,14-dihydroxymorphinan derivatives was described by Sawa and Tada (9).

Results and Discussion

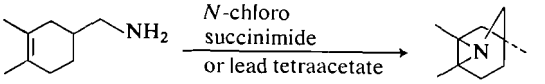
Our synthetic approach to various morphinan systems may be divided into two parts. The first consists in the successful practical synthesis of the unsaturated amine **3***a* a key intermediate analogous to the 3-unsubstituted analog already described (11). The starting material, 7-methoxy-1-tetralone (14) was alkylated by the method of Mousseron *et al.* (15) to give the spiro ketone **1** in high yield. Cyanomethylation of **1** (16) readily gave the hydroxy nitrile **2***a*, which was reduced *in situ* with lithium aluminum hydride to the amino alcohol **2***b*. Wagner–Meerwein rearrangement of **2***b* at 40° (in a refluxing mixture of concentrated hydrochloric acid and ether for 24 h), afforded unsaturated amine **3***a* in excellent yields. At room temperature, this reaction resulted in a 9:1 mixture of **3***a* and its positional isomer **4** which eventually rearranged to **3***a* at higher temperature. The characteristic n.m.r. absorptions of **3***a* at δ 5.71 (t, J = 3.5 Hz, olefinic proton at 10) and at δ 3.32 (broad singlet) for the benzylic protons can only be consistent with structure **3***a* (11). The isomeric olefin **4** was readily distinguished from **3***a* by the downfield shift of the olefinic proton signal (δ 5.35, J = 6 Hz) and the stronger coupling with its neighboring methylene protons (δ 3.43, J = 6 Hz). Attempted extension of the Wagner–Meerwein rearrangement to the homologous six-membered spiro intermediate **6***b* prepared from spiro ketone **5** by similar methods proved unsuccessful, the product of dehydration **6***c* as opposed to the rearranged product **7** being formed exclusively under our experimental conditions.

The second part of our synthesis consists in the oxidative cyclization of unsaturated amine **3***a* to the 14-hydroxymorphinan system **IV**. As far as we are aware, there are no direct methods for the conversion in a single step of γ,δ-unsaturated amines of general structure **V** to the corresponding 3-hydroxy piperidines **VI**. Accordingly, a stepwise approach had to be devised.



V VI

Our extensive experience in these laboratories with bromocyclizations of various β,γ- (17) and γ,δ-unsaturated systems (18, 19) proved of little use initially as regards the unsaturated amine **3***a*.[6] Attempts at the preparation of bridged aziridine systems such as **VIII** by the method of Nagata *et al.* (20) led mostly to the formation of intractable mixtures.

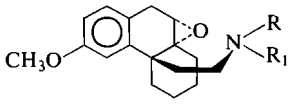


VII VIII

Our first successful formation of a morphinan functionalized at position 14 was accomplished by the method of Gassman *et al.* (21). The unsaturated amine **3***a* was first transformed into the *N*-ethoxycarbonyl derivative **3***b* followed by reduction to the *N*-methyl unsaturated amine **3***c*. This was converted to the chloramine **3***g* by reaction with *N*-chlorosuccinimide followed by methanolysis in hot methanol to give in low yield 3,14-dimethoxy-17-methylisomorphinan **9***l* (Scheme 3).

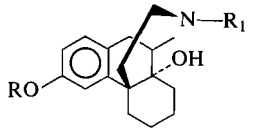
Another approach based on the intramolecular opening of an epoxide of **3***c* by the amino function was explored. In this respect it was essential to initially protect the amino function, followed by stereoselective epoxidation of the double bond in a *trans* fashion with respect to the amino ethane substituent. Next, deblocking of the nitrogen without affecting the epoxide function was desirable. Finally, it was necessary that the free amino group attack the epoxide ring regioselectively so as to give a 14-hydroxyisomorphinan rather than a 9α-hydroxyhasubanan. To this end, the unsaturated amine **3***c* was protected with a trifluoroacetyl group to give **3***f* which was then epoxidized with *m*-chloroperbenzoic acid to afford the α-epoxide **8***d* (Scheme 3). Hydrolysis of the amide function with potassium carbonate presumably gave the desired amino epoxide **8***e* which spontaneously cyclized to a 1:1 mixture of 14-hydroxyisomorphinan **9***f* and 9α-hydroxyhasubanan **10**. This approach was eventually modified so as to effect direct base-catalyzed cyclization of epoxy amides **8***a*, **8***b*, and **8***c* derived from the unsaturated amides **3***b*, **3***c*, and **3***d*. In this manner, these epoxy amides led to practical yields of the 14-hydroxy-

[6]However, subsequent experiments by Dr. T. T. Conway of these laboratories led to the successful bromocyclization of **3***a* to 9α-bromo-3-methoxyhasubanan hydrobromide, a key intermediate in our previously reported total synthesis of **11***b* (13).



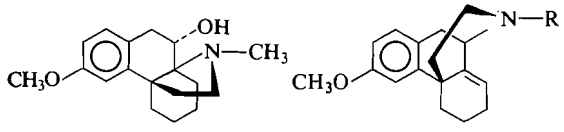
8

a R = H; R_1 = CO_2Et
b R = H; R_1 = $COCF_3$
c R = H; R_1 = CO-cyclopropyl
d R = CH_3; R_1 = $COCF_3$
e R = CH_3; R_1 = H



9

a R = CH_3; R_1 = CO_2Et
b R = CH_3; R_1 = $COCF_3$
c R = CH_3; R_1 = CO-cyclopropyl
d R = CH_3; R_1 = H
e R = CH_3; R_1 = CO-cyclobutyl
f R = CH_3; R_1 = CH_3
g R = CH_3; R_1 = CH_2-cyclopropyl
h R = CH_3; R_1 = CH_2-cyclobutyl
i R = H; R_1 = CH_3
j R = H; R_1 = CH_2-cyclopropyl
k R = H; R_1 = CH_2-cyclobutyl
l R = CH_3; R_1 = CH_3,14-OCH_3
m R = CH_3; R_1 = $CH_2CH{=}CH_2$
n R = H; R_1 = $CH_2CH{=}CH_2$



10 **11**

a R = CO_2Et
b R = H

SCHEME 3

isomorphinans **9***a*, **9***b*, and **9***c* when treated with sodium *t*-pentoxide in hot benzene (for **8***a* and **8***b*) or sodium hydride in DMSO (for **8***c*). Subsequent reduction of **9***a* and **9***c* with lithium aluminum hydride afforded the corresponding bases **9***f* and **9***g*. Alternatively, alkaline hydrolysis of **9***a* and **9***c* afforded the 14-hydroxy-3-methoxyisomorphinan **9***d* which was conveniently alkylated to **9***m* or acylated to **9***e* followed by reduction to **9***k*. Finally, cleavage of the ether function at the 3 position was accomplished with boron tribromide (22) in dichloromethane or with hot 48% hydrobromic acid. The 3,14-dihydroxyisomorphinans **9***j*, *k*, *n*, and **9***c* thus obtained, were tested for narcotic antagonist and analgesic activities in laboratory animals. Moderate activities comparable to those of pentazocine were observed with **9***j* and **9***h*.

While the general approach represented by scheme **3** → **8** → **9** provides a convenient entry into the 14-hydroxyisomorphinan system further modifications were required in order to synthesize the isomeric 14-hydroxymorphinans. This was initially accomplished by dehydrating **9***a* with phosphorus oxychloride in pyridine to give the $\Delta^{8,14}$-morphinan **11***a* which after hydrolysis to **11***b* was further transformed into various 14-hydroxymorphinans as previously described (13). Subsequently, a more elegant and practical synthesis of **11***a* was developed (see footnote 6).

Experimental

The melting points were determined on a Gallenkamp apparatus and are not corrected. The infrared (i.r.) spectra were recorded on a Unicam Sp-200G grating i.r. spectrometer. The n.m.r. spectra were recorded on a Varian A-60A spectrometer using deuteriochloroform as a solvent. The chemical shifts are expressed in δ values using tetramethylsilane as internal reference. Microanalysis were performed by Micro-Tech Laboratories Inc., Skokie, Ill.

3,4-Dihydro-7-methoxy-2,2-tetramethylene-1 (2H)-naphthalenone (1)

A suspension of sodium hydride (269 g of ≃56% washed with hexane) in benzene (3.75 l) was heated under reflux under nitrogen and to it was added dropwise *t*-amyl alcohol (220 g) followed by a solution of 7-methoxy-1-tetralone (440 g) in benzene (1.5 l). The mixture was stirred and heated under reflux for 45 min, followed by the rapid addition of a solution of 1,4-dibromobutane (650 g) in benzene (3 l). Stirring and heating were continued for 50 h, after which time the mixture was cooled and the excess of sodium hydride carefully decomposed with water. The benzene layer was washed with water, dried ($MgSO_4$), and concentrated *in vacuo*. The residual oil was fractionally distilled to give 455 g of **1**, b.p. 120–125°/0.1 Torr; i.r. (neat) 1725, 3340 cm^{-1}; n.m.r. δ 7.55 (1H, broad s), 7.05 (2H, m) 3.82 (3H, s), 2.9 (2H, t, J = 6 Hz), 2.0 (2H, t, J = 6 Hz), 1.1–2.3 (8H, m).

Anal. Calcd. for $C_{15}H_{18}O_2$: C, 78.22; H, 7.88. Found: C, 77.96; H, 7.93.

1-Hydroxy-7-methoxy-1,2,3,4-tetrahydro-2,2-tetramethylene-1-naphthaleneacetonitrile (2a) and 1-(2-Aminoethyl)-7-methoxy-1,2,3,4-tetrahydro-2,2-tetramethylene-1-naphtol (2b)

To a cooled (−80°), stirred solution of 1.6 *M* butyl lithium in hexane (1345 ml) under nitrogen was added anhydrous THF (1340 ml) followed by acetonitrile (88 g) in THF (1 l) and stirring continued for 1 h at −80°. To the resulting white suspension was added a solution of spiro ketone **1** (485 g) in THF (1.8 l). The cold bath was removed and the solution was stirred for 20 min. At this point the hydroxy nitrile *2a* can be isolated, or directly

reduced *in situ* to the amino alcohol **2***b*. Thus, the reaction mixture was poured onto cold dilute hydrochloric acid and extracted with benzene, followed by drying and evaporation of solvent to yield crude **2***a*. The pure product was obtained by recrystallization from chloroform (80% yield), m.p. 140–142°; i.r. (neat) 2260, 3420 cm^{-1}; n.m.r. δ 7.42 (1H, d, J = 2 Hz), 6.75–7.17 (2H, m), 3.85 (3H, s), 2.6–3.2 (4H, m), 1.1–2.2 (10H, m).

Anal. Calcd. for $C_{17}H_{21}NO_2$: C, 75.24; H, 7.80; N, 5.16. Found: C, 75.12; H, 7.91; N, 4.89.

Alternatively, to the above solution of **2***a* in THF was added lithium aluminum hydride (122 g) and the mixture was stirred for 2.5 h. It was then treated consecutively with water (122 ml), 5 *N* sodium hydroxide (122 ml), and again water (244 ml). The solids were removed by filtration, washed with ether, and the filtrate concentrated *in vacuo* to give 530 g of crude **2***b* as an oil which was used in the next step without further purification; i.r. (neat) 3200 cm^{-1}; n.m.r. δ 7.26 (1H, t, J = 2.5 Hz), 6.5–7.1 (2H, m), 3.83 (3H, s), 2.5–3.2 (4H, m), 1.0–2.2 (12H, m).

The oxalate salt was prepared in acetone and recrystallized from methanol, m.p. 179–180°.

Anal. Calcd. for $C_{17}H_{25}NO_2 \cdot C_2H_2O_4 \cdot CH_3OH$: C, 63.31; H, 7.70; N, 3.69. Found: C, 63.41; H, 7.43; N, 3.79.

4a-(2-Aminoethyl)-1,2,3,4,4a,9-hexahydro-6-methoxyphenanthrene (3a)

To a cooled and stirred solution of **2***b* (530 g) in ether (1 l) was added concentrated hydrochloric acid (530 ml). The cooling bath was removed and the two-phase mixture heated under reflux (steam bath) for 18 h. It was cooled, the ether layer separated, and the aqueous layer diluted with water (1 l) followed by stirring for 18 h. The deposited solid was collected by filtration, washed with acetonitrile, and dried to give 342 g of unsaturated amine hydrochloride **3***a*, m.p. 130°; i.r. (free base, neat) 3200 cm^{-1}; n.m.r. δ 6.6–7.2 (3H, m) 5.71 (1H, t, J = 3.5 Hz), 3.78 (3H, s), 3.32 (2H, broad s), 1.2–3.0 (12H).

The analytical sample was recrystallized from methanol–ether, m.p. 135°.

Anal. Calcd. for $C_{17}H_{23}NO \cdot HCl \cdot CH_3OH$: C, 66.34; H, 8.66; N, 4.29. Found: C, 66.34; H, 8.62; N, 4.26.

1-(2-Aminoethylidene)-1,2,3,4-tetrahydro-2,2-tetramethylenenaphthalene (4)

When the above rearrangement of **2***b* was carried out at room temperature for 24 h, **2***b* was all consumed but the yield of **3***a* was only 62%. However, the mother liquors contained a mixture of **3***a* and **4** in a 1:1 ratio. The unsaturated amine **4** was isolated by chromatography over alumina in 8% yield, as an oil; i.r. (neat) 3420 cm^{-1}; n.m.r. (CCl_4) δ 6.4–7.0 (3H, m), 5.35 (1H, t, J = 6 Hz), 3.67 (3H, s) 3.43 (2H, d, J = 6 Hz), 2.72 (2H, t, J = 7 Hz), 1.7 (2H, t, J = 7 Hz), 1.6 (8H, b, s).

The oxalate salt was recrystallized from methanol, m.p. 199°.

Anal. Calcd. for $C_{17}H_{23}NO \cdot C_2H_2O_4$: C, 65.69; H, 7.25; N, 4.03. Found: C, 65.81; H, 7.40; N, 4.04.

4a-[2-(Ethoxycarbonylamino)ethyl]-1,2,3,4,4a,9-hexahydro-6-methoxyphenanthrene (3b)

To a cooled (ice bath), stirred solution of unsaturated amine **3***a* (51.4 g, 0.2 mol) and triethylamine (22.2 g, 0.22 mol) in dichloromethane (200 ml) was added dropwise ethyl chloroformate (23.0 g, 0.21 mol). The mixture was stirred for 10 min and then washed with dilute hydrochloric acid (100 ml, 1 *N*) followed by water, dried, and evaporated *in vacuo*. The residual oil was dissolved in a 1:3 mixture of ether and petroleum ether (b.p. 30–60°) and the solution filtered through charcoal. The filtrate was concentrated to give 65.8 g of **3***b* as a pale yellow oil; i.r. (neat) 1725, 3340 cm^{-1}; n.m.r. δ 6.55–7.15 (3H, m), 5.7 (1H, t, J = 2.5 Hz), 4.56 (1H, m), 4.01 (2H, q, J = 7 Hz), 3.78 (3H, s), 3.25 (2H, s), 1.2–3.0 (12H, m), 1.15 (3H, t, J = 7 Hz).

Anal. Calcd. for $C_{20}H_{27}NO_3$: C, 72.9; H, 8.26; N, 4.25. Found: C, 72.71; H, 8.27; N, 4.25.

4a-[2-(Methylamino)ethyl]-1,2,3,4,4a,9-hexahydro-6-methoxyphenanthrene (3c)

To a suspension of lithium aluminum hydride (2.3 g) in dry ether (50 ml) was added dropwise under nitrogen a solution of urethane **2***b* (9.87 g) in ether (100 ml). The mixture was heated under reflux for 18 h, after which time it was worked-up in the usual manner to afford the unsaturated amine **3***c* as an oil (8.0 g); n.m.r. δ 5.60 (1H, t, J = 6 Hz, 10-H), 2.22 (3H, s, N—CH_3).

The hydrochloride salt was recrystallized from methanol–ether, m.p. 190–191°.

Anal. Calcd. for $C_{18}H_{25}NO \cdot HCl$: C, 70.22; H, 8.51; N, 4.55. Found: C, 70.39; H, 8.71; N, 4.48.

Amides 3d–3f

Amides **3***d*–**3***f* were prepared by a procedure similar to that described above for the preparation of **3***b*.

4a-[2-(Trifluoroacetylamino)ethyl]-1,2,3,4,4a,9-hexahydro-6-methoxyphenanthrene (3d)

White solid from ether – petroleum ether (89%), m.p. 99–101°.

Anal. Calcd. for $C_{19}H_{22}F_3NO_2$: C, 64.58; H, 6.28; N, 3.96. Found: C, 64.82; H, 6.25; N, 3.82.

4a-[2-(Cyclopropylcarbonylamino)ethyl]-1,2,3,4,4a,9-hexahydro-6-methoxyphenanthrene (3e)

White solid (79%) from methanol, m.p. 126–130°.

Anal. Calcd. for $C_{21}H_{27}NO_2$: C, 77.50; H, 8.36; N, 4.30. Found: C, 77.21; H, 8.40; N, 4.09.

3,4-Dihydro-2,2-pentamethylene-1(2H)-naphthalenone (5)

To a cooled stirred (ice-salt) suspension of sodium hydride (21.3 g of ≃ 56%, washed with hexane) in DMF (300 ml) was added dropwise a solution of 1-tetralone (36.55 g) and 1,5-dibromopentane (57.5 g) in DMF (150 ml) over a 2 h period. The internal temperature during the addition was maintained at 5–10°. When the addition was completed, the mixture was stirred for 30 min at 8–12° and then for 2 h at room temperature. It was then partitioned between water and petroleum ether and the organic layer washed with water, dried, and evaporated. The residual oil was distilled to give 29.5 g of spiro ketone **5**, b.p. 115–120°/0.05 Torr; i.r. (neat), 1680 cm^{-1}; n.m.r. (CCl_4), δ 7.9–8.1 (1H, m), 7.0–7.5 (3H, m), 2.93, (2H, t, J = 6 Hz), 20 (2H, t, J = 6 Hz), 1.15–2.0 (10H, m). This product was probably contaminated with some dibromopentane, as judged from the empirical analysis (carbon lower by 0.6%). It was used in the next step without further purification.

1-Hydroxy-1,2,3,4-tetrahydro-2,2-pentamethylen-1-naphthaleneacetonitrile (6a)

The hydroxynitrile **6***a* was obtained in 83% yield by a

similar procedure as given for the preparation of **2***a*, m.p. 128–131° (from benzene); i.r. 2260, 3440 cm^{-1}; n.m.r. ($CDCl_3$) δ, 7.7–7.9 (1H, m), 7.0–7.4 (3H, m), 2.6–3.1 (4H, m), 2.0–2.5 (2H, m), 1.1–1.9 (10H, m).

Anal. Calcd. for $C_{17}H_{21}NO$: C, 79.96; H, 8.29; N, 5.48. Found: C, 79.74; H, 8.28; N, 5.41.

1-(2-Aminoethyl)-1,2,3,4-tetrahydro-2,2-pentamethylene-1-naphtol (6b)

The amino alcohol **6***b* was obtained in a quantitative yield from hydroxynitrile **6***a* by the procedure described above for the preparation of **2***b*; i.r. (neat) 3220, 3470 cm^{-1}; n.m.r. ($CDCl_3$), δ 7.45–7.7 (1H, m), 6.9–7.4 (3H, m), 2.55–3.0 (4H, m), 0.8–2.5 (12H, m). The oxalate salt was prepared in ether, m.p. 167–171°.

Anal. Calcd. for $C_{17}H_{25}NO \cdot C_2H_2O_4 \cdot \frac{1}{2}H_2O$: C, 63.67; H, 7.67; N, 3.01. Found: C, 63.43; H, 7.53; N, 4.06.

1-(2-Amino-1-ethylidene)-1,2,3,4-tetrahydro-2,2-pentamethylenenaphthalene (6c)

A solution of the amino alcohol **6***b* (2.0 g) in methanol (60 ml) was added dropwise with stirring to concentrated hydrochloric acid (60 ml). The internal temperature during the addition was maintained at 30–36°. After addition was completed, stirring was continued for 15 min at the same temperature whereupon the mixture was poured onto water, basified with ammonium hydroxide, and extracted with benzene. The extract was dried and concentrated *in vacuo* to give 1.6 g of crude **6***c*; i.r. (neat) 3200 cm^{-1}; n.m.r. ($CDCl_3$) δ 7.1–7.4 (4H, m), 5.7 (1H, t, J = 7 Hz), 3.74 (2H, d, J = 7 Hz), 2.8 (2H, t, J = 6 Hz), 1.73 (2H, t, J = 6 Hz), 1.44 (10H, s).

The hydrochloride salt was prepared in ether and recrystallized from methanol–ether, m.p. 206–208°.

Anal. Calcd. for $C_{17}H_{23}N \cdot HCl$: C, 73.49; H, 8.71; N, 5.04. Found: C, 73.18; H, 8.89; N, 5.06.

10,10a-α-Epoxy-4a-[2-(ethoxycarbonylamino)ethyl]-1,2,3,4,4a,9,10,10a-octahydro-6-methoxyphenanthrene (8a)

To a cooled (5–10°) stirred solution of the urethane **3***b* (55.8 g) in dichloromethane (150 ml) was added in small portions 45 g of *m*-chloroperbenzoic acid (85% purity) and the mixture left at room temperature for 5 h. The precipitated solid was removed by filtration and the filtrate washed with aqueous sodium sulfite followed by 5% aqueous sodium bicarbonate and finally with water. Drying and evaporation of the solvent afforded an oil, which was dissolved in ether followed by the addition of petroleum ether. After filtration through Celite–charcoal and concentration of the filtrate *in vacuo*, there was obtained 65.8 g of epoxide **8***a* as an oil which solidified on standing, m.p. 75–77° (ether).

Anal. Calcd. for $C_{20}H_{27}NO_4$: C, 69.54; H, 7.77; N, 4.05. Found: C, 69.30; H, 7.95; N, 3.90.

10,10a-α-Epoxy-4a-[2-(trifluoroacetylamino)ethyl]-1,2,3,4,4a,9,10,10a-octahydro-6-methoxyphenanthrene (8b)

To a solution of amide **3***d* (7.06 g) in dichloromethane (140 ml) was added in small portions with stirring and cooling (5–10°) *m*-chloroperbenzoic acid (4.2 g, 85% purity). The mixture was left at room temperature for 18 h and then worked-up as described for the isolation of **8***a* to give 7.36 g of epoxide 7*b* as an amorphous solid. A sample was prepared for analysis by dissolving in ether followed by precipitation with excess petroleum ether; the syrup was dried under high vacuum to yield amorphous solid, m.p. 45–50°.

Anal. Calcd. for $C_{19}H_{23}F_3NO_3$: C, 61.79; H, 6.00; N, 3.79. Found: C, 62.02; H, 6.07; N, 3.74.

10,10a-α-Epoxy-4-[2-(cyclopropylcarbonylamino)ethyl]-1,2,3,4,4a,9,10,10a-octahydro-6-methoxyphenanthrene (8c)

The epoxide **8***c* was obtained in 78% yield from amide **3***c* by a procedure similar to that given for the preparation of **8***b* except that purification was accomplished by crystallization from ether, m.p. 130–132°.

Anal. Calcd. for $C_{21}H_{27}NO_3$: C, 73.87; H, 7.97; N, 4.10. Found: C, 73.71; H, 8.06; N, 4.20.

10,10a-α-Epoxy-4a-[2-(N-trifluoroacetyl-N-methylamino)ethyl]-1,2,3,4,4a,9,10,10a-octahydro-6-methoxyphenanthrene (8d)

The epoxide **8***d* was obtained as an oil in a quantitative yield by a procedure similar to that given for the preparation of **8***b*, except that the time required for completion of the reaction was 1 h.

Anal. Calcd. for $C_{20}H_{24}F_3NO_3$: C, 62.65; H, 6.31; N, 3.65. Found: C, 62.89; H, 6.48; N, 3.66.

17-Ethoxycarbonyl-14-hydroxy-3-methoxyisomorphinan (9a)

To a stirred boiling suspension of sodium hydride (3.15 g of ≃56%, washed with hexene) in dry benzene, under nitrogen atmosphere, was added a solution of anhydrous *t*-amyl alcohol (5.87 g) in benzene (50 ml). When the hydrogen evolution had subsided (*ca.* 15 min), a solution of epoxide **8***a* (23.0 g) in benzene (500 ml) was added dropwise over a 4 h period and stirring and heating were continued for 18 h. After cooling, the mixture was washed with water, dried, and concentrated *in vacuo*. The residual oil was dissolved in ether and the resulting solution was diluted with petroleum ether. The cloudy mixture was filtered through Celite–charcoal cake and the filtrate evaporated to dryness to give 20.0 g of the isomorphinan **9***a* as a yellow oil. A sample solidified after distillation at 100°/0.05 Torr, m.p. 50°; i.r. (Nujol) 1690, 3300 cm^{-1}; n.m.r. δ 6.5–7.2 (3H, m), 4.15 (2H, q, J = 7 Hz), 3.78 (3H, s), 2.3–3.8 (5H, m), 1.3–2.3 (10H, m), 1.26 (3H, t, J = 7 Hz).

Anal. Calcd. for $C_{20}H_{27}NO_4$: C, 69.54; H, 7.88; N, 4.05. Found: C, 69.21; H, 8.01; N, 3.95.

14-Hydroxy-3-methoxy-17-trifluoroacetylisomorphinan (9b)

The hydroxy amide **9***b*, an amorphous solid, was obtained from **8***b* in 68% yield together with the product of hydrolysis **8***d* (8%) by a procedure similar to that given for the preparation of **9***a* except that the reaction time was 3.5 h.

Mol. Wt. Calcd. for $C_{19}H_{23}F_3NO_3$: 369. Found (mass spectrometry): 369.

17-Cyclopropylcarbonyl-14-hydroxy-3-methoxyisomorphinan (9c)

To a stirred and cooled (5–8°) suspension of sodium hydride (1.8 g, hexane washed) in a mixture of anhydrous THF (200 ml) and DMSO (200 ml) was added epoxide **8***c* (13.08 g). The mixture was stirred at 5–8° for 3 h and

then for 1 h at room temperature. It was then poured onto water and extracted with benzene. The organic layer was washed with water several times, dried, and concentrated *in vacuo*. The residual oil was crystallized from ether to yield 6.56 g of isomorphinan **9c** (50%) as a white solid, m.p. 162–64°; i.r. (Nujol), 1640, 3410 cm^{-1}.

Anal. Calcd. for $C_{21}H_{27}NO_3$: C, 73.87; H, 7.97; N, 4.10. Found: C, 73.70, H, 8.13; N, 4.02.

14-Hydroxy-3-methoxyisomorphinan (9d)

A mixture of **9a** (10.0 g) and potassium hydroxide pellets (6.0 g) in 1-octanol (50 ml) was heated under reflux for 30 min under nitrogen. After cooling, the mixture was poured onto water and extracted with ether. The organic layer was extracted with 2 *N* hydrochloric acid (2 × 60 ml) and the extract washed with ether to remove 1-octanol. The aqueous layer was made alkaline and extracted with ether to give after drying and concentration 7.5 g of crude **9d** as an oil. The hydrochloride salt was recrystallized from isopropyl aclcohol – ether to afford 5.2 g (58%) of pure product, m.p. 261–271°; i.r. (free base), 3360 and 3460 cm^{-1}; n.m.r. ($CDCl_3$) δ 6.6–7.3 (3H, m), 3.78 (3H, s), 3.55 (1H, d, J = 7 Hz), 3.25 (1H, d, J = 7 Hz), 0.8–3.0 (13H, m).

Anal. Calcd. for $C_{17}H_{23}NO_2 \cdot HCl$: C, 65.90; H, 7.81; N, 4.52. Found: C, 65.57; H, 7.85; N, 4.27.

Alternatively, **9d** was obtained in a 53% overall yield from **8b** via **9b**, after treatment of the latter with 1.5 *N* NaOH in methanol–water (3:1) at reflux temperature for 3 h, without isolation of **9b**.

17-Cyclobutylcarbonyl-14-hydroxy-3-methoxyisomorphinan (9e)

To a stirred and cooled (ice) solution of **9d** (2.1 g) and triethylamine (1.0 g) in dichloromethane (20 ml) was added dropwise a solution of cyclobutanecarboxylic acid chloride (1.07 g) in dichloromethane (10 ml). The mixture was then washed with water, dried, and concentrated. The residual oil crystallized from ether to give **9e** (2.0 g) as a white solid, m.p. 136–138°.

Anal. Calcd. for $C_{22}H_{20}NO_3$: C, 74.33; H, 8.22; N, 3.94. Found: C, 74.53; H, 8.37; N, 3.78.

14-Hydroxy-3-methoxy-17-methylisomorphinan (9f)

To a solution of lithium aluminum hydride (3.8 g) in anhydrous ether (100 ml) was added dropwise under nitrogen atmosphere a solution of urethane **9a** (34.5 g) in ether (200 ml). The mixture was heated under reflux for 1 h and then worked-up in the usual manner. The crude product, an oil, was converted to its hydrochloride salt in methanol to give **9f** (23.0 g, 65%) as a white solid, m.p. 252–254°; i.r. (free base in $CDCl_3$) 3550 cm^{-1}; n.m.r. (free base in $CDCl_3$) δ 6.6–7.1 (3H, m), 3.76 (3H, s), 0.9–2.1 (10H, m).

Anal. Calcd. for $C_{18}H_{25}NO_2 \cdot HCl$: C, 66.76; H, 8.09; N, 4.32. Found: C, 67.03; H, 8.27; N, 4.18.

17-Cyclopropylmethyl-14-hydroxy-3-methoxyisomorphinan (9g)

A solution of **9c** (1.6 g) in THF (20 ml) was added dropwise to a solution of lithium aluminum hydride (0.47 g) in THF (10 ml) and the mixture was heated under reflux for 1 h. Work-up in the usual manner yielded **9g** as an oil which was converted to its hydrochloride salt in ether. Recrystallization from methanol afforded pure product (1.24 g, 71%) as a white solid, containing ½ mol of water of crystallization, m.p. 229–230°.

Anal. Calcd. for $C_{21}H_{29}NO_3 \cdot HCl \cdot \frac{1}{2}H_2O$: C, 67.67; H, 8.37; N, 3.72. Found: C, 67.63; H, 8.34; N, 3.65.

17-Cyclobutylmethyl-14-hydroxy-3-methoxyisomorphinan (9h)

The hydroxyisomorphinan **9h** was obtained in 74% yield from **9e** by a procedure similar to that given for the preparation of **9g**; hydrochloride salt, m.p. 239–241°.

Anal. Calcd. for $C_{22}H_{31}NO_2 \cdot HCl$: C, 69.91; H, 8.53; N, 3.71. Found: C, 69.71; H, 8.67; N, 3.48.

3,14-Dihydroxy-17-methylisomorphinan (9i)

A solution of **9f** (1.0 g) in 48% hydrobromic acid (10 ml) was heated under reflux for 10 min under nitrogen. After cooling, the mixture was diluted with water, made basic with ammonium hydroxide, and extracted with chloroform. The extract was dried, evaporated, and the residual oil crystallized from ether to afford **9i** (650 mg) as a white solid. Recrystallization from methanol–ether gave an analytical sample, m.p. 191–193°; n.m.r. ($CDCl_3$) δ 6.4–7.0 (3H, m), 2.4–3.0 (5H, m), 2.3 (3H, s), 0.8–2.2 (10H, m).

Anal. Calcd. for $C_{17}H_{23}NO_2$: C, 74.71; H, 8.48; N, 5.13. Found: C, 74.63; H, 8.52; N, 5.01.

17-Cyclopropylmethyl-3,14-dihydroxyisomorphinan (9j)

To a cooled (ice–salt) and stirred solution of boron tribromide (1.85 g) in anhydrous dichloromethane (10 ml) under nitrogen was added a solution of methoxyisomorphinan **9g** (0.80 g) in dichloromethane (10 ml) and the mixture stirred for 2 h at room temperature. It was then slowly poured onto ice–water, basified with ammonium hydroxide, and the layers separated. The organic layer was dried (Na_2SO_4), evaporated *in vacuo*, and the residual amorphous solid treated with dry hydrochloric acid in ether to give 0.59 g of hydrochloride salt of the dihydroxyisomorphinan **9j**. A sample for analysis was recrystallized from methanol, m.p. 222–224°.

Anal. Calcd. for $C_{20}H_{23}NO_2 \cdot HCl \cdot \frac{1}{4}CH_3OH$: C, 67.29; H, 8.27; N, 3.83. Found: C, 66.91; H, 8.35; N, 3.86.

17-Cyclobutylmethyl-3,14-dihydroxyisomorphinan (9k)

The dihydroxyisomorphinan **9k** was obtained in 68% yield from the methoxyisomorphinan **9h** as a white solid (free base), m.p. 162–164°, by a procedure similar to that given for the preparation of **9j**. Recrystallization from methanol gave an analytical sample, m.p. 170–171°.

Anal. Calcd. for $C_{21}H_{29}NO_2$: C, 77.02; H, 8.93; N, 4.28. Found: C, 77.17; H, 9.09; N, 4.11.

3,14-Dimethoxy-17-methylisomorphinan (9l)

A solution of chloramine **3g** (5.0 g) in methanol (150 ml) was heated under reflux for 24 h. The methanol was evaporated *in vacuo* and the residue extracted with petroleum ether. The extract was evaporated to give an oil (4.5 g), which was chromatographed on an alumina column (activity III to IV; eluent, dichloromethane) to give the dimethoxyisomorphinan **9l** (1.45 g) as an oil; n.m.r. ($CDCl_3$) δ 6.5–7.3 (3H, m), 3.84 (3H, s), 3.11 (3H, s), 2.38 (3H, s), 2.2–3.4 (5H, m), 0.8–2.2 (10H, m). The hydrochloride salt was recrystallized from isopropyl alcohol, m.p. 248–250°.

Anal. Calcd. for $C_{19}H_{27}NO_2 \cdot HCl$: C, 67.54; H, 8.35; N, 4.14. Found: C, 67.41; H, 8.35; N, 3.90.

17-Allyl-14-hydroxy-3-methoxyisomorphinan (9m)

A solution of **9d** (1.09 g), triethylamine (2.02 g), and allylbromide (0.73 g) in dry ethanol was heated under reflux and under nitrogen for 18 h. After cooling, it was partitioned between chloroform and dilute ammonium hydroxide. The organic layer was separated, dried, and evaporated to yield 1.20 g of **9m** as an oil; i.r. (neat) 3460 and 3560 cm^{-1}; n.m.r. ($CDCl_3$) δ 6.6–7.2 (3H, m), 5.0–6.4 (3H, m), 3.68 (3H, s), 0.8–3.2 (17H).

A sample for analysis was purified as the hydrochloride salt which was recrystallized from methanol–ether, m.p. 243–245°.

Anal. Calcd. for $C_{20}H_{27}NO_2 \cdot HCl$: C, 68.65; H, 8.07; N, 4.00. Found: C, 68.46; H, 8.18; N, 3.93.

17-Allyl-3,14-dihydroxyisomorphinan (9n)

To a cooled (ice–salt) solution of boron tribromide (1.75 g) in dichloromethane (10 ml) was added under nitrogen a solution of **9m** (1.1 g) in dichloromethane (10 ml) and the mixture was stirred for 1 h at room temperature. It was then treated with ice and concentrated ammonium hydroxide and the layers separated. The organic layer was dried (Na_2SO_4) and concentrated *in vacuo* to afford 1.0 g of **9n** as an oil; i.r. (neat) 3200 cm^{-1}; n.m.r. ($CDCl_3$) δ 6.1–7.1 (3H, m), 3.9–6.1 (3H, m), 0.5–3.2 (17H). The hydrochloride salt was recrystallized from 2-propanol, m.p. 248–250° (dec.).

Anal. Calcd. for $C_{19}H_{25}NO_2 \cdot HCl$: C, 67.94; H, 7.80; N, 4.17. Found: C, 67.75; H, 7.88; N, 3.96.

9α-Hydroxy-3-methoxy-17-methylhasubanan (10) and the Corresponding 14-Hydroxyisomorphinan (9f)

To a solution of *N*-trifluoroacetyl epoxide **8d** (5.4 g) in methanol (160 ml) was added a 10% aqueous solution of potassium carbonate (150 ml) and the mixture was stirred at room temperature for 2 h. It was then concentrated to a small volume, diluted with water, and extracted with ether to yield after drying and evaporation of the ether extract an oil (3.50 g). This was dissolved in methanol (50 ml) and the solution heated under reflux for 18 h under nitrogen. The solvent was then evaporated, and the residue chromatographed on an alumina column (activity III to IV; eluent, $CHCl_3$) to give at first 14-hydroxyisomorphinan **9f** (1.49 g) followed by 9α-hydroxyhasubanan **10** (1.52 g) as an oil; i.r. (neat) 3400 cm^{-1}; n.m.r. δ 6.6–7.2 (3H, m), 4.2 (1H, dd, J_1 = 6 Hz, J_2 = 9 Hz, 9-H), 3.79 (3H, s), 2.7–3.3 (4H, m), 2.62 (3H, s), 0.8–2.2 (10H, m).

The oxalate salt of **10** crystallized from methanol–acetone with ½ mol of methanol of crystallization, m.p. 109–111°.

Anal. Calcd. for $C_{18}H_{25}NO_2 \cdot C_2H_2O_4 \cdot \frac{1}{2}CH_3OH$: C, 62.58; H, 7.43; N, 3.56. Found: C, 62.69; H, 7.73; N, 3.31.

17-Ethoxycarbonyl-3-methoxy-$\Delta^{8,14}$-morphinan (11a)

To a cooled (ice–water) solution of hydroxyisomorphinan **9a** (48.0 g) in pyridine (96 ml) was added dropwise under nitrogen phosphorous oxychloride (48 ml) and the mixture was left at room temperature for 7 days. It was then diluted with benzene (200 ml) and carefully poured onto ice–water. The layers were separated and the water layer extracted with benzene (100 ml). The combined benzene extracts were washed with water, dried, and concentrated *in vacuo*. The residual brown oil was dissolved in ether followed by addition of petroleum ether. The turbid mixture was filtered through Celite–charcoal cake and evaporated to dryness to yield $\Delta^{8,14}$-morphinan **11a** (36.0 g; 79%) as a colorless oil; i.r. (neat) 1680 cm^{-1}; n.m.r. δ 6.6–7.2 (3H, m), 5.78 (1H, t, J = 4 Hz, 8-H), 4.16 (2H, q, J = 7 Hz), 3.82 (3H, s), 2.5–3.2 (5H, m), 1.28 (3H, t, J = 7 Hz), 1.2–2.4 (8H, m).

Anal. Calcd. for $C_{20}H_{25}NO_3$: C, 73.37; H, 7.70; N, 4.28. Found: C, 73.22; H, 7.33; N, 4.12.

3-Methoxy-$\Delta^{8,14}$-morphinan (11b)

A mixture of *N*-carbethoxymorphinan **11a** (32.7 g) and potassium hydroxide pellets (28.0 g) in 1-octanol (160 ml) was heated under reflux and under nitrogen for 45 min. The mixture was then worked-up as described above for the preparation of **9d** to give 20 g of a crude oily product. The oil was dissolved in acetone and treated with an acetone solution of oxalic acid. Addition of ether caused precipitation of a solid which was recrystallized from methanol–acetone to afford pure **11b** (12.0 g, 34.8%) as white crystals, m.p. 187–189°; n.m.r. (free base in CCl_4) δ 6.45–7.05 (3H, m), 5.5 (1H, t, J = 4 Hz), 3.71 (3H, s), 2.5–3.5 (5H, m), 1.2–2.5 (8H, m).

Anal. Calcd. for $C_{17}H_{21}NO \cdot C_2H_2O_4$: C, 66.07; H, 6.71; N, 4.06. Found: C, 66.28; H, 6.72; N, 4.11.

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