Synthetic morphinans and hasubanans. VI.[1] Total synthesis of 3-hydroxyisomorphinans, 3-hydroxyhasubanans, and 3,9-dihydroxyhasubanans

IVO MONKOVIĆ AND HENRY WONG
Bristol Laboratories of Canada, 100 Industrial Blvd., Candiac, Quebec J5R 1J1

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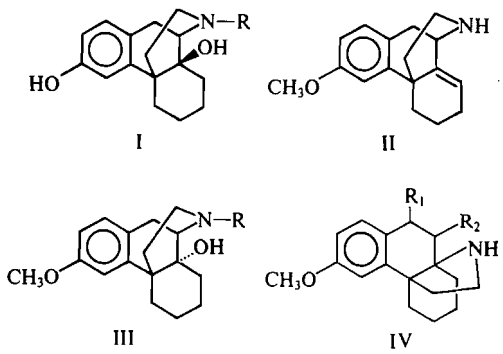
A new total synthesis of racemic 3-hydroxyisomorphinans (**3**), 3-hydroxyhasubanans (**9**), 3,9α-dihydroxyhasubanans (**5**), and 3,9β-dihydroxyhasubanans (**7**), via 4a-(2-aminoethyl)-1,2,3,4,4a,9-hexahydro-6-methoxyphenanthrene (**1***a*) is described.

IVO MONKOVIĆ et HENRY WONG. Can. J. Chem. **54**, 883 (1976).

On décrit une nouvelle synthèse totale des hydroxy-3 isomorphinanes (**3**), hydroxy-3 hasubananes (**9**), dihydroxy-3,9α hasubananes (**5**) et dihydroxy-3,9β hasubananes (**7**) par l'intermédiaire du (amino-2 éthyle)-4a hexahydro-1,2,3,4,4a,9 méthoxy-6 phénanthrène (**1***a*).
[Traduit par le journal]

Introduction

In the previous papers in this series, we have reported on the total synthesis of a number of 3,14-dihydroxymorphinans I (Chart 1), via 3-methoxy-$\Delta^{8,14}$-morphinan II, some of which have been found to possess valuable pharmacological properties as analgesics and narcotic antagonists (1, 2). We also reported on the total synthesis of various 3,14-dihydroxyisomorphinans III (3, 4) and several hasubanan alkaloids IV (4, 5). The common intermediate in all of the above syntheses is 4a-(2-aminoethyl)-1,2,3,4,4a,9-hexahydro-6-methoxyphenanthrene **1***a* (Chart 2).



R = H, CH_3, and various C_3H_5–C_5H_9 substituents.
R_1 = H, β-SH R_2 = H, α-OH, α-Br.

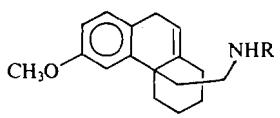
CHART 1

We now report on its utilization in the synthesis of isomorphinans **3** and various hasubanan alkaloids **5**–**9**.

Results and Discussion

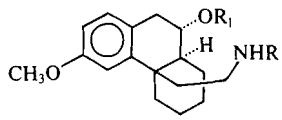
Several routes developed by Gates and coworkers led to the synthesis of the isomorphinan skeleton **3** (6, 7), the most practical being a modified Grewe approach (8). In view of potent analgesic and narcotic antagonist activity of some of these compounds, and a successful application of amine **1***a* in the synthesis of various related structures (1–5), we decided to attempt a total synthesis of the 3-hydroxyisomorphinan system **3** via the same intermediate. This was carried out in the following manner. Treatment of unsaturated amides (**1***b* and **1***c*) (4) with diborane in THF, followed by hydrogen peroxide and sodium hydroxide led to the stereo- and regioselective formation of B/C *trans*-fused α-hydroxyphenanthrenes **2***a* and **2***d* respectively, accompanied by some tertiary bases **2***b* and **2***e*. This stereochemical assignment is consistent with the reaction sequence described below. Treatment of **2***a* and **2***d* with methanesulfonyl chloride and pyridine afforded esters **2***c* and **2***f* which were cyclized to isomorphinans **3***a* and **3***c* respectively, by treatment with sodium hydride in DMF. Alkaline hydrolysis of **3***a* afforded 3-methoxyisomorphinan **3***b*, a versatile intermediate for the synthesis of various nitrogen substituted 3-hydroxyisomorphinans. Thus by a series of standard reactions, we prepared 17-

[1]For part V, see ref. 1.



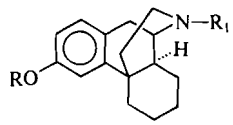
1

a R = H
b R = $COCF_3$
c R = CO—◁
d R = CO_2Et



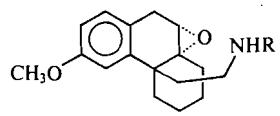
2

a R = $COCF_3$, R_1 = H
b R = CH_2CF_3, R_1 = H
c R = $COCF_3$, R_1 = SO_2CH_3
d R = CO—◁, R_1 = H
e R = CH_2—◁, R_1 = H
f R = CO—◁, R_1 = SO_2CH_3



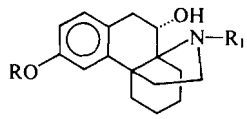
3

	R	R_1
a	CH_3	$COCF_3$
b	CH_3	H
c	CH_3	CO—◁
d	CH_3	CH_2—◁
e	H	CH_2—◁
f	CH_3	CO—◇
g	CH_3	CH_2—◇
h	H	CH_2—◇
i	CH_3	CO_2Et
j	H	CO_2Et
k	H	CH_3



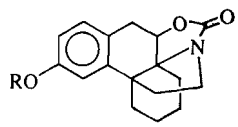
4

a R = CO_2Et
b R = CO—◁
c R = CH_3



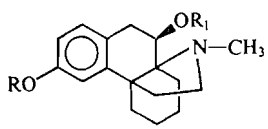
5

	R	R_1
a	CH_3	CO_2Et
b	H	CO_2Et
c	H	CH_3
d	CH_3	CO—◁
e	H	CO—◁
f	H	CH_2—◁
g	CH_3	CH_3



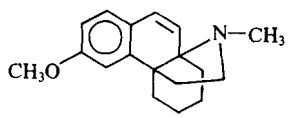
6

a R = CH_3
b R = H

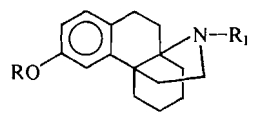


7

a R = CH_3 R_1 = H
b R = H R_1 = H
c R = CH_3 R_1 = SO_2CH_3



8



9

a R = CH_3 R_1 = CO_2Et
b R = CH_3 R_1 = CH_3
c R = CH_3 R_1 = H
d R = CH_3 R_1 = $COCF_3$
e R = CH_3 R_1 = CO—◁
f R = H R_1 = CO—◁
g R = H R_1 = CH_2—◁

CHART 2

cyclobutylmethyl-3-hydroxyisomorphinan **3***h* and 3-hydroxy-17-methylisomorphinan **3***k*, which was identical in every respect to an authentic specimen. Similarly, **3***c* was reduced to **3***d* and demethylated to **3***e*.

Our earlier experience with the acid-catalysed cyclizations of certain δ,ε-unsaturated systems (5, 9) led us to explore the reactivity of various epoxides, **4**, (4) and amides, **1**, under acidic conditions. These efforts gave rise to two new

synthetic approaches to the hasubanan skeleton. Thus, treatment of epoxy amides **4***a* and **4***b* with dilute perchloric acid in THF afforded 9α-hydroxy-3-methoxyhasubanans **5***a* and **5***b* respectively in good yields. Further transformations of these to the dihydroxyhasubanans **5***c* and **5***f* were easily accomplished by standard procedures, except that the usual reaction sequence, *i.e.* reduction of amide function followed by demethylation, was reversed. The reversed reaction sequence was applied after an unsuccessful demethylation attempt on the previously reported 9α-hydroxy-3-methoxy-17-methylhasubanan **5***g* (4).

The epimeric 3,9β-dihydroxyhasubanan **7***b* was prepared from **5***a* in three reaction steps as follows. (*i*) Treatment of **5***a* with phosphorus oxychloride in pyridine afforded oxazolidone **6***a* in an intramolecular displacement–inversion reaction.[2] (*ii*) Demethylation of **6***a* by treatment with boron tribromide to give **6***b*, followed by reduction with lithium aluminum hydride afforded 3,9β-dihydroxy-17-methylhasubanan **7***b*. (*iii*) Reduction of **6***a* (lithium aluminum hydride) to **7***a*, followed by treatment with methanesulfonyl chloride afforded an ester **7***c*, which was subjected to a reaction with sodium hydride in DMF, whereupon 3-methoxy-17-methyl-$\Delta^{9,10}$-hasubanan **8** was obtained.

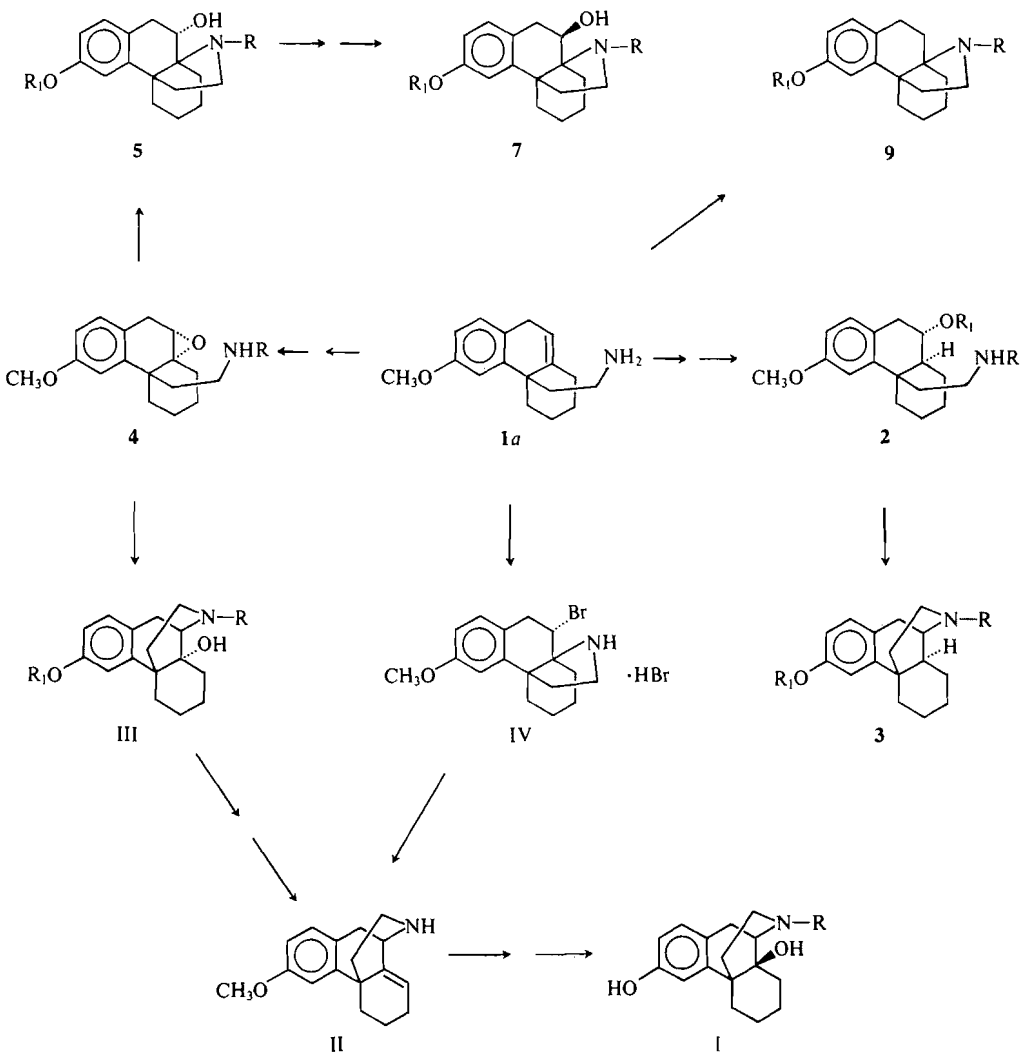
Our initial attempts to effect a one step synthesis of the hasubanan skeleton via acid-catalysed (sulfuric acid) cyclization of urethane **1***d* led to intractable mixtures. However, treatment of **1***b*, **1***c* and **1***d* with trifluoroacetic acid at reflux temperature afforded the corresponding hasubanans **9***a*, **9***b*, and **9***c* in good yields. Alkaline hydrolysis of **9***a* yielded 3-methoxyhasubanan **9***c* which could be easily transformed to the various N-substituted 3-hydroxyhasubanans. Alternatively, demethylation of **9***e* followed by reduction directly afforded 17-cyclopropylmethyl-3-hydroxyhasubanan **9***g*.

A summary of the various synthetic applications of the unsaturated amine **1***a* toward morphinan and hasubanan ring systems with structural correlations is shown in Scheme 1. We shall attempt to rationalize the high order of stereo- and regioselectivity of most of these reactions as follows. The stereospecific α-epoxidation and hydroboration of various acyl derivatives of **1***a* can be rationalized in terms of the steric effect of the amidoethano function. The bromocyclization of **1***a* to 9α-bromohasubanan IV rather than the respective 14-bromoisomorphinan is in accordance with the known preferential formation of five- to that of six-membered rings in the bromocyclization reactions (10, 11). Such preference in the case of **1***a* should be further enhanced by the fact that the probable intermediate bromonium ion should be asymmetric with higher charge distribution on the tertiary carbon (C_{14}) over that of the secondary one (C_9).

The regioselectivity of the epoxide ring opening reaction is influenced by several factors of steric and electronic nature, and it is usually difficult to assess the relative importance of each of these factors (12). However, due to the intramolecular nature of all the reactions studied, a number of important factors such as substitution of the epoxide ring, electrophilicity of the neighbouring group, and the size of the new ring to be formed, are easily recognized and the results can be rationalized as follows. The acid-catalysed reaction is expected to proceed by protonation of the epoxide oxygen atom and opening of the epoxide ring via neighbouring group participation of the acyl amine function. In such reactions, the tertiary carbocation intermediate as well as the size of the newly formed ring are expected to be dominant factors favoring 5-membered rings (hasubanans) over six-membered ones as pointed out in the course of the discussion of the bromocyclization reaction.

On the other hand, factors influencing the reactivity of aminoepoxide **4***c* (under non-catalyzed conditions) seem to be in a delicate balance resulting in equal amounts of the two possible products 9α-hydroxyhasubanan **5***g* and 14-hydroxyisomorphinan III (R = CH_3) (4). To put it another way, the preference (kinetic, or both kinetic and thermodynamic?) for formation of five- over six-membered rings successfully competes with the expected preferential opening of the epoxide with an amine at the less substituted carbon atom. However, this preference is insufficient when the nucleophilicity of the neighbouring group is enhanced such as in the case of base-catalysed cyclizations of various epoxides **4**, which result in exclusive formation

[2]Similar cyclizations in the cyclouridine series (18) using partially hydrolized phosphorus oxychloride, and in the series of β-hydroxyurethanes (19) using thionyl chloride and phosphorus pentoxide have been reported.



SCHEME 1

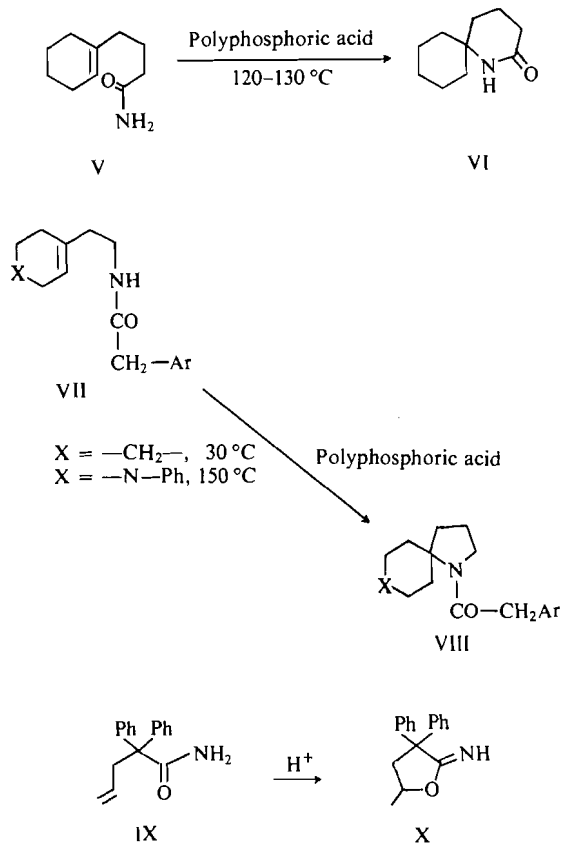
of 14-hydroxyisomorphinans III (4).

The preferred acid-catalysed cyclization of **1***b*, **1***c*, and **1***d* to hasubanan rather than morphinan ring systems is predictable on the basis of both ring size and a tertiary carbocation intermediate. This cyclization at the time of execution appeared to be a novel synthetic approach to a wide variety of heterocyclic compounds, particularly pyrrolidines and piperidines. Subsequently, we found two recorded examples in the literature describing the synthesis of spirolactams VI (Scheme 2) (13) and VIII (14, 15), from the respective cyclohexenyl derivatives V and VII.

It is interesting to note that some closely related systems such as IX under similar reaction conditions have been reported to give products of oxygen participation X. Similarly, various *N*-allylamides and related compounds give products of oxygen (sulfur) rather than nitrogen participation (5, 16, 17).

Pharmacological Results

A number of new compounds (in particular *N*-alkyl-3-hydroxy derivatives) have been screened for analgesic and narcotic antagonist activities



SCHEME 2

in mice by Dr. A. W. Pircio of the Bristol Laboratories, Syracuse, N.Y., according to the previously reported procedures (1). Some of the compounds have been found to possess moderate levels of activities as shown in Table 1, however, none was considered to be of therapeutic value.

Experimental

The melting points were determined on a Gallenkamp apparatus, and are uncorrected. The infrared (ir) spectra were recorded on a Unicam SP-200G grating ir spectrometer. The nmr spectra were recorded on a Varian A-60A spectrometer using deuteriochloroform. The chemical shifts are expressed in δ values using tetramethylsilane as internal reference. Microanalyses were performed by Micro-Tech Laboratories Inc., Skokie, Illinois.

Trifluoroacetamido Alcohol, 2a, and Trifluoroethylamino Alcohol, 2b

To a cooled (ice), stirred solution of **1***b* (4) (10.5 g) in dry THF (80 ml) was added dropwise 1 *M* solution of diborane in THF (75 ml). The mixture was allowed to stand for 18 h at 5 °C, followed by 4 h at room temperature. It was then treated successively with water (3 ml), 5 *N* sodium hydroxide (16 ml), and 30% hydrogen peroxide (4.4 ml), and the resulting mixture was heated to an internal temperature of 45–50 °C for 30 min. After cooling, it was diluted with ice cold water (100 ml), acidified with concentrated hydrochloric acid, and extracted with benzene. The acid layer was set aside and the benzene extract was dried and evaporated *in vacuo* to yield 11.7 g of crude **2***a* as an oil. The analytical sample was purified by chromatography on a silica gel column (eluent, benzene–ether 3:2); ir (neat), 3340, 3100, 1720 cm^{-1}; nmr δ 6.8–7.2 (3H, m), 3.82 (3H, s), 1.1–3.9 (16H, m). *Anal.* calcd. for $C_{19}H_{24}F_3NO_3$: C 61.44, H 6.51, N 3.77; found: C 61.60, H 6.74, N 3.63.

TABLE 1. Analgesic and narcotic antagonist activities (in mice) of some of the compounds studied

Compound	ED_{50} (mg/kg s.c.) Antagonist activity (oxymorphone-induced Straub tail)	ED_{50} (mg/kg s.c.) Analgesic activity (mouse writhing)
3*h*	7	0.3
5*c*	>40	20
5*f*	15	24
7*b*	>40	9
9*g*	>40	13

The aqueous acidic solution was made basic with ammonium hydroxide and extracted with dichloromethane. Drying and evaporation of solvent gave 450 mg of amino alcohol **2***b* as an oil; ir (neat) 3380 cm^{-1}; nmr ($CDCl_3$) δ 6.5–7.0 (3H, m), 3.9 (1H, m), 3.72 (3H, s), 1.1–3.5 (17H, m). The oxalate salt of **2***b* was recrystallized from methanol–ether; mp 170–172 °C. *Anal.* calcd. for $C_{19}H_{26}F_3NO_2 \cdot C_2H_2O_4$: C 56.37, H 6.31, N 3.13; found: C 56.41, H 6.61, N 3.17.

Methanesulfonyl Ester 2c

To a cooled and stirred mixture of crude amido alcohol **2***a* (11.2 g) and triethylamine (4.5 g) in benzene (50 ml) was added dropwise a solution of methanesulfonyl chloride (5.16 g) in benzene (10 ml). The reaction mixture was stirred for 3 h at room temperature and then partitioned between water and dichloromethane. The organic layer was dried and evaporated *in vacuo*. The residual oil was dissolved in a small amount of benzene and to this solution was added a large amount of ether. The solid deposited was collected by filtration to give 5.54 g of **2***c*. Recrystallization from 2-propanol gave an analytical sample; mp 118–120 °C; ir (Nujol) 3360, 1720 cm^{-1}; nmr δ 6.6–7.1 (3H, m), 4.6–5.1 (1H, m), 3.77 (3H, s), 3.03 (3H, s), 1.1–3.7 (15H, m). *Anal.* calcd. for $C_{20}H_{26}F_3NO_5S$: C 53.44, H 5.83, N 3.12; found: C 53.26, H 6.00, N 3.04.

Amido Alcohol 2d and Amino Alcohol 2e

To a solution of unsaturated amide **1***c* (9.75 g) in dry THF was added 1 *M* solution of diborane in THF (63 ml) and the mixture left at 5 °C for 18 h, at the end of which period, it was treated consecutively with water (1.5 ml), 5 *N* sodium hydroxide (13.5 ml), and 30% hydrogen

peroxide (4.4 ml). The mixture was heated under reflux for 30 min, cooled, diluted with water, and acidified with concentrated hydrochloric acid. The acidic solution was extracted with benzene and left aside. The benzene extract was dried and evaporated *in vacuo* to give an oil, which crystallized from ether. A yield of 65% (6.9 g) of **2***d* was obtained; mp 130–131 °C from dichloromethane–ether; ir (Nujol) 3480, 3280, 1630 cm^{-1}; nmr δ 6.6–7.2 (3H, m), 3.8 (3H, s), 3.7–4.1 (1H, m), 0.4–3.5 (20H, m). *Anal.* calcd. for $C_{21}H_{29}NO_3$: C 73.44, H 8.51, N 4.08; found: C 73.40, H 8.59, N 4.07.

The aqueous solution was made alkaline with ammonium hydroxide and extracted with dichloromethane to yield, after drying and evaporation, 1.4 g of amino alcohol **2***e* as an oil; ir (neat) 3380 cm^{-1}; nmr δ 6.6–7.2 (3H, m), 3.8 (3H, s), 3.8–4.2 (1H, m), 0.0–3.7 (22H, m).

A sample for analysis was purified as the oxalate salt by recrystallization from acetone; mp 193–195 °C. *Anal.* calcd. for $C_{21}H_{31}NO_2 \cdot C_2H_2O_4$: C 65.85, H 7.93, N 3.34; found: C 65.50, H 7.94, N 3.31.

Methanesulfonyl Ester 2f

The ester **2***f* was obtained in 93% yield from alcohol **2***d* by the procedure given for the preparation of **2***c*; mp 123–124 °C from dichloromethane–ether; ir (Nujol) 3280, 1640 cm^{-1}; nmr δ 6.6–7.1 (3H, m), 4.7–5.2 (1H, m), 3.8 (3H, s), 2.98 (3H, s), 0.4–3.6 (20H, m). *Anal.* calcd. for $C_{22}H_{31}NO_5S$: C 62.68, H 7.41, N 3.32; found: C 62.32, H 7.39, N 3.18.

3-Methoxy-17-trifluoroacetylisomorphinan 3a and 3-Methoxyisomorphinan 3b

To a cooled and stirred suspension of sodium hydride (580 mg of 55%, washed with hexane) in DMF (5 ml) was added dropwise a solution of methanesulfonyl ester **2***c* (4.05 g) in DMF (20 ml) and the mixture stirred at room temperature for 6 h. It was then cooled and partitioned between ice-cold water and a benzene–ether mixture. The organic layer was washed several times with cold water and extracted with dilute hydrochloric acid. The acidic extract was set aside, and the organic layer was washed with water, dried, and evaporated to dryness to give 1.25 g of isomorphinan **3***a* as an oil; bp 140–145 °C/0.02 torr; ir (neat) 1720 cm^{-1}; nmr δ 6.6–7.3 (3H, m), 4.1–4.6 (1H, m), 3.85 (3H, s), 0.8–3.6 (15H, m). *Anal.* calcd. for $C_{19}H_{22}F_3NO_2$: C 64.58, H 6.28, N 3.96; found: C 64.40, H 6.34, N 3.97.

The acidic extract was made basic with ammonium hydroxide and extracted with ether. The ethereal extract was dried, filtered with charcoal, and concentrated *in vacuo* to give 1.35 g of isomorphinan **3***b* as an oil; ir (neat) 3300 cm^{-1}; nmr δ 6.6–7.3 (3H, m), 3.83 (3H, s), 1.1–3.6 (15H, m), 0.85 (1H, d, $J \simeq 10$ Hz). The hydrochloride salt (1.42 g) was recrystallized from methanol–acetone; mp 293–295 °C. *Anal.* calcd. for $C_{17}H_{23}NO \cdot HCl$: C 69.49, H 8.23, N 4.77; found: C 69.48, H 8.38, N 4.62.

By varying the solvent composition and work-up temperature, the ratio of **3***a* and **3***b* can be adjusted. In another experiment, the starting material **2***c* (9.09 g) was dissolved in THF (25 ml) and added to a suspension of sodium hydride (1.6 g of 55%) in DMF (10 ml) under the same conditions as above. During work-up, the reaction mixture was cooled with an ice–salt bath. This procedure afforded 5.7 g of **3***a* and 1.1 g of **3***b*.

The hydrolysis of **3***a* to **3***b* is effected by treatment with sodium hydroxide in aqueous ethanol. A mixture of **3***a* (5.4 g) and 1 *N* sodium hydroxide in 80% aqueous ethanol (20 ml) was heated under reflux for 15 min. The usual work-up gave 4.0 g of **3***b*. This procedure can be applied to the crude mixture of **3***a* and **3***b* to obtain exclusively **3***b*.

17-Cyclopropylcarbonyl-3-methoxyisomorphinan 3c

The isomorphinan **3***c* (an oil) was similarly obtained in quantitative yield from **2***d*. The reaction time was 18 h. A sample for analysis was distilled at 165–170 °C/0.2 torr; ir (neat) 1630 cm^{-1}; nmr δ 6.6–7.2 (3H, m), 3.82 (3H, s), 3.8–5.0 (2H, m), 4.5–3.6 (19H, m). *Anal.* calcd. for $C_{21}H_{27}NO_2$: C 77.50, H 8.36, N 4.30; found: C 77.56, H 8.44, N 4.15.

17-Cyclopropylmethyl-3-methoxyisomorphinan 3d

To a solution of lithium aluminum hydride (0.23 g) in dry ether (10 ml) was added dropwise under nitrogen a solution of amide **3***c* (1.46 g) in ether (15 ml) and the mixture heated under reflux for 2 h. After cooling and the usual work-up, 1.17 g of **3***d* was obtained as an oil; nmr δ 6.6–7.1 (3H, m), 3.82 (3H, s), 0.0–3.3 (23H, m). A sample was purified as its hydrochloride salt by recrystallization from methanol–acetone; mp 237–239 °C. *Anal.* calcd. for $C_{21}H_{29}NO_2 \cdot HCl$: C 72.49, H 8.69, N 4.03; found: C 72.37, H 8.83, N 3.97.

3-Hydroxy-17-cyclopropylmethylisomorphinan 3e

A solution of 3-methoxyisomorphinan **3***d* (3.0 g) in hydrobromic acid (30 ml, 48%) was heated under reflux under nitrogen for 5 min. After cooling, the mixture was poured onto ice and ammonium hydroxide and extracted with dichloromethane. The extract was dried and evaporated *in vacuo*. The residual oil was dissolved in acetone and filtered over a celite–charcoal mixture. The filtrate was treated with a solution of hydrogen chloride in ether to give 2.05 g of the solid hydrochloride salt of **3***e*. Recrystallization from ethanol gave an analytical sample; mp 266–268 °C; ir (free base, neat) 3250 cm^{-1}; nmr δ 6.25–6.9 (3H, m), 0.0–3.2 (23H, m). *Anal.* calcd. for $C_{20}H_{27}NO \cdot HCl$: C 61.94, H 8.45, N 4.20; found: C 71.71, H 8.33, N 4.09.

17-Cyclobutylcarbonyl-3-methoxyisomorphinan 3f

To a cooled and stirred solution of **3***a* (5.0 g) and triethylamine (2.12 g) in dichloromethane (50 ml) was added dropwise a solution of cyclobutylcarbonyl chloride (2.49 g) in dichloromethane (10 ml). The mixture was then washed with water, dried, and evaporated *in vacuo* to give 5.98 g of **3***f* as an oil. A sample was distilled at 165–170 °C/0.2 torr; ir (neat) 1630 cm^{-1}; nmr δ 6.7–7.3 (3H, m), 4.0–5.3 (2H, m), 3.82 (3H, s), 1.2–3.7 (20H, m), 0.75–1.15 (1H, m). *Anal.* calcd. for $C_{22}H_{29}NO_2$: C 77.84, H 8.61, N 4.13; found: C 77.55, H 8.72, N 4.01.

17-Cyclobutylmethyl-3-methoxyisomorphinan 3g

A solution of amide **3***f* (5.67 g) in dry THF (40 ml) was added dropwise to a solution of lithium aluminum hydride (1.0 g) in THF (10 ml) and the mixture heated under reflux for 4.5 h. After cooling and the usual work-up, 4.55 g of **3***g* was obtained as an oil. A sample was distilled at 160–165 °C/0.01 torr; nmr δ 6.6–7.2 (3H, m), 3.8 (3H, s), 1.1–3.3 (24H, m), 0.86 (1H, d, m, poor

resolution, $J = 10$ Hz). *Anal.* calcd. for $C_{22}H_{31}NO$: C 81.18, H 9.60, N 4.30; found: C 81.30, H 9.67, N 4.18.

17-Cyclobutylmethyl-3-hydroxyisomorphinan 3h

A solution of methoxyisomorphinan **3g** (4.25 g) in dichloromethane (130 ml) was added dropwise over a period of 30 min to a cooled (ice–salt) and stirred solution of boron tribromide (6.77 g) in dichloromethane (10 ml). The mixture was stirred for another 30 min and then treated with cold water, followed by ammonium hydroxide, and the layers were separated. The organic layer was dried and evaporated to dryness. The residual oil was purified as its hydrochloride salt by two recrystallizations from 90% ethanol to give 2.1 g of **3h** hydrochloride; mp 263–265 °C; ir (neat) 3260 cm^{-1}; nmr δ 6.6–7.2 (3H, m), 1.1–3.3 (24H, m), 0.85 (1H, d, $J = 10$ Hz). *Anal.* calcd. for $C_{21}H_{29}NO \cdot HCl$: C 72.49, H 8.69, N 4.03; found: C 72.27, H 8.79, N 4.08.

17-Methoxycarbonyl-3-methoxyisomorphinan 3i

To a cooled (ice) stirred solution of 3-methoxyisomorphinan **3b** (1.80 g) and triethylamine (1.02 g) in dichloromethane (20 ml) was added dropwise a solution of methylchloroformate (0.66 g) in dichloromethane (5 ml). The mixture was then washed with water followed by dilute hydrochloric acid, dried, and evaporated *in vacuo* to give 1.84 g of **3i** as an oil; ir (neat) 1680 cm^{-1}; nmr δ 6.5–7.1 (3H, m), 4.1–4.5 (1H, m), 3.72 (3H, s), 3.65 (3H, s), 1.1–3.5 (14H, m), 0.9 (1H, d, $J = 10$ Hz). *Mol. Wt.* calcd. for $C_{19}H_{25}NO_3$; found (mass spectrum) 315.

3-Hydroxy-17-methoxycarbonylisomorphinan 3j

To a cooled (ice–salt) solution of boron tribromide (1.5 g) in dichloromethane (10 ml) a solution of methoxyisomorphinan **3i** (0.90 g) in dichloromethane (10 ml) was introduced dropwise under nitrogen. The mixture was stirred at room temperature for 4 h, and then worked up as usual to give 0.70 g of **3j** as an oil; ir (neat) 3340, 1675 cm^{-1}; nmr δ 6.4–7.0 (3H, m), 4.1–4.5 (1H, m), 3.63 (3H, s), 1.1–3.5 (14H, m), 0.85 (1H, d, $J = 10$ Hz). A sample solidified after distillation at 190 °C/0.05 torr; mp 102–105 °C. *Anal.* calcd. for $C_{18}H_{23}NO_3$: C 71.73, H 7.69, N 4.64; found: C 71.62, H 7.61, N 4.61.

3-Hydroxy-17-methylisomorphinan 3k

The hydroxyisomorphinan **3k** was obtained in quantitative yield by essentially the same procedure as given for the preparation of **3h**. At first an oil, it crystallized on standing. Recrystallization from ethyl acetate gave an analytical sample; mp 216–218 °C, reported mp 217–218.5 °C (6); ir (Nujol) 3100 cm^{-1}; nmr δ 6.5–7.0 (3H, m), 3.6–4.0 (1H, m), 2.32 (3H, s), 1.1–3.5 (14H, m), 0.98 (1H, d, $J = 10$ Hz). *Anal.* calcd. for $C_{17}H_{23}NO$: C 79.33, H 9.01, N 5.44; found: C 79.10, H 9.08, N 5.52.

17-Ethoxycarbonyl-9α-hydroxy-3-methoxyhasubanan 5a

To a cooled (ice), stirred solution of epoxy urethane **4a** (4) (4.5 g) in THF (40 ml) was added dropwise 30% perchloric acid (4 ml), and the mixture allowed to stand at room temperature for 2 h. It was then partitioned between aqueous ammonium hydroxide and benzene. The benzene layer was washed with water, dried, and evaporated to dryness. The residual oil crystallized from ether to yield 2.8 g of **5a**; mp 109–110 °C. Recrystallization from 2-propanol gave an analytical sample; mp 113–114 °C; ir (Nujol) 3340, 1665 cm^{-1}; nmr δ 6.6–7.1 (3H, m), 4.2 (1H, unresolved), 4.15 (2H, q, $J = 7$ Hz), 3.72 (3H, s), 2.6–3.8 (4H, m), 1.3 (3H, t, $J = 7$ Hz), 0.9–2.2 (10H, m). *Anal.* calcd. for $C_{20}H_{27}NO_4$: C 69.54, H 7.88, N 4.06; found: C 69.45, H 8.06, N 4.06.

3,9α-Dihydroxy-17-ethoxycarbonylhasubanan 5b

To a cooled (ice) stirred solution of **5a** (1.78 g) in dichloromethane (20 ml) was added in a few portions a solution of boron tribromide (2.75 g) in dichloromethane (10 ml). The mixture was allowed to stand at room temperature for 2 h and then it was treated with ice cold ammonium hydroxide and methanol. When all of solid was dissolved, the mixture was partitioned between water and dichloromethane. The organic layer was dried and evaporated *in vacuo* to give 950 mg of solid **5b**; mp 180–182 °C. Recrystallization from benzene afforded an analytical sample; mp 185–187 °C; ir (Nujol) 3220, 1645 cm^{-1}; nmr δ 6.5–7.0 (3H, m), 4.15 (2H, q, $J = 7$ Hz), 4.0–4.3 (1H, unresolved), 2.7–3.9 (4H, m), 0.9–2.2 (10H, m), 1.27 (3H, t, $J = 7$ Hz). *Anal.* calcd. for $C_{19}H_{25}NO_4$: C 68.86, H 7.60, N 4.23; found: C 68.60, H 7.63, N 4.14.

3,9α-Dihydroxy-17-methylhasubanan 5c

To a solution of lithium aluminum hydride (250 mg) in THF (20 ml) was added dropwise a solution of dihydroxyhasubanan **5b** (500 mg; containing 1 mol of benzene of crystallization) in THF (10 ml) and the mixture heated under reflux for 3 h. After cooling and the standard work-up procedure, the product was dissolved in a benzene–ether mixture and extracted with 1 *N* hydrochloric acid. The acidic extract was made basic with ammonium hydroxide and extracted with a benzene–ether mixture to give, after drying and evaporation of solvent, 360 mg of **5c** as a white solid; mp 183–186 °C. Recrystallization from acetone–benzene gave an analytical sample; mp 190–192 °C; ir (Nujol) 3270, 3440 cm^{-1}; nmr δ 6.4–6.9 (3H, m), 4.05 (1H, dd, $J_1 = 10$ Hz, $J_2 = 6$ Hz), 2.4–3.0 (4H, m), 2.4 (3H, s), 0.9–2.0 (10H, m). *Anal.* calcd. for $C_{17}H_{23}NO_2$: C 74.69, H 8.48, N 5.12; found: C 74.52, H 8.69, N 5.13.

17-Cyclopropylcarbonyl-9α-hydroxy-3-methoxyhasubanan 5d

The epoxide **4b** (4) was treated with perchloric acid as described above to give **5d** as an oil in 55% yield, which crystallized from ether; mp 99–101 °C. Another crop of 21% yield was obtained from mother liquors by column chromatography (silica gel, ether) for a total of 82%; ir (Nujol) 3200, 1610 cm^{-1}; nmr δ 6.6–7.1 (3H, m), 4.14 (1H, dd, $J_1 = 10$ Hz, $J_2 = 6$ Hz), 3.75 (3H, s), 3.6–4.0 (2H, m), 2.82 (3H, s, and d, $J = 3$ Hz), 0.6–2.3 (10H, m). *Anal.* calcd. for $C_{21}H_{27}NO_3$: C 73.87, H 7.97, N 4.10; found: C 73.66, H 8.09, N 4.01.

3,9α-Dihydroxy-17-cyclopropylcarbonylhasubanan 5e

The dihydroxyhasubanan **5e** was obtained in 76% yield, as a white solid containing 1 mol of benzene of crystallization, by treatment of methoxyhasubanan **5d** with boron tribromide as described for the preparation of **5b**. Recrystallization from acetone gave an analytical sample containing $\frac{1}{2}H_2O$ of crystallization; mp 193–194 °C; ir (Nujol) 3180, 1605 cm^{-1}; nmr δ 6.5–7.0

(3H, m), 3.6–4.4 (3H, m), 2.7–3.1 (3H, m), 0.6–2.4 (10H, m). *Anal.* calcd. for $C_{20}H_{25}NO_3 \cdot \frac{1}{2}H_2O$: C 71.40, H 7.79, N 4.16; found: C 71.19, H 7.63, N 4.28.

3,9α-Dihydroxy-17-cyclopropylmethylhasubanan 5f

The dihydroxyhasubanan **5f** was obtained in 83% yield, as a white solid, mp 82–92 °C from **5e** by a procedure given for the preparation of **5c**. Recrystallization from methanol gave an analytical sample containing $\frac{1}{2}CH_3OH$ of crystallization; mp 106–108 °C; ir (Nujol) 3420, 3295 cm^{-1}; nmr δ 6.4–7.0 (3H, m), 3.9 (1H, dd, J_1 = 10 Hz, J_2 = 6 Hz), 2.4–3.3 (6H, m), 0.0–2.1 (15H, m). *Anal.* calcd. for $C_{20}H_{27}NO_2 \cdot \frac{1}{2}CH_3OH$: C 75.19, H 8.71, N 4.18; found: C 75.19, H 8.89, N 4.22.

Oxazolidone 6a

To a cold (ice) solution of hydroxyurethane **5a** (1.56 g) in pyridine (10 ml) was added dropwise phosphorus oxychloride (3 ml) under nitrogen and the mixture allowed to stand at room temperature for 4 h. It was then poured carefully onto ice water and extracted with ether. The ether extract was washed with cold dilute hydrochloric acid followed by water, dried, and evaporated to dryness. The residual oil (1.30 g) was chromatographed over alumina (150 g, dry column eluent chloroform) to give 850 mg of **6a** as a heavy oil; ir (neat) 1752 cm^{-1}; nmr δ 6.5–7.1 (3H, m), 4.7 (1H, t, J = 3 Hz), 3.73 (3H, s), 1.1–3.3 (14H, m). A sample for analysis was distilled at 155 °C/0.05 torr to give an amorphous solid. *Anal.* calcd. for $C_{18}H_{21}NO_3$: C 72.22, H 7.07, N 4.68; found: C 72.34, H 7.16, N 4.57.

Oxazolidone 6b

To a cold (ice-salt) solution of boron tribromide (1.0 g) in dichloromethane (10 ml) was added dropwise a solution of oxazolidone **6a** (550 mg) in dichloromethane (10 ml) under nitrogen and the mixture was stirred at room temperature for 1.5 h. It was then poured onto ice – ammonium hydroxide and the layers separated. The organic layer was washed with water, dried (Na_2SO_4), and evaporated *in vacuo* to give 430 mg of solid **6b**. Recrystallization from ether gave an analytical sample; mp 234–236 °C; ir (Nujol) 3260, 1740 cm^{-1}; nmr δ 6.4–7.0 (3H, m), 4.78 (1H, t, J = 3 Hz), 1.1–3.3 (14H, m). *Anal.* calcd. for $C_{17}H_{19}NO_3$: C 71.56, H 6.71, N 4.91; found: C 71.29, H 6.60, N 4.76.

9β-Hydroxy-3-methoxy-17-methylhasubanan 7a

To a solution of lithium aluminum hydride (0.50 g) in THF (10 ml) was added dropwise a solution of oxazolidone **6a** (1.0 g) in THF (20 ml) and the mixture was heated under reflux for 18 h. Work-up as usual gave 900 mg of solid **7a**. It was purified as its hydrochloride salt by recrystallization from methanol–ether; mp 273–275 °C; ir (Nujol) 3200 cm^{-1}; nmr (free base) δ 6.5–7.1 (3H, m), 3.03 (1H, dd, J_1 = 8 Hz, J_2 = 5 Hz), 7.78 (3H, s), 2.44 (3H, s), 1.1–3.3 (14H, m). *Anal.* calcd. for $C_{18}H_{25}NO_2 \cdot HCl$: C 66.76, H 8.09, N 4.33; found: C 66.29, H 8.18, N 4.07.

3,9β-Dihydroxy-17-methylhasubanan 7b

This compound was prepared in 65% yield by the method described for the preparation of **6b**; an oil; nmr δ 6.4–7.0 (3H, m), 4.03 (1H, dd, poor resolution), 2.4 (3H, s), 1.1–3.2 (14H, m). A sample purified as its hydrochloride salt by recrystallization from methanol–ether contained 1 mol of water of crystallization; mp 273–275 °C; ir (Nujol) 3310, 3220 cm^{-1}. *Anal.* calcd. for $C_{17}H_{23}NO_2 \cdot HCl \cdot H_2O$: C 62.28, H 7.99, N 4.27; found: C 62.08, H 7.49, N 4.10.

3-Methoxy-17-methyl-$\Delta^{9,10}$-hasubanan 8

9β-Hydroxyhasubanan **7a** (350 mg) in benzene (5 ml) was treated with methanesulfonyl chloride (170 mg) and triethylamine (150 mg) for 4 h to give after the usual work-up, 440 g of 9β-methanesulfonate **7c** as an oil; nmr δ 6.5–7.1 (3H, m), 4.3 (1H, dd, J_1 = 11 Hz, J_2 = 6 Hz), 3.73 (3H, s), 3.03 (3H, s), 2.36 (3H, s), 1.1–3.8 (14H, m). This was treated with sodium hydride (100 mg) in DMF (10 ml) under reflux for 15 min to yield after work-up 260 mg of **8**, an oil, identical to an authentic sample prepared by another route.[3]

17-Ethoxycarbonyl-3-methoxyhasubanan 9a

A solution of urethane **1d** (1.2 g) in trifluoroacetic acid (12 ml) was heated under reflux under nitrogen for 10 min. The mixture was evaporated *in vacuo* and the residual oil was dissolved in ether and triturated with petroleum ether. This solution was filtered with charcoal and the filtrate concentrated *in vacuo* to give 1.08 g of **9a** as an oil, which solidified upon standing; mp 78–80 °C; ir (Nujol) 1695 cm^{-1}; nmr δ 6.6–7.1 (3H, m), 4.10 (2H, q, J = 7 Hz), 3.78 (3H, s), 1.3–3.6 (16H, m), 1.2 (3H, t, J = 7 Hz). *Anal.* calcd. for $C_{20}H_{27}NO_3$: C 72.90, H 8.26, N 4.25; found: C 73.00, H 8.21, N 4.15.

3-Methoxy-17-methylhasubanan 9b

Urethane **9a** was reduced to the *N*-methyl derivative **9b** by treatment with lithium aluminum hydride by the standard procedure. The product so obtained contained some of the 3-methoxyhasubanan **9c**. Formaldehyde was added to the mixture which was then hydrogenated with Raney Nickel as catalyst, to give a 72% yield of **9b**, isolated as its hydrochloride salt; mp 258–262 °C, identical by mixture mp determination with a sample of **9b** as previously reported (5).

3-Methoxyhasubanan 9c

To a solution of **9a** (3.29 g) in 1-octanol (20 ml) was added potassium hydroxide pellets (2.8 g) and the mixture was heated under reflux for 1 h. After cooling, ether (100 ml) was added and this solution was extracted several times with 1 *N* hydrochloric acid, followed by water (5 × 20 ml). The combined extracts were made basic with ammonium hydroxide and extracted with ether. The ether extract was dried and evaporated *in vacuo* and the residual oil **9c** was purified as its hydrochloride salt by recrystallization from methanol–ether to afford 1.5 g, mp 263 °C, identical to that previously reported (5).

3-Methoxy-17-trifluoroacetylhasubanan 9d

A solution of amide **1b** (2 g) in trifluoroacetic acid (20 ml) was heated under reflux under nitrogen for 30 min. The acid was then removed by evaporation *in vacuo* and the residual oil was treated with 5 *N* sodium hydroxide (10 ml) and ethanol (40 ml) at reflux temperature for 10 min. Then the mixture was cooled, diluted

[3]Unpublished work from these laboratories.

with water, acidified with hydrochloric acid, and extracted with ether to give, after drying and evaporation of ether, an oil which crystallized from ether – petroleum ether. Compound **9***d* (1.0 g) was obtained as a white solid; mp 102–104 °C (from ether); ir (Nujol) 1710 cm^{-1}; nmr δ 6.6–7.2 (3H, m), 3.78 (3H, s), 3.0–4.0 (3H, m), 1.2–3.0 (13H, m). *Anal.* calcd. for $C_{19}H_{22}F_3NO_2$: C 64.58, H 6.27, N 3.96; found: C 64.41, H 6.41, N 3.91.

17-Cyclopropylcarbonyl-3-methoxyhasubanan **9***e*

A solution of **1***c* (4.0 g) in trifluoroacetic acid (40 ml) was heated under reflux under nitrogen for 30 min. Then the mixture was concentrated to small volume, and the residue was partitioned between aqueous ammonium hydroxide and ether. The organic layer was dried, filtered over celite–charcoal, and evaporated *in vacuo* to give 3.9 g of solid **9***e*; mp 109–111 °C (from ether – petroleum ether); ir (Nujol) 1630 cm^{-1}; nmr δ 6.6–7.2 (3H, m), 3.85 (3H, s), 0.5–3.85 (21H, m). *Anal.* calcd. for $C_{21}H_{27}NO_2$: C 77.50, H 8.36, N 4.30; found: C 77.46, H 8.45, N 4.26.

17-Cyclopropylcarbonyl-3-hydroxyhasubanan **9***f*

The hydroxyamide **9***f* was obtained in quantitative yield, as a white solid from **9***e* by a procedure given for the preparation of **6***b*; mp 216–218 (from methanol); ir (neat) 3125, 1610 cm^{-1}; nmr δ 6.6–7.1 (3H, m), 0.4–3.8 (21H, m). *Anal.* calcd. for $C_{20}H_{25}NO_2$: C 77.14, H 8.09, N 4.50; found: C 77.13, H 8.21, N 4.39.

17-Cyclopropylmethyl-3-hydroxyhasubanan **9***g*

The hydroxyhasubanan **9***g* was obtained in 74% yield isolated as its hydrochloride salt, by reduction of **9***f* with lithium aluminum hydride as described above; mp 254–256 °C, from 2-propanol; ir (free base, neat) 3320 cm^{-1}; nmr δ 6.6–7.2 (3H, m), 0.0–3.6 (24H, m). *Anal.* calcd. for $C_{20}H_{27}NO \cdot HCl$: C 71.94, H 8.45, N 4.20; found: C 71.92, H 8.60, N 4.03.

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