5-Allyl-9-oxobenzomorphans. Part 4.[1] Synthesis of 3-hydroxy-8-oxyisomorphinans, 5-allyl-9α-hydroxy-6,7-benzomorphans, and related tetrahydrofuranobenzomorphans

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A series of 3-hydroxy-8-oxyisomorphinans (**11**, **16**) has been synthesized from the corresponding 5-allyl-9β-hydroxy-6,7-benzomorphans (**7**, **12**) via a hydroboration, oxidation, mesylation, and cyclization sequence of reactions. Selective reduction of and methylmagnesium iodide addition to 5-allyl-2′-methoxy-2-methyl-9-oxo-6,7-benzomorphan (**1**) gave the respective 9α-hydroxy-6,7-benzomorphans (**17**). These were transformed to a number of 2-substituted-5-allyl-2′,9β-dihydroxy-6,7-benzomorphans (**22**) and corresponding methyltetrahydrofurano analogs (**24**).

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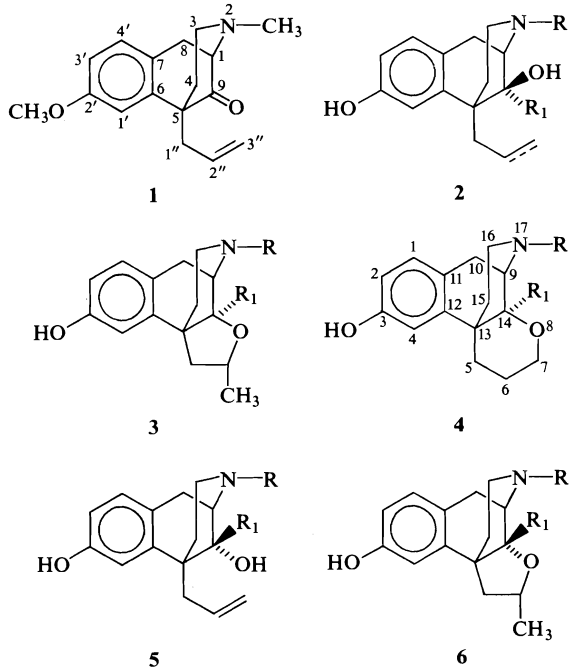
On a synthétisé une série d'hydroxy-3 oxy-8 isomorphanes (**11** et **16**) à partir des allyl-5 hydroxy-9β benzo-6,7 morphanes (**7**, **12**) correspondants par l'intermédiaire d'une hydroboration, d'une oxydation, d'une mésylation et d'une cyclisation. La réduction sélective et l'addition d'iodure de méthylmagnésium à l'allyl-5 méthoxy-2′ méthyl-2 oxo-9 benzo-6,7 morphane (**1**) conduisent respectivement aux hydroxy-9α benzo-6,7 morphanes (**17**) correspondants. Ceux-ci peuvent être transformés en un grand nombre d'allyl-5 dihydroxy-2′,9β benzo-6,7 morphanes (**22**) substitués en position 2 et de leurs analogues méthyltétrahydrofuranno correspondants (**24**).

[Traduit par le journal]

Introduction

In part 3 of this series (1) we have described the synthesis of a number of 5-propyl- and 5-allyl-2′,9β-dihydroxy-6,7-benzomorphans **2** as well as the corresponding tetrahydrofurano analogs **3**, via stereoselective reduction of, or organometallic addition to, 5-allyl-2′-methoxy-2-methyl-9-oxo-6,7-benzomorphan **1** (Scheme 1). In view of the fact that some of the compounds **2** have been found to possess high levels of analgesic and/or narcotic antagonist activities, comparable to reference agents in laboratory animal tests, we thought it desirable to explore the synthesis and pharmacological properties of isomeric 9-hydroxy-derivatives **5** in which orientation of the hydroxyl group is away from the nitrogen atom or α with respect to the aromatic ring. In addition, it was of interest to continue the investigation of C-ring oxygen-containing systems in both series, such as 8-oxyisomorphinans **4** and tetrahydrofuranobenzomorphans **6**.



SCHEME 1

Results and Discussion

The synthesis of 8-oxyisomorphinans **11** is shown in Scheme 2. 5-Allyl-9β-hydroxybenzomorphans **7***a* and **7***b* were converted to the corresponding diols **8***a* and **8***b* in good yields via a hydroboration and oxidation reaction

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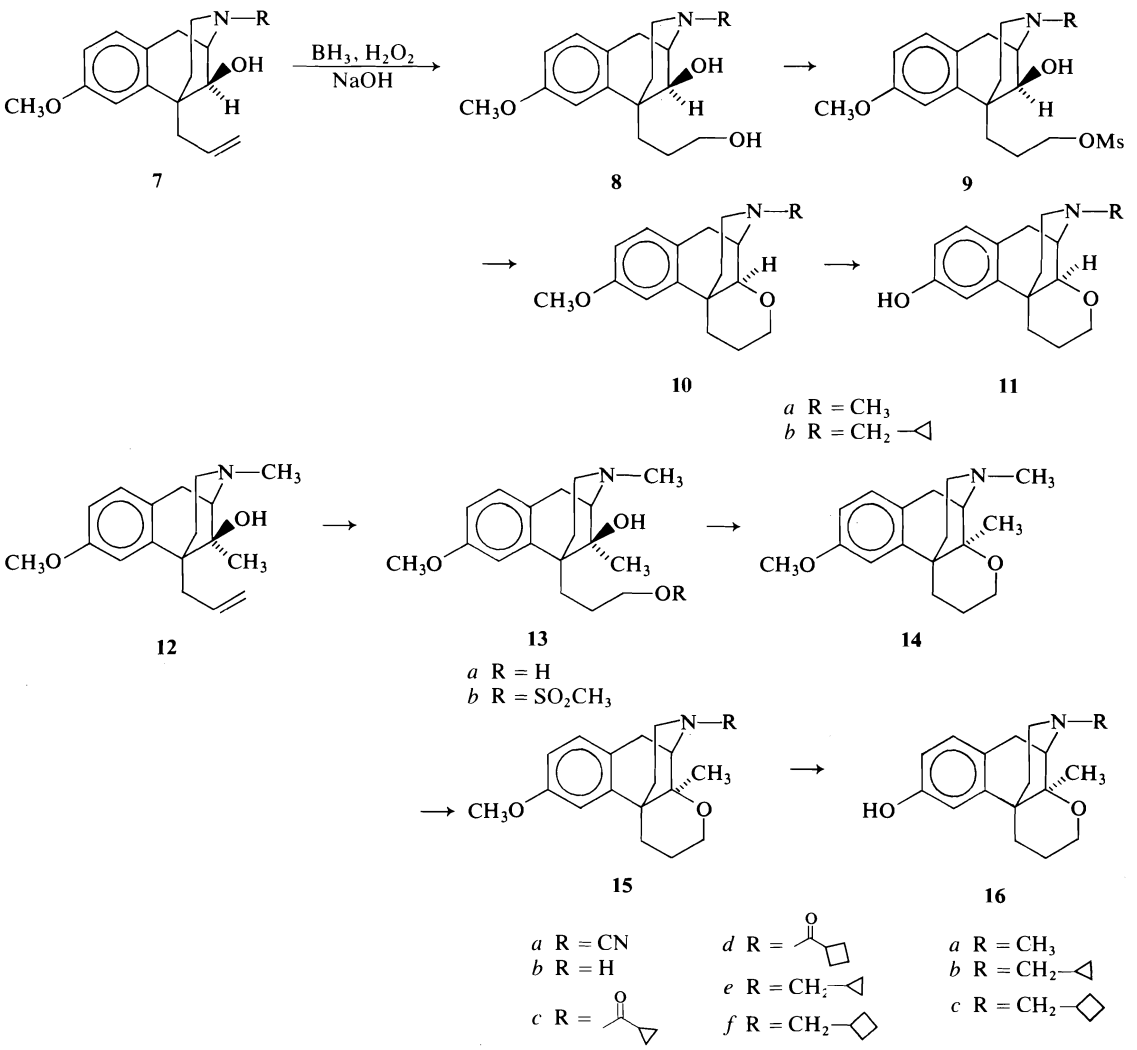
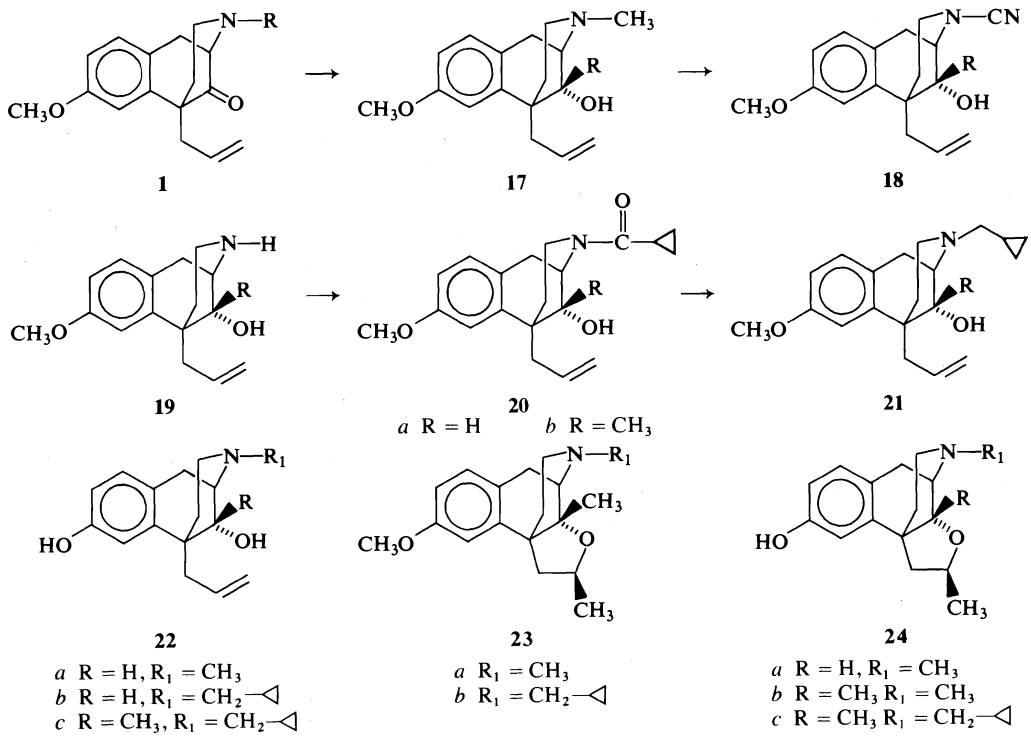


SCHEME 2

sequence. However the problem of formation of stable borane–nitrogen complexes required our attention. The complexed borane was decomposed thermolytically in a suitable hydroxylic solvent. The most convenient solvent was found to be ethylene glycol in which a reaction mixture was heated until hydrogen evolution ceased. The dihydroxy intermediates (**8***a* and **8***b*) were treated with methanesulfonyl chloride to give methanesulfonyl esters **9***a* and **9***b*, which were treated *in situ* with sodium hydride in DMF to give the respective 8-oxyisomorphinans **10***a* and **10***b*. These were demethylated by treatment with boron tribromide in dichloromethane to give **11***a* and **11***b*.

In a similar reaction sequence **12** was converted via **13***a* and **13***b* to the 3-methoxy-14-methyl-8-oxyisomorphinan **14**. A conversion of **14** to **15***e* and **15***f*, respectively, proceeded as expected via a well defined reaction sequence of von Braun demethylation, reduction, acylation, and again reduction. Demethylation of **14**, **15***e*, and **15***f* with boron tribromide gave poor yields of the corresponding phenolic products **16**, presumably due to opening of the tetrahydropyran ring. Better results were obtained with sodium thioethoxide in boiling DMF (2) or lithium diphenylphosphide in boiling THF (3).

Although a number of compounds in the 9α-hydroxy series have been prepared by May and



SCHEME 3

co-workers (4, 5) both by reduction and organometallic addition to tertiary amino ketones, from the start we were confronted with the following problems; firstly, catalytic reduction which is known to give α-alcohols could not be applied in our synthesis since it would be expected to reduce the double bond as well, which we need preserved. Secondly, addition of methyllithium to **1** has been demonstrated (1) to give selectively **12** instead of the expected **17***b* (Scheme 3). Consequently we had to investigate systematically these reactions in order to achieve the desired selectivity. We soon discovered that reduction of **1** with diisobutyl aluminum hydride does indeed give selectively **17***a* (better than 96% stereochemical purity) in quantitative yield.

While addition of methyllithium in ether to **1** gave selectively **12** (1) we observed that methylmagnesium iodide in the same solvent added to **1** to give a mixture of 45% **12** and 55% **17***b* as determined by nmr spectroscopy; in addition to a singlet at δ 1.1 due to **12**, a new singlet appeared at δ 1.58 due to **17***b*. Furthermore, the selectivity was lost when addition of methyllithium to **1** was conducted in a mixture of ether and petroleum ether (bp 30–60°C) 1:10, as observed by the product ratio of 60% **17***b* and 40% **12**, indicating, in addition to the observed large effect of the inorganic part of the organometallic reagent, a large solvent effect. These results also pointed a way in which further investigation should be directed; addition of the Grignard reagent in nonpolar solvent (petroleum ether) was expected and indeed found to give almost exclusively **17***b* (better than 95%).

In a recently published review article on the stereochemistry of organometallic compound addition to cyclic ketones Ashby and Laemmle (6) concluded that the stereochemical outcome of the addition is primarily a function of the entering groups and steric requirements of the particular ketone, which are controlled by steric and torsional strain in the transition state. Factors such as solvent, nature of the metal to which the entering group is attached, and others, result in only minor changes in overall observed stereochemistry. If this generalization is valid, it seems reasonable to assume that large metal and solvent effects observed by us must be related to the fact that our ketone is an amino ketone and therefore probably susceptible to a complexation with organometallic reagents via

a nitrogen lone electron pair. That such complexation would be more pronounced in a nonpolar solvent and consequently conducive to an intramolecular addition to give selectively *trans* amino alcohol (**17***b*) is not surprising, since a polar solvent could be expected to compete effectively with the bulky tertiary amine for the complexation of organometallic reagent. That complexation of a Grignard reagent is more effective than that of an organolithium compound is already known (7).

It is also conceivable that complex formation or lack of it plays an important role in the selective reduction of **1**. In a related study, Stevens *et al.* (8) concluded that primary and secondary 2-amino-2-phenylcyclohexanones form stable complexes with hydride reducing agents to give *trans* amino alcohols by an internal hydride transfer.

A conversion of **17***a* and **17***b* to **21***a* and **21***b* was accomplished by the standard reaction sequence shown in Scheme 3. Demethylation of **17***a*, **21***a*, and **21***b* (EtS^- or lithium diphenylphosphide) gave dihydroxybenzomorphans **22**. Compound **24***a* was obtained by hydrochloric acid-catalyzed cyclization of **22***a* (9) while **24***b* was obtained in two steps from **17***b*. Hydrochloric acid-catalyzed cyclization gave intermediate **23***a* which was demethylated to **24***b*. Similarly **24***c* was prepared from **21***b* via **23***b*.

Compounds **11**, **16**, **22**, and **24** were tested for analgesic and narcotic antagonist activities, and found to be considerably less active than corresponding compounds in the 9β-hydroxy series (1). Biological results will be discussed in more detail in another paper.

Experimental

The melting points were determined on 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 deuterochloroform. The chemical shifts are expressed in δ values using tetramethylsilane as internal reference. Microanalyses were performed by Micro-Tech Laboratories Inc., Skokie, IL.

9β-Hydroxy-2′-methoxy-2-methyl-5-[3′′-(1′′-hydroxypropyl)]-6,7-benzomorphan ***8a***

To a cooled (ice–salt bath) stirred solution of 5-allyl-9β-hydroxy-2′-methoxy-2-methyl-6,7-benzomorphan (**7***a*) (1) (2.24 g, 8.2 mmol) in THF (12 ml) was added dropwise a 1 *M* borane solution in THF (30 ml) and the mixture allowed to stand for 3 h at −10°C followed by 16 h at room temperature. This was cautiously treated with water (5 ml), followed by 20% sodium hydroxide (5 ml, 30 mmol) and 30% hydrogen peroxide (0.92 g, 8 mmol). The whole was stirred for 3 h and then extracted with chloroform (3 × 20 ml). The extract was concentrated *in vacuo* and the residue was boiled briefly with ethylene glycol (10 ml) to decompose a borane complex, cooled, diluted with water, and made basic with sodium hydroxide. The product, an oil, was isolated by extraction with chloroform, drying, and concentration *in vacuo*. The oil crystallized from ether – petroleum ether to give 1.34 g (50%) of **8***a*, mp 96–98°C. Another 15% of **8***a* was obtained from mother liquors by chromatography (Al_2O_3, $CHCl_3$ – 10% CH_3OH). An analytical sample was obtained by recrystallization from ether, mp 98–100°C; nmr δ 6.6–7.2 (3H, m), 3.8 (3H, s, O—CH_3), 3.5–4.0 (3H, m, 9-H and 3′′-H_2), 2.7–3.5 (3H, m), 2.37 (3H, s, N—CH_3), 1.0–2.7 (8H, m). *Anal.* calcd. for $C_{17}H_{25}NO_2$: C 70.07, H 8.65, N 4.81; found: C 70.16, H 8.79, N 4.79.

2-Cyclopropylmethyl-9β-hydroxy-2′-methoxy-5-[3′′-(1′′-hydroxypropyl)]-6,7-benzomorphan ***8b***

The diol **8***b* (an oil) was similarly prepared from **7***b* in 62% yield isolated as a hydrochloride salt. An analytical sample crystallized with ½CH_3OH of crystallization from methanol–acetone; mp 202–203°C. *Anal.* calcd. for $C_{20}H_{29}NO_3 \cdot HCl \cdot \frac{1}{2}CH_3OH$: C 64.13, H 8.40, N 3.65; found: C 64.50, H 8.35, N 3.49.

3-Methoxy-17-methyl-8-oxyisomorphinan ***10a***

To a cooled (ice bath) solution of **8***a* (1.08 g, 3.7 mmol) in dry CH_2Cl_2 (5 ml) was added a 1 *M* solution of methanesulfonyl chloride in benzene (4 ml) and the whole allowed to stand at room temperature for 1 h. Then the reaction mixture was concentrated *in vacuo* and the residue was stirred with a suspension of sodium hydride (420 mg of 50%, 9 mmol, washed with benzene) in DMF (6 ml) for 16 h at room temperature and then for 30 min at 60–70°C. After the usual work-up the crude product was chromatographed on an alumina column. Elution with chloroform gave an oil, which crystallized from ether – petroleum ether to give 0.53 g (62%) of **10***a*, mp 104–105°C; nmr δ 6.7–7.3 (3H, m), 4.05–4.5 (1H, m), 3.84 (3H, s, O—CH_3), 2.5–4.0 (7H, m), 2.44 (3H, s, N—CH_3), 0.8–2.5 (6H, m). *Anal.* calcd. for $C_{17}H_{23}NO_2$: C 74.69, H 8.48, N 5.12; found: C 74.74, H 8.58, N 5.11.

17-Cyclopropylmethyl-3-methoxy-14-methyl-8-oxyisomorphinan ***10b***

This compound (an oil) was similarly prepared from **8***b* in 65% yield, isolated as its oxalate salt. An analytical sample crystallized from methanol–acetone with ½MeOH of crystallization, mp 181–183°C. *Anal.* calcd. for $C_{20}H_{27}NO_2 \cdot C_2H_2O_4 \cdot \frac{1}{2}CH_3OH$: C 64.42, H 7.44, N 3.34; found: C 64.47, H 7.57, N 3.22.

3-Hydroxy-17-methyl-8-oxyisomorphinan ***11a***

To a cooled (ice bath) solution of **10***a* (547 mg, 2 mmol) in dry CH_2Cl_2 (8 ml) was added a 1 *M* boron tribromide solution in CH_2Cl_2 (5 ml) and the mixture allowed to stand at room temperature for 3 h. The excess boron tribromide was carefully decomposed with water. The mixture was made basic with ammonium hydroxide and layers were separated. The water layer was extracted with CH_2Cl_2 and the combined organic phase was dried and concentrated *in vacuo*. The residual orange colored solid

was recrystallized from acetone–CH_2Cl_2 to give 370 mg (64%) of **11***a* as an almost colorless solid, mp 218–220°C; nmr δ 6.7–7.3 (3H, m), 4.0–4.3 (1H, m), 2.5–3.8 (7H, m), 2.44 (3H, s), 0.8–2.4 (6H, m). *Anal.* calcd. for $C_{16}H_{21}NO_2$: C 74.10, H 8.16, N 5.40; found: C 74.21, H 8.37, N 5.25.

17-Cyclopropylmethyl-3-hydroxy-8-oxyisomorphinan ***11b***

The oxyisomorphinan **11***b* (an oil) was similarly prepared from **10***b* in 65% yield, isolated as the oxalate salt with $\frac{1}{2}CH_3OH$ of crystallization; mp 178–180°C (from methanol–acetone). *Anal.* calcd. for $C_{20}H_{27}NO_2 \cdot C_2H_2O_4 \cdot \frac{1}{2}CH_3OH$: C 64.42, H 7.44, N 3.44; found: C 64.47, H 7.57, N 3.22.

2,9α-Dimethyl-9β-hydroxy-2′-methoxy-5-[3″-(1″-hydroxypropyl)]-6,7-benzomorphan ***13a***

The diol **13***a* was prepared from **12** in 69% yield by the procedure given for the preparation of **8***a*; mp 146–148°C from *i*-propanol; nmr δ 6.5–7.1 (3H, m), 3.76 (3H, s), 3.4–3.8 (2H, m), 2.4–3.3 (5H, m), 2.32 (3H, s), 1.12 (3H, s), 0.9–2.3 (6H, m). *Anal.* calcd. for $C_{18}H_{27}NO_3$: C 70.79, H 8.91, N 4.59; found: C 70.78, H 9.05, N 4.61.

14,17-Dimethyl-3-methoxy-8-oxyisomorphinan ***14***

This compound was prepared from **13***a* in 64% yield, by the method given for the preparation of **10***a*: The hydrochloride salt of **14** crystallized from methanol–acetone with 1 mol of methanol of crystallization, mp 229–231°C; nmr (free base) δ 6.6–7.2 (3H, m) 3.8–4.1 (2H, m, 7-H_2) 3.78 (3H, s, O—CH_3), 2.4–3.6 (5H, m), 2.39 (3H, s, N—CH_3), 1.27 (3H, s, 14-CH_3), 0.7–2.4 (6H). *Anal.* calcd. for $C_{18}H_{25}NO_2 \cdot HCl \cdot CH_3OH$: C 64.12, H 8.50, N 3.93; found: C 63.98, H 8.40, N 3.85.

17-Cyano-3-methoxy-8-oxyisomorphinan ***15a***

To a solution of **14** (7.2 g, 25 mmol) in dry benzene (40 ml) was added cyanogen bromide (5.3 g, 50 mmol) and the mixture heated under reflux for 2 h. This was concentrated *in vacuo* and the residual oil was dissolved in CH_2Cl_2, washed with aqueous hydrochloric acid, and water, dried, and concentrated *in vacuo*. The residue was chromatographed (silica gel, ether) to give 5.4 g (72%) of solid **15***a*, mp 143–145°C (from acetone–ether); nmr δ 6.5–7.2 (3H, m), 3.8–4.1 (2H, m), 3.73 (3H, s), 1.15 (3H, s), 0.7–3.6 (11H). *Anal.* calcd. for $C_{18}H_{22}N_2O_2$: C 72.45, H 7.43, N 9.39; found: C 72.43, H 7.43, N 9.41.

3-Methoxy-14-methyl-8-oxyisomorphinan ***15b***

A solution of **15***a* (5.0 g, 16.7 mmol) in anhydrous THF (20 ml) was added dropwise over a 15 min period to a boiling solution of lithium aluminum hydride (2.5 g) in THF (60 ml). The whole was heated under reflux for 2 h, cooled, and treated with 1 *N* NaOH (12.5 ml). A solid was removed by filtration and washed several times with ether. The combined filtrate and washings were concentrated *in vacuo* to give 4.57 g (quantitative yield) of crude **15***b* as an oil. An analytical sample was purified as the oxalate salt by recrystallization from 95% ethanol. It crystallized as neutral oxalate with ½ mol of water of crystallization; mp 145–148°C. *Anal.* calcd. for $C_{17}H_{23}NO_2 \cdot \frac{1}{2}C_2H_2O_4 \cdot \frac{1}{2}H_2O$: C 66.03, H 7.70, N 4.28; found: C 65.69, H 7.76, N 4.15.

17-Cyclopropylcarbonyl-3-methoxy-8-oxyisomorphinan ***15c***

To a cooled (ice bath), stirred solution of **15***b* (1.48 g, 5.4 mmol) in dry CH_2Cl_2 (15 ml) and triethylamine (1 ml, 7.2 mmol) was added a solution of cyclopropane carboxylic acid chloride (0.62 g, 6 mmol) in dry CH_2Cl_2 (5 ml). The mixture was stirred for 10 min, and then washed with water followed by dilute hydrochloric acid. Drying and evaporation of solvent gave 1.82 g (quantitative yield) of **15***c* as an oil. A sample for analysis was purified by distillation at 220–230°C/0.5 Torr. *Anal.* calcd. for $C_{21}H_{27}NO_3$: C 73.87, H 7.97, N 4.10; found: C 74.03, H 8.11, N 3.99.

17-Cyclobutylcarbonyl-3-methoxy-8-oxyisomorphinan ***15d***

The amide **15***d* was similarly prepared from **15***b* in quantitative yield. An analytical sample was distilled at 220–230°C/0.4 Torr. *Anal.* calcd. for $C_{22}H_{29}NO_3$: C 74.35, H 8.22, N 3.94; found: C 74.02, H 8.32, N 3.65.

17-Cyclopropylmethyl-3-methoxy-8-oxyisomorphinan ***15e***

This compound was obtained by reduction of amide **15***c* in a procedure similar to that described for the preparation of **15***b*. The product (an oil) was isolated by column chromatography (Al_2O_3, ether) in 75% yield. The oxalate salt was recrystallized from methanol–acetone; mp 195–197°C; nmr δ 6.4–7.1 (3H, m), 3.75–4.05 (2H, m), 3.7 (3H, s), 1.15 (3H, s), 0.0–3.4 (18H). *Anal.* calcd. for $C_{21}H_{29}NO_2 \cdot C_2H_2O_4$: C 66.17, H 7.48, N 3.36; found: C 66.04, H 7.40, N 3.26.

17-Cyclobutylmethyl-3-methoxy-8-oxyisomorphinan ***15f***

This compound (an oil) was prepared similarly from **15***d* in 77% yield and purified as the oxalate salt; mp 204–206°C (from methanol–acetone); nmr δ 6.5–7.2 (3H, m), 3.88 (3H, s), 1.15 (3H, s), 0.6–4.2 (22H). *Anal.* calcd. for $C_{22}H_{31}NO_2 \cdot C_2H_2O_4$: C 66.80, H 7.71, N 3.25; found: C 66.58, H 7.68, N 3.15.

14,17-Dimethyl-3-hydroxy-8-oxyisomorphinan ***16a***

To a solution of **14** (0.73 g, 2.54 mmol) in dry THF (5 ml) was added under a nitrogen atmosphere a 0.78 *M* solution of lithium diphenylphosphide in THF (14 ml) and the whole heated under reflux for 6 h. The reaction mixture was treated with 0.5 *N* hydrochloric acid (40 ml) and extracted with ether (2 × 50 ml). The ether extract was discarded and the aqueous phase was made basic with ammonium hydroxide and extracted with CH_2Cl_2, to give after drying and evaporation 0.65 g of an oil. The oil crystallized from acetone to give 0.34 g (49%) of **16***a* as a white solid; mp 261–263°C, nmr δ 6.4–7.0 (3H, m), 3.7–4.0 (2H, m), 2.36 (3H, s), 1.15 (3H, s), 0.6–3.3 (11H). *Anal.* calcd. for $C_{17}H_{23}NO_2$: C 74.69, H 8.48, N 5.12; found: C 74.35, H 8.47, N 5.05.

17-Cyclopropylmethyl-3-hydroxy-14-methyl-8-oxyisomorphinan ***16b***

To a cooled (ice bath), stirred slurry of sodium hydride (580 mg, 24 mmol) in dry DMF (15 ml) was added ethane thiol (1.5 g, 24 mmol) followed by a solution of **15***e* (0.79 g, 2.4 mmol) in DMF (2 ml). The cooling bath was removed and the whole was heated under reflux for 4 h. After cooling, the reaction mixture was partitioned between water and CH_2Cl_2. The organic phase was washed with water, dried, and concentrated *in vacuo* to give an oil. This was dissolved in acetone and treated with a solution of dry HCl in ether to give 0.51 g (49%) of the hydrochloride of **16***b* as white solid. Recrystallization from ethanol–acetone–ether gave an analytical sample

containing 1 mol of ethanol of crystallization; mp 235–238°C. *Anal.* calcd. for $C_{20}H_{27}NO_2 \cdot HCl \cdot C_2H_5OH$: C 67.63, H 8.38, N 3.76; found: C 67.48, H 8.47, N 3.56.

17-Cyclobutylmethyl-3-hydroxy-14-methyl-8-oxyisomorphinan **16***c*

This compound was prepared from **15***f* by the procedure given for the preparation of **16***a*. It crystallized from acetone in 53% yield; recrystallization from methanol–acetone gave an analytical sample; mp 203–205°C. *Anal.* calcd. for $C_{21}H_{29}NO_2$: C 77.02, H 8.93, N 4.28; found: C 77.39, H 9.16, N 4.09.

5-Allyl-9α-hydroxy-2′-methoxy-1-methyl-6,7-benzomorphan **17***a*

To a cooled (−50°C), stirred 25% solution of diisobutyl aluminum hydride in hexane (50 ml, 77 mmol) was added dry THF (25 ml) followed by a solution of ketone **1** (10.5 g, 38.7 mmol) in dry THF (30 ml) over a period of 20 min. The whole was kept for 15 min at −50°C, treated cautiously with methanol (8 ml), and then poured onto a mixture of ice (200 g) and concentrated hydrochloric acid (40 ml). The layers were separated and the organic layer was extracted with 1 *N* hydrochloric acid (60 ml). The combined aqueous phase was extracted with CH_2Cl_2 (3 × 50 ml), and the extract washed with 2 *N* ammonium hydroxide (50 ml), dried, and concentrated *in vacuo* to give 10.5 g (100%) of essentially pure **17***a* as an oil which crystallized on standing. An analytical sample was prepared by recrystallization from ether – petroleum ether; mp 74–78°C; nmr δ 6.5–7.1 (3H, m), 5.0–6.5 (3H, m), 3.9 (1H, d, J = 5 Hz, 9-H), 3.82 (3H, s), 2.35 (3H, s), 1.1–3.3 (9H). *Anal.* calcd. for $C_{17}H_{23}NO_2$: C 74.69, H 8.48, N 5.12; found: C 74.26, H 8.73, N 5.19.

5-Allyl-1,9β-dimethyl-9α-hydroxy-2′-methoxy-6,7-benzomorphan **17***b*

A Grignard reagent was prepared by addition of a solution of iodomethane (26 g, 0.184 mol) in dry ether (30 ml) to a stirred suspension of magnesium turnings (3.71 g, 0.159 mol) in dry ether (30 ml) over a period of 2 h. Then the ether was evaporated *in vacuo* under a stream of nitrogen. To the dry solid was added in one portion a solution of **1** (9.78 g, 0.036 mol) in petroleum ether (250 ml, bp 30–60°C) and the whole vigorously stirred for 18 h. This was treated cautiously with water (70 ml) and p*H* was adjusted to 8 by addition of diluted (1:1) hydrochloric acid. The emulsified mixture was cleared by the addition of ammonium hydroxide and the layers were separated. The water layer was extracted with ether and the combined organic phase was dried and concentrated *in vacuo* to give 9.4 g (91%) of essentially pure **17***b* as an oil; nmr δ 6.5–7.1 (3H, m), 4.8–6.4 (3H, m), 3.73 (3H, s), 2.6–3.0 (5H, m), 2.3 (3H, s), 1.58 (3H, s), 1.0–2.5 (4H, m). A sample for analysis was purified as the oxalate salt by recrystallization from methanol–ether; mp 208–209°C. *Anal.* calcd. for $C_{18}H_{25}NO_2 \cdot C_2H_2O_4$: C 63.65, H 7.21, N 3.71; found: C 63.78, H 7.41, N 3.92.

5-Allyl-1-cyano-9α-hydroxy-2′-methoxy-6,7-benzomorphan **18***a*

This compound was prepared from **11***a* by the method given for the preparation of **15***a*. It crystallized from ether – petroleum ether in 70% yield as a white solid; mp 92–93°C. *Anal.* calcd. for $C_{17}H_{20}N_2O_2$: C 71.81, H 7.09, N 9.83; found: C 71.69, H 7.15, N 9.87.

5-Allyl-1-cyano-9α-hydroxy-2′-methoxy-9β-methyl-6,7-benzomorphan **18***b*

This compound was similarly prepared in 73% yield from **17***b*; mp 103–104°C (from chloroform–ether). *Anal.* calcd. for $C_{18}H_{22}N_2O_2$: C 72.45, H 7.43, N 9.39; found: C 72.56, H 7.48, N 9.23.

5-Allyl-9α-hydroxy-2′-methoxy-6,7-benzomorphan **19***a*

This compound (an oil) was obtained in quantitative yield from **18***a* by the method given for the preparation of **15***b*, except that dioxane was used as solvent. An analytical sample was purified by molecular distillation at 150°C/0.01 Torr; nmr δ 6.5–7.1 (3H, m), 5–6.5 (3H, m), 3.87 (1H, d, J = 3.5 Hz, 9-H), 3.78 (3H, s), 1.1–3.5 (9H). *Anal.* calcd. for $C_{16}H_{21}NO_2$: C 74.10, H 8.16, N 5.40; found: C 73.92, H 8.27, N 5.36.

5-Allyl-9α-hydroxy-2′-methoxy-9β-methyl-6,7-benzomorphan **19***b*

This compound was prepared similarly by reduction of **18***b* in THF, and isolated by column chromatography (silica gel; ether – 5% methanol) in 62% yield as an oil. The hydrochloride salt was recrystallized from methanol–ether; nmr δ 6.5–7.1 (3H, m), 4.8–6.4 (3H, m), 7.8 (3H, s), 1.55 (3H, s), 1–3.5 (9H). *Anal.* calcd. for $C_{17}H_{23}NO_2 \cdot HCl$: C 65.90, H 7.81, N 4.52; found: C 65.60, H 7.76, N 4.40.

5-Allyl-17-cyclopropylcarbonyl-9α-hydroxy-2′-methoxy-6,7-benzomorphan **20***a*

The hydroxyamide **20***a* was prepared from **19***a* in 80% yield by the procedure given for the preparation of **15***c*; white solid; mp 146–147°C (from benzene–ether). *Anal.* calcd. for $C_{20}H_{25}NO_3$: C 73.37, H 7.70, N 4.28; found: C 73.53, H 7.71, N 4.32.

5-Allyl-17-cyclopropylcarbonyl-9α-hydroxy-2′-methoxy-9β-methyl-6,7-benzomorphan **20***b*

The hydroxy amide **20***b* was similarly prepared in 65% yield from crude **19***b*; mp 144–145°C (from acetone). *Anal.* calcd. for $C_{21}H_{27}NO_3$: C 73.87, H 7.97, N 4.10; found: C 73.80, H 8.00, N 4.01.

5-Allyl-1-cyclopropylmethyl-9α-hydroxy-2′-methoxy-6,7-benzomorphan **21***a*

Reduction of **20***a* with lithium aluminum hydride in boiling dioxane in a procedure similar to that given for the preparation of **15***b* gave **21***a* (an oil) in 86% yield. An analytical sample was purified by molecular distillation at 180°C/0.01 Torr; nmr δ 6.6–7.1 (3H, m), 4.5–6.5 (3H, m), 3.9 (1H, d, J = 4 Hz), 7.78 (3H, s), 0.0–3.5 (16H). *Anal.* calcd. for $C_{20}H_{27}NO_2$: C 76.64, H 8.68, N 4.47; found: C 76.77, H 7.78, N 4.43.

5-Allyl-1-cyclopropylmethyl-9α-hydroxy-2′-methoxy-9β-methyl-6,7-benzomorphan **21***b*

This compound (an oil) was similarly prepared in 96% yield from **20***b*. The hydrochloride salt was recrystallized from methanol–ether; mp 236–238°C; nmr δ 6.5–7 (3H, m), 4.8–6.4 (3H, m), 3.7 (3H, s), 1.6 (3H, s) 0.0–3.1 (16H). *Anal.* calcd. for $C_{21}H_{29}NO_2 \cdot HCl$: C 69.31, H 8.31, N 3.81; found: C 69.08, H 8.44, N 3.79.

5-Allyl-2′,9α-dihydroxy-1-methyl-6,7-benzomorphan ***22a***

The diol **22***a* was prepared in 58% yield from **17***a* by the method given for the preparation of **16***b* and purified by recrystallization first from methanol–benzene and then from toluene; mp 154–156°C, nmr δ 6.4–7.1 (3H, m), 4.8–6.4 (3H, m), 3.88 (1H, d, J = 3.5 Hz), 2.4 (3H, s), 1–3.3 (9H). *Anal.* calcd. for $C_{16}H_{21}NO_2$: C 74.10, H 8.16, N 5.40; found: C 74.45, H 8.20, N 5.01.

5-Allyl-1-cyclopropylmethyl-2′,9α-dihydroxy-6,7-benzomorphan ***22b***

The diol **22***b* was similarly prepared in 87% yield from **21***a*, as an amorphous solid. It was purified by recrystallization from methanol–ether; mp 171–174°C. An analytical sample was purified by molecular distillation at 160°C/0.01 Torr, nmr δ 6.4–7.0 (3H, m), 4.9–6.3 (3H, m), 3.75 (1H, t, J = 4 Hz, 9-H), 0.0–3.5 (16H). *Anal.* calcd. for $C_{19}H_{25}NO_2$: C 76.22, H 8.42, N 4.68; found: C 76.19, H 8.50, N 4.72.

5-Allyl-1-cyclopropylmethyl-2′,9α-dihydroxy-9β-methyl-6,7-benzomorphan ***22c***

The diol **22***c* was similarly prepared in 67% yield from **21***b* and purified by recrystallization of the hydrochloride salt from methanol–acetone; mp 220–223°C; nmr δ 6.4–7.0 (3H, m), 4.9–6.3 (3H, m), 1.62 (3H, s), 0.0–3.2 (16H). *Anal.* calcd. for $C_{20}H_{27}NO_2 \cdot HCl$: C 68.65, H 8.07, N 4.00; found: C 68.64, H 8.06, N 3.96.

Tetrahydrofuranobenzomorphan ***24a***

The diol **22***a* (0.50 g, 1.9 mmol) was treated with concentrated hydrochloric acid (10 ml) at reflux for 5 min. The reaction mixture was concentrated to *ca.* 5 ml, made basic with ammonium hydroxide, cooled, and filtered to give crude solid **24***a*. This was purified by recrystallization first from toluene and then from ethanol to give 160 mg of pure **24***a*; mp 207–208°C; nmr δ 6.5–7.1 (3H, m), 3.7–4.1 (2H, m), 3.3–3.6 (1H, m), 2.8–3.0 (2H, m), 2.46 (3H, s), 1.5–2.6 (6H, m), 1.25 (3H, d, J = 5 Hz). *Anal.* calcd. for $C_{16}H_{21}NO_2$: C 74.10, H 8.16, N 5.40; found: C 73.81, H 8.08, N 5.12.

Tetrahydrofuranobenzomorphan ***24b***

This compound was obtained in two steps from **17***b* as follows. A solution of **17***b* (820 mg, 2.85 mmol) in concentrated hydrochloric acid (10 ml) was heated under reflux for 5 min, cooled, made basic with sodium hydroxide, and extracted with ether, to give after drying and concentration 800 mg of crude **23***a* as an oil; nmr δ 6.4–7.1 (3H, m), 3.65 (3H, s, O—CH_3), 3.4–3.9 (1H, m, 2′′-H), 2.6–3.0 (3H, m), 2.3 (3H, s, N—CH_3), 1.5–2.7 (6H, m), 1.45 (3H, s, 9-CH_3), 1.22 (3H, d, J = 6 Hz, 3′′-H_3). This was demethylated without further purification by the procedure given for the preparation of **16***a* to give crude solid **24***b*. This was purified by recrystallization from ethanol–water to give 530 mg (68%) of the pure product; mp 217–219°C; nmr δ 6.4–7.1 (3H, m), 3.4–3.9 (1H, m) 1.2–3.2 (11H, m) 1.52 (3H, s, 9-CH_3), 1.3 (3H, d, J = 6 Hz, 3′′-H_3). *Anal.* calcd. for $C_{17}H_{23}NO_2$: C 74.69, H 8.43, N 5.12; found: C 74.52, H 8.41, N 5.06.

Tetrahydrofuranobenzomorphan ***24c***

This compound was similarly prepared in two steps (via **23***b*) in 78% yield from **21***b*, isolated as the hydrochloride salt from acetone. Recrystallization from methanol–acetone gave an analytical sample; mp 246–249°C; nmr δ 6.5–7.0 (3H, m), 3.4–3.9 (1H, m, 2′′-H), 3.1–3.3 (1H, m, 9-H), 1.5–2.9 (10H, m), 1.55 (3H, s, 9-CH_3), 1.32 (3H, d, J = 6 Hz, 3′′-H_3), 0.0–1.1 (5H, m, c-C_3H_5). *Anal.* calcd. for $C_{20}H_{27}NO_2 \cdot HCl$: C 68.65, H 8.07, N 4.00; found: C 68.68, H 8.06, N 3.87.

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