corder (Grass Instruments Co., Quincy, MA). The bathing solution was aerated with 5% CO_2 in O_2. A 30-min equilibration period was allowed prior to all experiments.

In each experiment, control response to $PGF_{2\alpha}$ (10^{-6} M bath concentration), acetylcholine (AcCh; 5×10^{-7} M bath concentration), or KCl (15 mM bath concentration) was obtained by first exposing the tissue to the particular agonist and then washing the tissue three times over a 15-min period. Control response to the agonist was elicited three times prior to incubation of the tissue with any of the test compounds (1-4), to ensure viability of the tissue and stability of the response. The test compound was then added to the bath and left in contact with the ileum for 3 min. $PGF_{2\alpha}$, AcCh, or KCl was then added to the bath as before, and the resultant contraction was recorded. After 3 min, the bath was again washed three times and the control response to $PGF_{2\alpha}$, AcCh, or KCl was reestablished. All values were calculated as percent of the average of the initial control responses. Control responses to the concentrations of $PGF_{2\alpha}$, AcCh, and KCl used represented, respectively, 45.7 ± 11.4, 53.6 ± 2.3, and 52.6 ± 9.4% of the maximum response obtainable with each spasmogen.

To determine if variation of the calcium concentration in the medium would affect the antispasmodic actions of compounds 1-4, the following method was used.[19] The tissue was incubated for 10 min with the chosen concentration of calcium chloride to allow the spontaneous contractile activity to subside. The agonist (AcCh, 5×10^{-7} M; KCl, 15 mM; $PGF_{2\alpha}$, 10^{-6} M) was added to the bath and a control contraction was recorded. The tissue was washed and reincubated for 10 min with the same concentration of calcium used to obtain the control response to the agonist. One of the test compounds (1-4) was then added and left in contact with the tissue for 3 min before the reintroduction of the agonist. The tissue was then washed and allowed to relax, and the entire procedure was repeated at a higher concentration of bath calcium (the concentrations of agonists and test compounds were kept constant).

Analgesic Narcotic Antagonists. 5. 7,7-Dimethyldihydrocodeinones and 7,7-Dimethyldihydromorphinones[1]

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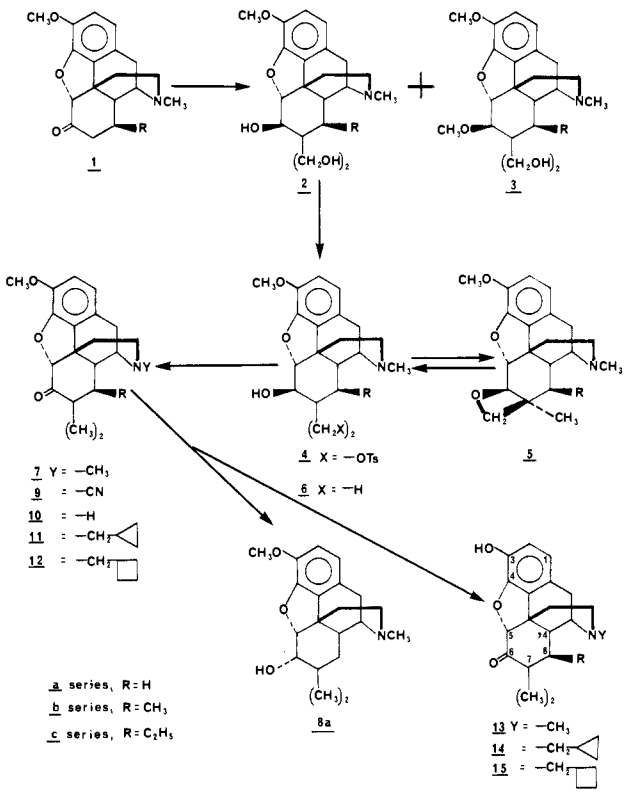
Treatment of dihydrocodeinone (**1a**) or the 8β-methyl (**1b**) or 8β-ethyl (**1c**) analogues with formaldehyde-$Ca(OH)_2$ in aqueous dioxane gave the corresponding 7,7-bis(hydroxymethyl)-6β-ols **2a-c**. Ditosylation of **2**, followed by $LiEt_3BH$ reduction, gave either the 7,7-dimethyl-6β-ol (**6a**) or 7α-methyl-6β,7β-oxetane compounds (**5b,c**). Compounds **5b** and **5c** were cleaved to **6b** or **6c** using $LiAlH_4$-$AlCl_3$. The configuration of the C6-alcohol group of **6a** was confirmed by an oxidation-reduction sequence which gave the 7,7-dimethyl-6α-ol **8a**. Oxidation of **6** gave the C6-ketones **7a-c**, which were converted to *N*-(cycloalkylmethyl) derivatives **11** and **12** and their corresponding 3-hydroxy compounds **14** and **15**. The 3-methoxy-7,7-dimethyl-6-ones **7** were as active as dihydrocodeinone in agonist assays. One compound of this series, *N*-(cyclopropylmethyl)-7,7-dimethyldihydronorcodeinone (**11a**), was a potent mixed agonist-narcotic antagonist.

We have recently reported that the agonist and narcotic antagonist properties of 17-(cycloalkylmethyl)morphinan-6-ones can be modified by the introduction of short alkyl groups into the 7 and 8 positions of the C ring.[2] In order to further explore the effect of other modifications on pharmacological profiles, we sought additional methods for the formation of carbon-carbon bonds within this portion of the opiate nucleus.

Examination of the literature revealed that Mannich and Schulte[3] reported in 1938 the facile aldol condensation-Cannizzaro reduction of dihydrocodeinone to give a 7,7-bis(hydroxymethyl)-6-hydroxy derivative. Our prior experience with a similar reaction in the carbohydrate area[4] prompted us to explore this method for the preparation of intermediates for conversion to 7,7-dimethyl-*N*-(cycloalkylmethyl)dihydronorcodeinones. This paper reports the chemistry of the title compounds and the results of the pharmacological evaluation of these modified opiates.

Chemistry. Reaction of dihydrocodeinone (**1a**) with formaldehyde, in the presence of calcium hydroxide in 1:2 methanol-water as reported,[3] gave a bis(hydroxymethyl) derivative (Scheme I) which was isolated as the hydro-

Scheme I



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chloride salt in good yield. We originally assigned the α configuration to the C6-alcohol function by analogy with codeine. Later studies, as described below, did not confirm this assignment and, in fact, showed that in **2a** the C6-alcohol is of the β or isocodeine configuration.

The 8β-alkylated-dihydrocodeinones[2a] **1b,c**, when treated with formaldehyde under the same conditions, gave the desired **2b,c** together with a second product. This component was identified as **3b,c** by NMR spectroscopy which indicated the presence of an extra methoxyl group at about δ 3.4. The position (δ 4.55) and coupling constant (7.5 Hz) observed for the C5 proton in these spectra suggest that the 6-methoxyl group in **3b,c** is also of the β configuration. The amount of **3b,c** formed was found to be dependent upon the amount of methanol in the reaction mixture. For example, in 50% aqueous methanol **1c** gave an approximately 1:10 mixture of **2c** and **3c**, while in water containing 15% methanol about a 1:1 mixture was obtained. The presence of an 8β-alkyl substituent evidently introduces a change in the C ring which results in the observed products. Formation of **3b,c** could be avoided by utilizing aqueous dioxane as the solvent for the condensation reaction.

Reaction of **2** with 3 equiv of tosyl chloride in pyridine solution for several days gave mainly the disubstituted compounds **4** which were difficult to obtain in a pure state. Displacement of the tosyl groups in **4a** with lithium triethylborohydride[5] proceeded slowly to give a good yield of the 7,7-dimethyl-6β-hydroxy compound **6a**. Unexpectedly, treatment of the 8β-alkyl derivatives **4b,c** under the same conditions quickly gave new products which were identified as the 7α-methyl-6β,7β-oxetane compounds **5b,c**. The NMR spectra of compound **5b** revealed the 7α-methyl group as a singlet at δ 1.08. The signal for the nonequivalent 7β-methylene protons was observed as a doublet centered at δ 4.53. Both H5 and H6 were observed as doublets, J = 6 Hz, at δ 4.42 and 4.17, respectively. The oxetane derivative **5a** could be obtained from **4a** if the reaction with $LiEt_3BH$ was conducted in refluxing tetrahydrofuran for a short time.

Reductive cleavage of the strained 6,7-epoxymethano bridge in **5b,c** was accomplished by use of a 3:1 mixture of lithium aluminum hydride–aluminum chloride[6] in refluxing ether. There was no indication for scission of the 4,5α-epoxy bond under these conditions. The resulting 7,7-dimethyl-6β-hydroxy compounds **6** were cleanly oxidized to the corresponding C6-ketones by use of dimethyl sulfoxide–trifluoroacetic anhydride.[7]

In order to confirm the configuration of the C6-alcohol group in **2a** and derivatives, the reduction of **7a** with sodium borohydride in 95% ethanol was investigated. A 4:1 mixture, as indicated by NMR, was obtained. The major product was the C6α-alcohol **8a**, in agreement with reports[8] that metal hydride reductions of C6-ketones in the dihydrocodeinone series produce both isomers, with the C6α-alcohol being obtained as the predominant isomer. For this major product **8a**, the NMR signal for H5 was observed at δ 4.75, a position downfield from that observed for the same proton in **6a** (δ 4.43). This result, that the C5 proton signal for α-alcohols appears at a lower field position than in the β-alcohols, is in agreement with observations in similar dihydrocodeine isomers.[9] The sequence **2a** → **4a** → **6a** involves reactions which do not effect the C6-hydroxy group. Therefore, **2a** must be of the C6β-hydroxy (dihydroisocodeine) series. The similar positions and coupling constants observed for the C5 proton in **6b** and **6c** implies that these compounds are also of the dihydroisocodeine configuration. The direct observation of the signal for H5 in the original adducts **2** is hampered by a general broadening and overlapping of signals.

The formation of C6β-alcohols in the condensation–reduction of **1** with formaldehyde and the formation of 6β-methoxy compounds from **1b** and **1c** may be explained by an elimination–addition sequence. The initial monocondensation product with formaldehyde is reduced to a C6α-alcohol which undergoes β-elimination. The molecule then adds solvent to the more accessible β face to relieve strain inherent in the unsaturated intermediate. Further condensation of the 6β-hydroxy(methoxy)-7-aldehyde, followed by reduction, yields the observed derivatives **2** or **3**. A similar mechanism has been invoked to explain results obtained with the aldol–Cannizzaro sequence in the carbohydrate area.[10]

The *N*-methyl compounds **7a–c** were converted to *N*-(cycloalkylmethyl) derivatives using the modified cyanogen bromide–acid hydrolysis–alkylation procedures we have previously reported.[2] The 3-methoxy function was cleaved to give the 3-phenols **13–15** by use of either refluxing 48% hydrobromic acid or boron tribromide.

Pharmacological Results

The 7,7-disubstituted morphinans were evaluated for agonist activity in the acetic acid induced mouse writhing[11] and heat stimulus rat tail-flick assays.[12] Narcotic antagonist activity was determined against an ED_{80} of morphine in the modified rat tail-flick procedure.[12] The test results are reported in Table I.

No activity was observed in these assays with the 7,7-bis(hydroxymethyl)isocodeines **2a–c**. The 6β,7β-oxetane compounds **5a** and **5b** are about equipotent with dihydrocodeinone in the mouse writhing procedure, whereas the 8β-ethyl derivative **5c** is only one-fifth as potent. The 7,7-dimethyl-6β-ols **6a–c** are less potent than dihydrocodeinone in both assays. The C6-ketones **7a–c** are about twice as potent as the 6β-ols **6a–c** and about equipotent with dihydrocodeinone. The two phenolic derivatives **13a** and **13c** are about equipotent with dihydromorphinone.

In the 3-methoxy-*N*-antagonist series, compounds **11a** and **12b** had mixed agonist–antagonist effects. The more potent compound **11a** had these activities with an agonist/antagonist ratio of 0.8. Compound **12b** was not considered a sufficiently potent agonist to warrant further study. The 3-hydroxy-*N*-(cyclopropylmethyl) series **14** were potent antagonists, devoid of agonist activity. The 3-hydroxy-*N*-(cyclobutylmethyl) series **15** did not possess sufficiently potent mixed activity required for a useful

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Table I. Analgesic and Narcotic Antagonist Activity[a]

compd	ED_{50}, μmol/kg sc (95% CL)		
	analgesic: mouse writhing	analgesic: rat tail flick	antagonist:[b] rat tail flick
2a	IA[c] at 25	IA at 25	
2b	>26	IA at 26	
2c	IA at 25	IA at 25	
5a	1.9 (0.87-4.2)	>30	
5b	1.8 (0.59-5.6)	>23	
5c	11.1 (6.6-18.8)	>28	
6a	6.5 (4.2-12.1)	30.4	
6b	3.8 (2.9-4.9)	15.6	
6c	21.5 (10.2-45)	>22	
7a	3.9 (2.7-5.9)	9.8 (4.2-22.5)	
7b	2.5 (2.3-2.9)	4.2 (3.0-5.9)	
7c	4.4 (2.4-7.9)	13.9 (6.6-29.3)	
8a	12.7 (5.3-30.6)		
13a	0.19 (0.096-0.96)	0.99 (0.61-1.7)	
13c	0.60 (0.44-0.75)	0.62 (0.42-0.91)	
11a	5.3 (1.4-20.3)		6.7 (3.2-13.8)
11b	>26		7.3 (3.6-14.8)
11c	IA at 20		>20
12a	IA at 26		>26
12b	17.2 (10.5-23.6)		4.7 (2.6-8.2)
12c	>23		>23
14a	IA at 28		1.2 (0.11-13.6)
14b	IA at 23		0.38 (0.06-2.3)
14c	IA at 16		2.4 (1.9-3.1)
15a	2.2 (0.53-9.2)		>24
15b	>25		>25
15c	18.5 (11.7-29.2)		2.8 (1.1-6.9)
codeine	10.3 (2.7-40)	75 (19-293)	
morphine	2.1 (1.1-4.0)	19.3 (9.2-41)	
dihydrocodeinone	2.4 (1.6-3.6)	5.2 (3.6-7.5)	
dihydromorphinone	0.25 (0.12-0.44)	1.3 (1.2-1.5)	
butorphanol	0.34 (0.13-0.90)		2.0 (0.97-9.4)
cyclazocine	0.41 (0.11-1.7)		0.81 (0.48-1.4)
nalorphine	3.51 (0.58-21)		2.47 (0.46-13)
pentazocine	13.0 (8.5-19)		36.4 (13.6-100)

[a] Compounds which were prepared as salts (see Experimental Section) were administered in distilled water; free bases were dissolved by the addition of 1 N HCl and then further diluted. [b] Determined using an intraperitoneal ED_{80} of morphine. [c] IA = inactive at dose indicated.

agent.

In an attempt to provide criteria which supplement potency considerations for the selection of useful compounds, we have suggested that the agonist/antagonist ratio may be an indicator of morphine substitution liability in the monkey.[2] The objective of these previous studies was to determine from our readily available, preliminary mouse and rat tests what the agonist/antagonist ratio should be in order for a compound not to substitute for morphine in the monkey and, by extrapolation, man. Our previous studies demonstrated that agents with a ratio of less than 0.4 substitute for morphine in drug-dependent monkeys, while those with ratios greater than 0.44 do not substitute.[2c] Compound **11a** (ratio 0.8), in contrast to the previous findings, completely substituted, albeit briefly, for morphine in dependent monkeys at doses above 3 mg/kg.[13] Thus, our proposal that agonist/antagonist ratios are useful predictors of morphine substitution is not generally valid.

These results, presented in Table I, indicate that, as we have previously observed,[2] the introduction of alkyl groups into the C ring of opiate derivatives does modify the magnitude of the effects observed. These changes in potency depend on the specific alkyl group introduced both at C7 and C8 and, for potential mixed agonist–antagonists, on the *N*-alkyl and 3-O substituents as well. Our studies directed toward the modification of pharmacological activity of opiate derivatives by exploring the chemistry of the C ring continues.

(13) We are indebted to the Committee on Problems of Drug Dependence, Dr. A. E. Jacobson, Biological Coordinator, for these studies. See Aceto, M. D.; Harris, L. S.; Dewey, W. L.; May, E. L. *NIDA Res. Monogr.*, in press.

Experimental Section

Methods have previously been described.[2] Processing in the usual manner implies that the organic extracts were combined, washed with dilute NH_4OH solution, dried over anhydrous $MgSO_4$, and evaporated to dryness under water aspirator vacuum on a rotary evaporator at a 40–45 °C bath temperature. The residue was further dried at 50–60 °C bath temperature using a mechanical vacuum pump. Column chromatography was carried out over silica gel 60 G (E. Merck) usually using a loading factor of ~1.0 g of crude material to 100 g of gel and $CHCl_3$–MeOH mixtures (2:1 to 20:1) containing 2.0 to 0.5% v/v concentrated NH_4OH as eluant. NMR spectra were recorded in $CDCl_3$ unless otherwise noted. Only certain characteristic NMR data are presented. The presence of solvent of crystallization was usually verified by NMR in an appropriate solvent. Where analyses are indicated only by symbols of elements, the analytical results obtained for those elements are within ±0.4% of the theoretical values.

7,7-Bis(hydroxymethyl)-4,5α-epoxy-3-methoxy-17-methylmorphinan-6β-ol (2a). To a solution of 4,5α-epoxy-3-methoxy-17-methylmorphinan-6-one (**1a**; 30.0 g, 0.10 mol) in dioxane (500 mL) was added H_2O (600 mL), $Ca(OH)_2$ (14.0 g, 0.19 mol), and 37%, w/w, formaldehyde solution (140 mL, 1.86 mol). The mixture was stirred at room temperature overnight and then concentrated under reduced pressure. The residue was diluted with H_2O and extracted with EtOAc. Processing in the usual manner gave a white foam, which was converted to the HCl salt. Crystallization from aqueous EtOH gave 28.7 g (72%) of **2a** in

three crops. Recrystallization from aqueous EtOH gave pure **2a**·HCl, mp >265 °C. Anal. ($C_{20}H_{27}NO_5$·HCl) C, H, N.

7,7-Bis(hydroxymethyl)-8β,17-dimethyl-4,5α-epoxy-3-methoxymorphinan-6β-ol (2b). A solution of **1b** (31.4 g, 0.10 mol) in dioxane (600 mL)/H_2O (600 mL) containing $Ca(OH)_2$ (14.0 g) and 37% formaldehyde solution (140 mL) was stirred overnight at room temperature and then evaporated to a small volume. Dilution with water was followed by extraction with EtOAc, and processing in the usual manner gave a foam. A combination of crystallization and chromatography gave 29.2 g (78%) of crystalline **2b**. Recrystallization from EtOH gave analytically pure **2b** as the hemihydrate: mp 109–111 °C; NMR ($CDCl_3$–CD_3OD) δ 6.70 (m, 2 H, aromatic), 4.73 (d, 1 H, H5, J = 7 Hz), 3.88 (s, 3 H, CH_3O), 2.43 (s, 3 H, CH_3N), 0.92 (unsymmetrical d, 3 H, 8β-CH_3). Anal. ($C_{21}H_{29}NO_5$·0.5H_2O) C, H, N.

7,7-Bis(hydroxymethyl)-4,5α-epoxy-8β-ethyl-3-methoxy-17-methylmorphinan-6β-ol (2c). Compound **1c** was reacted with formaldehyde in the presence of $Ca(OH)_2$ in dioxane–H_2O as indicated above for 24 h, and the reaction mixture was processed as described. A portion of the resulting foam was converted to the HCl salt, which crystallized from aqueous EtOH to give pure **2c**·HCl, mp >265 °C. Anal. ($C_{22}H_{31}NO_5$·HCl) C, H, N.

7,7-Bis(hydroxymethyl)-3,6-dimethoxy-4,5α-epoxy-8β-ethyl-17-methylmorphinan (3c). To a warm solution of **1c** (3.27 g, 10 mmol) in MeOH (60 mL) was added H_2O (70 mL), $Ca(OH)_2$ (1.40 g), and 37% formaldehyde solution (14 mL). The mixture was stirred overnight at room temperature and then concentrated to remove MeOH. The residual solution was diluted with brine and extracted three times with EtOAc. The EtOAc extracts were processed in the usual fashion to give 4.17 g of a foam, which was chromatographed. Fractions containing the faster migrating component were evaporated to give 2.41 g (60%) of **3c** as a foam. Latter fractions gave 0.21 g (5%) of **2c**, identical by TLC and NMR with material prepared above. Crystallization of **3c** from EtOAc–Et_2O gave pure material: mp 157–158 °C; NMR δ 6.70 (s, 2 H, aromatic), 4.55 (d, 1 H, H5, J = 7.5 Hz), 3.83 (s, 3 H, 3-CH_3O), 3.37 (s, 3 H, 6-CH_3O), 2.45 (s, 3 H, CH_3N). Anal. ($C_{23}H_{33}NO_5$) C, H, N.

7,7-Bis[(tosyloxy)methyl]-4,5α-epoxy-3-methoxy-17-methylmorphinan-6β-ols (4a–c). A solution of **2a** (35.7 g, 97 mmol) in dry C_5H_5N (200 mL) was cooled in an ice–salt bath and p-TsCl (55.4 g, 290 mmol) was added portionwise. The dark solution was then stirred at room temperature for 1 to 2 days, quenched by the addition of water, and evaporated to a small volume. The residue was diluted with H_2O and extracted with $CHCl_3$. The $CHCl_3$ extracts were processed to give a dark syrup, which was chromatographed. Fractions containing the desired product were pooled to give 51.6 g (78%) of **4a** as a tan foam: NMR δ 7.87–6.97 (m, 8 H, 2 tosyl groups), 6.60 (s, 2 H, aromatic), 4.30 (d, 1 H, H5). Compounds **4b** (66%) and **4c** (56%) were prepared in a similar manner and isolated as foams.

4,5α-Epoxy-3-methoxy-7α,8β,17-trimethyloxetano[b-6β,7β]morphinan (5b). To a solution of **4b** (35.5 g, 51.9 mmol) in THF (425 mL) cooled in an ice–salt bath under argon was added dropwise $LiEt_3BH$ (208 mL of a 1 M solution in THF). The mixture was removed from the bath and stirred at ambient temperature for 3 h. After the mixture cooled, the excess of hydride was destroyed by the addition of H_2O (25 mL). Following the dropwise addition of 3 N NaOH (50 mL) and 30% H_2O_2 solution (50 mL), the mixture was refluxed for 2 h. The solution was cooled, the layers were separated, and the aqueous phase was washed with $CHCl_3$. The combined organic phases were evaporated and the residue was chromatographed to yield 15.8 g (89%) of crystalline **5b**. Recrystallization from EtOAc gave pure **5b**: mp 161–162.5 °C; NMR δ 6.68 (m, 2 H, aromatic), 4.53 (d, 2 H, (β-CH_2, J = 9 Hz), 4.42 (d, 1 H, H5), 4.17 (d, 1 H, H6, J = 6 Hz), 3.90 (CH_3O), 2.50 (CH_3N), 1.08 (s, 3 H, 7α-CH_3), 0.77 (d, 3 H, 8β-CH_3). Anal. ($C_{21}H_{27}NO_3$) C, H, N.

7α,17-Dimethyl-4,5α-epoxy-8β-ethyl-3-methoxyoxetano[b-6β,7β]morphinan (5c). A solution of **4c** (62.7 g, 90 mmol) in THF (800 mL) was reacted with $LiEt_3BH$ (360 mmol) as above for 3 h and the excess of hydride was destroyed with H_2O (40 mL). After the solution was refluxed with 3 N NaOH (80 mL) and 30% H_2O_2 (80 mL), processing gave a syrup which was chromatographed to give 24.5 g (77%) of **5c** as a glass. Crystallization from ether gave pure material: mp 144–146 °C; NMR δ 4.6–4.0 (complex m, 4 H), 3.91 (s, CH_3O), 2.50 (s, CH_3N), 1.15 (s, 7α-CH_3). Anal. ($C_{22}H_{29}NO_3$) H, N; C: calcd, 74.33; found, 73.92.

4,5α-Epoxy-3-methoxy-7,7,17-trimethylmorphinan-6β-ol (6a). A solution of **4a** (41.4 g, 61.7 mmol) in THF (400 mL) was cooled in an ice bath under an argon atmosphere and then treated dropwise with $LiEt_3BH$ (250 mmol). The mixture was stirred for 6 h at room temperature, after which an additional portion of hydride (125 mmol) was added. Stirring was continued for an additional 24 h, after which water (100 mL) was added cautiously to the cooled solution. To this clear solution was added 3 N NaOH (100 mL), followed by 30% H_2O_2 solution (100 mL). The mixture was refluxed for 2 h and cooled, and the layers were separated. The aqueous layer was extracted twice with $CHCl_3$, and the combined organic extracts were evaporated to give 22.2 g of **6a** as a foam: NMR δ 6.69 (s, 2 H, aromatic), 4.43 (d, 1 H, H5, J = 7 Hz), 3.86 (s, CH_3O), 2.42 (s, CH_3N), 0.93 (d, 6 H, 7-CH_3's, J = 1.5 Hz). A portion of this foam was converted to the HCl salt, which was twice crystallized from MeOH–EtOAc to give **6a**·HCl, mp >265 °C. Anal. ($C_{20}H_{27}NO_3$·HCl) C, H, N.

4,5α-Epoxy-3-methoxy-7,7,8β,17-tetramethylmorphinan-6β-ol (6b). To a suspension of $AlCl_3$ (6.17 g, 46.3 mmol) in Et_2O (500 mL) stirred in an ice bath under argon was added portionwise $LiAlH_4$ (5.27 g, 139 mmol). The mixture was stirred for 30 min in the cold, after which a solution of **5b** (15.8 g, 46.3 mmol) in Et_2O (1 L) was added. The mixture was refluxed for 24 h, cooled, and water was added cautiously. The mixture was made basic with 3 N NaOH and filtered through Celite. The organic phase of the filtrate was separated and the aqueous phase was extracted twice with $CHCl_3$. The combined organic phases were evaporated to give 15.3 g (96%) of crystalline **6b**. Two recrystallizations from $CHCl_3$–hexane gave **6b** as the $CHCl_3$ solvate: mp 110–112 °C; NMR δ 6.65, 4.43 (d, 1 H, H5), 3.85, 2.45, 1.07–0.67 (m, 9 H, CH_3's). Anal. ($C_{21}H_{29}NO_3$·$CHCl_3$) H, N; C: calcd, 57.09; found, 57.60.

4,5α-Epoxy-8β-ethyl-3-methoxy-7,7,17-trimethylmorphinan-6β-ol (6c). A mixture of $AlCl_3$ (8.0 g, 60 mmol) and $LiAlH_4$ (6.8 g, 180 mmol) was prepared in Et_2O (600 mL) as described above. To this was added **5c** (21.3 g, 60 mmol) in Et_2O (1 L), and the mixture was refluxed for 36 h. Processing as described gave a foam. Crystals of **6c** (10.0 g) as the $CHCl_3$ solvate, mp 104–108 °C, were obtained from $CHCl_3$–hexane: NMR δ 6.70 (s, 2 H, aromatic), 4.40 (d, 1 H, H5, J = 7.5 Hz), 3.87, 2.45, 0.93, 0.85 (sharp s, 7-CH_3's). An additional 2.7 g of **6c** (59% overall yield) was obtained by processing the mother liquor. Anal. ($C_{22}H_{31}NO_3$·0.75$CHCl_3$) C, H, N.

4,5α-Epoxy-3-methoxy-7,7,17-trimethylmorphinan-6-one (7a). To a solution of Me_2SO (6.3 mL, 88 mmol) in CH_2Cl_2 (80 mL) under argon cooled in a dry ice-acetone bath was added slowly, dropwise, trifluoroacetic anhydride (9.3 mL, 66 mmol) in CH_2Cl_2 (35 mL) while keeping the temperature below −60 °C. To this was added **6a** (14.5 g, 44 mmol) in CH_2Cl_2 (80 mL) slowly, dropwise, so that the temperature remained below −55 °C. The mixture was stirred in the bath for 90 min, after which TEA (18 mL, 245 mmol) was added dropwise. The mixture was allowed to warm to room temperature and extracted twice with H_2O. Evaporation of the organic phase gave a residue, which was purified by chromatography to give 14.9 g of **7a** as a glass: NMR δ 6.63, 4.87 (s, 1 H, H5), 3.93, 2.43, 1.27 (s, 3 H, 7β-CH_3), 0.95 (s, 3 H, 7α-CH_3). A portion of this material was converted to the HCl salt, which was also obtained as a foam. Anal. ($C_{20}H_{25}NO_3$·HCl·0.5H_2O) C, H, N.

4,5α-Epoxy-3-methoxy-7,7,8β,17-tetramethylmorphinan-6-one (7b). Compound **6b** (710 mg, 2 mmol) in CH_2Cl_2 (10 mL) was oxidized using Me_2SO (0.35 mL, 5 mmol) and trifluoroacetic anhydride (0.70 mL, 3.75 mmol) in CH_2Cl_2 (8 mL) at −55 °C as described above. After the addition of TEA (1 mL), workup gave a residue, which was purified by chromatography to give 474 mg (67%) of **7b** as a glass: NMR δ 5.0 (s, 1 H, H5), 1.23–0.80 (3-CH_3's). This material was converted to the HCl salt, which crystallized from MeOH–EtOAc to give analytically pure **7b**·HCl, mp 246–248 °C. Anal. ($C_{21}H_{27}NO_3$·HCl) C, H, N.

4,5α-Epoxy-8β-ethyl-3-methoxy-7,7,17-trimethylmorphinan-6-one (7c) was prepared by oxidation of **6c** (22.6 mmol) in toluene (200 mL), using Me_2SO (45.2 mmol) and trifluoroacetic anhydride (33.9 mmol) in CH_2Cl_2 (50 mL), for 90 min at dry ice–acetone bath temperature. Workup by the addition of TEA (5 mL), followed by processing in the usual manner, gave

a foam which crystallized from EtOAc to give analytically pure **7c**: mp 154–156 °C; NMR δ 4.94 (s, 1 H, H5). Anal. ($C_{22}H_{29}NO_3$) C, H, N.

4,5α-Epoxy-3-methoxy-7,7,17-trimethylmorphinan-6α-ol (8a). To a solution of **7a** (818 mg, 2.5 mmol) in 95% EtOH (50 mL) was added $NaBH_4$ (284 mg, 7.5 mmol). The mixture was stirred at room temperature for 1 h and then the excess of hydride was destroyed by the addition of HOAc. The mixture was concentrated to a small volume, diluted with H_2O, and made basic with concentrated NH_4OH. The solution was extracted with $CHCl_3$, and the extracts were processed in the usual fashion to give 808 mg of a 4:1 mixture of **8a** and **6a** as indicated by NMR. The mixture was chromatographed to give 643 mg (78%) of **8a** followed by 90 mg (11%) of **6a** identical (TLC and NMR) with material previously prepared. The NMR of **8a** showed δ 6.68 (s, 2 H, aromatic), 4.75 (d, 1 H, H5, J = 5.5 Hz), 3.88 (s, CH_3O), 2.42 (s, CH_3N), 0.95 (br s, 7-CH_3's). Crystals of **8a**, mp 121–123 °C, were obtained from EtOAc–hexane. Anal. ($C_{20}H_{27}NO_3$) C, H, N.

17-Cyano-7,7-dimethyl-3-methoxymorphinan-6-ones (9a–c). To a rapidly stirred mixture of **7** (1.0 equiv) in $CHCl_3$ (1 g in 15 mL) containing powdered K_2CO_3 (1.5 equiv) was added dropwise a solution of BrCN (1.2 equiv) in $CHCl_3$ (1 g in 15 mL). The mixture was refluxed for 2 h and cooled, and the insoluble material was removed by filtration. The filtrate was evaporated to dryness and coevaporated with EtOH until crystals formed. After cooling, the crystals were collected and hydrolyzed as indicated below. **9a**: 77% yield; mp 194–197 °C. **9b**: 76% yield; mp 160–162 °C. **9c**: 79% yield; mp 195–198 °C.

7,7-Dimethyl-3-methoxymorphinan-6-ones (10a–c). A suspension of **9** in 2 N HCl (1 g, 15–25 mL) was refluxed for 5 to 7 h. The solution was cooled and the nor HCl salt was collected. This was used as is or converted to the free base for subsequent use in alkylation reactions as described below. **10a**·HCl: 76% yield; mp >265 °C. **10b**·HCl: 86% yield; mp >265 °C. **10c** was obtained as the glassy free base in 97% yield by extraction from aqueous solution after the addition of concentrated NH_4OH.

17-(Cycloalkylmethyl)-7,7-dimethyl-4,5α-epoxy-3-methoxymorphinan-6-ones (11a–c and 12a–c). A mixture of **10** (free base or HCl salt) in DMF (1 g in 20 mL) with $NaHCO_3$ (2.5 equiv) and cycloalkylmethyl bromide (1.2 equiv) was heated in an oil bath at 100 °C under argon. Reactions utilizing the free base usually required 3 to 4 h for completion, while those employing the HCl salt were carried out for 16 to 22 h. The cooled mixture was filtered to remove insolubles and the filtrate was evaporated using an oil pump. The residue was dissolved in H_2O, and the solution was adjusted to pH 10–11 with concentrated NH_4OH and extracted with three portions of toluene. The organic phase was evaporated and the residue was processed as described.

17-(Cyclopropylmethyl)-7,7-dimethyl-4,5α-epoxy-3-methoxymorphinan-6-one (11a). The residual foam (90%) was twice crystallized from EtOAc to give pure **11a**, mp 146.5–147.5 °C. Anal. ($C_{23}H_{29}NO_3$) C, H, N.

17-(Cyclopropylmethyl)-4,5α-epoxy-3-methoxy-7,7,8β-trimethylmorphinan-6-one (11b). The glass obtained (99%) was crystallized from EtOH to give **11b**, mp 127–128 °C, containing 0.25 mol of water. Anal. ($C_{24}H_{31}NO_3 \cdot 0.25H_2O$) C, H, N.

17-(Cyclopropylmethyl)-7,7-dimethyl-4,5α-epoxy-8β-ethylmorphinan-6-one (11c). This compound was obtained as a glass in 88% yield. Both the HCl and tartrate hydrate salts were obtained as foams. Anal. ($C_{25}H_{33}NO_3 \cdot C_4H_6O_6 \cdot H_2O$) C, H, N.

17-(Cyclobutylmethyl)-7,7-dimethyl-4,5α-epoxy-3-methoxymorphinan-6-one (12a). The glass obtained in 72% yield was twice crystallized from EtOH to give pure **12a**, mp 155–156 °C. Anal. ($C_{24}H_{31}NO_3$) C, H, N.

17-(Cyclobutylmethyl)-4,5α-epoxy-3-methoxy-7,7,8β-trimethylmorphinan-6-one (12b). Evaporation of the toluene solution gave crystals which were twice crystallized from 95% EtOH to give **12b** as needles, mp 163–164 °C. Anal. ($C_{25}H_{33}NO_3$) C, H, N.

17-(Cyclobutylmethyl)-7,7-dimethyl-4,5α-epoxy-8β-ethylmorphinan-6-one (12c). The toluene solution on evaporation gave an 85% yield of a glass. The HCl salt of **12c** resited crystallization and was obtained as a foam on evaporation from EtOAc. Anal. ($C_{26}H_{35}NO_3 \cdot HCl \cdot 0.25EtOAc$) C, H, N.

7,7-Dimethyl-3-hydroxymorphinan-6-ones (13a–c, 14a–c, and 15a–c). Method A. A suspension of the 3-methoxy compound in 48% HBr (1 g in 10 mL) was placed in a preheated 140 °C oil bath, and the mixture was refluxed for 15–20 min. The cooled solution was diluted with H_2O and then made basic by the addition of concentrated NH_4OH and extracted with three portions of EtOAc. The EtOAc extracts were evaporated and the residue was purified by chromatography.

Method B. To a stirred solution of BBr_3 (40 mmol) in $CHCl_3$ (50 mL) under argon cooled to 0 °C was added the 3-methoxy compound (6.60 mmol) in $CHCl_3$ (50 mL). The mixture was stirred for 30 min at room temperature, recooled to 0 °C, and MeOH (10 mL) was added slowly, dropwise. The solution was evaporated to a small volume and diluted with H_2O. Concentrated NH_4OH was added and the mixture was extracted with three portions of $CHCl_3$. The organic extracts were further processed in the usual fashion and evaporated to a residue, which was chromatographed.

7,7,17-Trimethyl-4,5α-epoxy-3-hydroxymorphinan-6-one (13a) was prepared by method A. Chromatography yielded 89% of a tan foam, which crystallized from MeOH–EtOAc to give pure **13a**, mp 251.5–253.5 °C. Anal. ($C_{19}H_{23}NO_3$) C, H, N.

7,7,17-Trimethyl-4,5α-epoxy-8β-ethyl-3-hydroxymorphinan-6-one (13c) was prepared by method B and obtained in 73% yield after chromatography. Conversion to the HCl salt, followed by crystallization from MeOH–EtOAc, gave pure **13c**·HCl, mp >265 °C. Anal. ($C_{21}H_{29}NO_3 \cdot HCl \cdot 0.25H_2O$) C, H, N.

17-(Cyclopropylmethyl)-4,5α-epoxy-7,7-dimethyl-3-hydroxymorphinan-6-one (14a) was prepared by method A and obtained as crystals in 44% yield. Recrystallization from MeOH–EtOAc gave pure **14a**, mp 252–255 °C. Anal. ($C_{22}H_{27}NO_3$) C, H, N.

17-(Cyclopropylmethyl)-4,5α-epoxy-3-hydroxy-7,7,8β-trimethylmorphinan-6-one (14b). The free base of **14b** was prepared by method B and obtained as a foam in 72% yield. The hemi-*d*-tartrate salt, mp 240–242 °C, was purified by crystallization from aqueous EtOH. Anal. ($C_{23}H_{29}NO_3 \cdot 0.5C_4H_6O_6$) C, H, N.

17-(Cyclopropylmethyl)-7,7-dimethyl-4,5α-epoxy-8β-ethyl-3-hydroxymorphinan-6-one (14c) was obtained by method B as the glassy free base in 78% yield after chromatography. This was converted to the *d*-tartrate salt, which was recrystallized twice from MeOH–EtOAc to give the EtOAc solvate, mp 165–180 °C. Anal. ($(C_{24}H_{31}NO_3 \cdot C_4H_6O_6 \cdot C_4H_8O_2)$ C, H, N.

17-(Cyclobutylmethyl)-7,7-dimethyl-4,5α-epoxy-3-hydroxymorphinan-6-one (15a) was prepared by method A and the free base was obtained in 64% yield after chromatography. An analytic sample of the hygroscopic HCl salt of **15a**, mp sinters 228 °C, melts 255 °C with dec, was obtained by two crystallizations from MeOH–EtOAc. Anal. ($C_{23}H_{29}NO_3 \cdot HCl \cdot 0.75H_2O$) C, H, N.

17-(Cyclobutylmethyl)-4,5α-epoxy-3-hydroxy-7,7,8β-trimethylmorphinan-6-one (15b) was obtained in 88% yield as a foam when prepared by method B. This was twice crystallized from EtOAc to give pure **15b**, mp 195–196 °C. Anal. ($C_{24}H_{31}NO_3$) C, H, N.

17-(Cyclobutylmethyl)-7,7-dimethyl-4,5α-epoxy-8β-ethyl-3-hydroxymorphinan-6-one (15c). The free base was obtained in 72% yield by use of method B. The hygroscopic HBr salt of **15c** was recrystallized twice from MeOH–EtOAc and had mp >265 °C. Anal. ($C_{25}H_{33}NO_3 \cdot HBr \cdot 0.25H_2O$) C, H, N.

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