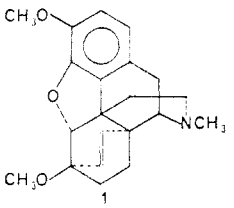
Analgesic Narcotic Antagonists. 6.[1] 7β,8β-Methano- and 7β,8β-Epoxydihydrocodeinone

Michael P. Kotick

Chemistry Department, Corporate Research Division, Miles Laboratories, Inc., Elkhart, Indiana 46515.
Received October 20, 1980

Reaction of codeinone (**2**) with CH_2N_2 in the presence of $Pd(OAc)_2$ yielded mixtures of starting material (**2**) and 7β,8β-methanodihydrocodeinone (**3**). Initial resolution of this mixture was achieved via carbonyl reduction followed by chromatography to give pure 7β,8β-methanodihydrocodeine (**4**), which was oxidized to **3**. Reaction of the mixture containing **2** and **3** with mercaptoethanol and NaOH [**2** → 8β-[(hydroxyethyl)thio]dihydrocodeinone (**5**)] allowed selective crystallization of **3**. The β configuration of the cyclopropane ring in **3** was established by cleavage with aqueous HCl to give the 8β-(chloromethyl) compound **6**, followed by carbonyl reduction and dehalogenation to 8β-methyldihydrocodeine (**8**). Reaction of the *N*-(cycloalkylmethyl) derivatives (**13** and **18**) of **2** with $CH_2N_2/Pd(OAc)_2$ gave potential mixed agonist–antagonists **14** and **19**, which were purified by reduction–oxidation (**14**) or mercaptoethanol-base treatment (**19**). Compound **2**, on oxidation with alkaline peroxide, gave the previously reported 7β,8β-epoxydihydrocodeinone (**22**) as the hemimethanol ketal (**21**). Compound **3** was about ninefold more potent an agonist than dihydrocodeine, and the *N*-(cyclopropylmethyl)-7β,8β-methano compound **19** had moderately potent, mixed agonist–narcotic antagonist properties.

The most attractive hypothesis advanced to explain the high analgesic potency of tertiary alcohol derivatives of Diels–Alder adducts of thebaine involves interaction with a specific lipophilic site on the opiate receptor.[2] This site is proposed to specifically bind the alkyl portion of the tertiary alcohol appendage in the C ring of these modified morphine structures. It has, however, been observed that the parent compound of this series, 6,14-*endo*-ethenotetrahydrothebaine (**1**), is 40 times more potent an anal-



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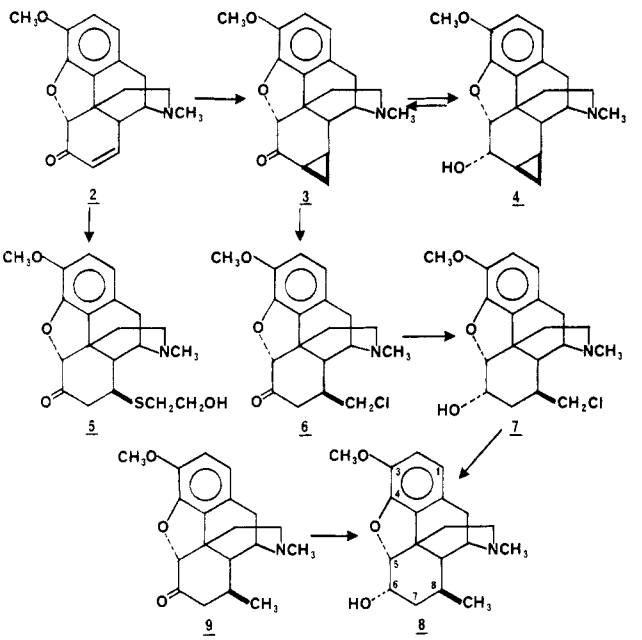
gesic than morphine. Interaction with the lipophilic site, which model-building studies indicate extends outward several angstroms from the morphine C ring, thus cannot be used to explain the potency of the parent compound. It is more likely that, in this case, a restriction of the conformation in this portion of the molecule to a more rigid structure accounts for the observed increase in potency.

We have reported that introduction of alkyl groups into the 7[1,3] or 8[4] positions in the C ring of morphinan-6-one compounds can result in a modulation of activity. In order to extend these observations, combined with an attempt to restrict the conformation of the C ring, we have now synthesized the 7β,8β-methano analogue of dihydrocodeinone. The similarity of olefins and cyclopropane derivatives with regard to chemical properties,[5] and thus perhaps to biological activities, gave added impetus to this work. The attempted preparation of this novel cyclopropane ring containing compound, by reaction of codeinone with dimethyloxosulfonium methylide, has been

Scheme I



reported to yield the oxirane derivative of 6-methylisocodeine.[6] Also included in this report is an observation on the preparation of the recently reported, related, 7β,8β-epoxydihydrocodeinone.[7]

Chemistry. Attempts to react codeinone (**2**) with numerous carbene or dihalogenocarbene sources resulted in either recovery of starting material or in a complex mixture from which a major component with expected properties could not be isolated. Eventual reaction of **2** with CH_2N_2, in the presence of $Pd(OAc)_2$,[8] in THF–Et_2O solution gave an insoluble precipitate which migrated as a homogeneous major spot on TLC. Carbonyl reduction with $NaBH_4$ gave variable mixtures of two products, resolvable by chromatography. The minor product was identified as codeine, while the spectral characteristics of the major product were consistent with the cyclopropane ring containing alcohol **4** (Scheme I). In addition to the loss of olefinic NMR signals in the spectrum of **4** relative to **2**, a complex

(1) For paper 5, see Leland, D. L.; Kotick, M. P. *J. Med. Chem.*, preceding paper in this issue.
(2) Lewis, J. W.; Bentley, K. W.; Cowan, A. *Annu. Rev. Pharmacol.* **1971**, *11*, 241. Bentley, K. W.; Lewis, J. W. In "Agonist and Antagonist Actions of Narcotic Analgesic Drugs"; Kosterlitz; H. W., Collier; H. O. J., Villarreal, J. E., Eds.; University Park Press: Baltimore, MD, 1973; p 7.
(3) Leland, D. L.; Kotick, M. P. *J. Med. Chem.* **1980**, *23*, 1427.
(4) (a) Kotick, M. P.; Leland, D. L; Polazzi, J. O.; Schut, R. N. *J. Med. Chem.* **1980**, *23*, 166. (b) Polazzi, J. O.; Schut, R. N.; Kotick, M. P.; Howes, J. F.; Osgood, P. F.; Razdan, R. K.; Villarreal, J. E. *Ibid.* **1980**, *23*, 174.
(5) de Meijere, A. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 809.
(6) Sargent, L. J.; Jacobson, A. E. *J. Med. Chem.* **1972**, *15*, 843.
(7) Uba, K.; Miyata, N.; Watanabe, K.; Hirobe, M. *Chem. Pharm. Bull.* **1979**, *27*, 2257.
(8) Kottwitz, J.; Vorbrüggen, H. *Synthesis* **1975**, 636. Mende, U.; Radüchell, B.; Skuballa, W.; Vorbrüggen, H. *Tetrahedron Lett.* **1975**, 629.

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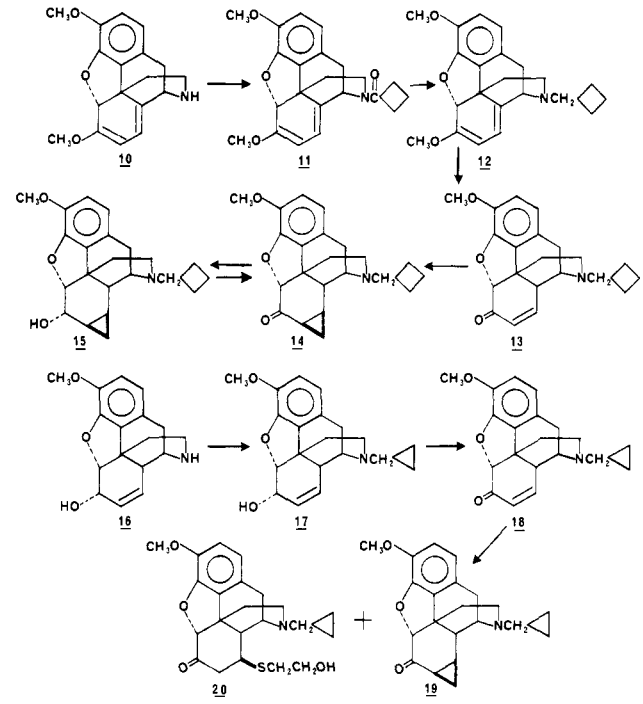
multiplet was observed for the cyclopropyl protons between δ 0.1 and 1.0.[9] Oxidation of 4 using Me_2SO–Ac_2O[10] at 65 °C gave relatively insoluble 3, which could be purified by recrystallization from DMF. The IR spectrum of 3 showed carbonyl absorption at 1695 cm^{-1}, characteristic of a cyclopropyl ketone. The mass spectrum of 3 gave a correct molecular ion (*m/e* 311, 100%), followed by loss of methyl (296, 41%) and methylene groups (282, 34%). The NMR spectra of 3 obtained in CD_3COOD solution showed H5 as a sharp singlet, δ 4.70, and a 4 proton multiplet between δ 0.9 and 1.8. In contrast, the H5 signal for 2 is observed at δ 4.94[11] in this solvent. This difference in the signal for H5 was a useful method for the assay of crude cyclopropylation reactions containing 2 and 3 prior to $NaBH_4$ reduction.

An efficient separation of 3 from 2 was obtained by selective reaction. Work in our laboratory[13] has shown that 2 is an excellent acceptor in Michael-type addition reactions. Compound 2, on treatment with mercaptoethanol and aqueous base, was completely converted to the polar 8β-[(hydroxyethyl)thio] derivative 5. When mixtures containing 2 and 3 were processed by the addition of these reagents, 3 could easily be isolated free of 5 by crystallization from EtOH.

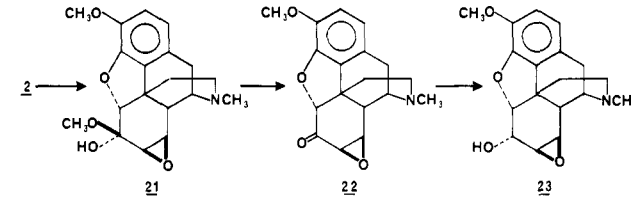
Removal of the *N*-methyl group in 3, by treatment with cyanogen bromide followed by acid hydrolysis, yielded a product in which the cyclopropyl ring was cleaved. Hydrolysis of the intermediate *N*-cyano compound under basic conditions gave a mixture of products. Investigation showed that 3 was quickly cleaved in refluxing 2 N HCl to the chloromethyl compound 6 in quantitative yield. This was most unexpected, in that usually strenuous conditions are required for opening of cyclopropyl rings fused α,β to cyclic ketones.[14] The conversion of 3 to 6 under these mild conditions reflects the very strained nature of the cyclopropane ring in this system. Compound 4 was stable to the same acid conditions.

The facile cleavage of 3 to 6 allowed confirmation that formation of the cyclopropane ring did occur on the β face of the molecule as expected. Reduction of 6 with $NaBH_4$ gave a 4:1 mixture of isomeric C6 alcohols. The major α isomer 7 was partially converted to the 8β-methyl compound 8 by refluxing with tri-*n*-butyltin hydride in EtOH solution containing a radical initiator. This product 8 was identical with the major product obtained on borohydride reduction of 8β-methyldihydrocodeinone (9).[4a] Direct *n*-Bu_3SnH reduction of 6 gave predominantly a 4,5-epoxy ring cleaved product via a 6β-OH derivative,[15] while cleavage of the cyclopropane ring in 3 with the same reagent[16] was not successful.

Scheme II



Scheme III



The α,β-unsaturated ketone 2 and the corresponding 17-(cycloalkylmethyl) derivatives are relatively unstable compounds which do not readily lend themself to extensive synthetic transformations or chromatography.[11] The *N*-(cycloalkylmethyl) derivatives 14 and 19 were, therefore, prepared by the indirect routes shown in Scheme II. Generation of the enone system was reserved as the penultimate step. Northebaine hydrochloride[17] (10) was treated with cyclobutanecarboxylic acid chloride in the presence of TEA to yield 11, which was then reduced with $LiAlH_4$ to 12 in a manner modified from that reported for the corresponding *N*-(cyclopropylmethyl) derivative.[18] The enone system was generated by treatment of 12 with HBr in CH_2Cl_2[4a,19] and the syrupy 13 was converted to a mixture containing 14. Reduction with $NaBH_4$ gave 15 and *N*-(cyclobutylmethyl)dihydronorcodeine, which were resolved by chromatography. Oxidation of 15 by use of Me_2SO–Ac_2O gave a moderate yield of pure 14.

The *N*-(cyclopropylmethyl)-7β,8β-methano derivative 19 was prepared by starting with norcodeine[20] (16). Alkylation with cyclopropylmethyl bromide under standard conditions[4] gave 17, which was oxidized at low temperature using Me_2SO–trifluoroacetic anhydride[21] to the enone 18.

(9) Bovey, F. A. "Nuclear Magnetic Resonance Spectroscopy"; Academic Press: New York, 1969; p 71.
(10) Albright, J. P.; Goldman, L. *J. Am. Chem. Soc.* **1967**, *89*, 2416.
(11) The NMR spectra of 2 in CD_3COOD changes with time to show two H5 protons attributable to a mixture of 2 and the 8,14 double bond isomer neopinone. The equilibrium is ca 1:1. Chromatography of 2 over silica gel G using $CHCl_3$–MeOH–NH_4OH mixtures also resulted in isomerization but not to as large an extent. See ref 12.
(12) Barber, R. B.; Rapoport, H. *J. Med. Chem.* **1976**, *19*, 1175.
(13) Kotick, M. P.; Polazzi, J. O., to be published.
(14) Giacomini, E.; Loreto, M. A.; Pellacani, L.; Tardella, P. A. *J. Org. Chem.* **1980**, *45*, 519. Loreto, M. A.; Pellacani, L.; Tardella, P. A. *J. Heterocycl. Chem.* **1979**, *16*, 1233. Pellacani, L.; Tardella, P. A.; Loreto, M. A. *J. Org. Chem.* **1976**, *41*, 1282.
(15) Chatterje, N.; Uman, J. G.; Inturrisi, C. E.; Chen, W. C.; Clarke, D. D.; Bhatnagar, S. P.; Weiss, U. *J. Org. Chem.* **1978**, *43*, 1003.
(16) Godet, J. Y.; Pereyre, M. *C. R. Hebd. Seances Acad. Sci., Ser. C* **1971**, *273*, 1183.
(17) Pohland, A.; Sullivan, H. R. U.S. Patent 3342824; *Chem. Abstr.* **1966**, *65*, 15441d.
(18) Bentley, K. W.; Bower, J. D.; Lewis, J. W. *J. Chem. Soc. C* **1969**, 2569.
(19) Gavard, J. P.; Krauz, F.; Rüll, T.; Delfly, M. *Bull. Soc. Chim. Fr.* **1965**, 486.
(20) von Braun, J. *Chem. Ber.* **1914**, *47*, 2312.
(21) Omura, K.; Sharma, A. K.; Swern, D. *J. Org. Chem.* **1976**, *41*, 957. Huang, S. L.; Omura, K.; Swern, D. *Ibid.* **1976**, *41*, 3329.

Reaction of 18 with $CH_2N_2/Pd(OAc)_2$ gave a mixture containing 19, which was resolved by conversion of unreacted 18 to the 8β-[(hydroxyethyl)thio] derivative 20, allowing the desired product 19 to be isolated by chromatography.

The formation of mixed crystals of 2 and 3 and the comigration on TLC of the enone–cyclopropyl ketone pairs 2 and 3, 13 and 14, and 18 and 19 indicate that the physical properties of the 7,8-methano molecules are not radically altered from that of the parent unsaturated ketones. The acid liability of the cyclopropyl ring in 3 reflects the strain induced in this system by restriction in the conformation of the C ring.

In connection with other work in the morphine alkaloid area, the related 7β,8β-epoxy derivative of codeinone, 22, was required as a synthetic intermediate. After completion of our work, the preparation[7] of 22 and the isolation of 23 as a metabolite of codeine in a liver microsomal preparation,[22] as well as the X-ray crystallographic structure[7] of 23, were reported. Compound 22, prepared in our laboratory utilizing reaction conditions similar to those reported, was, however, isolated as the hemimethanol ketal 21 (Scheme III). The free ketone 22 could easily be obtained, with properties as reported, by treatment of 21 with Ac_2O and crystallization from EtOAc. Recrystallization of the ketone 22 from MeOH gave the hemimethanol ketal 21 in good yield. Reduction of methyl hemiketal 21 with $LiAlH_4$ directly gave 23. The facile addition of MeOH across the C6 ketone of 22 is a reflection of the strain induced by the incorporation of a three-membered ring into the 7,8 position of the morphine nucleus. Evidently, the C ring dihydrocodeinone derivative 22 prefers a situation in which the C6 position is sp^3 hybridized. We have not observed this facile solvation in other morphinan-6-one compounds.

Results

The compounds prepared were tested for agonist[23] and narcotic antagonist activity.[24] The results are reported in Table I. The 7β,8β-methano compound 3 was more potent than dihydrocodeine and dihydrocodeinone and was a potent agonist in the rat tail-flick assay. Reduction of 3 to the C6α-alcohol 4 decreases potency about fourfold. Compound 5, which has a large hydrophilic group at the 8β position, was inactive, in agreement with the observation of bulk intolerance in this region.[4] The 6-oxo-8β-(chloromethyl) derivative 6 was about equipotent with codeine.

The 17-(cyclobutylmethyl) ketone 14 was an agonist, devoid of antagonist properties. The previously reported corresponding 7,8-unsubstituted 17-(cyclobutylmethyl)-norcodeinone[4a] was also an agonist (ED_{50} = 20.3 μmol/kg) and, likewise, inactive as an antagonist. The 7,8-methano-17-(cyclopropylmethyl) compound 19 had analgesic and antagonist properties in about a 1:1 ratio. This compound is 4 times more potent an agonist than the corresponding 7,8-unsubstituted compound, but both of these compounds had about the same antagonist potency. The 7β,8β-epoxy compound 21 was less potent than codeine, while the remaining compounds 22 and 23 were inactive at higher doses. No attempts were made to prepare the corresponding 3-phenols from any of the compounds reported, due to their instability to O-demethylating conditions.

Table I. Analgesic and Narcotic Antagonist Activity

compd	ED_{50}, μmol/kg sc (95% CL) analgesic: mouse writhing	analgesic: rat tail flick	antagonist:[a] rat tail flick
3	0.43 (0.04–4.14)	4.7 (0.30–7.35)	
4	1.79 (1.26–2.54)	IA at 65	
5	>25	IA at 25[b]	
6	12.2 (10.4–40.1)	IA at 25	
14	12.4 (4.0–40.1)		IA at 50
15	>55		IA at 55
19	9.0 (4.6–17.6)		8.7 (4.8–15.7)
20	3.4 (0.9–13.2)		>30
21	18.0 (10.5–30.8)	IA at 30	
22	IA at 32	>30	
23	IA at 32	IA at 32	
codeine	10.3 (2.7–39.9)	75.1 (19.1–293)	
dihydrocodeine	3.8 (1.1–14.7)	>22	
codeinone (2)	IA at 10[c]	IA at 3[c]	
dihydrocodeinone	2.4 (1.6–3.6)	5.2 (3.6–7.5)	
butorphanol	0.34 (0.13–0.90)		2.0 (0.9–9.4)
pentazocine	13.0 (8.5–19)		36.4 (13.6–100)

[a] Determined using an intraperitoneal ED_{80} of morphine. [b] IA = inactive at dose shown. [c] Caused convulsions at doses higher than those indicated.

Discussion

Cyclopropane rings have considerable double bond characteristics and, thus, may act as biological isosteres. This point is demonstrated by the similarlity in pharmacological effects of the narcotic antagonists naloxone and naltrexone [N-allyl- and N-(cyclopropylmethyl)-14-hydroxydihydrocodeinone, respectively]. The present work shows that introduction of a cyclopropane ring in the 7β,8β portion of the codeine nucleus does increase analgesic potency about sevenfold over the corresponding unsubstituted compounds. However, no major differences are seen with regard to the pharmacologic properties of the 17-(cycloalkylmethyl) derivatives. The 7β,8β-epoxy compounds are considerably less active than the corresponding parent drug. Thus, in these compounds, within which the conformation of the C ring has been restricted, exceptional analgesic activity is not observed. Work aimed at delineating the determinants of the high potency of the *endo*-enthenotetrahydrooripavine derivatives continues in our laboratory.

Experimental Section

Methods have previously been described.[1] Mass spectra were determined by using a Hewlett-Packard 5985A GC/MS system and are reported as m/e (relative intensity). Only selected, significant peaks are reported. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

For pharmacological testing, salts of the compounds were administered in distilled H_2O; free bases were dissolved by the dropwise addition of 1 N HCl and then further diluted.

4,5α-Epoxy-7β,8β-methano-3-methoxy-17-methylmorphinan-6-one (3). A stirred solution of 2 (5.00 g, 16.8 mmol)

(22) Uba, K.; Miyata, N.; Watanabe, K.; Hirobe, M. *Chem. Pharm. Bull.* **1980**, *28*, 356.
(23) Acetic acid induced mouse writhing assay. Whittle, B. A. *Br. J. Pharmacol.* **1964**, *22*, 246.
(24) Heat stimulus rat tail-flick method. Harris, L. S.; Pierson, A. K. *J. Pharmacol. Exp. Ther.* **1964**, *143*, 141.

in THF (200 mL) was cooled in an ice–salt bath to 0 °C and $Pd(OAc)_2$ (0.50 g, 2.2 mmol) was added. To this mixture was added dropwise a cold solution of CH_2N_2 [~70 mmol, prepared from *N*-nitroso-*N*-methylurea (15 g) in Et_2O (150 mL)][25] over a period of about 45 min. The suspension was stirred in the cold for 30 min and then at ambient temperature for 30 min. To this was added mercaptoethanol (2.56 g, 32.8 mmol) and 1 N NaOH (20 mL). After stirring for 15 min, the suspension was evaporated. The residue was taken up in CH_2Cl_2 and dried over $MgSO_4$. Filtration, followed by evaporation, gave a brown solid which contained a 2:1 mixture of **3** and **5** as indicated by NMR in CD_3COOD. The mixture was boiled with EtOH (50 mL) and, after cooling, yellow crystals of **3** (2.90 g, 55%), mp 245–246 °C, were collected. Recrystallization from DMF (45 mL) gave 2.32 g of **3**, mp 255–257 °C. Recrystallization of a portion of this material from DMF and then $CHCl_3$–EtOH gave analytically pure **3**: mp 257.5–259 °C; NMR (CD_3COOD) δ 6.83, (s, 2 H, aromatic), 4.70 (s, 1 H, H5), 4.38 (br, 1 H), 3.86 (s, 3 H, OCH_3), 3.03 (s, 3 H, NCH_3), 1.8–0.9 (m, 4 H, cyclopropyl protons). Anal. ($C_{19}H_{21}NO_3$) C, H, N.

4,5α-Epoxy-7β,8β-methano-3-methoxy-17-methylmorphinan-6α-ol (4). Compound **3** (1.00 g, 3.2 mmol) was partially dissolved in boiling 95% EtOH (150 mL) and the mixture was cooled to 50 °C. With continued stirring in an ice bath, $NaBH_4$ (0.15 g, 4 mmol) was added in one portion. The solution was further cooled to 20 °C and stirred at this temperature for 2 h, after which HOAc was added to destroy the remaining hydride. The mixture was evaporated and the residue was dissolved in H_2O, which was made basic by the addition of concentrated NH_4OH. Extraction with CH_2Cl_2, followed by processing of the organic phase in the usual fashion, gave 1.01 g of **4** as a foam. Crystallization of the foam from EtOAc gave 756 mg (75%) of **4**, mp 173–176 °C. Recrystallization from EtOAc gave pure **4**: mp 178–179 °C; NMR δ 6.63 (sharp d, 2 H, aromatic), 4.60 (d, 1 H, H5, J = 4 Hz), 3.85 (OCH_3), 2.43 (NCH_3), 1.0–0.1 (4 H, cyclopropyl H's). Anal. ($C_{19}H_{23}NO_3$) C, H, N.

Oxidation of 4 to 3. A mixture of Ac_2O (17 mL) and Me_2SO (26 mL) was heated at 65 °C for 20 min. To this was added **4** (2.76 g, 8.8 mmol), and the mixture was stirred at 65 °C for 1 h, during which time crystals of **3** formed in the reaction mixture. The mixture was evaporated under high vacuum, and the crystalline residue was triturated with EtOH. Crystalline **3** (1.92 g, 70%), mp 255–257 °C, was obtained, which on recrystallization from DMF had mp 257–259 °C and was identical with material prepared above.

4,5α-Epoxy-8β-[(hydroxyethyl)thio]-3-methoxy-17-methylmorphinan-6-one (5). To a solution of **2** (3.00 g, 10 mmol) in dioxane (100 mL) was added mercaptoethanol (2.23 g, 28.5 mmol), followed by 1 N NaOH (10 mL). The mixture was stirred for 15 min and then evaporated to a small volume. The residue was diluted with water and extracted with $CHCl_3$. Evaporation of the organic extracts gave a foam (4.03 g), which was chromatographed to give 3.68 g (100%) of **5** as a foam: NMR δ 6.70 (s, 2 H, aromatic), 4.70 (s, 1 H, H5), 3.93 (s, OCH_3), 3.70 (t, SCH_2, J = 6.5 Hz), 2.45 (s, NCH_3). The foam was dissolved in EtOH and concentrated HCl was added until the solution was acidic. Concentration of the solution, followed by standing overnight in the cold, yielded 3.74 g of white crystals, mp 224–227 °C, of **5**·HCl as the 0.5EtOH solvate. Anal. ($C_{20}H_{25}NO_4S$·HCl·0.5EtOH) C, H, N.

8β-(Chloromethyl)-4,5α-epoxy-3-methoxy-17-methylmorphinan-6-one (6). A mixture of **3** (1.00 g, 3.2 mmol) and 2 N HCl (10 mL) was refluxed for 2 h. The cooled solution was made basic with NH_4OH and extracted with $CHCl_3$. Evaporation of the dried organic phase gave 1.20 g of **6** as a foam. Crystallization from EtOH gave 815 mg (73%) of **6**, mp 167–168.5 °C. Recrystallization from EtOH gave pure **6**, mp 168–170 °C; NMR δ 6.70 (s, aromatic), 4.68 (s, H5), 3.93 (OCH_3), 3.76–3.50 (m, CH_2Cl), 2.45 (NCH_3). Anal. ($C_{19}H_{23}ClNO_3$) C, H, N.

8β,17-Dimethyl-4,5α-epoxy-3-methoxymorphinan-6α-ol (8). To a solution of **6** (1.95 g, 5.6 mmol) in 95% EtOH (100 mL) was added $NaBH_4$ (213 mg, 5.6 mmol) and the mixture was stirred for 30 min. The solution was made acidic by the addition of HOAc and evaporated to a small volume. The residue was dissolved in water, NH_4OH was added, and the product was extracted with $CHCl_3$. Evaporation of the organic extracts gave 2.30 g of a foam, which was shown by TLC to consist of two products. The foam was chromatographed to give the pure α isomer **7** (1.48 g, 75%) as a foam: NMR δ 4.60 (d, H5, J = 5 Hz). Further elution gave the corresponding 6β-ol (0.47 g, 24%): NMR δ 4.36 (d, H5, J = 7 Hz).

Compound **7** (1.40 g, 4.0 mmol) was dissolved in EtOH (35 mL) under an argon atmosphere and n-Bu_3SnH (1.76 g, 6 mmol) was added followed by azobis(isobutyronitrile) (100 mg). The mixture was refluxed for 12 h and the solvent was removed by evaporation. The residue was dissolved in 1 N HCl and extracted with several portions of Et_2O. The aqueous phase was made basic with NH_4OH and extracted with $CHCl_3$. Processing gave 1.24 g of a foam which was chromatographed. First eluted was unreacted **7** (575 mg, 41%) followed by **8** (535 mg, 42%) which was obtained as a glass: NMR δ 6.65 (s, 2 H, aromatic), 4.56 (d, 1 H, H5, J = 5 Hz), 3.87 (OCH_3), 2.42 (NCH_3), 0.94 (unsymmetrical d, 8β-CH_3). This material was identical (NMR, TLC) with the major product obtained upon borohydride reduction of 8β,17-dimethyl-4,5α-epoxy-3-methoxymorphinan-6-one (**9**).

17-(Cyclobutylcarbonyl)-3,6-dimethoxy-4,5α-epoxy-6,7,8,14-tetradehydromorphinan (11). To a suspension of **10**·HCl (33.4 g, 0.1 mol) in CH_2Cl_2 (400 mL) was added TEA (41 mL, 0.3 mol) followed by the dropwise addition of cyclobutanecarboxylic acid chloride (11.86 g, 0.1 mol) in CH_2Cl_2 (25 mL) at a rate such that the temperature did not rise above 30 °C. After the addition was complete, the suspension was stirred for 30 min and then poured into H_2O (300 mL). The organic layer was separated, washed twice with 2 N HCl, dried, and evaporated to give a quantitative yield of **11** as a foam.

17-(Cyclobutylmethyl)-3,6-dimethoxy-4,5α-epoxy-6,7,8,14-tetradehydromorphinan (12). Compound **11** (37.9 g, 0.1 mol) in THF (400 mL) was added dropwise over a period of 45 min to a stirred suspension of $LiAlH_4$ (5.3 g, 0.14 mol) in THF (300 mL). Upon completion of the addition, the mixture was stirred for 10 min, cooled, and quenched by the careful dropwise addition of H_2O (6 mL), 15% NaOH (6 mL), followed by H_2O (18 mL). The mixture was stirred for 1 h and then filtered from insoluble material. The filtrate was evaporated, and the residue was taken up in CH_2Cl_2 and washed several times with H_2O. Evaporation of the organic phase gave syrupy **12** (34.5 g, 94%) on evaporation. TLC indicated the presence of trace impurities: NMR δ 6.80 (s, 2 H, aromatic), 5.48 (d, 1 H, H7), 5.25 (s, 1 H, H5), 4.98 (d, 1 H, H8, $J_{7,8}$ = 6 Hz), 3.83 (s, 3-OCH_3), 3.56 (s, 6-OCH_3).

Compound **12** prepared in another reaction was obtained in crystalline form, mp 102–104 °C, upon two crystallizations from EtOH. Anal. ($C_{23}H_{27}NO_3$) C, H, N.

17-(Cyclobutylmethyl)-7,8-didehydro-4,5α-epoxy-3-methoxymorphinan-6-one (13). A solution of **12** (34.5 g) in CH_2Cl_2 (500 mL) was cooled in an ice–salt bath to 5 °C and rapidly saturated with HBr. The temperature of the reaction rose to ~18 °C and began to drop when the reaction was complete. The mixture was recooled to 5 °C and poured into saturated $NaHCO_3$ solution (600 mL). With continued stirring, the pH was adjusted to 14 by the addition of 50% NaOH. The organic phase was separated and washed twice with H_2O. Evaporation gave 40.1 g of the HBr salt of **13** as a foam. The foam was dissolved in H_2O and NH_4OH was added until the mixture was strongly basic. The basic aqueous solution was decanted and extracted once with CH_2Cl_2. The residue was dissolved in CH_2Cl_2 and the combined organic solutions were washed twice with 10% aqueous NH_4OH. Evaporation of the dried organic phase gave 33.3 g (100%) of **13** as a brown foam: NMR δ 6.67 (m, 3 H, aromatic and H7), 6.08 (d of d, 1 H, H8, $J_{7,8}$ = 11 Hz, $J_{8,14}$ = 3 Hz), 4.70 (s, 1 H, H5), 3.87 (s, OCH_3). TLC indicated the presence of trace impurities.

17-(Cyclobutylmethyl)-4,5α-epoxy-7β,8β-methano-3-methoxymorphinan-6α-ol (15). To a mixture of **13** (10.70 g, 30.4 mmol) and $Pd(OAc)_2$ (500 mg, 2.2 mmol) in THF (200 mL) cooled in an ice bath was added portionwise CH_2N_2 (~90 mmol) in Et_2O (200 mL). Upon completion of the addition, the mixture was stirred for 15 min and then filtered through Celite. The filtrate was evaporated to a dry residue, which was taken up in CH_2Cl_2 and washed with several portions of dilute NH_4OH. Evaporation

(25) Arndt, F. "Organic Syntheses"; Blatt, A. H., Ed.; Wiley: New York, 1943; Collect Vol. 2, p 165.

of the CH_2Cl_2 phase gave 10.7 g of a dark foam, which was shown by NMR to be an ca. 2:1 mixture of **13** and **14**. This residue was again dissolved in THF, $Pd(OAc)_2$ was added, and the mixture was retreated with CH_2N_2 (~90 mmol) as above. Workup as before gave 10.6 g of a foam which was an ca. 1:3 mixture of **13** and **14**. The foam was dissolved in 95% EtOH (350 mL) with warming and cooled in ice, and $NaBH_4$ (1.00 g, 26.4 mmol) was added portionwise. After the mixture was stirred for 30 min, excess HOAc was added and the mixture was evaporated. The residue was dissolved in H_2O, made basic by the addition of NH_4OH, and extracted with CH_2Cl_2. Processing in the usual fashion yielded a syrup, which was azeotroped with EtOH. Upon standing in the cold overnight, crystals of **15** (2.02 g, mp 166.5–167.5 °C) were obtained. Chromatography of the mother liquors, followed by crystallization from EtOH, gave an additional 1.94 g of **15** for an overall yield of 35%. An analytical sample of **15**, mp 168–170 °C, was prepared by recrystallization from EtOH. NMR δ 6.63 (d, 2 H aromatic, J = 2 Hz), 4.59 (d, H5, J = 4 Hz), 3.87 (OCH_3), 1.1–0.1 (m, 4 H, cyclopropyl H). Anal. ($C_{23}H_{29}NO_3$) C, H, N.

17-(Cyclobutylmethyl)-4,5α-epoxy-7β,8β-methano-3-methoxymorphinan-6-one (14). A mixture of Ac_2O (6 mL) and Me_2SO (9 mL) was heated at 65 °C for 20 min. To this was added **15** (1.00 g, 2.72 mmol) and heating continued at 65 °C for 40 min. The cooled solution was evaporated using high vacuum at 60–70 °C and the residue (947 mg) was chromatographed. Fractions containing the major product were pooled to give 495 mg (50%) of **14** as a glass: NMR δ 6.68 (s, 2 H, aromatic), 4.37 (s, 1 H, H5), 3.85 (OCH_3). A portion of this material was dissolved in EtOH and treated with an equivalent of 1 N HCl. The solution was evaporated and then coevaporated with EtOH–C_6H_6 followed by C_6H_6 until crystals formed. Crystals of pure **14**·HCl, mp sinters 172–173 °C, foams 178–179 °C, were collected with the aid of C_6H_6. Anal. ($C_{23}H_{27}NO_3$·HCl) C, H, N.

17-(Cyclopropylmethyl)-7,8-didehydro-4,5α-epoxymorphinan-6α-ol (17). A mixture of **16**·HCl·$3H_2O$ (32.0 g, 85 mmol), $NaHCO_3$ (21.0 g, 250 mmol), and cyclopropylmethyl chloride (10.9 g, 120 mmol) in DMF (200 mL) was heated at 100 °C under argon for 18 h. The cooled suspension was filtered, the filtrate was evaporated to dryness, and the residue was partitioned between dilute NH_4OH and toluene. Processing of the organic phase in the usual manner gave 27.0 g (93%) of **17** as a brown foam. This material was oxidized as described below without further purification.

17-(Cyclopropylmethyl)-7,8-didehydro-4,5α-epoxymorphinan-6-one (18). To a solution of Me_2SO (3.0 mL, 42 mmol) in CH_2Cl_2 (30 mL) at −60 °C was added dropwise over a period of 40 min a solution of trifluoroacetic anhydride (4.4 mL, 31 mmol) in CH_2Cl_2 (10 mL). After the solution stirred for 10 min, a solution of **17** (6.25 g, 18.4 mmol) in CH_2Cl_2 (50 mL) was added slowly over 30 min. The mixture was stirred at −60 °C for 2 h and then TEA (8 mL) was added slowly dropwise. After the mixture warmed to room temperature, the solution was diluted with CH_2Cl_2 and washed several times with H_2O. Drying, followed by evaporation, gave 6.18 g (99%) of **18** as a foam: NMR δ 6.87–6.60 (m, 3 H, aromatic and H8), 6.08 (pair of doublets, H8, $J_{7,8}$ = 11 Hz, $J_{7,14}$ = 3 Hz), 4.70 (s, H5). TLC indicated traces of several impurities. This material was used without further purification in the following reactions.

17-(Cyclopropylmethyl)-4,5α-epoxy-7,8-methano-3-methoxymorphinan-6-one (19). A solution of **18** (5.20 g, 15.4 mmol) in THF (150 mL) containing $Pd(OAc)_2$ (0.5 g, 2.2 mmol) was cooled to 0 °C and a solution of diazomethane (~70 mmol) in Et_2O (150 mL) was added dropwise over 45 min. The mixture was stirred in the ice bath for 30 min and then mercaptoethanol (20 mL, 28.5 mmol) and 1 N NaOH (20 mL) were added. The mixture was stirred for 15 min at room temperature and then evaporated to a small volume. The residue was diluted with H_2O and extracted with $CHCl_3$. Processing of the $CHCl_3$ extracts gave 5.64 g of a glass which contained a 2:1 mixture of **19** and **20** as indicated by NMR. Chromatography gave 1.73 g (32%) of **19** as a glass. Crystallization from EtOH gave 780 mg of **19** as fluffy white needles, mp 109–111 °C. Recrystallization from EtOH gave analytically pure **19**: mp 110–111 °C; NMR δ 6.67 (s, aromatic), 4.38 (s, H5), 3.87 (s, OCH_3). Anal. ($C_{22}H_{25}NO_3$) C, H, N.

17-(Cyclopropylmethyl)-4,5α-epoxy-8β-[(hydroxyethyl)thio]-3-methoxymorphinan-6-one (20). To a solution of **18** (975 mg, 2.89 mmol) in dioxane (40 mL) was added mercaptoethanol (0.7 mL, 10 mmol) and 1 N NaOH (3 mL). After stirring at room temperature for 15 min, the mixture was evaporated, and the residue was diluted with water and extracted with $CHCl_3$. The $CHCl_3$ extracts were processed to yield a foam, which was chromatographed to give 705 mg (59%) of **20** as a foam: NMR δ 6.62 (s, aromatic), 4.64 (s, H5), 3.87 (s, OCH_3), 3.63 (t, SCH_2). This foam was converted to the HCl salt, which gave crystals, mp 162–164 °C, from EtOH–EtOAc. Recrystallization from MeOH gave the MeOH solvate of **20**·HCl with indefinite melting point. The presence of MeOH was confirmed by NMR in Me_2SO-d_6. Anal. ($C_{23}H_{29}NO_4S$·HCl·CH_3OH) C, H; N: calcd, 2.89; found, 3.61.

4,5α:7β,8β-Diepoxy-3,6β-dimethoxy-17-methylmorphinan-6α-ol (21). A solution of **2** (18.00 g, 60 mmol) in CH_2Cl_2 (180 mL) and MeOH (450 mL) was cooled in an ice–salt bath below 5 °C and 30% H_2O_2 (18 mL, 210 mmol) was added followed by the dropwise addition of 5 N NaOH (6 mL). The mixture was stirred in the cold for 2 h and then poured into ice-cold brine (400 mL). The organic phase was separated and the aqueous phase was extracted twice with CH_2Cl_2. Evaporation of the organic phase gave 16.0 g of **21** as a foam, which was obtained as crystals (11.15 g, 54%), mp 193–195 °C, on boiling with MeOH. Recrystallization from MeOH gave pure **21** with mp 195–196.5 °C on rapid heating. With slow heating, a change in the crystal form was noted at about 155 °C: NMR δ 6.65 (sharp d, $J \approx 2$ Hz, 2 H, aromatic), 5.33 (br s, 1 H, OH), 4.55 (s, 1 H, H5), 3.90 (s, 3 H, 3-OCH_3), 3.53 (s, 3 H, 6β-OCH_3), 2.43 (NCH_3); mass spectrum, m/e 345 (35), 313 (100), 297 (79), 285 (73). Anal. ($C_{19}H_{23}NO_5$) C, H, N.

4,5α:7β,8β-Diepoxy-3-methoxy-17-methylmorphinan-6-one (22). A suspension of **21** (3.00 g, 8.7 mmol) in Ac_2O (50 mL) was stirred at ambient temperature for 3 h to yield a clear solution. The solution was evaporated under high vacuum below 40 °C, the residue was diluted with H_2O, concentrated NH_4OH was added, and the mixture was extracted with $CHCl_3$. Processing of the organic phases in the usual manner gave 2.76 g of a white crystalline solid. Crystallization from EtOAc gave **22** (1.84 g, 68%) as crystals: mp 194.5–196 °C (lit.[7] mp 199–200 °C); NMR δ 6.83 (s, 2 H, aromatic), 4.70 (s, 1 H, H5), 3.90 (s, OCH_3), 3.13 (s, 2 H), 3.03 (m, 2 H), 2.44 (s, NCH_3). Anal. ($C_{18}H_{19}NO_4$) C, H, N.

Recrystallization of **22** (800 mg, mp 194.5–196 °C) from MeOH gave 840 mg of **21**, mp sinters ~160 °C, melts 195.5–196.5 °C, whose NMR spectrum was identical with **21** obtained above.

4,5α:7β,8β-Diepoxy-3-methoxy-17-methylmorphinan-6α-ol (23). To a stirred suspension of $LiAlH_4$ (228 mg, 6 mmol) in freshly distilled THF (20 mL) was added a solution of **21** (1.04 g, 3 mmol) in THF (40 mL). The mixture was stirred for 20 min and then cooled. The excess hydride was destroyed by the sequential dropwise addition of H_2O (0.5 mL), 15% NaOH (0.5 mL), and H_2O (1.5 mL). After stirring for 20 min, the mixture was filtered through Celite and the filtrate was evaporated to dryness. The residue was dissolved in H_2O, concentrated NH_4OH was added, and the mixture was extracted with $CHCl_3$. Processing in the usual manner gave 1.02 g of **23** as a foam. Crystallization from Et_2O gave **23** (743 mg, 79%), mp 187–188.5 °C. Recrystallization from EtOH–Et_2O gave **23**, mp 188.5–190 °C (lit.[7] mp 189–190 °C).

Acknowledgment. The author is indebted to J. O. Polazzi and D. L. Leland for their advice and encouragement and to Dr. J. F. Howes, SISA, Inc., for the pharmacological results.