emptied by catheterization and the study was commenced by administration of compound or placebo. Compounds were given in gelatin capsules and the animals were maintained in metabolism cages for collection of spontaneously voided urine. Spontaneous urine was combined with bladder urine collected by catheterization at the end of 6 h. Urine volumes were measured, and aliquots were analyzed for sodium, potassium, and chloride content by standard methodology. Values are reported as geometric means.

**Oral Activity in SH Rat.** Antihypertensive activity was estimated in vivo in spontaneously hypertensive (SH) rats as described by Watson and Ludden.[23]

**Topical Rat Activity.** Female rats (Charles-River, 150–170 g) were maintained overnight on a sugar diet with water ad libitum. The substance was dissolved in a mixture of 70% ether, 25% pyridine, and 5% $H_2O$ such that each 0.2-mL aliquot contains the doese to be evaluated. At the time of the test, each animal was given 5 mL of $H_2O$ po and 0.2 mL of drug mixture in the vehicle topically to the shaved back. Warm air (using a hair dryer) was blown across the back for 1 min to evaporate moisture. Rats were housed in groups of three in metabolism cages. Urine was collected for 0 to 5 h and 5 to 24 h in graduated cylinders and was analyzed for sodium, potassium, and chloride content. Animals receiving placebo (vehicle) were run concurrently. Results were tabulated as milliequivalents (or milliliters) per cage and were the geometric means (±SE) of the number of cages for each dose level.

(23) Watson, L. S.; Ludden, C. T. In "New Antihypertensive Drugs"; Scriabine, A.; Sweet, C. S., Eds.; Spectrum Publications: Holliswood, N.Y., 1976; pp 87–96.

**Acknowledgment.** It is a pleasure to thank Dr. J. M. Sprague (retired), Dr. C. A. Stone, and Dr. R. Hirschmann for their guidance and encouragement throughout the course of this investigation. The authors are indebted to K. B. Streeter and Mrs. Jan Stranick for microanalyses, A. Augenblick for GLC analysis, Dr. D. W. Cochran for $^{13}C$ NMR spectra, and to W. R. McGaughran (retired) and Mrs. J. Murphy for the $^1H$ NMR spectra.

# Analgesic Narcotic Antagonists. 4.[1] 7-Methyl-*N*-(cycloalkylmethyl)-3-hydroxymorphinan-6-ones and -isomorphinan-6-ones

David L. Leland and Michael P. Kotick*

*Chemistry Department, Corporate Research Division, Miles Laboratories, Inc., Elkhart, Indiana 46515.*
*Received June 16, 1980*

3,6-Dimethoxy-7β,17-dimethyl-4-hydroxy-5,6,8,14-tetradehydromorphinan (**2**) was converted to the 4-deoxy compound **4** and hydrolyzed to a mixture of the B/C-cis (C series) and B/C-trans (T series) isomers of 7,8-didehydromorphinan-6-one, **5**. Hydrogenation of the separated isomers gave 7-methyl-6-oxo derivatives **6a**. 7,8-Dimethyl- (**6b**) or 7-methyl-8-ethylmorphinan-6-one (**6c**) was prepared by reaction of **5** with lithium organocuprates. The analgesic *N*-methyl compounds **6** were converted to 17-(cyclopropylmethyl) or 17-(cyclobutylmethyl) derivatives **10–13**. Some of these compounds had mixed profiles of narcotic agonist–antagonist effects. Studies with drug-dependent monkeys indicated that several of these compounds with an analgesic–antagonist ratio of less than 0.4 substitute for morphine.

The modification of opiate compounds continues to be an actively investigated area of medicinal chemistry. The goal of these studies is to prepare analgesic compounds, based on naturally occurring structures, which do not possess addiction liability and do not have other undesirable side effects. As part of our program directed toward this goal, we have studied the influence of alkyl groups in the 8 position of various *N*-(cycloalkylmethyl)morphinans.[2,3] During work to extend these studies, we unexpectedly found that thebaine (**1**) reacts with lithium dimethylcuprate to yield 7β-methyldihydrothebaine-φ (**2**).[4] This unique starting material offered entry into a series of 7-methyl- and 7-methyl-8-alkylmorphinan- and -isomorphinan-6-ones. These derivatives could be converted to potential mixed analgesic narcotic antagonists. This report concerns the results of our studies in this area.

**Chemistry.** It is recognized that 4-hydroxymorphinans are less potent analgesic agents than the corresponding 4-deoxy derivatives. Removal of this group from **2** was carried out in a manner analogous to that reported by Sawa and co-workers for dihydrothebaine-φ.[5] Compound **2** was converted to the 4-phenyl ether **3** by reaction with bromobenzene and cleaved to yield **4** by use of sodium in a liquid ammonia–toluene mixture (Scheme I).

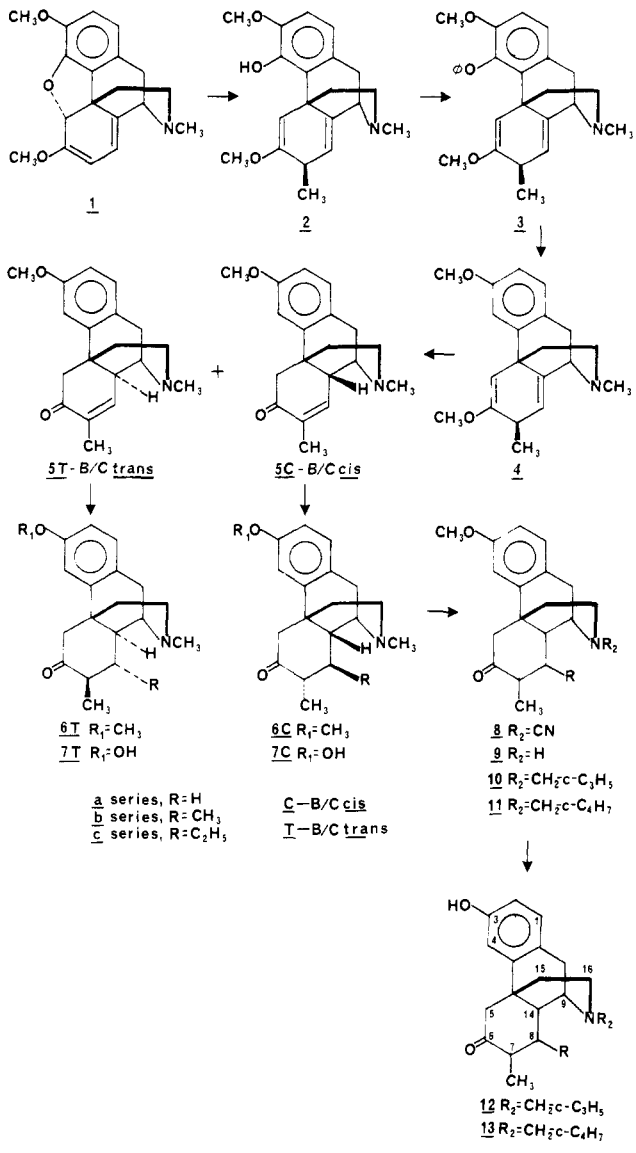
Various acidic conditions were investigated for hydrolysis of enol ether **4**. Treatment of **4** with hot 25% HCl gave an equimolar mixture of the B/C-cis and -trans isomers, **5C** and **5T**. On a preparative scale, 90% aqueous acetic acid produced an approximately 2:1 mixture of **5C** and **5T**. The separated isomers **5** were hydrogenated to give saturated compounds **6**. The assignment of stereochemistry to the B/C juncture in **6Ta** and **6Ca**, and thus in **5**, is based on the characteristic *m/e* 59 ion found in the mass spectral fragmentation pattern of ring C saturated B/C-cis isomers and by the relative abundance of the molecular ions (trans > cis).[6] In the spectrum of **6Ca**, *m/e* 59 was the base peak with a low observable $M^+$ peak; for **6Ta**, the molecular ion was usually the base peak. The 7-methyl group is assigned the more stable equatorial configuration[4] in each case.

Reaction of **5** with $Me_2CuLi$ proceeded smoothly to give good yields of the 7,8-dimethyl compounds, **6b**. In contrast, the reaction of **5** with $Et_2CuLi$ did not proceed in

(1) A portion of this work was previously presented. See Leland, D. L.; Kotick, M. P. In "Abstracts of Papers", 180th National Meeting of the American Chemical Society, Las Vegas, NV, August, 1980; American Chemical Society: Washington, D.C., 1980; Abstr MEDI 59.
(2) Kotick, M. P.; Leland, D. L.; Polazzi, J. O.; Schut, R. N. *J. Med. Chem.* **1980**, *23*, 166.
(3) Polazzi, J. O.; Schut, R. N.; Kotick, M. P.; Howes, J. F.; Osgood, P. F.; Razdan, R. K.; Villarreal, J. E. *J. Med. Chem.* **1980**, *23*, 174.
(4) Leland, D. L.; Polazzi, J. O.; Kotick, M. P. *J. Org. Chem.*, in press.
(5) Sawa, Y. K.; Tsuji, N.; Maeda, S. *Tetrahedron* **1961**, *15*, 154.
(6) Mandelbaum, A.; Ginsberg, D.; *Tetrahedron Lett.* **1965**, 2479. Inoue, H.; Takeda, M.; Kugita, H. *Chem. Pharm. Bull.* **1973**, *21*, 2004.

0022-2623/80/1823-1427$01.00/0 

Scheme I



a satisfactory manner, and mixtures which still contained substantial amounts of starting material were obtained. Lithium divinylcuprate reacted with **5** to yield a mixture of the 1,2 and desired 1,4 adducts. Hydrogenation of this mixture, followed by chromatography, gave the desired 8-ethyl compounds **6c** in low overall yield. These dialkylated products are assigned the diequatorial configuration in accord with results obtained in the 7-unsubstituted 8-alkyl series.[3]

Replacement of the *N*-methyl group with cycloalkylmethyl moieties was carried out by the cyanogen bromide–acid hydrolysis–alkylation sequence previously utilized. The *N*-(cycloalkylmethyl)-3-methoxy compounds **10** and **11** were demethylated by refluxing with HBr.

## Results and Discussion

The compounds prepared were tested for analgesia in the mouse writhing[7] and rat tail-flick assays. Narcotic antagonist activity was determined against an $ED_{80}$ of morphine by the modified rat tail-flick test as we have previously described.[2] The appropriate 7,8-dihydro-*N*-methyl or -*N*-(cycloalkylmethyl) compounds are included in the tables for comparative purposes.

Table I. Analgesic Activity

| compd | $ED_{50}$, μmol/kg, sc injectn (95% CL) mouse writhing | rat tail flick |
|---|---|---|
| 6C[a] | 1.72 (0.91-3.23) | 2.32 (1.89-2.84) |
| a | 0.50 (0.27-0.97) | 1.60 (8.61-37.0) |
| b | 2.16 (1.34-3.54) | 17.9 (8.61-37.0) |
| c | 0.49 (0.14-1.84) | 2.75 (1.95-5.11) |
| 6T | 5.54 (4.00-7.68) | >70 |
| a | 15.7 (12.0-20.5) | IA/33[b] |
| b | 3.72 (2.48-5.52) | IA/29 |
| c | 7.42 (3.84-14.8) | IA/27 |
| 7C | 0.52 (0.35-0.76) | 70 |
| a | 0.39 (0.21-0.88) | 1.82 (0.49-6.62) |
| b | 0.40 (0.20-0.83) | 12.4 (5.34-29.4) |
| c | 0.14 (0.05-0.35) | 1.50 (1.08-2.33) |
| 7T | 0.75 (0.49-1.14) | 1.33 (0.97-1.82) |
| a | 0.91 (0.60-1.51) | 1.09 (0.74-1.61) |
| b | 0.58 (0.37-0.97) | 0.68 (0.45-1.05) |
| c | 7.53 (6.19-9.18) | 7.45 (4.89-11.4) |
| codeine | 10.2 (2.7-40) | 75 (19-293) |
| morphine | 2.1 (1.1-4.0) | 19.3 (9.2-40.6) |
| dihydrocodeinone | 2.36 (1.56-3.60) | 5.2 (3.6-7.5) |
| dihydromorphinone | 0.25 (0.12-0.44) | 1.34 (1.18-1.52) |

[a] Compounds for which no suffix is indicated refer to the 7,8-unsubstituted compound. Data taken from ref 3. [b] IA, inactive at dose indicated.

Most of the *N*-methyl-3-methoxy and -3-hydroxy compounds **6** and **7** are potent analgesic agents (see Table I). In general, the introduction of a 7-methyl group, or a 7-methyl-8-short-alkyl group, does not substantially alter the analgesic potency of the parent 7,8-unsubstituted compounds. We limited the 8-alkyl substituent to methyl or ethyl to avoid the sharp drop in potency observed with longer alkyl groups at this position.[2]

For compounds which have a cycloalkylmethyl group on nitrogen, **10–13**, the introduction of alkyl groups in the C ring results in fluctuations in activity (see Table II). For the 3-methoxy compounds **10** and **11**, the analgesic activity decreases as the size of the 8 substituent is increased from hydrogen to methyl to ethyl. The same trend is noted in the 3-hydroxy B/C cis series, **12C** and **13C**. In the trans series, **12T** and **13T**, the 8-alkyl compounds are somewhat more potent analgesics than the reference 7,8-unsubstituted structures. In general, the cyclobutylmethyl compounds **11** and **13** are analgesic agents devoid of antagonist properties. For the *N*-(cyclopropylmethyl)-3-methoxy compounds **10C**, the introduction of a 7-methyl group causes a decrease in antagonist potency which is regained with a short alkyl group in the 8 position. In the corresponding trans series, **10T**, the 7-methyl group does not significantly alter antagonist activity. In this series, the 8-alkyl group causes a loss of antagonist properties. The same trend is evident in the *N*-(cyclopropylmethyl)-3-hydroxy series **12C**. For the trans series **12T**, antagonist activity observed for the 8-hydrogen and 8-methyl compounds is lost with an 8-ethyl group.

Three compounds of this series, **12Ca**, **12Ta**, and **13Cb**, had mixed agonist–antagonist properties within an appropriate potency range and were further studied in secondary pharmacological screens. Compound **12Ca** was studied in these systems as the more easily crystallizable tartrate salt, which had an analgesic $ED_{50}$ of 1.77 μmol/kg (1.25–2.52) and an antagonist $ED_{50}$ of 6.04 μmol/kg (0.80–45.8). This compound did not cause primary dependence or substitute for morphine in the rat infusion model.[8] Studies with morphine-dependent monkeys,[9]

(7) Whittle, B. A. *Br. J. Pharmacol.* **22**, 246 (1964).

(8) Teiger, D. T. *J. Pharmacol. Exp. Ther.* **1974**, *190*, 408.

Table II. Analgesic and Narcotic Antagonist Activity

| compd | $ED_{50}$, μmol/kg (95% CL) analgesic: mouse writhing, sc injectn | antagonist: rat tail flick, ip injectn | agonist/ antagonist |
|---|---|---|---|
| 10C[a] | 0.66 (0.19-2.37) | 14.9 | 0.04 |
| a | 1.60 (0.93-2.76) | 42.6 (10.1-1.79) | 0.04 |
| b | 2.64 (1.90-3.67) | 12.1 (7.31-19.8) | 0.22 |
| c | 8.04 (3.56-18.1) | 15.7 (7.87-31.4) | 0.51 |
| 10T | >25 | 3.60 (1.6-8.2) | |
| a | >40 | 3.19 (1.81-5.67) | |
| b | >26 | >26 | |
| c | >25 | >25 | |
| 11C | 0.58 (0.21-1.57) | IA[b]/25 | |
| a | 3.58 (2.28-6.51) | >25 | |
| b | 15.8 (11.9-21.3) | >25 | |
| c | 18.7 (12.8-27.0) | >24 | |
| 11T | 20.3 (10.7-38.4) | IA/30 | |
| a | 7.31 (2.44-21.3) | >38 | |
| b | >25 | >25 | |
| c | >25 | >25 | |
| 12C[c] | 3.28 (1.29-8.39) | 7.4 (4.1-13.2) | 0.44 |
| a | 2.40 (0.69-8.43) | 14.4 | 0.17 |
| b | 23.0 (12.4-42.4) | 0.35 (0.041-3.00) | 65 |
| c | >25 | 2.23 (0.64-7.74) | |
| 12T | 8.9[d] | 2.24 (1.06-4.71) | 4.0[e] |
| a | 1.77[d] (0.19-15.1) | 1.18 (0.47-3.05) | 1.5 |
| b | 4.50 (2.90-6.95) | 1.02 | 4.4 |
| c | >25 | >25 | |
| 13C | 0.047 (0.006-0.342) | IA/25 | |
| a | 0.35 (0.21-0.53) | >30 | |
| b | 2.21 (1.30-3.76) | 5.66 (0.67-47.5) | 0.40 |
| c | 8.19 (1.37-49.4) | 4.84 (0.97-24.1) | 1.7 |
| 13T | 2.6 (0.97-6.88) | 13.8 (5.0-38) | 0.20 |
| a | 0.93 (0.38-2.28) | >24 | |
| b | 0.79 (0.19-3.25) | >25 | |
| c | >25 | >25 | |
| butorphanol | 0.34 (0.13-0.90) | 2.0 (0.96-9.4) | 0.17 |
| cyclazocine | 0.41 (0.11-1.66) | 0.81 (0.48-1.44) | 0.50 |
| pentazocine | 12.9 (8.68-19.3) | 36.4 (13.6-100) | 0.36 |
| nalorphine | 3.51 (0.58-21.4) | 2.47 (0.46-13.5) | 1.42 |
| naloxone | IA | 0.11 (0.03-0.30) | |

[a] Compounds for which no suffix is indicated refer to the 7,8-unsubstituted compound. Data taken from ref 3. [b] IA, inactive at dose indicated. [c] The secondary pharmacology of this compound has been reported. See ref 11. [d] Short duration, $ED_{50}$ at 5 min. [e] Based on analgesic $ED_{50}$ at 5 min.

however, indicated partial substitution effects. The corresponding 7,8-unsubstituted compound, **12C**, has been reported to cause precipitated withdrawal in the same system.[10]

The isomeric trans compound, **12Ta**, is a short-acting analgesic with narcotic antagonist properties in the mouse and rat systems.

In morphine-dependent monkeys,[9] **12Ta** promptly precipitated dose-related withdrawal signs and further exacerbated withdrawal in the dose range of 0.25–1.0 mg/kg. The 7,8-dimethyl-*N*-(cyclobutylmethyl) compound **13Cb** completely substituted for morphine in monkeys. The corresponding 7-unsubstituted-8β-methyl compound was reported previously[3] to partially substitute for morphine in the monkey.[10]

The analgesic–antagonist ratios observed in the mouse and rat for **12Ca**·tartrate, **12Ta**, and **13Cb** (0.3, 1.5, 0.4 respectively), combined with our previously reported ratios for *N*-(cyclopropylmethyl)-8β-ethyl-4,5α-epoxy-3-methoxymorphinan-6-one (2.7, does not substitute for morphine)[2] and *N*-(cyclobutylmethyl)-8β-methyl-3-hydroxymorphinan-6-one (0.1, partial substitution),[3] indicate that compounds with a ratio of less than 0.4 in our assays may substitute for morphine in drug-dependent monkeys. However, the report[10] that the 7,8-unsubstituted **12C** (ratio 0.44) does precipitate a dose-related withdrawal syndrome places a limitation on this theory. Studies aimed at the prediction of monkey substitution liability from our readily available mouse and rat test data continues.

Our previous work with 8-alkyl-*N*-(cycloalkylmethyl)-morphinan-6-ones[2,3] indicated that the 8-substituent tended to modify the narcotic antagonist component of action. The results obtained in the present study do not allow a firm statement to be made regarding the effect on the pharmacology of 7-methyl or 7-methyl-8-lower-alkyl groups in the C ring of the morphinan nucleus. Our studies aimed at clarifying the effect of ring C modifications of opiate derivatives on pharmacological profiles are continuing.

## Experimental Section

Methods have previously been described.[2] For pharmacological testing, compounds which were prepared as salts were administered in distilled $H_2O$; free bases were dissolved by the dropwise addition of 1 N HCl and then further diluted. NMR spectra were recorded in $CDCl_3$. Mass spectra (MS) were determined using a Helwitt-Packard 5985A GC/MS system and are reported as *m/e* (relative intensity). Column chromatography was carried out over silica gel G using the indicated $CHCl_3$–MeOH–concentrated

(9) We are indebted to the Committee on Problems of Drug Dependence for these studies. Aceto, M. D.; Harris, L. S.; Dewey, W. L.; May, E. L. *NIDA Res. Monogr.* **1980**, *no. 28*, in press.
(10) Aceto, M. D.; Harris, L. S.; Dewey, W. L.; May, E. L. *NIDA Res. Monogr.* **1979**, *no. 27*, 336.
(11) Hirose, K.; Matsushita, A.; Kojima, Y.; Eigyo, M.; Joyama, H.; Shiomi, T.; Tsukinoki, Y.; Hatakeyama, H.; Matsubara, K.; Kawasaki, K. *Arch. Int. Pharmacodyn. Ther.* **1979**, *241*, 79.

$NH_4OH$ (v/v/%) mixtures as eluents. Where analyses are indicated only by symbols of elements, the analytical results obtained for those elements were within ±0.4% of the theoretical values.

**3,6-Dimethoxy-7β,17-dimethyl-4-phenoxy-5,6,8,14-tetradehydromorphinan (3).** Chloroform was removed from 2·$CHCl_3$ (18.80 g, 42 mmol) by azeotropic distillation several times with pyridine, and the residue was then dissolved in pyridine (100 mL). To this solution was added $C_6H_5Br$ (4.90 mL, 46 mmol), powdered $K_2CO_3$ (6.40 g, 46 mmol), and 40 μ Cu powder (1.34 g, 21 mmol), and the resulting mixture was refluxed under argon for 48 h. The solution was filtered while hot, the insoluble material was washed with warm pyridine, and the filtrate was evaporated to dryness. The residue was dissolved in $C_6H_6$, treated with charcoal, and evaporated to a crystalline residue. Crystallization from EtOAc gave 14.33 g (85%) of **3** as tan needles, mp 177–178 °C. Recrystallization from EtOAc gave analytically pure **3**: mp 177–178 °C; NMR δ 7.43–6.67 (m, 7, aromatic), 4.47 (m, 2, H-5 and H-8), 3.60 (3-$OCH_3$), 3.03 (6-$OCH_3$), 2.42 (N-$CH_3$), 1.17 (d, 3, 7-$CH_3$, $J$ = 7 Hz). Anal. ($C_{26}H_{29}NO_3$) C, H, N.

**3,6-Dimethoxy-7β,17-dimethyl-5,6,8,14-tetradehydromorphinan (4).** To liquid $NH_3$ (500 mL) at −78 °C was added dropwise a solution of **3** (17.20 g, 43 mmol) in toluene (150 mL). To the stirred biphasic system was added Na (2.94 g, 0.128 g-atoms) and the resulting blue solution was stirred at −78 °C for 1 h. Excess $NH_4Cl$ was added to quench the blue color, and the $NH_3$ was allowed to evaporate at room temperature. The residual suspension was diluted with 5% NaOH and extracted three times with $Et_2O$. Evaporation of the dried organic phase gave **4** as a tan syrup: NMR δ 7.17–6.53 (m, 3, aromatic), 5.47 (d, 1, H-8, $J_{7,8}$ = 4 Hz), 5.10 (s, 1, H-5), 3.78, 3.65, 2.43 (singlets), 1.23 (d, 3, 7-$CH_3$, $J$ = 7 Hz).

**7,8-Didehydro-7,17-dimethyl-3-methoxymorphinan-6-one (5C) and 7,8-Didehydro-7,17-dimethyl-3-methoxyisomorphinan-6-one (5T).** A solution of **4** (2.70 g) in 25% HCl (15 mL) was heated at 90–100 °C (preheated oil bath) for 1 h. The cooled solution was made basic by the addition of concentrated $NH_4OH$ and extracted three times with $CHCl_3$. The $CHCl_3$ extracts were evaporated to give a foam, which was chromatographed (10:1). The first major fraction gave 0.89 g (35%) of crystalline material, which was recrystallized from $Et_2O$–EtOAc to give pure **5T**: mp 118.5–120 °C; NMR δ 7.27–6.67 (m, 4, aromatic and H-8), 3.80, 2.40 (singlets), 1.90 (m, 3, 7-$CH_3$). Anal. ($C_{19}H_{23}NO_2$) C, H, N.

The second major fraction gave 0.93 g (36%) of **5C**, which was recrystallized from EtOAc to give an analytical sample of **5C**: mp 148–150 °C; NMR δ 7.11–6.32 (4 H), 3.75, 2.45 (singlets), 1.58 (m, 3, 7-$CH_3$). Anal. ($C_{19}H_{23}NO_2$) C, H, N.

**7α,17-Dimethyl-3-methoxymorphinan-6-one (6Ca).** Compound **5C** (10.0 g) was hydrogenated at an initial pressure of 50 psi over 10% Pd/C (1.0 g) in 95% EtOH (250 mL) containing concentrated HCl (0.5 mL) for 3 h. After the catalyst was removed, the filtrate was evaporated to a small volume and partitioned between dilute $NH_4OH$ and $CHCl_3$. Evaporation of the $CHCl_3$ gave a crystalline residue, which was recrystallized from EtOAc–$Et_2O$ to give 6.90 g (69%) of pure **6Ca**: mp 148.5–150 °C; NMR δ 0.87 (d, 3, 7-$CH_3$, $J$ = 7 Hz); MS, $m/e$ (relative intensity) 299 (25), 242 (11), 171 (21), 128 (17), 115 (17), 59 (100). Anal. ($C_{19}H_{25}NO_2$) C, H. N.

**7β,17-Dimethyl-3-methoxyisomorphinan-6-one (6Ta).** A solution of **5T** (10.8 g, 36.3 mmol) in 95% EtOH (250 mL) containing concentrated HCl (0.5 mL) was hydrogenated over 10% Pd/C (1.0 g) at 50 psi. Workup as above gave a crystalline residue, which was recrystallized from EtOAc to give 8.7 g (81%) of **6Ta** as white needles: mp 175–176.5 °C; NMR δ 1.08 (d, 3, 7-$CH_3$, $J$ = 6 Hz); MS, $m/e$ (relative intensity) 299 (100), 256 (60), 228 (68), 178 (75), 122 (40), 59 (0.7).

**3-Methoxy-7α,8β,17-trimethylmorphinan-6-one (6Cb).** To a solution of $Me_2CuLi$ (63 mmol) prepared in ether (400 mL), under argon at ice–salt bath temperature, was added **5C** (15.0 g, 50 mmol) in warm $C_6H_6$ (350 mL) rapidly in a thin stream. The cooling bath was removed and the reaction mixture was stirred at ambient temperature for 1 h. Workup in the usual manner gave a residue, which was crystallized from $Et_2O$–EtOAc to give 5.83 g of **6Cb**. Chromatography of the mother liquors gave an additional 7.29 g (83% overall yield) of crystalline **6Cb**. Recrystallization from $Et_2O$ gave analytically pure **6Cb**: mp 101–102 °C; NMR δ 7.07–6.15 (aromatic), 3.77, 2.47 (singlets), 1.08 (unsymmetrical d, 3, 8-$CH_3$), 0.88 (d, 3, 7-$CH_3$). Anal. ($C_{20}H_{27}NO_2$) C, H, N.

**3-Methoxy-7β,8α,17-trimethylisomorphinan-6-one (6Tb).** To a solution of $Me_2CuLi$ (6.3 mmol) in $Et_2O$ (75 mL) was added compound **5T** (1.50 g, 5 mmol) in $C_6H_6$ (75 mL). After 1 h at 0 °C, workup in the usual manner followed by column chromatography gave 1.35 g (86%) of **6Tb** as a foam: NMR δ 1.13 (d, 7- and 8-$CH_3$, $J$ = 6 Hz). This was converted to the HCl salt, which crystallized from EtOH–EtOAc to give pure **6Tb**·HCl, mp >265 °C. Anal. ($C_{20}H_{27}NO_2$·HCl) C, H, N.

**7α,17-Dimethyl-8β-ethyl-3-methoxymorphinan-6-one (6Cc).** Vinyllithium was prepared at −78 °C under argon by stirring vinyl bromide (3.0 mL, 42 mmol) with *tert*-butyllithium (63 mL of 1.35 M solution in pentane) for 1 h. The resulting suspension was transferred to a suspension of CuI (4.00 g, 21 mmol) in $Et_2O$ (100 mL) kept at −78 °C. The mixture was allowed to warm to −40 °C and, while maintaining this temperature, a solution of **5C** (5.00 g, 17 mmol) in $CH_2Cl_2$ (100 mL) was added rapidly dropwise. After stirring for 15 min at −40 °C, the mixture was allowed to warm to 20 °C and processed in the usual manner. Evaporation gave a residue which showed two major spots by TLC for the 1,2- and 1,4-addition products. The residue was dissolved in 95% EtOH (250 mL) and concentrated HCl (0.5 mL) and 10% Pd/C (1.0 g) was added, and the mixture was hydrogenated at 50 psi for 4 h. After the catalyst was removed, the filtrate was evaporated to a small volume and partitioned between dilute $NH_4OH$ and $CHCl_3$. The $CHCl_3$ solution was evaporated to dryness and the residue chromatographed (15:1:0.5). Fractions containing the desired 1,4 product were pooled to give 2.29 g of **6Cc** as a glass. The glass was converted to the HCl salt which was obtained as a foam for analysis. Anal. ($C_{21}H_{29}NO_2$·HCl) C, H, N.

**7β,17-Dimethyl-8α-ethyl-3-methoxyisomorphinan-6-one (6Tc).** Vinyllithium (42 mmol) was prepared in $Et_2O$ (60 mL) as above and added to a −78 °C suspension of CuI (21 mmol) in $Et_2O$ (100 mL). The mixture was allowed to warm to −40 °C and a solution of **5T** (5.0 g, 16.8 mmol) in $CH_2Cl_2$ (100 mL) was added dropwise. The reaction mixture was kept at −40 °C for 15 min and then allowed to warm to room temperature. Workup gave a foam which consisted of two major spots by TLC for the 1,2 and 1,4 adducts. The foam was dissolved in 95% EtOH (250 mL) and concentrated HCl (0.5 mL) and 10% Pd/C (1.0 g) was added, and the mixture was hydrogenated at 50 psi for 8 h. Processing followed by chromatography gave 1.57 g (28%) of **6Tc** as a foam. This foam was converted to the HCl salt, which crystallized from MeOH–EtOAc to give pure **6Tc**·HCl, mp 249–250 °C dec. Anal. ($C_{21}H_{29}NO_2$·HCl) C, H, N.

**7α,17-Dimethyl-3-hydroxymorphinan-6-one (7Ca).** Compound **6Ca** (1.03 g) and 48% HBr (10 mL) were refluxed in a preheated oil bath (140 °C) for 10 min. The cooled solution was made basic by the addition of concentrated $NH_4OH$ and extracted twice with $CHCl_3$. The combined $CHCl_3$ solutions were extracted twice with 5% NaOH, and these extracts were then saturated with $CO_2$ gas and extracted twice with $CHCl_3$. Evaporation of the organic phase gave 0.35 g (36%) of crystalline **10**, which was recrystallized from EtOH to give pure material, mp 278–281 °C. Anal. ($C_{18}H_{23}NO_2$) C, H, N.

Prepared in the same manner were **7Cb** [91%, mp 203–205 °C (EtOAc). Anal. ($C_{19}H_{25}NO_2$) C, H, N] and **7Cc** [51%, mp 214–216 °C (95% EtOH). Anal. ($C_{20}H_{27}NO_2$) C, H, N].

**7β,17-Dimethyl-3-hydroxyisomorphinan-6-one (7Ta).** A mixture of **6Ta** (680 mg) and 48% HBr (15 mL) was refluxed for 15 min. The cooled solution was diluted with water, made basic by the addition of concentrated $NH_4OH$, and extracted with three portions of $CHCl_3$. The $CHCl_3$ extracts were backwashed, dried, filtered, and evaporated to give 596 mg (91%) of **6Ta**, which crystallized from EtOAc–$Et_2O$ to give off-white crystals, mp 188–190 °C. Anal. ($C_{18}H_{23}NO_2$) C, H, N.

**3-Hydroxy-7β,8α,17-trimethylisomorphinan-6-one Hydrobromide (7Tb).** The methoxy compound **6Tb** (950 mg) and 48% HBr (5 mL) was refluxed for 15 min. When the mixture cooled, crystals separated which were collected to give 777 mg (86%) of **7Tb**·HBr. Crystallization from aqueous EtOH gave pure **7Tb**·HBr, mp >275 °C. Anal. ($C_{19}H_{25}NO_2$·HBr) C, H, N. In the same manner, **6Tc** gave a 62% yield of **7Tc**, mp >265 °C (aqueous

Table III. 17-(Cycloalkylmethyl)-7-methyl- and 7-Methyl-8-alkyl-3-methoxymorphinan-6-one (10 and 11)

| no. | R | $R_2$ | yield, %, of free base[a] | recrystn solvent, HCl salt[b] | HCl salt mp, °C | formula[c] |
|---|---|---|---|---|---|---|
| 10Ca | H | $CH_2$-c-$C_3H_5$ | 66 | M-EA | >265 | $C_{22}H_{29}NO_2 \cdot HCl$ |
| b | $CH_3$ | $CH_2$-c-$C_3H_5$ | 32 | foam | | $C_{23}H_{31}NO_2 \cdot HCl$ |
| c | $CH_2CH_3$ | $CH_2$-c-$C_3H_5$ | 47 | M-EA | 124-130 | $C_{24}H_{33}NO_2 \cdot HCl$ |
| 10Ta | H | $CH_2$-c-$C_3H_5$ | 52[d] | M-EA | 174.5-177 | $C_{22}H_{29}NO_2 \cdot HCl$ |
| b | $CH_3$ | $CH_2$-c-$C_3H_5$ | 71[d] | M-EA | >265 | $C_{23}H_{31}NO_2 \cdot HCl$ |
| c | $CH_2CH_3$ | $CH_2$-c-$C_3H_5$ | 90 | M-EA | >270 | $C_{24}H_{33}NO_2 \cdot HCl$ |
| 11Ca | H | $CH_2$-c-$C_4H_7$ | 79 | M-EA | >275 | $C_{23}H_{31}NO_2 \cdot HCl$ |
| b | $CH_3$ | $CH_2$-c-$C_4H_7$ | 78 | M-EA | 215-218 | $C_{24}H_{33}NO_2 \cdot HCl$ |
| c | $CH_2CH_3$ | $CH_2$-c-$C_4H_7$ | 59 | foam | | $C_{25}H_{35}NO_2 \cdot HCl$ |
| 11Ta | H | $CH_2$-c-$C_4H_7$ | 88 | M-EA | 270-275 | $C_{23}H_{31}NO_2 \cdot HCl$ |
| b | $CH_3$ | $CH_2$-c-$C_4H_7$ | 86 | M-EA | >265 | $C_{24}H_{33}NO_2 \cdot HCl$ |
| c | $CH_2CH_3$ | $CH_2$-c-$C_4H_7$ | 85 | M-EA | >265 | $C_{25}H_{35}NO_2 \cdot HCl$ |

[a] Yield of purified free base after chromatography. [b] M = methanol; EA = ethyl acetate. [c] Compounds had C, H, and N analysis within ±0.4% of the calculated value. [d] Not chromatographed. Converted directly to HCl salt. Shows yield of HCl salt.

EtOH). Anal. ($C_{20}H_{27}NO_2 \cdot HBr$) C, H, N.

**Preparation of *N*-Cyano Derivatives 8.** These compounds were prepared as previously described.[2] In the case of the trans series **8T**, an additional 1–2 h at reflux was required for completion of the reaction. These compounds, and the nor bases obtained below, were not further characterized but used directly in the next reactions. **8Ca**: 71% yield as crystals; mp 188–192 °C, from EtOH. **8Cb**: 75% yield; mp 159–161.5 °C (EtOH). **8Cc**: 86% yield; as a foam after evaporation from EtOH. **8Ta** was obtained as crystals in 66% yield. **8Tb** and **8Tc** were obtained as foams, after chromatography, in yields of 45 and 52%, respectively.

**Preparation of Nor Bases 9.** Hydrolysis was carried out in 2 N HCl at reflux as previously described.[2] Hydrolysis of **8C** was complete in 5–6 h, while **8T** required 18–24 h. **9Ca**·HCl was obtained as a foam, homogeneous by TLC, in quantitative yield. **9Cb**·HCl was obtained as crystals, mp 235–240 °C, in 61% yield on trituration with EtOH. Likewise, **9Cc**·HCl, mp >265 °C, in 63% yield. The free bases of **9T** were obtained in nearly quantitative yield as foams, pure enough for further reaction, after the addition of excess $NH_4OH$ and extraction with $CHCl_3$.

**17-(Cycloalkylmethyl)-7-methyl- and 7-Methyl-8-alkyl-3-methoxymorphinan-6-one (10 and 11).** A mixture of **9** (free base or HCl salt) in DMF (1 g/10 mL) containing $NaHCO_3$ (2.2 equiv) and cycloalkylmethyl bromide (1.5 equiv) was heated at 100 °C under argon for 16–22 h. The cooled mixture was filtered to remove insolubles and the filtrate was evaporated using an oil pump. The residue was dissolved in $H_2O$, adjusted to pH 10–11 with concentrated $NH_4OH$, and extracted with three portions of $C_6H_6$ or toluene. The organic layer was processed in the usual fashion and the residue chromatographed. Pure fractions were combined and the product crystallized as the free base or HCl salt. See Table III.

**17-(Cycloalkylmethyl)-7-methylmorphinan-6-ones (12 and 13).** The 3-methoxy compound **10** or **11** (salt or free base) in concentrated HBr (1.0 g/15 mL) was refluxed in a preheated oil bath (~140 °C) for 10 to 20 min. The solution was cooled, diluted with $NH_4OH$, and extracted three times with $CHCl_3$. After removal of the solvent, the residue was processed as described. **12Ca** was obtained as a glass in 43% yield after chromatography. The HCl salt, **12Ca**·HCl, mp 217–220 °C dec, crystallized from MeOH. Anal. ($C_{21}H_{27}NO_2 \cdot HCl$) C, H, N. **12Cb** was twice chromatographed to give a 26% yield of a white foam. Anal. ($C_{22}H_{29}NO_2$) H, N; C: calcd, 77.84; found, 76.82. **12Cc** was obtained as a foam in 46% yield after chromatography. The HCl salt also obtained as a foam. Anal. ($C_{23}H_{31}NO_2 \cdot HCl$) C, H, N. **12Ta**, after reflux, on cooling gave 73% of the crystalline HBr salt, mp >265 °C, which was recrystallized from EtOH. Anal. ($C_{21}H_{27}NO_2 \cdot HBr$) C, H, N. **12Tb** was obtained in the same manner as the crystalline HBr salt, mp >270 °C, in 76% yield. Anal. ($C_{23}H_{31}NO_2 \cdot HBr$) C, H, N. **12Tc** was obtained in 42% yield after chromatography and converted to the HCl salt. Recrystallization from MeOH–EtOAc gave pure **12Tc**, mp >270 °C. Anal. ($C_{23}H_{31}NO_2 \cdot HCl$) C, H, N.

**13Ca** was obtained as crystals by evaporation of the $CHCl_3$ extracts. Recrystallization from $CHCl_3$ gave 71% of the $CHCl_3$ solvate. Recrystallization from MeOH gave solvent-free **13Ca**, mp 175–177 °C. Anal. ($C_{22}H_{29}NO_2$) C, H, N. **13Cb** was obtained as a foam in 76% yield after chromatography. Anal. ($C_{23}H_{31}NO_2$) C, H, N. **13Cc** was obtained as a foam from the $CHCl_3$ extracts. Crystallization from EtOH gave 79% of the EtOH solvate. Drying gave **13Cc** as the 0.75EtOH solvate, mp 120–122 °C. Anal. ($C_{24}H_{33}NO_2 \cdot 0.75EtOH$) C, H, N. **13Ta** was obtained as crystals in 85% yield upon cooling of the reaction mixture. Recrystallization from EtOH gave **13Ta**·HBr, mp >265 °C. Anal. ($C_{22}H_{29}NO_2 \cdot HBr$) C, H, N. **13Tb** was obtained as a foam in 69% yield after chromatography. The HCl salt, mp >265 °C, crystallized from EtOH. Anal. ($C_{23}H_{31}NO_2 \cdot HCl$) C, H, N. **13Tc** was obtained in 43% yield after chromatography. The HCl salt, mp >270 °C, was crystallized from MeOH–EtOAc. Anal. ($C_{24}H_{33}NO_2 \cdot HCl$) C, H, N.

**Acknowledgment.** The authors thank J. O. Polazzi and Drs. R. N. Schut and J. E. Villarreal for the continued interest and encouragement. The authors are indebted to Drs. Howes, Osgood, and Razdan, SISA, Inc., Cambridge, MA, for the analgesic and antagonist data. We also thank the Committee on Problems of Drug Dependence, Dr. A. E. Jacobson, Biological Coordinator, for the results of the monkey studies.