

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% H₂O such that each 0.2-mL aliquot contains

the dose to be evaluated. At the time of the test, each animal was given 5 mL of H₂O 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 (\pm SE) of the number of cages for each dose level.

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 ¹³C NMR spectra, and to W. R. McGaughan (retired) and Mrs. J. Murphy for the ¹H NMR spectra.

(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.

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-7 β ,17-dimethyl-4-hydroxy-5,6,8,14-tetrahydromorphinan (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 7 β -methyl-dihydrothebaine- 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).

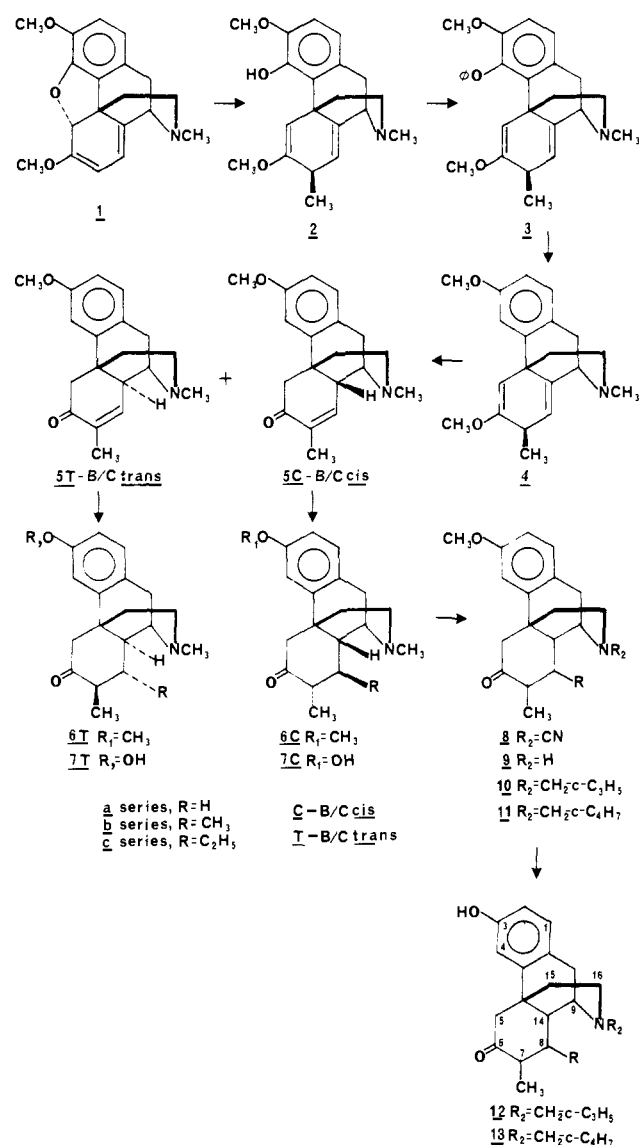
Various acidic conditions were investigated for hydrolysis of enol ether 4. Treatment of 4 with hot 25% HCl gave an equimolar mixture of the B/C-cis and -trans isomers, 5C and 5T. On a preparative scale, 90% aqueous acetic acid produced an approximately 2:1 mixture of 5C and 5T. The separated isomers 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 configuration⁴ in each case.

Reaction of 5 with Me₂CuLi proceeded smoothly to give good yields of the 7,8-dimethyl compounds, 6b. In contrast, the reaction of 5 with Et₂CuLi 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.

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 writhing⁷ and rat tail-flick assays. Narcotic antagonist activity was determined against an ED₈₀ 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) |
| dihydro-codeinone | 2.36 (1.56-3.60) | 5.2 (3.6-7.5) |
| dihydro-morphinone | 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 ED₅₀ of 1.77 μmol/kg (1.25-2.52) and an antagonist ED₅₀ 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, ED₅₀ at 5 min. ^e Based on analgesic ED₅₀ 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 previously³ 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 mor-

phine)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 report¹⁰ 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 H₂O; free bases were dissolved by the dropwise addition of 1 N HCl and then further diluted. NMR spectra were recorded in CDCl₃. Mass spectra (MS) were determined using a Hewlett-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 CHCl₃-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.

NH₄OH (v/v/%) mixtures as eluents. Where analyses are indicated only by symbols of elements, the analytical results obtained for those elements were within $\pm 0.4\%$ of the theoretical values.

3,6-Dimethoxy-7 β ,17-dimethyl-4-phenoxy-5,6,8,14-tetrahydro-morphinan (3). Chloroform was removed from 2-CHCl₃ (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 C₆H₅Br (4.90 mL, 46 mmol), powdered K₂CO₃ (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 C₆H₆, 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-OCH₃), 3.03 (6-OCH₃), 2.42 (N-CH₃), 1.17 (d, 3, 7-CH₃, J = 7 Hz). Anal. (C₂₆H₂₉NO₂) C, H, N.

3,6-Dimethoxy-7 β ,17-dimethyl-5,6,8,14-tetrahydro-morphinan (4). To liquid NH₃ (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 NH₄Cl was added to quench the blue color, and the NH₃ was allowed to evaporate at room temperature. The residual suspension was diluted with 5% NaOH and extracted three times with Et₂O. 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-CH₃, 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 NH₄OH and extracted three times with CHCl₃. The CHCl₃ 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 Et₂O–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-CH₃). Anal. (C₁₉H₂₃NO₂) 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-CH₃). Anal. (C₁₉H₂₃NO₂) C, H, N.

7 α ,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 NH₄OH and CHCl₃. Evaporation of the CHCl₃ gave a crystalline residue, which was recrystallized from EtOAc–Et₂O to give 6.90 g (69%) of pure 6Ca: mp 148.5–150 °C; NMR δ 0.87 (d, 3, 7-CH₃, J = 7 Hz); MS, m/e (relative intensity) 299 (25), 242 (11), 171 (21), 128 (17), 115 (17), 59 (100). Anal. (C₁₉H₂₅NO₂) C, H, N.

7 β ,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-CH₃, J = 6 Hz); MS, m/e (relative intensity) 299 (100), 256 (60), 228 (68), 178 (75), 122 (40), 59 (0.7).

3-Methoxy-7 α ,8 β ,17-trimethylmorphinan-6-one (6Cb). To a solution of Me₂CuLi (63 mmol) prepared in ether (400 mL), under argon at ice-salt bath temperature, was added 5C (15.0 g, 50 mmol) in warm C₆H₆ (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 Et₂O–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. Re-

crystallization from Et₂O 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-CH₃), 0.88 (d, 3, 7-CH₃). Anal. (C₂₀H₂₇NO₂) C, H, N.

3-Methoxy-7 β ,8 α ,17-trimethylisomorphinan-6-one (6Tb). To a solution of Me₂CuLi (6.3 mmol) in Et₂O (75 mL) was added compound 5T (1.50 g, 5 mmol) in C₆H₆ (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-CH₃, J = 6 Hz). This was converted to the HCl salt, which crystallized from EtOH–EtOAc to give pure 6Tb·HCl, mp >265 °C. Anal. (C₂₀H₂₇NO₂·HCl) C, H, N.

7 α ,17-Dimethyl-8 β -ethyl-3-methoxymorphinan-6-one (6Cc). Vinylolithium 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 Et₂O (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 CH₂Cl₂ (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 NH₄OH and CHCl₃. The CHCl₃ 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. (C₂₁H₂₉NO₂·HCl) C, H, N.

7 β ,17-Dimethyl-8 α -ethyl-3-methoxyisomorphinan-6-one (6Tc). Vinylolithium (42 mmol) was prepared in Et₂O (60 mL) as above and added to a -78 °C suspension of CuI (21 mmol) in Et₂O (100 mL). The mixture was allowed to warm to -40 °C and a solution of 5T (5.0 g, 16.8 mmol) in CH₂Cl₂ (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. (C₂₁H₂₉NO₂·HCl) C, H, N.

7 α ,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 NH₄OH and extracted twice with CHCl₃. The combined CHCl₃ solutions were extracted twice with 5% NaOH, and these extracts were then saturated with CO₂ gas and extracted twice with CHCl₃. 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. (C₁₈H₂₃NO₂) C, H, N.

Prepared in the same manner were 7Cb [91%, mp 203–205 °C (EtOAc). Anal. (C₁₉H₂₅NO₂) C, H, N] and 7Cc [51%, mp 214–216 °C (95% EtOH). Anal. (C₂₀H₂₇NO₂) C, H, N].

7 β ,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 NH₄OH, and extracted with three portions of CHCl₃. The CHCl₃ extracts were backwashed, dried, filtered, and evaporated to give 596 mg (91%) of 6Ta, which crystallized from EtOAc–Et₂O to give off-white crystals, mp 188–190 °C. Anal. (C₁₈H₂₃NO₂) C, H, N.

3-Hydroxy-7 β ,8 α ,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. (C₁₉H₂₅NO₂·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 ₃ H ₇ | 66 | M-EA | > 265 | C ₂₂ H ₂₉ NO ₂ ·HCl |
| b | CH ₃ | CH ₂ -c-C ₃ H ₇ | 32 | foam | | C ₂₃ H ₃₁ NO ₂ ·HCl |
| c | CH ₂ CH ₃ | CH ₂ -c-C ₃ H ₇ | 47 | M-EA | 124-130 | C ₂₄ H ₃₃ NO ₂ ·HCl |
| 10Ta | H | CH ₂ -c-C ₃ H ₇ | 52 ^d | M-EA | 174.5-177 | C ₂₂ H ₂₉ NO ₂ ·HCl |
| b | CH ₃ | CH ₂ -c-C ₃ H ₇ | 71 ^d | M-EA | > 265 | C ₂₃ H ₃₁ NO ₂ ·HCl |
| c | CH ₂ CH ₃ | CH ₂ -c-C ₃ H ₇ | 90 | M-EA | > 270 | C ₂₄ H ₃₃ NO ₂ ·HCl |
| 11Ca | H | CH ₂ -c-C ₄ H ₉ | 79 | M-EA | > 275 | C ₂₃ H ₃₁ NO ₂ ·HCl |
| b | CH ₃ | CH ₂ -c-C ₄ H ₉ | 78 | M-EA | 215-218 | C ₂₄ H ₃₃ NO ₂ ·HCl |
| c | CH ₂ CH ₃ | CH ₂ -c-C ₄ H ₉ | 59 | foam | | C ₂₅ H ₃₅ NO ₂ ·HCl |
| 11Ta | H | CH ₂ -c-C ₄ H ₉ | 88 | M-EA | 270-275 | C ₂₃ H ₃₁ NO ₂ ·HCl |
| b | CH ₃ | CH ₂ -c-C ₄ H ₉ | 86 | M-EA | > 265 | C ₂₄ H ₃₃ NO ₂ ·HCl |
| c | CH ₂ CH ₃ | CH ₂ -c-C ₄ H ₉ | 85 | M-EA | > 265 | C ₂₅ H ₃₅ NO ₂ ·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. (C₂₀H₂₇NO₂·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 NH₄OH and extraction with CHCl₃.

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 NaHCO₃ (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 H₂O, adjusted to pH 10-11 with concentrated NH₄OH, and extracted with three portions of C₆H₆ 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 NH₄OH, and extracted three times with CHCl₃. 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. (C₂₁H₂₇NO₂·HCl) C, H, N. 12Cb was twice chromatographed to give a 26% yield of a white foam. Anal. (C₂₂H₂₉NO₂) 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. (C₂₃H₃₁NO₂·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. (C₂₂H₂₇NO₂·HBr) C, H, N. 12Tb was obtained in the same manner as the crystalline HBr salt, mp >270 °C, in 76% yield. Anal. (C₂₃H₃₁NO₂·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. (C₂₃H₃₁NO₂·HCl) C, H, N.

13Ca was obtained as crystals by evaporation of the CHCl₃ extracts. Recrystallization from CHCl₃ gave 71% of the CHCl₃ solvate. Recrystallization from MeOH gave solvent-free 13Ca, mp 175-177 °C. Anal. (C₂₂H₂₉NO₂) C, H, N. 13Cb was obtained as a foam in 76% yield after chromatography. Anal. (C₂₃H₃₁NO₂) C, H, N. 13Cc was obtained as a foam from the CHCl₃ extracts. Crystallization from EtOH gave 79% of the EtOH solvate. Drying gave 13Cc as the 0.75EtOH solvate, mp 120-122 °C. Anal. (C₂₄H₃₃NO₂·0.75EtOH) 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. (C₂₂H₂₉NO₂·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. (C₂₃H₃₁NO₂·HCl) C, H, N. 13Tc was obtained in 43% yield after chromatography. The HCl salt, mp >270 °C, was crystallized from MeOH-EtOAc. Anal. (C₂₄H₃₃NO₂·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.