tensity). All organic layers after extractions were dried with Na_2SO_4. Except as noted, all reagents and solvents were used as obtained from the supplier. Tetrahydrofuran was distilled from sodium ketyl.

7-Acetyldihydrocodeinone (4a). A solution of dihydrocodeinone (**2a**; 996 mg, 3.3 mmol), morpholine (2.5 mL, 28 mmol), and *p*-toluenesulfonic acid monohydrate (5 mg) in benzene (50 mL) was heated at reflux through 3 Å molecular sieves for 3 days. The mixture was then concentrated in vacuo to afford crude **3a** as a solid.

To a stirred, cooled (ice bath) solution of this crude enamine (600 mg, 1.6 mmol) in trichloroethylene (50 mL) was added sequentially triethylamine (0.35 mL, 2.5 mmol) and acetyl chloride (0.6 mL, 8 mmol). A fine white solid precipitated from the solution, and after 15 min, the solution was removed from the ice bath and heated at reflux for 6 h. During this time, the color changed to orange and then to red. Water (25 mL) was added, and the mixture was heated at reflux for 1 h. After cooling, the mixture was made basic with 50% NH_4OH, extracted with chloroform, dried, and concentrated. The resulting oil was column chromatographed to afford **4a** (300 mg, 55% yield) and recovered **2a** (170 mg, 27% yield). Recrystallization (MeOH) afforded pure **4a**: mp 195–196 °C; NMR δ 2.10 [s, 3 H, $C(O)CH_3$], 2.45 (s, 3 H, NCH_3), 3.88 (s, 3 H, OCH_3), 4.93 (s, 1 H, H-5), 6.73 (AB q, J = 8 Hz, 2 H, aryl); IR (KBr) 1620 (br) cm^{-1}; MS, m/e 341 (100, M^+), 326 (13, $M^+ - CH_3$), 298 [18, $M^+ - C(O)CH_3$]. Anal. ($C_{20}H_{23}NO_4$) C, H, N.

The other diketones of structure **4** were prepared by essentially the same procedure, starting with either **2a** or **2b**.[8] One change which was made was to stir a methanol solution of the crude product (i.e., prior to chromatography) with 1 g of K_2CO_3 for 3–5 h. This solution was then concentrated, diluted with water, extracted with $CHCl_3$, dried, concentrated, and then chromatographed.

Isolation of the Enol Isobutyrate, 5. A trichloroethylene solution of **3b** (2.95 mmol), triethylamine (0.5 mL, 3.6 mmol), and isobutyryl chloride (1.3 mL, 12 mmol), prepared as above, was heated at reflux for 9 h. After hydrolysis and the usual workup, an oil was obtained which contained a substantial amount of **5**. After several chromatographs, 100 mg (7% yield) of **5** was obtained: NMR δ 0.2 and 0.6 (m, 5 H, c-C_3H_5), 0.93 [d, J = 7 Hz, 6 H $C(CH_3)_2$], 1.22 and 1.25 [doublets, J = 7 Hz, 6 H, $C(CH_3)_2$], 3.88 (s, 3 H, OCH_3), 5.20 (s, 1 H, H-5), 6.72, 6.75 (AB q, 2 H, aryl); IR (film) 1755 (s), 1700–1610 (several) cm^{-1}; MS, m/e 479 (9, M^+), 408 [8, $M^+ - C(O)C_3H_7$], 392 [1, $M^+ - OC(O)C_3H_7$], 43 (100). Treatment of a methanol solution of a mixture of **4g** and **5** with K_2CO_3 (as above) for 2 h afforded only **4g**.

***N*-(Cyclopropylmethyl)-7-acetyldihydronormorphinone (6d).** To a stirred solution of distilled BBr_3 (0.3 mL, 3 mmol) in $CHCl_3$ (6 mL) was added, dropwise, **4d** (100 mg, 0.26 mmol) in $CHCl_3$ (1 mL). After 0.5 h, the mixture was poured onto a 1:1 ice–NH_4OH mixture and stirred for 1 h. The layers were then separated, and the aqueous layer was extracted with $CHCl_3$. The $CHCl_3$ layers were combined, dried, and concentrated. Column chromatography afforded **6d** (80 mg, 84% yield): mp 135 °C (MeOH); NMR δ 0.2 and 0.6 (m, 5 H, c-C_3H_5), 2.17 (s, 3 H, Ac), 4.4 (br s, OH), 4.88 (s, 1 H, H-5), 6.67, 6.65 (AB q, J = 8 Hz, aryl); MS, m/e 367 (30, M^+), 55 (100). Anal. ($C_{22}H_{25}NO_4 \cdot 0.5CH_3OH$) C, H, N. The other compounds of structure **6** were prepared in a similar fashion.

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Novel Opiates and Antagonists. 5.[1] 7-Carbethoxy-*N*-(cycloalkylmethyl)-3-hydroxymorphinan-6-ones and -isomorphinan-6-ones

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SISA Inc., Cambridge, Massachusetts 02138. *Received January 4, 1982*

A direct conversion of deoxydihydrothebaine-ϕ (1) to 3-methoxymorphinan-6-one (**3Ca**) and its trans isomer **3Ta** was achieved in excellent yield by the catalytic reduction of 1 in AcOH containing CF_3COOH. Treatment of **3Ca** or **3Ta** with NaH and diethyl carbonate formed the corresponding 7-carbethoxy derivatives **4a** which, on O-demethylation, furnished the 3-hydroxy compounds **4b**. The analgesic *N*-methyl compounds **3** were converted to the 17-(cyclopropylmethyl) or 17-(cyclobutylmethyl) derivatives **6–8**. Two of these compounds, one in the cis (**7Ca**) and the other in the trans (**7Ta**) series, showed mixed agonist/antagonist activity in the pentazocine range.

The search for opioid analgesics of the mixed agonist/antagonist type continues to be of intense interest to medicinal chemists. Pentazocine, a benzomorphan derivative, was the first analgesic belonging to this class of compounds to be introduced to the market. Since then, others, such as nalbuphine, butorphanol, and buprenorphine, have followed with the main clinical objective of decreasing the incidence of undesirable side effects and increasing the efficacy.[2]

As part of our program directed toward this goal, we have studied 7-acyldihydromorphinones.[1] These compounds were prepared on the basis of our interest in determining the effect of 7-substitution on the analgesic activity of less rigid nonbridged compounds. To extend these studies, we prepared the 7-carbethoxy derivatives of morphinan-6-ones. During the course of this work it became apparent that the corresponding isomorphinan-6-ones were also easily accessible. This provided us an opportunity to study the effect of 7-carbethoxy substitution on analgesia in both the *cis*- and the *trans*-morphinan-6-ones. Recently, the influence of 7-alkyl substitution on analgesia in *cis*- and *trans*-morphinanones has been reported.[3] Further chemical elaboration of the carbethoxy group to give novel compounds was attempted; however, except for a few limited cases, the chemistry proved to be unrewarding and was not pursued. Our findings in this area are described in this paper.

(1) For paper 4, see Quick, J.; Herlihy, P.; Razdan, R. K.; Howes, J. F. *J. Med. Chem.*, preceding paper in this issue.

(2) See, for example, "Narcotic Antagonists"; Braude, M.; Harris, L. S.; May, E. L.; Smith, J. P.; Villarreal, J. E., Eds.; Raven Press: New York, 1973. Jaffe, J. H.; Martin, W. R. In "The Pharmacological Basis of Therapeutics"; Goodman, L. S.; Gilman, A., Eds.; Macmillan: London, 1980; p 521.

(3) Leland, D. L.; Kotick, M. P. *J. Med. Chem.* **1980**, *23*, 1427.

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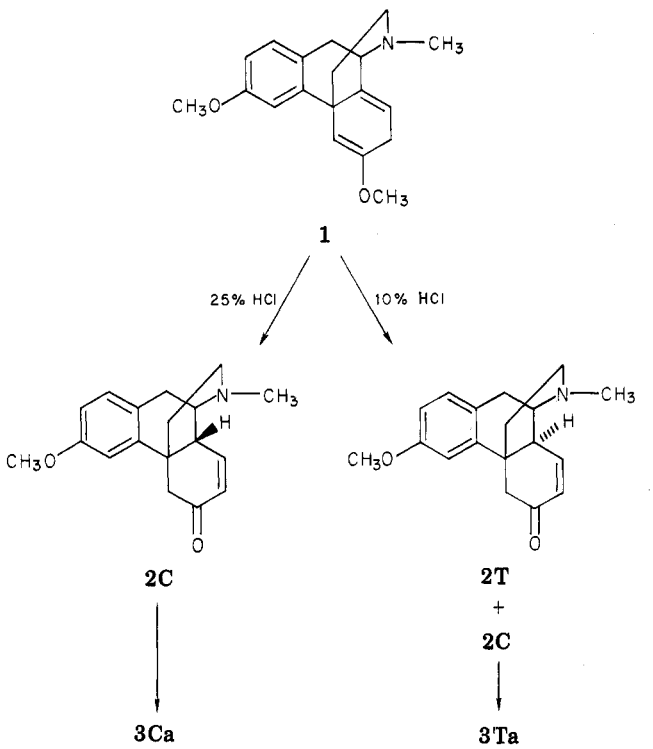
Scheme I[a]



[a] For C, B/C ring junction cis; for T, B/C ring junction trans.

Chemistry. In 1961, Sawa and co-workers[4] described the synthesis of 4-deoxydihydrothebaine-ϕ (**1**) from thebaine. They also reported[5] that treatment of **1** (Scheme I) with 25% HCl gave 3-methoxy-6-oxo-17-methyl-Δ^7-morphinan (**2C**), which on catalytic reduction over Pd/C formed 3-methoxymorphinan-6-one (**3Ca**, i.e., a B/C-cis ring junction, the same as in morphine). However, hydrolysis of **1** with 10% HCl gave a mixture containing 43% **2T** (B/C-trans ring junction) and 14% **2C** (cis isomer). Separation of the trans isomer **2T**, followed by reduction (Pd/C), provided the 3-methoxyisomorphinan-6-one (**3Ta**).[6]

We have found that catalytic reduction (Pd/C) of **1** in AcOH containing CF_3COOH directly formed **3a** (mixture of **3Ca** and **3Ta**), which on column chromatography afforded the two isomers **3Ca**[5] (54%) and **3Ta**[6] (33%) in excellent yield (Scheme II). Reaction of **3Ca** or **3Ta** with NaH and diethyl carbonate in refluxing C_6H_6 formed the corresponding 7-carbethoxy derivatives **4a** (diastereoisomeric mixture), which on treatment with BBr_3 in $CHCl_3$ furnished the 3-hydroxy compounds **4b**. Conversion of **3Ca** or **3Ta** to the *N*-(cycloalkylmethyl) compounds **5c** and **5d** was carried out via the *N*-cyano compound **5a** and the nor compound **5b**, followed by alkylation with the appropriate alkyl bromide as reported by us earlier.[7] These were then converted to **6a** and **6b** and demethylated to **7a** and **7b**, respectively, as described above.

To prepare 17-(cyclopropylmethyl)-7-(1-hydroxy-1-methylethyl)morphinan-3,6-diols (**8C** and **8T**), the ketone group in **7a** was reduced with $NaBH_4$ in C_2H_5OH. It gave a mixture of 6-ols (α and β), which without further purification, was treated with CH_3Li in THF. After column chromatography, the diols **8C** and **8T** (diastereoisomeric mixture of 6-ols) were isolated as their hydrochlorides. Attempts to prepare other analogues of **8** were not pursued, since reaction with other alkyllithium compounds gave complex mixtures. Compounds **9** and **3b** have been reported[7] by us earlier.

Pharmacological Results

The compounds were tested for analgesic activity in the acetic acid mouse writhing assay.[8] Narcotic antagonist activity was determined against an ED_{80} dose of morphine using the rat tail-flick assay.[9] These procedures have been described by us previously.[10] The compounds are listed in Table I, and the appropriate 7-unsubstituted *N*-methyl or *N*-(cycloalkylmethyl) precursors are also included for comparative purposes.

Since the number of examples in each class is limited, only trends in SAR are discussed. Both the *cis*- and *trans*-*N*-methyl-3-hydroxy compounds **4Cb** and **4Tb** are fairly potent analgesics (same as morphine) but are somewhat weaker than the parent 7-unsubstituted compounds (**3Cb** and **3Tb**). This is more pronounced with the corresponding 3-methoxy analogues, particularly in the trans series (compare **4Ta** and **3Ta**).

In the case of *N*-(cyclopropylmethyl) compounds, in the cis series both the 7-substituted compound **7Ca** and the parent unsubstituted compound **9Ca** were mixed agonist/antagonists. In the trans series, the 7-substitution gave compounds with a stronger agonist component. Compound **7Ta** showed a mixed agonist/antagonist profile, whereas the parent 7-unsubstituted compound **9Ta** had moderately potent antagonist activity only. When the N-substitution was cyclobutylmethyl, only the cis series was examined and there 7-carbethoxylation decreased the agonist activity considerably (compare **7Cb** and **9Cb**). The diol analogues **8** did not show interesting activity.

The apparent effect of 7-carbethoxy substitution on analgesia is substantially very similar to that observed for 7-methyl substitution.[3] It is noteworthy that two compounds, one in the cis (**7Ca**) and the other in the trans (**7Ta**) series, showed mixed agonist/antagonist activity in the pentazocine range.

Experimental Section

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. NMR spectra were recorded on a Varian T-60 spectrometer, using tetramethylsilane as an internal standard. Infrared spectra were obtained on a Perkin-Elmer 700 spectrometer. HPLC analyses were performed on a Waters Associates A 202 chromatograph (μ-Porasil column). Microanalyses were performed by Atlantic Microlab, Inc., Atlanta, GA. Mass spectra were obtained from the Mass Spectrometry Facility, Cornell University, Ithaca, NY. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. All compounds showed appropriate NMR spectra. Except as noted, all reagents and solvents were used as obtained from the supplier. THF was distilled from sodium ketyl. Benzene was passed through a neutral alumina column and stored over molecular sieves.

3-Methoxy-17-methylmorphinan-6-one (3Ca) and 3-Methoxy-17-methylisomorphinan-6-one (3Ta). A solution of **1** (20.0 g, 0.067 mol) and CF_3COOH (8.1 mL, 0.011 mol) in 15 mL of H_2O

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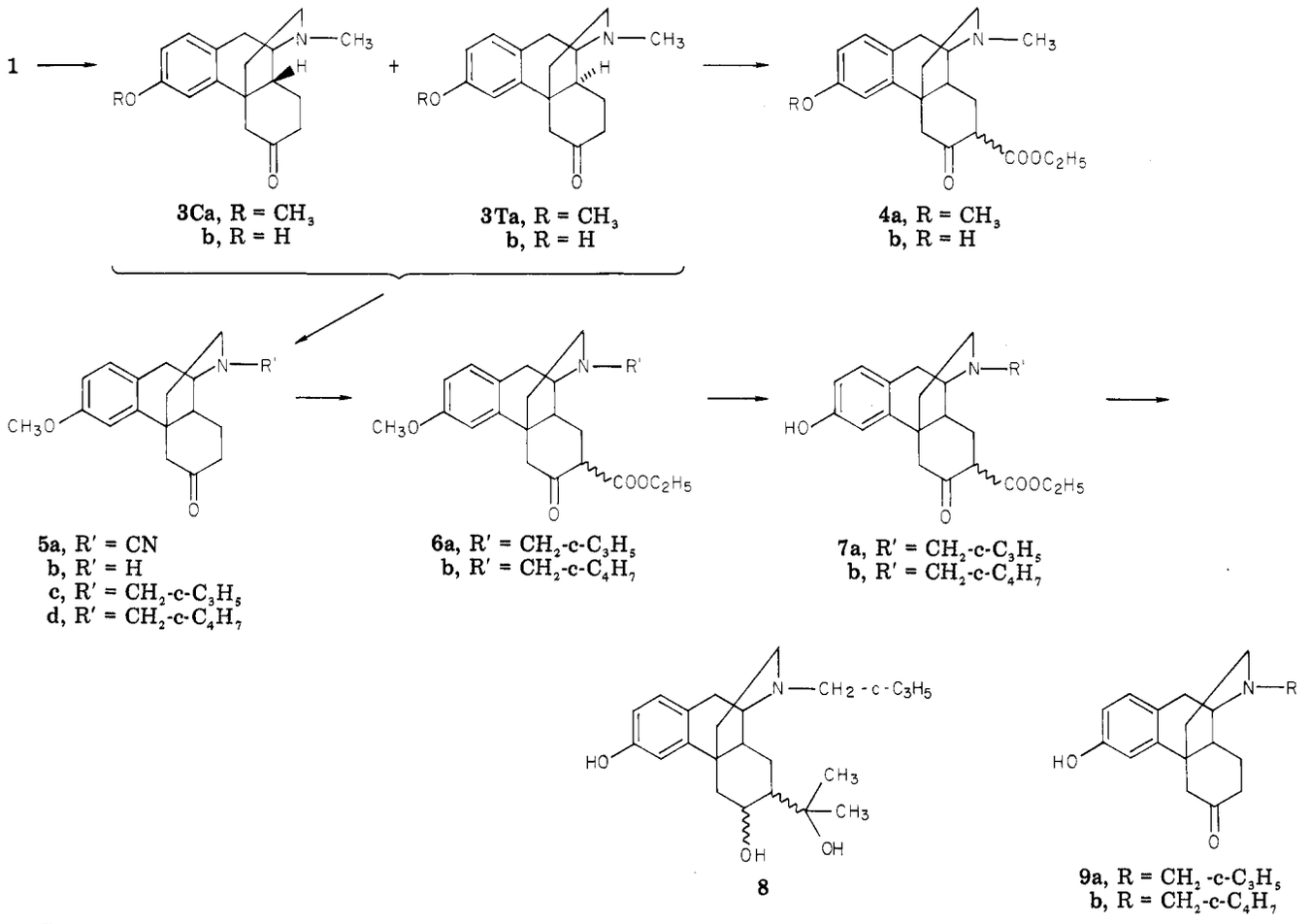
Table I

compd	% yield of free base	mp, °C	formula	anal.[a]	analgesic and narcotic antagonist act.:[b] ED_{50}, mg/kg (95% CL) agonist,[c] mouse writhing	antagonist,[d] rat tail flick
3Ca	54				0.49 (0.26-0.92)	
3Cb					0.15 (0.10-0.22)	
3Ta	33				1.58 (1.14-2.19)	
3Tb					0.23 (0.15-0.35)	
4Ca	38	gum	$C_{21}H_{27}NO_4 \cdot 0.75H_2O$	C, H, N	4.6 (3.6-6.0)	
4Cb	100	foam	$C_{20}H_{25}NO_4 \cdot H_2O$	C, H, N (MS)	0.72 (0.46-1.13)	
4Ta	86	154-157[e]	$C_{21}H_{27}NO_4 \cdot HCl \cdot C_2H_5OH$	C, H, N, Cl[f]	>10.0[g]	
4Tb	89	186-188	$C_{20}H_{25}NO_4 \cdot 0.5H_2O$	C, H, N	0.6 (0.30-1.21)	
5Cc					0.24 (0.07-0.86)	>3.0
5Cd					0.22 (0.08-0.59)	>10.0
5Tc					>10.0	1.3 (0.57-2.98)
5Td					6.9 (3.64-13.1)	>10.0
6Ca	31	foam[e]	$C_{24}H_{31}NO_4 \cdot 2HCl$	H, N; C[h] (MS)	>10.0[g]	>3.0
6Cb	61	foam[e]	$C_{25}H_{33}NO_4 \cdot 1.5HCl \cdot 0.75H_2O$	C, H, N, Cl (MS)	>10.0[g]	>3.0
6Ta	69	foam[e]	$C_{24}H_{31}NO_4 \cdot HCl$	(MS)	>10.0[g]	>10.0
7Ca	66	foam[e]	$C_{23}H_{29}NO_4 \cdot HCl \cdot 1.5H_2O$	C, H, N	4.9 (1.76-13.6)[g]	3.12 (1.45-6.69)
7Cb	90[i]	foam[e]	$C_{24}H_{31}NO_4 \cdot HCl \cdot 1.5H_2O$	C, N; H[j]	1.15 (0.50-2.66)[g]	>10.0
7Ta	64[i]	215-220[e,k]	$C_{23}H_{29}NO_4 \cdot HCl \cdot 0.75H_2O$	C, H, N	3.7 (1.01-13.52)[g]	2.54 (1.40-4.62)
8C	39	foam>200[e]	$C_{23}H_{33}NO_3 \cdot HCl \cdot 0.5CHCl_3$	C, H, N (MS)	6.9 (2.9-16.4)[g]	>10.0
8T	14	180[k]	$C_{23}H_{33}NO_3 \cdot 0.5H_2O$	C, H, N (MS)	>10.0	>10.0
9Ca					1.02 (0.40-2.61)	2.3 (1.28-4.12)
9Cb					0.017 (0.002-0.124)	>10.0
9Ta					>10.0	0.78 (0.37-1.64)
morphine sulfate					0.8 (0.4-1.5)	
nalorphine					1.22 (0.19-7.46)	0.86 (0.16-4.71)
pentazocine					3.70 (2.45-5.58)	10.4 (3.9-28.7)

[a] MS indicates that the molecular weight has been confirmed by high-resolution mass spectrometry, AEI-MS-092, and results are within 3.0 mmμ error. These compounds have a strong tendency to retain solvents. [b] Compounds that were prepared as salts were administered in distilled water; free bases were dissolved by the addition of 1 N HCl and then further diluted. [c] The drug was injected subcutaneously.[8] [d] The drug was injected intraperitoneally and the ED_{80} dose of morphine was given subcutaneously.[9] [e] The HCl salt. [f] H: calcd, 7.78; found, 7.10. [g] The compound was tested as the HCl salt. [h] C: calcd, 61.27; found, 60.80. N: calcd, 2.98; found, 3.46. [i] Yield after purification by chromatography (Florisil; $MeOH/CHCl_3$). [j] H: calcd, 7.65; found, 7.13. [k] Decomposition.

Scheme II[a]



[a] For C, B/C ring junction cis; for T, B/C ring junction trans.

and 150 mL of glacial AcOH was stirred at room temperature under N_2 for 0.5 h. Palladium (10%) on charcoal catalyst (0.57 g) was added, and H_2 was bubbled through the solution for 6.5 h; the reaction mixture was then left stirring at ambient temperature overnight. The catalyst was removed by suction filtration through Celite and washed thoroughly with H_2O. The filtrate was made basic (pH 8) by adding solid $KHCO_3$ and was then extracted with CH_2Cl_2 (4 times). The organic fractions were combined, dried over Na_2SO_4, and concentrated under reduced pressure to give 23.2 g of a mixture. The cis and trans isomers were separated from the crude product by column chromatography on Florisil with graded MeOH/$CHCl_3$ as eluant to give 10.41 g (54%) of the cis isomer **3Ca** and 6.3 g (33%) of trans isomer **3Ta**, identical in all respects with those reported by Sawa and coworkers.[5,6]

General Procedure for 7-Carbethoxylation. This is illustrated by the conditions used for the preparation of **7-carbethoxy-3-methoxy-17-methylmorphinan-6-one (4Ca).** NaH (50% oil dispersion; 3.5 g, 84 mmol) was introduced into a reaction flask, under a N_2 atmosphere, washed twice with hexane to remove mineral oil, and then suspended in 100 mL of dry C_6H_6. Diethyl carbonate (6.62 g, 56.1 mmol) was added, and the mixture was heated at reflux. A solution of **3Ca** (4.0 g, 14 mmol) in 60 mL of dry C_6H_6 was added dropwise to the hot slurry over a period of 2 h; it was stirred for an additional 3 h at the reflux temperature and then left at ambient temperature overnight. The reaction was quenched by the addition of AcOH, followed by H_2O, and was then extracted with C_6H_6 (3 times), dried over Na_2SO_4, and concentrated in vacuo. The residue was taken up in CH_2Cl_2, washed twice with 5% $NaHCO_3$ and twice with H_2O, dried over Na_2SO_4, and concentrated under reduced pressure to 4.8 g of crude **4Ca**. Purification by chromatography on Florisil using graded MeOH/$CHCl_3$ as eluant provided 1.9 g (38%) of product as a brown gum, which was homogeneous by TLC: NMR ($CDCl_3$) δ 1.2 (t, J = 7 Hz, 3 H), 2.42 (s, 3 H, NCH_3), 3.75 (s, 3 H, OCH_3), 4.1 (q, J = 6 Hz, 2 H), 6.65–7.12 (m, 3 H, aromatics); IR (smear) 1650, 1720, 1750 cm^{-1}.

Compounds **4Ta**, **6Ca**, **6Ta**, and **6Cb** were similarly prepared and were homogenous by TLC (Table I). The hydrochlorides were prepared from the free base (dissolved in $CHCl_3$) by treatment with ethereal HCl.

General Procedure for Demethylation of the 3-Methoxy Group. This is illustrated by the conditions used for the preparation of **7-carbethoxy-3-hydroxy-17-methylisomorphinan-6-one (4Tb).** To a stirred solution of distilled BBr_3 (1.1 mL, 10.5 mmol) in 10 mL of $CHCl_3$ as added, dropwise, a solution of **4Ta** (312 mg, 0.87 mmol) in 10 mL of $CHCl_3$. After 0.5 h the reaction mixture was poured into an ice/NH_4OH mixture and then stirred at 0 °C for 1 h. The layers were separated, and the aqueous phase was extracted twice with $CHCl_3$. The organic fractions were combined, washed once with H_2O, dried over Na_2SO_4, and concentrated in vacuo. Purification by column chromatography over Florisil using graded MeOH/$CHCl_3$ as eluant provided 267 mg (89%) of **4Tb** as a white solid, mp 186–188 °C.

Compounds **4Cb**, **7Ca**, **7Ta**, and **7Cb** were similarly prepared and were homogeneous by TLC (Table I). The HCl salts were prepared from the free base, which was dissolved in $CHCl_3$, by treatment with ethereal HCl.

17-(Cyclopropylmethyl)-7-(1-hydroxy-1-methylethyl)-morphinan-3,6-diol (8C). Solid $NaBH_4$ (765 mg, 20.21 mmol) was added in small portions to a stirred solution of **7Ca** (1.55 g, 4.04 mmol) in 50 mL of EtOH. After the addition was complete, the reaction mixture was stirred at ambient temperature under a N_2 atmosphere for 4 h. The reaction was quenched by the addition of 10 mL of glacial AcOH; this mixture was stirred at room temperature for 1 h. The solvents were removed in vacuo; the residue was taken up in H_2O and made basic with concentrated NH_4OH. The solid obtained was extracted 3 times with $CHCl_3$. The organic fractions were combined, washed once with H_2O, dried over Na_2SO_4, and concentrated in vacuo to give 0.89 g of 7-car-

bethoxy-17-(cyclopropylmethyl)morphinan-3,6-diol. It was used in the next reaction without further purification.

CH_3Li (1.84 M, 6.14 mL, 11.3 mmol) was added to a cooled (ice bath) solution of the above diol (792 mg, 2.05 mmol) in 45 mL of THF. The brown reaction mixture was stirred at ambient temperature under N_2 overnight. The reaction was quenched by pouring it into 25 mL of cold 20% NH_4Cl and stirring it in an ice bath for 15 min. The layers were separated, and the aqueous phase was extracted twice with $CHCl_3$. The organic fractions were combined, washed once with H_2O, dried over Na_2SO_4, and concentrated in vacuo. Purification of the product by column chromatography over Florisil using graded MeOH/$CHCl_3$ as eluant afforded 295 mg (39%) of 8C: MS, *m/e* (relative intensity) 371 (M^+, 70), 330 ($M^+ - CH_2$-c-C_3H_5, 100), 313 ($M^+ - CH_3COCH_3$, 23), 272 (330 – CH_3COCH_3, 30); NMR ($CDCl_3$) δ 0.13–0.53 (br m, 4 H), 1.18 (s, 3 H), 1.28 (s, 3 H), 4.48 (br s, 1 H, exchangeable), 4.75 (br s, 1 H, exchangeable), 6.58–7.03 (m, 3 H); IR (smear) 1610 cm^{-1}. Treatment with ethereal HCl gave the hydrochloride salt as a brown solid, mp foams >200 °C.

17-(Cyclopropylmethyl)-7-(1-hydroxy-1-methylethyl)isomorphinan-3,6-diol (8T). The compound was prepared according to the same procedure as used for 8C. It was obtained as an off-white solid which begins to decompose at 180 °C (Table I): NMR ($CDCl_3$/MeOD) δ 0.08–0.58 (m, 4 H), 1.3 (s, 3 H), 1.37 (s, 3 H), 4.1 (br s, 2 H, exchangeable), 4.57 (br s, 1 H, exchangeable), 6.53–7.02 (m, 3 H); IR ($CHCl_3$) 1610 cm^{-1}.

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Aporphines. 39.[1] Synthesis, Dopamine Receptor Binding, and Pharmacological Activity of (*R*)-(–)- and (*S*)-(+)-2-Hydroxyapomorphine[2]

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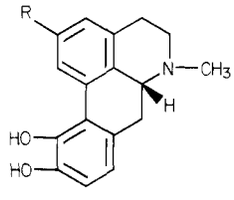
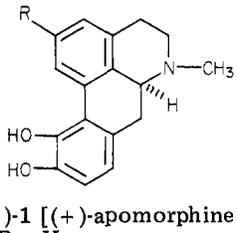
The enantiomers (6a*R* and 6a*S*) of 2,10,11-trihydroxyaporphine (THA) were synthesized from thebaine and bulbocapnine and evaluated pharmacologically in vitro in comparison with (–)-apomorphine [(–)-APO] and dopamine by competition with tritiated apomorphine, ADTN, and spiroperidol for binding to a membrane fraction of calf caudate nucleus, as well as for ability to stimulate adenylate cyclase. In all four tests, the rank order of potency was (–)-APO > (–)-THA ≫ (+)-THA. Thus, these results extend the impression that the 6a*R* configuration for hydroxyaporphines is preferred for interactions with putative dopamine receptors and that 2-hydroxylation reduces potency in comparison with 10,11-dihydroxyaporphines.

Since the discovery of therapeutically useful dopamine (DA) agonist activity in hydroxylated aporphine derivatives, such as apomorphine,[3] considerable interest has developed in delineating the portions of the aporphine molecular structure responsible for dopaminergic properties and the interactions with DA receptors.[4,5] The process of drug design could be considerably improved if receptors and their mode of interaction with active substances were known in precise molecular detail. Such information could then be used to design conformationally defined structures in which pharmacophoric groups are oriented in the appropriate spatial arrangement for optimal receptor interaction. Since DA is an achiral and conformationally flexible molecule, little information concerning interactions with DA receptors can be obtained with this neurotransmitter. Apomorphine [(–)-1, (–)-APO], the enantiomer obtained by the acid-catalyzed rearrangement of morphine, was reported by Saari et al.[6] to be the active enantiomer for dopaminergic and emetic activity. The *S*(+) enantiomer of apomorphine was shown to be inactive in producing postural asymmetrics in unilaterally caudate-lesioned mice.[6] Despite the complexities of interactions of apomorphine with presumed DA receptors and the status of apomorphine as a possible partial agonist or mixed agonist/antagonist in DA systems, including those in the central nervous system,[7–10] the apomorphine molecule has served as a good starting point for the study of DA receptor interactions. This proposal is supported by the facts that the catechol ring and the amino group analogous to those of DA are held in rigid conformation



(–)-1 [(–)-apomorphine, APO], R = H
(–)-2 [(–)-2-hydroxyapomorphine, (–)-THA], R = OH



(+)-1 [(+)-apomorphine], R = H
(+)-2 [(+)-2-hydroxyapomorphine, (+)-THA], R = OH

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(1) For Part 38, see R. J. Baldessarini, J. L. Neumeyer, A. Campbell, G. Sperk, V. J. Ram, G. W. Arana, and N. S. Kula, *Eur. J. Pharmacol.*, 77, 87 (1982).
(2) This paper has been presented in part. See "Abstracts of Papers", 182nd National Meeting of the American Chemical Society, New York, NY, Aug 1981, Chemical Society, Washington, DC, 1981, Abstr MEDI 22.

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