methanol was removed under vacuum, and the aqueous phase was extracted with Et$_2$O, which was discarded. The solution was acidified with 3 N HCl and extracted with Et$_2$O. The extracts were dried and evaporated to give 8.8 g (82%) of product, bp 130–134 °C (0.5 mm). Cyclization of 5-(2,5-dimethoxyphenyl)-pentanoic acid according to the procedure of Anderson[24] gave the ketone 15 in 45% yield.

5,8-Dimethoxy-1,4-dihydro-1,4-ethanonaphthalene Hydrochloride (16). A mixture of 18.8 g of the adduct between *p*-quinone and 1,3-cyclohexadiene[19] and 10.0 mL of 10% aqueous NaOH was stirred in an ice bath while 25 mL of dimethyl sulfate was added. After addition was complete, the mixture was stirred for 16 h at 25 °C. An additional 50 mL of 10% aqueous NaOH and 15 mL of dimethyl sulfate were added, and the mixture was again stirred for 16 h. The mixture was extracted well with Et$_2$O, and the extracts were washed, dried, and evaporated to give 17.3 g (80%) of the dimethyl ether 16 as a pale tan oil.

1,1a,6,6a-Tetrahydro-2,5-dimethoxycycloprop[a]indene-1-carboxylic Acid (19). Into 100 mL of MeOH was dissolved 6.5 g of 4,7-dimethoxy-1-indanone,[17] and 3 g of NaBH$_4$ was added in portions over 15 min. The mixture was stirred at 25 °C for 30 min, stripped of MeOH, and partitioned between EtOAc and

H$_2$O. The organic layer was separated, washed, dried, and evaporated to give 6.5 g (100%) of the alcohol as a white crystalline solid, mp 70–72 °C. A solution of 5.3 g (27 mmol) of this in 20 mL of pyridine was stirred at 25 °C while 3.54 g (30 mmol) of thionyl chloride was added. The reaction was stirred at 25 °C for 30 min and then refluxed for 2 h. It was poured into 200 mL of Et$_2$O and washed with H$_2$O. The organic layer was dried and evaporated onto 5 g of silica gel. It was chromatographed quickly on 60 g of silica using 1:1 hexane–Et$_2$O to give 2.3 g (48%) of white crystals of 18, mp 58–59 °C. A suspension of 1.05 g (6 mmol) of this and 200 mg of CuSO$_4$ in 10 mL of xylene was stirred in an oil bath maintained at 75 °C while ethyl diazoacetate in toluene was added dropwise until starting material was consumed (30 mmol of reagent). The reaction was filtered through Celite, and the filtrate was chromatographed on silica gel eluting with 90:10 hexane–ether to give 988 mg (63%) of the exo (19) and 236 mg (15%) of the endo adduct (20). The ^{1}H NMR of the endo isomer (20) showed a methylene quartet at δ 3.5, while that of the exo isomer (19) displayed a quartet at δ 4.3. Hydrolysis with ethanolic sodium hydroxide of the exo ester (19) and crystallization of the product from EtOAc gave 640 mg of white crystals, mp 177–179 °C (22% from the 1-indanone). Anal. (C$_{13}$H$_{14}$O$_4$) C, H.

(-)-4-Hydroxymorphinanones: Their Synthesis and Analgesic Activity

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A facile procedure is described for the conversion of morphine, via the diphosphate ester derivative 1 followed by catalytic reduction and treatment with Li/NH$_3$, to 3-deoxy-7,8-dihydromorphine (3). Oxidation with benzophenone *tert*-butoxide converted 3 to the ketone 4, which on treatment with Zn/NH$_4$Cl formed (-)-4-hydroxymorphinan-6-one 5. Reaction of 5 with diazomethane formed the methyl ether 6. The *N*-cyclopropylmethyl analogues of 4 and 5 were also prepared, i.e., 8c and 9 from 4. The antinociceptive activity of these compounds was tested. Compounds 5, 6, 8c, and 9 showed potent antiwrithing activity and, based on these data, a structure–activity relationship in morphinans is discussed.

As part of an ongoing program in our laboratories, to explore approaches to a practical synthesis of morphine, codeine, and related opioids, we needed a sample or (-)-4-hydroxymorphinan-6-one (5) for final comparison with the totally synthetic material. 4-Hydroxymorphinanones are relatively unexplored and represent an interesting series of morphinanones with a phenolic group at C$_4$. We achieved their synthesis from morphine and found (-)-4-hydroxymorphinan-6-one (5) to possess potent antinociceptive activity. This led us to prepare and examine the *N*-cyclopropylmethyl analogue 9, in the hope of developing a novel series of mixed agonist/antagonist type analgesics. While our work was in progress, Hsu et al.[1] described a facile synthesis of these compounds, albeit by a different route, and reported their antinociceptive activity.[2] This has prompted us to report our findings at this time. In this paper we report a novel route to the synthesis of 4-hydroxymorphinanones and discuss their antinociceptive activity.

We synthesized the key intermediate 3-deoxy-7,8-dihydromorphine (3) from morphine as shown in Scheme I,

utilizing the phosphate ester procedure for deoxygenation at C$_3$. Hsu et al.,[1b] Reden et al.,[3] and Bognar et al.,[4] prepared 3 via the *N*-phenyltetrazolyl ether derivatives. As pointed out by Hsu et al.,[1] compound 3 is an important intermediate, since it can lead to other 3-deoxyopioids,[3] as well as 4-hydroxymorphinanones.[1]

Morphine was treated with diethyl chlorophosphate and anhydrous K$_2$CO$_3$ in CH$_3$CN to give the diphosphate 1, which was immediately converted to the dihydromorphine 2 by catalytic reduction in ethanol in the presence of (10%) palladium on carbon. Cleavage of the 3-phosphate ester and hydrolysis of 6-ester was achieved by addition of 2 in THF to a 1 N solution of lithium in ammonia and maintaining the blue color for 15 min to give 3 as a colorless glass (75% overall from morphine). Oxidation of 3 by benzophenone–potassium *tert*-butoxide in benzene gave the ketone 4.[3,5] Treatment with Zn dust and NH$_4$Cl in refluxing ethanol gave the 4-hydroxymorphinan-6-one (5).[1] The corresponding methyl ether 6 was obtained by reaction of 5 with diazomethane.

The *N*-cyclopropylmethyl analogue 9 was prepared from 4 by a four-step process. Thus, reaction of 4 with cyanogen bromide in CH$_2$Cl$_2$ solution in the presence of K$_2$CO$_3$ gave the *N*-cyano compound 8a. Hydrolysis to 8b was accom-

(1) (a) F. Hsu, A. E. Jacobson, K. C. Rice, and A. Brossi, *Heterocycles*, 13, 259 (1979); (b) F. Hsu, K. C. Rice, and A. Brossi, *Helv. Chim. Acta*, 63, 2042 (1980); (c) M. D. Rozwadowska, F. L. Hsu, A. E. Jacobson, K. C. Rice, and A. Brossi, *Can. J. Chem.*, 58, 1855 (1980).
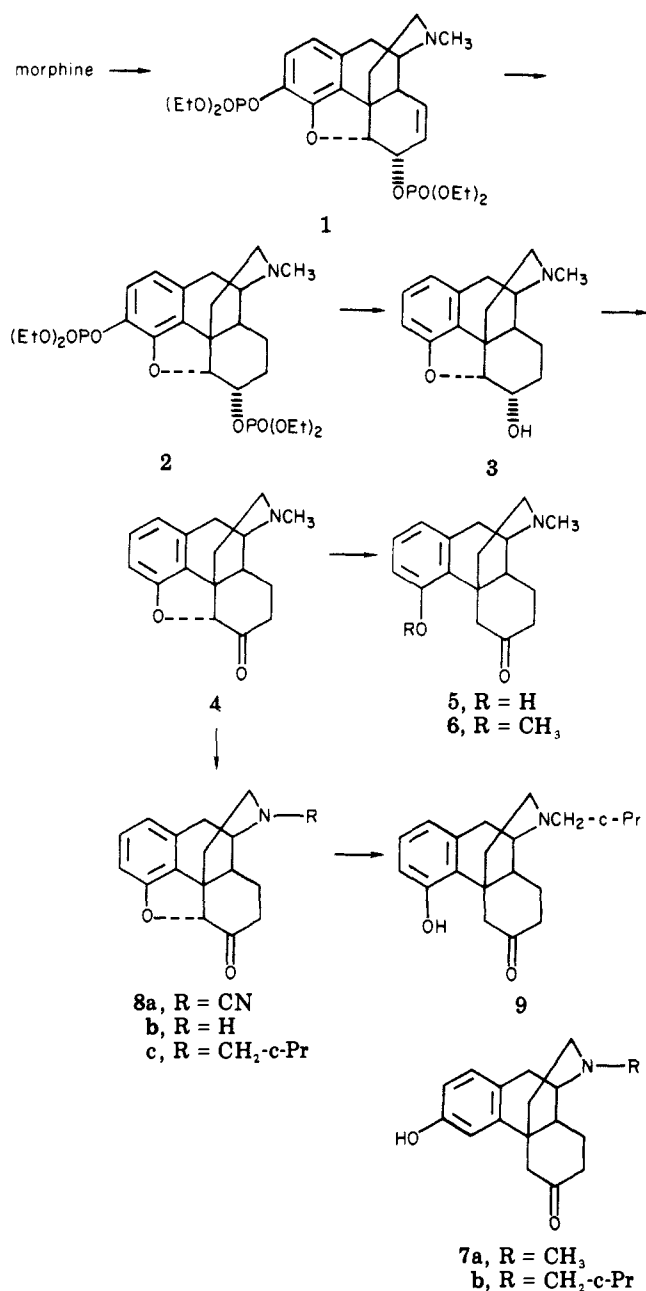
(2) Dr. Brossi has kindly informed us that the antinociceptive activity of these compounds is presently in press and was also presented at various meetings. See also footnotes in ref 1a and 1c.

(3) J. Reden, M. F. Reich, K. C. Rice, A. E. Jacobson, A. Brossi, R. A. Streaty, and W. A. Klee, *J. Med. Chem.*, 22, 256 (1979).

(4) R. Bognár, G. Y. Gaal, P. Kerekes, G. Horvath, and M. T. Kovacs, *Org. Prep. Proced. Int.*, 6, 305 (1974).

(5) Y. Sawa, R. Maeda, and J. Irisawa, U.S. Patent 3 707 470, 1972.

Scheme I

morphine ⟶

(EtO)₂OPO ⟶

$(EtO)_2OPO$

1

2

3

4

5, R = H
6, R = CH₃

8a, R = CN
b, R = H
c, R = CH₂-c-Pr

9

7a, R = CH₃
b, R = CH₂-c-Pr

plished by refluxing in 2 N HCl.[6,7] Alkylation of **8b** with cyclopropylmethyl bromide and K_2CO_3 in refluxing $CHCl_3$ formed **8c**, which on similar treatment as before with Zn dust/NH_4Cl gave **9**.

Results and Discussion

The antinociceptive activity of these compounds is shown in Table I. It was determined both in the acetic acid induced mouse writhing[8] and the heat stimulus rat tail-flick[9] tests. The narcotic antagonist activity was determined by the rat tail-flick method[9] against an ED_{80} of morphine.

On the basis of writhing data, both (-)-4-hydroxy-*N*-methylmorphinan-6-one (**5**) and its methyl ether **6** show

Table I. Analgesic and Narcotic Antagonist Activity[a]

compd	mouse writhing: ED_{50},[b] mg/kg	rat tail flick agonist ED_{50},[b] mg/kg	rat tail flick antagonist ED_{50},[b,c] mg/kg
5	0.18 (0.08–0.42)	19.2 (2.16–170)	
6	0.21 (0.09–0.46)		
7a	0.15 (0.1–0.3)	20.0 (9.8–41.2)	
7b (NIH-9466)	1.02 (0.4–2.6)		2.3 (1.3–4.1)
8c	0.06 (0.04–0.08)		12.5 (6.9–22.6)
9	0.64 (0.48–0.85)		inact at 10 mg/kg
morphine sulfate	0.8 (0.4–1.5)	7.3 (3.5–15.4)	
nalorphine	1.22 (0.19–7.46)		0.86 (0.16–4.71)

[a] 95% confidence limits are shown in parentheses.[17] [b] Subcutaneous injection in dilute HCl. [c] Determined using an intraperitoneal ED_{80} of morphine.

potent antinociceptive activity with very sharp dose–response curves. It is important to point out that although the writhing test gives false positives for nonanalgesics like lignocaine, antihistamines, pentylenetetrazole, etc., it detects the known clinical analgesics of the narcotic, narcotic antagonist, and antipyretic type.[10] In fact, it is a procedure of choice for screening the mixed agonist/antagonist type opioids.[14b] There are four narcotic antagonist analgesics which have been extensively studied in man, i.e., nalorphine, pentazocine, butorphanol, and nalbuphine. The relative analgesic potencies of these compounds are better predicted by the writhing test than any other widely used procedure. Furthermore, naloxone, which is a morphine antagonist, is not active in this procedure.

The present findings of potent antinociceptive activity of **5** and **6** are in contrast to the well-documented[11,12] structure–activity relationship (SAR) in morphinans where a phenolic group at C_3 is considered essential for biological activity. Thus (±)-3-hydroxy-*N*-methylmorphinan is about 12 times as potent as (±)-*N*-methylmorphinan.[11] In addition, it is known that moving the hydroxyl to C_2 or C_4 greatly reduces or abolishes activity.[11,12]

In the present *N*-methylmorphinan-6-one series, however, it appears that there is no difference in potency when the phenolic hydroxyl is at C_3 or C_4 (**7a**[13] vs. **5**). As yet, we have not studied the effect of complete removal of the phenolic group in this series.

In the rat tail-flick test, **5** is, however, less potent than morphine. We feel that this procedure generally gives higher ED_{50} values than the writhing test[14b] and correlates with the narcotic actions of the opiates.[9,14] Thus, compound **5** may have less of a narcotic component than

(6) H. Rapoport and M. Look, U.S. Patent 2890221 (1959); *Chem. Abstr.*, **54**, 612*f* (1960).

(7) M. Gates and T. A. Montzka, *J. Med. Chem.*, **7**, 127 (1964).

(8) B. J. R. Whittle, *Br. J. Pharmacol.*, **22**, 246 (1964).

(9) L. S. Harris and A. K. Pierson, *J. Pharmacol. Exp. Ther.*, **143**, 141 (1964).

(10) For a discussion, see, for example, (a) C. A. Winters, *Med. Chem. (Academic)*, **5**, 46 (1965); (b) M. R. Fennessy and J. R. Lee, *Methods Narc. Res.*, **5**, 73 (1975).

(11) E. L. May and S. L. Sargent, *Med. Chem. (Academic)*, **5**, 142 (1965).

(12) J. Hellerback, O. Schnider, H. Besendorf, and B. Pellmont, *Int. Ser. Monogr. Org. Chem.*, **8**, 74 (1966).

(13) Y. K. Sawa and S. Maeda, *Tetrahedron*, **20**, 2247 (1964); Japanese Patent 20863.

(14) (a) S. Archer, N. F. Albertson, L. S. Harris, A. K. Pierson, and J. G. Bird, *J. Med. Chem.*, **7**, 123 (1964); (b) J. Pearl, M. Aceto, and L. S. Harris, *J. Pharmacol. Exp. Ther.*, **160**, 217 (1968); W. L. Dewey and L. S. Harris, *Methods Narc. Res.*, **5**, 101 (1975).

morphine, although this would have to be examined more thoroughly. We wish to emphasize that the 3-hydroxy analogue **7a**, like **5**, is also less potent in this test, and both show nearly identical ED$_{50}$ values. These data are, therefore, consistent with the SAR results discussed above.

In the *N*-cyclopropylmethyl analogues, the 3-deoxy compound **8c** is a mixed agonist/antagonist with potent agonist activity, whereas the 4-hydroxy compound **9** is equipotent with morphine as an agonist and lacks antagonist activity up to 10 mg/kg. The corresponding analogue with a hydroxyl group at C$_3$, i.e., **7b**, is known (NIH 9466)[15] and is a mixed agonist/antagonist. It is slightly less potent than **9** in the writhing test, indicating that, although potent agonist activity is retained in moving the hydroxyl group from C$_3$ to C$_4$, the antagonist activity is lost.

Interestingly, however, we have observed that the lack of narcotic antagonist activity with the *N*-cyclopropylmethyl compound **9**, while not unique,[16] is accompanied by strong morphine-like effects (Straub tail and circling behavior). This is unusual and may reflect the influence of the 4-hydroxyl group on the interaction of the molecule with the receptor. (-)-4-Hydroxymorphinones are thus an interesting class of opioids worthy of further study.

Experimental Section

Melting points were determined in a Thomas-Hoover melting-point apparatus and are uncorrected. The IR spectra were recorded on a Perkin-Elmer Model 700 instrument, and the NMR spectra were measured in CDCl$_3$ on a Varian T-60 spectrometer. The high-pressure liquid chromatographic separations were made with a Waters Associates ALC-202 chromatograph equipped with a Model 6000 solvent delivery system.

4,5-Epoxy-17-methylmorphinan-6-ol (3). A mixture of morphine (12.4 g, 43.5 mmol), diethyl chlorophosphate (17.5 g, 100 mmol), anhydrous K$_2$CO$_3$ (25 g), and CH$_3$CN was stirred at room temperature for 72 h. The reaction mixture was filtered, the CH$_3$CN was evaporated on the rotary, and the residue was taken up in CH$_2$Cl$_2$. The CH$_2$Cl$_2$ was extracted with a saturated NaHCO$_3$ solution, dried over anhydrous Na$_2$SO$_4$, and concentrated to give 19.78 g of **1** as a colorless solid. The diphosphate **1** was hydrogenated in a Parr apparatus in ethanol (250 mL) using Pd/C (10%, 0.9 g). After the uptake of hydrogen was complete, the reaction mixture was filtered and concentrated to give **2** as a light yellow oil. Without further purification, this was then dissolved in anhydrous THF (freshly distilled, 100 mL) and added to a blue solution of Li (2 g, 0.28 g-atom) in NH$_3$ (300 mL), and the blue color was maintained for 15 min. Excess Li was decomposed by the addition of solid NH$_4$Cl, and NH$_3$ was allowed to evaporate off under N$_2$ stream. To the residue was added aqueous NH$_4$Cl (100 mL) and CH$_2$Cl$_2$ (200 mL), and the two layers were separated. The aqueous layer was extracted with more CH$_2$Cl$_2$ (2 × 200 mL). The combined CH$_2$Cl$_2$ layer was extracted with aqueous saturated NaCl, dried over Na$_2$SO$_4$, and concentrated to give **3** as a light yellow oil, 8.9 g (75% overall from morphine). Pure **3** was obtained by chromatography over silica gel as colorless glass but failed to crystallize. The product showed a single spot by TLC and a single peak by HPLC (μ-Porasil), and its spectral properties were identical with those reported.[1b,3,4]

4,5-Epoxy-17-methylmorphinan-6-one (4). Compound **3** was oxidized with benzophenone and potassium *tert*-butoxide in benzene by the procedure of Rapoport et al.[18] to give **4** as light

yellow needles, mp 242–243 °C (lit.[3,5] mp 246–247 °C). Anal. (C$_{17}$H$_{19}$NO$_2$) C, H, N.

4-Hydroxy-17-methylmorphinan-6-one (5). A mixture of **4** (0.4 g, 1.5 mmol), zinc dust (0.4 g), and NH$_4$Cl (0.4 g) in ethanol (75 mL) was heated at reflux in an oil bath for 4 h. The reaction mixture was allowed to cool to room temperature and filtered, and the filtrate was concentrated on the rotary evaporator. The residue was dissolved in water (15 mL) and basified with NH$_4$OH (1 N to pH 8–9). The reaction mixture was extracted with 3 × 50 mL of EtOAc. The EtOAc layer was extracted with saturated aqueous NaCl solution, dried over anhydrous Na$_2$SO$_4$, and concentrated to give 417 mg of crude product. It was crystallized from methanol to give colorless needles: mp 123–124.5 °C (lit.[1b] 119–121 °C); IR 3300 (OH), 1700 (C=O) cm^{-1}. Anal. (C$_{17}$H$_{21}$-NO$_2$·0.5H$_2$O) C, H, N.

4-Methoxy-17-methylmorphinan-6-one (6). The methyl ether **6** was prepared by the addition of an ethereal solution of diazomethane to a solution of **5** in 1:1 ether/CH$_2$Cl$_2$ at 0 °C and stirring at room temperature overnight. The crude methoxy compound **6** was obtained after concentration and was purified by chromatography (alumina activity IV with CH$_2$Cl$_2$). It was obtained as a light yellow solid: mp 140–141 °C; NMR [δ 3.78 (s, 3, OCH$_3$)] and IR were consistent with the structure. Anal. (C$_{18}$H$_{23}$NO$_2$·0.5H$_2$O) C, H, N.

17-(Cyclopropylmethyl)-4,5-epoxymorphinan-6-one (8c). A mixture of **4** (0.5 g, 1.85 mmol), CNBr (1.17 g, 11 mmol), CH$_2$Cl$_2$ (25 mL), and anhydrous K$_2$CO$_3$ (1.2 g) was heated in an oil bath at reflux for 20 h. After cooling, the reaction mixture was filtered. The CH$_2$Cl$_2$ layer was washed with water (20 mL), dried (Na$_2$SO$_4$), and concentrated under vacuum to give 0.535 g of **8a**.

8a (0.5 g) was dissolved in dilute HCl (2 N, 20 mL) and heated at reflux in an oil bath for 3 h. (TLC indicated complete conversion.) It was concentrated to dryness at reduced pressure, and residual H$_2$O was removed by codistillation with C$_6$H$_6$ (5 mL) to give 0.75 g of **8b**·HCl as a tan, partially solid residue. It was converted to the free base **8b** by neutralizing its aqueous solution (5 mL) with dilute NH$_4$OH and extraction with EtOAc (3 × 15 mL). The EtOAc extract was dried (Na$_2$SO$_4$) and concentrated to give 0.26 g of **8b** as a colorless solid. It was alkylated by heating with cyclopropylmethyl bromide (0.27 g) and anhydrous K$_2$CO$_3$ (0.5 g) in CHCl$_3$ (30 mL) in an oil bath (70 °C) for 24 h. The reaction mixture was filtered and concentrated to give 0.44 g (77% from **4**) of crude product. It was chromatographed over alumina using CH$_2$Cl$_2$ as the eluant to give **8c** as a colorless fluffy solid: mp 179–180 °C; pure by TLC and HPLC (μ-Porasil); NMR δ 7.07 (t, 1, *J* = 8 Hz, C$_2$ H), 6.73 and 6.67 (2 d, 2, *J* = 8 Hz, C$_1$ H and C$_3$ H), 4.62 (s, 1, C$_5$ H), 3.48 (m, 1, C$_9$ H), 1.0–3.3 (m, 13), 0.0–0.8 (m, 5) IR 1725 (C=O) cm^{-1}; mass spectrum, *m/e* 311.1855 (C$_{20}$H$_{25}$NO$_2$ requires 311.1885).

17-(Cyclopropylmethyl)-4-hydroxymorphinan-6-one (9). A mixture of **8c** (0.16 g, 0.52 mmol), Zn dust (0.2 g), NH$_4$Cl (0.2 g, 3.3 mmol), and ethanol (20 mL) was heated at reflux in an oil bath under N$_2$ for 6 h. After cooling, it was filtered through a pad of Celite, and the solvent was removed under vacuum. The residue was taken up in H$_2$O (10 mL) and extracted with CH$_2$Cl$_2$ (3 × 40 mL). The combined CH$_2$Cl$_2$ extract was dried (Na$_2$SO$_4$) and concentrated to give 0.11 g (73%) of a foam. It was chromatographed over alumina (Woelm activity IV, 5 g), eluting with 10% MeOH in CH$_2$Cl$_2$. The product gave a single spot by TLC and a single peak by HPLC (μ-Porasil): NMR δ 6.90 (dd, 1, *J* = 7 and 8 Hz, C$_2$ H), 6.58 and 6.60 (2 d, 2, *J* = 7 and 8 Hz, C$_1$ H and C$_3$ H), 6.1 (br s, 1, OH), 4.44 (d, 1, *J* = 13 Hz, C$_{5\alpha}$ H), 1.6–3.4 (m, 15), 0.0–1.0 (m, 5); mass spectrum, *m/e* 309.1721 (C$_{20}$H$_{23}$NO$_2$ requires 309.1729).

Acetic Acid Writhing Test.[8] Male albino Charles–River mice (18–22 g) were used for this study; five mice per dose and at least three doses of drug per ED$_{50}$ were determined. Salts of the test compounds were administered in distilled H$_2$O; free bases were dissolved by the dropwise addition of dilute HCl and then further diluted with H$_2$O. The test drug was given by subcutaneous injection 15 min prior to an intraperitoneal injection of 0.5% HOAc (0.4 mL). The number of writhes per group was counted for 20 min, starting 5 min after the HOAc injection. Analgesic potency was calculated from the difference between test groups and their controls. ED$_{50}$ values with 95% confidence limits were determined by the method of Litchfield and Wilcoxon.[17]

(15) Y. Sawa, A. Hyogo, R. Maeda, O. Osaka, and H. Tada, U.S. Patent 3 654 280, 1972.

(16) Many such examples are known in opioids; e.g., in the oripavine series, see K. W. Bentley, A. L. A. Boura, A. E. Fitzgerald, D. G. Hardy, A. McCoubrey, M. L. A. Aikman, and R. E. Lister, *Nature (London)*, **206**, 102 (1965). For a discussion, see H. F. Fraser and L. S. Harris, *Annu. Rev. Pharmacol.*, **7**, 277 (1967).

(17) J. T. Litchfield, Jr., and F. Wilcoxon, *J. Pharmacol. Exp. Ther.*, **96**, 99 (1949).

(18) H. Rapoport, R. Naumann, E. R. Bissell, and R. M. Benner, *J. Org. Chem.*, **15**, 1103 (1950).

Rat Tail-Flick Procedure.[9] Male albino rats (100–120 g) were used for this study. Two control reaction times were determined 30 min apart and prior to intraperitoneal injection of test drug. An ED_{80} dose of morphine was administered 10 min later subcutaneously, and reaction times were then determined 20 min later. The narcotic antagonist activity was determined from the difference between the groups and control groups which received morphine alone. For agonist activity, the drug was administered

subcutaneously, the ED_{80} of morphine was eliminated, and the animals were retested 20 min postdrug.

Aporphines. 36.[1] Dopamine Receptor Interactions of Trihydroxyaporphines. Synthesis, Radioreceptor Binding, and Striatal Adenylate Cyclase Stimulation of 2,10,11-Trihydroxyaporphines in Comparison with Other Hydroxylated Aporphines[2]

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The presence of the A ring of aporphines and the addition of substituents to it and to other portions of the aporphine ring systems can extend explorations of the dimensions and other characteristics of the dopamine receptor. Accordingly, the synthesis and some physical and pharmacological properties of a series of (−)-2,10,11-trihydroxyaporphines (**3a–g**) are described. Structure–activity relationships among mono-, di-, and trihydroxyaporphines were evaluated against the high-affinity (nanomolar) binding of [³H]apomorphine (APO) and [³H]spiroperidol (SPR) with a subcellular fraction (P_4) of caudate nucleus from bovine brain. In addition, DA-sensitive adenylate cyclase activity was evaluated in homogenates of rat brain striatal tissue. The rank order of displacement of [³H]APO by potent aporphines ($IC_{50} \leq 30$ nM) correlated approximately with their ability to stimulate cyclic AMP synthesis. Potency orders against the two ligands were dissimilar; for example, increasing the size of N^6-alkyl substituents *increased* potency vs. [³H]SPR but not vs. [³H]APO binding. Moreover, [³H]SPR binding correlated poorly with cyclase activity or [³H]APO binding, suggesting a closer relationship of [³H]APO binding to dopamine-sensitive adenylate cyclase activity.

The existence of receptor surfaces has been offered as an explanation for structure–activity relationships of various classes of drugs and their relative agonist or antagonist properties and toxicity. Rigid analogues have been prepared in attempts to constrain receptor-active molecules in an hypothesized receptor-preferred conformation, for example, by the addition of an extra ring system or the introduction of a triple bond to limit carbon-chain flexibility. We have applied such a rigid-analogue approach to the evaluation of the receptor-site-preferred conformation of dopamine (DA) by securing the catechol and the amino groups of DA in a rigid conformation in apomorphine (APO) and related aporphines, which have served as useful models for studying the characteristics of DA receptors.[3,4] While it is generally accepted that the catechol moiety is required to produce optimum interactions with the DA receptor,[5–9] the presence of a catechol group is not sufficient to confer agonist activity on aporphines or phenethylamines.[5] Thus, for example, (±)-isoapomorphine (9,10-dihydroxyaporphine) and (−)-1,2-dihydroxyaporphine were inactive in behavioral or biochemical tests designed to reflect DA-agonist activity.[7,8,10,11] In previous studies we evaluated 8-, 10-, or 11-hydroxylated aporphines and found that (±)-11-hydroxy-N-n-propylnoraporphine (**2b**) yields apparent DA-receptor agonist activity when administered to rats in vivo.[12,13] Our earlier studies using behavioral and striatal cyclase activities as indexes of DA-receptor agonist activity of monohydroxyaporphines, such as 8-, 10-, or 11-hydroxy-N-propylnoraporphines, suggested that a hydroxyl function at the 11

position of the aporphine ring may contribute more to receptor binding[5] and in vivo biological activity than at the 10 position.[8,12–16] The 8-hydroxy-substituted apor-

(1) For Part 35, see V. J. Ram and J. L. Neumeyer, *J. Org. Chem.*, **46**, 2830 (1981).

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