reaction was brought to reflux for 1.5 h. The solution was allowed to cool to room temperature, and 4 mL of 32% HBr–HOAc was slowly added. After stirring for 45 min, the mixture was filtered to yield 342 mg of crude product; an additional crop of 791 mg was obtained by triturating the mother liquor with petroleum ether. The two crops were crystallized from MeOH–ether, affording 721 mg (49%) of **1a**, no definitive melting point. Anal. ($C_{17}H_{26}FeN_2 \cdot 2HBr$) C, H, Fe, N.

Compounds **1b**, **2**, and **3** were prepared as described above for **1a** in yields of 31, 58, and 42%, respectively; none of the compounds, isolated and analyzed as the hydrobromides, had a definitive melting point. The number of equivalents of BH_3 used to reduce the polyamides was determined by adding the following: 2.4 for each secondary amide present and 3.2 for each primary. In the preparation of tetraamine **3**, HBr treatment did not yield a solid precipitate; however, the addition of petroleum ether did give rise to solid material which crystallized from MeOH–ether.

4-Ferrocenylbutyramide. 4-Ferrocenylbutyric acid (2.7 g, 10.0 mmol), 1-hydroxybenzotriazole hydrate (1.4 g, 10.0 mmol), and DCC (2.2 g, 11.0 mmol) were combined in 150 mL of ether and allowed to stir for 2 h at room temperature. The solid was removed by filtration and washed with ether. The combined ether filtrate was chilled in an ice bath and stirred while NH_3 was bubbled in during 1 h. The solid which formed was removed by filtration, and the filtrate was washed with 0.5 N NaOH and saturated NaCl. The dried ($MgSO_4$) ether was evaporated leaving a solid which crystallized from EtOH–H_2O to yield 2.3 g (85%) of the amide, mp 72–79 °C. An analytical sample obtained by recrystallization had mp 77.5–80 °C. Anal. ($C_{14}H_{17}FeNO$) C, H, N.

4-Ferrocenyl-1-aminobutane Hydrobromide. 4-Ferrocenylbutyramide (500 mg, 1.9 mmol) was reduced with 1 N BH_3 in THF (5.9 mL, 5.9 mmol) as described for **1a**. After acidification with 1.25 mL of 32% HBr–HOAc, petroleum ether was added to separate the product as a green oil. The solvent was decanted and the oil dried in a vacuum desiccator over P_2O_5. Crystallization of the oil from EtOH–ether afforded 56 mg of a slightly crude product; concentration of the mother liquor and crystallization of the resultant oil from acetone–ether yielded another 137 mg of product, elevating the yield to 31%. Repeated recrystallization from EtOH–ether afforded an analytical sample, mp 119–122 °C. Anal. ($C_{14}H_{19}FeN \cdot HBr$) C, H, N.

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References and Notes

(1) (a) A. H. Soloway, I. Agranat, A. R. Chase, R. E. Hernandez, E. S. Kimball, T. Cascieri, Jr., and C. H. Cox, *J. Med. Chem.*, **17**, 918 (1974); (b) A. H. Soloway, J. E. Wright, V. Subramanyam, and J. J. Gozzo, *ibid.*, **20**, 1357 (1977).
(2) (a) B. Rosenberg, *Cancer Chemother. Rep., Part 1*, **59**, 589 (1975); (b) S. K. Aggarwal, R. W. Wagner, P. K. McAllister, and B. Rosenberg, *Proc. Natl. Acad. Sci. U.S.A.*, **72**, 928 (1975).
(3) S. S. Cohen, "Introduction to the Polyamines", Prentice-Hall, Englewood Cliffs, N.J., 1971, p 109.
(4) T. J. Gill and L. T. Mann, Jr., *J. Immunol.*, **96**, 906 (1966).
(5) R. I. Geran, N. H. Greenberg, M. M. Macdonald, A. M. Schumacher, and B. J. Abbot, *Cancer Chemother. Rep., Part 3*, **3**, 1 (1972).
(6) It was suggested to us subsequent to the completion of this study that the mice used in the P-388 leukemia protocol might not be immunologically mature (~9 weeks old). In fact, the mice were ~6 weeks old. It should be noted, therefore, that the haptenic aspect of the test may not have been given a fair chance to exhibit itself.
(7) K. L. Rinehart, Jr., R. J. Curby, Jr., and P. E. Sokol, *J. Am. Chem. Soc.*, **79**, 3420 (1957).

2,3-Dihydroxy-9-amino-9,10-dihydrophenanthrene, a Rigid Congener of Dopamine and Isoapomorphine

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A rigid dopamine congener, 2,3-dihydroxy-9-amino-9,10-dihydrophenanthrene, was synthesized and tested for the ability to dilate the renal artery in dogs. The compound was found to be inactive in this assay at molar doses 1000 times greater than required for dopamine. This result is similar to isoapomorphine. The title compound was also examined for its ability to stimulate rat striatal adenylate cyclase. In concentrations of 10–100 μM no effect was observed. The phenanthrene also showed no ability to block dopamine-induced stimulation of adenylate cyclase.

Cannon et al.[1] have reported the synthesis and preliminary biological evaluation of 3,4-dihydroxy-9-*N*,*N*-dimethylamino-9,10-dihydrophenanthrene, a congener of apomorphine. This compound, however, possessed relatively low emetic activity and was completely devoid of apomorphine-like activity on heart and blood pressure. On the basis of the NMR spectra of this and related compounds, Cannon concluded that the lack of activity could be due to the fact that the dimethylamino group exists primarily in the pseudoaxial conformation. This conclusion is in agreement with a later study dealing with conformational preferences of 9-substituted 9,10-dihydrophenanthrenes.[2]

Isoapomorphine (**1**) has little or no central emetic action and does not elicit a gnawing response in rats at ten times the median effective dose of apomorphine.[3] However, Pinder et al.[4] found that the simpler aminotetralin congener of isoapomorphine, 6,7-dihydroxy-2-aminotetralin (ADTN, **2**), was more potent than dopamine in hyperpolarization and inhibition of neurons in the snail, *Helix aspersa*. Most important was the finding that ADTN possessed potent vasodilator activity in the kidney.[5] Isoapomorphine (**1**), however, does not produce renal vasodilation.

We decided to prepare 2,3-dihydroxy-9-amino-9,10-dihydrophenanthrene (**3**) in order to complete the de-

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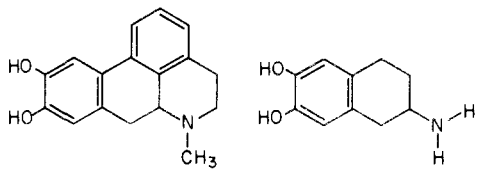

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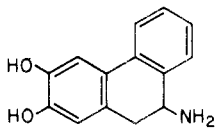

3

scription of this series of dopamine congeners. It was anticipated that the conformational equilibrium would also favor a pseudoaxial amino substituent in the case of the proposed compound.

Chemistry. The precedented[1] approach to the synthesis of the target compound involves Pschorr cyclization of (*E*)-2-phenyl-3-(2-amino-4,5-dimethoxyphenyl)propenoic acid (**5**), as shown in Scheme I. Reduction of the 9,10 bond, followed by Curtius rearrangement and ether cleavage, led to the desired compound **3**. Two major attempts were made to modify this route. The nitro acid **4** was reduced directly to the aminopropanoic acid **9**. It was anticipated that cyclization might lead directly to the 9,10-dihydrophenanthrene **7**. Instead, cyclization gave a mixture of products, none of which appeared to be the desired acid.

Attempts to use catalytic hydrogenation[6] to reduce the 9,10 bond in the phenanthrenecarboxylic acid **6**, under a variety of conditions, were unsatisfactory.

Results and Discussion

The phenanthrene derivative **3** was evaluated for dopamine-like activity in three dogs anesthetized with pentobarbitol, 30 mg/kg. Dopamine given intraarterially in 3×10^{-9}–1.9×10^{-7} mol produced dose-related increases in renal blood flow. The phenanthrene derivative **3** did not appear to cause noticeable vasodilation in doses up to 3×10^{-6} mol, about 1000 times the threshold dose for dopamine.

The ability of the phenanthrene **3** to activate adenylate cyclase in rat straital homogenates was also examined, using the method described by Kebabian et al.[7] The cAMP was measured using the protein kinase binding assay of Gilman,[8] and protein was determined by the method of Lowry et al.[9] The results are presented in Table I.

We are not able to tell whether this lack of activity is due to an unfavorable conformational equilibrium, as proposed by Cannon[1] for apomorphine congeners, or simply to the added steric bulk of the aromatic ring in comparison with the tetralin derivative **2**. The coupling constant $J_{9,10} = J_{9,10'} = 3.9$ Hz, measured for **3**, indicates that the amino group preferentially exists in the pseudoaxial conformation. We also examined the NMR spectrum for the *N*-benzoyl derivative of **8**. One would anticipate that the relatively larger *N*-benzoyl group would be forced predominately to assume the pseudoaxial conformation due to a more unfavorable peri interaction with the hydrogen at C-8. This is borne out by the average observed coupling constant of 4.7 Hz for the benzylic protons. If the *N*-benzoyl resided in the pseudoequatorial conformation, one would have expected to observe two different coupling constants of widely different magnitude as shown by Joshua et al.[10] For the rigid isomers of 9-dimethylamino-9,10-dihydro-4,5-dimethylphenanthrene, these workers observed the coupling constants for the benzylic protons of the isomer with the pseudoaxial dimethylamino to be $J_{ee} = 2.6$ Hz and $J_{ea} = 3.5$ Hz. On the other hand, for the isomer with the pseudoequatorial amino group, the observed coupling constants were $J_{ae} = 3.21$ Hz and $J_{aa} = 13.23$ Hz.

Scheme I

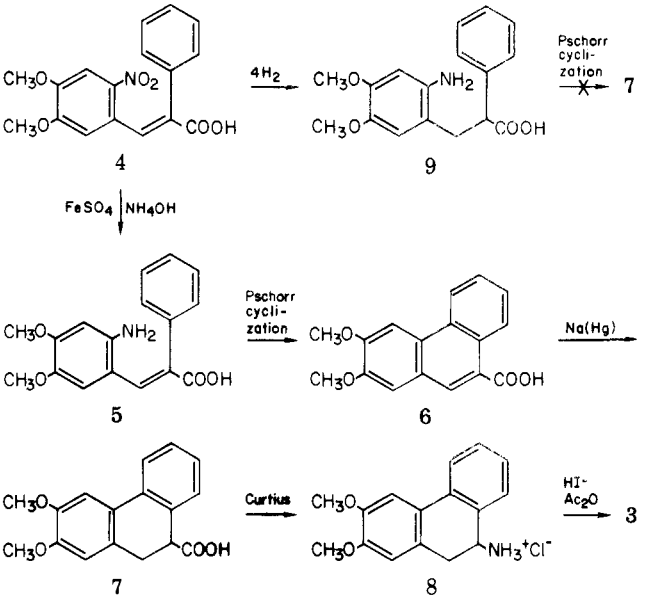

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Table I. Activity of Phenanthrene 3 on Rat Striatal Adenylate Cyclase[a]

Test substance (μM)	Adenylate cyclase act. (% of control[b])
Dopamine (100)	150 ± 1*
3 (10)	100 ± 5
3 (100)	92 ± 12
3 (100) + dopamine (100)	149 ± 8*

[a] Data represent the mean ± SEM for adenylate cyclase activity measured in four separate tissue homogenates. Enzyme activity was measured in three replicate samples from each homogenate. It can be seen that the phenanthrene **3** had no effect at concentrations between 10 and 100 μM and it also did not block dopamine-induced stimulation of adenylate cyclase. [b] In the absence of dopamine, cAMP levels were 98 ± 5 pmol/min/mg of protein. An asterisk indicates $p < 0.01$.

Experimental Section

Melting points were determined on a Thomas-Hoover Uni-Melt or Mel-Temp apparatus and are uncorrected. Infrared spectra were determined with a Beckman IR-33 instrument, and 60-MHz nuclear magnetic resonance spectra were recorded on a Varian EM-360 spectrometer and are recorded in parts per million using tetramethylsilane as an internal standard. Conformational studies were done using a Varian FT-80 spectrometer. Low-resolution mass spectra were obtained on a Du Pont 21-492 spectrometer. Thin-layer chromatography (TLC) was performed on Baker-flex silica gel IB2-F precoated sheets. Elemental analyses were performed by the Purdue Microanalytical Laboratory and were within ±0.4% of the calculated values.

Pharmacology. Renal Blood Flow. Mongrel dogs of either sex weighing 15–20 kg were anesthetized with pentobarbital, 30 mg/kg iv. A tracheotomy was performed and the animals were placed on a respirator with room air. The carotid artery was cannulated and blood pressure recorded using a Statham P23D transducer amplified by a Beckman type R dynograph. The jugular vein was cannulated to provide an intravenous line for fluid replacement and anesthetic supplementation.

The procedure described by McNay and Goldberg[11] was followed. Renal blood flow was measured with a Statham elec-

tromagnetic flow probe and an M4001 flow meter. A 23-gauge needle, bent about 90° 5 mm from the tip, was placed in the artery for injection of drugs. Phenoxybenzamine (POB), 5–10 mg/kg, was infused into the renal or femoral artery during a 15–20 min period; 10–20 mL/kg of 0.9% sodium chloride was administered intravenously to maintain blood pressure. After systemic blood pressure and blood flow had stabilized, the test compound was injected intraarterially in a constant volume of 0.2 mL. The compound was administered in fourfold dosage increments over a range of 1.8 log units.

(*E*)-2-Phenyl-3-(2-nitro-4,5-dimethoxyphenyl)propenoic Acid (4). This was prepared according to Fieser's directions.[12] A slurry of 13.6 g (0.1 mol) of 6-nitroveratraldehyde,[13] 10 mL of acetic anhydride, and 10 mL of triethylamine was heated with stirring at 160 °C for 1 h. To the cool, but liquid reaction mixture was added 20 mL of concentrated hydrochloric acid. The resulting solid was transferred to a separatory funnel with dichloromethane, washed with water (3 × 20 mL), and extracted with a 5% sodium hydroxide solution (300 mL and 3 × 150 mL). The combined basic extract was acidified with acetic acid to precipitate 24.0 g (73%) of **4**: mp 217–220 °C (lit.[14] mp 219 °C); IR (KBr) 3340 and 1710 cm^{-1}; NMR (TFA) δ 3.53 (s, 3, Ar-OCH_3), 4.05 (s, 3, Ar-OCH_3), 4.05 (s, 3, Ar-OCH_3), 6.56 (s, 1, Ar-H), 7.37 (br s, 5, Ar-H), 7.92 (s, 1, Ar-H), 8.57 (s, 1, Ar-H).

(*E*)-2-Phenyl-3-(2-amino-4,5-dimethoxyphenyl)propenoic Acid (5). The method of Pschorr[15] was used. To a solution of 135 g of ferrous sulfate heptahydrate in 450 mL of water was added 300 mL of concentrated ammonium hydroxide, and the resulting suspension was heated to reflux. To this was added, over 20 min, a solution of 20.0 g (0.061 mol) of **4** in 500 mL of dilute ammonium hydroxide. The reaction mixture was heated at reflux for 1 h after the addition was complete and was set aside for 3 h at room temperature. The hydroxides were removed by filtration through a Celite pad, and the solution was adjusted to pH 5.4 with concentrated hydrochloric acid. The precipitated solid was collected, dried, and dissolved in dry acetone. Insoluble ammonium sulfate was removed by filtration and the acetone was removed at reduced pressure to yield 17.5 g (95%) of **5**: mp 189 °C dec (lit.[15] mp 209 °C); homogeneous by TLC (chloroform–methanol, 8:2).

2,3-Dimethoxyphenanthrene-9-carboxylic Acid (6). The modification of the Pschorr cyclization reported by Chauncey and Gellert was employed.[16] To a solution of 16.0 g (54 mmol) of **5**, in 1600 mL of dry acetone, was added 29 mL of 20% sulfuric acid. The white suspension of the hydrogen sulfate salt was diazotized between 0 and 5 °C by the addition of 14 mL of isoamyl nitrite; stirring was continued at ice-bath temperature for 1.25 h. Solid sodium iodide (32 g) was then added. After the evolution of gas ceased (15 min), the mixture was poured into 1.5 L of hot water. Continued heating (steam bath) caused evaporation of the acetone and, after cooling, the precipitated solid was collected. Fractional recrystallization from ethanol yielded 8.15 g (54%) of **6** as tan needles: mp 268–270 °C (lit.[15] mp 272 °C). Evaporation of the mother liquor gave a crude solid which yielded 3.15 g (14.5%) of 2-iodo-4,5-dimethoxy-α-phenylcinnamic acid upon recrystallization from ethyl acetate (charcoal): mp 213–216 °C (lit.[16] mp 223–224 °C).

2,3-Dimethoxy-9,10-dihydrophenanthrene-9-carboxylic Acid (7). The reduction was carried out by the method of Schlittler and Muller.[17] To a vigorously stirred solution of 8.6 g (0.031 mol) of **6**, in 300 mL of water and 30 mL of 2 N sodium hydroxide, was added 174 g of 4% sodium amalgam in small pieces over 30 min. Periodically during the reduction sufficient 2 N hydrochloric acid was added to maintain some flocs of undissolved acid. After 6 h, enough 2 N sodium hydroxide was added to give complete solution, and the liquid was decanted from the still active amalgam. The supernatant was filtered and acidified with concentrated hydrochloric acid. The product was collected by suction filtration and dried to give a quantitative yield of **7**, mp 171–173 °C (with prior softening). Several recrystallizations from acetone–hexane raised the melting point to 172–174 °C: IR (KBr) 3400 (br), 1715 and 1690 cm^{-1}; NMR (Me_2SO-d_6) δ 3.03 (apparent t, 2, ArCH_2CH–), 3.65–3.90 (two overlapping s obscuring the methine signal, 7, Ar-OCH_3 and Ar-CH_2CH–), 6.87 (s, 1, Ar-H), 7.12–7.48 (m, 4, Ar-H), 7.65–7.90 (m, 1, Ar-H), 12.21 (br s, –CO_2H). Anal. ($C_{17}H_{16}O_4$) C, H.

2,3-Dimethoxy-9-amino-9,10-dihydrophenanthrene Hydrochloride (8). To a solution of 4.10 g (14.5 mmol) of **7** in 45 mL of dry acetone, maintained at –5 to –10 °C (salt–ice bath), was added 1.73 g (17 mmol) of triethylamine in 14 mL of dry acetone and then 2.12 g (19.5 mol) of ethyl chloroformate in 7 mL of dry acetone. Stirring was continued at –5 to –10 °C for 1.5 h. A solution of 1.45 g (22.3 mmol) of sodium azide in 4.4 mL of water was then added over 5 min. After stirring for 1 h at –5 to –10 °C, the suspension was poured into cold water and extracted with toluene (4 × 60 mL). The combined extract was dried over magnesium sulfate. The magnesium sulfate was then removed by filtration and the toluene solution was heated on a steam bath until evolution of nitrogen ceased (40 min). The toluene was removed at reduced pressure. The oily residue was treated with 25 mL of water and 30 mL of concentrated hydrochloric acid and heated at reflux for 3.5 h. Volatiles were removed at reduced pressure and the residue was treated with 100 mL of 3.5 N sodium hydroxide solution. The resulting suspension was extracted with ether (4 × 100 mL). The combined extract was dried over magnesium sulfate. The ether solution was filtered and the volume was reduced to 50 mL. This solution of the free amine was treated with an excess of ethereal hydrogen chloride and the resulting solid was recrystallized from 2-propanol–hexane to yield 2.85 g (67%) of **8**: mp 253–255 °C (with prior softening); IR (KBr) 3420 (br) and 2020 cm^{-1}; NMR (Me_2SO-d_6) δ 3.17 (d, 2, Ar-CH_2CH–), 3.82 (s, 3, Ar-OCH_3), 3.90 (s, 3, Ar-OCH_3), 4.52 (t, 1, Ar-CH_2CH-Ar), 7.00 (s, 1, Ar-H), 7.29–7.80 (m, 4, Ar-H), 7.89–8.17 (m, 1, Ar-H), 8.79 (s, 2+, D_2O exchangeable, –NH_3^+). Anal. ($C_{16}H_{18}ClNO_2$) C, H, N.

2,3-Dihydroxy-9-amino-9,10-dihydrophenanthrene Hydroiodide (3). This was prepared using Neumeyer's procedure.[3] To a slurry of 583 mg (2 mmol) of **8** in 7.0 mL of 48% hydriodic acid under nitrogen was slowly added 5.0 mL of 98% acetic anhydride. The mixture was heated in an oil bath at 140 °C for 1 h. The solid gradually went into solution with the development of a slightly yellow color. The solution was cooled to room temperature and the volatiles were removed at reduced pressure (steam bath). The resulting tan solid was slurried in water and the water was removed at reduced pressure. After several such treatments, the solid was dried, washed with ethyl acetate, and thoroughly dried to yield 587 mg (82%) of **3**·HI: mp 155–156 °C (with prior softening from 150 °C). Recrystallization from ethanol–ethyl acetate–hexane raised the melting point to 163–164 °C: IR (KBr) 3600–2400 cm^{-1}; NMR (Me_2SO-d_6) δ 2.83 (apparent d, 2, Ar-CH_2CH–), 4.40 (apparent t, 1, Ar-CH_2CH), 6.63 (s, 1, Ar-H), 7.09–7.80 (m, 5, Ar-H), 8.23 (br s, 5, D_2O exchangeable, Ar-OH and –NH_3^+). Anal. ($C_{14}H_{14}INO_2$) C, H, N.

2,3-Dimethoxy-(*N*-benzoylamino)-9,10-dihydrophenanthrene. To a solution of 50 mg (0.17 mM) of **8** in 1 mL of dry pyridine was added 48 mg (0.34 mM) of benzoyl chloride. The reaction was stirred at room temperature for 24 h and then poured into 20 mL of 6 N HCl. The aqueous acid solution was extracted repeatedly with 5-mL portions of $CHCl_3$. The $CHCl_3$ extracts were combined, washed with 10% Na_2CO_3 and water, and dried ($MgSO_4$). Removal of the solvent under reduced pressure gave 50.4 mg (82%) of solid material which was recrystallized from EtOAc–hexane: mp 253–254 °C; NMR ($CDCl_3$) δ 3.14 (d, 2, Ar-CH_2CH–), 3.90, 3.98 (2 s, 6, Ar-OCH_3), 5.46 (m, 1, Ar-CH_2CH-Ar), 6.29 (d, 1, –NH–), 6.77 (s, 1, Ar-H), 7.14–7.79 (m, 10, Ar-H). Chemical-ionization mass spectrometry showed an M + 1 ion at *m/e* 360.

References and Notes

(1) J. G. Cannon, R. V. Smith, M. A. Aleem, and J. P. Long, *J. Med. Chem.*, **18**, 108 (1975).
(2) G. R. Harvey, P. W. Rabideau, and P. P. Fu, *J. Org. Chem.*, **41**, 3722 (1976).
(3) J. L. Neumeyer, M. McCarthy, S. P. Battista, F. J. Rosenberg, and D. G. Teiger, *J. Med. Chem.*, **16**, 1228 (1973).
(4) R. M. Pinder, D. A. Buxton, and G. N. Woodruff, *J. Pharm. Pharmacol.*, **24**, 903 (1972).
(5) J. H. Crumly, Jr., R. M. Pinder, W. B. Hinshaw, and L. I. Goldberg, *Nature (London)*, **259**, 584 (1976).
(6) D. D. Phillips, "Organic Syntheses", Collect. Vol. IV, N. Rabjohn, Ed., Wiley, New York, N.Y., 1963, p 313.
(7) J. W. Kebabian, G. L. Petzold, and P. Greengard, *Proc. Natl.*

Acad. Sci. U.S.A., 69, 2145 (1972).
(8) A. G. Gilman, Proc. Natl. Acad. Sci. U.S.A., 67, 305 (1970).
(9) O. H. Lowry, N. J. Rosebrough, A. L. Farr, and R. J. Randall, J. Biol. Chem., 193, 265 (1951).
(10) H. Joshua, R. Gans, and K. Mislow, J. Am. Chem. Soc., 90, 4884 (1968).
(11) J. L. McNay and L. I. Goldberg, J. Pharmacol. Exp. Ther., 151, 23 (1966).
(12) L. Fieser, "Experiments in Organic Chemistry", 3rd ed, D. C. Heath, Boston, Mass., 1957, p 182.
(13) C. A. Fletscher in ref 6, p 735.
(14) J. W. Cook, J. D. Loudon, and R. K. Razdan, J. Chem. Soc., 4235 (1954).
(15) R. Pschorr and W. Buckow, Ber. Dtsch. Chem. Ges., 33, 1829 (1900).
(16) B. Chauncey and E. Gellert, Aust. J. Chem., 22, 993 (1969).
(17) E. Schlittler and J. Muller, Helv. Chim. Acta, 31, 1119 (1948).

Studies in the (+)-Morphinan Series. 5.[1] Synthesis and Biological Properties of (+)-Naloxone

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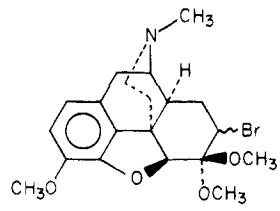
(+)-Naloxone was prepared in 26% overall yield in eight steps from (+)-7-bromodihydrocodeinone dimethyl ketal by a synthesis which excluded enantiomeric contamination. (+)-Naloxone was examined in three assay systems and found to have no more than $^1/_{1000}$–$^1/_{10\,000}$th the activity of (−)-naloxone; it can, thus, serve to test the stereospecificity of the biochemical and pharmacological actions of (−)-naloxone.

(−)-Naloxone (the enantiomer of **9**), prepared from natural thebaine (enantiomer of **2**), is in many assay systems a pure narcotic antagonist with no agonist activity. It is, therefore, widely used clinically to reverse opiate overdose symptoms and biochemically as a test for opiate receptor mediated phenomena. Since (−)-naloxone may exhibit pharmacological actions of its own,[2,3] reversal of a particular biological response by (−)-naloxone is not necessarily evidence that this activity is mediated by opiate receptors. Such ambiguities could be resolved by parallel experiments with the enantiomer, (+)-naloxone (**9**). This enantiomer would presumably not interact with the opiate receptor and would not share the specific actions of (−)-naloxone (enantiomer of **9**). Accordingly, we have prepared (+)-naloxone by a stereochemically controlled synthesis from (−)-sinomenine and have compared its activity to that of (−)-naloxone in several in vitro systems.



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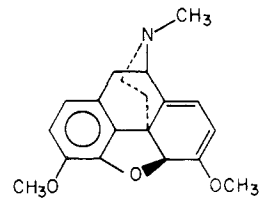

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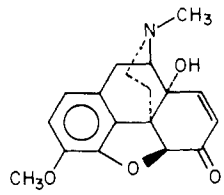

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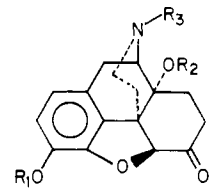

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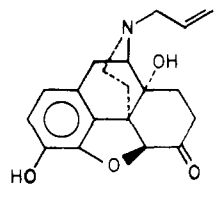

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Chemistry. Our goal could be achieved only after marked improvements had been made in the synthesis of (+)-dihydrocodeinone from natural (−)-sinomenine[1] and in the conversion of (−)-dihydrocodeinone into natural (−)-thebaine.[4] Bromo ketal **1**, prepared in five steps from sinomenine,[1] was the intermediate of choice since its (−) enantiomer had successfully been converted into (−)-thebaine,[4] starting material for the commercial synthesis of (−)-naloxone.[5] Starting with bromo ketal **1**, reactions carried out in the (+) series were as follows. Treatment of **1** with *t*-BuOK[4] in Me_2SO at 80–90 °C afforded (+)-thebaine (**2**), identical with the natural alkaloid except for its opposite optical rotation. Model experiments carried out in the (−) series suggested that oxidation of **2** with peroxide could be performed best with performic acid prepared in situ, affording the desired 14-hydroxy ketone **3** in excellent yield.[6] Catalytic hydrogenation of unsaturated ketone **3** gave saturated ketone **4** which, upon O-demethylation with BBr_3, gave phenolic hydroxy ketone **5**. Protection of the hydroxy groups by acetylation, followed by N-demethylation with cyanogen bromide in chloroform, yielded the *N*-cyano derivative **7**, via diacetoxy compound **6**. Refluxing the *N*-cyano compound **7** in 25% sulfuric acid effected deacetylation, hydrolysis, and decarboxylation and led to the desired secondary amine **8** in high yield. Since amine **8** is difficult to purify, it is a prerequisite in this synthesis that its precursors are chemically and optically pure. Synthesis of (+)-naloxone (**9**) was completed by routine N-allylation which gave the final product **9** as colorless prisms. This material was identical in every respect with a commercial sample of (−)-naloxone, except for its opposite optical rotation.[7]

Biological Results. (+)-Naloxone, prepared by a synthesis which excludes enantiomeric contamination, was examined in a brain receptor binding assay, in the guinea pig ileum assay, and in the neuroblastoma × glioma hybrid cell adenylate cyclase assay.

Rat Brain Receptor Binding Assay. Comparison of displacement of [^{3}H]-(−)-naloxone from opiate receptors