1. The atom labeled "H?" was placed at an approximate position for the hypothetical N(3) hydrogen atom [1 Å from N(3) along the bisector of the C(2)-N(3)-C(4) angle]. This is a very improbable location for a H atom because the 1.6-Å H···H? approach illustrated in Figure 1 is *ca.* 0.8 Å shorter than the sum of the H van der Waals radii (2.4 Å).

The structure of chlorguanide hydrochloride has been clarified by the experimental determination of the six biguanidinium hydrogen atoms Because of the extensive delocalization in the cation, it was not possible to locate the two C-N double bonds shown in structure **1b**. However, the structure of chlorguanide hydrochloride can be thought of as the resonance hybrid of the cation formed by protonation of **1b** at N(5).

Finally, the expected structural similarity between the conjugate acids of chlorguanide (**1b**·HCl) and the cycloguanil analog (**2b**·HCl) has been verified.

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References

(1) R. M. Pinder, "Medicinal Chemistry," Part 1, 3rd ed, A. Burger, Ed., Wiley-Interscience, New York, N. Y., 1970, p 499; A. Brossi, *Pure Appl. Chem.*, **19**, 171 (1969).
(2) C. J. Brown, *J. Chem. Soc. A*, 60 (1967).
(3) "The X-ray System-Version of June 1972," Technical Report TR-192 of the Computer Science Center, University of Maryland, June 1972.
(4) A. Damiani, E. Giglio, and A. Ripamonti, *Acta Crystallogr.*, **22**, 692 (1967).

Synthesis and Biological Activity of (6a*S*)-10,11-Dihydroxyaporphine, the Optical Antipode of Apomorphine

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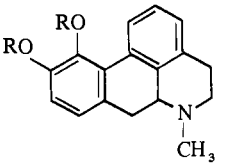
Apomorphine, (−)-**1**, has been shown to stimulate the dopaminergic system in the rat corpus striatum[1] and to produce a dopamine-like renal vasodilation in dogs.[2] On the basis of its dopamine receptor-stimulating properties, apomorphine has been investigated for the treatment of Parkinson's disease.[3,4] We have now prepared the previously undescribed optical antipode of apomorphine and have compared it with apomorphine in these dopaminergic systems.

The dimethyl ether of racemic apomorphine, **2**, prepared essentially by the method of Neumeyer, *et al.*[5] (for other syntheses of the racemic dimethyl ether, see ref 6), was resolved using the tartaric acid enantiomers. The dextrorotatory tartrate salt of **2**, which precipitated when the unnatural (−)-tartaric acid was used, was recrystallized until resolution was judged complete by comparison with a sample of authentic levorotatory dimethyl ether **2**. Levorotatory **2** was prepared by the action of diazomethane on apomorphine.[6d] It could also be obtained from *rac*-**2** through the use of natural (+)-tartaric acid as the resolving agent. Demethylation of (+)-**2** with a mixture of hydriodic acid and acetic anhydride gave (+)-**1** in 49% yield. Since apomorphine, (−)-**1**, has been shown to have an absolute stereochemistry designated as 6a*R*,[7-9] the newly prepared dextrorotatory isomer, (+)-**1**, as well as (+)-**2**, must have 6a*S* absolute configuration.



1, R = H
2, R = CH_3

Biological Results. The dihydroxyaporphine, (+)-**1**, its dimethyl ether, (+)-**2**, and the dimethyl ether of apomorphine, (−)-**2**, were examined for both apomorphine-like activity and as apomorphine antagonists using the caudate brain lesioned mouse preparation described by Lotti.[10] In this preparation apomorphine produces characteristic postural asymmetries which can be specifically blocked by apomorphine antagonists. The compounds were administered intraperitoneally, at a minimum of four dose levels, to groups of at least ten mice per dose and the mice observed for postural asymmetries 10, 20, and 60 min later. The highest dose of each compound tested was in excess of 25 times the dose of apomorphine (0.96 mg/kg ip) necessary to produce postural asymmetries in 50% of the lesioned mice.

Unlike apomorphine, none of the compounds were effective in producing postural asymmetries in caudate-lesioned mice. Similarly, when administered 1 hr prior to apomorphine, they were ineffective in antagonizing the response to apomorphine (4.0 mg/kg ip) in this preparation.

The dihydroxyaporphine (+)-**1** was additionally examined for its ability to induce emesis in dogs. Emesis was not observed in a group of six dogs administered (+)-**1** (0.14 mg/kg iv), whereas apomorphine was 100% effective when administered at $^1/_{10}$ this amount. When (+)-**1**, at doses of 1.0 and 100 μg/kg/min, was infused directly into a renal artery of an anesthetized dog, no increases in renal blood flow and no effect on blood pressure or heart rate were observed.

The results suggest that the optical antipode of apomorphine, (+)-**1**, its dimethyl ether, (+)-**2**, and the dimethyl ether of apomorphine,† (−)-**2**, do not possess significant apomorphine-like activity nor are they effective apomorphine antagonists.

Experimental Section

All melting points were obtained on a calibrated Thomas-Hoover Unimelt capillary melting point apparatus using open capillaries. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4 % of the theoretical values. Nmr spectra were recorded with Varian A-60A and HA-100D spectrophotometers (Me_4Si) and uv spectra with a Cary recording spectrophotometer, Model 11MS, in O_2 free EtOH. Optical rotations were determined with a Zeiss photoelectric precision polarimeter or a Perkin-Elmer polarimeter, Model 141. Tlc's

†The conclusion that the dimethyl ether of apomorphine, (−)-**2**, does not possess significant apormorphine-like activity is supported by the observation of Bergell and Pschorr[11] that this compound is "free of emetic action."

were performed on fluorescent silica gel G plates, spots detected by uv or exposure to I_2 vapor.

(6a*S*)-10,11-Dimethoxyaporphine Hydrogen (2*S*,3*S*)-Tartrate (2). A solution of 3.0 g (20 mmol) of (−)-tartaric acid in 20 ml of 50% EtOH-EtOAc was added to a solution of 5.0 g (17 mmol) of *rac*-10,11-dimethoxyaporphine base[5] in 10 ml of EtOAc. After adding more EtOAc and cooling, the insoluble crude tartrate salt was recrystallized several times from EtOH-EtOAc-hexane to give 0.85 g of (+)-10,11-dimethoxyaporphine hydrogen (−)-tartrate with a constant melting point of 179–184° dec, $[\alpha]^{25}D$ +64.0° (*c* 1, H_2O).‡ The nmr (D_2O) of this tartrate salt and tlc R_f (5% MeOH-$CHCl_3$) of the corresponding base were identical with those of the 6a*R* isomer.[6d] *Anal.* ($C_{19}H_{21}NO_2 \cdot C_4H_6O_6$) C, H, N.

(6a*R*)-10,11-Dimethoxyaporphine Hydrogen (2*R*,3*R*)-Tartrate (2). Mother liquors from isolation of the 6a*S* isomer were combined, concentrated, and converted to 3.7 g of base with 5% NaOH and Et_2O extraction. After addition of 3 g of (+)-tartaric acid and several recrystallizations from EtOH-EtOAc-hexane, 500 mg of (−)-10,11-dimethoxyaporphine hydrogen (+)-tartrate, mp 177–183° dec, $[\alpha]^{25}D$ −59.6° (*c* 1, H_2O), was obtained and found to be identical by nmr (D_2O), tlc (5% MeOH-$CHCl_3$ on the base), and mixture melting point with an authentic sample prepared from apomorphine.[6d] *Anal.* ($C_{19}H_{21}NO_2 \cdot C_4H_6O_6$) C, H, N.

(6a*S*)-10,11-Dihydroxyaporphine Hydrochloride (1). The base obtained from 100 mg (0.224 mmol) of (6a*S*)-10,11-dimethoxyaporphine hydrogen (2*S*,3*S*)-tartrate by neutralization with saturated $NaHCO_3$ solution and EtOAc extraction was dissolved in 1.5 ml of Ac_2O and added to a mixture of 1.0 ml of 57% HI and 1.0 ml of Ac_2O. The HI-Ac_2O mixture was decolorized by warming on the steam bath with a few drops of H_3PO_2 and cooling to room temperature before addition of the aporphine. The mixture was stirred at reflux under CO_2 for 2 hr and cooled and 3 ml of H_2O was added. After concentrating under reduced pressure at 80–90°, 5 ml of H_2O was added and the solution was concentrated again. Excess saturated $NaHCO_3$ was added to the residue and the crude product extracted with EtOAc which was then washed (saturated NaCl-H_2O), dried (Na_2SO_4), and filtered. Excess EtOH-anhydrous HCl solution (7 *N*) was added and after complete removal of solvent under reduced pressure at 40–50°, the residue was dissolved in 8 ml of 50% MeOH-EtOAc and filtered. The filtrate was concentrated at 15 mm of pressure and 40–50° until solid began to precipitate. After cooling, the product was filtered and dried immediately at 100° and 0.2 mm to give 35 mg (49%) of (6a*S*)-10,11-dihydroxyaporphine hydrochloride hydrate, mp 178–180° shrink, 220° darken, 258–268° dec. An analytical sample was obtained by drying at 138° (0.2 mm): mp 200° darken, 265.0–268.0° dec; $[\alpha]^{25}$ 5780 Å +55.3°, 5460 Å +68.7°, 4360 Å +69.4° (*c* 0.15, O_2 free EtOH); λ max 2745 Å (ε 17,300), 3126 (3960), sh 2640–2700, 2810–2870.§ The nmr (DMSO-d_6) of this sample and tlc R_f (5% MeOH-$CHCl_3$) of the corresponding base were identical with those of an authentic sample of (6a*R*)-10,11-dihydroxyaporphine (apomorphine) hydrochloride hemihydrate. *Anal.* ($C_{17}H_{17}NO_2 \cdot HCl$) C, H, N.

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References

(1) A. M. Ernst and P. G. Smelik, *Experientia*, 22, 837 (1966); N. E. Andén, A. Rubenson, K. Fuxe, and T. Hökfelt, *J. Pharm. Pharmacol.*, 19, 627 (1967).
(2) L. I. Goldberg, P. F. Sonneville, and J. L. McNay, *J. Pharmacol. Exp. Ther.*, 163, 188 (1968).
(3) G. C. Cotzias, P. S. Papavasiliou, C. Fehling, B. Kaufman, and E. Mena, *N. Engl. J. Med.*, 282, 31 (1970); S. Daley, G. C. Cotzias, A. Steck, and P. S. Papavasiliou, *Fed. Proc., Fed. Amer. Soc. Exp. Biol.*, 30, 216 (1971).
(4) P. Castaigne, D. Laplane, and G. Dordain, *Res. Commun. Chem. Pathol. Pharmacol.*, 2, 154 (1971).
(5) J. Neumeyer, B. Neustadt, and K. Weinhardt, *J. Pharm. Sci.*, 59, 1850 (1970).
(6) (a) S. Sugasawa and R. Tachikawa, *Tetrahedron*, 4, 205 (1958); (b) D. Hey and A. Palluel, *Chem. Ind. (London)*, 40 (1955); (c) D. Hey and A. Palluel, *J. Chem. Soc.*, 4123 (1956); (d) E. Späth and O. Homatka, *Chem. Ber.*, 62, 325 (1929).
(7) H. Corrodi and E. Hardegger, *Helv. Chim. Acta*, 38, 2038 (1955).
(8) J. Cymerman Craig and S. K. Roy, *Tetrahedron*, 21, 395 (1965).
(9) M. Shamma in "The Alkaloids," Vol. 9, R. H. F. Manske, Ed., Academic Press, New York, N. Y., 1967, p 30.
(10) V. J. Lotti, *Life Sci.*, 10, 781 (1971).
(11) P. Bergell and R. Pschorr, *Ther. Gegenw.*, 45, 247 (1906).

‡ A sample of (6a*R*)-10,11-dimethoxyaporphine hydrogen (2*R*,3*R*)-tartrate, mp 177–182° dec, prepared from apomorphine and CH_2N_2,[6d] was found to have $[\alpha]^{25}D$ −65.9° (*c* 1, H_2O).

§ Found for an authentic sample of (6a*R*)-10,11-dihydroxyaporphine (apomorphine) hydrochloride hemihydrate: mp 220° darken, 258–268° dec; $[\alpha]^{25}$ 5780 Å 62.0°, 5460 Å 68.1°, 4360 Å 79.4° (*c* 0.15, O_2 free EtOH); λ max 2750 Å (ε 18,200), 3132 (3750), sh 2650–2680, 2810–2855.

5-Benzoyl-1-methylpyrrole-2-acetic Acids as Antiinflammatory Agents. 2. The 4-Methyl Compounds

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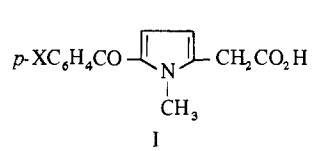
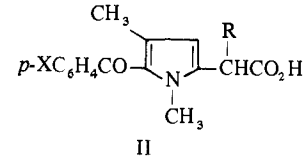
We recently disclosed some 5-benzoyl-1-methylpyrrole-2-acetic acids (I) which had antiinflammatory activity.[1] The potency of these compounds was intermediate between phenylbutazone and indomethacin (III).

We would like to report on a structural modification that gives compounds with significantly greater potency. When a methyl group is introduced at the 4 position of the pyrrole ring, certain of the compounds (II) have a potency comparable to indomethacin.

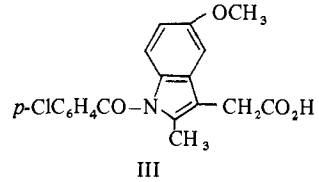
Compounds of type I were designed as isosteres of the portion of the indomethacin molecule responsible for the activity. In both indomethacin and the compounds of type II, the aroyl group is flanked on both sides by a carbon substituent. The steric influence of the carbon substituents on the conformation of the aroyl group might account for the potency of these compounds.



I



II



III

Pharmacology. The relative potency of compounds of type II in the kaolin- and carrageenan-induced edema tests is shown in Table I. Further aspects of the pharmacology of these compounds will be published elsewhere.

Chemistry. The preparation of an appropriate pyrrole starting material VI was carried out by a modification of the Hantzch pyrrole synthesis. Upon mixing diethyl acetonedicarboxylate and aqueous methylamine, a transient precipitate of a white crystalline solid is formed. If chloroacetone is added rapidly with cooling before the disappearance of the precipitate, a good yield of ethyl 1,4-dimethyl-3-