Aspergillus niger (ATCC 16888), and *Trichophyton mentagrophytes* (ATCC 9129).

The primary screening plates were prepared using Eugon agar (BBL) for bacteria and Mycophil agar (BBL) for fungi as complete media and Davis minimal agar (Difco) for bacteria and Czapek agar (Difco) for fungi as the minimal media.

The agar culture media were autoclaved, cooled to 45°, inoculated with bacterial or fungal suspensions, mixed thoroughly, and poured into Petri plates (100 × 15 mm) so that each plate contained 15 ml of agar culture media seeded with the test microorganism. Agar wells 10 mm in diameter were prepared in the plates and the samples (0.1 ml) were pipeted into the well. The solutions used were: D-cycloserine, 0.2 mg/ml; **3**, 20 mg/ml; **1**, 20 mg/ml.

The plates were incubated at 37° for bacteria or 25° for fungi and read for activity at 24-hr intervals. The results were expressed as the distance from the edge of the well to the outer edge of the clear zone of inhibition.

Acknowledgment. This work was supported by the Research Institute of Pharmaceutical Sciences, School of Pharmacy, University of Mississippi. We wish to acknowledge Dr. Stephen Billets for aid in mass spectral interpretations and Mrs. Sheida White for assistance in biological evaluations.

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Centrally Acting Emetics. 8. Conformational Aspects of Certain Dihydrophenanthrene Congeners of Apomorphine[1,†]

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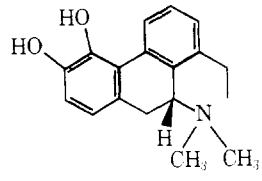
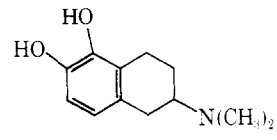
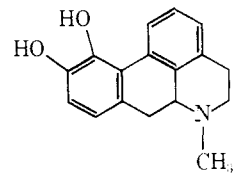
A prior communication[1] described the synthesis and biological effects of a ring-cleavage derivative (**1**) of apomorphine (**3**). The low order of emetic activity of **1**, which is



1



2

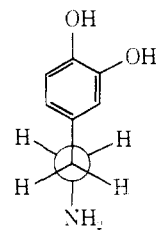


3

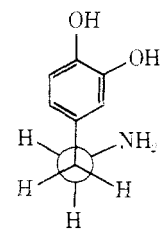
also closely related structurally to the potent emetic 5,6-dihydroxy-2-dimethylaminotetralin (**2**), was rationalized on conformational grounds. Rekker, *et al.*,[2] presented arguments that an anti disposition (**4**) of the catechol ring and the amino group of dopamine is the biologically active one. The dopamine portions of **2** and apomorphine exhibit this anti disposition.[1] It was proposed[1] that serious steric interaction between the dimethylamino group in a pseudo-equatorial conformation and the ethyl group at position 8 in compound **1** induces a conformational "flip" in the dihydrophenanthrene ring, to place the amino group in the less sterically crowded pseudo-axial arrangement. This conformation presents the dopamine portion of **1** in a gauche arrangement (**5**), and the molecule cannot interact optimally with the emetic receptor.

Inspection of molecular models led to the speculation that a phenanthrene system (**6**) lacking the ethyl group at position 8 would accommodate the dimethylamino group in the presumably more stable pseudo-equatorial disposition, in which the catechol ring and the amino group are in the biologically favorable anti conformation. Accordingly, it was predicted that **6** would exhibit potent emetic and peripheral apomorphine-like effects. Preparation of **6** was accomplished by a multistep sequence beginning with 3,4-dimethoxyphenanthrene-9-carboxylic acid. Spectral (ir, nmr) data were consistent with proposed structures of all compounds prepared.

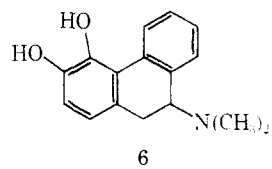
Pharmacology. Compound **6** was evaluated in five dogs anesthetized with barbital sodium (200 mg/kg). The arterial pressure was measured using the right femoral artery and the compound was administered into the left femoral vein. In doses up to 2 mg/kg, **6** did not alter the blood



4, anti



5, gauche



6

†This investigation was supported by Grant NS04349, National Institute of Neurological Diseases and Stroke.

pressure, heart rate, or the pressor response induced by bilateral carotid occlusion. There was no alteration of the pressor response of epinephrine. In contrast, 2 and apomorphine exert dramatic effects in these assays at dose levels of the order of μg/kg.[3]

Compound 6 in intramuscular doses of 40–160 mg (119–476 μmol)/kg produced vomiting in four pigeons. The estimated threshold emetic dose for apomorphine in the pigeon is 56.1 μmol/kg, and for 1 is 101.6 μmol/kg.[1] The pigeons were also sedated with 10 and 20 mg/kg doses of 6, but only mild sedation was noted. In three pigeons, pretreatment with 40 mg/kg of 6 did not antagonize pecking induced by 1.64 μmol/kg of apomorphine.

Discussion

The relatively low emetic activity and the absence of apomorphine-like activity on heart and blood pressure of 6 was initially puzzling. However, inspection of Dreiding models and reference to nmr spectra of 6 and certain congeners revealed unique conformational features of 6 which could unfavorably affect its biological potency.

Comparisons of the nmr spectra of 1, 3, and 6 reveal that similar conformations are assumed by 1 and 6. Table I lists nmr data for the NCH_3 and $C_{6a}H$ of apomorphine hydrochloride and the free base of its dimethyl ether; also tabulated are the corresponding NCH_3 and methine signals of 1 and 6 (as their HBr salts) and of the free bases of their dimethyl ethers. The *N*-methyl signals of 6, the dimethyl ether of 6, 1, and the dimethyl ether of 1 appear upfield relative to the corresponding *N*-methyl protons of apomorphine and its dimethyl ether. In contrast, the methine protons of apomorphine and its dimethyl ether appear upfield relative to the C_9H and $C_{10}H$ proton signals of the dihydrophenanthrene analogs. Since the C_{6a}-methine proton in apomorphine and its dimethyl ether is known to be pseudo-axial,[4] these data indicate that the dimethylamino groups in 1 and 6 and in their dimethyl ethers are pseudo-axial. The pseudo-axial conformation of the amino groups in these compounds forces their methyl protons into the shielding cones of both aromatic rings, thereby accounting, in part, for their higher field positions. The downfield signals of the methine protons in 1 and 6 and their dimethyl ethers, relative to the corresponding proton signals in apomorphine and its dimethyl ether, indicate pseudo-equatorial conformations for these atoms in 1 and 6. These assignments are corroborated by the coupling constants observed for the methine triplets of the dimethyl ethers of 1 and 6. For the dimethyl ether of 6, $J_{AX} = J_{BX} = 4.9$ Hz, while in the dimethyl ether of 1, $J_{AX} = J_{BX} = 4.0$ Hz. These data are in accord with $J_{a,e} \approx J_{e,e} \cong 3$–5 Hz reported for similar systems[5,6] and are in contrast with the coupling constants associated with the known pseudo-axial $C_{6a}H$ in the dimethyl ether of apomorphine ($J_{AX} = 3$ Hz; $J_{BX} = 7$ Hz). Thus, the apparent steric strain caused by the dimethylamino functions and the peri-hydrogen and ethyl groups at C_8 in 6 and 1 is sufficient to retain these compounds in conformations unfavorable for maximal apomorphine-like activity.

Experimental Section

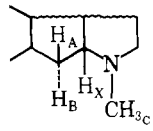
Melting points were determined in open capillaries on a Mettler automated melting point apparatus programmed for a 2°/min temperature rise and are corrected. Elemental analyses were performed by the Microanalytical Service, College of Pharmacy, The University of Iowa. Where analyses are indicated by the symbols of the elements, the analytical results were within ±0.4% of the theoretical values. Ir spectra were recorded on a Beckman IR-5A instrument, and nmr spectra were recorded on a Varian Associates T-60 instrument (Me_4Si).

3,4-Dimethoxy-9,10-dihydrophenanthrene-9-carboxylic Acid (7). A procedure of Schlittler and Müller[7] was employed. 3,4-Dimethoxyphenanthrene-9-carboxylic acid[8] (2.82 g, 0.01 mol) in 7 ml of 2 *M* NaOH was diluted with 200 ml of water and 275 g of 5% Na·Hg[9] was added in small pieces with efficient stirring over 1.5 hr. Sufficient 2 *N* HCl was added from time to time during the reduction to maintain some flocs of undissolved acid. The reaction mixture was stirred at room temperature for 36 hr; then HCl was added to destroy excess amalgam. The resulting mixture was basified with NaOH and this solution was extracted with ether and cooled, and excess concentrated HCl was added. The gum which separated was crystallized from aqueous ethanol and then from hexane in a Soxhlet apparatus to afford 1.89 g (66%) of shiny needles, mp 122–124°. *Anal.* ($C_{17}H_{16}O_4$) C, H.

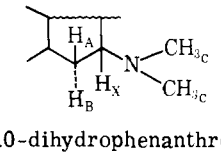
9-Amino-3,4-dimethoxy-9,10-dihydrophenanthrene Hydrochloride (8). A modification of a method of Weinstock[10] was employed. Compound 7 (5.77 g, 0.02 mol) was suspended in 4 ml of water, and acetone was added until all of the solid dissolved. To this cooled (0°), well-stirred solution was added 2.6 g (0.024 mol) of triethylamine in 30 ml of acetone and then 2.9 g (0.027 mol) of ethyl chloroformate in 30 ml of acetone was added dropwise. A copious white precipitate formed within 3–4 min; this mixture was stirred at 0° for 0.5 hr; then 2.6 g (0.04 mol) of NaN_3 in 10 ml of water was added dropwise with stirring. The resulting mixture was stirred at 0° for 1 hr; then it was poured into ice-water. A finely divided white solid separated; this mixture was extracted several times with ether, and the pooled extracts were dried (Na_2SO_4). The extract was filtered into a large round-bottom flask containing 200 ml of toluene, and the resulting solution was heated on a steam bath for 6 hr or until effervescence ceased. Volatiles were removed under reduced pressure (steam bath) to leave a viscous yellow oil: ir ($CHCl_3$) 2240 cm^{-1} (N=C=O). To this oil was added 70 ml of water and 70 ml of concentrated HCl, and refluxing was continued for 6 hr. Volatiles were removed under reduced pressure (steam bath) to leave a dirty gray solid. This material was treated with excess 5% NaOH and the resulting mixture was extracted repeatedly with ether. The combined extracts were dried (Na_2SO_4) and filtered, and excess ethereal HCl was added to the filtrate. The copious white precipitate was recrystallized from 2-propanol–heptane (charcoal) to afford 2.12 g (36%) of white plates. An attempted melting point determination (block) revealed crystal structure change to needles at 220° and gradual decomposition up to 275°. *Anal.* ($C_{16}H_{18}ClNO_2$) C, H, N.

9-Dimethylamino-3,4-dimethoxy-9,10-dihydrophenanthrene Hydrochloride (9). A method of Borch and Hassid[11] was employed. The free base of 8 (0.86 g, 0.003 mol) was obtained by treatment of 0.89 g (0.00305 mol) of 8 with excess NaOH and extraction with ether. The ether was evaporated and the syrupy residue was treated with 15 ml of acetonitrile and 4 ml of 37% formaldehyde solution; a copious white precipitate formed. Acetonitrile (10 ml) was added, followed by 0.302 g (0.005 mol) of $NaBH_3CN$ (99%; Ventron-Alpha), and this mixture was stirred at room temperature for 0.5 hr; then glacial acetic acid was added dropwise until the reaction mixture was approximately pH 7 when spotted on moist pH paper. Monitoring of the pH and addition of acetic acid was continued for 4 hr; then the reaction mixture was stirred overnight. Volatiles were stripped from the reaction mixture under reduced pressure, and the dark residue was treated with 100 ml of 25% KOH. The resulting mixture was ex-

Table I. Nmr Data on Apomorphine Systems and Certain 9,10-Dihydrophenanthrenes



apomorphine



9,10-dihydrophenanthrene

Compound	H_X, ppm	H_C, ppm
1·HBr[a]	4.80	2.78
1 dimethyl ether[b]	3.72	2.15
3·HCl[a]	4.17	3.14
3 dimethyl ether[b]	3.21	2.56
6·HBr[a]	4.68	2.74
6 dimethyl ether[b]	3.43	2.23

[a] Run in CD_3OD (Me_4Si). [b] Run in $CDCl_3$ (Me_4Si).

tracted repeatedly with ether; the pooled extracts were extracted once with 5% KOH (which was discarded) and then several times with 1 *N* HCl. The combined HCl extracts were washed with ether, then they were basified with KOH, and the resulting suspension was extracted repeatedly with ether. The pooled ethereal extracts were dried (Na_2SO_4) and filtered, and excess ethereal HCl was added. A limpid, off-white liquid separated, which was induced to crystallize by successive washing with 1-butanol and heptane. The resulting solid was recrystallized from acetone–heptane to afford 0.700 g (71%) of feathery crystals: mp 208–210° (at *ca.* 170° the feathery crystals sublimed to form rosettes of needles); nmr (DMSO) δ 2.60 [s, 6 H, $N(CH_3)_2$], 3.75 and 3.90 (2 s, 3 H each, OCH_3). *Anal.* ($C_{18}H_{22}ClNO_2$) C, H, N.

9-Dimethylamino-3,4-dihydroxy-9,10-dihydrophenanthrene Hydrobromide (6). Compound **9** (0.48 g, 0.0015 mol) was heated in 25 ml of 48% HBr under N_2 at 120–125° for 3 hr. Volatiles were then removed under reduced pressure (steam bath) and residual amounts of water were removed by repeated azeotroping with toluene. The solid residue was taken up in hot ethanol and was treated with charcoal. The solvent was removed under reduced pressure and the almost-white solid residue was recrystallized from 1-butanol–heptane to afford 0.440 g (87%) of a light buff powder, mp 222–224° dec. *Anal.* ($C_{16}H_{18}BrNO_2$) C, H, N.

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Centrally Acting Emetics. 9. Hofmann and Emde Degradation Products of Nuciferine[1,†]

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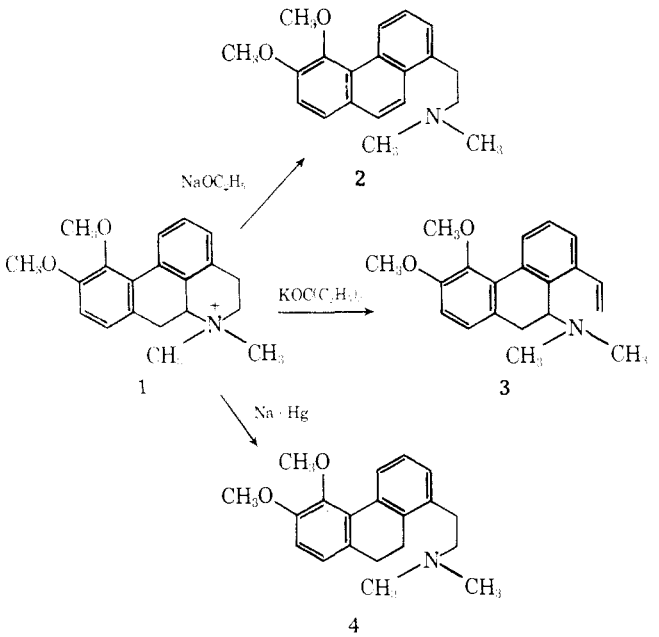
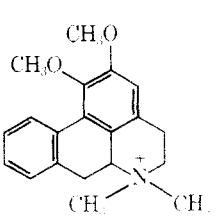
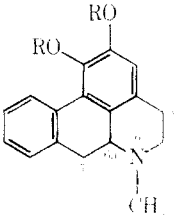
A prior communication[2] from this laboratory described procedures by which the direction of Hofmann elimination of a quaternary apomorphine derivative **1** could be controlled so as to obtain predominantly **2** or **3** (Scheme I). It was also demonstrated that Emde degradation of **1** gave a single product, **4**. Cooke and Haynes[3] stated that the direction of Hofmann elimination of quaternary aporphines appears to depend on the distribution of substituents and that small changes in reaction conditions may affect the course of the reaction. It was of interest to determine whether the selectivity of eliminations demonstrated for **1** was operative in other aporphine systems, and the *N*-methyl quaternary derivative **5** of nuciferine (1,2-dimethoxyaporphine) was selected for study.

Scheme I. Degradation of Quaternary Apomorphine Derivatives





5



6, R = H
9, R = CH3

Neumeyer, *et al.*,[4] have reported that the ether cleavage product **6** of (*R*)-nuciferine (which possesses the same absolute configuration as the biologically active enantiomer of apomorphine[5]) exhibits no emetic activity in the dog. Like apomorphine, **6** contains the elements of the dopamine structure, which is concluded to be the biologically significant portion of the apomorphine molecule.[2] We rationalize the emetic inactivity of **6** on the basis that the dopamine portion of the molecule is held rigidly with the catechol ring and the amino group in a gauche disposition (**7**). In apomorphine, the dopamine moiety exists in an anti arrangement (**8**) which we conclude is necessary for maximal emetic effect. In the present work, it was speculated that Hofmann cleavage of **5** between the nitrogen and carbon 6a would permit preparation of **12b**, in which

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