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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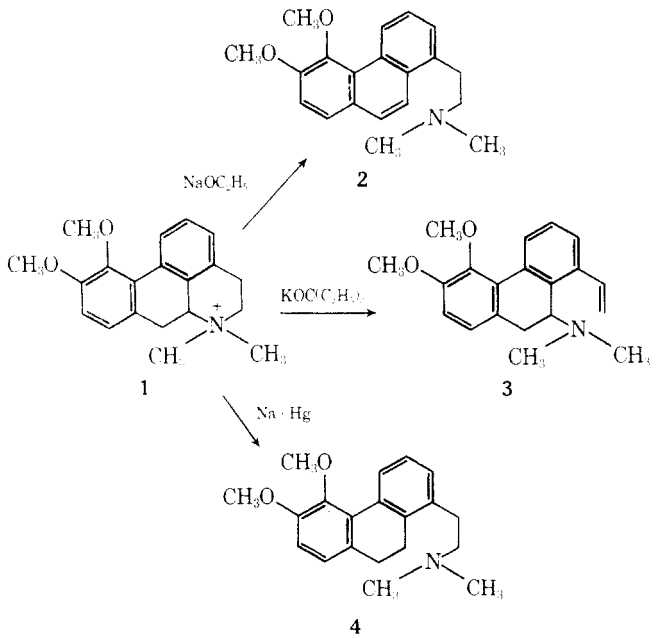
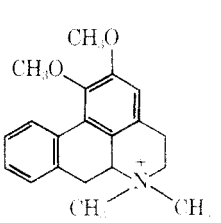
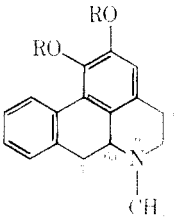
A prior communication[2] from this laboratory described procedures by which the direction of Hofmann elimination of a quaternary apomorphine derivative **1** could be controlled so as to obtain predominantly **2** or **3** (Scheme I). It was also demonstrated that Emde degradation of **1** gave a single 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 = CH_3

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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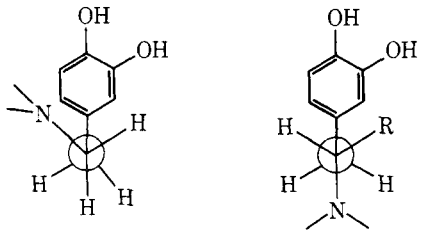
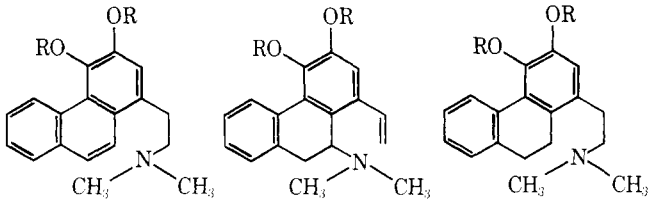


the flexible dopamine chain could assume the anti conformation (8) for proper interaction with the emetic receptor and with certain peripheral dopamine receptors.

Preparation of (±)-nuciferine (9) followed a literature method;[6] a modification of the Pschorr cyclization step (compound 14), in which freshly prepared copper powder was employed as the catalyst, permitted isolation of *N*-benzylnornuciferine in 60% yield. This represents one of the highest yields for a classical Pschorr cyclization reported to date.



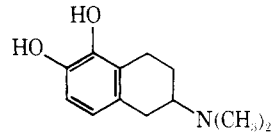
Yunoussoff, *et al.*,[7] refluxed 5 with alcoholic KOH and isolated modest amounts of trimethylamine and 1-vinyl-3,4-dimethoxyphenanthrene, plus a 73% yield of **10a** as a "semi-liquid mass." Cook and Haynes[3] repeated this reaction and concluded that the direction of elimination proceeds exclusively to give **10a.** In the present work, the reactions demonstrated for apomorphine in Scheme I were accomplished on the (±)-nuciferine derivative 5 to give comparable yields of **10a, 11a,** and **12a,** whose structures were confirmed by nmr data. (*R*)-Nuciferine methiodide was treated with the potassium salt of triethylcarbinol, to afford an optically active elimination product, which further verifies the structure of **11a,** the only possible product retaining an asymmetric center. The procedure[2] for directing Hofmann ring cleavages in aporphine systems seems to be a general one.

Vavrek, *et al.*,[6] have reported that treatment of nuciferine (9) with HI in glacial acetic acid permitted selective cleavage of the methoxy group at position 1. In the present work, treatment of nuciferine, **10a,** and **12a** with 48% HBr produced the 1,2-diphenolic systems.

Pharmacology. 10b, 12b, and *dl*-**6** were evaluated for biological activity by dissolving them in 50% propylene glycol–water. Control injections of the solvent system did not alter biological responses. The compounds, when administered to four anesthetized dogs, in doses of 1 mg/kg, did not alter the arterial pressure, heart rate, or the pressor response of epinephrine. The pressor response induced by bilateral carotid occlusion was not altered by 1 mg/kg doses of these compounds. Apomorphine produces dramatic responses in these assays at dose levels of a few μg/kg.[8] In pigeons, **6** and **10b,** in doses up to 40 mg (~115 μmol)/kg, did not induce pecking or vomiting, or alter the pecking rate induced by apomorphine. The estimated threshold pecking dose for apomorphine in the pigeon is 1.64 μmol/kg[2]. **12b** produced sedation at 10 mg/kg and sleep at 40 mg/kg in pigeons but no pecking or emesis.

Discussion

The prior report[4] of emetic inactivity of *O,O'*-desmethylnuciferine (6) in the dog was verified in the pigeon. The inactivity of **12b,** for which emetic and peripheral dopaminergic potency had been predicted, may be rationalized on the basis that this system, unlike the potent emetics apomorphine and 5,6-dihydroxy-2-dimethylaminotetralin (13),[9] and unlike dopamine itself, possesses a bulky substituent at the 5,6 positions of the dopamine ring. It is appealing to speculate that this bulk cannot be accommodated at the dopaminergic receptors under consideration. A similar argument may be proposed for the inactivity of **10b.**



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Experimental Section

Melting points were determined in open glass capillaries on a Thomas-Hoover Uni-Melt apparatus and are corrected. Elemental analyses were performed by the Microanalytical Service, College of Pharmacy, University of Iowa. Where analyses are indicated by symbols of the elements, the analytical results were within ±0.4% of the theoretical values. Ir spectra were recorded with a Beckman IR-10 instrument, and nmr spectra were recorded on a Varian Associates T-60 instrument (Me_4Si).

dl-***N*-Benzylnornuciferine (14).** 1-(2-Aminobenzyl)-2-benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline[6] (20 g, 0.52 mol) in 200 ml of glacial acetic acid and 15 ml of concentrated H_2SO_4 was cooled until solid material began to separate (10–15°); then $NaNO_2$ (5 g) in 36 ml of water was added dropwise over 10 min. The resulting deep red solution was stirred at 3–5° for 0.75 hr; then the reaction vessel was removed from the ice bath, 0.337 g of sulfamic acid, 22.9 g of freshly prepared copper powder,[10] and 400 ml of acetone were added, and the mixture was refluxed for 0.75 hr. The hot solution was filtered, cooled, and basified with 14% NH_4OH. The resulting mixture was extracted with ether. The extract was washed with saturated NaCl, dried (Na_2SO_4), and filtered, and the solvent was removed from the filtrate to give a viscous, red oil. This was chromatographed on neutral alumina and eluted with ether to afford a yellow oil which solidified upon addition of methanol. The solid was recrystallized from methanol to yield 11.5 g (60%) of crystals, mp 97–99° (lit.[6] mp 98–99°).

dl-**Nornuciferine (15).** This was prepared from 14 by the procedure of Weisbach and Douglas,[11] mp 120–123° (lit.[12] mp 124–125°).

dl-**Nuciferine (9).** This was prepared from 15 by the method of Vavrek, *et al.*,[6] mp 162–164° (lit.[13] mp 165.5°).

dl-**Nuciferine Methiodide (5).** Compound 9 (3 g, 0.01 mol) in 100 ml of ether was treated with excess MeI and was stored overnight at 10°. The resulting white solid was recrystallized from anhydrous ethanol to afford 4.5 g (97%) of material, mp 222–224° (lit.[7] mp 164–167° from acetone–benzene). *Anal.* ($C_{20}H_{23}INO_2$) C, H, N.

1-(2-Dimethylaminoethyl)-3,4-dimethoxyphenanthrene Hydrochloride (10a). Compound 5 (1.0 g, 0.002 mol) was refluxed with 4.76 g (0.207 g-atom) of Na in 48 ml of anhydrous ethanol. The reaction mixture was filtered and the filtrate was taken to dryness under reduced pressure. The solid residue was suspended in water and was extracted several times with ether. The pooled extracts were washed with saturated NaCl and dried (Na_2SO_4). Ethereal HCl was added; the oil which separated was triturated with 2-propanol and then was recrystallized from this solvent to afford 0.5 g (68%) of product: mp 195–197° (Cook and Haynes[3] characterized this compound as its picrate and HI salts); nmr ($CDCl_3$) δ 2.88 [s, 6 H, $N(CH_3)_2$], 3.20–3.77 (m, 4 H, CH_2CH_2), 3.95 and 4.03 (2 s, 6 H, OCH_3), 7.38–7.97 (m, 6 H, ArH), 9.57–9.80 (m, 1 H, ArH). *Anal.* ($C_{20}H_{24}ClNO_2$) C, H, N.

1-(2-Dimethylaminoethyl)-3,4-dimethoxy-9,10-dihydrophenanthrene Hydrochloride (12a). Compound 5 (1.5 g, 0.0036 mol) in 75 ml of water was treated with 10.7 g of 5% Na-Hg, added in small portions over 2 hr. The reaction mixture was permitted to stand overnight at room temperature; then it was extracted sev-

eral times with ether. The combined extracts were dried (Na_2SO_4) and filtered. The solvent was removed from the filtrate, leaving an oily residue which was treated with ethereal HCl. The solid which separated was taken up in pentane–anhydrous ethanol (2:1) and upon cooling, 0.90 g (72%) of product separated: mp 187–189°; nmr ($CDCl_3$) δ 2.73 [s, 6 H, $N(CH_3)_2$], 2.83–3.40 (broadened m, 8 H, aliphatic H), 3.67 and 3.90 (2 s, 6 H, OCH_3), 6.70–8.17 (m, 4 H, ArH), 8.20–8.47 (m, 1 H, ArH). *Anal.* ($C_{20}H_{26}ClNO_2$) C, H, N.

***dl*-1-Vinyl-3,4-dimethoxy-10-dimethylamino-9,10-dihydrophenanthrene Hydrochloride (11a).** Compound **5** (1.34 g, 0.0032 mol) was refluxed for 6 hr in a solution of 0.955 g (0.024 g-atom) of K in freshly distilled triethylcarbinol (Eastman, white label). The cooled mixture was treated with excess 10% HCl and was extracted with ether. The aqueous layer was treated with excess $NaHCO_3$ and the resulting mixture was extracted several times with ether. The pooled extracts were dried (Na_2SO_4) and filtered, and the ether was removed from the filtrate under reduced pressure. The residual oil was chromatographed on silica gel and eluted with ether. Evaporation of the eluate afforded an oily residue which was treated with ethereal HCl to give 0.40 g (53%) of a solid: mp 182–184°; nmr ($CDCl_3$) δ 2.02 [s, 6 H, $N(CH_3)_2$], 3.62 and 3.88 (2 s, 6 H, OCH_3), 5.15–5.85 (m, 2 H, vinyl H), 7.00–8.00 (m, 5 H, ArH + vinyl H), 8.28–8.55 (m, 1 H, ArH). *Anal.* ($C_{20}H_{24}ClNO_2$) C, H, N.

(*R*)-1,2-Dimethoxyaporphine (Nuciferine, 9). This was isolated from *Nelumbo lutea* (yellow water lily, collected from a lily pond in the Amana Colonies in eastern Iowa, by an isolation procedure reported by Kupchan, *et al.*:[13] nmr ($CDCl_3$) δ 2.53 (s, 3 H, NCH_3), 3.67 and 3.86 (s, 6 H, OCH_3), 6.63 (s, 1 H, ArH), 7.17–7.37 (m, 3 H, ArH), 8.27–8.50 (m, 1 H, ArH).

(*R*)-1-Vinyl-3,4-dimethoxy-10-dimethylamino-9,10-dihydrophenanthrene Hydrochloride (11a). (*R*)-**5**, prepared from (*R*)-**9** as described for (±)-**5**, was treated as described for *dl*-**11a**: $[\alpha]^{32}D$ −97.70° (*c* 0.174, ethanol).

***dl*-1,2-Dihydroxyaporphine Hydrobromide (*dl*-6).** Compound *dl*-**9** (1.0 g, 0.003 mol) was heated at 110–125° under N_2 with 16 ml of 48% HBr for 4 hr. After removal of volatiles, the solid residue was recrystallized from ethanol to yield 0.60 g (57%) of product, mp 226–228° (Neumeyer, *et al.*,[4] characterized this base as its HI salt). *Anal.* ($C_{17}H_{18}BrNO_2$) C, H, N.

(*R*)-1,2-Dihydroxyaporphine Hydrobromide [(*R*)-6]. This was prepared from (*R*)-**9** as described for *dl*-**6**: $[\alpha]^{32}D$ −272° (*c* 0.300, water).

1-(2-Dimethylaminoethyl)-3,4-dihydroxy-9,10-dihydrophenanthrene Hydrobromide (12b). Compound **12a** (0.60 g, 0.002 mol) was treated as described for *dl*-**6**, and the crude product was recrystallized from ethanol–ether (2:1) to give 0.45 g (72%) of product, mp 180–183°. *Anal.* ($C_{18}H_{22}BrNO_2$) C, H, N.

1-(2-Dimethylaminoethyl)-3,4-dihydroxyphenanthrene Hydrobromide (10b). Compound **10a** (0.60 g, 0.002 mol) was treated as described for *dl*-**6**, and the crude product was recrystallized from ethanol to give 0.34 g (44%) of product, mp 238° dec. *Anal.* ($C_{18}H_{20}BrNO_2$) C, H, N.

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Antagonism of Slow Reacting Substance in Anaphylaxis (SRS-A) and Other Spasmogens on the Guinea Pig Tracheal Chain by Hydratropic Acids and Their Effects on Anaphylaxis

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The anaphylactic reaction in the guinea pig is accompanied by the release of histamine,[1,2] slow reacting substance in anaphylaxis (SRS-A),[3-7] bradykinin,[8] and prostaglandins (PG) E_2 and $F_{2\alpha}$[9] and possibly other humoral factors which may or may not contribute to the pathological effect.[10,11] There is evidence that at least histamine, SRS-A, and bradykinin contribute to the anaphylactic bronchospasm in the guinea pig[7,8,12] and that the last two mediators but not histamine are involved in anaphylaxis in cattle.[13] Proof of participation of specific mediators in human asthma is much more difficult but it has been shown that human lung is exquisitely sensitive to SRS-A[14] responding with a prolonged, intense contraction and that SRS-A as well as histamine is released from sensitized human lung when challenged.[15,16]

While the pharmacological properties of histamine and bradykinin are well known, those of SRS-A may be less generally appreciated. SRS-A was first identified as a mediator in anaphylaxis in 1940 by Kellaway and Trethewie[3] but its structure is still unknown. It may be that the SRS released by 48/80 and the SRS-A released during various anaphylactic procedures are not identical but pharmacologically they are very similar.[17,18] Strandberg and Uvnas[19] have shown that SRS from cat paw is a carboxylic acid with hydroxyl groups and one or more double bonds but is probably not a prostaglandin.

SRS-A causes a slowly developing contraction in a limited number of smooth muscles including guinea pig and human bronchial muscle and guinea pig ileum.[20] Antihistamines abolish the bronchoconstrictor response to histamine in the guinea pig but have no effect on that induced by SRS-A or bradykinin. On the other hand, aspirin, sodium flufenamate, sodium mefenamate, and certain other antipyretics antagonize the response to both kinins and SRS-A without affecting the response to histamine.[21]

Antihistamines are of relatively little use in human asthma although they offer limited benefit when administered prophylactically especially in mild cases. They are also of little benefit in human systemic anaphylaxis. It is possible that other autacoids are more important than histamine as mediators in this reaction. Antipyretic

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