EtOAc was washed with water, 10% HCl, and Na_2CO_3 solution, successively, dried (Na_2SO_4), and then concentrated under reduced pressure. Recrystallization of the residue from EtOH gave 15.7 g of 11, mp 151–152°.

(II) 2-Benzyloxycarbonylaminoacetamido-3-benzoylthiophenes (Table II, 22–39). 2-Benzyloxycarbonylaminoacetamido-3-*o*-chlorobenzoyl-5-ethylthiophene (24). Benzyloxycarbonylaminoacetyl chloride (27.3 g, 0.12 mol) was added, with ice cooling, to a solution of **4** (26.6 g, 0.1 mol) in $CHCl_3$ (150 ml). After standing overnight in an ice box, the mixture was concentrated under reduced pressure. Recrystallization of the residue from EtOH gave 27.9 g of **24**, mp 118–119°.

(III) 2-Haloacetamido-3-benzoylthiophenes. (a) Cl or Br Derivatives (Table III, 40–51). **2-Chloroacetamido-3-*o*-chlorobenzoyl-5-ethylthiophene (43).** A solution of **4** (26.6 g, 0.1 mol) and chloroacetyl chloride (11.3 g, 0.11 mol) in $CHCl_3$ (130 ml) was refluxed for 1 hr. The solvent was concentrated under reduced pressure and the residue was recrystallized from EtOH to give 27.6 g of **43**, mp 99–100°.

(b) Iodo Derivatives (Table III, 52–59). **2-Iodoacetamido-3-*o*-chlorobenzoyl-5-ethylthiophene (55).** Sodium iodide (16.5 g, 0.11 mol) was added to a stirred solution of **43** (34.2 g, 0.1 mol) in Me_2CO (200 ml) and the mixture was refluxed for 30 min. After cooling, the inorganic salt was filtered off and the filtrate was concentrated under reduced pressure. Recrystallization of the residue from EtOH gave 37.3 g of **55**, mp 100–101°.

(IV) 2-Aminoacetamido-3-benzoylthiophenes (Table IV, 60–80). Method A. 2-Aminoacetamido-3-*o*-chlorobenzoyl-5-ethylthiophene (63). A solution of **24** (45.7 g, 0.1 mol) in 20% HBr–AcOH (200 ml) was stirred at room temperature for 1 hr. Isopropyl ether (1 l.) was added to the mixture and the precipitated crystals were collected by filtration and washed with three 100-ml portions of isopropyl ether. A suspension of the crystals in water was made alkaline with $NaHCO_3$ and extracted with $CHCl_3$. The extract was dried (Na_2SO_4) and concentrated under reduced pressure. Recrystallization of the residue from EtOH gave 20.3 g of **63**, mp 146–148°.

Method B. 2-Aminoacetamido-3-*o*-bromobenzoyl-5-ethylthiophene (64). Ammonia gas was introduced, with ice cooling, to a solution of **56** (20 g, 0.042 mol) in $CHCl_3$ (50 ml) and MeOH (5 ml) during 2 hr. After stirring at room temperature for additional 2 hr, the mixture was washed with ice–water and $NaHCO_3$ solution, successively, dried (Na_2SO_4), and then concentrated under reduced pressure. Recrystallization of the residue from EtOH gave 11.7 g of **64**, mp 160–161°.

(V) 5-Phenylthieno[2,3-*e*][1,4]diazepines (Table V, 81–104). 5-*o*-Chlorophenyl-7-ethyl-1,3-dihydro-2*H*-thieno[2,3-*e*][1,4]diazepin-2-one (85). A solution of **63** (10.0 g, 0.031 mol) in a mixture of pyridine (50 ml), AcOH (1.9 g, 0.031 mol), and C_6H_6 (20 ml) was refluxed for 10 hr in a flask fitted with a water separator. The mixture was concentrated under reduced pressure. A suspension of the mixture in water was made alkaline with $NaHCO_3$ and extracted with $CHCl_3$. The extract was dried (Na_2SO_4) and concentrated under reduced pressure. Crystallization of the residue from toluene gave 5.9 g of **85**, mp 204–206°.

(VI) 1-Substituted 5-Phenylthieno[2,3-*e*][1,4]diazepines (Table V, 105–122). 1-Methyl-5-*o*-chlorophenyl-7-ethyl-1,3-dihydro-2*H*-thieno[2,3-*e*][1,4]diazepin-2-one (109). A 50% suspension of NaH in mineral oil (2.9 g, 0.06 mol) was added portionwise to a solution of **85** (15.3 g, 0.05 mol) in DMF (100 ml). After stirring for 15 min at 50°, MeI (8.5 g, 0.06 mol) was added dropwise to the mixture with ice cooling and the solution was stirred for additional 30 min at room temperature. A suspension of the mixture in water was extracted with EtOAc. The extract was washed with water, dried (Na_2SO_4), and then concentrated under reduced pressure. Recrystallization of the residue from hexane gave 8.8 g of **109**, mp 105–106°.

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Centrally Acting Emetics. 7. Hofmann and Emde Degradation Products of Apomorphine†,[1]

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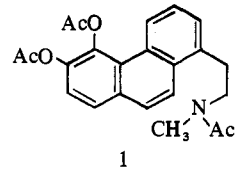
Hofmann elimination of quaternary apomorphine derivatives has been studied with respect to direction of ring opening. Specificity of opening has been attained by choice of a suitable base, and some confusion and error existing in the older literature on the subject have been resolved. Emde degradations have been found to proceed smoothly and the structure of the product has been determined by nmr. Derivatives of the Hofmann and Emde products have been evaluated for emetic effects and these biological data have been rationalized on conformational grounds.

Tiffeneau and Porcher[2] first prepared "triacetylapomorphine" **1** by prolonged heating of apomorphine with excess acetic anhydride, and they reported it to be devoid of emetic activity; this observation was verified in this laboratory.[3] Since the diacetate ester **2** of apomorphine has emetic activity nearly identical with that of apomorphine itself,[3] it was speculated that the inactivity of triacetylapomorphine might be referrable, at least in part, to the masking of the basicity of the nitrogen by the amide link. The great differences in emetic activity produced by relatively minor



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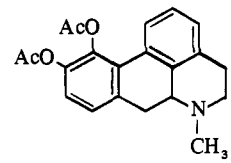

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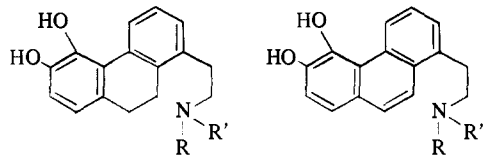
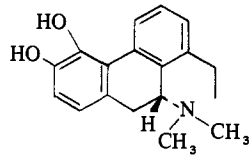
†This investigation was supported in part by Grants No. NS-04349 and NS-1396, National Institute of Neurological Diseases and Stroke. Abstracted in part from a thesis submitted by R. J. B. in partial fulfillment of the requirements for the Ph.D. degree, The University of Iowa, 1970.

changes in N-substitution on apomorphine[4] suggest that the chemoreceptor trigger zone ("CTZ") in the brain is highly sensitive to structural changes in the vicinity of the nitrogen of apomorphine. Compounds **3–7** were chosen for investigation in attempts to determine (1) whether it is mandatory that the nitrogen atom be a part of or be attached directly to a ring system and (2) whether it is essential to maintain a fixed steric relationship between the nitrogen atom and the catechol OH groups as in compound **7** or whether compounds **3–6**, having a flexible "tail" which can assume a conformation having the same intergroup distance and the same geometry as in apomorphine, would be emetic agents. An *N*-ethyl group was placed in compounds **4** and **6** on the basis that replacement of the *N*-methyl of apomorphine by ethyl increases the emetic effect.[4] Pschorr, *et al.*,[5] reported that a single product (the "methine base" **9**) results from Hofmann degradation of the methiodide salt of *O,O'*-dimethylapomorphine (**8**). However, Gadamer[6] noted that the Hofmann elimination in the apomorphinium system can in theory afford two products (depending upon which of the two positions β to the nitrogen—4 or 7—is attacked by the base): the methine base **9** and the "isomethine base" **10**. This worker refluxed an aqueous solution of apomorphine with excess potassium hydroxide and dimethyl sulfate; he isolated a product which demonstrated optical activity and on this basis, he assigned it the "isomethine" structure **10**, since elimination in the other direction would destroy the asymmetric center. No other structure elucidation or verification was reported.



3, R = R' = Me
4, R = Me; R' = Et

5, R = R' = Me
6, R = Me; R' = Et



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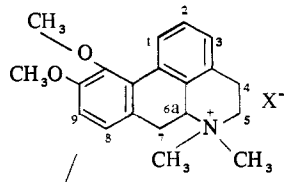

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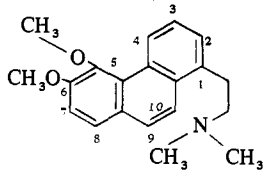

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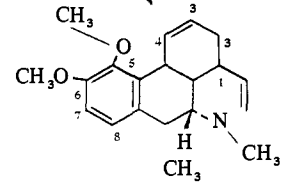

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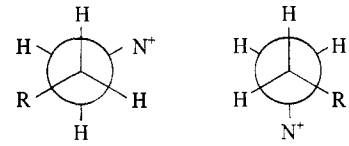
In the present study, when *N,O,O'*-trimethylapomorphinium methosulfate (**8**, X = $MeOSO_3^-$) was refluxed with sodium ethoxide in ethanol, the methine base **9** was obtained in 79% yield. The structure of this product was verified by its nmr spectrum, which was quite definitive: the aromatic protons at positions 2, 3, 7, 8, 9, and 10 appeared as a multiplet centered at δ 7.85. The proton at position 4 appeared downfield at δ 9.60. The other possible Hofmann product **10** (the isomethine) could not be isolated nor detected.

Examination of Dreiding models of *N,O,O'*-trimethylapomorphinium revealed that, of the two positions β to the quaternary nitrogen (4 and 7), only position 4 (structure **12**) has the trans relationship of a hydrogen atom to the quaternary, which favors Hofmann-type eliminations. Two other factors seem significant. (1) Space-filling models suggest that the hydrogens on position 7 of apomorphinium are somewhat more sterically shielded and are less accessible to approach by a base than are the hydrogens at position 4. (2) When the methine structure **9** is formed, there is a change in the dihedral angle between the planes of the two aromatic rings in the conversion from the aporphine (29.9°, ref 7) to the planar phenanthrene system. This results in greater nonbonded interaction between the methoxyl group at position 5 and the hydrogen at position 4 of **9**. Indeed, examination of nmr spectra, which will be discussed later, confirms this. In sum, these three factors would seem to direct apomorphinium elimination to the isomethine **10** rather than to the methine **9**. However, formation of the methine base involves extension of the aromaticity of the system, which might be expected to be a potent driving force. Smissman, *et al.*,[8] found that treatment of several aporphines with cyanogen bromide resulted in ring-cleavage reactions with aromatization to phenanthrenes, rather than to the desired N-demethylated (noraporphine) systems. These workers stated that, of the two factors which seem to determine the reaction path, the benzylic character of the bond cleaved and the formation of a fully aromatized phenanthrene ring, it is the second which seems to be the more critical in determining the nature of the product. This explanation must be invoked to rationalize the isolation in the present work of high yields of the methine base **9** upon treatment of apomorphinium cation with ethoxide anion. Cooke and Haynes,[9] in a review of Hofmann degradations of aporphine alkaloids, concluded that small changes in reaction conditions may affect profoundly the course of the reaction and that the distribution of substituents within the ring system may also be a significant factor.



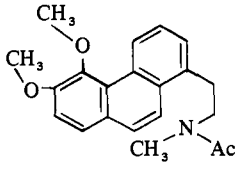
11 carbon 7 → 6a

12 carbon 4 → 5

It was envisioned in the present work that if the quaternary apomorphine system **8** were treated with an extremely bulky anionic base (resulting in even greater inaccessibility to the hydrogens at position 7), it might be possible to control the elimination reaction such that attack by the base occurs predominantly on the 4 position, forming the isomethine base **10**. Upon refluxing **8** with the potassium salt of triethylcarbinol in triethylcarbinol, **10** was obtained in 74% yield. Its nmr spectrum demonstrated a multiplet at δ 5.49, assignable to two vinylic protons; four aromatic protons and the one remaining vinyl proton appeared as a multiplet centered at δ 7.04, and the position 4 aromatic

proton appeared at δ 8.34. A small amount of a second product was detected in the crude reaction mixture and was identified by tlc as the methine **9**. This is the first report which demonstrates that it is possible to exercise control over the course and direction of the Hofmann degradation of an aporphine system.

As a matter of interest, the dimethyl ether of apomorphine was treated with acetic anhydride under the conditions of the Tiffeneau-Porcher elimination reaction.[2] An excellent yield of the acetylaminoethylphenanthrene (**13**) resulted.



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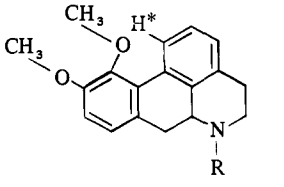
The Emde degradation, as modified by Faltis and Krausz,[10] was employed in conversion of apomorphinium systems to the 9,10-dihydrophenanthrene-4-ethylamines **3** and **4**. The dimethyl ethers of **3** and **5** were quaternized and subjected to an additional Hofmann elimination to give known products, thus verifying further their chemical structures. For biological evaluation, the ether groups of all products were removed with HBr.

Comparison of the chemical shifts of the *O*-methyl protons and of the position 1 proton (H*) of the aporphine system **14** with those found for the corresponding protons in the phenanthrene **17** and the 9,10-dihydrophenanthrene **15**, **16** systems revealed a consistent and characteristic downfield shift of the signal of the H* from the region δ 8.19-8.34 in the aporphine and the 9,10-dihydrophenanthrene systems to the region δ 9.60-9.66 for the completely aromatic phenanthrene system. Baarschers, *et al.*,[11] have attributed this same effect in aporphine systems having a proton at position 11 opposed by a methoxyl at position 1 to deshielding of the 11-proton by the neighboring aromatic ring, as well as to anisotropic effects of the C-O single bond, since the H* is held very close to the opposing oxygen atom. This downfield shift effect on the H* signal increases as the ring system becomes completely planar, as in the phenanthrene system **17**; Mollov and Dutschewska[12] noted the same type of downfield shift in 6a,7-dehydroaporphine (**18**).



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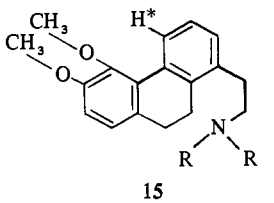

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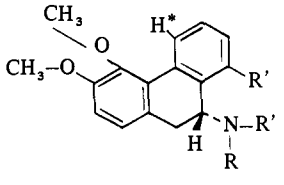

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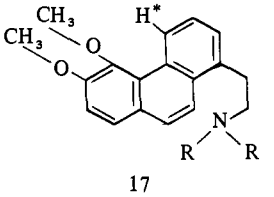

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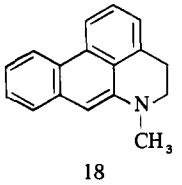

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Pharmacology. Preparations. HBr salts of the new compounds and apomorphine HCl were dissolved in appropriate volumes of physiological saline. Solutions were prepared immediately before use or were stored in amber containers in a freezer. Compounds were administered ip to mice, im to pigeons, and sc to dogs.

Acute Toxicity in Mice. Graded doses of each compound were administered to groups of three mice; when supplies of test compound permitted, 95% confidence limites were determined. Animals were observed for 6 hr following injection. Animals died within 30 min of administration of **6**, while in the case of **4** and **7**, most deaths occurred within 1-1.3 hr. Compound **6** was decidedly more toxic than the others (see Table I).

Compulsive Gnawing in Mice. Groups of three mice were used. The compulsive gnawing syndrome elicited by low doses of apomorphine in rodents[13] was observed for **3**, **4**, and **5**, which were somewhat weaker than apomorphine (see Table I).

Pecking and/or Emesis in Pigeons. Pigeons of both sexes, weighing 200-550 g, were used. Groups of three birds were used at each dose level. All compounds induced pecking; all except **6** (which was toxic) induced vomiting in doses roughly equivalent to those of apomorphine (see Table I).

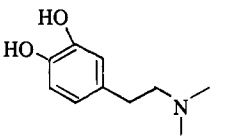
Emesis in Dogs. Female dogs weighing 8-12 kg were employed. Graded doses of all new compounds consistently failed to evoke vomiting in all dogs, but preemetic symptoms were apparent, characterized by excitability, salivation, retching, and enhanced respiration. Doses more than 100 times TED of apomorphine were not attempted. Compound **4** was more potent than **7**, and **6** was inert at low doses and toxic at higher doses.

Discussion

The modest activity of **3** and **4** in the spectrum of test species can be rationalized on the basis that the flexible aminoethyl side chain can assume a conformation (as shown below) such that the overall shape and dimensions of the molecule resemble those of apomorphine and in which the nitrogen-to-phenolic group distance approximates that in the proposed[1] active conformation for dopamine, **19**.

The inactivity of the phenanthrene ethylamine **6** seems referrable to the aromatization of the ring system, although a convincing detailed explanation is not apparent; a similar conformation for **6** may be shown as was invoked for **3** and **4**, which would seem to favor some degree of emetic activity.

The comparatively low emetic activity of **7** was unexpected, in that it is closely related structurally to the 5,6-



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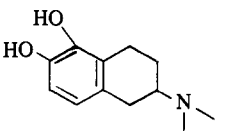

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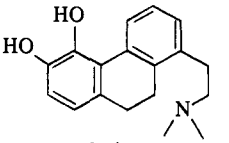

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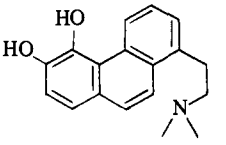

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Table I. Biological Activities of Hofmann and Emde Derivatives

Compd no.	Mouse gnawing		Pigeon pecking		LD_{50}, μmol/kg	95% confidence limits, μmol/kg	RP[b]	Pigeon emesis		Dog preemetic symptoms, μmol/kg
	GD_{50}, μmol/kg[a]	RP[b]	MED,[c] μmol/kg	RP[b]				MED,[c] μmol/kg	RP[b]	
3	30	0.28	>2.0	<0.8	>84		<7.0	28	2.0	1.50
4	16	0.52	1.8	0.9	317	269-370	1.8	50.6	1.1	0.31
5	56	0.15	>2.0	<0.8	>100		<6.0	77.0	0.7	4.00
6	e		>2.0	<0.8	76	72-81	7.9	f		g
7	100 × TED for apomorphine		>2.0	<0.8	1032	972-1099	0.5	101.6	0.5	0.70
Apomorphine HCl	8.4	1.0	1.64	1.0	600		1.0	56.1	1.0	0.07[d]

[a] In terms of free base. [b] Potency relative to apomorphine. [c] Estimated threshold dose. [d] Emetic dose. [e] Doses higher than 77 μmol/kg were not attempted because of severe toxicity in this range. [f] Death occurred at 203 μmol/kg and no higher doses were attempted. No preemetic symptoms were noted at this dose level. [g] No preemetic symptoms were seen in lower doses; higher doses killed the animals.

dihydroxy-2-aminotetralins **20** which have been shown[1] to be violent emetics and in that it differs from apomorphine only in that the heterocyclic ring is broken, and the nitrogen bears two methyl groups rather than one. Molecular models indicate that if the 9-dimethylamino group of **7** is in the pseudo-equatorial conformation in which it exists in apomorphine (and, presumably, in the 2-aminotetralins[1]), there is a serious steric interaction between the dimethylamino group and the ethyl group at position 8. This interaction is much less severe if the amino group assumes a pseudo-axial disposition, which can occur if the 9,10-dihydrophenanthrene system undergoes a conformational "flip." The resulting pseudo-axial 9-dimethylamino system can no longer be superimposed upon the apomorphine molecule, and it might be expected that it would not be accommodated optimally by the emetic receptor, analogous to the situation described previously[1] for 4,5-dihydroxy-2-aminoindans. Pullman, *et al.*,[14] have utilized X-ray crystallographic data and molecular orbital calculations to conclude that dopamine possesses three stable conformations: two folded forms and one extended form in which the plane of the side chain is approximately perpendicular to the plane of the ring. This extended confirmation cannot be reconciled with the proposed[1] conformation of dopamine analogs and congeners required for attachment to the emetic receptor. The Pullman group have cautioned that conformations calculated for molecules in their free state need not be the same as those of the molecules bound to their receptors.

Experimental Section

Melting points were determined in open capillaries on a Thomas-Hoover Uni-Melt apparatus and are corrected. Differential thermal analyses (dta) were performed on a Du Pont 900 instrument. Elemental analyses were performed by Galbraith Laboratories, Wheatridge, Colo., and 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). Optical rotations were determined on a Carl Zeiss circular polarimeter.

1-(2-Dimethylaminoethyl)-5,6-dimethoxyphenanthrene Hydrochloride (9). *N,O,O'*-Trimethylapomorphinium methosulfate[15] (2.1 g, 0.005 mol) was refluxed for 4 hr with a solution of 10 g (0.43 g-atom) of sodium in 100 ml of anhydrous ethanol. The reaction mixture was filtered and the filtrate was taken to dryness under reduced pressure. The solid residue was extracted with several portions to ether which were combined and washed with 50 ml of water. After drying (Na_2SO_4), ethereal hydrogen chloride was added; the solid which separated was recrystallized from 2-propanol giving 1.37 g (79%) of product: mp 219° (lit.[5] mp 220–221°); nmr (DMSO-d_6) δ 2.90 (s, 6 H, $-N(CH_3)_2$), 3.44 (m, 4 H, $-CH_2CH_2-$), 3.89 and 4.00 (2 s, 6 H, OCH_3), 7.85 (m, 6 H, Ar H), and 9.60 (m, 1 H, Ar H).

Anal. ($C_{20}H_{24}ClNO_2$) C, H, Cl, N.

1-(2-Dimethylaminoethyl)-5,6-dimethoxy-9,10-dihydrophenanthrene (21). This was obtained by a modification of a method of Faltis and Krausz.[10] To 2.105 g (0.005 mol) of *N,O,O'*-trimethylapomorphinium methosulfate[15] in 75 ml of water was added 15 g of 5% sodium amalgam in small portions over 2 hr. The organic material that separated from the reaction mixture was taken up in ether and dried (Na_2SO_4). The ether was evaporated, leaving a solid residue which was recrystallized from pentane to yield 1.26 g (85%) of cubes: mp 71.5–72° (lit.[10] mp 70.5–71.5°); nmr (CCl_4) δ 2.24 (s, 6 H, $-N(CH_3)_2$), 2.70 (broadened s, 4 H, 9,10-dihydro H), 3.64 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 6.57–7.17 (m, 4 H, Ar H), and 8.19 (d of d, 1 H, Ar H).

1-Vinyl-5,6-dimethoxyphenanthrene (22). To 3.09 g (0.01 mol) of 9 in 50 ml of ether, cooled to −5°, was added 3 g (0.032 mol) of methyl bromide in 50 ml of ether. The white solid which separated was collected, washed with ether, and dried under reduced pressure, mp 260–261° dec. This salt was dissolved in 100 ml of water and 30 g of sodium hydroxide was added, raising the

temperature to 90°. The oil which separated was taken up in ether and dried (Na_2SO_4), and, upon evaporation, a solid remained which was recrystallized from ether to yield 2.08 g (78%) of a slightly yellow product: mp 75–77° (lit.[10] mp 76–77°); nmr ($CDCl_3$) δ 3.94 and 4.0 (2 s, 6 H, OCH_3), 5.60 (m, 2 H, vinyl H), 7.17–7.97 (m, 8 H, Ar H and vinyl H), and 9.67 (d of d, 1 H, Ar H).

1-Vinyl-5,6-dimethoxy-9,10-dihydrophenanthrene (23). Compound **21** (3.11 g, 0.01 mol) was quaternized with 3 g (0.032 mol) of methyl bromide and the product was recrystallized from ethanol, mp 239–240°. It was treated with 30 g of sodium hydroxide in 100 ml of water as described for **22**, and the product was recrystallized from ether to give 2.28 g (86%) of product: mp 83.5–84° (lit.[10] mp 83.5–84°); nmr (CCl_4) δ 2.74 (broadened s, 4 H, 9,10-dihydro H), 3.64 and 3.84 (2 s, 6 H, OCH_3), 5.45 (m, 2 H, vinyl H), 7.02 (m, 4 H, Ar H and vinyl H), and 8.31 (d of d, 1 H, Ar H).

1-(2-Dimethylaminoethyl)-5,6-dihydroxyphenanthrene Hydrobromide (5). Compound 9 (1.424 g, 0.004 mol) in 20 ml of 48% hydrobromic acid was heated under nitrogen at 120–125° for 1.5 hr. The yellow solid which separated upon cooling was collected, washed with water, and was fractionally recrystallized from ethanol to yield 0.743 g (50%) of material. Dta under nitrogen showed a sharp endotherm at 242°: nmr (DMSO-d_6) δ 2.94 (s, 6 H, $-N(CH_3)_2$), 3.49 (m, 4 H, aliphatic H), 7.68 (m, 6 H, Ar H), and 9.97 (m, 3 H, Ar H and 2 OH). After D_2O exchange, the multiplet at δ 9.97 integrated for 1 H.

Anal. ($C_{18}H_{20}BrNO_2$) C, H, N.

1-(2-Dimethylaminoethyl)-5,6-dihydroxy-9,10-dihydrophenanthrene Hydrobromide (3). Compound **21** (3.257 g, 0.01 mol) was treated with 70 ml of 48% hydrobromic acid as described for **5**, and the product was recrystallized from ethanol to give 1.57 g (42%) of crystals. Dta under nitrogen showed a sharp endotherm at 243°: nmr (DMSO-d_6) δ 2.67 (m, 4 H, 9,10-dihydro H), 2.87 (s, 6 H, $-N(CH_3)_2$), 3.17 (m, 4 H, aliphatic H), 6.95 (m, 4 H, Ar H), 8.34 (d of d, 1 H, Ar H), 9.43 (broad m, 2 H, OH). After D_2O exchange, the signal at δ 9.43 disappeared.

Anal. ($C_{18}H_{22}BrNO_2$) C, H, Br, N.

1-Vinyl-5,6-dimethoxy-10-dimethylamino-9,10-dihydrophenanthrene (10). *N,O,O'*-Trimethylapomorphinium methosulfate[15] (2.105 g, 0.005 mol) was refluxed for 6 hr with a solution of 1.5 g (0.04 g-atom) of potassium in 15 ml of triethylcarbinol. The mixture was cooled and excess 10% hydrochloric acid was added, followed by extraction with ether. The water solution was treated with excess sodium bicarbonate and the resulting mixture was extracted with ether. This extract was dried (Na_2SO_4); removal of the solvent left an oil which was taken up in 5 ml of ether and was chromatographed on silica gel and eluted with ether to afford 1.15 g (74%) of an oil: $[\alpha]^{32.5}D$ +186.2° (*c* 1.571, anhydrous EtOH) (lit.[6] [α]D +138.6°); nmr (CCl_4) δ 2.07 (s, 6 H, $-N(CH_3)_2$), 2.82 (m, 2 H, position 9 H), 3.65 (s, 3 H, OCH_3), 3.70 (m, 1 H, methine H), 3.85 (s, 3 H, OCH_3), 5.49 (m, 2 H, vinyl H), 7.04 (m, 5 H, Ar H and vinyl H), and 8.34 (d of d, 1 H, Ar H).

Anal. ($C_{20}H_{23}NO_2$) C, H, N.

A picrate salt was recrystallized from ethanol, mp 167–168°.

Anal. ($C_{26}H_{26}N_4O_9$) C, H, N.

1-Ethyl-5,6-dimethoxy-10-dimethylamino-9,10-dihydrophenanthrene (24). Compound 10 (4.20 g, 0.0136 mol) in ethanol was hydrogenated in a Parr shaker at room temperature with 0.2 g of 5% palladium on charcoal at 3.5 kg/cm². After 2 hr, the reaction was complete. The reaction mixture was filtered through a Celite pad and upon removal of the solvent from the filtrate, the residual oil was taken up in 5 ml of ether, chromatographed on silica gel, and eluted with ether to afford 3.82 g (90%) of a yellow oil: $[\alpha]^{32.5}D$ +151.2° (*c* 1.048, anhydrous EtOH); nmr (CCl_4) δ 1.25 (t, 3 H, CH_3), 2.07 (s, 6 H, $-N(CH_3)_2$), 2.17 (m, 4 H, aliphatic H), 3.64 (broad s, 4 H, OCH_3 and methine H), 3.85 (s, 3 H, OCH_3), 6.94 (m, 4 H, Ar H), and 8.27 (d of d, 1 H, Ar H).

Anal. ($C_{20}H_{25}NO_2$) C, H, N.

1-[(2-Acetylmethylamino)ethyl]-5,6-dimethoxyphenanthrene (13). 10,11-Dimethoxyaporphine[15] (2.105 g, 0.0071 mol), 30 ml of acetic anhydride, and 0.5 ml of acetic acid were refluxed for 4 hr; then the volatiles were removed under reduced pressure. The oily residue was poured over ice and the resulting mixture was extracted with chloroform. This extract was washed with 5% sodium bicarbonate and then with water and was dried (Na_2SO_4). Evaporation of the chloroform yielded an oil which crystallized upon standing and was recrystallized from ethyl acetate to yield 1.9 g (71%) of material: mp 143–144°; ir (KBr) 1635 cm^{-1} (amide C=O); nmr ($CDCl_3$) δ 1.93 (d, 3 H, $NCOCH_3$), 2.89 (d, 3 H, NCH_3), 3.50 (m, 4 H, aliphatic H), 3.95 (s, 3 H, OCH_3), 4.04 (s, 3 H, OCH_3), 7.71 (m, 6 H, Ar H), and 9.66 (m, 1 H, Ar H).

Anal. ($C_{21}H_{23}NO_3$) C, H, N.

***N*-Ethyl-*O,O*-dimethylapomorphinium Iodide (25).** 10,11-Dimethoxyaporphine[15] (0.421 g, 0.0014 mol) and 0.437 g (0.0028 mol) of ethyl iodide were refluxed in 50 ml of acetone for 2 hr. The solid which separated was collected on a filter and washed with acetone and then was recrystallized from water to give 0.536 g (85%) of product: mp 227–228°; nmr (DMSO-d_6) δ 1.36 (t, 3 H, CCH_3), 3.37 (s, 3 H, NCH_3), 3.62 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 4.97 (m, 1 H, methine H), 7.30 (m, 4 H, Ar H), and 8.24 (d of d, 1 H, Ar H).

Anal. ($C_{21}H_{26}INO_2$) C, H, N.

1-[2-(Methylethylamino)ethyl]-5,6-dimethoxy-9,10-dihydrophenanthrene Hydrobromide (26). Compound **25** (0.451 g, 0.001 mol) was treated with 15 g of 5% sodium amalgam in 25 ml of water as described for **21**. The crude oily product was treated with 10 ml of 48% hydrobromic acid and 10 ml of water. The resulting solution was extracted three times with chloroform and the extracts were dried (Na_2SO_4). Upon evaporation of the chloroform, a solid remained which was recrystallized from water to give 0.325 g (80%) of product: mp 208–210°; nmr (DMSO-d_6) δ 1.27 (t, 3 H, CH_3), 2.72 (broadened s, 4 H, 9,10-dihydro H), 2.87 (s, 3 H, NCH_3), 3.20 (m, 6 H, 3($-CH_2-$)), 3.60 (s, 3 H, OCH_3), 3.83 (s, 3 H, OCH_3), 7.15 (m, 4 H, Ar H), and 8.21 (d of d, 1 H, Ar H).

Anal. ($C_{21}H_{28}BrNO_2$) C, H.

1-[2-(Methylethylamino)ethyl]-5,6-dimethoxyphenanthrene Hydrobromide (27). Compound **25** (0.451 g, 0.001 mol) was treated with 200 ml of 30% sodium hydroxide solution as described for **22**. The crude oily product was dissolved in 5 ml of 48% hydrobromic acid, and this solution was diluted with 5 ml of water. The resulting solution was extracted with 60 ml of chloroform; this extract was dried (Na_2SO_4) and evaporated under reduced pressure to leave a crystalline residue which was recrystallized from ethanol to yield 0.372 g (92%) of crystals: mp 191–192°; nmr (DMSO-d_6) δ 1.32 (t, 3 H, CH_3), 2.94 (s, 3 H, NCH_3), 3.44 (m, 6 H, 3 ($-CH_2-$)), 3.87 (s, 3 H, OCH_3), 4.0 (s, 3 H, OCH_3), 7.82 (m, 6 H, Ar H), and 9.61 (m, 1 H, Ar H).

Anal. ($C_{21}H_{26}BrNO_2$) C, H, N.

1-[2-(Methylethylamino)ethyl]-5,6-dihydroxyphenanthrene Hydrobromide (6). Compound **27** (1.0 g, 0.0025 mol) was treated with 20 ml of 48% hydrobromic acid as described for **5** and the crude product was recrystallized from 2-propanol to give 0.57 g (61%) of crystals: mp 190–192°; nmr (CD_3OD) δ 1.30 (t, 3 H, CH_3), 2.90 (s, 3 H, NCH_3), 3.14 (m, 6 H, aliphatic H), 7.50 (m, 6 H, Ar H), 9.88 (d of d, 1 H, Ar H); nmr (DMSO-d_6) δ 8.84 and 10.00 (broad m, 2 H, phenolic OH), both signals disappeared upon treatment with D_2O.

Anal. ($C_{19}H_{22}BrNO_2$) C, H, N.

1-[2-(Methylethylamino)ethyl]-5,6-dihydroxy-9,10-dihydrophenanthrene Hydrobromide (4). Compound **26** (1.8 g, 0.0044 mol) was treated with 48% hydrobromic acid as described for **5**, and the crude product was recrystallized from water to give 0.86 g (52%) of material: mp 173–176°; nmr (DMSO-d_6) δ 1.26 (t, 3 H, CH_3), 2.67 (m, 4 H, 9,10-dihydro H), 2.86 (s, 3 H, NCH_3), 3.00 (m, 6 H, 3 ($-CH_2-$)), 6.94 (m, 4 H, Ar H), 8.38 (m, 2 H, Ar H plus 1 H), and 9.39 and 9.84 (broad, 2 H). After D_2O exchange, the signals at δ 9.39 and 9.84 disappeared and the 8.38 signal became a sharp d of d integrating for 1 proton.

Anal. ($C_{19}H_{24}BrNO_2$) C, H, N.

1-Ethyl-5,6-dihydroxy-10-dimethylamino-9,10-dihydrophenanthrene Hydrobromide (7). Compound **24** (1.0 g, 0.0032 mol) was treated with 20 ml of 48% hydrobromic acid as described for **5**, and the crude product was recrystallized from 2-propanol–ether to give 0.732 g (63%) of product: mp 195–196°; nmr (CD_3OD) δ 1.26 (t, 3 H, CH_3), 2.77 (s, 6 H, $-N(CH_3)_2$), 7.18 (m, 4 H, Ar H), and 8.56 (d of d, 1 H, Ar H); nmr (DMSO-d_6) δ 8.91 and 9.72 (broad, 2 H, OH). After D_2O exchange, both signals disappeared.

Anal. ($C_{18}H_{22}BrNO_2$) C, H, N.

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Conformational Effects on the Activity of Drugs. 4.[1] Cyclic Analogs of 1-(*p*-Nitrophenyl)-2-isopropylaminoethanol. Synthesis and Evaluation of the Adrenergic β-Receptor Blocking Activity of 2-(*p*-Nitrophenyl)-4-isopropylmorpholine

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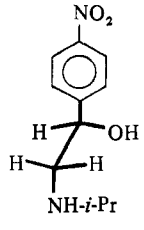
In order to obtain information about the conformation-activity relationship in the β-adrenergic blocking drugs, a cyclic analog, 2-(*p*-nitrophenyl)-4-isopropylmorpholine, and the *N*-methyl, *O*-methyl, and *N,O*-dimethyl derivatives of INPEA have been synthesized. The pharmacological results obtained by assaying these compounds on isolated muscle preparations, such as isolated rabbit atria and guinea-pig colon, and on rat blood pressure demonstrate that these products do not possess the specific β-receptor blocking properties of INPEA.

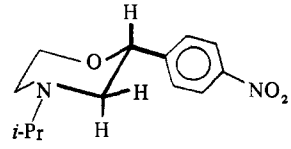
The pharmacological study of molecules in which the presumed active groups of a drug are locked in a rigid structure or contained in a semirigid system may present some disadvantages. Steric and electronic effects arising from the additional neighboring atoms necessary to maintain the rigid conformation might well influence the physical and chemical properties of the molecule to the extent that biological activity is altered.[2,3] However, such an approach can be useful toward the investigation and prediction of drug receptor interactions.[4]

Although much work has been done on β-adrenergic blocking agents, very little attention has been paid to their conformational aspects.[4d,5-7] In order to extend the knowledge of molecular conformation-biological activity relationships in drugs of this class, we have undertaken the investigation of derivatives of 1-(*p*-nitrophenyl)-2-isopropylaminoethanol (INPEA, **1**) with emphasis on conformationally rigid or semirigid analogs.[8]

Studies on compounds structurally similar to **1**, *e.g.*, isoproterenol, have shown that the preferred conformation about the C–C bond of the ethyl side chain is that with the aromatic ring and the amino group trans to each other.[9-11] Analogously, the preferred conformation of INPEA should be that shown in **1**.† 2-(*p*-Nitrophenyl)-4-isopropylmorpholine (**2**) illustrates one of the simplest ways in which INPEA can be incorporated in a cyclic structure. Although **2** is not conformationally rigid, however, it should exist mostly in the shown conformation corresponding to the assumed preferred conformation of **1**.‡



1

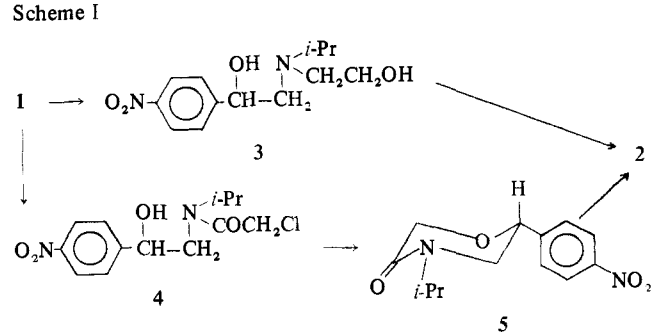


2

In the present paper we report the synthesis and evaluation of the β-receptor blocking activity of **2**; this compound contains a *tert*-amino group in addition to the etherification of the hydroxyl group and there may be some doubt about the possibility of a comparison with INPEA. Since modification of this kind in some β-adrenergic blocking drugs has been shown to bring about decreased activity or even total inactivation,[5,7,12-15] we also prepared the *N*-methyl (**6**), *O*-methyl (**9**), and *N,O*-dimethyl (**10**) derivatives of **1** in order to compare their biological activity with that of **2**.

Chemistry. Compound **2** was obtained by two independent methods. In the first, **1** was treated with 2-chloroethanol to give the *N*-(2-hydroxyethyl) derivative **3** which was converted into **2** by acid-catalyzed cyclization. Treatment of **1** with $CH_2ClCOCl$ and NaOH in CH_2Cl_2–H_2O yielded amide **4** which gave the morpholinone **5** by SN2 displacement using KOH in EtOH; subsequent reduction with B_2H_6 led to **2** (Scheme I). The expected preferred conformation of **2** was confirmed by the resonance of the benzylic proton which appears as a quartet with apparent coupling constants

Scheme I



†Nmr and X-ray studies are progressing on this subject.

‡All materials are racemic although only a single isomer is drawn.