chloride (from MeOH–Me_2CO) melted at 217–220° and had $[\alpha]^{20}D$, +39.3°. *Anal.* ($C_{16}H_{24}ClNO$) C, H.

The combined filtrate and washings from the 1.1 g of precipitate above were concentrated to 5–6 ml and made basic with NH_4OH–H_2O giving 0.9 g of a mixture of α-(−)- and (±)-**1d**; mp 192–210°. This was digested with 12–15 ml of boiling Me_2CO. Rapid cooling in ice and filtration gave 0.4 g of α-±-**1d**, mp 213–219°. The filtrate was concentrated to 3–5 ml (to the appearance of crystals), cooled to −5°, and filtered giving 0.45 g of α-(−)-**1d**, mp 196–203°. It was suspended in a little MeOH and acidified with HCl gas. Acetone was added, and solvents were distilled with periodic addition of Me_2CO until crystals began separating. Cooling to 0° gave 0.45 g (55%) of α-(−)-**1d**·HCl, mp 218–221°, $[\alpha]^{20}D$ −39.1° after recrystallization from MeOH–Me_2CO. *Anal.* ($C_{16}H_{24}ClNO$) C, H. Treatment of this hydrochloride with MeOH–NH_4OH gave α-(−)-**1d**, prisms from Me_2CO; mp 205–206°, $[\alpha]^{20}D$ −60.8°.

(+)-5-*m*-Hydroxyphenyl-2-methylmorphan [(+)-2] and the (−) Isomer [(−)-2].—*d*-Mandelic acid (0.8 g, Aldrich), 1.1 g of (±)-**2**,[9] and 10 ml of Me_2CO were warmed to disappearance of solid. On cooling, a sirup separated and was dissolved by addition of a few drops of MeOH (slight warming). Crystals separated and the mixture was cooled overnight at −5° to give 1.9 g of *d*-mandelate salts. These were dissolved in 55 ml of boiling MeOH. The solution was concentrated to the appearance of crystals (to 10–15 ml) and left at room temperature for 1 hr to give 0.9 g of the *d*-mandelate salt of (+)-**2**, mp 212–215°. Another similar recrystallization gave 0.8 g, mp 216–218°. It was suspended in boiling H_2O and treated dropwise with NH_4OH to give an oil which crystallized on cooling; yield of (+)-**2** 0.4 g (74%) mp 153–154° before and after recrystallization from MeOH, $[\alpha]^{20}D$ +12.4°. *Anal.* ($C_{15}H_{21}NO$) C, H. The **hydrochloride** (from *i*-PrOH–HCl gas) melted at 233–235° and had $[\alpha]^{20}D$, +4.4° (*c* 1.8). *Anal.* ($C_{15}H_{22}ClNO$) C, H.

The combined filtrates and washings from the 1.9-, 0.9-, and 0.8-g fractions above were concentrated to *ca.* 5 ml and diluted strongly with H_2O and NH_4OH to give 0.5 g of a mixture of (−)- and (±)-**2**. This and 0.4 g of *d*-mandelic acid were heated briefly in 5 ml of MeOH giving crystals immediately. Cooling to −5°, filtering, and washing the precipitate with cold MeOH gave 0.6 g of (−)-**2** *d*-mandelate, mp 212–214° dec. It was converted into 0.35 g (65%) of (−)-**2** as described for (+)-**2**; mp 153–154°, unchanged by recrystallization from EtOH–H_2O or MeOH. It had $[\alpha]^{20}D$ −12.7°. *Anal.* ($C_{15}H_{21}NO$) C, H. The hydrochloride (from *i*-PrOH–HCl gas) melted at 233–235° and had $[\alpha]^{20}D$ −4.8°. *Anal.* ($C_{15}H_{22}ClNO$) C, H.

(9) E. L. May and J. G. Murphy, *J. Org. Chem.*, **20**, 1197 (1955).

Tricyclic Norephedrine Analogs. The Isomeric 9-Hydroxy-10-amino-1,2,3,4,4a,9,10,10a-(*trans*-4a,10a)-octahydrophenanthrenes[1a]

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The syntheses of the 4 isomeric 9-hydroxy-10-amino-1,2,3,4,4a,9,10,10a-(*trans*-4a,10a)-octahydrophenanthrenes (**1**, **2**, **3**, and **4**) are described. Spectral and chemical evidence are presented for the structures of the title compounds. Biological data are recorded for α-adrenergic receptor activity and α-adrenergic blocking activity.

A number of studies have been performed to aid in the delineation of the architectural features of adrenergic receptors, each providing some evidence concerning the steric and electronic requirements for analogs of norepinephrine to produce effects in various tissues.[2] More recently studies have been directed at determining the conformational specifications of the agonist drug–receptor complex, with the idea that conformational differences in the drug–receptor interaction of a single drug with different receptors may be at least a partial explanation for different actions of a single drug, and/or different potencies of the same drug, on various tissues. Little has been offered in terms of the architectural features of this complex, although speculation, consistent with the facts, does exist, determined primarily for conformationally mobile agonists.[2c,3] Adrenergic activity of a phenethylamine moiety, and a benzylic hydroxyl group of a given absolute stereochemistry have been defined. In addition stereochemical relationships between the ephedrines and ψ-ephedrines for agonist and antagonist activity have been determined.[4] In this nonrigid system little can be said concerning specific conformational requirements of the drug–receptor complex. Studies by Smissman and coworkers have shown some adrenergic activity in the 2-phenyl-3-amino-*trans*-2-decalols,[5a] although little difference is noted in the isomers and amine depleting activity in the 3-phenyl-3-hydroxy-*trans*-decahydroquinolines.[5b]

In this study we prepared norephedrine analogs **1**, **2**, **3**, **4**, in which 9-(e)-hydroxy-10(e)-amino-1,2,3,4,4a,9,-10,10a-(*trans*-4a,10a)-octahydrophenanthrene (**1**), and the 9(a)-hydroxy-10(a)-amino compound, (**3**) represent *threo* configurations of norephedrine and the 9(a)-hydroxy-10(e)-amino compound (**2**), and the 9(e)-hydroxy-10(a)-amino analog (**4**), represent *erythro* configurations.[6]

(1) (a) Presented to the Division of Medicinal Chemistry, 158th National Meeting of the American Chemical Society, New York, N. Y., Sept 7–12, 1969, MEDI-33; (b) taken in part from the dissertation presented by D. D. Miller, July 1969, to the Graduate School, University of Washington, in partial fulfillment of the Ph.D. degree; (c) U. S. Public Health Service Fellowship, 1-F1-GM-33,942, 1966–1969.

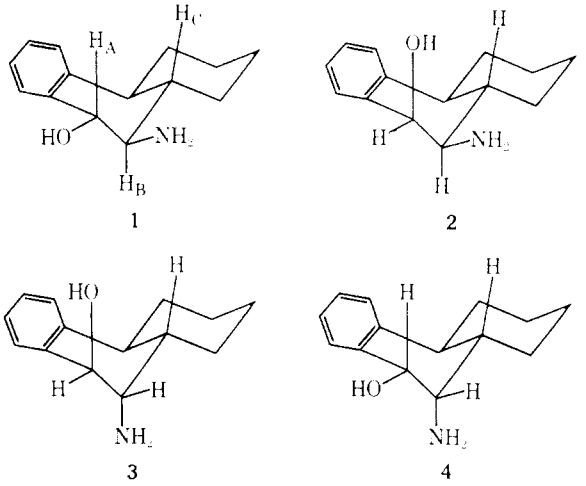
(2) For recent reviews see (a) R. P. Ahlquist, *J. Pharm. Sci.*, **55**, 359 (1966); (b) A. M. Lands and T. G. Brown, Jr., *Drugs Affecting Peripheral Nerv. Syst. 1967*, **1**, 399 (1967); (c) B. Belleau, *Ann. N. Y. Acad. Sci.*, **139**, 580 (1967).

(3) (a) B. M. Bloom and I. M. Goldman, *Advan. Drug. Res.*, **3**, 121 (1966); (b) G. A. Robinson, R. W. Butcher, and E. W. Sutherland, *Ann. N. Y. Acad. Sci.*, **139**, 606 (1967); (c) L. B. Kier, *J. Pharmacol. Exp. Ther.*, **75**, 164 (1968); (d) L. B. Kier, *J. Pharm. Pharmacol.*, **21**, 93 (1969); (e) P. S. Portoghese, *J. Med. Chem.*, **10**, 1057 (1967).

(4) J. B. LaPidus, A. Tye, P. Patil, and B. A. Modi, *ibid.*, **6**, 76 (1963).

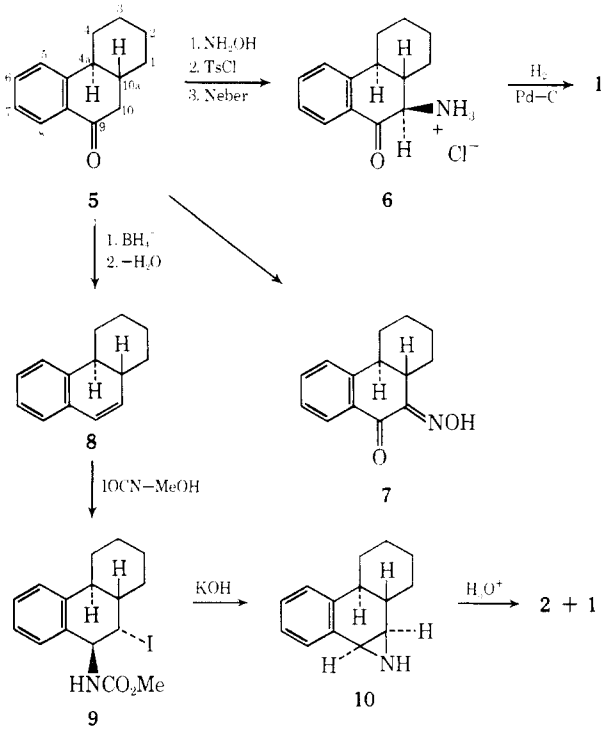
(5) (a) E. E. Smissman and W. H. Gastrock, *ibid.*, **11**, 860 (1968); (b) E. E. Smissman and G. H. Chappell, *ibid.*, **12**, 429 (1969).

(6) (a) The central ring is arbitrarily assigned the half-chair conformation where the equatorial (e) and axial (a) substituents at C-9 are in fact *pseudo*-equatorial and *pseudo*-axial respectively; (b) All materials are racemic although only a single isomer is drawn; (c) Consistently throughout nmr discussions of the 9,10-disubstituted compounds, the proton at C-9 will be designated A, the proton at C-10, B, and the C-10a axial proton, C.



Octahydrophenanthrone (**5**)[7] was the starting material for preparation of the isomeric amino alcohols. The relative stereochemistry of the hydrogens at 4a and 10a; *i.e.*, the *trans*-ring junction, is determined by the synthetic method (Scheme I).

Scheme I



Compound **1** was prepared from **5** by Neber rearrangement of the ketone oxime tosylate. Only small amounts of amino ketone **6** were isolated, partly due to the lack of solubility of the starting material in suitable reaction solvents. The nmr spectrum of **6** showed a doublet at δ 4.35, J_{BC} = 12 Hz, similar in coupling constant to the 10-axial proton in ketone **5**.[8] These data clearly demonstrate the equatorial disposition of the amino group; however, the stereochemistry of **6** is not necessarily due to the stereospecificity of the rearrangement, but could be a result of acid-catalyzed enolization of the epimeric amino ketone.[9] We were unsuccessful in several attempts to isolate the possible azirine or amino ketal intermediates of the rearrangement.

The α-amino ketone **6** was reduced (Pd–C) to provide **1**, having equatorial OH and amino groups. Because of the insolubility of **1** in suitable nmr solvents the *N,O*-diacetyl derivative (**1A**) was prepared for nmr work. The nmr spectrum of **1A** showed CH at δ 6.05, J_{AB} = 9 Hz, and at δ 4.17, J_{BC} = 10 Hz, assigned to axial protons H_A and H_B, respectively.[6c] An additional coupling of H_B with N–H of 10 Hz was removed by deuterium exchange.

Attempted catalytic (Pt) reduction of **6** in acid, failed to produce **2**, although this has been reported.[10] In our hands, only **1**·HCl was isolated. More conveniently, α-oximino ketone **7**, which was readily prepared from **5** by nitrosation, could be reduced to **6** and then to **1** without difficulty.

Hexahydrophenanthrene **8** was the starting material for preparation of **2**. Addition of iodine isocyanate (INCO), followed by methanolysis afforded **9**. The assignment of net *trans* diaxial addition is consistent with reports of INCO addition in other systems,[11] and from nmr evidence, which showed small coupling constants for J_{AB} and J_{BC} consistent with dihedral angles, $\phi_{AB} \simeq \phi_{BC} \simeq$ *ca.* 50–70°, and diequatorial disposition of H_A and H_B.[6a,12] Methanolic KOH was used to convert **9** into **10**, the *syn*-aziridine.[13] On treating **10** with refluxing aq 5% H_2SO_4, **2** was isolated in 56% yield. On repeating this procedure carefully it could be demonstrated that **1** was also present in the crude reaction mixture. This observation is consistent with other reports of isolation of *cis*- and *trans*-amino alcohols as products of styryl aziridine openings; *e.g.*, from 2-phenyl-3-methylaziridine[14a] and 5,6-imino-6,7-dihydro-5*H*-dibenz[*a,d*]cycloheptadiene.[14b] The intermediary of a carbonium ion or carbonium ion-like species would be expected in these systems.[15]

The nmr spectrum of the *N,O*-diacetyl derivative, **2A**, was consistent with the *cis* disposition of substituents showing a doublet for H_A at δ 6.19, J_{AB} = 4 Hz, and a multiplet at 4.26, which collapsed into a quartet, J_{BC} = 11 Hz, when D exchange was performed; at the same time a doublet at δ 6.80 for the N-H proton, $J_{B,NH}$ = 9 Hz, disappeared. The dihedral angles ϕ_{AB} and ϕ_{BC} are *ca.* 70 and 190°, respectively, in Dreiding models.[16]

Believing that **3**, containing an axial amino group, could be best prepared from *syn*-epoxide **11**,[13] by

(7) (a) W. E. Backmann and E. J. Fornefeld, *J. Amer. Chem. Soc.*, **72**, 5529 (1950); (b) D. Ginsburg and R. Pappo, *ibid.*, **75**, 1524 (1953); (c) C. D. Gutsche and W. S. Johnson, *ibid.*, **68**, 2239 (1946).

(8) W. L. Nelson, D. D. Miller, and R. S. Wilson, *J. Heterocycl. Chem.*, **6**, 131 (1969).

(9) D. F. Morrow, M. E. Butler, and E. C. Y. Huang, *J. Org. Chem.*, **30** 579 (1965).

(10) G. Drefahl and D. Martin, *Chem. Ber.*, **93**, 2497 (1960).

(11) (a) A. Hassner and F. W. Fowler, *J. Amer. Chem. Soc.*, **90**, 2869 (1968); (b) A. Hassner and C. Heathcock, *Tetrahedron Lett.*, 1125 (1964); (c) A. Hassner and C. Heathcock, *J. Org. Chem.*, **30**, 1748 (1965).

(12) (a) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959); (b) M. Karplus, *J. Amer. Chem. Soc.*, **85**, 2870 (1963).

(13) *Syn* and *anti* refer to the hetero three-membered ring as being on the same, or opposite side, of the tricyclic skeleton as the C-10a H atom.

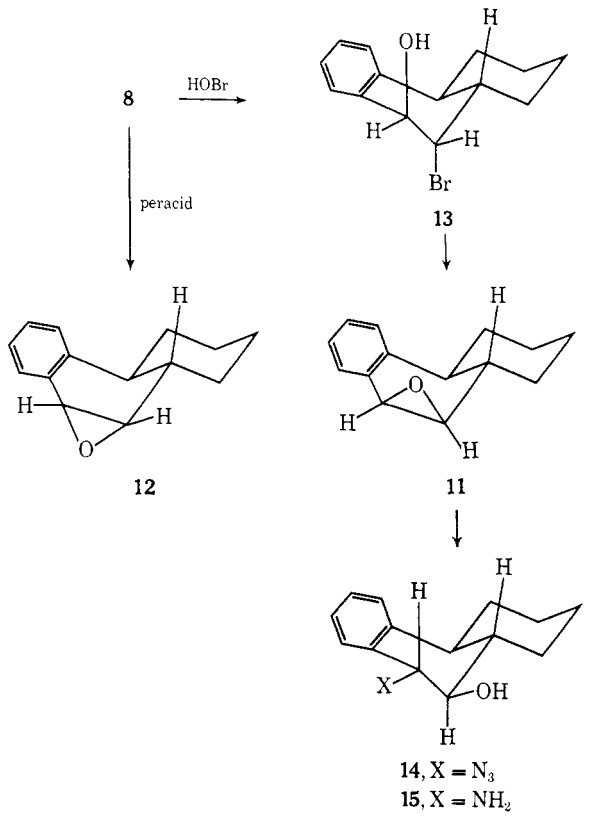
(14) (a) K. Kotera, M. Motomura, S. Miyazaki, T. Okada, and Y. Matsukawa, *Tetrahedron*, **24**, 1717 (1968); (b) K. Kotera, T. Okada, and S. Miyazaki, *ibid.*, **24**, 5677 (1968).

(15) R. E. Parker and N. S. Isaacs, *Chem. Rev.*, **59**, 737 (1959).

(16) Dihedral angles of 60 and 180° are not observed because of the *pseudo* nature of the substituent at C-9 in the substituted cyclohexene system,[6a] and an additional conformational constraint due to a *trans* ring fusion between C-4a and C-10a.

opening with an appropriate nucleophile, we sought routes to the desired epoxide. Epoxidation with *m*-chloroperbenzoic acid afforded *anti*-epoxide **12**,[13] and no trace of **11**. Formation of **11** was accomplished by addition of HOBr to **8**, followed by epoxide formation using NaOH (see Scheme II). Assignment of structure **13** to the bromohydrin was made based on the nmr spectrum. A doublet at δ 5.93, $J_{OH,A}$ = 5.5 Hz, was assigned to the OH which disappeared on addition of small amounts of F_3CCO_2H, a quartet for H_A at δ 4.75, J_{AB} = 2.3 Hz, and a multiplet for H_B, W_h = 5 Hz. The small coupling constants J_{AB} and J_{BC} are consistent with dihedral angles, ϕ_{AB} and ϕ_{BC} *ca.* 60–70°.[6a,12]

SCHEME II



Exposure of the bromohydrin to OH^- for short periods afforded **11**, although longer periods afforded no epoxide but only mixtures of 1,2,3,4,4a,9,10,10a-(*cis*- and *trans*-4a,10a)-10-ketooctahydrophenanthrenes, which probably arises from the epoxide.[15,17]

Having both epoxides, **11** and **12**, it was not difficult to distinguish between them based on their nmr spectra. The *anti*-epoxide (**12**) shows a doublet at δ 3.69, J_{AC} = 4.3 Hz, and another doublet for H_B a δ 2.82 indicating $J_{BC} \approx 0$ Hz. The *syn*-epoxide (**11**) showed a doublet at δ 3.59, J_{AB} = 4 Hz, and a *broadened* doublet at 3.14 for H_B, J_{BC} = 0–1.5 Hz. The difference of marked line broadening in the H_B signal in **11** and in **12** is consistent with dihedral ϕ_{BC} measurements of *ca.* 120° in **11** and 90° in **12**.

Opening of **11** with NaN_3 or NH_3 as nucleophiles provided products of ring opening at the benzylic position, **14** and **15**, respectively. Structure assignment to **14** became readily apparent from nmr data. A doublet at δ 4.49, J_{AB} = 9 Hz, a sextet at 3.65, $J_{BC} \approx$ 10 Hz, and a doublet at 2.93, $J_{B,OH}$ = 10 Hz are observed. The latter signal disappeared upon addition of D_2O and the sextet collapsed to a quartet indicating H_B is attached to the carbon bearing the OH group. Structure **3**, with OH at the benzylic position, is inconsistent with the quartet observed in the nmr spectrum, thus allowing the alternative assignment.

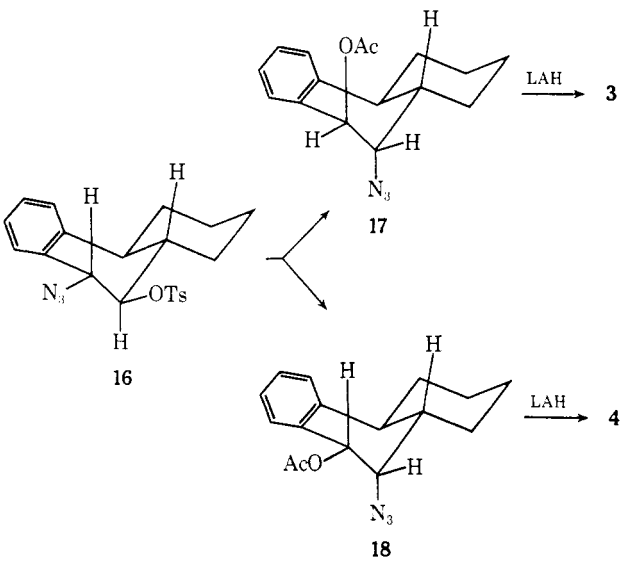
Compound **14** was converted into **15**, thus indicating both nucleophiles entered from the benzylic position.

It is not obvious from Dreiding models that attack of the nucleophile would be sterically less hindered at the benzylic C; in fact, no obvious differences in ease of attack at C-9 and C-10 are observed. However, if some degree of C–O bond fission takes place prior to C-nucleophile bond formation, *i.e.*, there is some polarization and charge separation in the transition state, then approach at the benzylic position would probably be more favorable due to increased stability of this carbonium ion, or partially polarized transition state at this center.[18] Similar results leading to diequatorial opening of epoxides have been reported in certain steroidal systems.[15,19]

Pursuit of amino alcohol **3**, by this route, was not abandoned. Resourceful use of azido alcohol **14** led to successful routes to both **3** and **4**.

Azido alcohol **14** was converted into the corresponding tosylate **16**, which was solvolyzed in AcOH. Long-term solvolysis (7 days) afforded a 9:1 mixture of azido acetates **17** and **18**. Column chromatography afforded samples of pure **17**, but allowed for isolation of only small amounts of **18**. No conclusive nmr evidence was available to distinguish between these two structures as only small differences in ϕ_{AB} are discernable from models, both near 60°. If the azide group participates in the solvolysis of the tosylate and/or formation of an azidonium ion[20] occurs then **17** would be expected to predominate (Scheme III).

SCHEME III



(17) (a) C. J. Thomas, S. J. and I. M. Hunsberger, *J. Org. Chem.*, **33**, 2852 (1968); (b) R. E. Lyle and W. E. Drueger, *ibid.*, **32**, 2873 (1967).

(18) C. A. VanderWerf, R. Y. Heisler, and W. E. McEwen, *J. Amer. Chem. Soc.*, **76**, 1231 (1954).

(19) (a) F. G. Bordwell, R. R. Frame, and J. G. Strong, *J. Org. Chem.*, **33**, 3385 (1968); (b) D. H. R. Barton, D. A. Lewis, and J. F. McGhie, *J. Chem. Soc.*, 2907 (1957).

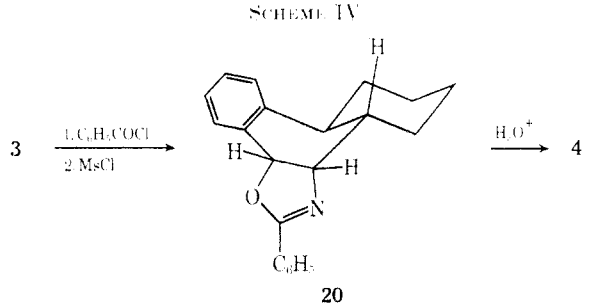
(20) A. Streitweiser, Jr., and S. Pulver, *J. Amer. Chem. Soc.*, **86**, 1587 (1964).

The two azido acetates, **17** and **18**, were converted into their corresponding amino alcohols, **3** and **4**, respectively, and then to their *N,O*-diacetyl derivatives, **3A** and **4A**. In order to isolate useful quantities of **4A**, LAH reduction was performed on a mixture of **17** and **18**, followed by acetylation and chromatographic separation of the resulting mixture of **3A** and **4A**.

Slight differences in J_{AB} were noted in these compounds. In **4A** J_{AB} = 5 Hz and in **3A** J_{AB} = 3 Hz, similar in magnitude to the corresponding azido acetates. In Dreiding models ϕ_{AB} in **4A** is *ca.* 50°, and in **3A** about 70°, consistent with these assignments. An additional coupling constant $J_{B,NH}$ = *ca.* 10 Hz was removed by D exchange. This fact, and the fact that the benzylic proton, H_A, did not change in multiplicity allows for assignment of the location of the amino function at C-10, further confirming the structure of the azido acetates and of **3A** and **4A**.

Because both J_{AB} and J_{BC} were small in both **3A** and **4A**, no absolute assignments based on nmr data could be made to their relative stereochemistry. Chemical evidence was found by converting **3** into **4** by a stereospecific route. Compound **3** was converted into the corresponding *N*-benzoyl derivative **19** which upon treatment with $MeSO_2Cl$ spontaneously formed oxazoline **20**, resulting from intramolecular carbonyl O displacement of the mesylate. Hydrolysis, under carefully controlled conditions, afforded **4** (see Scheme IV). *N,O*-Diacetyl derivatives prepared by both routes were identical spectrally.

Scheme IV



20

Hydrochloride salts of **1**, **3**, and **4** were submitted for testing in the vas deferens preparation reported by Patil, *et al.*[21] The insolubility of salts of **2** precluded screening of this compound. None of the compounds showed intrinsic activity of greater than 10% of (−)-norepinephrine in this assay. This is probably due to the large C-skeleton attached to the basic phenethylamine being present, especially the large β substituent.

Two of the compounds, **1** and **3**, showed adrenergic blocking activity, the former demonstrating both competetive and noncompetetive antagonism (Figure 1). The effects of **3** were less dramatic, showing only a slight diminution in the maximal response to (−)-norepinephrine at 4×10^{-4} *M* (Figure 2).

Compound **4** exhibited potentiation at 1×10^{-4} *M* (Figure 3) while a noncompetetive type interaction was evident at higher concentrations. It is possible that this agent may be acting at the adrenergic nerve terminal as well as at the effector site.

(21) P. N. Patil, J. B. LaPidus, and A. Tye, *J. Pharmacol. Exp. Ther.*, **155**, 1 (1967).

Experimental Section[22]

1,2,3,4,4a,9,10,10a-(*trans*-4a,10a)-Octahydro-9-oxophenanthrene (5).[7c]—2-Phenylcyclohexylacetic acid, 25 g (0.114 mole), was placed into an ice-cooled, stirred solution of 200 ml of liquid HF (Matheson Co., Inc.) in a 500-ml polyethylene container. The HF was allowed to evaporate, leaving a brown residue. Caution should be taken that this reaction be performed in a hood and one should always wear rubber gloves when handling the polyethylene container. The residue was dissolved in Et_2O and washed with aq saturated $NaHCO_3$, aq 10% HCl, and H_2O. The Et_2O layer was then dried (Na_2SO_4) and evapd *in vacuo* to give 24 g of white solid material. After recrystallization in MeOH 22.8 g of white plate-like crystals were collected (88%): mp 95° (lit.[7c] mp 95–96°); uv max (95% EtOH) 250 (ε 11,200), 292 mμ (ε 1,720); ir (KBr) 5.95 μ (C=O); nmr ($CDCl_3$) δ 8.22 (m, 1, C-8 aromatic proton), 7.8–7.2 (m, 3, aromatic protons); nmr (C_6H_6) δ 2.50 (q, 1, J_{gem} = 16 Hz, J_{ea} = 3.3 Hz, equatorial proton at C-10), 2.20 (q, 1, J_{gem} = 16 Hz, J_{aa} = 11.5 Hz, axial proton at C-10), 2.5–1.0 (m, 10, CH_2–CH envelope).

1,2,3,4,4a,9,10,10a-(*trans*-4a,10a)-Octahydro-9-oximinophenanthrene *O*-*p*-Toluenesulfonate.—To a solution of 20.0 g (0.10 mole) of ketone **5** in 77 ml of MeOH was added 13.9 g (0.20 mole) of $H_2NOH \cdot HCl$ in one portion, followed by the slow addition of 13.0 g (0.09 mole) of K_2CO_3 in 30 ml of H_2O over a 10-min period. The mixture was refluxed 2 hr, allowed to cool, and then poured into 300 ml of ice–H_2O. The white ppt 10.0 g (88.5%) was collected by filtration, mp 175°. A small portion was recrystallized from EtOAc and Et_2O giving colorless needles: mp 177° (lit.[10] mp 178°); uv max (95% EtOH) 253 mμ (ε 11,200); nmr (pyridine) δ 3.23 (q, 1, J_{gem} = 17.9 Hz, J_{ea} = 4 Hz, equatorial at C-10, 2.9–1.0 (broad CH_2–CH envelope).

The oxime, 9.0 g (0.04 mole), was placed in 36 ml of anhyd pyridine and this solution was kept at −25° (Dry Ice–Me_2CO bath). To the pyridine solution was added 11.4 g (0.06 mole) of TsCl and the mixture was stirred for 20 min, then allowed to warm to room temp, and stirred overnight. The reddish-brown solution was then poured in 300 ml of ice–H_2O and the resulting ppt 13.8 g (89%) was collected by filtration. After 2 recrystallizations from MeOH–EtOAc–H_2O clear needle-like crystals were collected: mp 177° (lit.[10] mp 174.5°); uv max (95% EtOH) 255 (ε 13,600); nmr (pyridine) δ 3.18 (q, 1, J_{gem} = 19 Hz, J_{ea} = 4 Hz, equatorial proton H_A), 2.24 (s, 3, CH_3), 2.5–0.9 (m, 10, CH_2–CH envelope).

9-Keto-10(e)-amino-1,2,3,4,4a,9,10,10a-(*trans*-4a,10a)-octahydrophenanthrene (6). A. Neber Rearrangement.—A solution of KOEt prepared by dissolving 1.12 g (0.0286 g-atom) of K in 15 ml of abs EtOH was added to a stirred solution of 10 g (0.027 mole) of the oxime tosylate in 100 ml of C_6H_6 at 10° under N_2. After the addition of the EtO^- solution another 100 ml of abs EtOH was added. The yellow suspension was then stirred and maintained at 10° for the next 10 hr and then allowed to warm to room temp. After 24 hr the brown mixture was filtered affording 4 g of a purple ppt (KOTs). The brown filtrate was evaporated *in vacuo* with the temp of the water bath maintained below 40°. To the green suspension was added 20 g of basic Al_2O_3, Brockmann activity I (Brinkmann), and the mixture evapd to give a brownish green colored solid. The solid was placed on 200 g of basic Al_2O_3 Brockman activity I (Brinkmann). After elution with 2 l. of (1:1 Et_2O), 1 l. of Et_2O, and 500 ml of C_6H_6, $CHCl_3$ was placed on the column and the next 800 ml was collected. Evaporation afforded 4.0 g of a light red oil. The red oil contained 5 components when inspected with the (silicic acid plates, 1:1 Et_2O–hexane, I_2 as indicator).

The red oil (4.0 g) was placed on a dry column of 400 g of neutral Al_2O_3, Brockmann activity II (Brinkmann). The column was eluted with 1:1 Et_2O–hexane. After the first 225 ml of solvent eluted from the column, the next 175 ml was collected and evaporated *in vacuo* to give 900 mg of a red oil. This was

(22) Melting points were obtained on a calibrated Thomas-Hoover Uni-Melt and are corrected. Uv spectra were recorded on a Cary 14 spectrometer. Ir data were recorded on Beckman IR-5A, IR-8, and IR-20 spectrophotometers. Nmr spectra were determined with Varian A-60 and Varian T-60 spectrophotometers using Me_4Si as an internal standard. In nmr descriptions, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Mass spectra were recorded on AEI MS-9. Microanalyses were conducted by Dr. Weiler and Dr. F. B. Strauss, Oxford, England. Where analyses are indicated only by symbols of the elements, analytical results were obtained for those elements within ±0.4% of the theoretical values.

dissolved in Et_2O and added to a 10% aq HCl. The Et_2O layer was added to the aq HCl to prevent self-condensation.[23] The aq layer, which contained some brown ppt which was removed by filtration, was separated. The light yellow filtrate was evapd *in vacuo* affording 120 mg of a light green solid. The solid was dissolved in MeOH, Et_2O was added until the solution turned cloudy, and the soln was placed in the refrigerator overnight. The mixture was filtered and 100 mg (1%) of colorless crystals of **6** was collected: mp 215–217° (lit.[10] mp 210–212°); ir (KBr) 3.1 to 4.0 ($-NH_3^+$ stretching, broad ammonium band)[24] a weak band at 5.1 (combination of $-NH_3^+$ torsional oscillation and asym $-NH_3^+$ deformations);[24] 5.9 μ (C=O stretching); nmr (CD_3OD) δ 8.25 (m, 1, C-8 aromatic proton), 8.0–7.4 (m, 3, aromatic protons), 4.34 (d, 1, axial proton H_A); uv max (95% EtOH) 251 mμ (ϵ 11,300). *Anal.* ($C_{14}H_{18}ClNO$) calcd C, 66.79; found C, 66.29, H, N.

B. Reduction of Keto Oxime 7.—Keto oxime **7** (500 mg, 2.18 mmoles), was placed in 50 ml of abs EtOH and to this solution was added 0.80 ml of concd HCl in 10 ml of abs EtOH along with 100 mg of 10% Pd–C. The mixture was hydrogenated at a maximum pressure of 1.05 kg/cm^2. Uptake of H_2 was complete in 10 min and the mixture was then filtered through Celite to give a clear filtrate. The filtrate was evapd *in vacuo* to give white solid, mp 210–212°. This material had identical spectral properties (ir, nmr, uv) as the amino ketone·HCl prepared by the Neber rearrangement.

9-Keto-10-oximino-1,2,3,4,4a,9,10,10a-(*trans*-4a,10a)-octahydrophenanthrene (7).[10]—To a solution of 7.0 g (0.035 mole) of ketone **5** and 4.1 g (0.035 mole) of isoamylnitrite in 10 ml of anhyd toluene was added a solution of KOEt, prepared by dissolving 1.36 g (0.035 g-atom) of K in 10 ml each of abs EtOH and anhyd toluene. During the addition the mixture was kept below 10°, utilizing an ice bath. The resulting purple suspension was stirred for an additional hour with the ice bath and then allowed to come to room temp. To the purple suspension was added 50 ml of anhyd Et_2O and this mixture was then poured into 300 ml of anhyd Et_2O. The white ppt that formed was collected by filtration and dissolved in H_2O and from the resulting yellow solution a ppt formed which was removed by filtration. The filtrate was cooled in an ice bath and carefully acidified to pH 5 with cold 10% aq HCl. After chilling for 6 hr 3.9 g (49%) of crude **7**, mp 115–120°, was collected. A small portion of this material was recrystallized 3 times from 95% EtOH to give yellow needles: mp 140–141° (lit.[10] 158–159°); uv max (CH_3OH), neutral, 272 (ϵ 10,700); uv max (CH_3OH), alkaline, 265 and 323. *Anal.* ($C_{14}H_{15}NO_2$): C, H, N.

9(e)-Hydroxy-10(e)-amino-1,2,3,4,4a,9,10,10a-(*trans*-4a,10a)-octahydrophenanthrene Hydrochloride (1).—A mixture of 430 mg (1.7 mmoles) of the α-amino ketone **6** and 200 mg of 10% Pd–C in 100 ml of EtOH was hydrogenated at a maximum pressure of 2.45 kg/cm^2 and room temp. Uptake of H_2 was complete in 72 hr. The mixture was filtered through Celite to give a clear EtOH solution. The EtOH solution was evaporated *in vacuo* to give a white powder. The powder was taken up in MeOH, and Et_2O was added to the boiling solution until it turned cloudy, and then it was refrigerated for crystallization, affording 298 mg (69%) of white crystalline **1**: mp 234° (lit.[10] 240–242°); ir (KBr) 3.20–3.60 ($-NH_3^+$ stretching, broad), 5.0 μ (broad, combination of $-NH_3^+$ torsional oscillation and asym $-NH_3^-$ deformation).[25]

9(e)-Acetoxy-10(e)-acetamido-1,2,3,4,4a,9,10,10a-(*trans*-4a,-10a)-octahydrophenanthrene (1A).—A mixture of 220 mg (0.87 mmole) of the HCl salt of amino alcohol **1**, 5 ml of pyridine, and 3 ml of Ac_2O was allowed to stand 15 hr at room temp. Excess pyridine and Ac_2O were removed *in vacuo* and the residual oil was mixed with 10 ml of 3% aq HCl and allowed to stand 30 min. The acidic solution was extracted with Et_2O several times and the Et_2O layers were combined and washed with satd solution of $NaHCO_3$, 3% aq HCl, and H_2O. The Et_2O layer was dried (Na_2SO_4) and then evapd *in vacuo* affording 258 mg of light yellow solid. The solid material was recrystallized from C_6H_6 to give 232 mg (89%) of white needles: mp 168–169°; ir (KBr), 3.04 (N-H stretching), 3.41 and 3.50 (aliphatic C-H stretching), 5.82 (C=O stretching), 6.1 (amide C=O stretching), 6.5-6.6 (broad), 7.31, 8.15, 9.83, 10.35, and 13.43 μ; nmr ($CDCl_3$), δ 7.3–7.0 (m, 4 aromatic protons), 6.75 (d, 1, $J_{B,NH}$ = 10 Hz, amide N-H), 6.05 (d, 1, J_{AB} = 9 Hz, benzylic H_A proton) 4.17 (q, 1, J_{BC} = 10 Hz, CH H_B proton), 2.07 (s, 3, CH_3), 1.98 (s, 3, CH_3). *Anal.* ($C_{18}H_{23}NO_3$) C, H, N.

9(ξ)-Hydroxy-1,2,3,4,4a,9,10,10a-(*trans*-4a,10a)octahydrophenanthrene.—At room temperature 2.28 g (0.053 mole) of

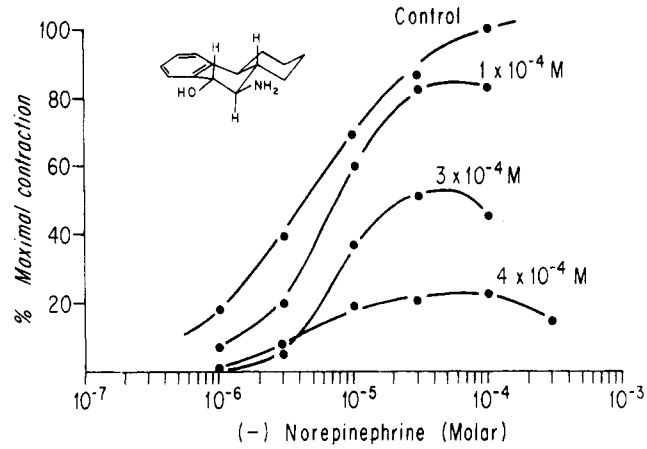


Figure 1.—Cumulative dose–response curve of (−)-norepinephrine before and after addition of **1**, on isolated rat vas deferens.

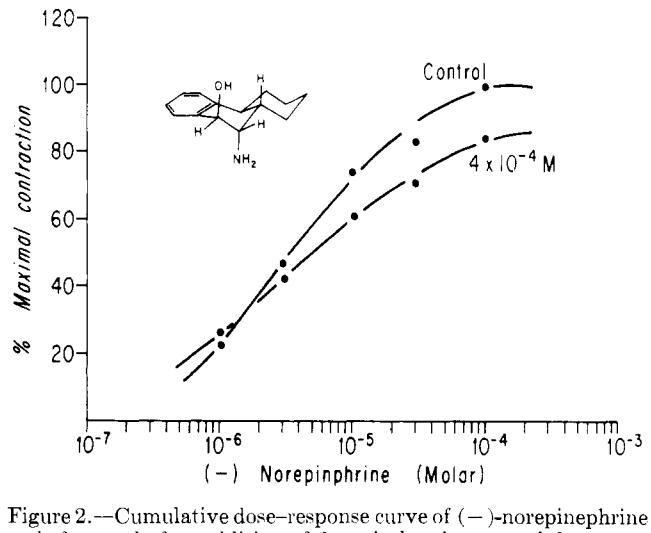


Figure 2.—Cumulative dose–response curve of (−)-norepinephrine before and after addition of **3**, on isolated rat vas deferens.

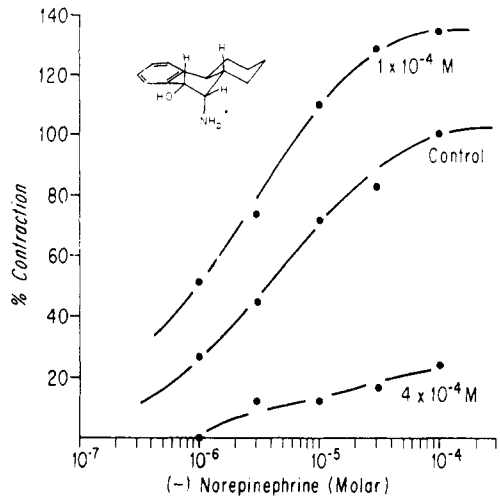


Figure 3.—Cumulative dose–response curve of (−)-norepinephrine before and after addition of **4**, on isolated rat vas deferens.

(23) H. E. Baumgarten and J. M. Petersen, *J. Amer. Chem. Soc.*, **82**, 459 (1960).

(24) K. Nakanishi, "Infrared Absorption Spectroscopy," Holden-Day, Inc., San Francisco, Calif., 1964, p 39.

(25) N. B. Colthup, L. H. Daley, and S. E. Wiberly, "Introduction to Infrared and Raman Spectroscopy," Academic Press, New York, N. Y., 1964, p 281.

$NaBH_4$ (Alfa Inorganics, Inc.) in 20 ml of H_2O was added slowly over a 20-min period to 20 g (0.10 mole) of **5** in 1 l. of 95% EtOH. The mixture was stirred 19 hr. After the addition of 10 ml of 1 *N* NaOH the EtOH was removed *in vacuo*. The oily residue was dissolved in Et_2O, washed with H_2O, dried (Na_2SO_4), and evapd *in vacuo* to give 19.5 g (92%) of white solid material, mp 102°. An analytical sample was prepared by recrystallization from petroleum ether (bp 30–60°), mp 102°. *Anal.* ($C_{14}H_{18}O$) C, H.

A *p*-nitrobenzoate derivative was prepared, mp 130–131°.

1,2,3,4,4a,10a-(*trans*-4a,10a)-Hexahydrophenanthrene (8).—A mixture of 24.0 g (0.12 mole) of the alcohol and 500 mg (2.4 mmoles) of 2-naphthalenesulfonic acid (Eastman Organic Chemicals) in 1 l. of C_6H_6 was refluxed with an attached Dean–Stark trap for 48 hr. The mixture was evapd *in vacuo* and the remaining residue was dissolved in Et_2O and washed with several portions of an aq satd $NaHCO_3$ solution and H_2O. The Et_2O layer was dried (Na_2SO_4) and then evapd *in vacuo* to give 25 g of a yellow oil. Column chromatography on 900 g of silica gel (Brinkmann); Brockmann Activity III, using hexane as eluent afforded 20.6 g of colorless alkene (93%) in the first 750 ml of hexane collected: uv max (95% C_2H_5OH) 262 (ϵ 8200); nmr ($CDCl_3$) δ 7.26 (m, 4, aromatic protons), 6.55 (q, 1, J_{AB} = 10 Hz, J_{AC} = 2 Hz, C-9 vinyl proton), 5.85 (d, 1, J_{BC} = 0–1 Hz, C-9 proton, H_B); mass spectrum (70 eV) *m/e* 184.

9(a)-Carbomethoxyamino-10(a)-iodo-1,2,3,4,4a,9,10,10a-(*trans*-4a,10a)-octahydrophenanthrene (9).—To a cold (−5 to −10°) solution of 3.9 g (0.02 mole) of hexahydrophenanthrene **8** in 200 ml of anhyd Et_2O was added 4.2 g (0.028 mole) of freshly prepared AgOCN. To this was added 5.04 g (0.021 mole) of solid I_2 in one portion. The slurry was stirred for 2 hr in the cold and then at room temperature for an additional 6 hr. The inorganic salts were removed by filtration and the solution was diluted with 200 ml of anhyd MeOH and the mixture was refluxed for 2 hr. The light brown ppt was removed by filtration and washed with Et_2O. The ppt was then recrystd from CH_3OH giving 5.35 g (70%) of white needles: mp 138°; uv max (95% C_2H_5OH) 217, (ϵ 7000); ir (KBr) 3.05 (N-H stretching), 3.25 (aromatic C-H stretching), 3.39 and 3.49 (aliphatic C-H stretching), 5.90 (very broad, C=O stretching); nmr (pyridine), δ 5.59 (q, 1, J_{AB} = 2 Hz, $J_{A,NH}$ = 8 Hz, benzylic proton H_A) 4.84 (m, W_h = 4 Hz, C-10, H_B proton), 2.70–0.7 (m, 10, CH_2—CH envelope). *Anal.* ($C_{16}H_{20}INO_2$): C, H, N.

***syn*-9,10-Imino-1,2,3,4,4a,9,10,10a-(*trans*-4a,10a)-octahydrophenanthrene (10).**—A mixture of 5.0 g (0.13 mole) of the carbamate **9** and 12.9 g of KOH in 130 ml of abs EtOH was refluxed for 3 hr. The EtOH was then removed *in vacuo* and the remaining solid was dissolved in 500 ml of Et_2O and washed with cold H_2O until the washings were neutral. The Et_2O layer was dried (Na_2SO_4) and evapd *in vacuo* to 50 ml and then refrigerated overnight. A total of 2.49 g (93.5%) of white needles, mp 128–129°, was collected. A small portion of the aziridine was recrystd from Et_2O for an analytical sample: mp 129–130°; nmr ($CDCl_3$), δ 7.55–6.90 (m, 4, aromatic protons), 2.79 (d, J_{AB} = 6 Hz, benzylic H_A proton). *Anal.* ($C_{14}H_{19}N$) C, H, N.

9(a)-Hydroxy-10(e)-amino-1,2,3,4,4a,9,10,10a-(*trans*-4a,10a)-octahydrophenanthrene (2).—The aziridine **10** (1 g, 5 mmoles), in 75 ml of 5% aq H_2SO_4 was heated at reflux for 1 hr. The purple solution was made alkaline with 10% aq NaOH and extracted several times with $CHCl_3$. The $CHCl_3$ layers were combined, dried (Na_2SO_4), and evapd *in vacuo* to give a light yellow solid. The solid was recrystd from C_6H_6 to give 606 mg (56%) of white fluffy material: mp 180–181°; ir (KBr), 2.95, 3.2 (broad), 3.45 (broad), 6.95, 9.81, 10.6 (broad), 10.25, 10.9, and 11.6. *Anal.* ($C_{14}H_{19}NO$) C, H, N.

9(a)-Acetoxy-10(e)-acetamino-1,2,3,4,4a,9,10,10a-(*trans*-4a,10a)-octahydrophenanthrene (2A).—From a sample of 400 mg (1.84 mmoles) of β-amino alcohol **2**, the *N,O*-diacetyl derivative was prepared as described for **1A**, affording 422 mg (76%) of very fine colorless needles (from C_6H_6), mp 196–197°; ir (KBr), 3.00 (N-H stretching), 3.25 (aromatic C-H stretching), 3.39 and 3.49 (aliphatic C-H stretching), 5.80 (acetoxy C=O stretching), 6.07 (broad amide C=O stretching), 6.50 (broad), 6.90, 7.29, 8.10 (broad), 9.73, 10.39, 10.55, 12.25, 13.25, and 13.45 μ; nmr ($CDCl_3$) δ 7.27 (m, 4, aromatic protons), 6.80 (d, 1, J_{BC} = 9 Hz, amide proton), 6.10 (d, 1, J_{AB} = 4 Hz, benzylic proton, H_A), 4.26 (m, 1, proton H_B) 2.02 (s, 3, CH_3), 1.99 (s, 3 CH_3) 2.70–0.70 (m, 10, CH_2—CH envelope); after exchange (D_2O) of the amide proton, proton H_A remains constant, proton H_B is now a quartet, J_{BC} = 11 Hz; mass spectrum (70 eV) *m/e* 302.16. *Anal.* ($C_{18}H_{23}NO_3$) C, H, N.

***anti*-9,10-Epoxy-1,2,3,4,4a,9,10,10a-(*trans*-4a,10a)-octahydrophenanthrene (12).**—To a cold soln (0°, ice–salt bath) of 4.69 g (27.2 mmoles) of *m*-chloroperbenzoic acid (Research Organic Inorganic Chemical Co.) in 60 ml of $CHCl_3$ was added slowly 5.0 g (27.2 mmoles) of alkene **8** in 15 ml of $CHCl_3$ and the cloudy mixture was stirred at room temp for 2 hr. The mixture was then washed with 5% aq NaOH and H_2O and dried (Na_2SO_4). The $CHCl_3$ layer was evapd *in vacuo* to give 5.2 g of a yellow oil which solidified upon standing overnight. A small portion of the solid was recrystd from EtOH containing a small amount of KOH[26] which has been reported to eliminate an acidic impurity which catalyzes the reaction of epoxides with EtOH. The recrystallization gave colorless needles, mp 53°. A second recrystallization from EtOH gave needles with mp 55–56°. This procedure was very inefficient and it was observed that recrystallization from hexane gave material with identical melting point in better yields but this material turned yellow upon standing for long periods. A total of 2.5 g (46%) of the epoxide was collected from both recrystallizations: ir (KBr), 3.40 and 3.48 (aliphatic C-H stretching), 6.70, 6.90, 10.00, 10.50, 11.32, 11.50, 12.60, and 13.08 μ; nmr ($CDCl_3$) δ 7.45–6.95 (m, 4, aromatic protons), 3.67 (d, 1, J_{AB} = 4.3 Hz, benzylic proton, H_A), 2.82 (d, 1, C-10 proton, H_B), 1.8–0.7 (m, 10, CH_2—CH envelope). *Anal.* ($C_{14}H_{16}O$) C, calcd 83.96; found 83.33, H.

9(a)-Hydroxy-10(a)-bromo-1,2,3,4,4a,9,10,10a-(*trans*-4a,10a)-octahydrophenanthrene (13).—A mixture of 50 ml of H_2O, 50 ml of dioxane, 4.9 g (0.027 mole) of *N*-bromosuccinimide (Eastman), and 5.0 g (0.027 mole) of **8** was stirred vigorously for 2.5 hr. A white fluffy ppt formed during this period which was removed by filtration and washed with H_2O. A total of 4.8 g (63%) of the bromohydrin was isolated: mp 104–106°; nmr (DMSO-d_6) δ 7.25 (s, 4, aromatic protons), 5.93 (d, 1, $J_{A,OH}$ = 5.5 Hz), 4.75 (q, 1, J_{AB} = 2.3 Hz, benzylic proton, H_A), 4.36 (m, 1, W_h = 5 Hz, C-10 proton H_B), 3.0–0.8 (M, 10, CH_2—CH envelope); D exchange (D_2O) proton H_A appeared as a doublet. *Anal.* ($C_{17}H_{17}BrO$) C, H.

***syn*-9,10-Epoxy-1,2,3,4,4a,9,10,10a-(*trans*-4a,10a)-octahydrophenanthrene (11).**—To 3.0 g (0.011 mole) of bromohydrin **13** in 100 ml of MeOH being stirred was added 0.64 g (0.016 mole) of NaOH in 10 ml of H_2O and 10 ml of MeOH over a 5-min period. After the addition a white ppt formed which turned yellow in the next 15 min of stirring. The mixture was immediately poured into a large volume of H_2O and extracted with several portions of Et_2O. The Et_2O extracts were combined, dried (Na_2SO_4), and evapd *in vacuo* to give 2.1 g of solid material. The material was recrystd from Et_2O–hexane to give 800 mg (37%) of very fine needles of **11**: mp 100°; ir (KBr), 3.38 and 3.48 (aliphatic C-H stretching), 6.72, 6.90, 7.30, 8.76, 10.95, 11.50, 11.60, 11.78, 12.23, 12.50, 12.85, 13.50, and 13.68 μ; nmr ($CDCl_3$) δ 8.75–6.7 (m, 4, aromatic protons), 3.59 (d, J_{AB} = 4 Hz, benzylic proton, H_A) 3.14 (broadened d, C-10 proton, H_B), 2.6–0.7 (m, 10, CH_2—CH envelope). *Anal.* ($C_{14}H_{16}O$) C, H.

1,2,3,4,4a,9,10,10a-(*cis*- and *trans*-4a,10a)-Octahydro-10-oxophenanthrene.[7c]—The bromohydrin **13**, 3.0 g (10.7 mmoles), was dissolved in 25 ml of MeOH and to this mixture was added 3.4 g (32 mmoles) of Na_2CO_3 in 25 ml of H_2O. The cloudy mixture was heated at reflux for 13.5 hr. After this the MeOH was removed *in vacuo* and the remaining oil–H_2O mixture was extracted with several portions of Et_2O. The Et_2O layers were combined and washed (H_2O) until neutral, dried (Na_2SO_4), and evapd *in vacuo* to give 2.1 g of light orange oil. The oil possessed a strong C=O absorption at 5.85 μ. Attempts at crystallization of the oil from Et_2O–hexane failed. The oil, 1.8 g, was placed on 55 g of silica gel (Brinkmann), Brockmann Activity I, and eluted with 30% Et_2O in hexane to give 1.3 g of ketone. Attempts at crystallizing the ketone from CH_3OH gave a very small amount of colorless needles, mp 63.5° (lit.[7c] mp 66–66.5°), which decomposed upon standing; nmr ($CDCl_3$) δ 7.2–6.7 (m, 4, aromatic protons), 3.34 (s, 2, benzylic protons), and 2.6–0.7 (m, 10, CH_2—CH envelope). *Anal.* ($C_{14}H_{16}O$) C, calcd 83.96, found 83.32; H.

9(e)-Azido-10(e)-hydroxy-1,2,3,4,4a,9,10,10a-(*trans*-4a,10a)-octahydrophenanthrene (14).—A mixture of 500 mg (2.5 mmoles) of epoxide **11**, 668 mg (12.5 mmoles) of NaN_3, 668 mg (12.5 mmoles) of NH_4Cl, 60 ml of EtOH, and 18 ml of H_2O was refluxed for 24 hr. It was allowed to cool and then poured into a large volume of H_2O. The aq mixture was extracted with several portions of Et_2O, the Et_2O extracts were combined and dried

(26) G. Berti, B. Macchia, and F. Macchia, *Tetrahedron*, **24**, 1755 (1968).

(Na_2SO_4), and the solvent removed *in vacuo* to give 510 mg of light reddish colored solid. The solid was passed over a 40-g silica gel column (Brinkman), Brockman Activity II, using 30% Et_2O in hexane as solvent. A total of 481 mg (80%) of **14** was collected, mp 100–101°. Recrystallization of a small sample for analysis from Et_2O–hexane gave colorless needles: mp 101–102°; nmr (DMSO-d_6) δ 7.40–7.05 (m, 4, aromatic protons), 4.49 (d, 1, J_{AB} = 9 Hz, benzylic proton, H_A), 3.65 (octet, 1, J_{BC} = 10 Hz, $J_{B,OH}$ = 4.5 Hz, C-10 proton, H_B), 2.93 (d, 1, O-**H**), 2.8–0.7 (m, 10, CH_2—CH envelope); deuterium exchange, C-10 proton H_B absorbs as a quartet. *Anal.* ($C_{14}H_{17}N_3O$) C, H, N.

9(e)-Amino-10(e)-hydroxy-1,2,3,4,4a,9,10,10a-(*trans*-4a,10a)-octahydrophenanthrene (15).—Epoxide **11** (1.0 g, 5 mmoles), was placed into a steel bomb (cooled in Dry Ice–Me_3CO) along with 25 ml of liquid NH_3. The bomb was sealed and heated at 115° for 24 hr. The bomb was then cooled (Dry Ice–Me_2CO) and the yellow residue was dissolved in $CHCl_3$ and evapd to give 1.2 g of a yellow solid. The solid material was placed on a 60-g silica gel (Brinkmann), Brockmann Activity III column and eluted with $CHCl_3$–Et_2O, 1:1. The fractions collected between 25 and 45 ml contained an unidentified brown oil. The following 130-ml eluent contained 564 mg of a yellow solid. The solid material was recrystd from C_6H_6 yielding 548 mg (50%) of fluffy white plates: mp 157–158°; ir (KBr), 2.95, 3.01, 3.15 (broad N-H and O-H stretching), 3.40 and 3.50 (aliphatic C-H stretching), 6.30, 6.72, 6.95, 7.40, 9.15, 9.51, 9.69, 10.41, 10.68, and 13.35 μ. *Anal.* ($C_{14}H_{19}NO$) C, H, N.

9(e)-Azido-10(e)-*O*-*p*-toluenesulfonoxy-1,2,3,4,4a,9,10,10a-(*trans*-4a,10a)-octahydrophenanthrene (16).—A solution of 2.0 g (8.25 mmoles) of **14**, 2.1 g (11.2 mmoles) of TsCl, and 150 ml of pyridine was placed in the refrigerator for 5 days. The mixture was then poured into a large volume of stirred H_2O and the resulting solid material was filtered to give 2.3 g (71%) of the *trans*-azido tosylate **16**, mp 155–156°. A small portion of this material was recrystd for an analytical sample from Et_2O–hexane to give colorless needles: mp 156–157°; nmr ($CHCl_3$) δ 7.91 (d, 2, aromatic protons), 7.39 (d, 2, aromatic protons), 7.28 (s, 4, aromatic protons), 4.71 (t, 1, J_{AB} = J_{BC} = 8 Hz, C-10 proton, H_B), 4.49 (d, 1, benzylic proton, H_A), 2.44 (s, 3, C**H**$_3$), 2.80–0.70 (m, 10, CH_2—CH envelope). *Anal.* ($C_{21}H_{23}NO_3S$) C, H, N.

Acetolysis of 16.—A solution of 3.5 g (8.8 mmoles) of tosylate **16** and 720 mg (8.8 mmoles) of anhyd NaOAc in 87.5 ml of glacial HOAc was heated at reflux for 7 days. The mixture was then allowed to cool to room temp and then poured into a large volume of ice–H_2O. The aq solution was extracted several times with Et_2O and the extracts were combined, washed with satd aq $NaHCO_3$, dried (Na_2SO_4), and evaporated *in vacuo* to give 2.9 g of a clear oil. The oil contained a mixture of 2 azido acetates (9:1) (9(a) and 9(e)-acetoxy-10(a)-azido-1,2,3,4,4a,9,10,10-(*trans*-4a,10a)-octahydrophenanthrene (**17** and **18**). The oil was placed on a 500-g silica gel column (Brinkmann silica gel 0.05–0.2 mm) Brockmann Activity I. The product was eluted with 2 l. of C_6H_6–hexane (1:1), followed by 760 ml of C_6H_6 in which no product was isolated. The next 30-ml fraction of C_6H_6 afforded 20 mg of an oil, 9(e)-acetoxy-10(a)-azido-1,2,3,4,4a,-9,10,10a-(*trans*-4a,10a)-octahydrophenanthrene (**18**); ir (neat) 3.35, 3.41, 4.67 (-N_3 stretching), 5.68 (ester C=O stretching), 7.20, 8.15 (-N_3 stretching), 13.20 μ; nmr ($CDCl_3$) δ 7.25 (s, 4, aromatic protons), 6.18 (broadened d, 1, J_{AB} = 4.5 Hz, benzylic proton H_A), 4.00 (d, 1, $J_{BC} \simeq 0$, C-10 proton, H_B) 2.9–0.6 (CH_2—CH envelope).

The next 120 ml of C_6H_6 afforded 326 mg of a mixture of the *cis*- and *trans*-azido acetates (**18** and **17**). In the following 740 ml of C_6H_6 a total of 1.72 g of *trans*-**17** was isolated: ir (neat) 3.39, 3.48, 4.62, (-N_3 stretching), 5.71 (ester C=O stretching), 7.29, 8.10 (-N_3 stretching), 9.80, 10.30, 13.3 μ; nmr ($CDCl_3$) δ 7.25 (s, 4, aromatic protons), 5.95 (d, 1, J_{AB} = 3 Hz, benzylic proton, H_A), 3.87 (d, 1, J_{BC} = 0–1, proton H_B) 1.99 (s, 3, C**H**$_3$ 2.9–0.7 (m, 10, CH_2—CH envelope).

9(a)-Hydroxy-10(a)-amino-1,2,3,4,4a,9,10,10a-(*trans*-4a,10a)-octahydrophenanthrene (3).—A mixture of 400 mg (1.4 mmoles) of crude **17** and 185 mg (5 mmoles) of LAH in 100 ml of anhyd Et_2O was heated at reflux for 24 hr. H_2O (1 ml) was added to the mixture and the white solid that formed was removed by filtration. The clear Et_2O solution was evapd *in vacuo* to give 301 mg (98%) of an oil that turned solid upon standing. A portion of the solid was recrystd from $CHCl_3$–Et_2O to give colorless fine needles of the *trans*-amino alcohol **10**, mp 114° (lit.[9] 190–191°): ir (KBr) 3.21 (broad), 3.45 and 3.52 (aliphatic C-H stretching), 6.34, 6.95, 7.70, 7.84, 9.75, 10.75, 13.25, and 13.60 μ. *Anal.* ($C_{14}H_{19}NO$) C, calcd 77.38, found 76.97, H, N.

9(a)-Acetoxy-10(a)-acetamido-1,2,3,4,4a,9,10,10a-(*trans*-4a,-10a)-octahydrophenanthrene (3A).—From a sample of 200 mg (0.92 mmoles) of *trans*-amino alcohol **3**, the *N*,*O*-diacetyl derivative was prepared as described for **1A**, affording 206 mg (76%) from $CHCl_3$–Et_2O: mp 172–173°; ir (KBr) 3.05 (N-H stretching), 3.29 (aromatic C-H stretching), 3.42 and 3.50 (aliphatic C-H stretching), 5.79 (ester C=O stretching), 6.10 (amide C=O stretching), 6.58 (broad), 9.85, 10.50, 12.95, 13.35, 13.68, and 14.10 μ; nmr ($CDCl_3$) δ 7.50–7.00 (m, 4, aromatic protons), 6.25 (d, 1, $J_{NH,B}$ = 10 Hz, amide N-**H**), 5.78 (d, 1, J_{AB} = 3 Hz, benzylic proton, H_A), 4.26 (multiplet composed of 2 broad doublets, J_{BC} = 1–2 Hz, H_B proton), 2.00 (s, 3, CH_3), 1.83 (s, 3, CH_3), and 2.80–0.90 (m, 10, CH_2—CH envelope); after D exchange of amide proton, proton H_B absorbs as a broad multiplet W_h = 7 Hz. *Anal.* ($C_{18}H_{23}NO_3$) C, H, N.

9(e)-Acetoxy-10(a)-acetamido-1,2,3,4,4a,9,10,10a-(*trans*-4a,-10a)-octahydrophenanthrene (4A).—A mixture of 160 mg of solid material composed of *cis*- and *trans*-9-hydroxy-10(a)-amino-1,2,3,4,4a,9,10,10a-(*trans*-4a,10a)-octahydrophenanthrene (4:1), 2 ml of Ac_2O, and 4 ml of pyridine was allowed to stand at room temp overnight. Excess Ac_2O and pyridine was evaporated *in vacuo* to give 180 mg of an oil that was treated with 20 ml of 3% aq HCl for 30 min. The mixture was then poured into a separatory funnel and extracted with several portions of $CHCl_3$. These extracts were combined, washed with aq 10% $NaHCO_3$, H_2O, and dried (Na_2SO_4) and evaporation *in vacuo* of the $CHCl_3$ solution gave a light green oil that was dissolved in $CHCl_3$–Et_2O and allowed to stand overnight at 4°. A mixture of 2 types of crystals was collected (17 mg of hard spherical crystals, mp 170–171°, and 68 mg of square plate-like crystals, mp 161°) and sepd using a microspatula. The square plate-like crystals were recrystd 3 times from $CHCl_3$–Et_2O to give 38 mg of clear plate-like crystals of **4A**: mp 178°; ir (KBr) 2.95 (N-H stretching), 3.27 (aromatic C-H stretching), 3.41 and 3.50 (aliphatic C-H stretching), 5.80 (ester C=O stretching), 6.08 (broad, amide C=O stretching), 6.55 (broad), 6.93, 7.32, 8.15 (broad), 9.85, 10.15, 10.25, 13.3, and 13.85 μ; nmr ($CHCl_3$) δ 7.50–7.00 (m, 4, aromatic protons), 6.60 (d, 1, J_{AB} = 5 Hz, benzylic proton H_A), 5.20 (d, 1, $J_{B,NH}$ = 10 Hz, amide proton N-H), 4.60 (q, 1, J_{BC} = 0, C-10 proton, H_B), 2.10 (s, 3, CH_3) 1.90 (s, 3, CH_3), and 2.80–0.90 (m, 10, CH_2—CH envelope); D exchange of amide proton, proton H_B absorbs as a sharp doublet. *Anal.* ($C_{18}H_{23}NO_3$) C, H, N.

10(a)-Hydroxy-9(a)-benzamido-1,2,3,4,4a,9,10,10a-(*trans*-4a,10a)-octahydrophenanthrene (19).—A solution of the *trans*-amino alcohol **3** (500 mg, 2.3 mmoles), 600 mg of NaOH, 485 mg (3.45 mmoles) of BzCl, 10 ml of H_2O, and 400 ml of C_6H_6 was stirred rapidly in an ice bath for 30 min. To this mixture was added 80 ml of hexane and a white gummy material formed on the inside of the flask. The C_6H_6–hexane–H_2O mixture was poured from the flask and the white gummy material was dissolved in $CHCl_3$. The benzene–hexane layers were sepd from the H_2O and combined with the $CHCl_3$ layer, dried (Na_2SO_4), and evaporated *in vacuo* to give 750 mg of an oil. This turned to a solid upon standing at room temperature and was recrystd ($CHCl_3$–Et_2O) to give 628 mg (83%) of the benzamide, mp 140–141°. *Anal.* ($C_{21}H_{23}NO_2$) C, H, N.

2-Phenyloxazoline of 9(e)-Hydroxy-10(a)-amino-1,2,3,4,4a,-9,10,10a-(*trans*-4a,10a)-octahydrophenanthrene (20).—A solution of 600 mg (1.8 mmoles) of benzamide **19** and 412 mg (3.6 mmoles) of MsCl in 10 ml of pyridine was kept in an ice bath for 30 min. The mixture was then allowed to warm and stand at room temp during the next 4 hr. To the pyridine solution was then added 50 ml of ice–H_2O and the cloudy mixture was allowed to stand at room temperature for an additional 2 hr. The solid material was removed by filtration to give 224 mg of the oxazoline, mp 105°. The filtrate was then extracted with $CHCl_3$ and the $CHCl_3$ layer was washed with H_2O, dried (Na_2SO_4), and evapd *in vacuo* to give 260 mg of a light yellow oil. The oil was passed over a 60-g alumina column (Merck reagent Al_2O_3, neutral) using C_6H_6 as the solvent. In the first 220 ml of C_6H_6 eluted an additional 140 mg of the oxazoline was isolated (67%). A small sample of the material was recrystd from Et_2O–hexane to give colorless plate-like crystals: mp 111°; nmr ($CDCl_3$) δ 8.1–7.9 (m, 2, aromatic protons), 7.6–7.2 (m, 7, aromatic protons), 5.72, (d, 1, J_{AB} = 10 Hz proton H_A), 4.53 (q, 1, J_{BC} = 4 Hz, C-10 proton H_B), 2.8–0.8 (m, 10, CH_2—CH protons). *Anal.* ($C_{21}H_{21}NO$) C, H, N.

9(e)-Hydroxy-10(a)-amino-1,2,3,4,4a,9,10,10a-(*trans*-4a,10a)-octahydrophenanthrene (4).—Oxazoline **20** (200 mg, 0.70 mmole) was dissolved in 100 ml of 10% aq HCl. The mixture was heated at reflux with stirring for 3 hr. The aq solution was allowed to cool and was then extracted with Et_2O to remove $PhCO_2H$. The aq layer was neutralized with aq 10% NaOH and extracted with $CHCl_3$. The $CHCl_3$ layer was dried (Na_2SO_4) and evapd *in vacuo* to give 68 mg of an oil. The oil was dissolved in $CHCl_3$-Et_2O-hexane and placed in a refrigerator overnight. Yellow square-like crystals of **4** were collected: mp 144°; ir (KBr) 3.22 (broad-OH, N-H stretching), 3.45 and 3.52 (aliphatic C-H stretching), 6.33, 6.80, 6.95, 7.50, 9.70, 11.00, 13.35 μ. A diacetyl derivative **4A** was prepared which had identical melting point and spectral data, as previously prepared by LAH reduction and acetylation of 9(e)-acetoxy-10(a)-azido-1,2,3,4,4a,9,10,10a-(*trans*-4a,10a)-octahydrophenanthrene (**18**).

Pharmacological Testing.—Experiments were performed on isolated rat vas deferens[21] *in vitro* at 37°. The cumulative dose response curves of (−)-norepinephrine were obtained before and after experimental agents. The tissue incubation time of the experimental compounds was 5 min and the dose response curve of (−)-norepinephrine was obtained in the presence of the drug. Experiments were repeated a minimum of 3 times.

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Synthesis and Hypotensive Activity of N-Substituted 1-Trimethoxybenzyl-3-butenylamines and Related Compounds

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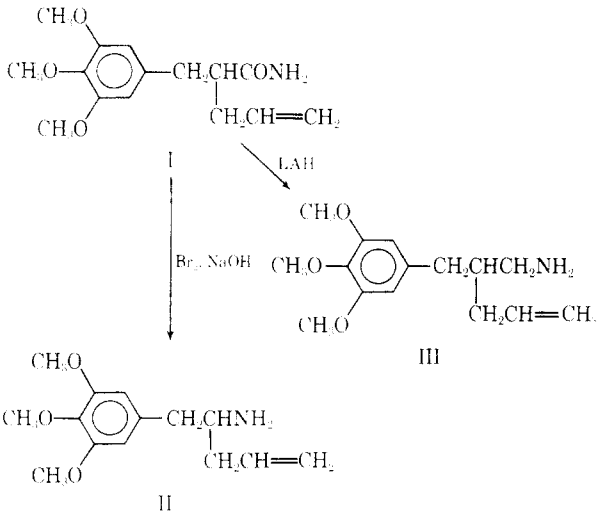
A series of N-substituted 1-trimethoxybenzyl-3-butenylamines was prepared and evaluated for hypotensive, analgetic, and antiinflammatory activity. *N*-Methyl-1-(3,4,5-trimethoxybenzyl)-3-butenylamine·HCl (**2**) was selected for further pharmacological and clinical investigation as a hypotensive agent. Certain of the *N*-acyl-1-trimethoxybenzyl-3-butenylamines were cyclized by the Bischler–Napieralski reaction to form 3-allyl-1-substituted-6,7,8-trimethoxy-3,4-dihydroisoquinolines.

Previous[1,2] reports from these laboratories disclosed that certain compounds of the 1-aralkyl-3-butenylamine series possess hypotensive activity. The most interesting compound of this series was 1-(3,4,5-trimethoxybenzyl)-3-butenylamine (II), which, like reserpine, possesses mild hypotensive activity. The close structural relationship of this amine to the centrally acting compound, mescaline, suggested to us that a central component might be involved in the mechanism of the hypotensive action of II. Since we considered a central mechanism to be a desirable mode of action for a hypotensive agent, we were prompted to prepare a series of analogs of II. In the present investigation we have modified structure II, principally, by substitution on N, in an attempt to obtain a more effective, orally active agent.

Chemistry.—1-(3,4,5-Trimethoxybenzyl)-3-butenylamine (II) (**1**, Table I) was prepared as previously described[1] (Scheme I) by a Hofmann rearrangement of 2-(3,4,5-trimethoxybenzyl)-4-pentenamide (I). Substitution of the primary N of II to prepare compounds of Table I was carried out by conventional reactions with the appropriate acyl chloride, anhydride, sulfonyl chloride, alkyl chloride, cyanate, or thioisocyanate. Certain of the amides resulting from the use of acyl chlorides were subsequently reduced with LAH to form the amine. LAH reduction of the amide I produced 2-(3,4,5-trimethoxybenzyl)-4-pentenylamine (III).[1] Three *N*-acyl derivatives of III were prepared (Table II).

Scheme I



Certain of the *N*-acyl-1-(3,4,5-trimethoxybenzyl)-3-butenylamines were refluxed with $POCl_3$ in PhMe resulting in Bischler–Napieralski cyclodehydration and

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