(5) C. F. Hiskey, *Anal. Chem.*, **21**, 1440(1949).
(6) H. L. Pardue and P. A. Rodriguez, *ibid.*, **39**, 901(1967).
(7) H. L. Pardue and S. N. Deming, *ibid.*, **41**, 986(1969).
(8) D. H. Follett, *Proc. Phys. Soc.*, **46**, 499(1934).
(9) R. Mavrodineanu, *J. Res. Nat. Bur. Stand.*, **76A**, 405(1972).
(10) R. W. Burke, E. R. Deardorff, and O. Menis, *ibid.*, **76A**, 469(1972).
(11) G. Östling, *Chem. Instrum.*, **5**, 1(1973).
(12) B. Gabaric, I. Piljac, and I. Filipovic, *Anal. Chem.*, **45**, 1932(1973).
(13) C. Eisenhart, *Science*, **160**, 1201(1968).
(14) R. W. Burnett, *Anal. Chem.*, **45**, 383(1973).

**ACKNOWLEDGMENTS AND ADDRESSES**

Received May 7, 1973, from *Eli Lilly and Company, Indianapolis, IN 46206*

Accepted for publication March 29, 1974.

*NOTES*

# Amphetamine Derivatives: 10(e)- and 10(a)-Amino-1,2,3,4,4a,9,10,10a-(*trans*-4a,10a)-octahydrophenanthrene

**WENDEL L. NELSON** [x] **and BOB E. SHERWOOD** *

**Abstract** □ Amphetamine analogs 10(e)- and 10(a)-amino-1,2,3,4,4a,9,10,10a-(*trans*-4a,10a)-octahydrophenanthrene, I and II, respectively, were prepared. Hydrogenolysis (methanolic hydrochloric acid) of 9(a)-hydroxy-10(e)-amino-1,2,3,4,4a,9,10,10a-(*trans*-4a,10a)-octahydrophenanthrene afforded I. A similar procedure for the preparation of II from 9(a)-hydroxy-10(a)-amino-1,2,3,4,4a,9,10,10a-(*trans*-4a,10a)-octahydrophenanthrene was followed, except the more drastic conditions of a mixture of acetic and perchloric acids were necessary. The compounds were inactive when assayed for amphetamine behavioral and hyperthermia effects.

**Keyphrases** □ 10(e)- and 10(a)-Amino-1,2,3,4,4a,9,10,10a-(*trans*-4a,10a)-octahydrophenanthrene—synthesized and evaluated for amphetamine behavioral and hyperthermia effects □ Amphetamine derivatives—synthesis of 10(e)- and 10(a)-amino-1,2,3,4,4a,9,10,10a-(*trans*-4a,10a)-octahydrophenanthrene, evaluated for amphetamine behavioral and hyperthermia effects

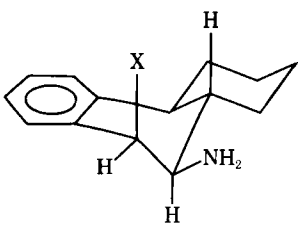
Conformationally rigid analogs have been used to study drug receptor systems, but few studies have been reported (1–5) with respect to amphetamines. In the cyclopropane series, the *trans*-isomer shows equivalent peripheral amphetamine-like effects, *e.g.*, pressor response, moderate central nervous system stimulation, and increased monoamine oxidase inhibition when compared to amphetamine. Some differences were noted in other rigid analogs, although only changes in motor activity and $LD_{50}$ data have been reported (3, 4). The norephedrine analogs in the octahydrophenanthrene system were reported previously (6), in which a potentiation and blockade of the effects of norepinephrine were noted; a logical extension of this work was the preparation of these analogous amphetamine derivatives.

## DISCUSSION

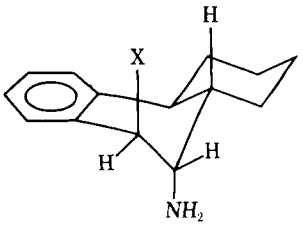
In a related study, the isomeric 9-hydroxy-10-amino-1,2,3,4,-4a,9,10,10a-(*trans*-4a,10a)-octahydrophenanthrenes were prepared (6). The alcohols[1] III and IV were subjected to hydrogenolysis conditions. The conversion of III-HCl occurred smoothly using palladium-on-carbon in methanol containing hydrochloric acid. Similar results were obtained in a related tricyclic system (7). Attempted hydrogenolysis of the IV-HCl under these conditions failed. More rigorous conditions, acetic acid–hydrochloric acid, also failed. However, when using acetic acid–perchloric acid, hydrogenolysis did occur.

The mass spectra of 10(e)- and 10(a)-amino-1,2,3,4,4a,9,10,10a-(*trans*-4a,10a)-octahydrophenanthrene, I and II, respectively, showed parent peaks at *m/e* 201.1494 and 201.1502, respectively (calculated 201.1518). The NMR spectra were not useful in assigning the relative stereochemistry because of similar chemical shifts of several protons in each spectrum. The small quantities of compound precluded preparation of suitable derivatives. When using a TLC developing system of ether–methanol–aqueous ammonia (90:8:2) and silica gel plates, $R_f$ values of 0.46 and 0.28 were found for I and II, respectively, demonstrating that the potential hazard of dehydration to the intermediate enamine is not a likely process during the hydrogenolysis step.

The behavioral effects of amphetamine in mice (25 mg/kg), *e.g.*,




I: X = H
III: X = OH




II: X = H
IV: X = OH

[1] All materials are racemic, although only a single isomer is shown.

increased motor activity, piloerection, and salivation (3, 4, 8), were not observed when I and II were administered intraperitoneally to mice. Compound I produced decreased motor activity and sedation at doses of 50–100 mg/kg. Compound II produced slight tremors at 25–50 mg/kg and marked tremors and ataxia at 80–100 mg/kg. Significant hypothermia was also noted with the larger doses. No amphetamine-like hyperthermia (9) was noted in rabbits.

From these results, it was concluded that neither compound produces amphetamine-like effects. The pharmacology of II is under further investigation.

## EXPERIMENTAL[2]

**10(e)-Amino-1,2,3,4,4a,9,10,10a-(*trans*-4a,10a)-octahydrophenanthrene Hydrochloride (I-HCl)**—A mixture of 195 mg (0.9 mmole) 9(a)-hydroxy-10(e)-amino-1,2,3,4,4a,9,10,10a-(*trans*-4a,10a)-octahydrophenanthrene (III) (6), 90 mg palladium-on-carbon (10%), and 0.7 ml of concentrated aqueous hydrochloric acid in 35 ml absolute methanol was reduced at an initial hydrogen pressure of 30 psi. After 24 hr the catalyst was removed by filtration, the solvent was evaporated, and the residue was crystallized from ether and recrystallized from isopropanol to give I-HCl, 185 mg (86% of theory), mp 290–300° dec.; IR (KBr): 3430 (NH), 2950 broad (CH), 1590, 1490, 1445, 770, and 735 $cm^{-1}$; NMR (dimethyl sulfoxide-$d_6$): $\delta$ 8.47 (s, broad, 3, $^+NH_3$), 7.37–7.07 (m, 4, ArH), 3.33–3.00 (m, 3, $H_9$, $H_{9'}$, $H_{10}$), 2.60–2.27 (m, 2, $H_{10a,4a}$), and 2.13–0.97 (m, 8, $CH_2$—CH envelope), addition of $D_2O$ removed the absorption at 8.47, replaced by HOD at $\delta$ 3.65; mass spectrum (70 ev): *m/e* (relative intensity, fragment) 202 (14, M + 1), 201 (81, M), 200 (8, M − H), 184 (100, $C_{14}H_{16}$), 142 (51, $C_{11}H_{10}$), 141 (64, $C_{11}H_9$), 115 (33, $C_9H_7$), 91 (26, $C_7H_7$), and 77 (16, $C_6H_5$). Calc. *m/e* for $C_{14}H_{19}N$: 201.1518. Found: 201.1494.

*Anal.*—Calc. for $C_{14}H_{20}ClN$: C, 70.72; H, 8.48; N, 5.89. Found: C, 71.09; H, 8.58; N, 5.97.

**10(a)-Amino-1,2,3,4,4a,9,10,10a-(*trans*-4a,10a)-octahydrophenanthrene Hydrochloride (II-HCl)**—A mixture of 63 mg (250 mmoles) 9(a)-hydroxy-10(a)-amino-1,2,3,4,4a,9,10,10a-(*trans*-4a,10a)-octahydrophenanthrene hydrochloride (IV) (6), 63 mg palladium-on-carbon (10%), and 0.5 ml of 70% aqueous perchloric acid in 30 ml acetic acid (99%) was reduced under an initial hydrogen pressure of 30 psi. After 24 hr the catalyst was removed by filtration and washed with water. The filtrate and washings were combined and made alkaline by slow addition of 10% aqueous sodium hydroxide. Ether was added, and the phases separated. The ether extract was washed with water, dried (magnesium sulfate), concentrated to 50 ml, and treated with hydrogen chloride gas. The precipitate was removed to give II-HCl, 37 mg (63%), mp 261–263° dec.; IR (KBr): 3450 (NH), 3050 (ArCH), 2900 (CH), 1600, 1500, 1445, 1380, 765, and 740 $cm^{-1}$; NMR (dimethyl sulfoxide-$d_6$): $\delta$ 8.03 (s, broad, 3, $^+NH_3$), 7.47–7.10 (m, 4, ArH), 3.47 (m, 1, $H_{10}$), 3.18 (m, 2, $H_{9,9'}$), 2.77–2.40 (m, 2, $H_{10a,4a}$), and 2.03–1.13 (m, 8, $CH_2$—CH envelope), addition of $D_2O$ removed the signal at 8.03, replaced by HOD at 3.92; mass spectrum (70 ev): *m/e* (relative intensity, fragment) 202 (6, M + 1), 201 (82, M), 200 (4, M − H), 184 (100, $C_{14}H_{16}$), 142 (67, $C_{11}H_{10}$), 141 (86, $C_{11}H_9$), 115 (23, $C_9H_7$), 91 (15, $C_7H_7$), and 77 (11, $C_6H_5$). Calc. *m/e* for $C_{14}H_{19}N$: 201.1518. Found: 201.1502.

*Anal.*—Calc. for $C_{14}H_{20}ClN$: C, 70.72; H, 8.48; N, 5.89. Found: C, 70.90; H, 8.62; N, 5.71.

**TLC Separation of I and II**—About 2 mg of each amine hydrochloride salt was added to 10% aqueous sodium hydroxide and then extracted with ether. The ether solutions were evaporated and the amines were spotted on 20-cm silica gel TLC plates and developed with ether–methanol–aqueous ammonia (90:8:2). The $R_f$ values (iodine visualization) were 0.46 for I and 0.28 for II. A mixture of the two amines produced similar results.

**Pharmacological Testing**—The compounds were screened for amphetamine-like effects by the method of Campbell and Richter (8) and for hypothermia by the method of Hill and Horita (9).

[2] IR data were recorded on a Beckman IR-5A spectrophotometer, and NMR data were determined from Varian A-60 and T-60 spectrometers. The solvents used are stated and tetramethylsilane was the internal standard. Mass spectra were determined using the AEI-MS9 mass spectrometer and a DEC PDP-12 computer equipped with suitable programs for data collection and reduction (Mass Spectrometry Laboratory, Department of Chemistry, University of Washington). Melting points were taken on a Thomas-Hoover capillary melting-point apparatus and are corrected. Microanalyses were performed by Dr. F. B. Strauss, Oxford, England.

## REFERENCES


(1) A. Burger and W. L. Yost, *J. Amer. Chem. Soc.*, **70,** 198(1948).

(2) J. H. Biel, in "Proceedings of International Symposium on Amphetamines and Related Compounds," E. Costa and S. Garattini, Eds., Raven Press, New York, N.Y., pp. 3–19.

(3) E. E. Smissman and T. L. Pasdernik, *J. Med. Chem.*, **16,** 15(1973).

(4) *Ibid.*, **16,** 18(1973).

(5) A. S. Horn and S. H. Snyder, *J. Pharmacol. Exp. Ther.*, **180,** 523(1972).

(6) W. L. Nelson and D. D. Miller, *J. Med. Chem.*, **13,** 807(1970).

(7) J. G. Murphy, *J. Org. Chem.*, **26,** 3104(1961).

(8) D. E. S. Campbell and W. Richter, *Acta Pharmacol. Toxicol.*, **25,** 345(1967).

(9) H. F. Hill and A. Horita, *J. Pharm. Pharmacol.*, **23,** 715(1971).


## ACKNOWLEDGMENTS AND ADDRESSES


Received January 29, 1974, from the *Department of Pharmaceutical Sciences, School of Pharmacy, University of Washington, Seattle, WA 98195*

Accepted for publication March 29, 1974.

Abstracted in part from a dissertation submitted by B. E. Sherwood to the University of Washington in partial fulfillment of the Doctor of Philosophy degree requirements.

Supported in part by a Career Development Award (5-K4-GM-70,023) to W. L. Nelson from the National Institute of General Medical Sciences. Funds for partial support of the mass spectrometric faculty were provided by the National Science Foundation.

The authors thank Professor Akira Horita, Department of Pharmacology, University of Washington, for the hyperthermia data and discussions concerning the observed pharmacological effects.



* Present address: Battelle Memorial Institute, Columbus, OH 43201

[x] To whom inquiries should be directed.