pears downfield at δ 7.77 (*cf.*, 7.82 in II*b*) and one of the methoxy groups appears upfield at δ 3.68 (*cf.*, 3.60 in II*b*), a methoxy can be placed at C-1 and a hydrogen at C-11 (5, 10, 11)[6]. The UV spectrum [λ_{max} (CH_3OH) nm (log ϵ): 217 (4.65), 280 (4.08), 307 (4.16), and 313 sh (4.16)] is characteristic of a 1,2,3,9,10-pentaoxygenated aporphine (12, 13) and distinctly different from a 1,2,8,9,10-pentaoxygenated aporphine (10). Thus, the only substitution pattern for Alkaloid B that is consistent with both the UV and NMR spectra (singlets for the two aromatic hydrogens) is a C-1,2,3,9,10-pentaoxygenated aporphine with a C-1 methoxy group.

The methylenedioxy group could be located at C-2,3 or C-9,10. The location of the methylenedioxy group at C-9,10 and the methoxy groups at C-2 and C-3 is preferred since a 2H singlet at δ 5.87 is observed for the methylenedioxy protons in Alkaloid B (*cf.*, 5.85 in II*b*). The protons of a methylenedioxy group located at C-2,3 form an *AB* quartet (14) just as they do when located at C-1,2 (5). Additional evidence for this oxygenation pattern comes from observing the chemical shifts of the methoxy resonances. When methoxy groups are located at C-9 and C-10, they usually appear as overlapping signals near δ 3.9 (5, 11); but when methoxy groups are located at C-1, 2, and 3, they appear as discrete signals (14) as observed in the NMR spectrum of Alkaloid B.

Based on this evidence, we propose that Alkaloid B be represented as (+) -3-methoxy-*N*-acetylnornantenine (II*e*). The absolute stereochemistry at C-6*a* follows by noting the large positive Cotton effect in the circular dichroism spectrum[4] at 243 nm ([θ] = +199,000; 1.80 mg/50 ml), which has been correlated with the *S*-configuration at C-6*a* (6). To our knowledge, these alkaloids (II*b* and II*e*) represent the first two examples of naturally occurring *N*-acetylaporphine alkaloids.

(1) M. A. Buchanan and E. E. Dickey, *J. Org. Chem.*, **25**, 1389(1960).

(2) J. Cohen, W. Von Langenthal, and W. I. Taylor, *ibid.*, **26**, 4143(1961).

(3) W. I. Taylor, *Tetrahedron*, **14**, 42(1961).

(4) M. Tomita and H. Furukawa, *Yakugaku Zasshi*, **82**, 1199(1962).

(5) M. Shamma, "The Isoquinoline Alkaloids," Academic, New York, N.Y., 1972, chap. 14, pp. 195, 220–222.

(6) K. Kotera, Y. Hamada, and R. Mitsui, *Tetrahedron*, **24**, 2463(1968).

(7) S. R. Johns, J. A. Lamberton, and A. A. Sioumis, *Aust. J. Chem.*, **20**, 1457(1967).

(8) C. R. Ghoshal and S. K. Shah, *Chem. Ind. (London)*, **1972**, 889.

(9) T. Kametani, "The Chemistry of the Isoquinoline Alkaloids," Elsevier, New York, N.Y., 1969, chap. 9, p. 81.

(10) M. Shamma, R. J. Shine, and B. S. Dudoc, *Tetrahedron*, **23**, 2887(1967).

(11) W. H. Baarschers, R. R. Arndt, K. Pachler, J. A. Weisbach, and B. Douglas, *J. Chem. Soc.*, **1964**, 4778.

(12) R. H. F. Manske, in "The Alkaloids," vol. 9, R. H. F. Manske, Ed., Academic, New York, N.Y., 1967, p. 28.

(13) P. E. Sonnet and M. Jacobson, *J. Pharm. Sci.*, **60**, 1254(1971).

(14) M. P. Cava, Y. Watanabe, K. Bessho, M. J. Mitchell, A. I. da Rocha, B. Hwang, B. Douglas, and J. A. Weisbach, *Tetrahedron Lett.*, **1968**, 2437.

[6] The NMR spectrum of ocoteine (II*d*) is reported in Ref. 11. It shows $-OCH_2O-$ at C-1,2 as an *AB* quartet and signals for three methoxy groups at δ 3.91, 3.91, and 3.99.

Charles D. Hufford[x]
*Mary Jo Funderburk**

Department of Pharmacognosy
School of Pharmacy
University of Mississippi
University, MS 38677

Received February 11, 1974.

Accepted for publication May 10, 1974.

Supported in part by the Committee on Faculty Research, University of Mississippi, and the Research Institute of Pharmaceutical Sciences, School of Pharmacy, University of Mississippi.

* National Sciences Foundation Undergraduate Research Participant, 1973.

[x] To whom inquiries should be directed.

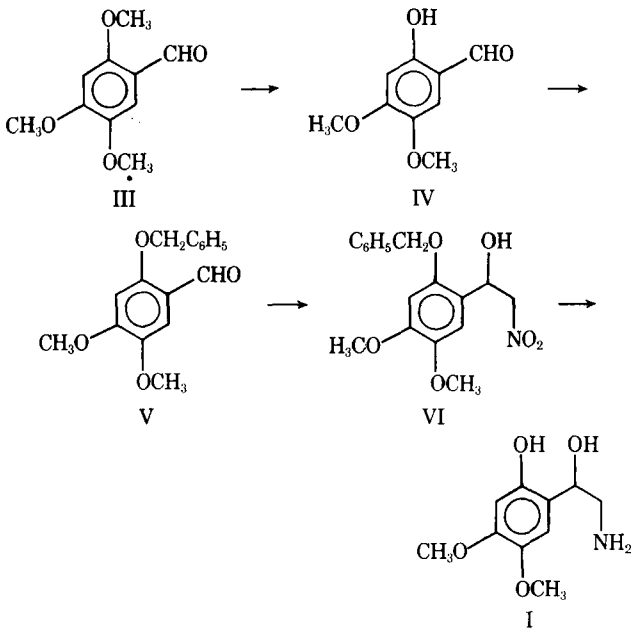
Synthesis and Psychotropic Activity of 2-Hydroxy-4,5-dimethoxyphenethanolamine, a Potential Endogenous Psychotogen, and Its Methylenedioxy Analog

Keyphrases □ 2-Hydroxy-4,5-dimethoxyphenethanolamine and methylenedioxy analog—synthesis and psychotropic activity, potential endogenous psychotogen □ Phenethylamine derivatives—synthesis and psychotropic activity of 2-hydroxy-4,5-dimethoxyphenethanolamine, role in schizophrenia □ Schizophrenia—synthesis and psychotropic activity of 2-hydroxy-4,5-dimethoxyphenethanolamine, a potential endogenous psychotogen

To the Editor:

Currently, there is renewed and active interest in elucidating the biochemical etiology of schizophrenia (1). Based on a hypothesis put forth by Osmond and Smythies (2) that an aberration in the metabolism of catecholamines could produce an endogenous psychotogen structurally related to mescaline, several investigators proposed various derivatives of phenethylamine as potential endogenous toxins responsible for psychosis (1, 3–5). Shulgin *et al.* (4) recently carried out a detailed analysis of structure–activity relationships among 40 phenethylamine derivatives and proposed 2-hydroxy-4,5-dimethoxyphenethanolamine (I) as a potential endogenous psychotogen. However, no report has appeared on the synthesis and psychotogenic evaluation of I.

In continuing investigations on peyote and related alkaloids (6, 7), the authors extended the work to the study of I and its methylenedioxy analog (II). The synthesis of racemates of I and II is reported here



Scheme I

along with their behavioral response in mice, which could be correlated with hallucinogenic activity in humans (8).

Under base-catalyzed conditions, the reaction of nitromethane with aromatic aldehydes usually yields a mixture of nitrostyrene and the corresponding 1-phenyl-2-nitroethanol. The authors recently observed that the yield of nitro-alcohol could be increased by varying reaction conditions such as temperature and workup procedure (9, 10). The nitro-alcohol could then be reduced to the corresponding phenethanolamine as reported earlier for the synthesis of β-hydroxymescaline (11). The modified procedure for the preparation of 1-phenyl-2-nitroethanols has now been applied in the synthesis of the phenethanolamines I and II.

Scheme I outlines the synthesis of the proposed endogenous psychotogen (I). Demethylation of 2,4,5-trimethoxybenzaldehyde (III) by boron trichloride (12) gave the requisite benzaldehyde (IV), which was converted to its 2-benzyloxy derivative (V) and reacted with nitromethane at 0–5° for 30 min in the presence of potassium hydroxide to yield on acidification the key intermediate, 1-(2-benzyloxy-4,5-dimethoxyphenyl)-2-nitroethanol (VI), mp 75–77°. Hydrogenation of VI in the presence of 10% palladium-on-carbon catalyst furnished (±)-2-hydroxy-4,5-dimethoxyphenethanolamine (I), mp 151–152° dec., in 43% overall yield; mass spectrum: *m/e* 213 (M^+), 195 ($M-H_2O$), and 183 ($M-CH_2NH_2$); NMR (solvent, *CDCl*$_3$ containing a few drops of CD_3OD): δ 2.96–3.06 (m, 2, α-CH_2), 3.82 (s, 3), 3.86 (s, 3) (C_4 and C_5 di OCH_3), 4.68–4.78 (t, 1, β-CH), 6.46 (s, 1, aromatic C_6-H), and 6.65 (s, 1, aromatic C_3-H) ppm.

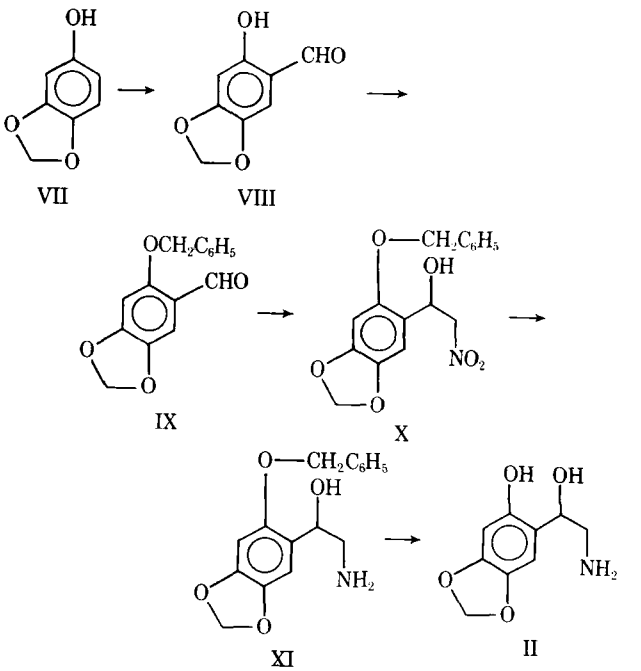
Anal.—Calc. for $C_{10}H_{15}NO_4$: C, 56.33; H, 7.09; N, 6.57. Found: C, 56.26; H, 7.04; N, 6.43.

The synthesis of the methylenedioxy analog II is described in Scheme II. Formylation of sesamol (VII) with *N*-methylformanilide and phosphorus oxychloride furnished the benzaldehyde (VIII), which was converted to its 2-benzyloxy derivative (IX). Compound IX was reacted with nitromethane at 0–5° in the presence of potassium hydroxide to afford on acidification the key nitroethanol intermediate (X), mp 120–122°. Compound X was first reduced to the corresponding amine (XI) (hydrochloride, mp 155–156° dec.) by hydrogen over platinum oxide. The benzyloxyamine (XI) was then hydrogenolyzed in the presence of 10% palladium-on-charcoal catalyst to give (±)-2-hydroxy-4,5-methylenedioxyphenethanolamine (II) (hydrochloride, dec. ~150°) in 36% overall yield; mass spectrum: *m/e* 197 (M^+), 179 ($M-H_2O$), and 167 ($M-CH_2NH_2$); NMR (D_2O solvent): δ 3.33–3.42 (m, 2, α-CH_2), 5.22–5.27 (m, 1, β-CH), 6.05 (s, 2, aromatic OCH_2O at C_4, C_5), 6.66 (s, 1, aromatic C_6-H), and 7.03 (s, 1, aromatic C_3-H) ppm.

Anal.—Calc. for $C_9H_{11}NO_4$·HCl: C, 46.25; H, 5.13; N, 5.99. Found: C, 46.45; H, 5.16; N, 5.93.

The hallucinogenic potencies of the synthetic compounds I and II were determined according to the method of Corne and Pickering (8), which has shown a good correlation between drug-induced hallucinations in humans and head twitches in mice. Male mice, weighing 20–40 g (5 g weight variation in each group), were injected with a single intraperitoneal dose of the test compounds in water and observed for head twitches over 30 min. Twelve mice were used at each dose level, and each compound was tested at four different doses ranging from 2.5 to 40 mg/kg. Mescaline was used as a positive control. The ED_{50} values (with 95% limits) were estimated according to the method of Litchfield and Wilcoxon (13).

The head twitch responses produced by the test compounds in mice are given in Table I. Onset of head twitch in individual animals following drug administration occurred within 18 min, and the effect lasted up to 28 min. The racemic phenethanolamine



Scheme II

Table I—Head Twitch Responses in Mice Produced by Phenethylamine Derivatives

Compound	ED_{50} (95% Limits), mg/kg ip[a]	Onset, min	Duration, min
(±)-2-Hydroxy-4,5-dimethoxyphenethanolamine (I)	17 (12.1–23.8)	2–18	2–24
(±)-2-Hydroxy-4,5-methylenedioxyphenethanolamine (II)	56 (25.4–123.2)	2–6	2–22
Mescaline	5.3 (3.6–7.3)	2–14	2–28

[a] The ED_{50} values reported are calculated for the free base concentrations of the test compounds.

derivatives I and II were about one-third and one-tenth as active as mescaline, respectively. From these results it appears that I could be an endogenous psychotogen responsible for schizophrenic manifestations as postulated by Shulgin *et al.* (4).

(1) A. A. Boulton, *Nature*, **231**, 22(1971).
(2) H. Osmond and J. Smythies, *J. Ment. Sci.*, **98**, 309(1952).
(3) A. J. Friedhoff and E. Van Winkle, *Nature*, **194**, 897(1962).
(4) A. T. Shulgin, T. Sargent, and C. Naranjo, *ibid.*, **221**, 537(1969).
(5) R. E. Dill and K. M. Campbell, *Res. Commun. Chem. Pathol. Pharmacol.*, **6**, 975(1973).
(6) M. L. Sethi, G. S. Rao, and G. J. Kapadia, *J. Pharm. Sci.*, **62**, 1802(1973).
(7) G. J. Kapadia and M. B. E. Fayez, *Lloydia*, **36**, 9(1973).
(8) S. J. Corne and R. W. Pickering, *Psychopharmacologia*, **11**, 65(1967).
(9) G. J. Kapadia, M. B. E. Fayez, M. L. Sethi, and B. K. Chowdhury, *Lloydia*, **35**, 469(1972).
(10) G. J. Kapadia, M. B. E. Fayez, G. S. Rao, and B. K. Chowdhury, *ibid.*, **36**, 442(1973).
(11) G. J. Kapadia, M. H. Hussain, B. K. Chowdhury, and G. S. Rao, *Proc. Int. Congr. Pharm. Sci.*, **31**, 103(1971).
(12) F. M. Dean, J. Goodchild, L. E. Houghton, J. A. Martin, R. B. Morton, B. Parton, A. W. Price, and N. Somvichien, *Tetrahedron Lett.*, **1966**, 4153.
(13) J. T. Litchfield, Jr., and F. Wilcoxon, *J. Pharmacol. Exp. Ther.*, **95**, 99(1949).

Govind J. Kapadia[x]
Bejoy K. Chowdhury
*G. Subba Rao**
Department of Biomedicinal Chemistry
College of Pharmacy and Pharmacal Sciences
Howard University
Washington, DC 20001

S. N. Pradhan
Department of Pharmacology
College of Medicine
Howard University
Washington, DC 20001

Received February 26, 1974.
Accepted for publication May 3, 1974.
Presented in part to the American Society of Pharmacognosy, 13th Annual Meeting, Columbus, Ohio, July 1972.
Supported in part by Grant MH 15573, National Institutes of Health, U.S. Public Health Service, Bethesda, Md.
The authors thank Mr. B. K. De, College of Medicine, Howard University, Washington, D.C., for his cooperation in obtaining ED_{50} data.

This communication is Part XVII in the series Peyote and Related Alkaloids.

* Present address: Laboratory of Chemical Pharmacology, National Heart and Lung Institute, Bethesda, MD 20014
[x] To whom inquiries should be directed.

Chemical Constituents of Gentianaceae XI: Antipsychotic Activity of Gentianine

Keyphrases □ Gentianine—antipsychotic activity evaluated □ Gentianaceae—chemical constituents, antipsychotic activity of gentianine evaluated □ Antipsychotic activity—gentianine screened, chemical constituents of Gentianaceae

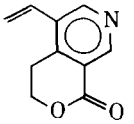
To the Editor:

In an attempt to locate the active principle(s) of *Swertia chirata* (1), we examined the psychopharmacological profile of its major alkaloid, gentianine (I). The first report (2) on the central nervous system (CNS) activity of this compound was limited to the observation that "in weak doses it appears to stimulate the central nervous system, but in larger amounts it shows a paralyzing action." Preliminary pharmacological screening of the alkaloid, however, reflected its CNS depressant activity even in small doses (3). The results obtained in the present investigation point to a persuasive explanation of this activity and prompt us to report the antipsychotic profile of action of this compound.

Pharmacological studies were conducted on albino mice[1] (18–25 g) and albino rats[1] (80–120 g). The animals were fed on standard pellet diet[2]. All experiments were conducted at ambient temperature of 28 ± 2°. Unless stated otherwise, gentianine was used in a dose of 20 mg/kg ip and pretreatment time was 1 hr. At least 10 animals were used for drug-treated and control groups, the latter receiving only the vehicle, distilled water.

In primary observational tests (4), gentianine, in small doses (10–20 mg/kg ip), markedly diminished spontaneous motility and produced sedation and ptosis in albino mice and rats, but reflexes were intact and the animals responded to external stimuli. On increasing the dose (50–100 mg/kg), hind-limb paralysis and catalepsy were produced. The cataleptic animals remained stationary when placed on a vertical wire netting and maintained the awkward posture when one hind limb was placed on a cork. However, they responded to painful stimuli and retained the righting reflex. Gentianine produced hypothermia in albino rats as recorded by a rectal thermister probe. Since these observations are indicative of antipsychotic activity, gentianine was subjected to further pharmacological screening as follows.

The effects of gentianine on hexobarbital hypnosis, amphetamine toxicity and stereotypy, and lysergide-induced symptoms were evaluated. Gentianine sig-



I

[1] B. N. Ghosh & Co, Calcutta, India.
[2] Hindusthan Levers, Calcutta, India.