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Alkaloids of *Banisteria caapi* and *Prestonia amazonicum*

BY F. A. HOCHSTEIN AND ANITA M. PARADIES

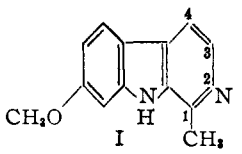
RECEIVED JUNE 17, 1957

The hallucinogenic plant *Banisteria caapi* contains, in addition to harmine, the alkaloids harmaline and *d*-tetrahydroharmine. *Prestonia amazonicum* leaves have yielded another psychotomimetic amine, N,N-dimethyltryptamine.

The plant *Banisteria caapi* Spruce has been examined repeatedly by workers who were attracted by the hallucinogenic activity of this drug.[1,2] Three names, telepathine, yageine (yajeine) and banisterine were assigned to the alkaloids isolated by early workers. Several subsequent investigators agree that harmine is the sole alkaloid of *B. caapi*, though Oryekhov[3] reported that harmaline also is present. The properties reported for yageine,[2,4] however, are quite unlike those of harmine or harmaline. Undoubtedly, some of these inconsistencies resulted from errors in botanical identification and confusion of the common names of the several species of plants used in northern South America as hallucinogens.[2]

We have recently had occasion to examine this plant anew.[5]

The availability of modern investigational techniques, especially paper chromatography, has enabled us to extend the earlier work. In our hands, *Banisteria caapi* "Ayahuasca" has yielded harmine (I) as its major alkaloid. We have found in addition, lesser quantities of harmaline (3,4-dihydroharmine), and a third alkaloid, previously unde



I

scribed. The new alkaloid, colorless crystals, m.p. 198–200°, $[\alpha]D$ +32°, was isolated in quantities inadequate for degradative study. The ultraviolet absorption spectrum clearly indicated it to be a 6-methoxyindole, and the analyses suggested that it was N,N-dimethyl-6-methoxytryptamine. The optical activity observation was discounted and the substituted tryptamine was accordingly synthesized, but found to be different. The slight difference between the ultraviolet spectra of the new alkaloid and 6-methoxy-N,N-dimethyltryptamine suggested that our compound was an α,β-disubstituted indole. Tetrahydroharmine appeared to be the only likely alternate structure, though it seemed improbable that the reported m.p. (199–200°) of the synthetic material would be the same as that of our dextrorotatory alkaloid. Careful comparison of the isolated alkaloid with racemic 1,2,3,4-tetrahydroharmine leaves no doubt that the two compounds differ only in the optical activity of the naturally occurring material.

The presence of these three alkaloids, differing only in their state of oxidation in the same plant is of biogenetic interest. In view of the low degree of psychotomimetic activity reported for harmine,[1b] and the effectiveness ascribed to *Banisteria caapi* extracts, it seems likely that the harmaline or *d*-tetrahydroharmine may have substantial psychotomimetic activity in their own right.

A second plant, "Yage," *Prestonia amazonicum* (*Haemadictyon amazonicum* Spruce) was made available to us as an aqueous extract of the leaves. The natives of the area of collection commonly consume a mixed extract of the *B. caapi* vine and *P. amazonicum* leaves, in the belief that the latter suppresses the more unpleasant hallucinations associated with pure *B. caapi* extracts. This plant is reported to be the source of the alkaloid "yageine,"[4] m.p. 206°, $C_{14}H_8N_3O$, though others attributed it to *B. caapi*.[2] This *P. amazonicum* extract yielded substantial amounts of another psychotomimetic amine, N,N-dimethyltryptamine, an alkaloid which has been identified recently as a component of the seeds of certain *Piptadenia* species.[6] Its psychotomimetic effect in man has also been demonstrated by recent work.[7] No other alkaloids were detected in this plant extract.

ADDED IN PROOF.—R. R. Paris, F. Percheron, J. Manil and R. Goutarel, *Bull. Soc. Chim., France*, 780 (1957), have reported that the alkaloid leptaflorine is the racemic form of tetrahydroharmine.

Experimental

Extraction of Crude Alkaloids of *Banisteria caapi*.—Fifteen hundred grams of the ground vine of *Banisteria caapi* was stirred under reflux with 3 liters of methanol for five hours, filtered and washed with methanol. The extraction was twice repeated in the same manner, and the combined extracts were then concentrated to dryness *in vacuo* to yield 120 g. of total extracted solids.

This crude extract was suspended in 1 liter of 5% ammonium hydroxide, and extracted with four 400-ml. portions of chloroform. Centrifuging was necessary to break the stable emulsions. The combined chloroform extracts were then dried over sodium sulfate, and concentrated *in vacuo* to yield 15 g. of crude alkaloids (A). A partially crystalline solid (20 g.) was filtered from the aqueous phase, dried and extracted overnight in a Soxhlet with chloroform to yield an additional 9 g. of crude alkaloids (B).

(1) (a) T. A. Henry, "The Plant Alkaloids," 4th Ed., Blakiston Co., Philadelphia—Toronto, 1949, p. 488, lists a reasonably complete bibliography on this subject through 1939; (b) H. H. Pennes and P. H. Hoch, *Am. J. Psychiatry*, **113**, 887 (1957), have reported on the psychotomimetic effect of harmine in man.

(2) W. B. Mors and P. Zaltzman, Boletim do Insituto de Quimica Agricola (Brazil) No. 34, p. 17 (1954), covers the botanical question thoroughly, as well as other aspects.

(3) A. P. Oryekhov, *Byull-Nauch. Issledovatel Khim-Farm. Inst.*, 3 (1930); *C. A.*, **26**, 5699 (1932).

(4) A. M. Barriga Villalba, *J. Soc. Chem. Ind.*, **44**, 205T (1925).

(5) We are indebted to Mr. D. H. Allen for a supply of the plant material studied here. Both the *Banisteria caapi* "Ayahuasca" and the *Haemadictyon amazonicum* (*Prestonia amazonicum*), "Yage," were collected on the Napo River, near Iquitos, Peru. The botanical identification was made by Dr. R. Ferreyra, of the University of San Marcos, Lima. It might be noted that both of the trivial names, or variants of them, have previously been quoted as referring to *Banisteria caapi*. See ref. 1 and 2.

(6) M. S. Fish, N. M. Johnson and E. C. Horning, THIS JOURNAL, **77**, 5892 (1955).

(7) St. Szára, *Experientia*, **XII**, 441 (1956).

Isolation of Harmine.—Direct crystallization of (B) from hot chloroform (with concentration) yielded 5 g. of crude harmine. A similar crystallization of (A) yielded 3 g. of crude harmine. These two lots were combined and recrystallized twice from methanol to yield 5 g. (0.3%) of pure harmine, m.p. 261.8–262.4°; mixture m.p. with an authentic sample[8] not depressed. The infrared absorption spectrum and the paper chromatographic behavior were identical with that of the pure synthetic sample.

Isolation of Harmaline and *d*-Tetrahydroharmine.—A second crop of alkaloids (2 g.) obtained by concentration of the mother liquors from A and B above, contained, in addition to harmine, larger quantities of two other alkaloids, which were detected readily by their paper chromatographic behavior. On a chloroform–formamide system,[9] harmine shows R_f 0.64, harmaline has R_f = 0.07, and tetrahydroharmine has R_f 0.13. All three compounds fluoresce brightly under ultraviolet light. Attempts to separate the three components by an 8-tube countercurrent distribution between chloroform and *p*H 4.6 phosphate buffer showed limited separation. The crude mixture sublimed completely at 185° (0.1 mm.). Chromatography of 0.5 g. of this mixture over 30 g. of "Florisil," utilizing chloroform with increasing increments of methanol, finally pure methanol for elution, yielded first harmine, then tetrahydroharmine, finally harmaline.

The tetrahydroharmine, of which about 50 mg. (0.003%) was isolated in pure form, had m.p. 198.4–199.8° (*in vacuo*), $[\alpha]^{25}D$ +32° ($CHCl_3$, or 5% acetic acid). The mixed m.p. with racemic tetrahydroharmine,[10] m.p. 199.4–199.8° (*in vacuo*) was not visibly depressed. Further, the infrared spectra of the natural and synthetic materials were identical, both in chloroform solution and in KBr pellets. The papergram characteristics of the two forms were indistinguishable.

Harmaline (25 mg.), the last component eluted from the column, was purified by sublimation, and melted at 227–229°. The mixture m.p. with an authentic sample, prepared from a commercial product, m.p. 228.5–231°, was not depressed. Identity was confirmed by ultraviolet and infrared absorption spectra, and by paper chromatographic comparison.

An aqueous extract of *B. caapi*, "as used by the natives," was supplied to us at a different time. It contained the same three alkaloids, but it appeared to be richer in *d*-tetrahydroharmine and harmaline. One liter of this extract contained 3.3 g. of chloroform extractable solids, from which about one gram of pure harmine was isolated.

Isolation of Dimethyltryptamine from *Prestonia amazonicum* Extract.—The aqueous extract of the leaves was received as a turbid suspension, *p*H 5.5, with a faintly aromatic odor. Two liters of extract were adjusted to *p*H 10.5 with sodium hydroxide, and extracted with three one-liter portions of chloroform. The chloroform extracts were washed with water, and concentrated *in vacuo* to yield 4.3 g. of a viscous oil which was readily soluble in dilute acetic acid or mineral acid. Distillation at 170° (0.01 mm.) yielded 3 g. of colorless oil which crystallized spontaneously on standing, m.p. 44–46°. A second distillation yielded purified N,N-dimethyltryptamine, m.p. 44.6–46.8°, pK_a (ethanol–water), 8.68, eq. wt. 190, calcd. 188. The identity, which was immediately suspected from the analysis and the ultraviolet absorption spectrum, was established by preparation of the picrate, m.p. 169.5–170°, and of the methiodide, m.p. 216–217°.

Examination of the crude total alkaloids by paper chromatography revealed only dimethyltryptamine.

N,N-Dimethyl-6-methoxytryptamine.—Oxalyl chloride (0.5 g., 6 mmoles) was added to a solution of 0.44 g. (3 mmoles) of 6-methoxyindole[11] in 15 ml. of ether at 0°. An orange-red crystalline precipitate separated within a few minutes. After 30 minutes the crude 6-methoxy-3-indoleglyoxychloride, 0.66 g., was separated by filtration, washed with ether and added with vigorous stirring to 20 ml. of 35% aqueous dimethylamine. After 15 minutes the clear yellow solution was concentrated *in vacuo* to a few ml., and 0.57 g. of crystalline 6-methoxyindoleglyoxyldimethylamide separated and dried, m.p. 194–195°. A portion, 75 mg., was recrystallized from 15 ml. of benzene to yield 55 mg. of pure compound, m.p. 195.1–196.8°.

Anal. Calcd. for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.00; H, 5.79; N, 11.53.

One-half gram of the crude amide was dissolved in 35 ml. of dry tetrahydrofuran, 0.50 g. of lithium aluminum hydride in 20 ml. of tetrahydrofuran added, and the resulting suspension was heated under reflux for three hours. The excess hydride was decomposed with 100 ml. of water and the product extracted several times with methylene chloride. Concentration of the combined, water-washed extracts yielded 0.47 g. of colorless crystals, of crude N,N-dimethyl-6-methoxytryptamine, m.p. 68–75°. Two recrystallizations from ligroin yielded a pure product, m.p. 76–77.2°.

Anal. Calcd. for $C_{13}H_{18}N_2O$: C, 71.52; H, 8.31; N, 12.83. Found: C, 71.18; H, 8.00; N, 13.40.

The ultraviolet absorption spectra, which show peaks in methanol at 223 mμ, ε 21,200, 273 mμ, ε 2600 and 294 mμ, ε = 3180, is very similar but not identical with those of such α,β-disubstituted 6-methoxyindoles as tetrahydroharmine or methyl reserpate.

Acknowledgments.—We should like to express our thanks to Mr. W. H. Boegemann for his invaluable assistance with paper chromatography. We are indebted also to Dr. R. L. Wagner and his colleagues for the physical measurements and analytical data, and to Dr. L. Nickell for his continuing help with the botanical aspects of the problem.

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(8) The authentic sample was prepared by the nitric acid oxidation of commercial (E. Merck, Darmstadt) harmaline by the procedure of V. V. S. Iyer and R. Robinson, *J. Chem. Soc.*, 1635 (1934).

(9) F. A. Hochstein, K. Murai and W. H. Boegemann, THIS JOURNAL, **77**, 3551 (1955).

(10) Tetrahydroharmine was prepared by the sodium–amalgam reduction of harmaline hydrochloride, following the procedure of W. H. Perkin and R. Robinson, *Chem. Soc.*, **115**, 961 (1919), for the reduction of harmine.

(11) We are indebted to Dr. R. B. Woodward for this material.

[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, WEIZMANN INSTITUTE OF SCIENCE]

Reaction of Acylamino Acids with Paraformaldehyde

BY DOV BEN-ISHAI*

RECEIVED JUNE 3, 1957

Carbobenzoxy derivatives of simple α-amino acids, hippuric and phenaceturic acids have been found to react with paraformaldehyde in the presence of a sulfonic acid catalyst to give N-acyl-5-oxazolidones (II). The reaction of the oxazolidinones with amines is described.

Primary amides and primary urethans are known to react with formaldehyde or paraformaldehyde under acidic conditions to give methylenediamides (I) and methylenediurethans[1] (I, R = OR_1)

$$2RCONH_2 + CH_2O \xrightarrow{H^+} (RCONH)_2CH_2 + H_2O$$
$$\text{I}$$

* Department of Chemistry, Israel Institute of Technology, Haifa, Israel.

(1) J. F. Walker, "Formaldehyde," Amer. Chem. Soc., Monograph Series, Reinhold Publ. Corp., New York, N. Y., 1944, Chapter 14.