[CONTRIBUTION FROM THE RESEARCH AND DEVELOPMENT DIVISION, SMITH KLINE AND FRENCH LABORATORIES]

Indole Alkaloids of *Acer saccharinum* (the Silver Maple), *Dictyoloma incanescens*, *Piptadenia colubrina*, and *Mimosa hostilis*

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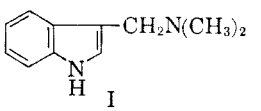
Gramine was isolated from the leaves of *Acer saccharinum* L., *N,N*-dimethyl-5-methoxytryptamine from the bark of *Dictyoloma incanescens* D.C., bufotenine from the seeds of *Piptadenia colubrina* Benth., and *N,N*-dimethyltryptamine from the roots of *Mimosa hostilis* Benth.

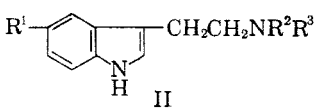
Several plants which we have studied recently have, by coincidence, yielded indole alkaloids of simple structure. Four of these are described in the present paper.

Although numerous members of the maple family, Aceraceae, have been studied chemically in considerable detail, none has been known to produce alkaloids. When we learned, through qualitative tests, that alkaloids occur in the leaves of the silver maple tree, *Acer saccharinum* L. it was of considerable interest to us to learn their nature.

Extraction of 3.75 kg. of dried, ground maple leaves[2] with ethanol and concentration of the alkaloid gave a mass of large crystals in 0.05% yield. The ultraviolet spectrum of the material was almost identical with those of 3-substituted indoles such as gramine and tryptamine. Upon recrystallization from benzene, the alkaloid melted at 131–132° and was found to be identical with a synthetic specimen of the alkaloid gramine (I). As far as we know, gramine has been found to occur naturally only in the grass family and its occurrence in maple leaves was quite unexpected. The Aceraceae may now be included in the growing number of plant families known to produce indole alkaloids.



I



II

Another plant family not known to produce simple indole derivatives is the Rutaceae. Although more complex indoles such as harmine,[3] canthinone,[4] and hortiamine[5] occur in certain of its species, indoles unsubstituted at the 2-position have not been found.

The bark of the Brazilian tree *Dictyoloma incanescens* D.C.[6] yielded a new alkaloid, *N,N*-dimethyl-5-methoxytryptamine (II, $R^1 = OCH_3$; $R^2 = R^3 = CH_3$) in 0.04% yield. This product was prepared some years ago by Hoshino and Shimodaira[7] during the course of their synthetic studies on bufotenine (II, $R^1 = OH$; $R^2 = R^3 = CH_3$) and related compounds. The *Dictyoloma* alkaloid was identified through analysis, comparison of its ultraviolet spectrum with that of a sample of 5-methoxytryptamine,[8] comparison of the melting point of the alkaloid and its picrate with those previously reported[7] and finally through preparation of the methiodide, identical by melting point, mixed melting point and infrared spectrum with the methiodide prepared by exhaustive methylation of 5-methoxytryptamine.[7]

The occurrence of *N,N*-dimethyl-5-methoxytryptamine rather than the corresponding phenolic compound, bufotenine, in *Dictyoloma incanescens* is in keeping with the observation of Briggs and Cambie[9] that the presence of methoxy and methylenedioxy groups rather than free phenolic groups is a common characteristic of the family Rutaceae.

Wilkinson[10] has recently mentioned that of the series of tryptamines (II, R^1 = H, OH or OCH_3; R^2 = H or CH_3; R^3 = H or CH_3) all except 5-methoxytryptamine and *N,N*-dimethyl-5-methoxytryptamine occur naturally. It may now be stated that of these nine alkaloids, only 5-methoxytryptamine still remains to be discovered in nature.

A narcotic plant used by the Indians of Brazil came to our attention through the late Dr. J. G. Kuhlmann. The roasted seeds of the plant, identified as *Piptadenia colubrina* Benth., are powdered and taken as a snuff. Stromberg[11] and later Fish,

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(2) Collected in the Philadelphia area in midautumn and identified by Mr. J. W. Adams. A reference specimen, No. 8818, has been deposited at the Morris Arboretum of the University of Pennsylvania.

(3) W. O. Kermack, W. H. Perkin, Jr., and R. Robinson, *J. Chem. Soc.*, 1872 (1922).

(4) H. F. Haynes, E. R. Nelson, and J. R. Price, *Australian J. Sci. Research, Ser. A*, **5**, 387 (1952).

(5) I. J. Pachter, R. F. Raffauf, G. E. Ullyot, and O. Ribeiro, Abstracts, 132nd Meeting of the American Chemical Society, New York, September, 1957, p. 49P.

(6) Collected in the winter season in the environs of Rio de Janeiro and identified by the late Dr. J. G. Kuhlmann. A herbarium specimen, No. 863710, has been deposited at the Philadelphia Academy of Natural Sciences.

(7) T. Hoshino and K. Shimodaira, *Bull. Chem. Soc. Japan*, **11**, 221 (1936); *Chem. Abstr.*, **30**, 5982[9] (1936).

(8) R. A. Abramovitch and D. Shapiro, *J. Chem. Soc.*, 4589 (1956).

(9) L. H. Briggs and R. C. Cambie, *Tetrahedron*, **2**, 256 (1958).

(10) S. Wilkinson, *J. Chem. Soc.*, 2079 (1958).

(11) V. L. Stromberg, *J. Am. Chem. Soc.*, **76**, 1707 (1954).

Johnson and Horning[12] investigated *Piptadenia* and found bufotenine to be the major alkaloid of a number of species. Bufotenine is also the major alkaloid of *P. colubrina*.[13] It was identified through comparison with an authentic sample obtained from Dr. R. H. Levin of the Upjohn Co. The seeds of *P. colubrina* constitute an exceptionally rich source of the alkaloid, the yield of crystalline base, m.p. 146–147°, being 2.1%.

The Pancarú Indians of the interior of the State of Pernambuco, Brazil, use a beverage in their mystico-religious ceremonies which is described as one that transports individuals to strange worlds and permits them to contact the souls of the dead. The plant from which this beverage, called "wine of Jurema," is prepared was obtained by Gonçalves de Lima and identified as *Mimosa hostilis* Benth. The results of a chemical examination of the root bark were published in 1946.[14] An alkaloid named nigerine, m.p. 45.8–46.8°, was isolated in 0.51% yield. An empirical formula, $C_{13}H_9N_2O$, was assigned.

The nature of the alkaloid was not apparent from its formula and was considered worthy of further study. Prof. Gonçalves de Lima kindly furnished 2.7 kg. of the roots. The plant material yielded a single alkaloid, m.p. 48–49°, in 0.57% yield. In our hands, an analysis was obtained which suggested the formula $C_{12}H_{16}N_2$. The alkaloid was identified as *N,N*-dimethyltryptamine by its ultraviolet and infrared spectra and through preparation of the previously described[15] picrate and methiodide derivatives. *N,N*-Dimethyltryptamine has been reported to be a constituent of other species of the family Mimosaceae.[12]

EXPERIMENTAL

Gramine from Acer saccharinum. A 10-kg. sample of leaves of *Acer saccharinum*[2] was dried at 40° and milled to give 3.75 kg. of ground leaves. This material was stirred under reflux for 8 hr. with 20 l. of 95% ethanol. The mixture was filtered and the extraction repeated twice with fresh solvent. The combined alcoholic solutions were concentrated under reduced pressure to give 2.5 l. of a waxy alcoholic slurry.[16] To this was added 2.5 l. of hexane. The resulting mixture was then stirred slowly while 2 l. of water was added. It was allowed to stand for a day. The dark hexane layer gave a negative test for alkaloids and was discarded. A nonalkaloidal interphase, freed of solvent by centrifugation, also was discarded. The aqueous-alcholic layer was concentrated under reduced pressure to a thick sirup. This was stirred with 1.5 l. of 2% phosphoric acid and 1 l. of ether. The aqueous phase was retained. The ethereal layer was extracted with a fresh 1 l. portion of 2% phosphoric acid and discarded. The combined phosphoric acid solutions were washed with two 100-ml. portions of ether and then adjusted to *p*H 9 with concentrated aqueous ammonia.

The ammoniacal solution was extracted with four 1 l. portions of ether and finally with 1 l. of chloroform. The organic phases were combined, dried over magnesium sulfate, and evaporated to dryness. The residue was extracted with 500 ml. of boiling ether. A nonalkaloidal ether-insoluble residue remained and was discarded. The ethereal solution was extracted three times with 50-ml. portions of 2% hydrochloric acid and the combined acid solutions were adjusted to *p*H 9 with ammonia and extracted with three 100-ml. portions of ether. The ethereal solutions were dried over magnesium sulfate, filtered, and evaporated to dryness. The alkaloidal residue, weighing 1.9 g. (0.05% yield), solidified. It was recrystallized twice from benzene to give 1.1 g. (0.03% yield) of prismatic crystals, m.p. 131–132°. The alkaloid gave no depression of melting point upon admixture with synthetic gramine.

Anal. Calcd. for $C_{11}H_{14}N_2$: C, 75.82; H, 8.10; N, 16.08. Found: C, 75.83, 75.69; H, 8.29, 8.06; N, 16.02.

The picrate of the alkaloid, m.p. 141–142°, gave no depression of melting point upon admixture with a sample of picrate derived from synthetic gramine.

N,N-Dimethyl-5-methoxytryptamine from Dictyoloma incanescens. A 900-g. sample of the ground bark of *Dictyoloma incanescens*[6] was extracted for 8 hr. with 3 l. of boiling petroleum ether (b.p. 30–60°) and filtered. The petroleum ether extract was nonalkaloidal and was discarded. The residual bark was then heated under reflux with stirring for 3 hr. with 2 l. of ethanol containing 10% aqueous ammonia. The process was repeated twice with fresh solvent, the periods of extraction being extended to 8 hr.

The combined alcoholic extracts were concentrated to 500 ml. *in vacuo*, acidified with 5% tartaric acid, diluted with 1 l. of water and filtered with the aid of Supercel. The resulting solution was made basic with concentrated aqueous ammonia and extracted three times with 500-ml. portions of ethyl acetate. Evaporation to dryness left 4.4 g. of residue. This was dissolved in 20 ml. of methylene chloride and extracted three times with 20-ml. portions of 5% hydrochloric acid. The acid solutions were combined, adjusted to *p*H 9 with concentrated aqueous ammonia and extracted four times with 50-ml. portions of ether. The ethereal solutions were combined, dried over magnesium sulfate and evaporated to dryness to give 1.1 g. of crude alkaloid. Paper chromatography on Whatman 3MM paper, using 10:1:10 butanol:acetic acid:water, showed a single strong alkaloid spot, R_f 0.65.

The 1.1 g. of crude alkaloid was dissolved in methanol and treated with an equal weight of picric acid dissolved in methanol. There was obtained 0.70 g. of orange-yellow *picrate*, m.p. 176–177.5°, after three recrystallizations from methanol-acetone.

Anal. Calcd. for $C_{13}H_{18}N_2O \cdot C_6H_3N_3O_7$: C, 51.00; H, 4.73; N, 15.65. Found: C, 51.27; H, 5.05; N, 15.55.

The yield of alkaloid represented by 0.70 g. of picrate is 0.04%.

A 250-mg. sample of the picrate was treated with alkali to liberate the free base. The alkaloid crystallized, and upon recrystallization from hexane containing some ether, yielded 75 mg. of prisms, m.p. 67.5–68.5°, R_f 0.66 on Whatman 3MM paper using 10:1:10 butanol:acetic acid:water.

Anal. Calcd. for $C_{13}H_{18}N_2O$: C, 71.52; H, 8.31. Found: C, 71.29; H, 8.35.

The ultraviolet absorption spectrum in 95% ethanol, which shows maxima at 222 mμ, ε 25,100; 278 mμ, ε 6,300; 296 mμ, ε 5,100; 309 mμ (shoulder), ε 3,500 and minima at 212 mμ, ε 21,800; 248 mμ, ε 1,750; 294 mμ, ε 5,050 is virtually identical with that of synthetic 5-methoxytryptamine.[8]

(12) M. S. Fish, N. M. Johnson, and E. C. Horning, *J. Am. Chem. Soc.*, **77**, 5892 (1955).

(13) Collected in the autumn season in the environs of Rio de Janeiro and identified by the late Dr. J. G. Kuhlmann. A herbarium specimen, No. 859244, has been deposited at the Philadelphia Academy of Natural Sciences.

(14) O. Gonçalves de Lima, *Arquiv. inst. pesquisas agron.*, **4**, 45 (1946). In addition to the chemical study, this article contains a fascinating account of the ceremonial use of the plant and a botanical description by Dr. D. de Oliveira.

(15) F. A. Hochstein and A. M. Paradies, *J. Am. Chem. Soc.*, **79**, 5735 (1957).

(16) A pre-extraction with petroleum ether is recommended for future runs.

The alkaloid yields a methiodide, m.p. 183°, which does not depress the melting point of that prepared by exhaustive methylation of 5-methoxytryptamine.[7] The methiodide samples are identical by infrared spectroscopy.

Bufotenine from Piptadenia colubrina. A 2.26-kg. sample of ground seeds of *Piptadenia colubrina*[13] was extracted continuously with ethanol until exhausted of alkaloids. The alcoholic extract was evaporated to dryness and partitioned between 500 ml. of 5% aqueous ammonia and 500 ml. of chloroform. The layers were separated and the ammoniacal solution was extracted six times with 300-ml. portions of chloroform. The chloroform solutions were combined, concentrated to 1 l. and extracted five times with 350 ml. portions of 5% hydrochloric acid. Emulsions formed which were broken by centrifugation. The combined acid solutions were made basic with concentrated aqueous ammonia and extracted eight times with 300-ml. portions of chloroform. Evaporation of the chloroform solutions to dryness left 74 g. of total bases in the form of a solid brown resin.

The crude bases were powdered and boiled thoroughly with ethyl acetate. Insoluble black material was removed by filtration. The ethyl acetate solution was poured onto a column of alumina and the alkaloids were eluted by repeated washing with ethyl acetate. Dark-colored materials remained adsorbed on the column. The ethyl acetate eluates were concentrated and yielded 47 g. (2.1% yield) of bufotenine, m.p. 146–147°. The alkaloid gave no depression of melting point upon admixture with an authentic specimen of bufotenine obtained from the Upjohn Co., Kalamazoo, Mich. The two samples were spectrally identical.

N,N-Dimethyltryptamine from Mimosa hostilis. A 2.7-kg. sample of ground roots of *Mimosa hostilis*[14] was extracted continuously with ethanol until the marc was exhausted of alkaloids. The alcohol was removed and the residue stirred with 500 ml. of 5% aqueous ammonia and 2 l. of chloroform. The layers were separated by centrifugation and an interphase was extracted several more times with aqueous ammonia and chloroform until it no longer contained alkaloids. The combined aqueous solutions were extracted three additional times with 1 l. portions of chloroform. The chloroform solutions were combined, concentrated, and extracted with 2% hydrochloric acid until the acid solutions no longer gave positive tests with Mayer's reagent. The combined acid solutions (3 l.) were adjusted to *p*H 9 with concentrated aqueous ammonia and extracted three times with 500-ml. portions of chloroform. Emulsions were separated by centrifugation. The chloroform solutions were dried over magnesium sulfate and evaporated to dryness to give 18.5 g. of crude brown alkaloid.

Paper chromatography of the crude material on Whatman 3MM paper using 10:1:10 *t*-amyl alcohol:formic acid:water showed a single alkaloid, R_f 0.78.

A 12.0 g. sample of the total alkaloid was dissolved as completely as possible in boiling ether and filtered to remove black resinous matter. The ethereal filtrate was evaporated to dryness and the residue dissolved in 30 ml. of methanol. A solution of 15 g. of picric acid in 75 ml. of methanol was added to the alkaloidal solution and a crystalline picrate separated. This was filtered and dried to give 21.9 g. of picrate, m.p. 168–170°. Three crystallizations from benzene gave 16.9 g. of first crop material, m.p. 171–172°, and 3.8 g. of second crop material, m.p. 169–171°.

A 10 g. sample of the picrate was converted to the free base, which crystallized from hexane containing a little ethyl acetate to give 3.3 g. of *N,N*-dimethyltryptamine, m.p. 48–49°.

Anal. Calcd. for $C_{12}H_{16}N_2$: C, 76.55; H, 8.57; N, 14.88. Found. C, 76.88; H, 8.83; N, 14.71.

Based on the formula $C_{12}H_{16}N_2$ for the alkaloid, the combined weight of first and second crops of the aforementioned picrate derived from 65% of the total bases corresponds to a yield of 0.57%.

When warmed with methyl iodide in ethereal solution, the alkaloid yielded a crystalline methiodide which, upon recrystallization from ethanol, melted at 215–216°.

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[CONTRIBUTION FROM CENTRAL EXPERIMENT STATION, BUREAU OF MINES, U. S. DEPARTMENT OF THE INTERIOR]

Selective Hydrogenation of Polynuclear Aromatic Hydrocarbons

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It has been found that dicobalt octacarbonyl, in the presence of carbon monoxide and hydrogen, functions as a selective homogeneous hydrogenation catalyst for polynuclear aromatic hydrocarbons. Isolated benzene rings are stable in this system. Naphthalenes are slowly reduced to tetralins. Linearly condensed compounds, such as anthracene, are readily hydrogenated at the meso positions. Phenanthrene-type compounds are reduced very slowly at 200° to dihydro derivatives. More highly condensed systems are reduced to yield phenanthrene derivatives. In most cases, only one reduction product is obtained. The system provides a convenient synthetic method for preparing certain hydrogenated derivatives of polynuclear aromatic compounds.

Discovery of the hydroformylation reaction by Roelen[1] during World War II led to investigation of the reaction of various types of olefinic substances with carbon monoxide and hydrogen in the presence of a cobalt carbonyl. Since the 9,10-double bond in phenanthrene possesses considerable olefinic character, Adkins and Krsek[2] attempted to hydroformylate this compound at 125°, but no reaction was observed at this temperature. Wender, Levine, and Orchin[3] treated phenanthrene with carbon monoxide and hydrogen in the presence of a cobalt catalyst at a higher temperature and found that this compound was slowly hydrogenated. After 2 hr. at 180–185°, a 7% yield of 9,10-dihydrophenanthrene and a 1% yield of 1,2,3,4-tetrahydrophenanthrene were obtained; 81% of the starting compound was recovered unchanged.

(1) O. Roelen, U.S. Patent 2,327,066, Aug. 17, 1943.

(2) H. Adkins and G. Krsek, *J. Am. Chem. Soc.* 71, 3051 (1949).

(3) I. Wender, R. Levine, and M. Orchin, *J. Am. Chem. Soc.*, 72, 4375 (1950).