and recrystallization from methanol produced 0.16 g. of tetrahydroepiveatchine, m.p. 174–177°, undepressed upon admixture with authentic material. This almost certainly must have involved direct hydrogenation of VI rather than proceeding *via* the ketone IX, since the C_{19} carbonyl group is not reducible under those conditions.

DETROIT, MICHIGAN
MEXICO, D. F.

[CONTRIBUTION FROM THE LABORATORY OF CHEMISTRY OF NATURAL PRODUCTS, NATIONAL HEART INSTITUTE, NATIONAL INSTITUTES OF HEALTH]

Alkaloids of the Amaryllidaceae. V. Alkaloids of *Nerine falcata* Barker and *N. laticoma* (Ker) Dur. and Schinz.[1]

BY W. C. WILDMAN AND CAROL J. KAUFMAN

RECEIVED APRIL 9, 1955

Nerine falcata Barker and *N. laticoma* (Ker) Dur. and Schinz. have been found to contain lycorine, caranine and a new alkaloid which has been named falcatine. The empirical formula and functional groups of falcatine have been determined. Evidence is presented that the aromatic ring contains methylenedioxy and methoxyl groups.

The genus *Nerine* (Amaryllidaceae) recently was investigated by Boit,[2] who found in *N. sarniensis* tazettine, lycorine and a new alkaloid of empirical formula $C_{19}H_{25}NO_5$, named nerinine. This paper deals with the alkaloids of two *Nerine* species which were collected two years ago in South Africa. To date, the alkaloids of this genus appear to vary considerably with the species, since the alkaloids of *N. falcata* and *N. laticoma* are quite different from those found in *N. sarniensis*. Moreover, we have found that *N. kreigii* contains lycorine and two additional new alkaloids which will be reported in another paper.

The isolation procedures were similar to those of our previous work. The yields of lycorine, caranine and falcatine from the two *Nerine* species are shown in Table I. Lycorine and caranine were identified by melting point and comparison of infrared spectra with those of authentic samples.

TABLE I

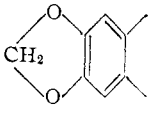
ALKALOIDAL CONTENT OF *Nerine* SPECIES BASED ON FRESH BULB WEIGHT

	N. falcata	*N. laticoma*
Lycorine, %	0.046	0.024
Caranine, %	.021	.006
Falcatine, %	.216	.042

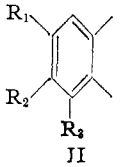
The new alkaloid, falcatine, was shown by analysis to have the molecular formula $C_{17}H_{19}NO_4$. Although relatively unstable to oxygen and light, the alkaloid showed no decomposition when stored for two months under nitrogen at 0° in a brown bottle. Analysis of the functional groups showed the presence of one methoxyl. The N-methyl group was absent. A band at 2.80 μ in the infrared spectrum of falcatine showed the presence of a hydroxyl group. An aliphatic hydroxyl was verified when it was found that falcatine gave a basic monoacetate showing carbonyl absorption at 5.81 μ. Bands at 9.55 and 10.70 μ indicated the presence of a methylenedioxyphenyl function. A positive Labat[3] test gave further proof of the methylenedioxyphenyl group. Upon catalytic reduction, falcatine absorbed one mole of hydrogen to give a crystalline dihydro derivative. No evidence of a second isomer was obtained. The relatively low yield of dihydrofalcatine is attributed to partial decomposition during purification. Falcatine gave two methiodides when treated with methyl iodide. The α-isomer, m.p. 250–255° dec., was formed in smaller amount. The β-isomer was non-crystalline.

Falcatine is isomeric with natalensine, coccinine, montanine and crinamine.[1,4] However, spectral comparisons of falcatine with these isomers show two important differences. It has been our observations that most alkaloids containing the methylenedioxyphenyl chromophore show ultraviolet maxima near 240 mμ (log ϵ ~3.6) and 295 mμ (log ϵ ~3.7) when no unsaturated group is conjugated with the aromatic ring. Crinamine and caranine differ slightly in the respect that the low wave length band appears as a shoulder near 235 mμ. The ultraviolet spectrum of falcatine clearly resembles that of hydrocotarnine (λ_{max} 287 mμ, log ϵ 3.23) more closely than those of crinamine and its isomers.

A study of the infrared spectra between 6.0 and 6.5 μ of compounds containing the system I shows very weak C=C stretching absorption near 6.25 μ when no unsaturation is conjugated with the phenyl group.



I



II

a, $R_1R_2 = O_2CH_2$ b, R_1 $R_2 = OCH_3$ c, R_1, R_2, $R_3 = OCH_3$
$R_3 = OCH_3$ $R_3 = H$

Strong absorption appears at 6.25 μ if conjugation is introduced. Oxyhydrastinine and piperonal show absorption at 6.25 μ almost as intense as that of the carbonyl band.[5] A similar intensification appears to occur in compounds of the type II even though no conjugation is present. Lycorenine, hydrocotarnine, mescaline, homoveratrylamine, 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and its 2-methyl derivative all show relatively strong bands

(1) Previous paper, L. H. Mason, E. R. Puschett and W. C. Wildman, THIS JOURNAL, **77**, 1253 (1955).

(2) H.-G. Boit, *Chem. Ber.*, **87**, 1704 (1954).

(3) J. A. Labat, *Bull. soc. chim. biol.*, **15**, 1344 (1932).

(4) W. C. Wildman and C. J. Kaufman, THIS JOURNAL, **77**, 1248 (1955).

(5) A more general discussion of this phenomenon is found in L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1954, pp. 59–63.

between 6.2 and 6.3 μ. The fact that falcatine shows strong absorption at 6.20 μ lends further support to the hypothesis that its methoxyl group is in the aromatic ring. The infrared spectra of natalensine, coccinine, montanine and crinamine show little, if any, absorption near 6.2 μ. Since their ultraviolet spectra agree well with those of alkaloids containing only methylenedioxyphenyl absorption, such as tazettine and lycorine, it is concluded that in these compounds the methoxyl group is aliphatic.

Experimental[6]

The bulbs of *N. falcata* were gathered early in 1953 in Transvaal, South Africa; those of *N. laticoma* were collected in the Cape Province. By our standard method of processing,[1] 1125 g. of *N. falcata* gave 9.14 g. (0.81%) of crude alkaloids. In a similar manner, 4195 g. of *N. laticoma* gave 12.87 g. (0.31%) of alkaloidal material. The low yield of crude alkaloid fraction from *N. laticoma* was surprising since a small quantitative test on 246 g. gave a yield twice as great as the run above.

A portion of the crude alkaloid fraction of *N. falcata* (3.49 g.) was heated to boiling with 100 ml. of benzene containing 10 ml. of chloroform. The insoluble material was separated by decantation and treated with boiling ethanol. Upon cooling, 124 mg. of crystalline lycorine, m.p. 233–244° dec., was removed by filtration. The infrared spectrum of this material was identical with that of an authentic sample. The ethanolic filtrate was combined with the benzene-soluble alkaloid fraction, concentrated to a dark gum that was dissolved in benzene containing a trace of chloroform and chromatographed on 360 g. of aluminum oxide (Merck). Elution with benzene–ethyl acetate (1:1) gave 1.458 g. of oil which crystallized upon the addition of ethyl acetate. Recrystallization from ether gave 0.930 g. of falcatine, m.p. 125–127.5°. Elution with ethyl acetate followed by chloroform gave 0.168 g. of oil that afforded 89 mg. of crude caranine, m.p. 167–174°, identical in infrared spectrum with authentic caranine. Further elution with ethanolic chloroform gave a series of oils from which 76 mg. of lycorine, m.p. 224–235° dec., was obtained by trituration with ethanol. Similar treatment of a portion of the crude alkaloid fraction of *N. laticoma* gave the same alkaloids in yields shown in Table I.

Falcatine.—The alkaloid showed a pronounced tendency to become yellow on standing in air in the presence of light. Recrystallization from ethyl acetate and other higher boiling solvents also tended to increase the amount of yellow impurity. The most satisfactory purification involved dissolving the falcatine in ether and removing the insoluble yellow material by filtration. Concentration of the ethereal solution gave colorless prisms of falcatine, m.p. 127–128°, $[\alpha]^{22}D$ −197.8° (*c* 1.05, chloroform), which was stored under nitrogen in a brown bottle at 0°. The alkaloid seemed quite stable under these conditions.

Anal. Calcd. for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65; CH_3O, 10.30; N-CH_3, 4.98; neut. equiv., 301.33. Found: C, 67.80; H, 6.31; N, 4.61; CH_3O, 10.13; N-CH_3, 0.72; neut. equiv., 303.3.

The ultraviolet absorption spectrum showed a maximum at 287 mμ (log ϵ 3.23).

Falcatine Picrate.—Aqueous picric acid was added to a hot ethanolic solution of 50 mg. of falcatine. Upon cooling, a quantitative yield of picrate precipitated, m.p. 178–183° dec. The solid was recrystallized from aqueous ethanol to give the pure picrate, m.p. 182–185° dec.

Anal. Calcd. for $C_{17}H_{19}NO_4 \cdot C_6H_3N_3O_7$: C, 52.07; H, 4.18; N, 10.56. Found: C, 52.03; H, 3.99; N, 10.60.

Falcatine Methiodide.—A solution of 113 mg. of falcatine in acetone was treated with 3 ml. of methyl iodide. The solvent and excess methyl iodide were removed from the gummy methiodide by boiling. When the residue was heated with absolute ethanol, 50 mg. of crystalline material separated, m.p. 240–250° dec. Two recrystallizations from 95% ethanol gave 34 mg. of a methiodide, m.p. 250–255° (gradual dec. from 220°). The remaining methiodide was non-crystalline.

Anal. Calcd. for $C_{17}H_{19}NO_4 \cdot CH_3I$: C, 48.77; H, 5.00; I, 28.63. Found: C, 48.67; H, 4.93; I, 28.42.

Falcatine Hydrochloride.—Addition of 6 *N* hydrochloric acid to a hot aqueous suspension of 98 mg. of falcatine gave, upon cooling, 95 mg. of the hydrochloride, m.p. 238–240° dec. Finely powdered crystals of the same material showed a m.p. 220–235° dec.

Anal. Calcd. for $C_{17}H_{19}NO_4 \cdot HCl$: C, 60.44; H, 5.97; N, 4.15. Found: C, 60.17; H, 6.15; N, 3.89.

O-Acetylfalcatine.—A solution of 30 mg. of falcatine in 2 ml. of dry pyridine and 1 ml. of acetic anhydride was allowed to stand two days at room temperature. The solvents were removed *in vacuo*. The residue was dissolved in chloroform and washed with dilute sodium carbonate solution followed by water. The chloroform was removed under reduced pressure. Trituration of the residue with ethanol gave 34 mg. of the acetate, m.p. 201–202°. Recrystallization from ethanol gave colorless prisms, m.p. 201–202°. The acetate showed basic properties.

Anal. Calcd. for $C_{19}H_{21}NO_5$: C, 66.46; H, 6.16; N, 4.08. Found: C, 66.16; H, 6.26; N, 4.10.

Dihydrofalcatine.—An ethanolic solution containing 117 mg. of falcatine absorbed one equivalent of hydrogen when reduced at room temperature and atmospheric pressure with 100 mg. of 10% palladium-on-charcoal catalyst. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure to a colorless oil. The oil was dissolved in ether and the solution was centrifuged to remove traces of a flocculent substance. Concentration of the ethereal solution gave 60 mg. of dihydrofalcatine, m.p. 127–129.5°. Recrystallization from ether afforded pure dihydrofalcatine, m.p. 128.5–129.5°. A second crop of 28 mg., m.p. 125–127°, was obtained. Like falcatine, the dihydro derivative was unstable to light and oxygen and gradually turned to an ether-insoluble yellow solid.

Anal. Calcd. for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.17; H, 7.00; N, 4.51.

Acknowledgment.—The procurement of samples and botanical aspects of this work were carried out by the Section of Plant Introduction, U. S. Agricultural Research Service. We are indebted to Mr. D. L. Rogerson of this Institute for the processing of the plant material.

BETHESDA, MARYLAND

(6) All melting points are corrected and were observed on a Kofler microscope hot-stage equipped with polarizer. Analyses were performed by Dr. W. C. Alford and his staff, National Institute of Arthritis and Metabolic Diseases, Bethesda, Md., and the Clark Microanalytical Laboratory, Urbana, Ill. Infrared spectra were recorded with a Perkin-Elmer model 21 double-beam spectrophotometer; ultraviolet spectra were recorded with a Cary model 11MS spectrophotometer. Unless otherwise noted, the ultraviolet spectra were run in Pharmco absolute ethanol. The spectral work was performed by Miss F. C. Bateman.