Two recrystallizations from ether yielded 32 mg. of crystals melting at 167–170°. The infrared spectrum showed the absence of any hydroxyl bands; ν^{Nujol} (OAc) 1735, 1238 cm.$^{-1}$; (NAc) 1643 s. cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{35}NO_3$: C, 74.76; H, 9.15; OAc, 11.16.[13] Found: C, 75.10, 74.76; H, 9.10, 9.24; Ac, 12.05.[13]

N-Acetate IV.—A solution of the O,N-diacetate III in 60% ethanol containing 0.5 g. of sodium hydroxide was left at 50° for one hour. After evaporation to dryness the residue was taken up in water and extracted with chloroform. The chloroform extract yielded a resin which crystallized from ether. Recrystallization from acetone gave material melting at 222–225°. The infrared spectrum in Nujol showed the presence of a hydroxyl band at 3421 cm.$^{-1}$ and an N-acetate band at 1639 s. cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{33}NO_2$: C, 76.92; H, 9.68. Found: C, 76.88; H, 9.36.

Condensation of the $C_{20}H_{31}NO$ Base (II) with Ethylene Chlorohydrin.—A solution of 70 mg. of II in 3 ml. of dry ethylene chlorohydrin and 10 ml. of dry methanol containing 300 mg. of anhydrous sodium carbonate was boiled under reflux for 18 hours. After evaporation to dryness *in vacuo* the residue was taken up in water and extracted repeatedly with chloroform. The chloroform extract yielded a resin which was dissolved in methanol and treated with Norite. When concentrated to 3 ml., diluted to incipient turbidity and seeded, the solution yielded 53 mg. of feathery needles of dihydroatisine, m.p. 155–159°. Recrystallization from aqueous methanol gave 44 mg. of pure dihydroatisine, m.p. 156–159°, undepressed with an authentic sample. The infrared spectrum in Nujol was identical with that of authentic dihydroatisine.

Dihydroatisine Diacetate (VI). A.—The above dihydroatisine (35 mg.) in 3 ml. of acetic anhydride was boiled under reflux for 13 minutes. After evaporation to dryness *in vacuo*, the residue was taken up in water, treated with sodium bicarbonate and extracted with chloroform. The extract yielded a residue which crystallized from ether as heavy prisms. Recrystallization gave material melting at 122–123°, undepressed with a sample of the authentic diacetate described below. The infrared spectra (Nujol) of the two samples were also identical.

B.—Dihydroatisine prepared by the sodium borohydride reduction of atisine was acetylated in acetic anhydride as described above. The diacetate crystallized from ether as heavy prisms, m.p. 123.5–124°, $[\alpha]^{27}D$ −84° (*c* 1.5 in chf.). The infrared spectrum showed the absence of hydroxyl bands; ν^{Nujol} (OAc) 1739 cm.$^{-1}$; (>C=CH$_2$) 1660, 907 cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{39}NO_4$: C, 72.69; H, 9.15; OAc, 19.99. Found: C, 72.76; H, 9.27; OAc, 20.30.

Conversion of Dihydroatisine (V) to Isoatisine (VII).—To a solution of 665 mg. of dihydroatisine in 100 ml. of absolute ether was added 486 mg. of osmium tetroxide.[3] After standing for three days at 0° the black mixture was filtered and the filtrate concentrated to dryness. The residue (290 mg.) crystallized from ether as unchanged dihydroatisine, m.p. 154–157°. The precipitate of osmium ester was decomposed by boiling for 90 minutes in 100 ml. of 50% ethanol containing 3 g. of potassium hydroxide and 1.5 g. of mannitol. After evaporation to dryness *in vacuo* the residue was taken up in water and extracted with chloroform. The extract yielded 340 mg. of a brown resin which was chromatographed in benzene over 7 g. of alumina. The material obtained from the first eight 50-ml. fractions was combined (172 mg.) in benzene, filtered from insoluble material, and rechromatographed over 3 g. of alumina. The material eluted with the first 50 ml. of benzene (140 mg.) was crystallized twice from dilute acetone to give 98 mg. of prisms. Two more recrystallizations from acetone gave pure isoatisine, m.p. 145–149°. The infrared spectrum in KBr was identical with that of an authentic sample of isoatisine.

Infrared spectra were determined in the appropriate phase without compensation on a Perkin–Elmer model 21 double beam spectrometer, with sodium chloride optics, set at resolution 927, response 2, gain 6, suppression 2 and a scanning speed of 0.2 μ per minute.

Acknowledgment.—Analytical data have been obtained by Mr. D. Rigakos of this Laboratory. The technical assistance of Miss Vera Bohan is also gratefully acknowledged.

NEW YORK 21, N. Y.

(13) The sample was rather insoluble in the *p*-toluenesulfonic acid solution. Under the conditions of the hydrolysis only the O-acetate was cleaved.

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

Alkaloids of the Amaryllidaceae. VIII. The Structures of Narcissamine, Pseudolycorine and Methylpseudolycorine[1]

BY H. M. FALES, LAURA D. GIUFFRIDA AND W. C. WILDMAN

RECEIVED MARCH 21, 1956

The bulbs of the King Alfred daffodil (*Narcissus pseudonarcissus* L.) have been found to contain a new alkaloid named methylpseudolycorine, as well as the known alkaloids galanthamine, galanthine, lycorenine, homolycorine, haemanthamine and narcissamine. Narcissamine has been shown to be N-demethylgalanthamine. Structures are proposed for pseudolycorine and methylpseudolycorine.

In spite of the availability of horticultural varieties of daffodils, the first comprehensive report on the alkaloids in the common daffodil (*Narcissus pseudonarcissus* L.) was published this year by Boit and Ehmke.[2] While our results are essentially in agreement with their findings, we wish to record the occurrence of a new alkaloid in the King Alfred daffodil not mentioned by these authors and assign a structural formula to it. Incidental to this research, it was possible to assign a structure to the known alkaloid pseudolycorine.

The preparation of a crude alkaloid fraction from the bulbs followed the method used in our earlier work. Isolation of the pure alkaloids was accomplished by chromatography on alumina. Lycorenine[3] and haemanthamine[4] had been isolated previously in this Laboratory, and the specimens obtained from *N. pseudonarcissus* were identified by melting points, mixed melting points and infrared spectra. Galanthamine was identified by its melting point, rotation, analysis and the preparation of two derivatives that agreed well

(1) Paper VII, Carol K. Briggs, Patricia F. Highet, R. J. Highet and W. C. Wildman, THIS JOURNAL, **78**, 2899 (1956).

(2) H.-G. Boit and H. Ehmke, *Chem. Ber.*, **89**, 163 (1956).

(3) R. J. Highet and W. C. Wildman, THIS JOURNAL, **77**, 4399 (1955).

(4) W. C. Wildman and Carol J. Kaufman, *ibid.*, 1248 (1955).

with values reported in the literature. Galanthine and narcissamine were identified by similar methods. In addition to the alkaloids reported by Boit and Ehmke,[2] we were able to isolate the known homolycorine[5] and in low yield a new alkaloid that we named methylpseudolycorine.

Narcissamine was isolated by Boit and Ehmke[2] from several of the garden varieties of daffodils, but their analytical results did not allow a decision to be made between the formulas $C_{16}H_{19}NO_3$ and $C_{16}H_{21}NO_3$. The alkaloid was characterized as a secondary amine containing one methoxyl but no N-methyl group. We have verified their finding that the base is a secondary amine by the formation of an O,N-diacetate. Our analyses on this derivative and the alkaloid itself pointed to the molecular formula $C_{16}H_{19}NO_3$ for narcissamine. On the basis of the expanded formula $C_{15}H_{14}O(OCH_3)(NH)(OH)$ for narcissamine, it seemed probable that the base was either N-demethylgalanthamine or N-demethyl base IX.[6] When narcissamine was methylated with methyl iodide, N-methylnarcissamine methiodide was formed. The product was identical in melting point, optical rotation and infrared spectrum with authentic galanthamine methiodide and did not depress the melting point of an admixture.

In the chromatographic isolation of the pure alkaloids, a strongly fluorescent solid was the first basic material to be eluted from the column. This base (and its picrate) analyzed correctly for a compound $C_{17}H_{17}NO_2$ and is represented by IIIa. The ultraviolet spectrum (Fig. 1) of IIIa was almost identical with that of anhydrolycorine (IIIb), and

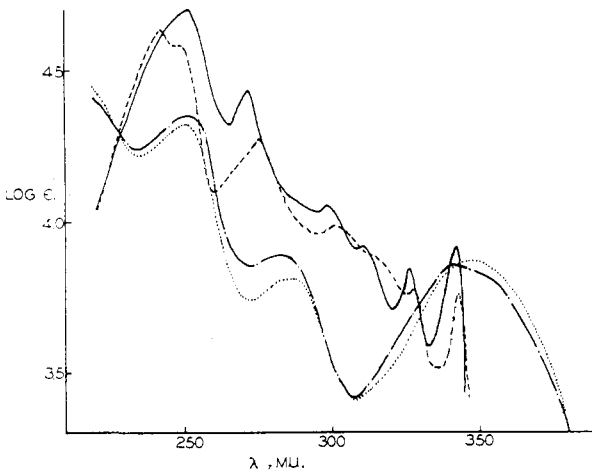


Fig. 1.—Ultraviolet absorption spectra in ethanol of IIIa, — · — · —; IIIb, ...; IVa, ——; IVb ------.

its melting point behavior and stability were similar to the properties reported by Cook, Loudon and McCloskey[7] for IIIb.

Air oxidation occurred during determination of the melting point, and the decomposition point finally observed was that of the phenanthridone IVa. Finally, IIIa and IVa were synthesized from 1-(6'-nitroveratroyl)-2,3-dihydroindole (V) by procedures now considered standard.[7-9] Synthetic IIIa was identical with the sample isolated by chromatography of the crude alkaloid mixture.

Methylpseudolycorine possessed the molecular formula $C_{17}H_{21}NO_4$ and contained two methoxyl groups as determined by analysis. Two hydroxyl groups were present as proven by the formation of a diacetate. No enolic properties were observed. Periodate titration indicated that the hydroxyl functions were vicinal. The facile preparation of a basic diacetate showed the nitrogen to be tertiary. Upon catalytic hydrogenation, the alkaloid formed a dihydro derivative with an ultraviolet absorption spectrum that was identical with that of the parent alkaloid. Methylpseudolycorine perchlorate showed no absorption in the 6 μ region attributable to an enamine salt.[10] These preliminary characterizations parallel similar reactions of lycorine (IIb), and it was suspected that the new alkaloid was the dimethoxy analog IIa of lycorine. This correlation was strengthened by the fact that the infrared spectrum of methylpseudolycorine was quite similar to that of lycorine.[11] When methylpseudolycorine was dissolved in dilute base, concentrated to dryness and heated under reduced pressure, dehydration occurred and crystals of IIIa were obtained as a sublimate. This conversion established the entire ring system of methylpseudolycorine and located the two methoxyl groups in the 9- and 10-positions.[12]

Methylpseudolycorine was oxidized by selenium dioxide to the hydroxyphenanthridinium chloride (VIa) which showed physical and spectral properties that resembled very closely those of VIb.[9] A similar correlation was present in the basic forms VIIa and VIIb. The spectral comparison is shown in Fig. 2. This oxidation established the presence of one hydroxyl in the 2-position. The positive periodate test requires the 1- or 3-position for the second hydroxyl. At this point the problem of assigning positions to the remaining hydroxyl and the double bond was comparable to that presented by lycorine.[8] Since hot ethanolic sulfuric acid caused dehydration and oxidation to IVa, attempts to isomerize the double bond (if located in 3a–4)

(5) Our isolation of homolycorine by chromatography of the crude mixture on alumina does not constitute proof that the alkaloid exists in the bulbs of the King Alfred daffodil, since the alkalinity of the alumina may be sufficient to cause disproportionation of some lycorenine to homolycorine. Reference 1 reports a similar transformation with the alkaloid krigeine.

(6) Authentic base IX [H. Kondo, S. Ishiwata and S. Okayama, *J. Pharm. Soc. Japan*, **53**, 149 (1933)], m.p. 190°, has been isolated in our Laboratory from *Lycoris squamigera*. Our analytical data revealed that the molecular formula should be revised to $C_{17}H_{21}NO_4$. Base IX seems identical with galanthamine except in the configuration of the hydroxyl group, since the same α,β-unsaturated ketone, m.p. 188–192° (semicarbazone, m.p. 230–240° dec.), was obtained from each alkaloid upon manganese dioxide oxidation. Experimental details will be published at a later date.

(7) J. W. Cook, J. D. Loudon and P. McCloskey, *J. Chem. Soc.*, 4176 (1954).

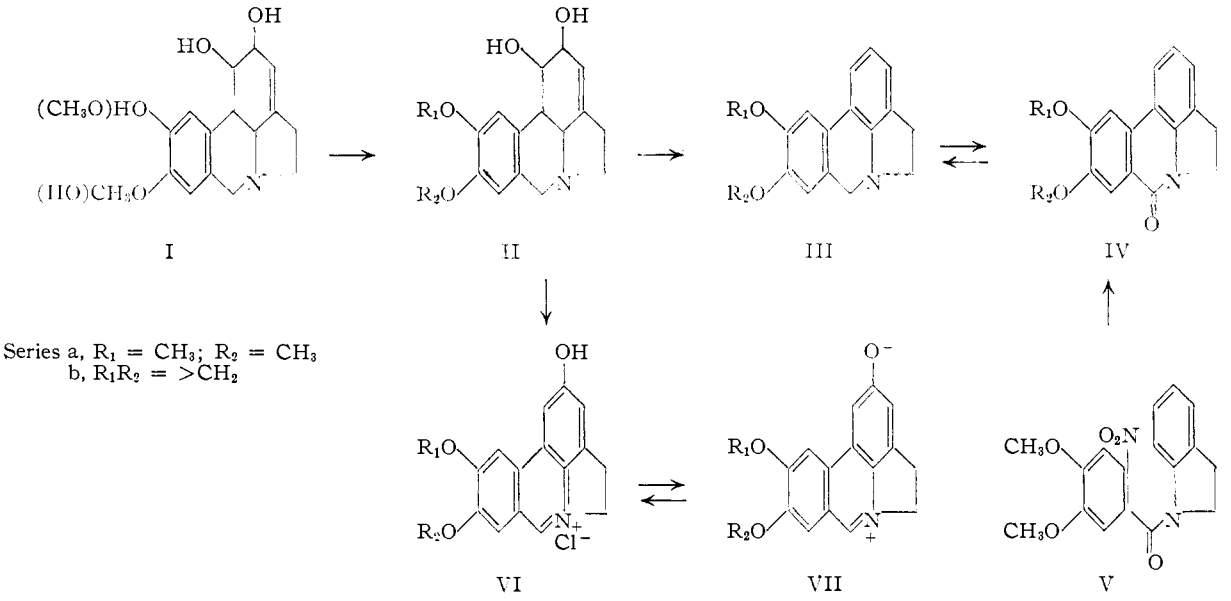
(8) L. G. Humber, H. Kondo, K. Kotera, S. Takagi, K. Takeda, W. I. Taylor, B. R. Thomas, Y. Tsuda, K. Tsukamoto, S. Uyeo, H. Yajima and N. Yanaihara, *ibid.*, 4622 (1954).

(9) H. M. Fales, E. W. Warnhoff and W. C. Wildman, THIS JOURNAL, **77**, 5885 (1955).

(10) N. J. Leonard and V. W. Gash, *ibid.*, **76**, 2781 (1954).

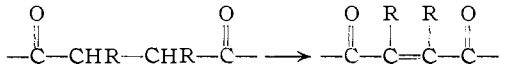
(11) Methylpseudolycorine bears a superficial resemblance to pluviine[2] but differs in analysis, rotation and color test with sulfuric acid.

(12) It is very unlikely that compounds IIIa and IVa exist as such in the plant. IIIa probably is formed from methylpseudolycorine by spontaneous dehydration under the influence of the basic alkaloid mixture itself and the anhydrous alkaline conditions of the chromatogram. IVa is formed by subsequent air oxidation.

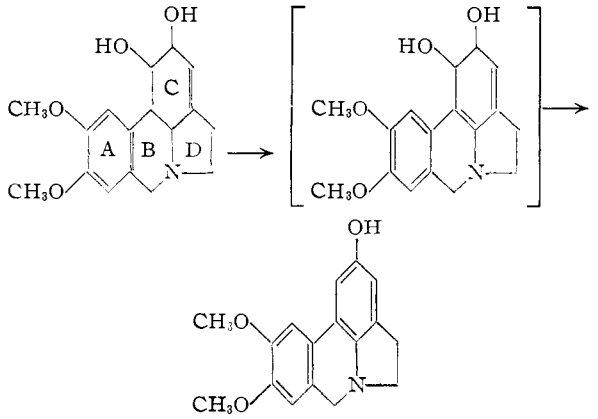


were to no avail. The chemical and physical data (*vide supra*) require the double bond to be located either in position 3–3a or 3a–4. Location of the double bond in 3a–4 would permit the hydroxyl to be in either position 1 or 3. A 3–3a location for the double bond requires the second hydroxyl to be in position 1, and methylpseudolycorine would be the dimethoxy analog of lycorine. While complete chemical proof has not been possible because of insufficient quantities of alkaloid, the similarities between the infrared spectra of methylpseudolycorine and lycorine and the excellent rotational correlations (Table I) justify a tentative assignment of formula IIa to methylpseudolycorine.

It has been suggested[13] that selenium dioxide oxidations of the type



require a *cis* configuration of the abstracted hydrogen atoms. Thus the oxidation of methylpseudolycorine by selenium dioxide may indicate the presence of a *cis* B:C ring junction by the path



A similar ring fusion in lycorine has been suggested

(13) C. S. Barnes and D. H. R. Barton, *J. Chem. Soc.*, 1419 (1952).

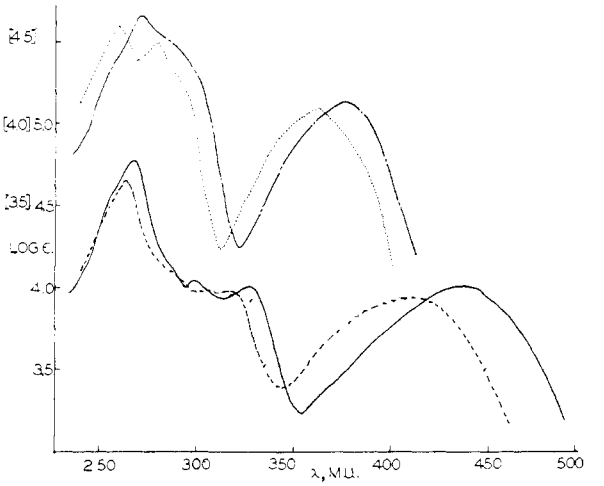


Fig. 2.—Ultraviolet absorption spectra of: VIa in 0.01 *N* ethanolic hydrochloric acid, — · —; VIb in 0.1 *N* hydrochloric acid, ...; VIa in 0.01 *N* ethanolic sodium hydroxide, ——; VIb in 0.1 *N* sodium hydroxide -----.

TABLE I

ROTATIONAL DATA[a]

Alkaloid	M.p., °C.	$[\alpha]^{25}D$	M_D
Lycorine	250–255 d.	−42°	−120°
Pseudolycorine[15]	245 d.	−41.5	−120
Methylpseudolycorine	228–233 d.	−40	−121
Dihydrolycorine	225–230 d.	−71	−205
Dihydromethylpseudolycorine	192–196 d.	−65	−198

[a] Rotations were run in dimethylformamide with the exception of pseudolycorine which was observed in ethanol.

on other grounds.[14] It is noteworthy that lycorine is oxidized in the same fashion.

The alkaloid pseudolycorine was isolated from *Lycoris radiata* Herb. nearly 30 years ago.[15] Other than a report of its probable occurrence in

(14) S. Takagi, W. I. Taylor, S. Uyeo and H. Yajima, *ibid.*, 4003 (1955).

(15) H. Kondo, K. Tomimura and S. Ishiwata, *J. Pharm. Soc. Japan*, **52**, 51 (1932).

Cooperia pedunculata,[16] there has been no further evidence of its isolation from any plant source. The base, $C_{16}H_{17}NO_4$, was reported to contain three hydroxyl groups, one of which was phenolic. The alkaloid contained one methoxyl but no N-methyl group.[15] It seemed to us that the analytical results presented by Kondo could be explained equally as well on the basis of the formula $C_{16}H_{19}NO_4$.[17] In this case, pseudolycorine might be represented by formula I. Pseudolycorine[18] was treated with diazomethane. The product was identical with the alkaloid methylpseudolycorine. Pseudolycorine then can be represented by I.

Acknowledgment.—The procurement of samples and botanical aspects of this work were carried out by Dr. B. G. Schubert of 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.

Experimental[19]

Isolation of Crude Alkaloid Fractions.—In a typical experiment, 7 kg. of bulbs of the King Alfred daffodil (*Narcissus pseudonarcissus* L.) were ground in a Ball and Jewell grinder and extracted twice with 10 l. of 1% ethanolic tartaric acid solution for two hours at room temperature. The filtered extract was concentrated to 2 l. and diluted with 8 l. of water. The mixture was acidified with 400 ml. of 2 *N* hydrochloric acid and washed with chloroform. The chloroform solution gave a positive silicotungstic acid test, so it was washed further with eleven 200-ml. portions of 2 *N* hydrochloric acid. These washings were added to the original aqueous acid layer; the combined solutions were basified with sodium carbonate and extracted with twenty-two 200-ml. portions of chloroform. These extracts were dried and evaporated leaving 20.205 g. (0.288%) of a brown gum. Subsequent shipments of bulbs were processed by similar procedures to give comparable yields of crude alkaloid mixtures.

Isolation of Alkaloids.—(a) A 5.00-g. sample of the crude alkaloid fraction was refluxed with an excess of benzene and ethyl acetate for several hours. The insoluble material (0.420 g.) which remained was removed by filtration, and the solution was chromatographed on 400 g. of aluminum oxide (Merck).

(b) A portion (3.25 g.) of a second crude alkaloid fraction was heated several times with warm water. The water-insoluble gum remaining was triturated with acetone to give 0.835 g. (25.7%) of lycorenine, m.p. 189–193°. The water-soluble material was partly extracted into chloroform. The chloroform solution was evaporated and chromatographed on alumina. Homolycorine (0.190 g., 5.8%) was eluted with ethyl acetate and was the only crystalline product obtained. The remaining water raffinate was evaporated leaving 0.819 g. of an unidentified oil.

(c) A crude alkaloid fraction (51.4 g.) was dissolved in an excess of 10% hydrochloric acid solution until *p*H 1 was reached. The acidic solution was extracted with nine 500-ml. portions of chloroform. The chloroform extracts were evaporated and treated with aqueous alkali. The aqueous solution was extracted with chloroform and ethyl acetate. The chloroform solution was evaporated leaving 10.02 g. of a brown oil which was triturated with ethyl acetate to give 0.340 g. of crystalline lycorenine, m.p. 188–194°. The filtrate was chromatographed on 500 g. of aluminum oxide (Merck). The dihydrophenanthridine IIIa (0.089 g.) was eluted with ethyl acetate. Further elution with ethyl acetate afforded 0.940 g. (1.8% of crude alkaloid) of galanthine which melted at 132–134°, recrystallized on the hot-stage, and finally remelted at 160–170°. Further elution with ethyl acetate yielded 0.604 g. of galanthamine and finally 0.929 g. of haemanthamine.

Fraction	Eluent (100-ml. fractions)	Product from eluate
1–10	Benzene	0.050 g. colorless wax
11–18	Benzene	0.010 g. colorless oil
19–43	15–25% ethyl acetate in benzene	0.088 g. IIIa, m.p. 145°, 270°
44–78	25–30% ethyl acetate in benzene	0.711 g. oil which yielded 0.21 g. galanthamine, m.p. 122–128°
79–108	30–50% ethyl acetate in benzene	1.967 g. crude haemanthamine, m.p. 197–199°
109–178	(1) 2 l. ethyl acetate (2) 2 l. 50% chloroform in ethyl acetate (3) 2.5 l. chloroform	1.560 g. crude narcissamine, m.p. 158–163°, 193–199°
179–253	1–10% ethanol in chloroform	0.040 g. crude methylpseudolycorine, m.p. 217–233° dec.

Haemanthamine (Natalensine).—Haemanthamine was recrystallized from ethyl acetate to yield prisms, m.p. 199–200°, which did not depress the melting point of authentic haemanthamine,[4] $[\alpha]^{22}D$ +19.5° (*c* 3.77, methanol), (reported[4] $[\alpha]^{25}D$ +19.6°). The infrared spectrum was identical with that of the authentic alkaloid.

Galanthamine (Lycorenine).—The alkaloid crystallized after prolonged trituration with ether. It was recrystallized from ether or cyclohexane and then sublimed at 120° (5 μ), m.p. 130–131° (reported 127–129°,[20] 126–127°,[21] 127–129°[22]), $[\alpha]^{26}D$ − 120° (*c* 0.99, ethanol) (reported $[\alpha]^{22}D$ − 122°,[20] $[\alpha]D$ −118.8°,[21] $[\alpha]^{32}D$ −121.4°[22]).

Anal. Calcd. for $C_{17}H_{21}NO_3$: C, 71.05; H, 7.37; N, 4.87. Found: C, 71.08; H, 7.45; N, 4.84.

The ultraviolet absorption spectrum (ethanol) showed a maximum at 288 mμ (log ϵ 3.41).

Galanthamine methiodide formed instantaneously when methyl iodide was added to galanthamine in ether solution. The product was recrystallized from water and dried at 100° (1 mm.), m.p. 280–284° dec. (reported 286°,[20] 279°,[21] 289–291°[22]), $[\alpha]^{22}D$ −94.4°, $[\alpha]^{22}_{436}$ −196° (*c* 0.67, 75% ethanol).

Anal. Calcd. for $C_{17}H_{21}NO_3 \cdot CH_3I$: N, 3.26; I, 29.56. Found: N, 2.98; I, 29.66.

Dihydrogalanthamine (lycoramine) was obtained by allowing 0.200 g. of galanthamine to absorb one mole of hydrogen over 40 mg. of 10% palladium-on-charcoal in ethanol. The catalyst was removed by filtration, and the filtrate was treated with alkali and extracted with chloroform to give 0.176 g. (88%) of a product which melted at 122–124° and did not depress the m.p. of an authentic sample of lycoramine.

Lycorenine.—The crude alkaloid was recrystallized several times from ethyl acetate and ethanol, m.p. 198–200°. A sample did not depress the m.p. of authentic lycorenine (m.p. 198–200°), and the infrared spectrum was identical with that of authentic lycorenine.

Homolycorine.—The ethyl acetate eluate mentioned in (b) was evaporated and triturated with ethanol to induce crystallization. The product was recrystallized from ethanol as long prisms, m.p. 176–177°, which did not depress the m.p. of an authentic specimen, $[\alpha]^{26}D$ +93.5° (*c* 1.2, chloroform) (reported[3] $[\alpha]^{25}D$ +93.6°).

Anal. Calcd. for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; 2 OCH_3, 19.68; NCH_3, 4.77. Found: C, 68.43; H, 6.57; OCH_3, 19.45; NCH_3, 4.27.

Galanthine.—The ethyl acetate eluate mentioned in (c) was evaporated, and the residue was triturated with ethyl

(16) G. A. Greathouse and N. E. Rigler, *Am. J. Botany*, **28**, 702 (1941).

(17) In a private communication, Prof. S. Uyeo has kindly informed us that an authentic sample of pseudolycorine analyzed correctly for a base of the formula $C_{16}H_{19}NO_4$. Full experimental details of this work will be published at a later date.

(18) We are indebted to Prof. S. Uyeo for an authentic sample of pseudolycorine.

(19) 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 staff, National Institute of Arthritis and Metabolic Diseases, Bethesda, Md.; the Clark Microanalytical Laboratory, Urbana, Ill.; Dr. W. Manser, Zurich, Switzerland; and Mr. J. F. Alicino, Metuchen, N. J. Ultraviolet absorption spectra were recorded with a Cary model 11 MS spectrophotometer, and infrared absorption spectra were recorded with a Perkin-Elmer model 21 spectrophotometer. The spectral work was performed by Mr. H. F. Byers and Miss Catherine Monaghan.

(20) H.-G. Boit, *Chem. Ber.*, **87**, 681 (1954).

(21) N. F. Proskurnina and A. P. Yakovleva, *Zhur. Obshchei Khim.*, **22**, 1899 (1952).

(22) S. Uyeo and S. Kobayashi, *Pharm. Bull.*, **1**, 139 (1953).

acetate. Crude galanthine crystallized, m.p. 160–170°. When this product was recrystallized from ethyl acetate, long, pale green prisms formed which lost birefringence at 93–105°, but regained birefringence from 105–134°, and melted rapidly from 134–136°. The completely fused mass recrystallized as long prisms which melted at 166–167°. The m.p. was unchanged after the compound had been recrystallized from water and dried at 76° (5 μ), $[\alpha]^{27}D$ −81.6° (*c* 0.21, ethanol) (reported[2] $[\alpha]^{22}D$ −81°).

Anal. Calcd. for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.31; N, 4.41; 3 OCH_3, 29.34; neut. equiv., 317. Found: C, 67.90; H, 7.55; N, 4.50; OCH_3, 29.48; neut. equiv., 315. No N-CH_3 was present.

The ultraviolet spectrum (ethanol) showed a maximum at 284 mμ (log ε 3.41).

Galanthine perchlorate was prepared in ether–methanol by the addition of 70% perchloric acid and recrystallized as long prisms from ethanol–ethyl acetate; m.p. 211–213°, recrystallized 218°, and finally decomposed completely 280°[23] (reported[2] 218°), $[\alpha]^{27}D$ +42.3° (*c* 0.85, 95% ethanol) (reported[2] $[\alpha]^{22}D$ +39°).

Anal. Calcd. for $C_{18}H_{23}NO_4 \cdot HClO_4 \cdot {}^1/_2H_2O$: C, 50.65; H, 5.90; Cl, 8.31. Found: C, 50.68; H, 5.74; Cl, 8.40.

The ultraviolet absorption spectrum (ethanol) showed maxima at 235 mμ (log ε 3.90) and 283 mμ (log ε 3.58).

Galanthine picrate was prepared and recrystallized from ethanol, m.p. 182–190° dec., m.p. (capillary) 188–190° dec. (reported[2] 199–200° dec.).

Anal. Calcd. for $C_{18}H_{23}NO_4 \cdot C_6H_3N_3O_7$: C, 52.74; H, 4.80; N, 10.25. Found: C, 52.81; H, 4.87; N, 10.21.

Narcissamine.—This base crystallized easily when the ethyl acetate and chloroform eluates mentioned in (a) were evaporated. Boit[2] has reported a m.p. of 195–196°. Our material initially showed a m.p. of 158–163° after recrystallization from water; after recrystallization from xylene, the m.p. was 193–199°. Another recrystallization from water failed to change the latter m.p. When a fusion of the lower-melting form was seeded at 165° with the higher-melting form, recrystallization occurred, followed by final melting at 193–199°. Once the higher-melting polymorph had been obtained, the lower-melting form was never recovered again during recrystallizations; $[\alpha]^{27}D$ −9.8°, $[\alpha]^{27}_{436}$ −24.7° (*c* 0.99, 95% ethanol).[24]

Anal. Calcd. for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.13; 1 OCH_3, 11.35; mol. wt., 273. Found: C, 70.07; H, 7.27; N, 4.92 (Dumas), 4.98 (perchloric acid titration); OCH_3, 11.53; NCH_3, 0.00; C-CH_3, 0.00; mol. wt., 282 (Rast).

The ultraviolet absorption spectrum (ethanol) showed a maximum at 287 mμ (log ε 3.38).

O,N-Diacetylnarcissamine.—The derivative was prepared by allowing 0.100 g. of narcissamine to stand overnight in a mixture of 1 ml. of pyridine and 0.5 ml. of acetic anhydride. Water and sodium bicarbonate were added, and the precipitate was collected and dried, 0.090 g. (69%), m.p. 208–209°. A sample was recrystallized from benzene–cyclohexane, m.p. 208–209°, $[\alpha]^{22}D$ +19.3°, $[\alpha]^{22}_{436}$ +44.2° (*c* 0.62, chloroform).

Anal. Calcd. for $C_{20}H_{23}NO_5$: C, 67.21; H, 6.49; N, 3.92; CH_3CO, 24.09. Found: C, 67.11; H, 6.42; N, 4.01; CH_3CO, 23.89.

The infrared spectrum showed absorption at 5.78 and 6.12 μ.

N-Methylnarcissamine Methiodide (Galanthamine Methiodide).—A solution of 50 mg. of narcissamine in ethyl acetate was treated with excess methyl iodide. The precipitate was removed by filtration and recrystallized twice from ethanol, 15 mg., m.p. 279–282° dec., $[\alpha]^{22}D$ −93.2, $[\alpha]^{22}_{436}$ −196° (*c* 0.68, 75% ethanol). A mixture melting point determination with galanthamine methiodide was not depressed. The infrared absorption spectrum (KBr) was identical with that of galanthamine methiodide.

Anal. Calcd. for $C_{17}H_{21}NO_3 \cdot CH_3I$: C, 50.36; H, 5.63. Found: C, 50.43; H, 5.66.

Methylpseudolycorine (IIa).—(a) This compound was obtained in very low yield as a chloroform-insoluble precipitate from the final ethanol–chloroform eluates of the alumina column mentioned in (a). Trituration with chloroform caused the product to crystallize in dark yellow clusters that were slightly soluble in cold water and very soluble in chloroform–ethanol mixtures. Recrystallization from ethanol or *n*-butyl alcohol gave a poor recovery of colorless prisms, m.p. 228–233° dec. The compound could be sublimed unchanged at 160° (1 μ), m.p. 234–242° dec., $[\alpha]^{26}D$ −40° (*c* 0.21, dimethylformamide).

Anal. Calcd. for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62; 2 OCH_3, 20.46. Found: C, 67.36; H, 6.90; N, 4.42; OCH_3, 20.67; NCH_3, 0.00; glycol, 0.70 mole (periodate).

The alkaloid gave no reaction with a mixture of sulfuric and chromotropic acids or with sulfuric acid alone. An infrared absorption peak at 10.7 μ, characteristic of the methylenedioxy group, was absent. The ultraviolet absorption spectrum (ethanol) showed a maximum at 285 mμ (log ε 3.58).

(b) A solution of 10 mg. of pseudolycorine in 10 ml. of methanol was treated with an ethereal solution of diazomethane prepared from 2 g. of N-nitrosomethylguanidine. The mixture was allowed to stand two hours and then was evaporated under a current of nitrogen. The crystalline product, m.p. 225–230° dec., was judged impure on the basis of its infrared curve. The mixture was washed with dilute alkali and water and finally sublimed at 150° (< 1 μ to give 2 mg. of a product, m.p. 223–228° dec., that did not depress the m.p. of IIa and had an infrared spectrum (KBr) identical with that of IIa.

Methylpseudolycorine perchlorate was prepared by the addition of 70% perchloric acid to a solution of the free base in ethanol–ether. Recrystallization from the same solvent mixture gave a sample that sintered at 180° and decomposed extensively at 230°.

Anal. Calcd. for $C_{17}H_{21}NO_4 \cdot HClO_4$: C, 50.56; H, 5.49; N, 3.47. Found: C, 50.50; H, 5.61; N, 3.63.

The infrared absorption spectrum of the salt in a Nujol mull showed no intense absorption in the 6.0 μ region. The ultraviolet absorption spectrum showed maxima at 235 mμ (log ε 3.87) and 283 mμ (log ε 3.59).

Diacetylmethylpseudolycorine was prepared by allowing 25 mg. of the base to dissolve overnight at room temperature in a mixture of two drops of acetic anhydride and four drops of pyridine. The reaction mixture was decomposed with water and dilute potassium carbonate solution and was extracted with chloroform. The extracts were dried over anhydrous sodium sulfate and evaporated in a current of nitrogen. The basic product (15 mg., 47%) was recrystallized from benzene–cyclohexane, m.p. 174–175°, and finally sublimed at 140° (5 μ).

Anal. Calcd. for $C_{21}H_{25}NO_6$: CH_3CO, 22.22. Found: CH_3CO, 20.94.

A qualitative ultraviolet absorption spectrum showed a maximum at 285 mμ. The infrared spectrum exhibited a broad band at 5.75 μ but none at 6.0–6.3 μ.

Dihydromethylpseudolycorine was formed when 33.7 mg. of the parent base absorbed one equivalent of hydrogen over 50 mg. of pre-reduced platinum oxide in 15 ml. of glacial acetic acid. The excess acetic acid was removed from the filtered product in a stream of nitrogen. Aqueous alkali was added to the residue, and the dihydro derivative crystallized, 29 mg., 85%, m.p. 190–198°. A sample was recrystallized from aqueous ethanol and sublimed at 130° (1 μ), m.p. 192–196°, $[\alpha]^{25}D$ −65° (*c* 0.22, dimethylformamide).

Anal. Calcd. for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59. Found: C, 66.92; H, 7.66; N, 5.03.

The ultraviolet absorption spectrum (ethanol) showed a maximum at 283 mμ (log ε 3.55). In 0.01 *N* ethanolic hydrochloric acid, maxima appeared at 235 mμ (log ε 3.89) and 283 mμ (log ε 3.53).

Anhydromethylpseudolycorine (IIIa).—(a) The fluorescent oil which was eluted from the column deposited diamond-shaped crystals from ethanol. The material could be recrystallized from ethanol with little air oxidation. However, it was transformed to the phenanthridone IVa when allowed to stand in thin films even at room temperature.

(23) The melting at 211–213° occurs with some decomposition, and it is likely that the recrystallization and final m.p. at 280° would be overlooked unless the observations were made using a microscope hot-stage.

(24) The rotation reported by Boit[2] was $[\alpha]^{22}D \pm 0°$ (*c* 0.25, chloroform). It is quite likely that the observed rotation of our material would be negligible at that concentration.

The material sintered below 100° and at 145° was transformed almost completely to the crystalline phenanthridone (IVa) which then remelted at 260–270° dec.

Anal. Calcd. for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.54; H, 6.41; N, 5.30.

(b) The same material (IIIa) was obtained when 10 mg. of pure methylpseudolycorine (IIa) was evaporated to dryness with several drops of dilute sodium hydroxide, then heated to 150–200° at 1 mm. The anhydro base (2 mg.) was sublimed and was found to have the same infrared spectrum in chloroform and ultraviolet spectrum in ethanol as synthetic IIIa. Its action on melting was the same as that of IIIa, and a small sample was converted on the hot-stage to the phenanthridone IVa which showed the same ultraviolet spectrum in ethanol as did synthetic IVa.

(c) Synthetic phenanthridone IVa (0.839 g.) was extracted over 24 hours from the thimble of a Soxhlet apparatus into a suspension of 2 g. of lithium aluminum hydride in 20 ml. of tetrahydrofuran. The fluorescent suspension which resulted was decomposed with ethyl acetate and treated with hydrochloric acid. Air was passed into the suspension in an effort to convert the product to the more stable phenanthridinium chloride, but the hydrochloride which resulted (0.554 g., 69%) proved to be the unchanged dihydrophenanthridinium salt. The dihydrophenanthridine IIIa precipitated when a solution of the salt was neutralized with ethanolic ammonia. A sample was recrystallized from ethanol, m.p. 145°, 270° as above. The infrared and ultraviolet spectra were identical with those of IIIa obtained from natural sources.

The picrate of IIIa was prepared in ethanol, recrystallized from dimethylformamide, and digested with ethanol; m.p. 234–252° dec.

Anal. Calcd. for $C_{17}H_{17}NO_2 \cdot C_6H_3N_3O_7$: C, 55.64; H, 4.06; N, 11.29. Found: C, 55.56; H, 3.99; N, 11.21.

1-(6′-Nitroveratroyl)-2,3-dihydroindole (V).—A solution of 6-nitroveratroyl chloride was prepared by refluxing 31 g. of 6-nitroveratric acid and 25 ml. of oxalyl chloride in 100 ml. of benzene for two hours. The solvents were removed under reduced pressure, and the crystalline acid chloride was treated directly with a chilled solution of 15 g. of 2,3-dihydroindole in 40 ml. of pyridine. The suspension was warmed on a steam-bath after the initial reaction had subsided and finally was digested with methanol and filtered. A total of 36.7 g. (82% based on the acid) of yellow amide was obtained. One recrystallization from ethanol produced analytically pure material, m.p. 180–183°.

Anal. Calcd. for $C_{17}H_{16}N_2O_5$: C, 62.19; H, 4.91. Found: C, 62.50; H, 4.66.

1-(6′-Aminoveratroyl)-2,3-dihydroindole.—A suspension of 36 g. of V in 75 ml. of 50% ethanol–ethyl acetate was shaken in an atmosphere of hydrogen with 1 g. of 10% palladium-on-charcoal. The solution absorbed three moles of hydrogen when heated to 50–60°. The catalyst was removed by filtration, and the product crystallized on cooling. One recrystallization from ethanol gave 30 g. (92%) of colorless plates. A sample was sublimed at 120° (1 μ) for analysis, m.p. 157–158°.

Anal. Calcd. for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08. Found: C, 68.43; H, 6.03.

4,5-Dihydro-9,10-dimethoxypyrrolo[de]-7-phenanthridone (IVa).—(a) A suspension of 4.647 g. of 1-(6′-aminoveratroyl)-2,3-dihydroindole in 10 ml. of 12 *N* hydrochloric acid was treated with a slight excess of nitrous acid during vigorous agitation at 0°. The solution afforded a red, positive diazo reaction with alkaline β-naphthol. Copper metal (0.1 g.) was added, and the mixture was warmed on a steam-bath until evolution of nitrogen ceased. A precipitate formed and was extracted from the acidic mixture by chloroform. Evaporation of the chloroform left a brown solid which was triturated with benzene and filtered. The precipitate remaining (0.841 g., 4.4%) was recrystallized from chloroform–ethanol as long prisms. A sample was sublimed at 150° (5 μ) for analysis, m.p. 272–274°.

(b) A solution of 10 mg. of anhydromethylpseudolycorine (from natural sources) was evaporated in a sublimation tube and heated to 180° with free access to air. The mass then was sublimed at 150° (5 μ) as above, m.p. 272–274° alone or when mixed with the synthetic product. The two samples possessed identical ultraviolet spectra in ethanol and infrared spectra both in chloroform solution and as Nujol mulls.

Anal. Calcd. for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.65; H, 5.53; N, 4.84.

The benzene filtrates from the synthetic lactam were chromatographed over aluminum oxide (Merck). Elution with benzene furnished 2.60 g. (59%) of a neutral amide which was presumed to be **1-veratroylindole**, m.p. 105–106° from cyclohexane.

Anal. Calcd. for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37. Found: C, 72.43; H, 5.21.

4,5-Dihydro-9,10-dimethoxy-2-hydroxypyrrolo[de]phenanthridinium Chloride (VIa).—A solution of 30 mg. of methylpseudolycorine and 22 mg. of selenium dioxide in 5 ml. of ethanol was warmed gently on a steam-bath for one hour. The precipitated selenium metal was removed by centrifugation, and the yellow solution was concentrated under an air jet. Dilute hydrochloric acid was added to the residue, and an additional quantity of selenium metal was removed. The hydrochloride VIa crystallized from water in long, pale-yellow, hydrated prisms, m.p. 235–240° dec. The sample was dried at 160° for 12 hours in vacuum.

Anal. Calcd. for $C_{17}H_{15}NO_3 \cdot HCl \cdot H_2O$: C, 60.80; H, 5.40; 2 OCH_3, 18.48. Found: C, 60.69; H, 5.61; OCH_3, 18.46.

Another sample was dried over phosphoric anhydride and appeared to be a hemihydrate.

Anal. Calcd. for $C_{17}H_{15}NO_3 \cdot HCl \cdot {}^1/_2H_2O$: C, 62.48; H, 5.25; N, 4.29. Found: C, 62.84; H, 5.48; N, 4.38.

The free betaine (VIIa) precipitated as yellow prisms when the hydrochloride was treated with aqueous ammonia. Upon exhaustive drying the material became red, but when moist air was admitted the sample regained its original yellow hue. This phenomenon has been observed also with VIIb. Analysis indicated VIIa to be approximately a trihydrate, m.p. 225–232° dec.

Anal. Calcd. for $C_{17}H_{15}NO_3 \cdot 3H_2O$: C, 60.88; H, 6.31. Found: C, 60.40; H, 5.92.

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