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

Interconversions of Amaryllidaceae Alkaloids by Sodium and Amyl Alcohol[1]

BY H. M. FALES AND W. C. WILDMAN

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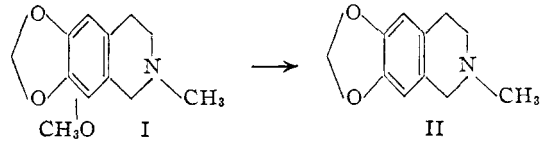
Sodium with amyl alcohol has been found effective for interrelating a number of Amaryllidaceae alkaloids. With the aid of this reagent, partial structures have been assigned to the alkaloids falcatine and narcissidine; lycorine and methylpseudolycorine have been converted to caranine and pluviine, respectively. The conversions of powelline and buphanidrine to dihydroepicrinine and buphanisine, respectively, by this reagent, have provided additional proof for the structures assigned earlier to powelline, buphanidrine and buphanisine.

Through empirical correlations in infrared spectra and by the use of certain classification reagents such as manganese dioxide,[1,2] selenium dioxide and mercuric acetate,[3-5] an Amaryllidaceae alkaloid of unknown constitution may be placed tentatively within one of the six fundamental ring systems which have been established for the family. Within each given ring system, a number of alkaloids may stem from simple variations in the type of aromatic and aliphatic ring substitution.[1,4-8] Since many of these alkaloids are obtainable only in quantities insufficient for detailed degradative study, chemical methods which would permit the conversion of a scarce alkaloid to an alkaloid of proven structure would be of great value. We have found that the action of sodium and amyl alcohol on certain alkaloids of the family is most useful in this respect. This paper reports our observations concerning the effect of this reagent on a number of alkaloids at our disposal.

The methylenedioxy and methylenedioxymethoxy groups constitute two of the most prevalent types of aromatic substitution within the family. These two types of substitution may be recognized by differences in the ultraviolet absorption spectra and by the presence of an intense, sharp band at 6.2μ in the infrared spectra of alkaloids containing the methylenedioxymethoxyphenyl function.[9] It has been our observation that alkaloids with the latter type of substitution give a deep violet color in concentrated sulfuric acid while colors no deeper than orange result from alkaloids containing the methylenedioxyphenyl group.

The alkaloid derivatives hydrocotarnine (I) and hydrohydrastinine (II) may be cited as simple examples of these types of substitution. The conversion of hydrocotarnine to hydrohydrastinine was reported first by Pyman and Remfry.[10] Nearly fifty years later this conversion was reexamined by Clayson[11] who obtained a 60% yield of II by the addition of isoamyl alcohol to powdered sodium suspended in a xylene solution of I under reflux. Degradative work in our laboratory had indicated that a similar relationship existed in the aromatic substitution of the alkaloids powelline (III, R = OCH_3) and crinine (III, R = H).[1,7] Powelline contains the functional groups of crinine



and, in addition, one methoxyl group which was placed in the aromatic ring for the spectral reasons mentioned earlier. Since the formation of crinine by the *ar*-demethoxylation of powelline would constitute additional chemical proof of the structure of powelline, it seemed desirable to study the effect of sodium and isoamyl alcohol on powelline. The infrared spectrum of the crude reaction mixture indicated that *ar*-demethoxylation was essentially complete, since only weak absorption was observed at 6.2 μ. However, chromatography of the mixture on alumina afforded no crinine. The most strongly adsorbed substance was identified as dihydroepicrinine (IV).[1] Preceding this material, two isomeric, non-crystalline substances (V) of molecular formula $C_{16}H_{17}NO_2$ were eluted. Each of these isomers gave (−)-crinane upon the absorption of one equivalent of hydrogen under catalytic conditions. The nature of these products is chemical evidence that (a) powelline is derived from 5,10b-ethanophenanthridine, the ring system of crinine, (b) the methylenedioxy group of powelline is in the 8,9-position as in crinine, and (c) the hydroxyl group of powelline is in position 3 as in crinine. The reaction products can be explained readily only on the basis of structure III (R = OCH_3) for powelline.

The isomeric desoxycrinines Va and Vb may be derived from the hydrogenolysis of the allylic 3-hydroxyl group. The formation of the intermediate radical (IX, R = OCH_3 or H), followed by reduction of the resonance hybrid would explain the formation of two isomers. Such a mechanism is supported by the observation that dihydroepicrinine is the sole product of the action of sodium and isoamyl alcohol on dihydroepipowelline (VIII).

The formation of dihydroepicrinine may occur by one of two paths. The reaction may proceed

(1) Paper XII in a series on the alkaloids of the Amaryllidaceae; previous paper, W. C. Wildman, THIS JOURNAL, **80**, 2567 (1958).

(2) R. J. Highet and W. C. Wildman, *ibid.*, **77**, 4399 (1955).

(3) H. M. Fales, E. W. Warnhoff and W. C. Wildman, *ibid.*, **77**, 5885 (1955).

(4) H. M. Fales, Laura D. Giuffrida and W. C. Wildman, *ibid.*, **78**, 4145 (1956).

(5) H. M. Fales and W. C. Wildman, *ibid.*, **78**, 4151 (1956).

(6) Carol K. Briggs, Patricia F. Highet, R. J. Highet and W. C. Wildman, *ibid.*, **78**, 2899 (1956).

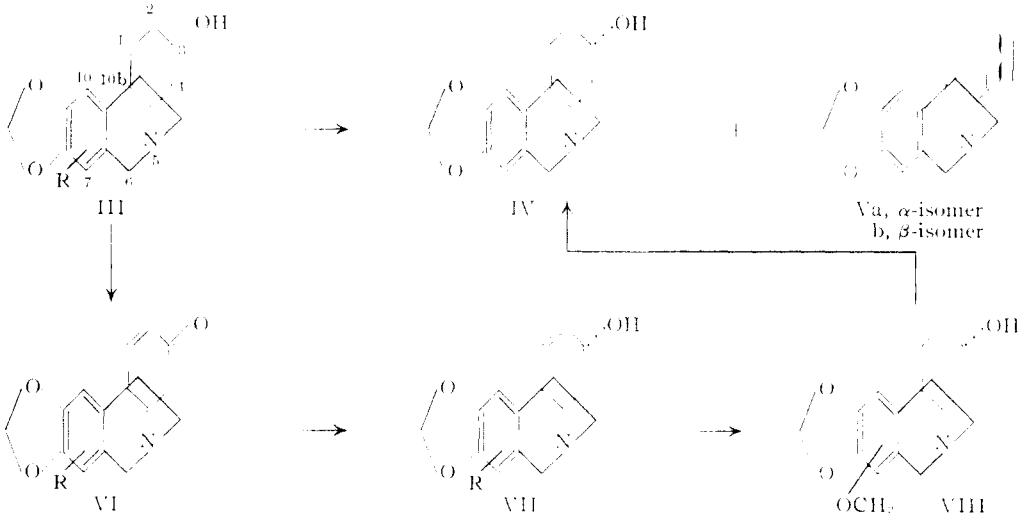
(7) W. C. Wildman, *Chemistry & Industry*, 1090 (1956).

(8) H.-G. Boit, H. Ehmke, S. Uyeo and H. Yajima, *Chem. Ber.*, **90**, 363 (1957).

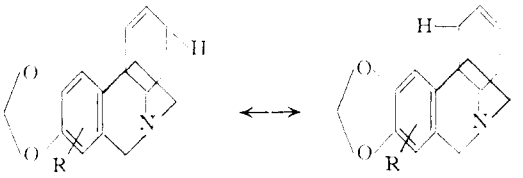
(9) W. C. Wildman and Carol J. Kaufman, THIS JOURNAL, **77**, 4807 (1955).

(10) F. L. Pyman and F. G. P. Remfry, *J. Chem. Soc.*, 1595 (1912).

(11) D. B. Clayson, *ibid.*, 2016 (1949).

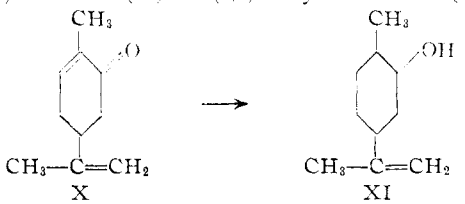


through VI, formed by the action of some carbonyl contaminant or other hydrogen acceptor upon III in the basic reaction medium.[12] Reduction of VI to the corresponding saturated ketone, followed by the reduction of the 3-carbonyl group would be expected to lead to that alcohol which is thermodynamically most stable.[13] From the observation[1]



IX

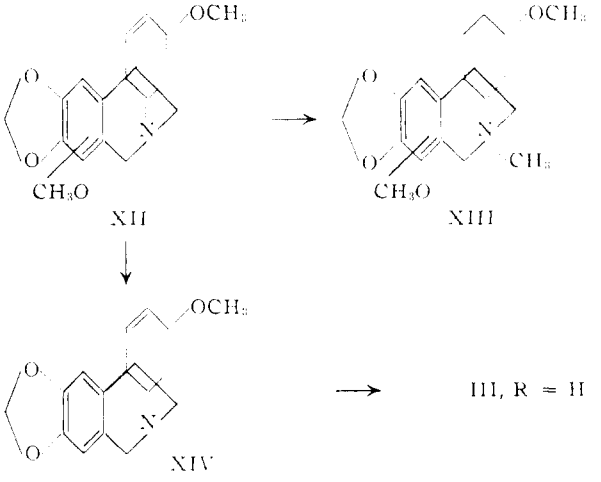
that oxopowelline (VI, R = OCH_3) and oxocrinine (VI, R = H) are reduced by lithium aluminum hydride or sodium borohydride to epipowelline (VII, R = OCH_3) and epicrinine (VII, R = H), respectively, it is likely that the hydroxyl groups of the epi series are the more stable and presumably of equatorial conformation. The latter phases of this mechanism have precedent in the conversion of (+)-carvone (X) to (+)-dihydrocarveol (XI).[14]



X XI

The demethoxylation of the aromatic ring occurs during these transformations, but there is no evidence to indicate whether it precedes, follows or is simultaneous with the reactions of ring C.[15]

Buphanidrine, an alkaloid closely related to powelline, was isolated first from the bulbs of *Boöphone fischeri* Baker in non-crystalline form by Renz, Stauffacher and Seebeck.[17] Subsequently, it was isolated in our laboratories as a crystalline solid, m.p. 88–89°, from an unidentified *Brunsvigia* species of South African origin and from an *Amaryllis* hybrid ($^3/_4$ *A. bella-donna* L. × $^1/_4$ *Brunsvigia gigantea* Heist.). The alkaloid has been assigned the structure XII from a consideration of its molecular formula, $C_{15}H_{13}N(O_2CH_2)(OCH_3)_2$, and from its conversion to powelline by mild acid hydrolysis.[1,7] The possibility that this hydrolysis was accompanied by allylic rearrangement has been minimized by the discovery that catalytic hydrogenation of dihydrobuphanidrine methine affords an optically inactive product (XIII).[18] Simple *ar*-demethoxylation occurred when buphanidrine was treated with sodium and isoamyl alcohol. The reaction mixture yielded a small amount of unreacted buphanidrine and a crystalline base, $C_{15}H_{14}N(O_2CH_2)(OCH_3)$, m.p. 123–124°. This material was found to be identical in all respects with buphanisine, a companion alkaloid of buphanidrine



(12) *Cf.* the necessity for trace amounts of carbonyl component in the equilibration of alcohols; W. E. Doering and T. C. Aschner, THIS JOURNAL, **71**, 838 (1949).

(13) (a) D. H. R. Barton, *Experientia*, **6**, 316 (1950); (b) G. Vavon, *Bull. soc. chim. (France)*, [4] **49**, 937 (1931).

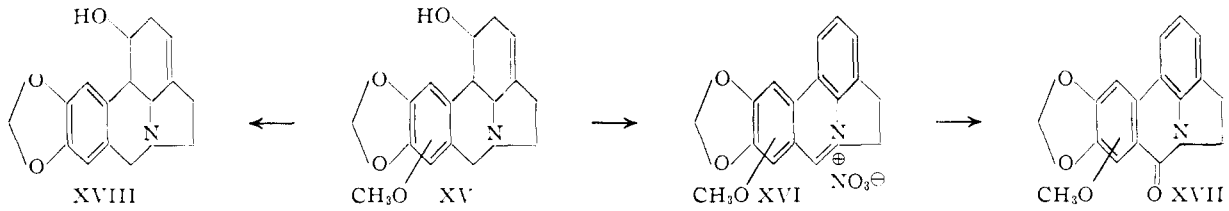
(14) R. G. Johnson and J. Read, *J. Chem. Soc.*, 233 (1934).

(15) Determination of the position of the methoxyl group in the aromatic ring is under investigation in these laboratories. It is of interest to note that the biogenetic proposals of Barton and Cohen[16] require the methoxyl group to be in the 10-position. *Cf.* E. W. Warnhoff, *Chemistry & Industry*, 1385 (1957).

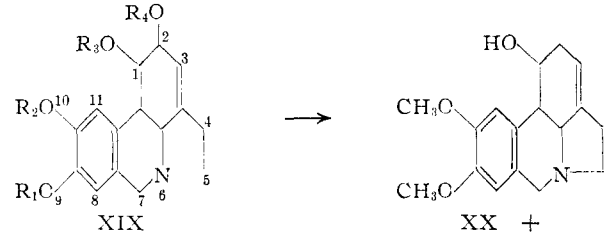
(16) D. H. R. Barton and T. Cohen, "Festschrift Arthur Stoll," Birkhäuser, Basel, 1957, p. 117.

(17) J. Renz, D. Stauffacher and E. Seebeck, *Helv. Chim. Acta*, **38**, 1209 (1955).

(18) E. W. Warnhoff, private communication.

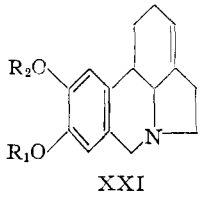


XVIII XV CH$_3$O XVI $NO_3^\ominus$ CH$_3$O O XVII



XIX XX +

a, $R_1,R_2 = >CH_2$; $R_3,R_4 = H$
b, $R_1,R_2 = CH_3$; $R_3,R_4 = H$
c, $R_1,R_2,R_4 = CH_3$; $R_3 = H$



XXI

in *B. fischeri* Baker. That aromatic demethoxylation occurred in this transformation was evident from the infrared and ultraviolet spectra of the product and the observation that buphanisine was converted by mild acid hydrolysis to the alkaloid crinine (III, R = H). Therefore, buphanisine could be assigned the structure XIV with certainty.

In a previous paper, the isolation and characterization of falcatine was reported.[9] This alkaloid is isomeric with powelline. It possesses one hydroxyl group and one double bond. The aromatic ring contains both a methylenedioxy and a methoxy group. However, degradative evidence showed clearly that falcatine did not possess the same basic ring system as powelline. Oxidation with selenium dioxide afforded a phenanthridinium nitrate (XVI) which could be oxidized by potassium ferricyanide to the phenanthridone (XVII). Analytical data and spectral comparisons of XVI and XVII with compounds of analogous structure derived from lycorine[19] and methylpseudolycorine[4,8] supported this assignment of the pyrrolo[de]-phenanthridine ring system to falcatine. With this preliminary evidence for the basic ring system of falcatine, it seemed possible that the alkaloid was *ar*-methoxycaranine. Inferences of this relationship had been derived from the similarities in the infrared spectra, the comparable rotations of the two alkaloids, and the observation that falcatine and caranine occur together in *Nerine falcata* and *N. laticoma*. Chemically, both alkaloids were found to decompose gradually in the presence of light and air; neither was oxidized by manganese dioxide. Since the limited quantities of falcatine at our disposal precluded extensive classical degradations, falcatine was treated with sodium and isoamyl alcohol in the expectation that, if XV represented the alkaloid, caranine (XVIII)[20] would be produced. The fact that caranine was isolated from the reaction mixture is convincing evidence that falcatine is represented correctly as XV.[21]

In order to examine the scope of this reaction, we undertook a study of the action of sodium and amyl alcohol on the more accessible disubstituted alkaloids, lycorine[22] and galanthine.[5] With these alkaloids, chunks of sodium were added to a boiling solution or suspension of the alkaloid in *n*-amyl alcohol.[23] No useful reaction products resulted from the action of this reagent on the dihydro derivatives of the alkaloids; dihydrolycorine and dihydronarcissidine were recovered from the reaction mixtures in 79 and 81% yields, respectively.

Lycorine (XIXa) or its O,O-diacetyl derivative and galanthine (XIXc)[24] each afforded two major crystalline products. Galanthine gave a demethoxygalanthine, $C_{17}H_{21}NO_3$, which was identical with pluviine (XX),[8] and a base, $C_{17}H_{21}NO_2$, which possessed no aliphatic oxygen-containing substituents. Completely analogous compounds were isolated from the action of sodium and *n*-amyl alcohol on lycorine or O,O-diacetyllycorine. The more highly oxygenated product, $C_{16}H_{17}NO_3$, was identified as caranine (XVIII) and both oxygen atoms of the second product, $C_{16}H_{17}NO_2$, were present as a methylenedioxy group. Pluviine and caranine may be formed, in part, from a direct hydrogenolysis of the respective allylic methoxyl or hydroxyl group of the starting alkaloid. Such an explanation has ample precedent in the chemical literature.

We propose that the second pair of products, $C_{16}H_{17}NO_2$ from lycorine and $C_{17}H_{21}NO_2$ from galanthine, is represented by XXIa and XXIb, respectively. Such structures may be considered to be derived from the basic ring systems lycorane (XXIVa) and methylpseudolycorane (XXIVb) by the

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

(20) E. W. Warnhoff and W. C. Wildman, THIS JOURNAL, **79**, 2192 (1957).

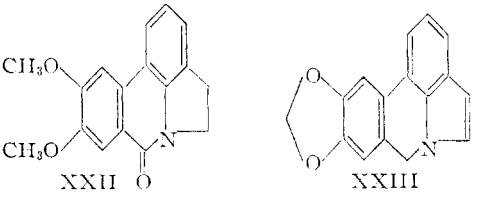
(21) The synthesis of XVI or XVII by the methods used in preparation of their dimethoxy or methylenedioxy analogs has not been undertaken because of the relative inaccessibility of the requisite 3,4-methylenedioxy-2-(or 5-)-methoxy-6-nitrobenzoic acid. Such a synthesis of either of the two phenanthridones represented by XVII would prove the position of the methoxyl group in falcatine. The fact that caranine and dihydrocaranine are oxidized by the Oppenauer method,[20] while falcatine is recovered in 96% yield under the same reaction conditions suggests that the latter oxidation is prevented by steric hindrance caused by an 11-methoxyl group.

(22) 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, *J. Chem. Soc.*, 4622 (1954).

(23) The Clayson technique (addition of isoamyl alcohol to a suspension of powdered sodium in a refluxing xylene solution of the alkaloid) was found to be rather rigorous treatment for alkaloids of the lycorine group. Cleavage of the methylenedioxy group and aromatization of ring C occurred to such an extent that the yields of useful degradation products were almost nil. Conversely, addition of sodium to a boiling *n*-amyl alcohol solution of an alkaloid containing the methylenedioxymethoxyphenyl group was not vigorous enough to effect *ar*-demethoxylation in good yield.

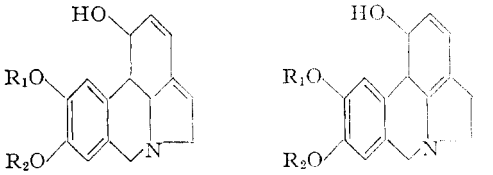
(24) Structure XIXc was assigned to galanthine from evidence presented in ref. 5. Additional proof for this structure has been found in the acid hydrolysis of galanthine to methylpseudolycorine (XIXb).

loss of two hydrogen atoms in ring C. For the sake of convenience, we have adopted the trivial names lycorene and methylpseudolycorene for these compounds. These structures are based on the following evidence. The basic ring systems, including the pattern of aromatic substitution, are those of the original alkaloids, since XXIb was converted to the known phenanthridone (XXII)[4,8] when heated above its melting point in air, and XXIa was dehydrogenated to the indole (XXIII)[19] by palladium-on-charcoal in *p*-cymene. From this information and the molecular formulas, it is evident that each base must contain one aliphatic double bond; this was verified by catalytic hydrogenation. The reduction of XXIa gave α-lycorane (XXIVa) which has been prepared recently by Takeda, Kotera and Mizukami[25] by another route. The unsaturation of XXIa and XXIb is assigned the 3,3a-position from the observation that neither compound shows any ultraviolet absorption characteristic of a styrene. Nor do the amine hydro-salts exhibit any new bands in the 6 μ region attributable to the $>C=C-\ddot{N}<$ $\rightarrow$ $>C-\overset{+}{C}=N<$ transformation.[26] It has been our observation that the infrared spectra of alkaloids of the Amaryllidaceae which contain the functional group RCH=CHR′ (crinine, powelline, buphanidrine, buphanisine and buphanamine) show well-defined carbon–hydrogen stretching bands at 3.30 μ at high concentrations in carbon tetrachloride. These bands are not present in the corresponding dihydro derivatives.[27] Neither XXIa nor XXIb (nor lycorine diacetate, galanthine, methylpseudolycorine, falcatine, narcissidine and caranine) shows such a band, thus indicating the probable absence of 1,2-, 2,3- or 4,5-unsaturation in these compounds. Of the remaining possible positions for the unsaturation, 3,3a and 3a,4, the latter is less likely since XXIa was recovered unchanged after treatment with boiling hydrochloric acid.[28]



XXIVa, $R_1,R_2 = >CH_2$
b, $R_1,R_2 = CH_3$

The structure of a third product, $C_{17}H_{19}NO_3$, which was isolated in minute yield from the action of sodium and *n*-amyl alcohol on galanthine has provided a plausible mechanism for the formation of XVIII and XXIa from lycorine and the analogous compounds XX and XXIb from galanthine. The same material had been isolated, again in low yield, from an earlier, unsuccessful attempt to oxidize galanthine in the presence of potassium *t*-butoxide and fluorenone. The fact that this substance was obtained from galanthine in the presence of both basic oxidizing and reducing reagents suggested that base was the reagent necessary for its formation. The correctness of this deduction was shown by the observation that galanthine, when treated with an excess of potassium *t*-amyl oxide in *t*-amyl alcohol at 100°, gave this substance in high yield. Subsequent experiments showed that lycorine or O,O-diacetyllycorine under the same conditions afforded an analogous compound, $C_{16}H_{15}NO_3$. These products, $C_{17}H_{19}NO_3$ obtained from galanthine and $C_{16}H_{15}NO_3$ derived from lycorine, have been given the trivial names dehydromethylpseudolycorine and dehydrolycorine and may be assigned the structures XXVb and XXVa, respectively, from the following facts. Both compounds showed hydroxyl absorption in the infrared at 2.88 μ (Nujol), and a normal O-acetyl derivative (λ 5.75 μ) was obtained from XXVa. Both bases formed normal methosalts, and XXVa formed a hydroperchlorate which exhibited no bands in the 6.0 μ region, characteristic of the $>C=\overset{+}{N}-$bond. Both XXVa and XXVb rapidly absorbed one mole of hydrogen over palladium-on-charcoal to afford caranine (XVIII) and pluviine (XX), respectively. The isolation of these products provided chemical proof that dehydrolycorine and dehydromethylpseudolycorine contain the caranine and pluviine nuclei, respectively, less two atoms of hydrogen. Characteristic of conjugated dienes, both XXVa and XXVb showed strong absorption maxima at 230 mμ when the appropriate aromatic chromophores were subtracted from the observed spectra.



XXVa, $R_1,R_2 = >CH_2$
b, $R_1,R_2 = CH_3$

XXVI

The alternative structures XXVIa and XXVIb can be eliminated on the basis of the wave length of these ultraviolet maxima and the fact that the position of these maxima did not shift more than 1 mμ in acid solution. Furthermore, a compound of the structure XXVIa or XXVIb would be expected to dehydrate readily under the conditions employed in its formation.[29] Although XXVb was recovered in 73% yield when treated with methanolic hydrochloric acid, under more stringent conditions (warm phosphorus oxychloride), it was possible to convert XXVb to an anhydro base (XXII, no O at C_7).[5]

Most convincing evidence that XXVa and XXVb are intermediates in the formation of XVIII and

(25) K. Takeda, K. Kotera and S. Mizukami, THIS JOURNAL, **80**, 2562 (1958).

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

(27) W. H. Tallent and I. J. Siewers, *Anal. Chem.*, **28**, 953 (1956).

(28) H. C. Brown, J. H. Brewster and H. Schechter, THIS JOURNAL, **76**, 467 (1954).

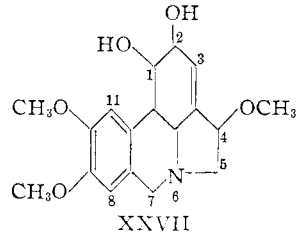
(29) *Cf.* the conversion of lycorine methohydroxide to anhydrolycorine methosalts.[22]

XXIa from lycorine and XX and XXIb from galanthine was obtained in the following manner. A solution of XXVb was treated with sodium and *n*-amyl alcohol under the same conditions initially employed for galanthine itself, and the same products, XX and XXIb, were obtained. Under similar conditions, XXVa gave caranine (XVIII) and XXIa. The formation of XXVa and XXVb probably takes place through a simple 1,4-elimination of alkoxyl, acetoxyl or even hydroxyl by the strong base. Conversion of these substances to caranine and pluviine would result from 1,4-reduction of the conjugated diene system, while in the formation of XXIa and XXIb, hydrogenolysis of the 1-hydroxyl group occurs prior to 1,4-reduction of the diene. Simple hydrogenolysis of XIXa and XIXc probably occurs simultaneously with this reaction path since XXVa reacts with sodium and *n*-amyl alcohol to afford a mixture of XVIII and XXIa having a higher ratio of the latter to the former than does the mixture obtained directly from lycorine. It is important to note that this over-all reaction mechanism involves no optically active centers except those subsequently converted to methylene carbon atoms. Since dihydrolycorine and dihydrocaranine have been shown to have the same stereochemistry at C_1, C_{3a}, C_{11b} and C_{11c},[30] any alternative mechanism would be required to neither invert nor racemize these centers.

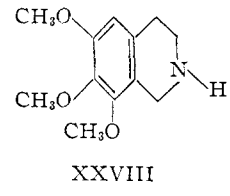
The foregoing products and principles have enabled us to come to a conclusion concerning the structure of narcissidine. The alkaloid narcissidine was isolated first from the bulbs of *Narcissus poeticus* L.[31] Subsequent isolations[32,33] have shown that the base is present in many *Narcissus species*. In our laboratory, it has been isolated in 0.015% yield from *Hymenocallis amancaes* (Ruiz and Pavon) Nichols. Boit and Stender[31] showed that the alkaloid possesses the expanded molecular formula $C_{15}H_{12}N(OCH_3)_3(OH)_2$ and contains one reducible double bond. Preliminary tests by these workers showed that it was not affected by diazomethane, hydroxylamine, dilute acid or dilute base. We have confirmed these results and have determined by periodate titration that the hydroxyl groups of dihydronarcissidine are vicinal.

A considerable amount of rather speculative evidence was available to indicate that narcissidine was an alkaloid of the pyrrolo[de]phenanthridine (lycorine) type, yet valid chemical proof of the ring system was difficult to obtain. The infrared spectrum of narcissidine showed many bands in common with methylpseudolycorine (XIXb) and, like many alkaloids of the same basic ring system, it gradually turned yellow in the presence of air and light. However, the Hofmann and Emde reactions were unsuccessful under conditions by which lycorine gave anhydro compounds. Like methylpseudolycorine and galanthine, narcissidine was oxidized by both selenium dioxide and mercuric acetate, but the initially yellow oxidation products darkened rapidly and no useful products could be recovered from the black reaction mixture. However, O,O-diacetyldihydronarcissidine was oxidized in good yield by potassium permanganate to a neutral, conjugated lactam. This type of reaction is characteristic of alkaloids derived from pyrrolo[de]phenanthridine and does not occur with alkaloids containing the 5,10b-ethanophenanthridine ring system (*e. g.*, crinine).

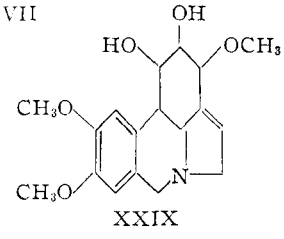
In view of these rather unpromising results, narcissidine was treated with sodium and *n*-amyl alcohol in the hope that more useful degradation products could be obtained. From the structures of the reaction products, all of which were known from earlier work, it has been possible to assign tentatively the structure XXVII to narcissidine. The reaction products were pluviine (XX), XXIb and XXVb. The isolation of these products made it certain that narcissidine contains the 9,10-dimethoxypyrrolo[de]phenanthridine nucleus and that one hydroxyl group of the alkaloid is located in the 1-position. Since the hydroxyl groups of dihydronarcissidine (and, therefore, of narcissidine also) are vicinal, the second hydroxyl must be located in position 2 or 11b. The latter position is not likely since narcissidine is stable toward acid and catalytic hydrogenolysis and forms a diacetyl derivative with ease. The position of the third methoxyl group is ambiguous, since the preceding experiments indicate that either aliphatic or aromatic methoxyl groups may be removed by sodium and amyl alcohol.



XXVII



XXVIII



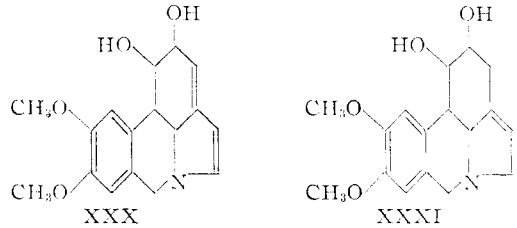
XXIX

Although the ultraviolet spectrum of narcissidine is identical with that of methylpseudolycorine (XIXb), the difference between the spectra of these alkaloids and that of anhalinine (XXVIII) is quite small. To determine the type of aromatic substitution, narcissidine was oxidized by potassium permanganate. The isolation of *m*-hemipinic acid from this oxidation proves that the aromatic ring of the alkaloid is substituted by methoxyl groups only in the 9- and 10-positions. From the foregoing data, it may be concluded that the two aromatic methoxyls and the two hydroxyl groups of narcissidine are in the same positions as in methylpseudolycorine (XIXb).

The only remaining problem in the structural determination of narcissidine is the placement of the double bond and the aliphatic methoxyl group. The positions of these two functions are mutually

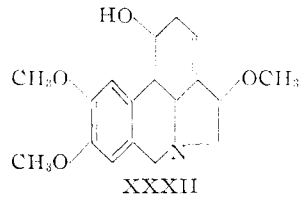
(30) K. Takeda and K. Kotera, *Pharm. Bull.*, **5**, 234 (1957).
(31) H.-G. Boit and W. Stender, *Chem. Ber.*, **87**, 624 (1954).
(32) H.-G. Boit, W. Döpke and Anita Beitner, *ibid.*, **90**, 2197 (1957).
(33) H.-G. Boit and H. Ehmke, *ibid.*, **89**, 163 (1956).

dependent. The ultraviolet spectrum of narcissidine and the infrared spectrum of O,O-diacetylnarcissidine hydroperchlorate show that the double bond is neither conjugated with the aromatic ring nor α,β to the nitrogen atom. Since narcissidine can be neither an enol (evidenced by its insolubility in alkali and the formation of a normal O,O-diacetate (λ 5.75 μ) but no reaction with hydroxylamine) nor an enol ether (shown by stability to dilute acid), only two positions, 3,3a and 3a,4, are possible for the double bond. These restrictions limit the possible structures for narcissidine to XXVII and XXIX. A choice between these two structures may be derived from considerations of the biogenesis of the alkaloid, the possible mechanisms by which XX and XXIb are formed by the action of sodium and *n*-amyl alcohol on the alkaloid, and by analogy with the structures of other alkaloids of the family containing this ring system. A double bond in position 3a,4 (as in XXIX) has not been found in any alkaloid of the lycorine type. Also, a compound of a structure such as XXIX would be expected to isomerize with dilute acid[28] to a $\Delta^{3,3a}$ structure and afford a dihydroxy ketone as a reaction product. As has been mentioned earlier, narcissidine is stable to dilute acid. From our previous studies, sodium and *n*-amyl alcohol would be expected to react with XXIX to afford either XXX or XXXI by 1,4-elimination or hydrogenolysis, respectively. Neither of these compounds is a promising intermediate for the observed formation of XX or XXIb. On the other hand, XXVII contains the double bond in the 3,3a-position which is common to the other alkaloids possessing this ring system, and such a structure



XXX

XXXI



XXXII

may be derived biogenetically from a *nor*-adrenalin-like precursor. The reaction with sodium and *n*-amyl alcohol would be expected to proceed *via* hydrogenolysis of the 2-hydroxyl group to yield XXXII. Base-catalyzed 1,4-elimination of the aliphatic methoxyl group of XXXII would afford the intermediate XXVb, which has been shown to be converted to XX and XXIb by sodium and *n*-amyl alcohol. Support for this route is provided by the actual isolation of XXVb from the reaction mixture and by the observation that narcissidine itself is stable to potassium *t*-amyl oxide, a reagent which converts galanthine to XXVb. From this reasoning, based on the existing chemical evidence, it would seem that XXVII is the most satisfactory structure for narcissidine. Other degradation methods are under investigation to confirm this proposal.

Acknowledgment.—The authors wish to thank Dr. B. G. Schubert of the Section of Plant Introduction, U. S. Department of Agriculture, for her help in obtaining the plant materials used in this study. We are indebted to Messrs. D. L. Rogerson, Jr., and J. D. Link for the isolation of the crude alkaloid mixture and to Miss Elizabeth Kielar for the isolation of several of the pure alkaloids. The skillful assistance of Miss Patricia Wagner and Mrs. L. C. Warren in the instrumental aspects of the work is acknowledged gratefully.

Experimental[34]

Isolation of Alkaloids.—Narcissidine was isolated from the *Narcissus* hybrid "Deanna Durbin" in yields comparable to those reported by Boit and Ehmke.[33] The alkaloid also was isolated from *Hymenocallis amancaes* (Ruiz and Pavon) Nichols by methods reported earlier.[4] Narcissidine, hippeastrine, lycorine and lycoramine were isolated in 0.015, 0.0015, 0.11 and 0.014% yields, respectively. The melting points and infrared spectra of the isolated alkaloids were compared with those of authentic samples, and mixture melting points gave no depression. The isolation and characterization of falcatine, lycorine, galanthine, buphanidrine and powelline have been described in previous papers of this series.

Narcissidine (XXVII).—The base crystallized from acetone as colorless prisms, m.p. 201–203° dec., $[\alpha]^{23}_{589}$ −31° (*c* 1.5); reported[31] m.p. 218–219° dec., $[\alpha]^{22}_{589}$ −32.0° (chloroform). In an evacuated capillary, narcissidine showed a m.p. 221–223° dec. The ultraviolet absorption spectrum showed an inflection at 227 mμ (log ϵ 3.96) and a maximum at 284 mμ (log 3.53).

Anal. Calcd. for $C_{18}H_{23}NO_5$: C, 64.85; H, 6.95; N, 4.20; 3 OCH_3, 27.93; neut. equiv., 333.4. Found: C, 64.63; H, 7.08; N, 4.23; OCH_3, 25.08; neut. equiv., 333.

The base was recovered in 80% yield after treatment with 6 *N* hydrochloric acid at 100° for 12 hours and in 50% yield from the action of warm phosphorus oxychloride for ten minutes. It was recovered in 80% yield from the action of lithium aluminum hydride in refluxing tetrahydrofuran overnight.

O,O-Diacetylnarcissidine hydroperchlorate was prepared from O,O-diacetylnarcissidine[31] and dilute, aqueous perchloric acid. One recrystallization from water afforded long prisms, m.p. 220–235° dec. The product exhibited absorption bands in the infrared spectrum (Nujol) at 5.72 and 5.75 μ due to the O-acetyl groups and at 6.18 and 6.26 μ due to the aromatic ring.

Anal. Calcd. for $C_{22}H_{27}NO_7 \cdot HClO_4$: C, 51.02; H, 5.45; Cl, 6.85. Found: C, 51.08; H, 5.43; Cl, 7.16.

Dihydronarcissidine.—A solution of 350 mg. of narcissidine in glacial acetic acid was hydrogenated at room temperature and atmospheric pressure in the presence of 100 mg. of prereduced platinum oxide. Slightly more than one mole of hydrogen was absorbed in 20 minutes. The solution was filtered, evaporated and basified with potassium hydroxide. The clear solution was extracted with chloroform, and the chloroform extracts were dried over sodium sulfate and evaporated. The product (280 mg., 80%) crystallized from ethyl acetate as fine, non-birefringent prisms, m.p. 158.5–160°, $[\alpha]^{28}_{589}$ −111°, $[\alpha]^{28}_{436}$ −241° (*c* 0.22, dimethylformamide).

Anal. Calcd. for $C_{18}N_{25}NO_5$: C, 64.46; H, 7.51; OCH_3, 27.76; glycol, 1.00. Found: C, 64.63; H, 7.68; OCH_3, 28.04; glycol, 0.97.

(34) All melting points were observed on a Kofler microscope hot-stage and are corrected. The boiling points are uncorrected. Unless otherwise noted, rotations were measured in chloroform solution on a Rudolph photoelectric polarimeter using a 2-dm. tube, and ultraviolet spectra were obtained in absolute ethanol solution on a Cary model 11 MS recording spectrophotometer. Infrared spectra were recorded on a Perkin–Elmer model 21 double-beam spectrophotometer, in chloroform solution unless noted to the contrary. Analyses were performed by Mr. J. F. Alicino, Metuchen, N. J.

O,O-Diacetyldihydronarcissidine.—A solution of 83 mg. of dihydronarcissidine in a mixture of 0.5 ml. of acetic anhydride and 0.5 ml. of pyridine was allowed to stand overnight. Water and potassium bicarbonate were added to the solution, and 94 mg. (90%) of fine prisms precipitated, m.p. 181–184°. Several recrystallizations from aqueous ethanol gave fine prisms, m.p. 181–183°, $[\alpha]^{24}_{589}$ −95° (*c* 0.79). The ultraviolet spectrum showed a maximum at 283 mμ (log ε 3.57) and an inflection at 227 mμ (log ε 3.94).

Anal. Calcd. for $C_{22}H_{29}NO_7$: C, 62.99; H, 6.97; $OCOCH_3$, 20.52. Found: C, 62.72; H, 7.01; $OCOCH_3$, 20.36.

O,O-Diacetyldihydronarcissidine Lactam.—A solution of 57 mg. of diacetyldihydronarcissidine in 2 ml. of acetone was treated with a solution of 50 mg. of potassium permanganate in 3 ml. of water and 5 ml. of acetone at 0°. The solution was nearly decolorized after 30 minutes. Water was added and sulfur dioxide was passed in until the solution was clear and acidic. The mixture was extracted with chloroform, and the extracts were dried over sodium sulfate and evaporated. The residual gum crystallized on trituration with ethyl acetate, and it was recrystallized from the same solvent to give 25 mg. (43%) of short prisms, m.p. 222.5–224°. The infrared spectrum exhibited typical conjugated lactam bands at 6.08 and 6.22 μ. The ultraviolet spectrum showed maxima at 225 mμ (log ε 4.53), 251 mμ (log ε 3.81), 264 mμ (log ε 3.85), 299 mμ (log ε 3.79) and a shoulder at 272 mμ (log ε 3.82).

Anal. Calcd. for $C_{22}H_{27}NO_8$: C, 60.96; H, 6.28. Found: C, 60.66; H, 6.16.

Oxidation of Narcissidine to *m*-Hemipinic Acid.—A suspension of 205 mg. of narcissidine in 30 ml. of water at 30–40° was treated dropwise with a solution of 1 g. of potassium permanganate in 100 ml. of water. The solution was still slightly red at the end of 0.5 hour. Sulfur dioxide was passed through the solution until the precipitate dissolved and the solution was strongly acidic. The aqueous solution was concentrated and extracted with ethyl acetate. Evaporation of this extract left 10 mg. of an optically inactive product, m.p. 250–260°, which was soluble in dilute potassium hydroxide. This material exhibited an intense maximum in the ultraviolet at 245 mμ. The infrared spectrum showed a peak at 5.76 μ, but an insufficient quantity was available for further study. The aqueous solution was extracted continuously with ether. Evaporation of the ether left a gum which was partially dissolved in potassium bicarbonate. The bicarbonate washes were acidified, extracted with a large amount of ethyl acetate and concentrated to a gum which was evaporated to dryness with acetic anhydride. The residue was sublimed to yield 15 mg. (12%) of crude *m*-hemipinic anhydride, m.p. 165–175°. Resublimation of this product raised the melting point to 170–175° (reported[35] 175°). A few drops of methylamine were added to the anhydride, and the product was sublimed again to yield N-methyl *m*-hemipinimide, m.p. 257–258° alone or when mixed with an authentic specimen, m.p. 257–258° (reported: 268°,[36] 258°[37]). The infrared spectra (KBr) of the derived and synthetic products were identical.

Anhydrofalcatinium Nitrate (XVI).—A solution of 40 mg. of falcatine in 5 ml. of ethanol was treated with 50 mg. of selenium dioxide and heated for 2 hours on a steam-bath. The yellow solution was filtered, evaporated under an air jet and treated with dilute nitric acid. An orange salt precipitated and was recrystallized from water (35 mg., 77%), m.p. 190–220° dec. One recrystallization from ethanol afforded rectangular orange plates which darkened from 210–220° and finally decomposed at 240° without evolving gas. The ultraviolet absorption spectrum showed maxima at 263 mμ (log ε 4.61 and 358 mμ (log ε 4.11) and a shoulder at a 277 mμ (log ε 4.42).

Anal. Calcd. for $C_{17}H_{14}N_2O_6$: C, 59.65; H, 4.12; N, 8.18; OCH_3, 9.07. Found: C, 59.79; H, 4.15; N, 8.01; OCH_3, 9.28.

Anhydrofalcatine Lactam (XVII).—A solution of 84 mg. of XVI in 3 ml. of water was treated with a solution of 220 mg. of potassium ferricyanide in 2 ml. of water. The yellow quaternary ammonium ferricyanide precipitated. This suspension was combined with 0.5 ml. of 50% potassium hydroxide and boiled for 2 minutes. The lactam was extracted into chloroform, washed with dilute hydrochloric acid and dried over sodium sulfate. Evaporation of the solvents left an oil which was crystallized from ethanol to give 43 mg. (59%) of long, very pale yellow prisms, m.p. 196–198°. A sample was recrystallized from ethanol–water and sublimed at 150° (0.1 mm.) for analysis, m.p. 198–201°. The infrared absorption spectrum exhibited bands at 6.05, 6.15 and 6.25 μ (KBr), while the ultraviolet absorption spectrum had maxima at 256 mμ (log ε 4.69), 273 mμ (log ε 4.32), 332 mμ (log ε 3.79), 347 mμ (log ε 3.86), and a shoulder at 300 mμ (log ε 4.00).

Anal. Calcd. for $C_{17}H_{13}NO_4$: C, 69.14; H, 4.44. Found: C, 68.89; H, 4.39.

Degradation of Alkaloids with Sodium and Amyl Alcohol. Powelline.—To a rapidly stirred suspension of 450 mg. of sodium in 30 ml. of boiling xylene was added 430 mg. of powelline. A solution of 3 ml. of redistilled isoamyl alcohol in 10 ml. of xylene was added in one portion. A vigorous reaction ensued, and after 3 minutes an additional 1 ml. of isoamyl alcohol in 3 ml. of xylene was added. The reaction mixture was stirred for 10 minutes in an atmosphere of nitrogen and then was allowed to cool. The basic materials were extracted from the xylene solution with several portions of dilute hydrochloric acid. The aqueous solutions were washed once with benzene and once with ether, then basified with ammonia and extracted four times with chloroform. The chloroform solutions were washed once with water and concentrated to a colorless oil that was chromatographed on 50 g. of Merck aluminum oxide. Elution with 20% ethyl acetate in benzene afforded 136 mg. of **α-crinene (Va)** which was evaporatively distilled at 180° (0.1 mm.), $[\alpha]^{25}_{589}$ −76.3°, $[\alpha]^{25}_{436}$ −192.5° (*c* 1.01).

Anal. Calcd. for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.46; H, 6.73; N, 5.46.

α-Crinene picrate formed yellow prisms from acetone–ethanol, m.p. 225–226°.

Anal. Calcd. for $C_{16}H_{17}NO_2 \cdot C_6H_3N_3O_7$: C, 54.54; H, 4.16; N, 11.57. Found: C, 54.50; H, 4.27; N, 11.60.

Elution with ethyl acetate gave 89 mg. of **β-crinene (Vb)** which was evaporatively distilled at 180° (0.1 mm.) for analysis; $[\alpha]^{25}_{589}$ −95.1°, $[\alpha]^{25}_{436}$ −206.3° (*c* 0.82).

Anal. Found: C, 75.41; H, 6.77; N, 5.54.

β-Crinene picrate formed yellow prisms, m.p. 201–202°, after recrystallization from ethanol.

Anal. Found: C, 54.54; H, 4.21; N, 11.44.

Elution with 10% ethanol in ethyl acetate gave 77 mg. of dihydroepicrinine which was crystallized from aqueous acetone to give colorless prisms, m.p. 103–105°, identical in all respects with authentic dihydroepicrinine prepared by the catalytic reduction of epicrinine.[1]

Reduction of an ethanolic solution of either α- or β-crinene in the presence of 10% palladium-on-charcoal catalyst occurred with the absorption of one equivalent of hydrogen to give (−)-crinane, m.p. 109–110°.[1] The reduction products were identified by comparison of their infrared spectra (liquid film) with that of authentic (−)-crinane, by mixture melting point determinations and by conversion to (−)-crinane picrate, m.p. 211–212°.[1]

Dihydroepipowelline.—Under conditions identical to those reported for powelline, 515 mg. of dihydroepipowelline afforded 317 mg. of a colorless oil which was identical in its infrared spectrum with that of dihydroepicrinine. For purification, the oil was converted to the perchlorate salt and recrystallized twice from water (Darco) to give 204 mg. of dihydroepicrinine hydroperchlorate, m.p. ~ 135° (reported[1] 135–140°). The free base (159 mg.), m.p. 102–107° (reported[1] 103–108°), was regenerated from the salt by alkali.

Buphanidrine.—To a refluxing solution of 2.26 g. of buphanidrine in 60 ml. of xylene was added 1.92 g. of sodium. The sodium was dispersed as a fine suspension by rapid stirring, and 8 ml. of redistilled isoamyl alcohol was added in one portion. The reaction mixture, covered with nitrogen, was stirred for 10 minutes. The solution was cooled to 100°, and ethanol was added to destroy any remaining traces of sodium. The reaction mixture was diluted with 200 ml. of water and acidified with dilute hydrochloric acid. The xylene layer was extracted four times with dilute hydrochloric acid. The combined aqueous solutions were extracted three

(35) Goldschmiedt, *Monatsh.*, **9**, 339 (1888).

(36) V. Prelog, K. Wiesner, H. G. Khorana and G. W. Kenner, *Helv. Chim. Acta*, **32**, 453 (1949).

(37) R. A. Labriola, V. Deulofeu and B. Berinzaghi, *J. Org. Chem.*, **16**, 90 (1951).

times with chloroform, and the chloroform extracts were washed with dilute ammonia and then water. Concentration of the chloroform under reduced pressure afforded 1.2 g. of buphanisine contaminated with some buphanidrine. The aqueous acid solution was basified with dilute ammonia and extracted four times with chloroform. The chloroform solution was washed with water and concentrated under reduced pressure to give 0.9 g. of crude buphanisine, m.p. 110–120°. The 1.2-g. fraction of crude buphanisine was dissolved in dilute hydrochloric acid and re-extracted with three portions of chloroform. The chloroform extracts and the aqueous acid solution were processed as above to yield an additional 951 mg. of crude buphanisine and 137 mg. of unreacted buphanidrine. The crude buphanisine fractions were chromatographed on 100 g. of Merck aluminum oxide. Elution with 5% ethyl acetate in benzene and recrystallization of the eluates with ether afforded 849 mg. of buphanisine, m.p. 124–126°. The filtrates from these recrystallizations contained both buphanidrine and buphanisine, and a third separation with chloroform and dilute hydrochloric acid was effected. From this oil there was obtained an additional 210 mg. of buphanidrine and 113 mg. of **buphanisine** m.p. 123–124°. The mixture melting point of our buphanisine with that kindly supplied by Dr. J. Renz was not depressed. The infrared spectra (KBr) were identical. The analytical sample was recrystallized from ether, m.p. 125–126°, $[\alpha]^{26}_{589}$ −24° (*c* 1.00, 95% ethanol), $[\alpha]^{23}_{589}$ −31.0° (*c* 1.08); reported[17] m.p. 122–124°, $[\alpha]^{20}_{589}$ −26° (ethanol).

Anal. Calcd. for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91; OCH_3, 10.87. Found: C, 71.62; H, 6.80; N, 4.83; OCH_3, 10.87.

Catalytic hydrogenation of a solution of 214 mg. of buphanisine in ethanol in the presence of palladium-on-charcoal afforded 158 mg. of **dihydrobuphanisine**, m.p. 95–96°. A portion of this material was recrystallized from ether for analysis, m.p. 95–96°, $[\alpha]^{23}_{589}$ −28.0° (*c* 1.3).

Anal. Calcd. for $C_{17}H_{21}NO_3$: C, 71.05; H, 7.37; N, 4.87. Found: C, 71.35; H, 7.24; N, 4.90.

Falcatine.—By the procedure described for powelline, 400 mg. of falcatine was converted to 375 mg. of a basic, brown oil that was chromatographed on 50 g. of Merck aluminum oxide. Elution with ethyl acetate afforded 80 mg. of **caranine**, m.p. 178–180°, $[\alpha]^{24}_{589}$ −186° (*c* 1.28). The infrared spectrum (KBr) of the product was identical with that of authentic caranine,[7] and a mixture melting point determination showed no depression.

Galanthine.—Small pieces of sodium totaling 500 mg. were added to 25 ml. of *n*-amyl alcohol under reflux in a nitrogen atmosphere. Immediately, 312 mg. of dry galanthine was added with vigorous stirring. When the reaction had subsided, an additional 200 mg. of sodium was added and allowed to dissolve. The cooled reaction mixture was acidified with 10% hydrochloric acid and extracted with ether. The aqueous acid solution was basified with ammonia, extracted with chloroform, and the extracts were dried over sodium sulfate. Evaporation of the solvent left 285 mg. of a crystalline mixture, m.p. 150–200°. Repeated fractional recrystallization from a variety of solvents failed to purify any component. The total crystalline product was recombined and chromatographed on Merck aluminum oxide. A mixture of 50% benzene in ethyl acetate eluted 70 mg. of flat plates, m.p. 168–173°, which was a mixture of pluviine and methylpseudolycorene. This material was fractionally sublimed. The first zone of sublimate formed at 100° (1 μ) while the second zone occurred at 150° (1 μ). The first zone of relatively pure **methylpseudolycorene** (**XXIb**) was recrystallized from cyclohexane, m.p. 165–175°. Several samples obtained in this fashion were combined and purified as described below. The second zone was removed and recrystallized from acetone, yielding slightly impure **pluviine** (**XX**), m.p. 192–203°. The infrared spectrum of this sample was identical with that of natural pluviine in spite of the low melting point. Recrystallization of the combination of several samples obtained in a similar manner yielded pure pluviine, m.p. 223–225° alone or when mixed with authentic pluviine, $[\alpha]^{23}_{589}$ −165° (*c* 0.14), reported[8] m.p. 225–227°, $[\alpha]^{21}_{589}$ − 151° (chloroform).

Anal. Calcd. for $C_{17}H_{21}NO_3$: C, 71.05; H, 7.37. Found: C, 70.92; H, 7.33.

Further elution of the original column with 10% ethanol in ethyl acetate gave 10 mg. of dehydromethylpseudolycorine (XXVb), identical in all respects with that obtained by the action of potassium *t*-butoxide or potassium *t*-amyl oxide on galanthine.

Lycorine.—Essentially the same results were obtained in the following reaction when lycorine was substituted for diacetyllycorine. However, the yield was slightly higher with the diacetyl derivative, and its solubility in the medium facilitated observation of the course of the reaction.

A solution of 2 g. of diacetyllycorine in 100 ml. of *n*-amyl alcohol was refluxed under nitrogen, and small pieces of sodium totaling 2 g. were added. When the sodium had reacted completely, the reaction mixture was cooled, diluted with water, acidified with dilute sulfuric acid and extracted with ether. The aqueous solutions were made basic with ammonia, extracted with chloroform, and the extracts were dried over sodium sulfate. Evaporation of the solvents left 1.105 g. of brown gum which was dissolved in benzene and chromatographed over Merck aluminum oxide. Elution with benzene produced 212 mg. (11%) of **lycorene** (**XXIa**), m.p. 118–120°. Elution with 50% ethyl acetate in benzene gave a few milligrams of a neutral solid, m.p. 163–168°, which was not investigated further. Finally, elution with 50% ethyl acetate in benzene produced 257 mg. (13%) of crude caranine. This was recrystallized from acetone and afforded 85 mg. of pure **caranine**, m.p. 176–180°, $[\alpha]^{24}_{589}$ −209° (*c* 1.01), reported[20] $[\alpha]^{27}_{589}$ −196.6° (chloroform). A mixture melting point with authentic material was not depressed. The infrared spectra, both in chloroform solution and as a KBr pellet, of the product and caranine were identical.

Dihydrolycorine.—A solution of 258 mg. of dihydrolycorine in 30 ml. of freshly distilled *n*-amyl alcohol was refluxed under nitrogen while 800 mg. of sodium chips were added. When all of the sodium had reacted, the solution was cooled, acidified with dilute sulfuric acid and extracted with ether. The aqueous layer was neutralized with sodium hydroxide and, on chilling, 185 mg. (72%) of dihydrolycorine crystallized, m.p. 230–237° dec. alone or when mixed with starting material. An additional 18 mg. (7%) was obtained by chloroform extraction of the water layer. The infrared spectrum of the product was identical with that of the starting material.

Dehydrolycorine (**XXVa**).—To a solution of 551 mg. of the diene XXVa in 50 ml. of refluxing *n*-amyl alcohol under nitrogen, chips of sodium totaling 2.50 g. were added continuously. The reaction mixture was cooled, acidified with dilute hydrochloric acid and extracted with ether. The aqueous layer was basified with ammonia and extracted with chloroform. The chloroform extracts were dried over magnesium sulfate and evaporated to yield 353 mg. of residue which was chromatographed over Merck alumina (by the method used for lycorine) to yield 114 mg. (22%) of crude **lycorene** (**XXIa**), m.p. 118–120°, followed by 150 mg. of an oil which was treated with methyl iodide to yield 53 mg. (6%) of **caranine β-methiodide**, m.p. 312–316° (reported[20] 312–314°). Both compounds failed to depress the melting points of authentic samples and exhibited infrared spectra identical with the respective authentic compounds.

Narcissidine.—A vigorously boiling solution of 300 mg. of narcissidine in 30 ml. of freshly distilled *n*-amyl alcohol was treated in a nitrogen atmosphere with 400 mg. of sodium chips. When the sodium had reacted completely, the cooled mixture was diluted with water, acidified with sulfuric acid and extracted with ether to remove amyl alcohol. The aqueous solution was basified with ammonia, extracted with chloroform, and the extracts were dried over sodium sulfate. Evaporation of the solvents left 275 mg. of residue which crystallized when triturated with acetone. As in the case of galanthine, fractional crystallization did not effect a purification of any of the components, so the mixture was dissolved in benzene and chromatographed on Merck aluminum oxide. Elution with 5% ethyl acetate–benzene gave 101 mg. (41%) of pure **methylpseudolycorene**, m.p. 175–178°, identical in all respects with that obtained from galanthine. Further elution with the same solvents gave 70 mg. of a mixture which was separated into its components by fractional crystallization to yield 3 mg. of **pluviine** and 5 mg. (2%) of **dehydromethylpseudolycorine**, both of which were identical in melting point and infrared spectrum (KBr) with the corresponding products obtained from galanthine. Further elution with 5% ethanol in ethyl acetate produced 37 mg. of an oil from which 7 mg. of pure **pluviine** was obtained by repeated recrystallization from acetone, m.p. 223–225° alone or when mixed with authentic material.[8] The infrared

spectra (KBr) of the product and authentic pluviine were identical. The very low yield of pluviine (3.8%) required proof of its absence in the narcissidine employed in the reaction. A prepared mixture of 3% pluviine in narcissidine gave an intense red color in 98% sulfuric acid as did pluviine itself. However, the narcissidine used in this experiment produced only a faint yellow color in the same reagent.

Dihydronarcissidine.—A solution of 258 mg. of dihydronarcissidine[31] in 30 ml. of boiling *n*-amyl alcohol was treated with 800 mg. of sodium chips. The reaction mixture was cooled, diluted with water and extracted with chloroform from which 210 mg. (81%) of dihydronarcissidine, m.p. 155–159°, was recovered.

Dehydromethylpseudolycorine (XXVb).—To a solution, of 25 mg. of the diene XXVb in 8 ml. of refluxing *n*-amyl alcohol under nitrogen, chips of sodium totaling 150 mg. were added continuously. After complete reaction of the sodium had occurred, the solution was cooled, water was added, and the mixture was extracted with chloroform. The chloroform extracts were dried over magnesium sulfate, filtered, and evaporated in a current of nitrogen. The crude product (15 mg.) crystallized from acetone, m.p. 199–205°. Although the infrared spectrum was very similar to that of pluviine, several important differences were noted. As in the case of galanthine, further recrystallization did not accomplish purification so the total product was dissolved in acetone and streaked horizontally on Whatman #3 filter paper. The chromatogram was developed overnight with 0.1 *N* hydrochloric acid. When test strips were removed from the main strip and developed with Dragendorf reagent, two basic zones appeared, one with R_f 0.73 and the other, R_f 0.87. The upper zone was eluted with ethanol, evaporated in a stream of nitrogen, basified with sodium hydroxide, extracted with chloroform and again evaporated. The residue (4 mg.) was sublimed at 150° (1 μ) and washed with ether to give a crystalline solid, m.p. 220–224°. The product exhibited an infrared spectrum (KBr) identical in all respects with that of authentic **pluviine**. The lower zone, treated in the same manner, afforded 2 mg. of **methylpseudolycorene (XXIb)**, m.p. 171–174°, having the same infrared spectrum (KBr) as XXIb obtained directly from galanthine.

Characterization of Reaction Products. Lycorene (XXIa).—Crude lycorene, obtained from lycorine as described above, was recrystallized from ether to afford fine needles, m.p. 120–121°, $[\alpha]^{24}_{589}$ −132° (*c* 2.97), λ_{max} 292 mμ (log ϵ 3.68). The infrared spectrum of the product exhibited no absorption bands in the 2.5–3.0 μ or 5–6 μ region.

Anal. Calcd. for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.15; H, 6.65; N, 5.39.

Lycorene was recovered unchanged after refluxing for 2 hours in a 5% perchloric acid solution. It also was unaffected by pyridine and acetic anhydride.

Lycorene picrate was prepared in 80% ethanol and recrystallized from the same solvent forming yellow prisms, m.p. 174–176° dec.

Anal. Calcd. for $C_{16}H_{17}NO_2 \cdot C_6H_3N_3O_7$: C, 54.54; H, 4.16. Found: C, 54.47; H, 3.97.

Lycorene hydriodide formed stout prisms from water, m.p. 255°. The infrared spectrum (Nujol) showed no bands characteristic of imine salts in the 6 μ region.

Anal. Calcd. for $C_{16}H_{18}NO_2I$: I, 33.12. Found: I, 33.27.

Lycorene methiodide was prepared by the quaternization of the free base in dry acetone with methyl iodide. The salt was recrystallized from water and dried at 100° (1 mm.) to give flat, non-birefringent prisms, m.p. 294–296° dec. $[\alpha]^{24}_{589}$ +124°, $[\alpha]^{24}_{436}$ +248° (*c* 0.157, 50% aqueous ethanol).

Anal. Calcd. for $C_{17}H_{20}NO_2I$: C, 51.40; H, 5.07; I, 31.95. Found: C, 51.48; H, 5.03; I, 31.84.

Lycorene hydroperchlorate was prepared by the addition of dilute perchloric acid to the free base, and then recrystallization of the precipitate from water to yield long prisms, which sintered at 244–250° and decomposed extensively at 250–260°.

Anal. Calcd. for $C_{16}H_{17}NO_2 \cdot HClO_4$: N, 3.94; Cl, 9.97. Found: N, 3.88; Cl, 9.80.

α-Lycorane (XXIVa).—A solution of 139 mg. of lycorene (XXIa) in 2 ml. of glacial acetic acid was added to 100 mg. of platinum oxide which previously had been equilibrated with hydrogen in 8 ml. of acetic acid. Hydrogen was absorbed very slowly (0.75 ml. per hour), but the addition of 3 ml. of 12 *N* hydrochloric acid accelerated the rate of hydrogenation. After 84% of the theoretical volume of hydrogen had been absorbed, the reaction appeared to stop. The filtered solution was evaporated slightly and sodium perchlorate was added. **The hydroperchlorate** crystallized immediately (75 mg., 39%). A sample was recrystallized from water and dried at 100° (1 mm.), m.p. 252–256° (brown discoloration, no gas evolution). The infrared spectrum (KBr) of this sample was distinctly different from that of lycorene hydroperchlorate.

Anal. Calcd. for $C_{16}H_{19}NO_2 \cdot HClO_4$: C, 53.71; H, 5.63. Found: C, 53.90; H, 5.63.

A portion of the hydroperchlorate was treated with alkali, extracted with ether and dried over sodium sulfate. The solvents were evaporated in a stream of nitrogen. The free base was recrystallized from hexane and sublimed at 60° (1 μ) to give short prisms of **α-lycorane** (XXIVa), m.p. 63–65°, $[\alpha]^{24}_{589}$ −52.3°, $[\alpha]^{24}_{436}$ −153° (*c* 0.66), $[\alpha]^{24}_{589}$ −100° (*c* 0.27, benzene). The infrared spectrum showed no absorption in the 2.5–3 μ or 5–6 μ region.

Anal. Calcd. for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; neut. equiv., 257. Found: C, 74.66; H, 7.71; neut. equiv., 260.

When a hexane solution of this lycorane, m.p. 63–65°, was seeded witha sample of α-lycorane,[25,38] the base crystallized as colorless plates, m.p. 82–83°. A mixture melting point with authentic α-lycorane, m.p. 82–83°, was not depressed. The infrared spectra (chloroform) of the two materials were identical.

Lycorane Picrolonate.—Prepared in ethanol and recrystallized twice from ethanol–water, the picrolonate afforded long yellow prisms, m.p. 219–224°.

Anal. Calcd. for $C_{26}H_{27}N_5O_7$: C, 59.87; H, 5.22. Found: C, 59.61; H, 5.42.

Dehydrogenation of Lycorene (XXIa).—A solution of 15 mg. of lycorene in 15 ml. of *p*-cymene was refluxed in a nitrogen atmosphere with 80 mg. of 10% palladium-on-charcoal catalyst for 2 hours. The *p*-cymene was removed from the filtered solution in a current of nitrogen, and the residue was triturated with methanol. The indole (XXIII) was recrystallized from methanol to give fine needles. Characteristically, the product sintered at 143° and melted from 149–161°, but then recrystallized as long prisms which melted at 205–212° (reported[19] 159–161°). This behavior was not changed when a sample of the product was mixed with authentic XXIII prepared by a similar dehydrogenation of anhydrolycorine (4,5-dihydro XXIII). Infrared and ultraviolet absorption spectra of the product and authentic XXIII were identical.

Methylpseudolycorene (XXIb).—The crude materials obtained from several degradations of galanthine with sodium and *n*-amyl alcohol were combined and recrystallized from acetone as long-bladed prisms, m.p. 179–180°, $[\alpha]^{23}_{589}$ −133°, $[\alpha]^{23}_{436}$ −283° (*c* 1.06), λ_{max} 283–287 mμ (split) (log ϵ 3.61). The infrared spectrum showed no absorption in the 2.5–3.0 μ or 5–6 μ region.

Anal. Calcd. for $C_{17}H_{21}NO_2$: C, 75.24; H, 7.80; neut, equiv., 271. Found: C, 75.32; H, 7.82; neut. equiv., 270.

When a melt of methylpseudolycorene was allowed to remain at 200° in the presence of air, it was converted in good yield to a crystalline substance which melted at 250–260°. This material was purified by sublimation at 150° (5 μ) and by recrystallization from aqueous ethanol. The pure material, in the form of fine, colorless prisms, m.p. 272–273°, showed no depression of melting point when mixed with authentic 4,5-dihydro-9,10-dimethoxypyrrolo[de]-7-phenanthridone (XXII).[4] The ultraviolet spectra of the two samples were identical, as were the infrared spectra (KBr) except for the presence of a very weak band at 5.95 μ in the pyrolysis product.

The methopicrate of XXIb was prepared by quaternization with methyl iodide in acetone and then addition of an aqueous solution of lithium picrate and subsequent recrystallization from aqueous dimethylformamide, m.p. 200–216°.

Anal. Calcd. for $C_{24}H_{26}N_4O_9$: C, 56.03; H, 5.09. Found: C, 56.09; H, 5.12.

(38) We are indebted to Dr. Ken'ichi Takeda for a sample of this material.

Conversion of Diacetyllycorine and Lycorine to Dehydrolycorine (XXVa).—Diacetyllycorine (953 mg.) was added to a solution prepared by heating 1 g. of potassium with 30 ml. of *t*-amyl alcohol. The mixture was refluxed under nitrogen for 1 hour. Water was added to the cooled mixture and the amyl alcohol layer separated. The aqueous solution was extracted with chloroform. The chloroform layer was combined with the amyl alcohol, dried over magnesium sulfate, filtered and evaporated to give 711 mg. of a brown oil. After trituration with ethyl acetate, 90 mg. of insoluble lycorine was removed. The filtrate slowly deposited 180 mg. (28%) of XXVa as brown crystals, m.p. 170–175°. Sublimation at 150° (1 μ) afforded a solid which was recrystallized from water to yield large prisms, m.p. 172–176°, $[\alpha]^{23}_{589}$ −517° (*c* 0.5). The ultraviolet absorption spectrum showed maxima at 231 mμ (log ϵ 4.24) and 290 mμ (log ϵ 3.70). When the ultraviolet spectrum of the compound was run against diacetyllycorine in a solution of the same molarity as a blank, one maximum was obtained, 231 mμ (log ϵ 4.13). The differential maximum shifted in acid to 232 mμ and increased in intensity to log ϵ 4.23.

Anal. Calcd. for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; neut. equiv., 269. Found: C, 71.11; H, 5.67; neut. equiv. (perchloric acid titration), 269.

When lycorine was substituted for diacetyllycorine and the reaction was run in the same manner, a 4.8% yield of XXVa was eluted from a column of Merck aluminum oxide with chloroform. Lycorine was recovered in 67% yield.

The free base XXVa acquired a green hue on standing in sunlight. A chloroform solution of XXVa when treated with activated manganese dioxide became of a bright blue-green color, but on evaporation only a black tar remained which could not be redissolved in organic solvents.

The O-acetyl derivative of XXVa was prepared by allowing a small sample of XXVa to stand overnight in a 1:1 mixture of pyridine and acetic anhydride. When the reaction mixture was decomposed with water and neutralized with sodium bicarbonate, a precipitate formed which was recrystallized from aqueous ethanol as fine, white needles, m.p. 162–164°. The infrared absorption spectrum of the product showed one peak at 5.75 μ, and the ultraviolet absorption spectrum was identical to that of XXVa.

Anal. Calcd. for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; $OCOCH_3$, 13.82. Found: C, 69.66; H, 5.72; $OCOCH_3$, 13.82.

The methiodide of XXVa was prepared in methanol and recrystallized from the same solvent to form opaque, flat hexagons, m.p. 270–271°. The infrared absorption spectrum exhibited no bands typical of imine salts in the 6 μ region.

Anal. Calcd. for $C_{17}H_{18}NO_3I$: C, 49.65; H, 4.41; I, 30.86. Found: C, 49.71; H, 4.35; I, 30.92.

The hydroperchlorate of XXVa was prepared by the addition of aqueous perchloric acid to the free base. The product was recrystallized from water to form plates, m.p. 213–220° dec. The infrared absorption spectrum (Nujol) exhibited no bands characteristic of imine salts in the 6 μ region.

Anal. Calcd. for $C_{16}H_{15}NO_3 \cdot HClO_4$: C, 51.97; H, 4.36; Cl, 9.59. Found: C, 51.76; H, 4.23; Cl, 9.40.

Hydrogenation of Dehydrolycorine.—A solution of 52 mg. of XXVa in 20 ml. of ethanol–acetic acid (5:1) was stirred under hydrogen with 52 mg. of prereduced palladium-on-charcoal catalyst. Slightly over one mole of hydrogen was absorbed in 5 minutes, and the reaction was stopped. The catalyst was removed by filtration, and the solution was basified with ammonia and extracted with chloroform. The extracts were dried and evaporated to 40 mg. of an oil which crystallized from ethyl acetate when seeded with caranine. One recrystallization from benzene gave pure **caranine** m.p. 176–180° alone or when mixed with authentic caranine.[20] The infrared absorption spectra (KBr) of the product and authentic caranine were identical. The filtrates were treated with methyl iodide, and an additional 20 mg. of **caranine β-methiodide**, m.p. 315–316° (reported[20] 312–314°), was obtained.

Conversion of Galanthine to Dehydromethylpseudolycorine (XXVb).—To a solution of potassium *t*-amyl oxide, prepared from 520 mg. of potassium and 25 ml. of *t*-amyl alcohol, was added 506 mg. of galanthine. The mixture was refluxed under nitrogen for one hour and then cooled. Water was added and the non-phenolic bases were extracted with chloroform. The chloroform extracts were dried with magnesium sulfate and concentrated to give 474 mg. of crystalline material, m.p. 190–205°. One recrystallization from chloroform–acetone gave 252 mg. (55%) of sparkling plates, m.p. 210–220°. A sample was sublimed at 150° (5 μ) for analysis, m.p. 226–229° (recrystallized on hot-stage at 200°), $[\alpha]^{23}_{589}$ −359°, $[\alpha]^{23}_{436}$ −823° (*c* 0.20, methanol). The compound is rather unstable in sunlight, becoming greenish-blue. The ultraviolet absorption spectrum showed maxima at 230 mμ (log ϵ 4.41) and 283 mμ (log ϵ 3.55). When a solution of the diene was run against galanthine in a solution of the same molarity as a blank, one maximum resulted at 230 mμ (log ϵ 4.03). The differential maximum shifted in acid solution to 231 mμ and increased in intensity (log ϵ 4.14).

Anal. Calcd. for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; 2 OCH_3, 21.75; neut. equiv., 285. Found: C, 71.64; H, 6.74; OCH_3, 20.96; NCH_3, 0.00; neut. equiv. (perchloric acid titration), 285.

The same product was obtained (along with recovered galanthine) from an attempt to oxidize galanthine under Oppenauer conditions with potassium *t*-butoxide and fluorenone.[39]

Dehydromethylpseudolycorine methiodide was prepared by allowing methyl iodide to react with the free base in acetone, and then one recrystallization of the product from ethanol, m.p. 242–246° dec.

Anal. Calcd. for $C_{18}H_{22}NO_3I$: C, 50.59; H, 5.19. Found: C, 50.40; H, 5.19.

Dehydration of Dehydromethylpseudolycorine (XXVb).—The diene (5 mg.) was covered with freshly distilled phosphorus oxychloride and heated on the steam-bath for 20 minutes. The cooled solution was hydrolyzed with water, neutralized with ammonia and extracted with chloroform. The extracts were dried over magnesium sulfate and evaporated. The yellow solid (XXII, no O at C_7), 2.5 mg., was sublimed at 100° (1 μ), m.p. 168–170° (recrystallized on hot-stage and remelted at 258–262°) alone or when mixed with authentic 9,10-dimethoxy-4,5,6,7-tetrahydropyrrolo[de]phenanthridine.[40] The infrared (KBr) and ultraviolet spectra (ethanol) also were identical.

Hydrogenation of Dehydromethylpseudolycorine.—A solution of 90 mg. of the diene XXVb in 10 ml. of ethanol containing 10% acetic acid was added to a previously equilibrated suspension of 90 mg. of 10% palladium-on-charcoal in 20 ml. of the same solvent under hydrogen. The mixture absorbed 7.10 ml. of hydrogen within the first 2 minutes, and the reduction was allowed to continue an additional 3 minutes. The total uptake of hydrogen was 7.33 ml. (104%). The solution was basified with sodium hydroxide and quickly filtered from a flocculent precipitate. The aqueous solution was extracted with chloroform, and the chloroform extracts were dried over magnesium sulfate and evaporated. The crude pluviine (68 mg., 75%), m.p. 198–203°, was recrystallized from methyl ethyl ketone to give pure, flat hexagonal crystals of **pluviine**, m.p. 223–225°, $[\alpha]^{22}_{589}$ −155° (*c* 0.24). The melting point of a mixture with authentic material was unchanged.

Conversion of Galanthine to Methylpseudolycorine (XIXb).—A solution of 182 mg. of galanthine (XIXc) in 10 ml. of 10% hydrochloric acid was heated under reflux in a nitrogen atmosphere for 5 hours. The solution was cooled and a precipitate of anhydromethylpseudolycorine hydrochloride (75 mg.) was removed by filtration and converted to the free base, m.p. 168–170°. The filtrates were neutralized with sodium hydroxide and extracted with chloroform–ethanol (10:1). The extracts were dried over sodium sulfate and evaporated to give 27 mg. of a white residue which was triturated with chloroform, filtered and recrystallized from chloroform–ethanol as fine prisms, m.p. 229–233° dec. alone or on admixture with authentic methylpseudolycorine (XIXb). The infrared spectrum (Nujol) was identical with that of authentic material.

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(39) We are indebted to Dr. E. W. Warnhoff for this observation.

(40) This material corresponds to the material, m.p. 174–177°, reported in ref. 8. The same substance had been obtained by us in a polymorphic form, m.p. 145°, in earlier work.[4] The infrared spectra (chloroform) of the two forms were identical.