(m.p. 211–213°); yield 5.42 g. (53%), b.p. 130–132°, $[\alpha]_D$ −71.0° (4.8%, $CHCl_3$).

Anal. Calcd. for $C_7H_{13}N$: N, 12.61. Found: N, 12.52.

Poly-*d*-conidine Boron Fluoride.—*d*-Conidine (b.p. 134–136°, *ca.* 1 g.) was added to a nitrogen-filled Carius tube. After boron fluoride had been bubbled through for 1.5 minutes, the liquid turned to yellow solid. After standing at room temperature for 5 days, the polymer was dissolved in 20 ml. of benzene, washed three times with 10% sodium hydroxide, and then with water, until the washing became neutral. The benzene layer was dried with anhydrous potassium carbonate and freeze-dried; yield, 1.0 g. of almost white poly-*d*-conidine boron fluoride, m.p. 73–75°, $[\alpha]_D$ +12.7° (1.5% $CHCl_3$), $[\eta]$ 0.047 in benzene at 26°, molecular weight 4300 (Rast).

Anal. Calcd. for $(C_7H_{13}N\cdot BF_3)_n$: C, 46.98; H, 7.27; N, 7.83. Found: C, 47.52; H, 7.44; N, 7.77.

Poly-*d*-conidine boron fluoride was soluble in benzene and chloroform and insoluble in ether, acetone and water at room temperature. It was soluble in boiling acetone and boiling water.

Poly-*d*-conidine.—*d*-Conidine (b.p. 134–136°, *ca.* 2 ml.) was added to a nitrogen-filled Carius tube and one to two drops of redistilled boron fluoride etherate was added. It was then sealed and kept at room temperature for five days. The white polymer was dissolved in 240 ml. of boiling benzene, cooled to room temperature, washed three times with 250-ml. portions of 10% aqueous sodium hydroxide, and then washed with water until the washings became neutral. The benzene layer was freeze-dried to yield 1.7 g. of white isotactic poly-*d*-conidine, m.p. 92–94°, $[\alpha]_D$ −140.8° (1.4%, $CHCl_3$), $[\eta]$ 0.33 in benzene at 26°.

Anal. Calcd. for $(C_7H_{13}N)_n$: C, 75.67; H, 11.71; N, 12.61. Found: C, 75.52; H, 11.76; N, 12.60.

Poly-*d*-conidine was highly crystalline by X-ray powder diagram (Table I). It was soluble in benzene, chloroform and carbon tetrachloride and fairly soluble in ethanol, boiling water and boiling pyridine, but it was insoluble in acetone and ether at boiling or room temperature.

Poly-*l*-conidine.—The above procedure was carried out on 2.81 g. of *l*-conidine (b.p. 130–132°), except the sealed tube was kept at room temperature for 14 days instead of 5 days; yield 2.56 g. (90.0%) of white isotactic poly-*l*-conidine, m.p. 92–94°, $[\alpha]_D$ +140.8° (1.4%, $CHCl_3$), $[\eta]$ 0.45 in chloroform at 25.0°.

Anal. Calcd. for $(C_7H_{13}N)_n$: C, 75.67; H, 11.71; N, 12.61. Found: C, 75.54; H, 11.54; N, 12.62.

Poly-*l*-conidine was soluble in benzene and chloroform and insoluble in water, pyridine, acetone, ether, N,N-dimethylformamide, nitromethane and nitrobenzene at room temperature. It was slightly soluble at boiling temperature in several solvents: water, pyridine, ethanol, N,N-dimethylformamide and nitrobenzene.

Racemic Isotactic Polyconidine.—Isotactic poly-*d*- and *l*-conidine (each m.p. 92–94°, 0.0756 g.) were mixed and dissolved in 35.0 ml. of warm benzene and freeze-dried; yield 0.12 g. of racemic isotactic polyconidine, m.p. 91–93°, $[\alpha]_D$ 0.00 (1%, chloroform).

Racemic isotactic polyconidine was highly crystalline. The calculated interplanar spacings (Å.) and intensities are cited in Table I.

Racemic Atactic Polyconidine.—When the above polymerization procedure was carried out on 2.0 ml. of *dl*-conidine, only yellow, translucent, tacky and soft polymer was formed.

PHILADELPHIA 4, PENNA.

[CONTRIBUTION FROM THE DEPARTMENT OF PHARMACEUTICAL CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Veratrum Alkaloids. XLII.[1] The Structures of Desacetylprotoveratrine A and Desacetylprotoveratrine B[2]

BY S. MORRIS KUPCHAN, C. IAN AYRES AND RUPRECHT H. HENSLER

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The structures of desacetylprotoveratrine A and desacetylprotoveratrine B have been elucidated. Desacetylprotoveratrine A is protoverine 3-(*d*)-2′-hydroxy-2′-methylbutyrate 6-acetate 15-(*l*)-2′-methylbutyrate (VIII). Desacetylprotoveratrine B is protoverine 3-(*d*)-*threo*-2′,3′-dihydroxy-2′-methylbutyrate 6-acetate 15-(*l*)-2′-methylbutyrate (XII).

Desacetylprotoveratrine A[3] and desacetylprotoveratrine B ("desacetylneoprotoveratrine")[4,5] are hypotensive triester constituents of alkaloidal extracts of veratrum species. Desacetylprotoveratrine A may be obtained by methanolysis[3] of the hypotensive tetraester protoveratrine A (VII)[6] and desacetylprotoveratrine B may be obtained by methanolysis[4] of protoveratrine B (IX).[6] Nevertheless, the isolation of the triesters from extracts made under mild conditions known to leave intact sensitive germine triesters such as germitrine and neogermitrine[5] would suggest that the desacetylprotoveratrines may be of primary origin in the plant.

Our interest in the desacetylprotoveratrines arose from a study of the mild mineral acid hydrolysis of protoveratrine A and protoveratrine B. It was shown that, in each case, an acetyl grouping could be selectively removed to yield the corresponding naturally occurring triester. Due to the closely related structures of the protoveratrines, it seemed reasonable to assume, as a working hypothesis, that the acid-labile acetyl grouping was attached to the same position in the nucleus, *i.e.*, either C_6 or C_7. A strong indication that the C_7-acetate was acid-labile came from the following sequence. Protoveratrine A 16-isobutyrate[6] (I) on acid hydrolysis afforded a desacetylprotoveratrine A 16-isobutyrate (II). The latter compound on chromic acid oxidation yielded dehydrodesacetylprotoveratrine A 16-isobutyrate (III). The rotatory dispersion curve of III was virtually superimposable upon that of 7-dehydroprotoverine 3,6,15,16-tetraacetate (VI) (Fig. 1).[7] The structure of VI was unequivocally determined by synthesis. Protoverine 3,6,16-triacetate (IV)[8] (so-

(1) Part XLI in the series: S. M. Kupchan and N. Gruenfeld, *J. Am. Pharm. Assoc., Sci. Ed.*, **48**, 737 (1959).

(2) This investigation was supported by research grants from the National Institutes of Health (H-2275 (C3)), Pitman–Moore Co., and The Wisconsin Alumni Research Foundation.

(3) G. S. Myers, W. L. Glen, P. Morozovitch, R. Barber, G. Papineau-Couture and G. A. Grant, THIS JOURNAL, **78**, 1621 (1956).

(4) M. W. Klohs, M. D. Draper, F. Keller, W. Malesh and F. J. Petracek, *ibid.*, **75**, 3595 (1953).

(5) G. S. Myers, P. Morozovitch, W. L. Glen, R. Barber, G. Papineau-Couture and G. A. Grant, *ibid.*, **77**, 3348 (1955).

(6) S. M. Kupchan and C. I. Ayres, *ibid.*, **82**, 2252 (1960).

(7) We thank Professor Carl Djerassi and Dr. E. J. Eisenbraun for the optical rotatory dispersion measurements.

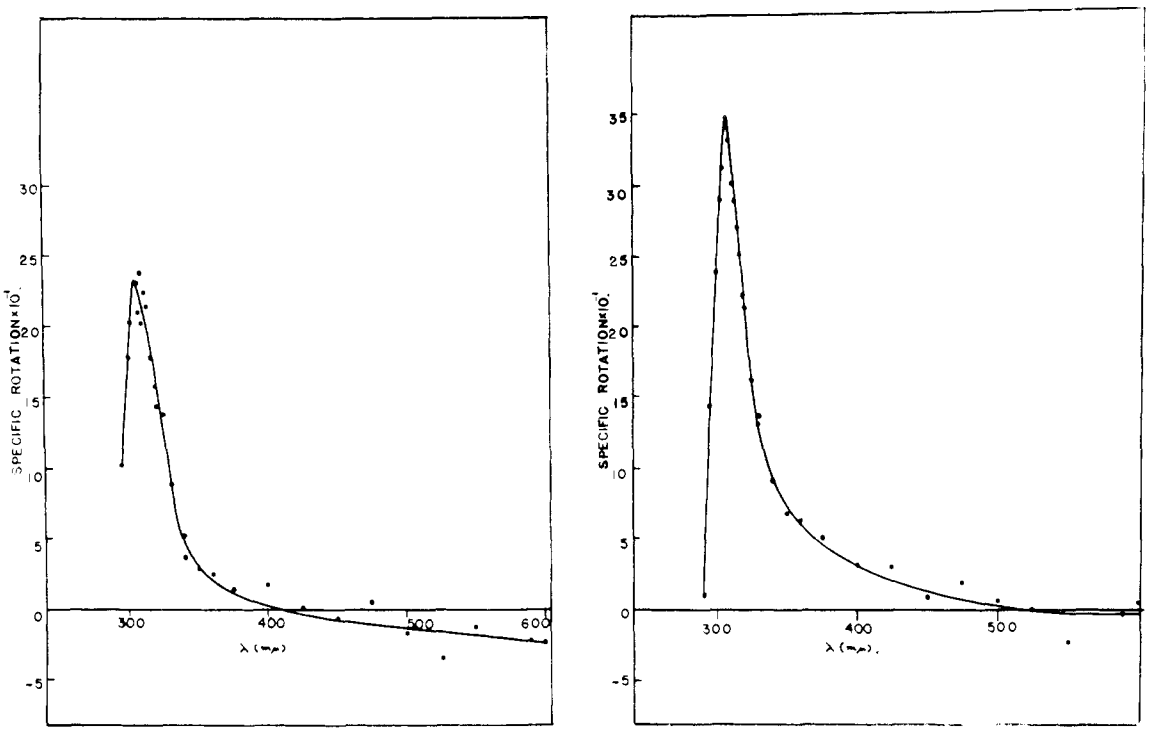


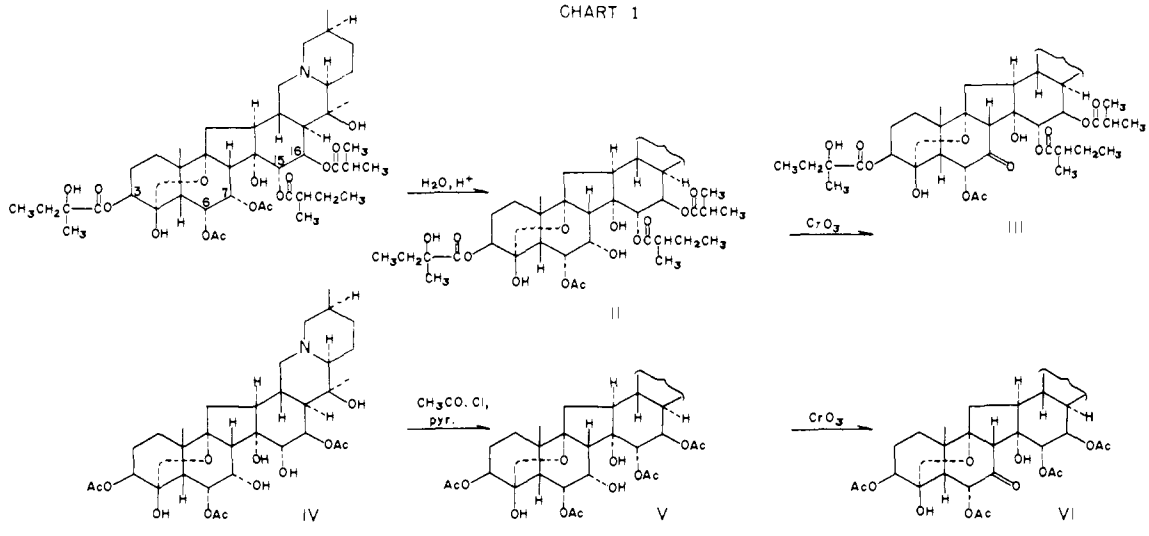
Fig. 1.—Optical rotatory dispersion curves in dioxane of: A, 7-dehydrodesacetylprotoveratrine A 16-isobutyrate (III) (*c* 0.100); B, 7-dehydroprotoverine 3,6,15,16-tetraacetate (VI) (*c* 0.095).

dium periodate consumption: 1 mole equivalent) was treated with a limited amount of acetyl chloride–pyridine to yield protoverine 3,6,15,16-tetraacetate (V) (stable to sodium periodate). V consumed 1 oxygen equivalent of chromic acid to give VI.

15-(*l*)-2′-methylbutyrate 6-acetate (XI) was synthesized for comparison purposes.

Protoverine 14,15-acetonide 3,6,16-triacetate (X)[8] upon prolonged mineral acid hydrolysis afforded protoverine 6,16-diacetate (XIV) in 20% yield. Treatment of X with sodium borohydride afforded

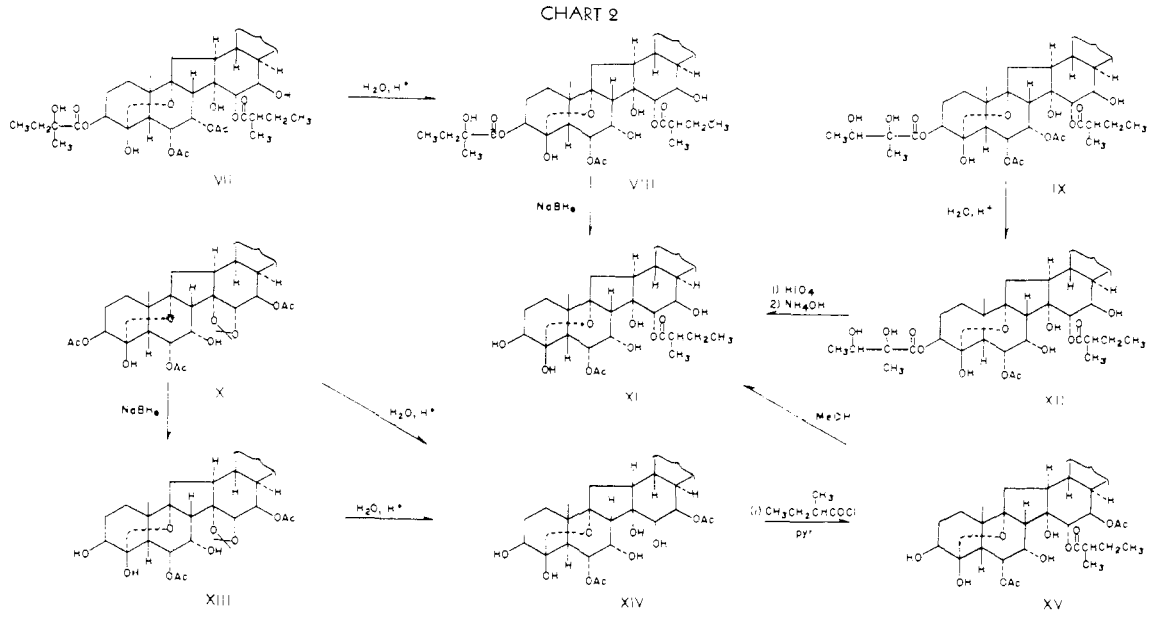
CHART 1



The removal of the butyryl moiety from C_3 in the desacetylprotoveratrines would afford the same protoverine 15-(*l*)-2′-methylbutyrate monoacetate. In anticipation that these conversions could be effected and on the strength of the rotatory dispersion comparison discussed above, protoverine a 40% yield of the known[8] protoverine 14,15-acetonide 6,16-diacetate (XIII) which on acid hydrolysis gave XIV. Treatment of XIV with a limited amount of (*l*)-2-methylbutyryl chloride gave protoverine 15-(*l*)-2′-methylbutyrate 6,16-diacetate (XV) (sodium periodate consumption: 1.1 mole equivalents). The amorphous product obtained upon periodate oxidation showed absorp-

(8) S. M. Kupchan, C. I. Ayres, M. Neeman, R. H. Hensler, T. Masamune and S. Rajagopalan, THIS JOURNAL, **82**, 2242 (1960).

CHART 2



tion at 3.65, 5.62 and 5.80 μ, characteristic of the aldehydo-γ-lactone produced by periodate cleavage in ring A.[8] Methanolysis of XV afforded the desired protoverine 15-(*l*)-2′-methylbutyrate 6-acetate (XI) which consumed 1.0 mole equivalent of sodium periodate and gave an oxidation product which again showed characteristic aldehydo-γ-lactone absorption.

Desacetylprotoveratrine B was treated with periodic acid followed by exposure of the crude oxidation mixture to dilute ammonium hydroxide. This treatment effectively removed the dihydroxybutyric acid moiety (*cf.* ref. 6). The product which resulted was identical with XI. Hence, desacetylprotoveratrine B has structure XII. Treatment of desacetylprotoveratrine A with sodium borohydride gave a complex mixture from which XI was isolated. Hence desacetylprotoveratrine A has structure VIII.

Experimental[9]

Acid Hydrolysis of Protoveratrine A. Desacetylprotoveratrine A (VIII).—Protoveratrine A (1 g.), m.p. 273–275° dec., was dissolved in 10% hydrochloric acid (50 ml.) and allowed to stand at room temperature for 24 hours. The cooled solution was basified with dilute ammonium hydroxide and extracted with chloroform. The chloroform extract was dried over anhydrous sodium sulfate and evaporated to yield a resin which was chromatographed on Merck acid-washed alumina (15 g.). The column yielded to mixtures of benzene–chloroform, starting material (300 mg.); to 1% methanol–chloroform, a resin (265 mg.). A paper chromatogram[10] indicated that the resin was homogeneous. The resin was crystallized from acetone–petroleum ether as needles (200 mg.), m.p. 200–201° dec. Recrystallization from acetone–petroleum ether gave long, colorless needles (175 mg.), m.p. 200–201° dec., $[\alpha]^{22}D$ −11° (*c* 1.05, pyr.). The m.p. was not depressed on admixture with an authentic sample[11] of desacetylprotoveratrine A. The paper chromatographic behavior[10] and infrared spectra of the respective samples were identical.

Acid Hydrolysis of Protoveratrine B. Desacetylprotoveratrine B (XII).—Protoveratrine B (1 g.), m.p. 267–269° dec., was dissolved in 10% hydrochloric acid (50 ml.) and allowed to stand at room temperature for 24 hours. The cooled solution was basified with dilute ammonium hydroxide and extracted with chloroform. The chloroform extract was dried over anhydrous sodium sulfate and evaporated to yield a resin which was crystallized from acetone–petroleum ether to yield starting material (440 mg.). The mother liquor was evaporated to yield a resin which was chromatographed on Merck acid-washed alumina (15 g.). The column yielded to chloroform and to 1% methanol–chloroform a material (100 mg.) which appeared from its paper chromatographic behavior[10] to be mainly starting material. The column yielded to 2% methanol–chloroform a resin (240 mg.) which was crystallized from acetone–petroleum ether as needles (213 mg.), m.p. 201–202° dec., $[\alpha]^{23}D$ −8° (*c* 1.00, pyr.). The melting point was not depressed on admixture with an authentic sample[11] of desacetylprotoveratrine B. The paper chromatographic behavior[10] and infrared spectra of the respective samples were identical.

7-Desacetylprotoveratrine A 16-Isobutyrate (II).—Protoveratrine A 16-isobutyrate[6] (1.1 g.), m.p. 273–275° dec., was dissolved in 10% hydrochloric acid (110 ml.) and allowed to stand at room temperature for 48 hours. The cooled solution was basified with dilute ammonium hydroxide and extracted with chloroform. The chloroform extract was dried over anhydrous sodium sulfate and evaporated to yield a resin which was chromatographed on Merck acid-washed alumina (40 g.). The column yielded to mixtures of benzene–chloroform, an oil; to chloroform, starting material (115 mg.); to 1% methanol–chloroform, a resin (390 mg.). The resin was crystallized from acetone–petroleum ether as needles (190 mg.), m.p. 235–238° dec. A sample was recrystallized for analysis from acetone–petroleum ether as colorless needles, m.p. 235–236° dec., $[\alpha]^{25}D$ −15° (*c* 1.00, pyr.).

Anal. Calcd. for $C_{43}H_{67}O_{14}N$: C, 62.83; H, 8.22. Found: C, 62.76; H, 8.26.

In a volatile acid determination,[12] 16.84 mg. of the compound yielded an amount of acid equivalent to 11.00 ml. of 0.004697 *N* sodium thiosulfate; calcd. for 1 mole of acetic acid, 1 mole of 2-methylbutyric acid and 1 mole of isobutyric acid, as expected for structure II, 13.1 ml.

(9) Melting points are corrected for stem exposure. Values of $[\alpha]D$ have been approximated to the nearest degree. Infrared spectra were determined on a Baird model B double beam infrared recording spectrophotometer and unless otherwise stated chloroform was used as a solvent. Microanalyses were carried out by Dr. S. M. Nagy and his associates at the Massachusetts Institute of Technology on samples dried under reduced pressure at 110°. "Petroleum ether" refers to the fraction of boiling point 60–80°.

(10) The paper chromatographic system used was that of J. Levine and H. Fischbach. *J. Am. Pharm. Assoc., Sci. Ed.*, **46**, 191 (1957); ethylene chloride-cellosolve acetate–pyridine, (15:10:1 by volume).

(11) We thank Dr. G. S. Myers of Ayerst, McKenna and Harrison, Ltd., for samples of desacetylprotoveratrines A and B, and Mr. Murle Klohs of Riker Laboratories for a sample of desacetylprotoveratrine B.

7-Dehydrodesacetylprotoveratrine A 16-Isobutyrate (III).—7-Desacetylprotoveratrine A 16-isobutyrate (100 mg.), m.p. 229–232° dec., was dissolved in acetic acid (10 ml.), treated with 0.66 *N* chromium trioxide in 98.5% acetic acid (1.5 ml.), and allowed to stand at room temperature for 1 hour. The cooled reaction mixture was treated with aqueous sodium bisulfite to destroy the excess of the oxidizing agent, carefully basified with dilute ammonium hydroxide and extracted with chloroform. The chloroform extract was dried over anhydrous sodium sulfate and evaporated to yield a resin which readily crystallized from ether as prisms (80 mg.), m.p. 226–227° dec. The compound was recrystallized from acetone–petroleum ether as prisms (70 mg.), m.p. 239–241° dec., $[\alpha]^{21}D$ −47° (*c* 1.00, pyr.).

Anal. Calcd. for $C_{43}H_{65}O_{14}N \cdot H_2O$: C, 61.63; H, 8.05. Found: C, 61.72; H, 7.96.

In a volatile acid determination,[12] 13.50 mg. of the compound yielded an amount of acid equivalent to 9.95 ml. of 0.004697 *N* sodium thiosulfate; calcd. for 1 mole of acetic acid, 1 mole of (*l*)-2-methylbutyric acid and 1 mole of isobutyric acid, as expected for structure III, 10.3 ml.

Protoverine 3,6,15,16-Tetraacetate (V).—Protoverine 3,6,16-triacetate[8] (3 g.), m.p. 236–238° dec., was dissolved in pyridine (35 ml.), cooled in ice and treated with acetyl chloride (0.7 ml.). The reaction mixture was allowed to warm to room temperature and stand overnight. The cooled solution was basified with dilute ammonium hydroxide and extracted with chloroform. The chloroform extract was dried over anhydrous sodium sulfate and evaporated to yield a resin which was chromatographed on Merck acid-washed alumina (70 g.). The column yielded to 50% benzene–chloroform, the known[8] protoverine 3,6,7,15,16-pentaacetate (300 mg.); to chloroform, a resin which was crystallized with difficulty from acetone–petroleum ether as prisms (1.4 g.), m.p. 228–231° dec. The compound was recrystallized from acetone–petroleum ether as colorless prisms (1 g.), m.p. 235–236° dec., $[\alpha]^{24}D$ −1° (*c* 1.05, pyr.).

Anal. Calcd. for $C_{35}H_{51}O_{13}N \cdot {}^1/_2H_2O$: C, 59.81; H, 7.46; acetyl, 24.50. Found: C, 59.92; H, 7.42; acetyl, 22.97.

7-Dehydroprotoverine 3,6,15,16-Tetraacetate (VI).—Protoverine 3,6,15,16-tetraacetate (1.35 g.), m.p. 233–234° dec., was dissolved in acetic acid (18 ml.), treated with 0.66 *N* chromium trioxide in 98.5% acetic acid (45 ml.) and allowed to stand at room temperature for 2 hours. The cooled reaction mixture was treated with aqueous sodium bisulfite to destroy the excess of the oxidizing agent, carefully basified with dilute ammonium hydroxide and extracted with chloroform. The chloroform extract was dried over anhydrous sodium sulfate and evaporated to yield a resin which was chromatographed on Merck acid-washed alumina (20 g.). The column yielded to mixtures of benzene–chloroform, a yellow oil; to chloroform and to 1% methanol–chloroform, a resin. The resin was crystallized from acetone–petroleum ether as needles (1.1 g.), m.p. 228–229° dec. The compound was recrystallized from acetone–petroleum ether as colorless needles (1 g.), m.p. 228–229° dec., $[\alpha]^{22}D$ −39° (*c* 1.18, pyr.).

Anal. Calcd. for $C_{35}H_{49}O_{13}N$: C, 60.75; H, 7.13; acetyl, 24.83. Found: C, 60.38; H, 7.09; acetyl, 25.96.

Protoverine 6,16-Diacetate (XIV). **A. From Protoverine 14,15-Acetonide 3,6,16-Triacetate.**—Protoverine 14,15-acetonide 3,6,16-triacetate[8] (18 g.), m.p. 261–262° dec., was dissolved in 2% hydrochloric acid (600 ml.) and allowed to stand at room temperature for 20 hours. The cooled solution was basified with dilute ammonium hydroxide and extracted with chloroform. The chloroform extract was dried over anhydrous sodium sulfate and evaporated to yield a resin which was crystallized from acetone to give prisms (2 g.), m.p. 246–248° dec. The mother liquor was evaporated to yield a resin which was dissolved in 2% hydrochloric acid (500 ml.) and allowed to stand at room temperature for 42 hours. An identical work-up afforded prisms (1.45 g.), m.p. 246–248° dec. A sample was recrystallized dec., $[\alpha]^{25}D$ −11° (*c* 1.03, pyr.).

Anal. Calcd. for $C_{31}H_{47}O_{11}N$: C, 61.06; H, 7.77; acetyl, 14.12. Found: C, 60.69; H, 8.01; acetyl, 14.48.

B. From Protoverine 14,15-Acetonide 6,16-Diacetate.—Protoverine 14,15-acetonide 6,16-diacetate (4.8 g.), m.p. 236–238° dec., was dissolved in 2% hydrochloric acid (180 ml.) and allowed to stand at room temperature for 16 hours. The cooled solution was basified with dilute ammonium hydroxide and extracted with chloroform. The chloroform extract was dried over anhydrous sodium sulfate and evaporated to yield a resin (4 g.). A paper chromatogram[10] indicated that this resin was virtually pure protoverine 6,16-diacetate and consequently the resin was used, without further purification, for synthetic purposes.

Protoverine 14,15-Acetonide 6,16-Diacetate (XIII).—A mixture of protoverin 14,15-acetonide 3,6,16-triacetate (11.5 g.), m.p. 261–262° dec., *t*-butyl alcohol (1 l.) and sodium borohydride (2.5 g.) was heated under reflux for 1 hour, cooled to 25° and treated with water (50 ml.). The solution was allowed to stand at room temperature for 15 minutes, acidified with acetic acid (75 ml.) and evaporated under reduced pressure. The residue was taken up in water, basified with dilute ammonium hydroxide and extracted with chloroform. The chloroform extract was dried over anhydrous sodium sulfate and evaporated to yield a resin which was chromatographed on Merck acid-washed alumina (180 g.). The column yielded to chloroform and to 1% methanol–chloroform, a resin which was crystallized from ether as prisms (7.8 g.), m.p. 230–235° dec. A paper chromatogram[10] indicated that the material contained a small amount of impurity. Three recrystallizations from acetone–petroleum ether yielded protoverine 14,15-acetonide 6,16-diacetate, 4.8 g., m.p. 236–238° dec.

Sodium Periodate Titrations.—The titrations were performed as described in an earlier paper.[8] The results are shown in Table I.

TABLE I

PERIODATE OXIDATIONS

Substrate	Mole equiv. of sodium periodate consumed[a] (hr.)
Protoverine	
6,16-diacetate (XIV)	1.9 (1.5), 2.2 (4.5)
15-(*l*)-2′-methylbutyrate 6,16-diacetate (XV)	0.9 (1.5), 1.0 (2.5)
15-(*l*)-2′-methylbutyrate	1.0 (1), 1.0 (2.5)
3,6,15,16-tetraacetate (V)	0.1 (5)

[a] The last uptake recorded in each case is the one beyond which no significant change occurred on further standing.

Chromic acid titration was performed as described in an earlier paper.[8] After 1 hour and after 3 hours, protoverine 3,6,15,16-tetraacetate (V) had consumed 0.7 and 0.8 oxygen equivalent of chromic acid, respectively.

Protoverine 15-(*l*)-2′-Methylbutyrate 6,16-Diacetate (XV).—A solution of protoverine 6,16-diacetate (1 g.), m.p. 248–249° dec., in pyridine (6 ml.) was cooled to 0°, treated with (*l*)-2-methyl-butyryl chloride[12] (0.3 ml.) and allowed to stand at room temperature for 16 hours. The cooled solution was basified with dilute ammonium hydroxide and extracted with chloroform. The chloroform extract was dried over anhydrous sodium sulfate and evaporated to yield a resin which was chromatographed on Merck acid-washed alumina (20 g.). The column yielded to chloroform, a resin (165 mg.); to 1% methanol–chloroform, a solid (600 mg.) which was crystallized from acetone–petroleum ether as needles (500 mg.), m.p. 217–219° dec. The compound was recrystallized from acetone–petroleum ether as long, colorless needles (475 mg.), m.p. 217–219° dec., $[\alpha]^{24}D$ −26° (*c* 0.95, pyr.). A paper chromatogram[10] indicated that the material was homogeneous.

Anal. Calcd. for $C_{36}H_{55}O_{12}N \cdot H_2O$: C, 60.74; H, 8.07. Found: C, 60.65; H, 7.69.

In a volatile acid determination[12] 6.24 mg. of the compound yielded an amount of acid equivalent to 2.75 ml. of 0.009375 *N* sodium thiosulfate; calcd. for 2 moles of acetic acid and 1 mole of (*l*)-2-methylbutyric acid, as expected for structure XV, 2.80 ml.

Upon acetylation, this compound afforded the known[6] protoverine 15-(*l*)-2′-methylbutyrate 3,6,7,16-tetraacetate.

A 10-mg. sample of the triester was oxidized with sodium periodate under conditions described for a sodium periodate titration.[8] After 2 hours, the solution was basified with

(12) F. L. Weisenborn, J. W. Bolger, D. B. Rosen, L. T. Mann, L. Johnson and H. L. Holmes, THIS JOURNAL, **76**, 1792 (1954).

dilute ammonium hydroxide and extracted with chloroform. The chloroform extract was dried over anhydrous sodium sulfate and evaporated. The amorphous residue (5 mg.) showed absorption at 3.65, 5.62 and 5.80 μ.

Protoverine 6-Acetate 15-(*l*)-2′-Methylbutyrate (XI).—A solution of protoverine 15-(*l*)-2′-methylbutyrate 6,16-diacetate (540 mg.), m.p. 217–219° dec., in methanol (15 ml.) was allowed to stand at room temperature for 11 hours. The methanol was evaporated under reduced pressure and the residue was chromatographed on Merck acid-washed alumina (10 g.). The column yielded to chloroform a resin (60 mg.). A paper chromatogram[10] indicated that this resin was mainly starting material. The column yielded to 1% methanol–chloroform a resin (230 mg.) which was crystallized from chloroform–petroleum ether as needles (200 mg.), m.p. 238–239° dec. Two recrystallizations from chloroform–petroleum ether gave fine colorless needles (150 mg.), m.p. 248–249° dec., $[\alpha]^{24}D$ −23° (*c* 1.01, pyr.).

Anal. Calcd. for $C_{34}H_{53}O_{11}N\cdot CHCl_3$: C, 54.51; H, 7.06. Found: C, 54.79; H, 7.02.

In a volatile acid determination,[12] 11.97 mg. of the compound yielded an amount of acid equivalent to 3.15 ml. of 0.009375 *N* sodium thiosulfate; calcd. for 1 mole of acetic acid and 1 mole of (*l*)-2-methylbutyric acid, as expected for structure XI, 3.31 ml.

A 10-mg. sample of this compound was oxidized with sodium periodate under conditions described for a sodium periodate titration.[8] After 2 hours, the solution was basified with dilute ammonium hydroxide and extracted with chloroform. The chloroform extract was dried over anhydrous sodium sulfate and evaporated. The amorphous residue (5.5 mg.) showed absorption at 3.65, 5.62 and 5.80 μ.

Conversion of Desacetylprotoveratrine B to Protoverine 6-Acetate 15-(*l*)-2′-Methylbutyrate.—A solution of desacetylprotoveratrine B (250 mg.), m.p. 201–203° dec., in 5% acetic acid (6 ml.) was treated with a solution of periodic acid (250 mg.) in a mixture of water (3 ml.) and *t*-butyl alcohol (18 ml.). The solution was allowed to stand at room temperature for 1 hour, the excess of the oxidizing agent was destroyed by rapid addition of 0.1 *N* aqueous sodium arsenite (25 ml.) and the solution was extracted with chloroform. The chloroform extract was dried over anhydrous sodium sulfate and evaporated to yield a resin which was chromatographed on Merck acid-washed alumina (8 g.). The column yielded to chloroform and to 2% methanol–chloroform, a yellow oil; to 5% methanol–chloroform, a white solid. The solid was crystallized from acetone as chunky rods (85 mg.), m.p. 241–242° dec. The compound was recrystallized from chloroform–petroleum ether as fine needles (62 mg.), m.p. 248–249° dec. The m.p. was not depressed on admixture with protoverine 6-acetate 15-(*l*)-2′-methlybutyrate. The paper chromatographic behavior[10] and infrared spectra (potassium bromide pellet) of the respective samples were identical.

Conversion of Desacetylprotoveratrine A to Protoverine 6-Acetate 15-(*l*)-2′-Methylbutyrate.—A solution of desacetylprotoveratrine A (130 mg.), m.p. 201–202° dec., and sodium borohydride (45 mg.) in a mixture of pyridine (10 ml.) and *t*-butyl alcohol (10 ml.) was allowed to stand at room temperature for 30 minutes. The excess of the borohydride was destroyed by addition of acetic acid (5 ml.), the solution basified with dilute ammonium hydroxide and extracted with chloroform. The chloroform extract was dried over anhydrous sodium sulfate and evaporated to yield a resin which was chromatographed on Merck acid-washed alumina (7 g.). The column yielded to chloroform and to 2% methanol–chloroform a starting material (55 mg.); to 5% methanol–chloroform, a resin. The resin was crystallized from chloroform–ether as needles (20 mg.). A paper chromatogram[10] indicated that the product was slightly impure. Two recrystallizations from chloroform–petroleum ether effectively purified the material and afforded colorless needles (6 mg.), m.p. 244–247° dec. The m.p. was not depressed on admixture with protoverine 6-acetate 15-(*l*)-2′-methylbutyrate. The paper chromatographic behavior[10] and infrared spectra (potassium bromide pellet) of the respective samples were identical.

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

The Alkaloids of *Nerine bowdenii* W. Wats. and *Crinum moorei* J. D. Hook.[1]

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The seeds of *Crinum moorei* J. D. Hook. have been found to contain the alkaloids lycorine, crinamidine, powelline, crinine and 1-acetyllycorine. 1-Acetyllycorine had not been isolated previously from natural sources. The bulbs of *Nerine bowdenii* W. Wats. have been shown to contain at least sixteen alkaloids, four of which have not been reported to date. The method of isolation is described in detail, and the new alkaloids from both sources are characterized. One of the new alkaloids was identified as (+)-epicrinine (III). The conversion of (+)-epicrinine to (±)-crinane is reported.

In the course of studies in this Laboratory on the structures of undulatine[3] and crinamidine,[4] we sought plant materials which would provide these alkaloids in quantity and at reasonable cost. The isolation of these alkaloids from the bulbs of *Nerine undulata* (L.) Herb.,[4] *N. flexuosa* Herb.,[5] *N. bowdenii* W. Wats.[6] and *Crinum moorei* Hook. f.[7] has been reported. Of these plant sources, only the latter two are relatively abundant in this country, and the yields of undulatine and crinamidine from them were reported to be less than 0.01%. Although we were unable to find plants that were appreciably richer in these bases, a number of interesting new alkaloids were discovered in the course of the exploratory studies.

Through the courtesy of Mr. N. F. Giridlian,[8] we were able to purchase quantities of the seeds of *Crinum moorei* J. D. Hook. In addition to the expected alkaloids crinamidine, powelline, lycorine and crinine, a new alkaloid, $C_{18}H_{19}NO_5$, was obtained, m.p. 220–221°, $[\alpha]^{28.5}_{589}$ −96° (chloroform). Degradative evidence, which will be presented later in this paper, established the alkaloid as 1-acetyllycorine (I, R = CH_3CO, R_1 = H).

The isolations from *N. bowdenii* were considerably more complex. In an earlier study of the alkaloids of this bulb, Boit and Ehmke[6] reported the

(1) Paper XV of a series on Amaryllidaceae alkaloids; previous paper: P. F. Highet and W. C. Wildman, *J. Org. Chem.*, in press.

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(3) E. W. Warnhoff and W. C. Wildman, *Chemistry & Industry*, 1293 (1958).

(4) H.-G. Boit, *Chem. Ber.*, **89**, 1129 (1956).

(5) H.-G. Boit and H. Ehmke, *ibid.*, **90**, 369 (1957).

(6) H.-G. Boit and H. Ehmke, *ibid.*, **89**, 2093 (1956).

(7) H.-G. Boit, *ibid.*, **87**, 1704 (1954).

(8) Oakhurst Gardens, Arcadia, Calif.