Veratrum Alkaloids L

Structure-Activity Relationships in a Series of Synthetic Hypotensive Analogs of the Protoveratrines

By S. MORRIS KUPCHAN, EIICHI FUJITA, JOHN C. GRIVAS, and LAWRENCE C. WEAVER

A study aimed at further elucidation of the relationship between hypotensive activity and structure among analogs of the protoveratrines is reported. A series of synthetic protoverine tetraesters, which differ from each other only in the nature of the acid residue affixed at C_{15}, have been prepared and subjected to preliminary pharmacological evaluation. The results indicate that alteration in the structure of the ester affixed at C_{15} in analogs of the protoveratrines profoundly affects hypotensive potency.

Two recent developments have stimulated studies involving the synthesis and pharmacological evaluation of analogs of the protoveratrines. On the chemical side, our elucidation of the complete structures and configurations of protoveratrine A (I) and protoveratrine B (II) (1) and several related hypotensive ester alkaloids (2, 3) made feasible the systematic alteration of the molecules. On the clinical side, recent work has demonstrated significant differences between protoveratrine A and protoveratrine B when the substances are administered orally, particularly with regard to hypotensive-emetic relationships (4–6). Since protoveratrines A and B differ only in the nature of the ester moiety at C_3, it was deemed desirable that new protoverine (III) (7) esters, which differ from the protoveratrines solely in the nature of the acid residues, should be prepared and subjected to pharmacological evaluation.

In our previous studies the compounds examined were protoverine derivatives with varying substitution at positions 3, 4, 6, 7, 14, 15, and 16 (8–10). The results supported the following generalizations (*a*) esterification at position 16 with acetate or isobutyrate is accompanied by a profound loss in activity, (*b*) esterification at positions 3 and 15 is required for high activity, (*c*) esterification at position 15 with a branched chain acid is advantageous, (*d*) the ester grouping at position 3 need not be branched, (*e*) positions 6 and 7 need not be esterified for good activity, (*f*) esterification at position 7 with a branched chain acid may be disadvantageous, (*g*) oxidation of the alcohol group at position 16 to a ketone group is accompanied by a loss in activity, (*h*) acetonide formation at positions 14 and 15 is accompanied by a profound loss in activity, (*i*) esterification at position 4 may be disadvantageous, and (*j*) considerable alteration can be made in the structure of the ester affixed at 3 without greatly altering hypotensive potency.

In view of the aforementioned facts that minor differences in the ester affixed at 3 significantly affect the hypotensive-emetic ratio of the protoveratrines and that changes in the structure of the ester at C_3 do not greatly alter hypotensive potency, it was deemed desirable that additional compounds which differ from each other only in the nature of the ester at C_{15} should be prepared and subjected to pharmacological evaluation. The present report details the synthesis and preliminary pharmacological evaluation of three new analogs of the protoveratrines. In the new analogs, the isobutyrate residue, previously demonstrated to be an effective substitute for the naturally-occurring substituted α-methylbutyrate residues (8), is affixed at C_3. Treatment of protoverine (III) with acetone and hydrochloric acid yielded the 14, 15-acetonide (IV), and acetylation then gave protoverine 14, 15-acetonide 3, 6, 16-triacetate (V). Upon treatment with sodium borohydride in *t*-butanol, protoverine 14, 15-acetonide 6, 16-diacetate (VIII) was obtained (7,11). Acylation with isobutyryl chloride in pyridine afforded the 14, 15-acetonide 6, 16-diacetate 3-isobutyrate (VII), and dilute acid gave protoverine 6, 16-diacetate 3-isobutyrate (VI). The latter triester served as the key intermediate for all the further synthesis. Partial acylation with the appropriate acid halide introduced the desired new ester at position 15 (IX, R = tosyl; XII, R = tigloyl; XV, R = nicotinyl). Treatment with acetic anhydride gave

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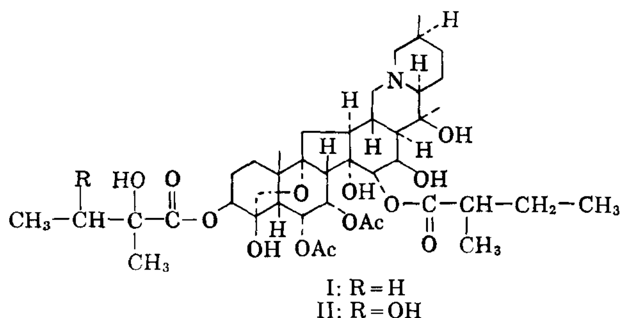

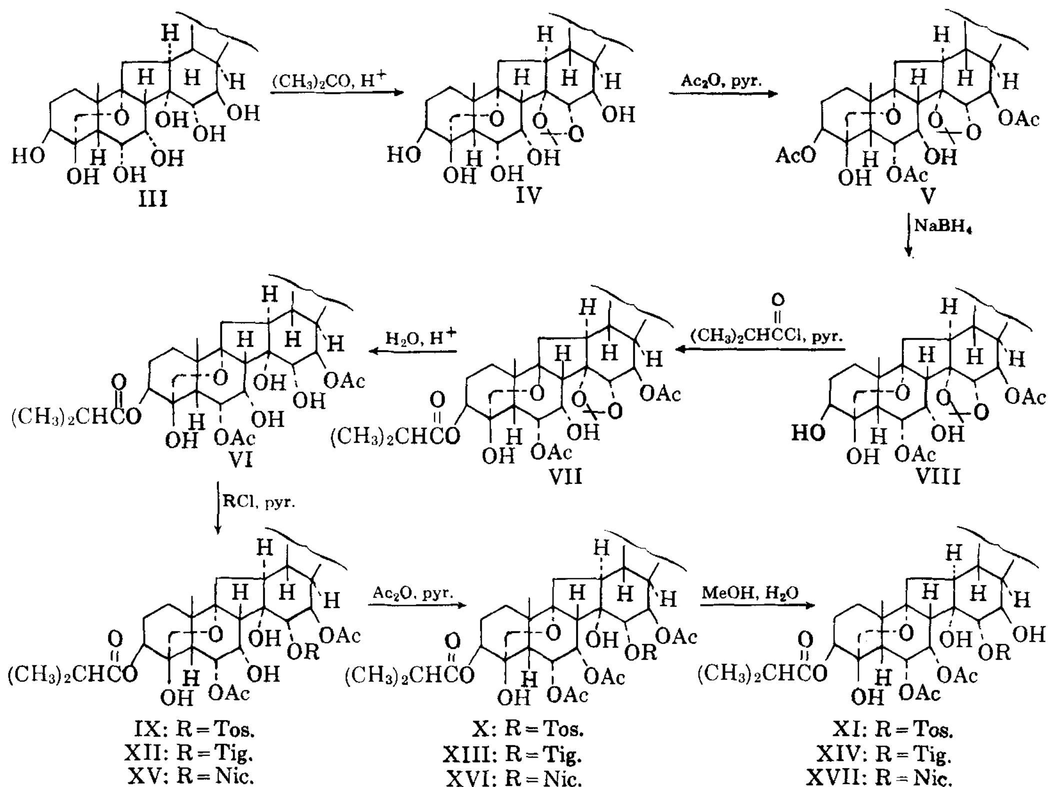

the 3, 6, 7, 15, 16-pentaesters X, XIII, and XVI, and methanolysis selectively removed the 16-acetate to yield the desired 3, 6, 7, 15-tetraesters XI, XIV, and XVII.

The three new protoveratrine analogs XI, XIV and XVII have been investigated for hypotensive activity in the unanesthetized dog and the results are presented in Table I. Adult mongrel dogs unselected as to sex were employed in all experiments described. The femoral artery of the unanesthetized dog was catheterized using locally administered procaine for anesthesia. A mercury manometer and smoked kymogram were used to record mean blood pressure. The dog was placed in an upright position. Test drugs were administered intravenously as freshly prepared aqueous solutions, usually acidic. The effects of these drugs on systemic blood pressure and on emesis production were determined and the results are summarized in Table I. Responses to protoveratrine A and B, and to protoverine 3, 15-diisobutyrate 6,7-diacetate (8) are included for comparison. The 15-isobutyrate was moderately potent as a hypotensive agent, although the activity was appreciably reduced as compared to the protoveratrines. The 15-tiglate (XIV) retained activity, but the order of activity was considerably lower than that of the 15-isobutyrate. When the ester affixed at position 15 was tosylate (XI) or nicotinate (XVII), there was almost complete loss of activity within the doses tested.

It is apparent from the data reported herein that alterations in the structure of the ester moiety affixed at position 15 greatly affect the hypotensive potency. The situation contrasts

TABLE I.—EMETIC AND HYPOTENSIVE ACTIVITIES OF PROTOVERINE DERIVATIVES IN UNANESTHETIZED DOGS

	Mcg./Kg., i.v.	No. Dogs	Mean Blood Pressure: Change, %	Mean Blood Pressure: Duration, min.	Emesis: No. Vomiting / No. Tested	Emesis: Onset, min.
Protoveratrine A (I)	1	5	−22	39	1/5	87
	2	3	−37	75	2/3	24, 61
Protoveratrine B (II)	2	6	−33	25	4/6	2, 21 95, 95
Protoverine 3,15-diisobutyrate 6,7-diacetate	2	2	0	0	0/2	
	4	3	−67	17	0/3	
	8	4	−62	8	0/4	
	16	2	−77	>30	2/2	17, 112
Protoverine 3-isobutyrate 6,7-diacetate 15-tosylate (XI)	4	1	0	0	0/1	
	16	1	−12	55	0/1	
	32	2	−37	1	0/2	
	64	2	−74	1	0/2	
Protoverine 3-isobutyrate 6,7-diacetate 15-tiglate (XIV)	2	3	0	0	0/2	
	64	2	−54	>40	1/2	4
	128	2	−71	40	1/2	1
Protoverine 3-isobutyrate 6,7-diacetate 15-nicotinate (XVII)	4	1	+43	5	0/1	
	64	1	0	...	0/1	
	128	2	−42	1	0/2	

with that of position 3-analogs of the protoveratrines, among which considerable alterations can be made in the structure of the ester without greatly altering hypotensive potency (10).

EXPERIMENTAL

Melting points are corrected for stem exposure. Values of $[\alpha]_D$ have been approximated to the nearest degree. 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°.

Protoverine 14,15-Acetonide 6,16-Diacetate (VIII).—A mixture of 16.2 Gm. of protoverine 14, 15-acetonide, 3, 6, 16-triacetate (V) (7), 1.52 L. of *t*-butanol and 3.8 Gm. of sodium borohydride was stirred at room temperature for three hours. A 70 ml. quantity of water was added, the solution was allowed to stand for 15 minutes, acidified with 105 ml. of acetic acid and evaporated under reduced pressure. The residue was taken up in water, made alkaline 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 272 Gm. of Merck acid-washed alumina. The column yielded to methanol-chloroform (0.3–1.7%) a resin which was crystallized from acetone as prisms, (8.74 Gm.), m.p. 236–238° decompn. (11). A paper chromatogram[1] indicated that the material was homogeneous.

Protoverine 14, 15-Acetonide 3-Isobutyrate 6, 16-Diacetate (VII).—A 13.73 Gm. quantity of protoverine 14, 15-acetonide 6, 16-diacetate (VIII) was dissolved in 135 ml. of pyridine, cooled in an ice bath, and isobutyryl chloride (6.66 ml., *ca.* 3 mole equivalents) was slowly added with stirring. The flask was protected from moisture with a calcium chloride tube. After completion of the acid chloride addition, the reaction mixture was allowed to stand at room temperature for 24 hours. The solution was treated with ice water, made alkaline with dilute ammonium hydroxide and extracted with chloroform. The chloroform extract was dried over anhydrous sodium sulfate and evaporated to dryness. To remove all of the pyridine, the residue was repeatedly dissolved in benzene and evaporated to dryness, whereupon a yellow resin weighing 14.42 Gm. was obtained. The material was chromatographed on 225 Gm. of Merck acid-washed alumina and yielded to chloroform-benzene (65–80% chloroform), to chloroform, and to methanol-chloroform (0.3–3.3% methanol) a material which was crystallized from ether as prisms, (10.96 Gm.), m.p. 173–178° decompn. A paper chromatogram[1] indicated that the material was homogeneous. A sample was twice recrystallized for analysis from ether to yield prisms, m.p. 175–177° decompn., $[\alpha]_D^{25}$ + 28° (c 1.06, pyr.).

Anal.—Calcd. for $C_{38}H_{57}NO_{12} \cdot H_2O$: C, 61.87; H, 8.00. Found: C, 61.67, H, 7.64.

Protoverine 3-Isobutyrate 6, 16-Diacetate (VI).—A 6.20 Gm. quantity of protoverine 14, 15-acetonide 6, 16-diacetate (VII) was dissolved in 160 ml. of dilute hydrochloric acid (1:4) and the solution was allowed to stand at room temperature for 40 minutes. The reaction mixture was treated with ice, made alkaline with dilute ammonium hydroxide and extracted with chloroform. The chloroform extract was dried over anhydrous sodium sulfate and evaporated under reduced pressure to yield an almost colorless residue. Chromatography on 75 Gm. of Merck acid-washed alumina yielded to chloroform-benzene (35–80%), to chloroform, and to methanol-chloroform (0.5–1.5%), a resin which was crystallized from acetone as rods (5.02 Gm.), m.p. 221–224° decompn. A paper chromatogram[1] indicated that the material was homogeneous. A sample was twice recrystallized from acetone as rods, m.p. 225-226° decompn., $[\alpha]_D^{25}$ − 19° (c 1.15, pyr.).

Anal.—Calcd. for $C_{35}H_{53}NO_{12} \cdot {}^1/_2\, H_2O$: C, 61.04; H, 7.84. Found: C, 60.80; H, 7.48.

Protoverine 3-Isobutyrate 6,16-Diacetate 15-Tosylate (IX).—A 1.9 Gm. quantity of tosyl chloride was added portionwise to a solution containing 679 mg. of protoverine 3-isobutyrate 6, 16-diacetate (VI) in 6 ml. of pyridine cooled in an ice bath. The mixture was allowed to stand at room temperature for 24 hours. The reaction mixture was treated with ice, water, and dilute ammonium hydroxide to

[1] The paper chromatographic system was that of Levine and Fischbach (12): the solution was prepared by adding 1 ml. of formic acid to the separated solvent layer of the system *n*-butylacetate: *n*-butanol: water (10:25:10 ml.).

pH 8.5 and extracted with chloroform. The chloroform extract was dried over anhydrous sodium sulfate and evaporated to dryness. The residue was repeatedly dissolved in benzene and evaporated to dryness to remove pyridine traces. Crystallization of the residue from acetone yielded prisms weighing 506 mg., m.p. 224–226° decompn. Paper chromatographic analysis[2] indicated the material was homogeneous. The product was twice recrystallized from acetone to yield prisms, m.p. 230–231° decompn., $[\alpha]_D^{26}$ − 5° (c 1.37 pyr.).

Anal.—Calcd. for $C_{42}H_{59}NO_{14}S$: C, 60.50; H, 7.08; S., 3.84. Found: C, 60.73; H, 7.01; S, 3.85.

Protoverine 3-Isobutyrate 6,7,16-Triacetate 15-Tosylate (X).—A solution containing 416 mg. of protoverine 3-isobutyrate 6,16-diacetate 15-tosylate (IX) in 3 ml. of pyridine was treated with 12 ml. of acetic anhydride and heated in a water bath at 80° for 2.5 hours. The reaction mixture was treated with ice, water, and dilute ammonium hydroxide to pH 8.5 and extracted with chloroform. The chloroform extract was dried over anhydrous sodium sulfate and evaporated to dryness. The residual resin was crystallized from acetone as prisms, (357 mg.), m.p. 245–247° decompn. A paper chromatogram[2] indicated the homogeneity of the material. Recrystallization from acetone gave prisms, m.p. 245–247° decompn., $[\alpha]_D^{27}$ − 38° (c 1.95, pyr.).

Anal.—Calcd. for $C_{44}H_{61}NO_{15}S$: C, 60.34; H, 6.97; S, 3.65. Found: C, 60.31; H, 7.04; S, 3.44.

Protoverine 3-Isobutyrate 6,7-Diacetate 15-Tosylate (XI).—A solution containing 350 mg. of protoverine 3-isobutyrate 6,7,16-triacetate 15-tosylate (X) in 30 ml. of methanol was allowed to stand at room temperature for 64 hours. Evaporation to dryness left a colorless solid which was crystallized from acetone, to yield prisms, (202 mg.), m.p. 194–195° followed by decomposition at 235–237°. Paper chromatographic analysis[3] indicated the principal product was contaminated with components of lower R_f. Two recrystallizations from acetone yielded prisms weighing 99 mg., m.p. 199–200° followed by decomposition at 215°, $[\alpha]_D^{25}$ − 31° (c 1.14 pyr.), and this material was demonstrated to be homogeneous by paper chromatography.

Anal.—Calcd. for $C_{42}H_{59}NO_{14}S$: C, 60.50; H, 7.08; S, 3.84. Found: C, 60.35; H, 7.19; S, 3.80.

Protoverine 3-Isobutyrate 6,16-Diacetate 15-Tiglate (XII).—A 0.15 ml. quantity of tigloyl chloride was added dropwise to a solution containing 340 mg. of protoverine 3-isobutyrate 6,16-diacetate (VI) in 3.4 ml. of pyridine cooled in an ice bath. The mixture was allowed to stand at 0° for 1 hour and then at room temperature for 18 hours. Workup as described for IX gave a yellow resin which was chromatographed on 12.5 Gm. of Merck acid-washed alumina. The column yielded to chloroform and to methanol-chloroform (0.5–1.5%) a resin which was crystallized from acetone to yield plates: first crop, 155 mg., m.p. 229–230° decompn.; second crop, 29 mg., m.p. 225–226° decompn. Paper chromatography[2] indicated that the first crop was homogeneous and that the second crop was contaminated with a small proportion of a second substance. Recrystallization of a sample of the first crop from acetone yielded plates, m.p. 232–233° decompn., $[\alpha]_D^{27}$ + 13° (c 1.85, pyr.).

Anal.—Calcd. for $C_{40}H_{59}NO_{13}$: C, 63.06; H, 7.75. Found: C, 63.17; H, 7.81.

Protoverine 3-Isobutyrate 6,7,16-Triacetate 15-Tiglate (XIII).—A solution containing 304 mg. of protoverine 3-isobutyrate 6,16-diacetate 15-tiglate (XII) in 2.4 ml. of pyridine was treated with 1.0 ml. of acetic anhydride as described for X. Workup in the usual manner gave a resin which was crystallized from acetone as prisms, (214 mg.), m.p. 260–261° decompn. A second crop weighing 49 mg., m.p. 255–259° decompn., was also obtained. Both crops were shown to be homogeneous by paper chromatography[2]. A sample was twice recrystallized for analysis from acetone to yield prisms, m.p. 264–265° decompn., $[\alpha]_D^{28}$ − 22° (c 1.55, pyr.).

Anal.—Calcd. for $C_{42}H_{61}NO_{14} \cdot H_2O$: C, 61.38; H, 7.67. Found: C, 61.63; H, 7.65.

Protoverine 3-Isobutyrate 6,7-Diacetate 15-Tiglate (XIV).—A solution containing 545 mg. of protoverine 3-isobutyrate 6,7,16-triacetate 15-tiglate (XIII) in 55 ml. of methanol was allowed to stand at room temperature for 27 hours. Evaporation to dryness left a colorless resin which was chromatographed on 11 Gm. of Merck acid-washed alumina. The column yielded to chloroform a resin which was crystallized from ether as prisms (116 mg.). Recrystallization from ether gave prisms weighing 80 mg., m.p. 229–233°, $[\alpha]_D^{28}$ − 22° (c 1.05, pyr.), shown to be homogeneous by paper chromatography.[4]

Anal.—Calcd. for $C_{40}H_{59}NO_{13}$: C, 63.06; H, 7.75. Found: C, 63.06; H, 7.76.

Protoverine 3-Isobutyrate 6,16-Diacetate 15-Nicotinate (XV).—A 0.26 ml. quantity of nicotinyl chloride was added dropwise to a solution containing 679 mg. of protoverine 3-isobutyrate 6,16-diacetate (VI) in 6.8 ml. of pyridine cooled in ice water. After 17 hours at room temperature, the reaction mixture was worked up by the procedure described for IX to yield a resin from chloroform. Crystallization from acetone gave prisms weighing 520 mg., m.p. 200–204° decompn., and a second crop weighing 76 mg., m.p. 195–202° decompn. Both fractions were shown to be homogeneous by paper chromatography.[4] A sample was recrystallized for analysis from acetone to yield prisms, m.p. 200–205° decompn., $[\alpha]_D^{28}$ + 28° (c 1.53, pyr.).

Anal.—Calcd. for $C_{41}H_{56}N_2O_{13} \cdot H_2O$: C, 61.27; H, 7.23; N, 3.49. Found: C, 61.50; H, 6.92; N, 3.62.

Protoverine 3-Isobutyrate 6,7,16-Triacetate 15-Nicotinate (XVI).—A solution containing 770 mg. of protoverine 3-isobutyrate 6,16-diacetate 15-nicotinate (XV) in 6 ml. of pyridine was treated with 2.5 ml. of acetic anhydride as described for X. Workup in the usual manner gave a resin which was crystallized from acetone as prisms weighing 663 mg., m.p. 253–254° decompn. A sample was twice recrystallized from acetone to yield prisms, m.p. 256–257° decompn., $[\alpha]_D^{27}$ − 23° (c 1.79, pyr.).

Anal.—Calcd. for $C_{43}H_{58}N_2O_{14}$: C, 61.98; H, 7.02; N, 3.38. Found: C, 61.80; H, 7.02; N, 3.33.

Protoverine 3-Isobutyrate 6,7-Diacetate 15-Nicotinate (XVII).—A solution containing 346 mg. of

[2] The paper chromatographic system used was *n*-butyl acetate : *n*-butanol : formic acid (25 : 5 : 1 by volume) (12).
[3] The solvent system used was : *n*-butyl acetate : *n*-butanol : formic acid (100 : 1 : 5 by volume), saturated with water.

[4] The solvent system used was: 2,2,4-trimethylpentane: 4-methyl-2-pentanone: pyridine (10:5 : 1 by volume).

protoverine 3-isobutyrate 6,7,16-triacetate 15-nicotinate (XVI) in 57 ml. of methanol was allowed to stand at room temperature for 16 hours. Evaporation to dryness left a resin which resisted attempts at purification by column chromatography, but which yielded to preparative paper chromatography. The resin was dissolved in chloroform and applied to Whatman No. 4 paper (19 sheets, 6 × 18 inches) pretreated with phosphate buffer of pH 3.5. After development for 2.5 hours with the isooctane solvent system[4] and drying, a chloroform solution of Bromphenol Blue was sprayed over the papers as usual. The desired band was cut from the sheets and extracted with 2% methanol-chloroform in a Soxhlet extractor for 2 hours. The extract was shaken with dilute ammonium hydroxide to liberate the free base and remove the dye, and the chloroform solution was washed with water. The chloroform solution was dried over anhydrous sodium sulfate and evaporated to yield a colorless resin weighing 205 mg., which was shown to be homogeneous by paper chromatography.[4] Crystallization from acetone-ether gave colorless prisms weighing 139 mg., m.p. 227–229° decompn. Recrystallization gave prisms, m.p. 229–230° decompn., $[\alpha]^{27}_{D}$ − 1° (c 1.08, pyr.).

Anal.—Calcd. for $C_{41}H_{56}N_2O_{13}\cdot{}^1/_2\ H_2O$: C, 62.04; H, 7.18; N, 3.53. Found: C, 61.89; H, 7.11; N, 3.84.

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Veratrum Alkaloids LI

Hypotensive-Emetic Relationships in the Unanesthetized Dog Among Analogs of the Protoveratrines

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A study aimed at elucidation of the relationship between hypotensive and emetic activities in the unanesthetized dog among synthetic analogs of the protoveratrines is reported. Preliminary data indicate that a partial dissociation of hypotensive and emetic activities is demonstrable.

Veratrum and related plants have been used for medicinal purposes for hundreds of years. Galenical preparations were used in the Middle Ages for purposes of sorcery and mystical rites. Subsequently, the crude extracts have been used in the treatment of fevers, as local counterirritants in neuralgia, as cardiac tonics, as emetics, as crow poisons, and as insecticides (1, 2). The use of veratrum in the control of hypertension, at least in the United States, dates from the report of Baker in 1859 (3). Several attempts were made to introduce the use of veratrum extracts into medical practice during the second half of the nineteenth century, but these attempts were unsuccessful. The treatments during this period continued to employ crude extracts containing many alkaloids. The results achieved with these crude extracts were erratic and the treatments fell into disrepute. Some 50 years later, during the late 1930's, purified alkaloidal preparations responsible for the hypotensive activity of veratrum became available for the first time. Poethke in Germany (4) and Jacobs and Craig in the United States (5) improved the extraction and purification procedures and made available the first crystalline powerfully hypotensive alkaloid preparation, protoveratrine. Careful pharmacological investigation of the crystalline preparations, spearheaded by Krayer and his associates, demonstrated that the drugs were suitable for clinical trials (6). These clinical

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