(4.66 g., 0.01 mole) in 500 ml. of ethanol was refluxed with stirring with 16 g. of activated Raney nickel.[9] After 15 minutes, the mixture was filtered and concentrated to dryness *in vacuo*. The residue was dissolved in ethanol, treated with charcoal, filtered and cooled whereupon large needle-like crystals were formed, 2.8 g. (64%), m.p. 135–136°; light absorption properties: (in ethanol), maxima at 230 and 274 mμ, shoulder at 280 mμ. Essentially similar ultraviolet absorption properties were exhibited by 1-*O*-acetyl-3,5-di-*O*-benzoyl-2-deoxy-D-ribose[28] (maxima at 230 and 272 mμ, shoulder at 280 mμ.

Anal. Calcd. for $C_{24}H_{28}N_2O_6$: C, 65.92; H, 5.76; N, 6.39. Found: C, 65.75; H, 5.94; N, 6.13.

N-(2-Deoxy-β-D-ribofuranosyl)-2-oxo-5-methylhexahydropyrimidine.—4-Thiothymidine[3] (770 mg.) in 200 ml. of absolute ethanol was refluxed with 5 g. (wet weight) of activated Raney nickel for 15 minutes. After filtration from catalyst, the filtrate was concentrated to dryness and the residue dissolved in a small amount of ethanol. After several weeks in the refrigerator, white, crystalline needles formed (0.2 g.) which were recrystallized from ethanol, m.p. 186–187°. This product was devoid of light absorption in the ultraviolet.

Anal. Calcd. for $C_{10}H_{18}O_4N_2$: C, 52.17; H, 7.83; N, 12.17. Found: C, 52.23; H, 7.87; N, 12.31.

N-(2,3,5-Tri-*O*-benzoyl-β-D-ribosyl)-2-oxo-hexahydropyrimidine (II, R = OBz, R′ = H).—1-(2,3,5-Tri-*O*-benzoyl-β-D-ribosyl)-4-thiouracil[3] (5.72 g., 0.01 mole) was treated with Raney nickel[9] as in the case of the thymidine analog (*vide supra*). The residue obtained by removal of solvent was dissolved in ethanol, treated with charcoal, filtered and cooled. Small needle-like crystals were obtained; 3.0 g. (55%), m.p. 143–145°; light absorption properties (in ethanol): maximum at 230 mμ, shoulders at 273 and 280 mμ.

Anal. Calcd. for $C_{30}H_{28}N_2O_8$: C, 66.17; H, 5.18; N, 5.15. Found: C, 66.22; H, 5.22; N, 5.41.

Debenzoylation of II (R = H, R′ = CH_3 or R = OBz, R′ = H) with alcoholic ammonia or with sodium ethoxide yielded a glass. Spectral analysis (in ethanol) showed no selective absorption in the ultraviolet region. They were not investigated further.

Reduction of Uracil with Raney Nickel. Synthesis of 5,6-Dihydrouracil.—Uracil (1.12 g., 0.01 mole) in 500 ml. of water was refluxed with 15 g. of activated Raney nickel. After two hours (the absorption spectrum of the solution indicated the presence of some uracil) the catalyst was removed by filtration and the filtrate concentrated to dryness. The residue was dissolved in ethanol and cooled, 560 mg. (53%), m.p. 269–270 (Batt, *et al.*,[10] report 272–275°).

Reduction of 1-Methyluracil. Synthesis of 1-Methyl-5,6-dihydrouracil.—1-Methyluracil (1.26 g.) in 400 ml. of ethanol was stirred under reflux with 20 g. of activated Raney nickel for 6 hr. Spectral analysis of the reaction mixture indicated the presence of some unchanged starting material. After filtration and concentration of the filtrate to dryness, the residue was dissolved in hot ethyl acetate from which 1-methyl-5,6-dihydrouracil crystallized; 0.47 g. (34%), m.p. 169–170° (reported[14] m.p. 170–172°).

A similar product in 86% yield may be obtained by reduction of 1-methyluracil in water with rhodium-on-alumina catalyst at atmospheric pressure. A theoretical uptake (1 mole in 30 min.) was noted, m.p. 169–170° (mixed-melting point with material obtained by Raney nickel reduction (*vide supra*) was undepressed.

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(28) J. J. Fox and I. Wempen, unpublished synthesis.

[CONTRIBUTION FROM THE DEPARTMENT OF PHARMACOLOGY, HARVARD MEDICAL SCHOOL]

N-Alkyl Derivatives of Veratramine

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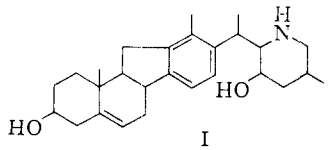
A description of the preparation of a series of N-alkyl derivatives of veratramine is given. Statements are made concerning the nature and significance of the pharmacological properties of the compounds.

Veratramine (I) has been shown to possess powerful cardiodecelerator properties which are manifested on the normal resting rate as well as on the elevated rate arising from accelerans stimulation or from the administration of sympathomimetic amines.[1] The pharmacodynamic effect, which appears to be mediated directly at the sino-atrial node of the mammalian heart, is neither annulled by the presence of atropine nor accompanied by a negative inotropic action (impairment of contractility) on the myocardium.



I

Following the original observations with the naturally occurring alkaloid, related compounds were found to harbor similar properties, although no other substance approached veratramine itself in absolute potency. Since the active alkanolamines of the early studies all were piperidine or pyrrolidine derivatives, it was considered for a time that the secondary degree of substitution of the nitrogen atom might be of prominence in those drug–receptor interactions which lead to evocation of the biological response. However, such a view became untenable when occasion arose to prepare, and to examine, N-methylveratramine, for the tertiary base was found to display a definite, although much attenuated, effect of the type characteristic of the parent compound.

On several counts, this finding was regarded of sufficient importance for further pursuit. Obviously, N-alkylation provides the opportunity of systematic modification of only a single variable in an extensible series of compounds suitable for comparative study. Moreover, the availability of highly active tertiary amines would permit greater ease of masking of the 3β- and 23-hydroxyl groups in less polar functions, a manner of alteration frequently of profound consequence for pharmacological behavior. In fact, considerable encouragement was offered by the very next compound to be synthesized, N-*n*-butylveratramine, which proved to be nearly as active as veratramine itself.

Additional N-alkylation products of the alkaloid

(1) O. Krayer, *J. Pharmacol. Expell. Therap.*, **96**, 422 (1949); **97**, 427 (1950).

then were prepared, including the ethyl, *n*-propyl, isobutyl, *n*-pentyl, *n*-hexyl and benzyl relatives. Of the total group of eight tertiary derivatives, N-*n*-butylveratramine remained the most outstanding member. It will be seen (Table I)[2] that cardiodecelerator activity increased regularly as the homologous set was ascended from N-methyl to N-*n*-butyl, whereupon it declined with the *n*-pentyl and *n*-hexyl compounds. With the latter two substances, dose–response curves disclosed a much slower rate of reaction than with the *n*-butyl and with its lower homologs. The isobutyl and benzyl tertiary bases showed only a very minimal grade of activity.

TABLE I

RELATIVE ACTIVITIES OF N-ALKYL DERIVATIVES

Veratramine = 100

	Heart–lung preparation of dog		Isolated guinea pig atrium		Acute toxicity in mice intravenous
	Resting rate	Elevated rate	Resting rate	Elevated rate	
Veratramine	100	100	100	100	100
Methyl	2	2	14	9	18
Ethyl	13	10	23	13	26
Propyl	53	27	62	39	..
Butyl	69	70	80	62	59
Pentyl	30	53	7	39	45
Hexyl	..	17	4	3	..
Isobutyl	9	8	2	2	6
Benzyl	..	1	..	2	..

In general, the acute toxicities of the compounds followed the order of their decelerator properties. Again, the *n*-pentyl and *n*-hexyl congeners were somewhat atypical in that the onset of lethal action was delayed, even after intravenous injection, as opposed to the usual prompt appearance of symptoms with the other substances.

At present, it is not possible to bring forward a persuasive mechanistic interpretation of the results. As expected, the pK_a values of the compounds were found to be virtually identical. Lipid–aqueous partition coefficients thus far have not been measured. In essence, the findings recall other homologous series which may be found throughout the pharmacological literature in which maximal activity is reached with a particular member. It must be conceded that most, if not all, of these earlier cases have, as yet, eluded rational explanation.

However, it is felt that the N-alkylveratramine derivatives give promise of furnishing an exemplary sequence for more penetrating study of this perplexing phenomenon. The possibility of pliant manipulation of a single, structurally quite simple change of pronounced influence within a large, complex molecule is readily apparent. Furthermore, the remarkably precise reproducibility of the pharmacodynamic response renders the situation a particularly attractive one for quantitative work.

The Experimental section of the present communication comprises a description of the preparation of the compounds which proceeded without exceptional incident by well established methods. N-Methylveratramine was procured by Clarke–Eschweiler methylation with formaldehyde and formic acid. The higher homologs were prepared by lithium aluminum hydride reduction, in ether or in tetrahydrofuran solution, of appropriate acyl amides. The latter, in turn, were obtained with acid anhydrides, or with acid chlorides, in anhydrous medium. Recourse to chromatography was required in certain instances in order to secure a crystalline product. A second source of N-*n*-butylveratramine was developed through direct alkylation with *n*-butyl bromide in *n*-butyl alcohol solution in the presence of sodium bicarbonate.

It is worthy of remark that the alkyl derivatives were found to be reluctantly soluble in 10% acetic acid, requiring a concentration of at least 20% for ready extraction by trituration of solid residues. Inasmuch as steroid amines, in general, form very slightly water-soluble salts with mineral acids, common practice in manipulative operations entails the use of 5 or 10% aqueous acetic acid in which even the weakest polycyclic bases are usually easily dispersed. In the investigation under discussion, however, the alkylation products were missed in the first experiments in which concentrations of acetic acid of no greater than 10% had been employed.

Experimental

The melting points were observed on a calibrated micro hot-stage. The microanalyses were performed by Dr. S. M. Nagy and associates of the Massachusetts Institute of Technology, Cambridge, Mass. The pK_a determinations were carried out by Dr. W. Simon of the Eidgenössische Technische Hochschule, Zürich, Switzerland. Woelm nonalkaline aluminum oxide was used for the chromatographic separations.

3β,23-Diacetyl-N-methylveratramine.—A mixture of 1.025 g. (0.0025 mole) of veratramine (pK 7.49), 0.50 ml. (0.01 mole) of 87% formic acid and 0.22 ml. (0.0028 mole) of 37% formaldehyde was maintained at reflux temperature for 21 hours. The solution was diluted with 10 ml. of water and acidified to *p*H 2 with acetic acid. The deposit was removed by gravity filtration with the aid of Filter-cel. The filtrate was basified with 6 *N* aqueous ammonium hydroxide. The precipitate was collected by filtration, washed with water and dried. A solution of this material in 10 ml. of acetic anhydride was maintained at reflux temperature for 15 minutes. The acetic anhydride was distilled under reduced pressure. The residue was treated with 20% aqueous acetic acid and extracted with ether. (The ether solution gave, following concentration, 0.37 g. of crude 3β,23,N-triacetylveratramine, m.p. 181–191°.) The aqueous phase was basified with 6 *N* aqueous ammonium hydroxide. The precipitate was collected by filtration, washed with water and dried; yield 0.66 g., m.p. 170–183°. Recrystallization from absolute ethanol afforded 0.49 g. (40%), m.p. 184–187°.

N-Methylveratramine.—A solution of 0.49 g. (0.001 mole) of 3β,23-diacetyl-N-methylveratramine in a mixture of 25 ml. of ethanol, 15 ml. of water and 0.50 ml. of 40% aqueous sodium hydroxide was maintained at reflux temperature for 2 hours. After 15 hours at 0°, the deposit was collected by filtration, washed with water and dried; yield 0.38 g. (89%), m.p. 220–222°. The analytical sample was recrystallized from absolute ethanol; m.p. 221–223°.

Anal. Calcd. for $C_{28}H_{41}NO_2$ (423.62): C, 79.38; H, 9.76; N, 3.31. Found: C, 79.19; H, 9.91; N, 3.37.

3β,23-Diacetyl-N-ethylveratramine.—To a stirred mixture of 0.53 g. of lithium aluminum hydride and 200 ml. of anhydrous ether was added, by means of a non-syphoning, direct flow Soxhlet apparatus, 1.22 g. (0.0023 mole) of 3β,23,N-triacetylveratramine.[3] After 2 hours at reflux tem-

(2) We are indebted to Drs. Dennis Hawkins and O. Krayer for this summary of results to be published in full in the *J. Pharmacol. and Exptl. Therapeutics*.

(3) K. Saito, *Bull. Chem. Soc. Japan*, **15**, 22 (1940).

perature, a few milliliters of water was added cautiously drop by drop to the cold solution. The mixture was stirred with 200 ml. of 10% aqueous sodium hydroxide for 1 hour. The ether phase was washed with water and concentrated under reduced pressure. The dry residue was dissolved in 5 ml. of acetic anhydride. After 15 minutes at reflux temperature, the acetic anhydride was distilled *in vacuo*. The solid residue was triturated with 60 ml. of 10% aqueous acetic acid. The precipitate was collected by filtration. The filtrate was basified with dilute aqueous ammonium hydroxide to give 285 mg., m.p. 156–163°. The insoluble residue (0.66 g.) from the 10% acetic acid extraction was treated with 35 ml. of 20% aqueous acetic acid under reflux. The cooled mixture was clarified by filtration with the aid of Filter-cel. The filtrate was basified with dilute aqueous ammonium hydroxide to give 0.44 g. which was combined with the material from the previous extraction with 10% acetic acid to afford a total yield of 61% of crude product which was recrystallized from absolute ethanol; m.p. 164–167°.[4]

N-Ethylveratramine.—A solution of 250 mg. of 3β,23-diacetyl-N-ethylveratramine and 0.60 ml. of 2.5 *N* aqueous sodium hydroxide in 5 ml. of ethanol was maintained at reflux temperature for 1 hour. After 15 hours at 0°, the precipitate was collected by filtration, washed with water and dried; fine matted needles, yield 0.20 g. (96%), m.p. 172–174°. The analytical sample was recrystallized from absolute ethanol; m.p. 174–175°, *pK* 7.40.

Anal. Calcd. for $C_{29}H_{43}NO_2$ (437.64): C, 79.58; H, 9.90; N, 3.20. Found: C, 79.40; H, 9.63; N, 3.28.

3β,23,N-Tripropionylveratramine.—A solution of 1.0 g. (0.0024 mole) of veratramine and 2 ml. of propionyl chloride in 12 ml. of pyridine was maintained at reflux temperature for 2 hours. The pyridine was distilled under reduced pressure. The residue was extracted with ether. The oil (2.0 g.) from vacuum evaporation of the dried (anhydrous sodium sulfate) ether solution was chromatographed over 60 g. of aluminum oxide. Fractions 5–8 which were eluted with benzene gave, from a mixture of ether and petroleum ether (b.p. 30–60°), flat needles, yield 200 mg. (14%), m.p. 177–178°.

Anal. Calcd. for $C_{36}H_{51}NO_5$ (577.78): C, 74.83; H, 8.90; N, 2.43. Found: C, 75.02; H, 8.96; N, 2.77.

N-Propylveratramine.—A solution of 140 mg. (0.00024 mole) of 3β,23,N-tripropionylveratramine in 15 ml. of anhydrous tetrahydrofuran was added to a stirred mixture of 300 mg. of lithium aluminum hydride in 10 ml. of tetrahydrofuran. After 5 hours at reflux temperature, a few ml. of water was added cautiously to the cooled mixture. The tetrahydrofuran was distilled under reduced pressure. The residue was treated with 2 *N* aqueous sodium hydroxide and extracted with ether. The material (115 mg.) remaining from vacuum evaporation of the washed and dried (anhydrous sodium sulfate) ether solution was chromatographed over 3.5 g. of aluminum oxide. Fractions 5–7 which were eluted with benzene–ether (95:5) gave, from ether–petroleum ether (b.p. 30–60°), 42 mg. (39%) of long needles, m.p. 182–183°, *pK* 7.20.

Anal. Calcd. for $C_{30}H_{45}NO_2$ (451.77): C, 79.75; H, 10.04; N, 3.10. Found: C, 78.38; H, 9.88; N, 3.20.

3β,23,N-Tributyrylveratramine.—A solution of 2.0 g. of veratramine in 20 ml. of butyric anhydride was maintained at 100° for 2 hours The butyric anhydride was distilled at 11 mm. The residue was crystallized from petroleum ether (b.p. 30–60°) to give 2.52 g. (83%), m.p. 80–120°. After two additional recrystallizations the analytical sample melted at 115–117°.

Anal. Calcd. for $C_{39}H_{57}NO_5$ (619.86): C, 75.56; H, 9.27; N, 2.26. Found: C, 75.40; H, 9.28; N, 2.62.

3β,23-Diacetyl-N-butylveratramine. A.—A solution of 1.00 g. (0.0016 mole) of 3β,23,N-tributyrylveratramine in 75 ml. of anhydrous tetrahydrofuran (prepared by distillation from lithium aluminum hydride) was added during a period of 2 hours to a stirred suspension of 0.50 g. of lithium aluminum hydride in 150 ml. of refluxing tetrahydrofuran. After 3 hours at reflux temperature, the unused reagent was decomposed by cautious dropwise addition of water to the cooled mixture. The stirred suspension was diluted with 100 ml. of 10% aqueous sodium hydroxide. After 0.5 hour most of the aluminum hydroxide had dissolved. The organic phase was separated, washed successively with water and with saturated aqueous sodium chloride, combined with an ether extract of the aqueous phase and dried over anhydrous magnesium sulfate. The residue (0.79 g.) from vacuum distillation of the solvents was dissolved in 5 ml. of acetic anhydride. After 0.5 hour at reflux temperature the acetic anhydride was distilled under reduced pressure. The residue was extracted twice with 40-ml. quantities of 10% aqueous acetic acid and once with 40 ml. of 20% aqueous acetic acid. The acid extracts were combined, clarified by filtration and basified with dilute aqueous sodium hydroxide. The precipitate was collected by filtration, washed with water and dried; yield 0.73 g. (82%). The analytical sample was recrystallized twice from absolute ethanol; m.p. 138–140°.

Anal. Calcd. for $C_{35}H_{51}NO_4$ (549.84): C, 76.46; H, 9.35; N, 2.55. Found: C, 76.09; H, 9.48; N, 2.55.

B.—A mixture of 0.82 g. (0.002 mole) of veratramine, 0.82 g. (0.006 mole) of *n*-butyl bromide, 0.20 g. of sodium bicarbonate and 5 ml. of *n*-butyl alcohol was maintained at reflux temperature for 70 hours. The mixture was diluted with ether. The organic phase was washed with water and dried over anhydrous magnesium sulfate. The residue from vacuum distillation of the ether was dissolved in 2 ml. of glacial acetic acid. The solution was diluted with 18 ml. of water. After 2 hours at 0° the mixture was clarified by filtration. The filtrate was basified with dilute aqueous ammonium hydroxide. The precipitate was collected by filtration, washed with water and dried. A solution of the material in 2 ml. of acetic anhydride was kept at reflux temperature for 15 minutes. The acetic anhydride was distilled under reduced pressure. The residue was extracted with 20% aqueous acetic acid. The solution was clarified by filtration. The filtrate was basified with dilute aqueous ammonium hydroxide. The precipitate was collected by filtration, washed with water and dried; yield 0.10 g. (9%), m.p. 133–137°.

N-Butylveratramine.—A solution of 250 mg. of 3β,23-diacetyl-N-butylveratramine and 0.60 ml. of 2.5 *N* aqueous sodium hydroxide in 5 ml. of ethanol was kept at reflux temperature for 1 hour. After 15 hours at 0°, the precipitate was collected by filtration, washed with water and dried. The analytical sample was recrystallized from absolute ethanol; m.p. 187–189°, *pK* 7.20.

Anal. Calcd. for $C_{31}H_{47}NO_2$ (465.70): C, 79.95; H, 10.17; N, 3.01. Found: C, 79.58; H, 10.15; N, 2.92.

3β,23-Diacetyl-N-isobutyrylveratramine.—A solution of 410 mg. (0.001 mole) of veratramine, 0.6 ml. of isobutyryl bromide (b.p. 116°) and 6 ml. of pyridine in 6 ml. of benzene was maintained at reflux temperature for 1 hour. The pyridine hydrobromide was removed from the cooled solution by filtration. The solvents were distilled *in vacuo*. The residue was extracted with dichloromethane. The organic phase was washed with 2 *N* aqueous hydrochloric acid, 2 *N* aqueous sodium carbonate and water. The residue (550 mg.) from distillation of the solvent was dissolved in 20 ml. of 2 *N* ethanolic potassium hydroxide. After 2 hours at reflux temperature, the ethanol was distilled under reduced pressure. The remainder was extracted with ether. The organic phase was washed with water and dried over anhydrous sodium sulfate. The residue from vacuum distillation of the ether was dissolved in 4 ml. of anhydrous pyridine and treated with 1 ml. of acetic anhydride. After 1 hour at reflux temperature the pyridine was distilled *in vacuo*. The residue was extracted with ether. The organic solution was washed successively with 2 *N* aqueous hydrochloric acid, 2 *N* aqueous sodium carbonate and water. The dried material (320 mg.) from distillation of the ether was chromatographed over 9.6 g. of aluminum oxide. Fractions 1–12 which were eluted with benzene–petroleum ether (9:1) gave, from a mixture of methanol and ether, 90 mg. (16%), m.p. 231–232°.

Anal. Calcd. for $C_{35}H_{49}NO_5$ (563.75): C, 74.56; H, 8.76. Found: C, 74.46; H, 8.80.

N-Isobutylveratramine.—A solution of 83 mg. (0.00015 mole) of 3β,23-diacetyl-N-isobutyrylveratramine in 5 ml. of anhydrous tetrahydrofuran was added to a stirred mix-

(4) This compound appears to be identical with the substance obtained following thionyl chloride–pyridine treatment of the lithium aluminum hydride reduction product of 3β,23,N-triacetylveratramine-5,6-epoxide; *cf.* W. A. Jacobs and Y. Sato, *J. Biol. Chem.*, **191**, 71 (1951).

ture of 150 mg. of lithium aluminum hydride and 5 ml. of tetrahydrofuran. After 11 hours at reflux temperature a few milliliters of water was cautiously added dropwise to the cooled suspension. The tetrahydrofuran was distilled under reduced pressure. The residue was treated with 2 *N* aqueous sodium hydroxide and extracted with ether. The residue from the washed and dried (anhydrous sodium sulfate) ether solution gave, from methanol, needles, m.p. 199–201°, yield 40 mg. (57%).

Anal. Calcd. for $C_{31}H_{47}NO_2$ (465.70): C, 79.95; H, 10.17; N, 3.01. Found: C, 77.60; H, 10.16; N, 3.05.

3β,23-Diacetyl-N-pentanoylveratramine.—A mixture of 1.0 g. (0.0024 mole) of veratramine, 4 ml. of valeric anhydride and 10 ml. of anhydrous pyridine was maintained at reflux temperature for 4 hours. The solution was concentrated under reduced pressure. The residue was diluted with water and extracted with ether. The organic phase was washed successively with 2 *N* aqueous hydrochloric acid, 2 *N* aqueous sodium carbonate and water. The remainder from vacuum distillation of the ether was dissolved in 100 ml. of 2 *N* ethanolic potassium hydroxide. After 2 hours at reflux temperature, the ethanol was distilled *in vacuo*. The residue was extracted with ether. The material (1.12 g.) from the washed and dried (anhydrous sodium sulfate) ether solution was dissolved in 10 ml. of anhydrous pyridine and treated with 2 ml. of acetic anhydride. After 1 hour at reflux temperature, the pyridine was distilled under reduced pressure. The residue was extracted with ether. After the organic phase had been washed with 2 *N* aqueous hydrochloric acid, 2 *N* aqueous sodium carbonate and water it was dried over anhydrous sodium sulfate. The residue from vacuum distillation of the solvent gave, from a mixture of ether and petroleum ether (b.p. 30-60°), 700 mg. (50%) of long needles, m.p. 183–184°.

N-Pentylveratramine.—A solution of 400 mg. (0.0007 mole) of 3β,23-diacetyl-N-pentanoylveratramine in 20 ml. of anhydrous tetrahydrofuran was added to a stirred mixture of 800 mg. of lithium aluminum hydride and 20 ml. of tetrahydrofuran. After 5 hours at reflux temperature the cooled mixture was treated cautiously with several milliliters of water. The tetrahydrofuran was distilled under reduced pressure. The residue was extracted with ether. The remainder (350 mg.) from the washed and dried (anhydrous sodium sulfate) ether solution was chromatographed over 10.5 g. of aluminum oxide. The material which was eluted in fractions 7–11 with ether–chloroform (98:2) gave, from methanol–ether 260 mg. (78%) of needles, m.p. 173–175°, *pK* 7.28.

Anal. Calcd. for $C_{32}H_{49}NO_2$ (479.72): C, 80.11; H, 10.30; N, 2.92. Found: C, 79.81; H, 10.54; N, 3.05.

3β,23-Diacetyl-N-hexanoylveratramine.—A mixture of 410 mg. (0.001 mole) of veratramine, 1 ml. of hexanoyl chloride (b.p. 151°) and 4 ml. of anhydrous pyridine was maintained at reflux temperature for 15 hours. The pyridine now was distilled under reduced pressure. The residue was treated with water and extracted with ether. The ether solution was washed with water and concentrated under reduced pressure. The remainder was dissolved in 5 ml. of 2 *N* ethanolic potassium hydroxide. After 2 hours at reflux temperature, the ethanol was distilled *in vacuo*. The residue was extracted with a mixture of ether and water. The residue (500 mg.) from the dried (anhydrous sodium sulfate) ether solution was dissolved in 4 ml. of anhydrous pyridine and treated with 1 ml. of acetic anhydride. The mixture was kept at reflux temperature for 1 hour. The pyridine was distilled under reduced pressure. The residue was extracted with ether. The organic solution was washed with 2 *N* aqueous sodium carbonate and with water. The remainder from the dried (anhydrous sodium sulfate) solution was recrystallized from a mixture of ether and petroleum ether (b.p. 30–60°); yield 310 mg. (52%), m.p. 175–176°.

Anal. Calcd. for $C_{37}H_{53}NO_5$ (591.81): C, 75.09; H, 9.01. Found: C, 74.98; H, 8.93.

N-Hexylveratramine.—A solution of 200 mg. (0.0034 mole) of 3β,23-diacetyl-N-hexanoylveratramine in 15 ml. of anhydrous tetrahydrofuran was added dropwise during 0.5 hour to a stirred suspension of 400 mg. of lithium aluminum hydride in 15 ml. of tetrahydrofuran. After 5 hours at reflux temperature a few milliliters of water was cautiously added dropwise to the cooled solution. The tetrahydrofuran was distilled under reduced pressure. The residue was treated with 2 *N* aqueous sodium hydroxide and was extracted with dichloromethane. The organic phase was washed with 2 *N* aqueous sodium hydroxide and with water. The remainder (180 mg.) from the dried (anhydrous sodium sulfate) solution was recrystallized 3 times from a mixture of ether and petroleum ether (b.p. 30–60°) to give 100 mg. (59%), m.p. 155–156°.

Anal. Calcd. for $C_{33}H_{51}NO_2$ (493.75): C, 80.27; H, 10.41; N, 2.84. Found: C, 80.23; H, 10.41; N, 2.94.

3β,23,N-Tribenzoylveratramine.—A mixture of 500 mg. (0.0012 mole) of veratramine, 0.50 g. (0.0036 mole) of benzoyl chloride, 6 ml. of anhydrous pyridine and 6 ml. of benzene was maintained at reflux temperature for 1 hour. The pyridine hydrochloride was removed by filtration. The filtrate was concentrated under diminished pressure. The residue was dissolved in chloroform. The solution was washed successively with 2 *N* aqueous hydrochloric acid, 2 *N* aqueous sodium carbonate and water. The residue (650 mg.) from the dried (anhydrous sodium sulfate) organic solution was chromatographed over 19.5 g. of aluminum oxide. The fraction which was eluted with benzene–ether (9:1) was crystallized from ethanol to give 210 mg. (24%), m.p. 215–216°.

Anal. Calcd. for $C_{48}H_{51}NO_5$ (721.90); C, 79.86; H, 7.12. Found: C, 80.06; H, 7.19.

N-Benzylveratramine.—A solution of 150 mg. of 3β,23,N-tribenzoylveratramine in 15 ml. of anhydrous tetrahydrofuran was added dropwise at 0°, during a period of 0.5 hour, to a suspension of 300 mg. of lithium aluminum hydride in 15 ml. of tetrahydrofuran. The mixture was maintained at reflux temperature for 5 hours. The suspension was cooled to 5° and cautiously treated dropwise with water. The tetrahydrofuran was distilled under reduced pressure. The residue was diluted with 15 ml. of 2 *N* aqueous sodium hydroxide and extracted with a mixture of ether and chloroform (3:1). The extract was washed with 2 *N* aqueous sodium hydroxide and with water. The residue (140 mg.) from the dried (anhydrous sodium sulfate) chloroform solution was chromatographed over 4.2 g. of aluminum oxide. The fraction (50 mg.) which was eluted with benzene–ether (4:1) was crystallized from a mixture of ether and petroleum ether (b.p. 30–60°) to give 42 mg. (40%) of long needles, m.p. 178–180°.

Anal. Calcd. for $C_{34}H_{45}NO_2$ (499.71): C, 81.71; H, 9.09; N, 2.80. Found: C, 81.51; H, 9.21; N, 2.87.

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