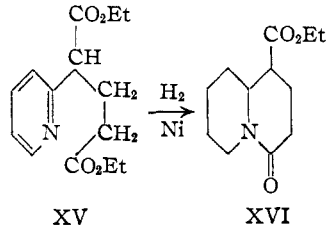
Anal. Calcd. for $C_{11}H_{22}NOI$: C, 42.45; H, 7.13. Found: C, 42.63; H, 7.26.

Diethyl α-(2-Pyridyl)-glutarate (XV).—This was prepared by the addition of ethyl acrylate to ethyl 2-pyridylacetate[12] according to the general procedure of Rogers.[8] To a solution of 0.2 g. of sodium in 50.0 g. of ethyl pyridylacetate maintained at 130–140°, there was added dropwise with stirring 10.0 g. of ethyl acrylate. After the mixture had been heated at 130–140° for two hours, it was cooled and diluted with benzene. The benzene solution was washed with water and then concentrated. Distillation of the residual oil gave 29.5 g. of recovered ethyl 2-pyridylacetate and 20.4 g. (82%) of a colorless oil, b.p. 140–146° at 1 mm., $n^{20}D$ 1.4964.

Anal. Calcd. for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.21. Found: C, 63.73; H, 6.99.

1-Carbethoxy-4-quinolizidone (XVI).—The conversion of diethyl α-(2-pyridyl)-glutarate to 1-carbethoxy-4-quinolizidone (XVI) was accomplished by hydrogenation over Raney nickel catalyst as illustrated below. A mixture containing 17.0 g. of diethyl α-(2-pyridyl)-glutarate, 2 g. of Raney nickel catalyst and 15 ml. of ethanol was subjected to hydrogenation at 175° and under 100 atm. pressure of hydrogen. When hydrogen was no longer absorbed, the reaction mixture was cooled and the catalyst and solvent were removed. Distillation of the residual oil gave 11.6 g. (80%) of a colorless oil; b.p. 155–158° at 2 mm., $n^{20}D$ 1.4949.

Anal. Calcd. for $C_{12}H_{19}NO_3$: C, 64.00; H, 8.44. Found: C, 64.04; H, 8.43.



XV XVI

Although 1-carbethoxy-4-quinolizidone was not actually converted to 1-hydroxymethylquinolizidine, such a conversion has previously been reported for 1-carbomethoxy-4-quinolizidone.[14]

In view of the high yields encountered in the preparation of XV and XVI, this would appear to be the best approach for a large scale preparation of *d,l*-lupinine or *d,l*-epilupinine.

(14) V. Boekelheide and J. P. Lodge, Jr., THIS JOURNAL, **73**, 3681 (1951).

ROCHESTER, NEW YORK

[CONTRIBUTION FROM THE LABORATORIES OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH]

The Veratrine Alkaloids. XXXV. Veracevine, the Alkanolamine of Cevadine and Veratridine[1]

BY S. W. PELLETIER AND WALTER A. JACOBS

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The gentle saponification of cevadine and so-called veratrine yields a new alkanolamine, veracevine. Further treatment with alkali progressively isomerizes veracevine to cevagenine and finally cevine. The mild saponification conditions used for its formation and a study of its ultraviolet and infrared spectra, demonstrate that *veracevine and not cevine or cevagenine* is the genuine alkanolamine present in ester form in the principal constituents of veratrine. Veracevine, like cevine, contains one double bond and eight hydroxyl groups. Germine has been similarly isomerized to an unsaturated base analogous to cevine, and given the trivial name pseudogermine.

In a previous paper Jaffe and Jacobs[2] presented data on the isomerism observed with the highly hydroxylated veratrine bases cevine, germine and protoverine. Under the influence of alkali these singly unsaturated bases, in which the double bond was assumed to be in the neighborhood of a hydroxyl bearing carbon atom, were observed to change from a normal form designated as the α-base to a β-base owing to a double bond shift with development of a characteristic absorption in the ultraviolet. This isomerization was followed in turn by a change to the carbonyl-containing iso bases. More recent studies have shown that other changes occur under the influence of alkali. This has been presented in part in two recent articles of Stoll and Seebeck[3] who correctly concluded that cevine which was previously assumed to be the parent base occurring in the natural ester alkaloids is itself a product of alkali isomerization. Under gentler conditions a ketonic base, cevagenine, was isolated which they concluded to be the original base occurring in the natural alkaloids. However, our more recent data have led us to a different conclusion.

We have found that crystalline cevadine, which was separated over alumina from commercial veratrine (E. Merck and Co.), when carefully saponified at 0° yields up to 90% of a new base which crystallized as needles from ether and which has been given the trivial name veracevine (m.p. 181–183°, $[\alpha]D$ −24° in abs. EtOH). A similar result was obtained with veratrine itself which is said to be principally a mixture of cevadine and veratridine, thus demonstrating that veratridine is also a veracevine ester. Analytical data were in accord with the formulation $C_{27}H_{43}NO_8$. In the ultraviolet it showed essentially uneventful end absorption as in the case of α-cevine. Although its infrared spectrum (Fig. 1) differed from that of α-cevine, it showed a weak band at 1635 cm.$^{-1}$ approximating the α-cevine band at 1625 cm.$^{-1}$ and both suggesting ethylenic absorption. Like cevine it showed no carbonyl absorption in the ultraviolet or infrared. When the saponification of cevadine was effected at a higher temperature (40°) some cevagenine was also isolated. It was subsequently found that veracevine itself was isomerized to cevagenine under the conditions of Stoll and Seebeck. The yield of cevagenine depends upon the temperature as well as the time and

(1) The essential data obtained by us concerning the isolation and characterization of veracevine as a precursor of cevagenine and cevine was contained in a manuscript received by THIS JOURNAL Oct. 22, 1952.

(2) H. Jaffe and W. A. Jacobs, *J. Biol. Chem.*, **193**, 325 (1951).

(3) A. Stoll and E. Seebeck, *Helv. Chim. Acta*, **35**, 1270, 1942 (1952).

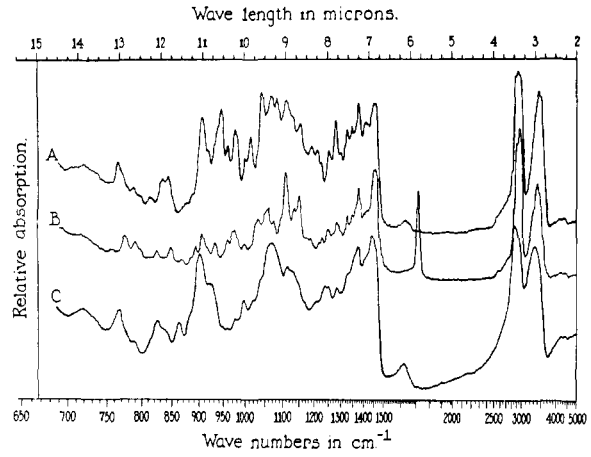

Fig. 1.—Infrared absorption spectra: A, veracevine; B, cevagenine (isoveracevine); C, α-cevine.

concentration of alkali used and is further affected by other changes leading finally to cevine. A schematic diagram of the formation and isomerization of veracevine is shown in Fig. 2.

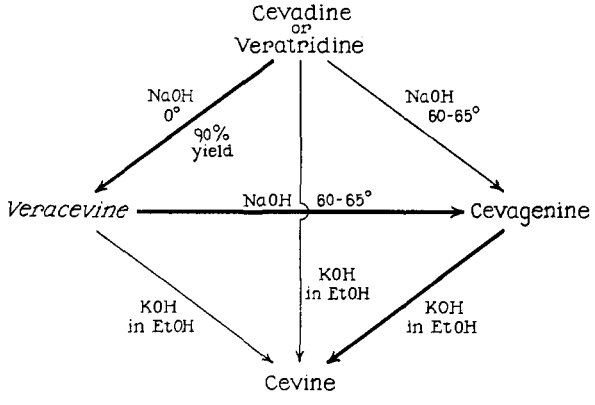

Fig. 2.—The formation and isomerization of veracevine.

Cevagenine was shown to be a carbonyl containing base by Stoll and Seebeck and this has received additional confirmation by our determination of its ultraviolet absorption spectrum: λ_{max}^{EtOH} 278–280 mμ, log ε 1.60. This more strongly levorotatory ketonic base thus bears a relationship to veracevine which resembles that found between the more strongly levorotatory oxobases isogermine and isoprotoverine and their precursors germine and protoverine. The rotations of these isomers are shown in Table I. Ethanol was the solvent except in the case of protoverine and isoprotoverine where pyridine was used.

TABLE I

COMPARATIVE ROTATIONS OF THE ALKAMINES AND THEIR ISOMERS

Veracevine	−23.7°	Isogermine	−46.5°
Germine	+ 4.8°	Isoprotoverine	−42° (pyridine)
Protoverine	−12° (pyridine)	Cevine	−17.5°
Cevagenin (Isoveracevine)	−47.8°	Pseudogermine	+11.4°

Since veracevine is a precursor of cevagenine and cevine and is formed under such gentle conditions, it must be the original base which occurs in ester form in the natural alkaloids. This was supported by our determination of the ultraviolet absorption of one of the hydrogenated isomers of cevadine, namely, the dihydrocevadine-I, first described by Stoll and Seebeck.[4] In the latter the strongly absorbing angelic acid group of the original alkaloid has been reduced to an isovaleryl group and as shown in Fig. 3, the curve obtained is not suggestive of carbonyl absorption. Instead, shoulders at 255–265 mμ and 280–295 mμ are evident. This curve is in close agreement with the ultraviolet curve previously obtained[2] with protoveratrine (containing only saturated acids) and which is presented again in Fig. 3 for comparison. The absence of a carbonyl group in cevadine and protoveratrine was further shown by the failure to obtain oximes from these ester alkaloids under the conditions used for the ready formation of oximes from isogermine,[2] isoprotoverine[2] and cevagenine,[3] namely, in solution with hydroxylamine hydrochloride and sodium acetate. These data demonstrate that *veracevine and not cevagenine* is the original base occurring in cevadine and veratridine.

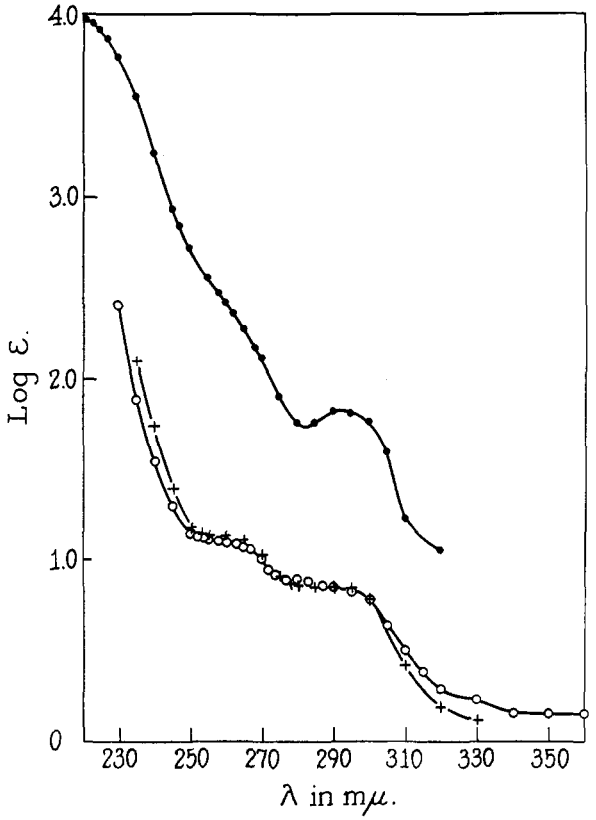

Fig. 3.—Ultraviolet absorption spectra: ●, cevadine; ○, dihydrocevadine-I; +, protoveratrine.

A few derivatives of veracevine have been prepared. Like α-cevine and cevagenine it yields an *oxide*. On acetylation with pyridine and acetic anhydride a triacetylveracevine resulted. However, by the use of acetic anhydride and perchloric acid, as used by Stoll and Seebeck in the case of

(4) The infrared absorption peak at 1707 cm.$^{-1}$ which is attributed by Stoll and Seebeck to ketonic absorption must therefore be due to an ester and not a ketonic carbonyl group in cevadine and dihydrocevadine.

cevagenine, a tetraacetylanhydroveracevine was obtained. Veracevine also forms a perchlorate.

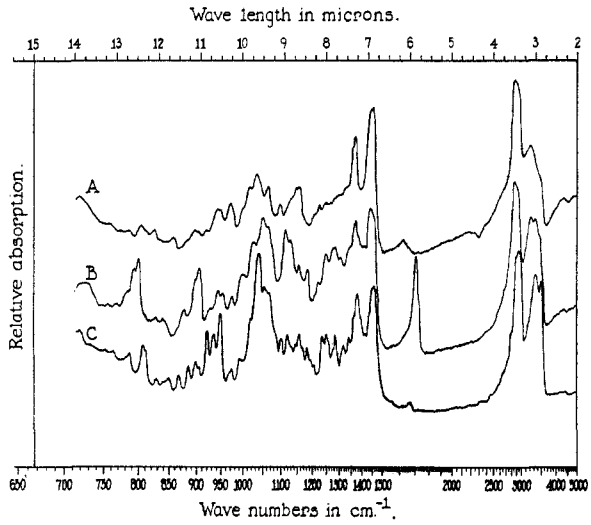

Fig. 4.—Infrared absorption spectra: A, α-germine; B, isogermine; C, pseudogermine.

In contrast to germine[5] and protoverine[6] which readily yield acetonyl derivatives, none could be obtained from veracevine under the same conditions. In all likelihood the proximal hydroxyl groups necessary for acetone condensation which are present in the former must be lacking in veracevine or else the condensation is prevented by a *trans*-configuration of the hydroxyl groups.

Although cevine is a product of alkali isomerization, the change involved in its formation must be independent of the α-β-isomerization previously discussed in the case of cevine, germine and protoverine.[2] This isomerization is apparently not reversible since we were unable to obtain cevagenine or veracevine again from cevine. Both germine[7] and protoverine[6] are the products of gentle saponification procedures and must be the original bases which occur in the corresponding ester alkaloids. This we have more recently substantiated by the isolation of germine and protoverine after saponification of the ester alkaloids at room temperature. The isomerization of veracevine to cevagenine proceeds more readily than the change from α-germine to isogermine. On the other hand, α-protoverine resembles veracevine in this regard.

Under the conditions used for the preparation of α-cevine from veratrine germine has been found to be similarly isomerized. From the mixture besides unchanged germine, an isomeric base, pseudogermine, has been obtained although in smaller yield. As seen in Table I, its rotation differs from that of α-germine by about the same amount which has been observed between veracevine and cevine. Protoverine was also changed under the same conditions with alkali, but in a more complicated manner and thus far no crystalline isomerization product corresponding to α-cevine has been obtained from the reaction mixture.

The striking analogy of the interrelationships between germine, isogermine and pseudogermine to those between veracevine and its isomers is evident from the ultraviolet data and is shown in the 6 μ region of the infrared curves presented in Figs. 1 and 4. A similar relationship between protoverine and isoprotoverine was shown in the infrared by the ethylenic absorption of the former at 1645 cm.$^{-1}$ and by the carbonyl absorption of the latter at 1708 cm.$^{-1}$.

(5) L. C. Craig and W. A. Jacobs, *J. Biol. Chem.*, **148**, 57 (1943).
(6) W. A. Jacobs and L. C. Craig, *ibid.*, **149**, 271 (1943).
(7) W. Poethke, *Arch. Pharm.*, **275**, 571 (1937).

Experimental[8]

Isolation of Cevadine from Veratrine.—An aqueous solution of 20 g. of veratrine hydrochloride (E. Merck and Co.) was emulsified with chloroform and treated with an excess of fresh sodium carbonate solution. After the separation, aided by addition of sodium chloride solution, the extraction was repeated. The chloroform phase was cleared with sodium sulfate and concentrated *in vacuo* to dryness. The resinous residue was dissolved in 50 ml. of benzene and added to a column of 400 g. of alumina. Attempted elution with benzene was without success but following the use of about 500 ml. of 1.5% methanol in benzene, material began to be eluted from the column. At this stage, material appeared at a fairly steady rate of about 0.25–0.27 g. for each 10-ml. fraction eluted. At proper intervals the fractions were tested to see whether after concentration and seeding crystallization could be induced from absolute ethanol. This was found true in varying degree with the first 30 fractions which were recombined. After concentration to dryness and solution in a small volume of absolute ethanol, crystallization occurred after seeding. The collected material was recrystallized from absolute ethanol to give 3.5 g. Small additional amounts were obtained from the mother liquor. It crystallized from ether as microplatelets or flat needles; m.p. 213–214.5°, $[\alpha]^{28}D$ +13° (*c* 0.97 in 95% EtOH).

Anal. Calcd. for $C_{32}H_{49}NO_9$: C, 64.95; H, 8.35. Found (dried at 120° *in vacuo*): C, 64.80; H, 8.37.

Veracevine from Crystalline Cevadine.—A solution of 1.0 g. of purified cevadine, m.p. 214–215°, in 25 ml. of methanol was treated with 1.0 ml. of 5 *N* aqueous sodium hydroxide and quickly cooled to 0°. After standing at 0° for 24 hours the colorless solution was diluted with 50 ml. of ice-water and promptly extracted ten times with 5-ml. portions of chloroform. The extract was washed with 10 ml. of water and then evaporated to dryness *in vacuo*. When dissolved in 25 ml. of boiling ether the colorless resin crystallized quickly as small needles; 676 mg. The substance loses birefringence at 85–110° and then melts to a clear resin at 180–185°; $[\alpha]^{27}D$ −24° (*c* 2.15 in abs. EtOH). Concentration of the mother liquor gave an additional 111 mg. of needles of the same melting point; $[\alpha]^{25}D$ −20° (*c* 1.91 in abs. EtOH). The total yield of veracevine amounted to 91%.

Anal.[9] Calcd. for $C_{27}H_{43}NO_8$: C, 63.63; H, 8.51; N, 2.75. Found: C, 63.53; H, 8.69; N, 2.74.

When veracevine was dissolved in a small volume of hot methanol, the solution concentrated to a sirup and then carefully diluted with eight volumes of boiling ether, the base crystallized slowly as rosettes of long needles, containing one-half a mole of methanol of crystallization; m.p. 179–185° (94% recovery), $[\alpha]^{27}D$ −23.9° (*c* 3.23 in abs. EtOH), $[\alpha]^{27}D$ −28.4° (*c* 3.49 in chf.).

Anal. Calcd. for $C_{27}H_{43}NO_8 \cdot {}^1/_2CH_3OH$: C, 62.83; H, 8.63. Found: C, 62,80, 62.80; H, 8.62, 8.64.

When the above methanol-containing crystals were recrystallized from ether, delicate feathery needles of pure veracevine were obtained free of solvent; m.p. 181–183°, $[\alpha]^{26}D$ −23.7°.

Anal. Found: C, 63.56; H, 8.30; N, 2.75.

The stability of veracevine toward alumina was demonstrated by allowing a solution of 35 mg. of the base in 2 ml. of benzene–chloroform (1:1) to stand four days in a column of 3 g. of alumina. Elution with chloroform–methanol (4:1) then gave unchanged veracevine, $[\alpha]^{27}D$ −24.4° (*c* 1.02 in abs. EtOH).

(8) All melting points are corrected.
(9) Samples of veracevine were dried at 60° (0.2 mm.). Drying temperatures above 80° caused sufficient decomposition to affect the analyses.

Saponification of Cevadine at 25°.—A solution of 1.0 g. of crystalline cevadine in 6 ml. of methanol was treated with 2.0 ml. (theory, 1.8 ml.) of 1 *N* sodium hydroxide and allowed to remain at 25° for 20 hours. When the reaction mixture was processed as described for veracevine and fractionally crystallized from methanol–ether, it yielded successively 228 mg. of crude cevagenine, $[\alpha]^{27}D$ −40° (*c* 3.11 in abs. EtOH) and 223 mg. of crude veracevine, $[\alpha]^{27}D$ −22° (*c* 3.95 in abs. EtOH).

Veracevine from Veratrine Hydrochloride.—A solution of 14.0 g. of veratrine hydrochloride (E. Merck and Co.) (av. mol. wt., 698) in 300 ml. of methanol was chilled to 10°, neutralized with 5 *N* sodium hydroxide with cooling, and then treated with 12 ml. of the same reagent. The brown solution was kept at 0° for 24 hours and diluted with 500 ml. of ice-water and extracted quickly with seven 50-ml. portions of cold chloroform. The chloroform extract yielded a tan resin which when dissolved in 200 ml. of boiling ether crystallized rapidly as delicate needles; 7.03 g. (69%), m.p. 180–182°, $[\alpha]^{24}D$ −23.6° (*c* 1.98 in abs. EtOH).

Anal. Found: C, 63.57; H, 8.59.

Concentration of the mother liquor gave an additional 250 mg. of veracevine; m.p. 179–181°, $[\alpha]^{24}D$ −23.3° (*c* 2.16 in abs. EtOH).

Veracevine Perchlorate.—A solution of 300 mg. of veracevine in 3 ml. of acetone was treated with 3 drops of 70% perchloric acid. Ether was added to initial turbidity and the perchlorate gradually separated as rosettes of delicate needles; 312 mg., m.p. 217–220° dec. Recrystallization from acetone–ether gave 211 mg. of spherical rosettes which melted to a clear golden liquid at 228–230° dec. Further recrystallization did not alter the melting point. The twice recrystallized perchlorate showed $[\alpha]^{26}D$ −9.6° (*c* 1.98 in abs. EtOH).

Anal. Calcd. for $C_{27}H_{43}NO_8 \cdot HClO_4$: C, 53.15; H, 7.27. Found: C, 53.25; H, 7.25.

Veracevine and Acetone.—Ninety mg. of veracevine was dissolved in 2 ml. of methanol and treated with a slight excess of hydrochloric acid. After concentration to 1 ml. it was gradually treated with 10 ml. of acetone. No crystallization occurred so the concentrated solution was diluted, then treated with an excess of dilute sodium carbonate solution and repeatedly extracted with chloroform. The recovered material crystallized as delicate needles from acetone and ether to give 49 mg. of unchanged veracevine which sintered at 172 and melted at 180–182°. An additional amount was recovered from the mother liquor. Found (dried at 60° *in vacuo*): C, 63.37; H, 8.47.

Veracevine Triacetate.—A solution of 255 mg. of recrystallized veracevine in 1.6 ml. of dry pyridine was treated with 1 ml. of acetic anhydride and allowed to remain at 0° for 44 hours. The mixture was treated gradually with ice-water and then evaporated to near dryness *in vacuo*. The oily residue was dissolved in 5 ml. of water and after treating with an excess of cold sodium bicarbonate solution, the solution was extracted with six 3-ml. portions of chloroform. The extract was concentrated *in vacuo* and the residue was evaporated with benzene to remove residual pyridine. The colorless resin was dissolved in a small volume of hot methanol and diluted with five volumes of ether. The acetate separated very slowly as microcrystals; 177 mg. of m.p. 259–265°. Two recrystallizations from methanol–ether gave 65 mg. melting at 273–274°; $[\alpha]^{27}D$ +7° (*c* 1.58 in abs. EtOH).

Anal. Calcd. for $C_{33}H_{49}NO_{11}$: C, 62.35; H, 7.76; sapon. equiv., 212. Found: C, 62.55; H, 8.07; sapon. equiv., 236.

Anhydroveracevine Tetraacetate.—A suspension of 1.0 g. of recrystallized veracevine in 8 ml. of acetic anhydride was cooled to 0° and treated dropwise, with cooling, with 0.3 ml. of 70% perchloric acid. The cold mixture was allowed to reach 25° and let stand for 18 hours. The initial pale pink color rapidly became a dark brown. Water was carefully added at 10° to decompose excess anhydride followed by dilution with 20 ml. of water. After concentration almost to dryness *in vacuo* to remove acetic acid, the residue was treated with water which caused gradual crystallization of the perchlorate. The brown mass was washed well with water, dissolved in 25 ml. of boiling ethanol and treated with Norit. After the faint yellow filtrate was concentrated to one fourth volume, it was diluted with 5 ml. of water and boiled to expel the alcohol. The salt gradually crystallized as light tan needles; 625 mg., m.p. 255–256° dec. Concentration of the mother liquor gave additional 395 mg. of the salt.

A concentrated solution of the product in hot methanol when diluted with water gave starlets of fine, colorless needles which contained two moles of water of crystallization; (68% recovery), m.p. 255–257° dec.

Anal. Calcd. for $C_{35}H_{49}NO_{11} \cdot HClO_4 \cdot 2H_2O$: C, 52.79; H, 6.84; Cl, 4.45. Found: C, 52.68; H, 6.62; Cl, 4.54.

A solution of 1.15 g. of the perchlorate in 25 ml. of chloroform was shaken with an excess of saturated sodium bicarbonate solution and the aqueous phase was re-extracted three times with 10-ml. portions of chloroform. The combined chloroform extracts were concentrated to a small volume and diluted with ether. When further concentrated, heavy prisms slowly deposited; 921 mg. of m.p. 185–190°. Concentration of the mother liquor gave an additional 72 mg.

Recrystallization from ether gave an 80% yield of large prisms which lost solvent at 90–110° and then melted to a clear resin at 185–190°. Analyses were unsatisfactory with this material. However, when a solution of the above material in warm methylene chloride was diluted with a large volume of light petroleum ether and subsequently concentrated to a small volume, the solvent-free anhydrotetraacetate separated as sandy prisms; m.p. 257.5–258.5°, $[\alpha]^{27}D$ +72.9° (*c* 2.52 in abs. EtOH).

Anal. Calcd. for $C_{35}H_{49}NO_{11}$: C, 63.71; H, 7.49; sapon. equiv., 165. Found: C, 63.81, 63.57; H, 7.55, 7.35; sapon. equiv., 173.

Veracevine Oxide.—Veracevine (220 mg.) was added to 1.5 ml. of 30% hydrogen peroxide and solution effected by gentle warming over the steam-bath. The mixture foamed considerably and after 30 minutes the reaction appeared to be complete. The colorless solution was evaporated to dryness *in vacuo* and the resulting resin dissolved in hot ethanol and treated with Norit. The clarified solution was concentrated to 1 ml. and diluted carefully with water. When seeded (with a trace of material which had dried on the upper part of the container), the oxide crystallized as a fine, sandy deposit of prisms; 156 mg. of m.p. 273–275° dec. A solution of the product in 8 ml. of boiling ethanol was concentrated to 1 ml., then diluted with 1 ml. of water and again concentrated until crystallization began. Stout prisms of the oxide separated which contained one mole of water; m.p. 271–274° dec. after preliminary sintering, $[\alpha]^{27}D$ −29.6° (*c* 1.67 in abs. EtOH).

Anal. Calcd. for $C_{27}H_{43}NO_9 \cdot H_2O$: C, 59.65; H, 8.34; N, 2.58. Found: C, 59.36; H, 8.11; N, 2.69.

Isomerization of Veracevine to Cevagenine.—A solution of 50 mg. of veracevine in 0.3 ml. of methanol was treated with 0.022 ml. of *N* sodium hydroxide and heated on the bath for 30 minutes. Extraction of the diluted mixture with chloroform yielded 50 mg. of resin which readily crystallized from methanol–ether as characteristic needles. Sixteen mg. was obtained in the first fraction.

Anal. Calcd. for $C_{27}H_{43}NO_8$: C, 63.63; H, 8.51. Found (dried at 100° *in vacuo*): C, 63.33; H, 8.42.

The ultraviolet spectrum showed maximal absorption at 280 mμ, log *e* 1.57.

After recrystallization, it showed m.p. 176–179°, subsequently crystallized and then melted at 240–244°, $[\alpha]^{27}D$ −43° (*c* 0.56 in abs. EtOH).

Isomerization of Veracevine to Cevine.—A solution of 500 mg. of veracevine in 2 ml. of ethanol was treated with 5 ml. of a saturated solution of potassium hydroxide in ethanol. After heating on the steam-bath for 30 minutes, the solution was allowed to stand for two hours. The potassium salt of cevine separated as fine, thread-like needles and was collected and washed with ether. The salt was decomposed with carbon dioxide in the usual way yielding crystalline cevine. When recrystallized from aqueous ethanol it formed prisms indistinguishable from those of authentic cevine; m.p. 166–173°, $[\alpha]^{25}D$ −18.5° (*c* 1.88 in abs. EtOH).

Anal. Calcd. for $C_{22}H_{43}NO_8$: C, 63.63; H, 8.51. Found: C, 63.34; H, 8.33.

Pseudogermine.—Two grams of germine was treated with a fresh 20% potassium hydroxide solution in absolute ethanol and the resin which formed was worked into solution with a rod. The solution was heated at 60° for 30 minutes during which time it became brown-colored. The cooled solution was diluted with an equal volume of water and extracted

10 times with chloroform. The latter was washed with a small volume of saturated sodium chloride solution, then cleared with sodium sulfate and concentrated finally *in vacuo*. The resin (1.57 g.) was dissolved in a small volume of methanol and induced to crystallize as small short prisms by careful dilution; 0.33 g. was collected with water, in which it was appreciably soluble. It consisted of germine contaminated with the isomer.

The mother liquor was concentrated *in vacuo* to remove methanol and the aqueous mixture when heated deposited a resin which redissolved on cooling. Soon micro needles or rods began to separate and gradually increased on standing. This fraction was collected with water and amounted to 0.46 g. It consisted largely of pseudogermine contaminated with germine. On careful dilution of the solution in a small volume of methanol, an initial fraction of 62 mg. of germine separated. The mother liquor was concentrated finally to dryness *in vacuo*. A solution of the residue in the minimum of methanol crystallized on addition of ether as small four-sided micro crystals; 0.3 g., m.p. 173–174°, $[\alpha]^{25}D$ +11.4° (*c* 1.05 in abs. EtOH). Contrary to germine this substance did not crystallize from chloroform.

Anal. Calcd. for $C_{27}H_{43}NO_5$: C, 63.63; H, 8.51. Found (dried at 100° *in vacuo*): C, 63.63; H, 8.48.

The above fractions of germine were dissolved in about 10 ml. of warm chloroform and after partial concentration allowed to crystallize as needles of the germine–chloroform adduct. The collected substance when recrystallized by concentration of the methanol solution was found to be unchanged germine; $[\alpha]^{28}D$ +5° (*c* 1.03 in abs. EtOH).

The residue obtained from the chloroform mother liquor yielded from methanol–ether 0.125 g. of pseudogermine; $[\alpha]^{8}D$ +12° (*c* 1.00 in abs. EtOH).

Anal. Found (dried at 100° *in vacuo*): C, 63.58; H, 8.49.

The original mother liquors gave additional fractions of germine and pseudogermine and contained appreciable amounts of unidentified material. No isogermine was isolated.

Infrared Spectra.—Samples were prepared as Nujol mulls and their spectra determined from 2 to 14.5 μ without compensation on a Perkin–Elmer model 21 double beam spectrometer with sodium chloride optics, set at resolution 5, response 3, gain 8, suppression 1 and a scanning speed of 0.12 μ per minute on a chart scale of 2 inches for 1 μ.

We wish to acknowledge the generous coöperation of Dr. T. F. Gallagher of the Sloan–Kettering Institute and of Dr. H. Jaffe of The Rockefeller Institute in obtaining the infrared data. All analytical results have been obtained by Mr. D. Rigakos of this Laboratory.

NOTE ADDED IN PROOF.—D. H. R. Barton and J. F. Eastham (*J. Chem. Soc.*, 424 (1953)) recently reported on the basis of ultraviolet absorption studies that cevine possesses an oxidic structure in place of a double bond and a hydroxyl group. Such a possibility could also be considered for veracevine, germine, pseudogermine and protoverine. However, the correctness of this conclusion is under further study in this Laboratory. They have also shown that so called β-cevine is cevine contaminated with an oxidation product which may possess a strongly absorbing diosphenol chromophore.

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The Conversion of Hecogenin to $\Delta^{7,9(11)}$-22-isoallospirostadiene-3β-ol[1]

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Hecogenin has been transformed to $\Delta^{9(11)}$-dehydrotigogenin and thence *via* 22-isoallospirostane-3(β),9(α),11(α)-triol to $\Delta^{7,9}$-22-isoallospirostadiene-3β-ol in good over-all yield.

The conversion of hecogenin (I) to $\Delta^{9(11)}$-dehydrohecogenin (V) *via* the 11,23-dibromide II has been reported recently[2]; reduction of V to $\Delta^{9(11)}$-dehydrotigogenin (VIIa) was accomplished[3] by the Wolff–Kishner reduction, a method which has been observed to give mixtures of $\Delta^{9(11)}$- and Δ^{11}-olefins in the bile acid series.[3,4] We have found that the conversion of I to V may be alternatively effected by the action of selenium dioxide on the 23-monobromide III,[5] derived from hecogenin, followed by reductive debromination of the intermediate 23-bromo-$\Delta^{9(11)}$-dehydrohecogenin acetate (IV). The conversion of $\Delta^{9(11)}$-dehydrohecogenin (V) to $\Delta^{9(11)}$-dehydrotigogenin (VIIa) was accomplished by Raney nickel hydrogenolysis of the crystalline ethylene dithioketal derivative VI to give VII in excellent yield.[6] The value M_D (VII) − M_D (VIIa) of −45° is in good agreement with the average value of −52° for $\Delta^{9(11)}$-steroid olefins (*trans* A/B).[7] Furthermore the infrared spectrum of $\Delta^{9(11)}$-dehydrotigogenin (VIIa) exhibited a well-defined band at 1647 cm.$^{-1}$ (6.06 μ)[8] and at 821 cm.$^{-1}$, characteristic of trisubstituted olefins.[9]

Attempts to dehydrogenate the $\Delta^{9(11)}$-olefin VII with mercuric acetate[3] or by low temperature bromination–dehydrobromination[10] were unsuccessful; the product in each instance was essentially unchanged starting material. Treatment of the $\Delta^{9(11)}$-olefin VII with osmium tetroxide, however, converted it smoothly and in good yield to

(1) Presented at the Meeting-in-Miniature of the North Jersey Section of the American Chemical Society on January 26, 1953, at Newark, N. J.

(2) C. Djerassi, H. Martinez and G. Rosenkranz, *J. Org. Chem.*, **16**, 303 (1951).

(3) C. Djerassi, H. Martinez and G. Rosenkranz, *ibid.*, **16**, 1278 (1951).

(4) H. B. Alther and T. Reichstein, *Helv. Chim. Acta*, **26**, 492 (1943); E. Seebeck and T. Reichstein, *ibid.*, **26**, 536 (1943); L. F. Fieser and S. Rajagopalan, THIS JOURNAL, **73**, 118 (1951); similar observations have been made in this Laboratory by Dr. Evelyn Wilson.

(5) R. E. Marker, R. B. Wagner, P. R. Ulshafer, E. L. Wittbecker, D. P. J. Goldsmith and C. H. Ruof, *ibid.*, **69**, 2167 (1947).

(6) It is interesting to note that M. Mujovic, W. Voser, H. Heusser and O. Jeger, (*Helv. Chim. Acta*, **35**, 964 (1952)) have recently observed retro-migration of the double bond during reduction of the monoethylenedithioketal derivative of acetoxylanostendione.

(7) D. H. R. Barton, *J. Chem. Soc.*, 813 (1945).

(8) We are indebted to Dr. K. Dobriner of the Sloan-Kettering Institute for Cancer Research, N. Y., for the determination of this spectrum.

(9) P. Bladon, J. Fabian, H. Henbest, H. Koch and G. Wood, *J. Chem. Soc.*, 2402 (1951); also H. Hirschmann, THIS JOURNAL, **74**, 5357 (1952).

(10) R. C. Anderson, R. Budziarek, G. T. Newbold, R. Stevenson and F. S. Spring, *Chemistry and Industry*, 1035 (1951).