[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA, BERKELEY 4, CALIF.]

The Structures of Two New Sesquiterpene Lactones from Artemisia[1]

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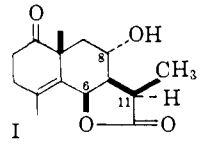
RECEIVED SEPTEMBER 26, 1959

A new sesquiterpene lactone was isolated from the mother liquors of ψ-santonin purifications. This new material was shown to be desoxy-ψ-santonin (II) by its synthesis from ψ-santonin (I); II upon treatment with potassium carbonate was epimerized from an 11β- to an 11α-methyl isomer. This latter material was shown to be identical with the lactone, finitin (X), previously isolated by Kawatani and Takeuchi from *A. finita*.

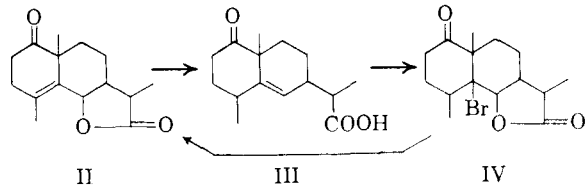
During the course of routine isolations of the sesquiterpene lactone, ψ-santonin (I), from semi-purified extracts of *Artemisia* it was found that by



I

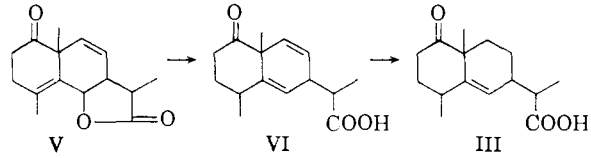
careful processing of the residual material, a new sesquiterpene lactone (II) could be obtained. This material, $C_{15}H_{20}O_3$, possessed three C–CH_3 groups (Kuhn–Roth) and the three oxygen atoms were present as an isolated carbonyl group (semicarbazone and infrared) and a lactone which reformed spontaneously upon generation of the hydroxy acid by acidification of the salt. Of particular interest were the spectral features of this new lactone since they were practically identical in all respects with those of ψ-santonin[4] except that the hydroxyl absorptions were lacking. In the infrared, bands were found at 1770, 1710 and 1650 cm.$^{-1}$ which are characteristic of a γ-lactone, an isolated saturated ketone and an olefinic double bond, respectively. In the ultraviolet, the low intensity maximum of a carbonyl was present at 290 mμ (ϵ 40) and the end absorption was ϵ_{210} 10,000. This latter value when compared with 8300 ϵ_{210} for ψ-santonin indicated the presence of a tetrasubstituted double bond as found in ψ-santonin. In view of this great similarity of the new lactone II with that of ψ-santonin (I), it was called desoxy-ψ-santonin and such a structure has been proved.

In order to locate the relative positions of the tetrasubstituted double bond and the lactone ring in II, the hydrogenation of the material was investigated. In the ψ-santonin series, it has been found that upon absorption of one mole of hydrogen, the lactone ring undergoes hydrogenolysis.[5] Concomitant with this cleavage, the double bond shifts from a tetrasubstituted position in ring A to a trisubstituted position in ring B. This product upon reaction with bromine in the presence of sodium carbonate yields a δ-bromo-γ-lactone which upon treatment with collidine yields ψ-santonin. When II was subjected to the same hydrogenation conditions, one mole of hydrogen was absorbed in 5 minutes and an unsaturated acid (III) was obtained. The rapidity of the hydrogenolysis reaction is characteristic of the presence of an allylic lactone and the infrared spectrum of III was almost identical, except for hydroxyl absorptions, with that of the acid derived from ψ-santonin. The change in intensity of the end absorption in going from II (ϵ_{210} 10,000) to III (ϵ_{210} 4600) also is characteristic of the migration of a double bond from a tetrasubstituted to a trisubstituted position. Direct chemical evidence from this migration was obtained when the δ-bromo-γ-lactone IV was obtained from III under the usual reaction conditions. When IV was treated with collidine, desoxy-ψ-santonin (II) was reformed. Hence, this reaction sequence completely parallels that found in ψ-santonin and establishes the presence of identical structural units of the double bond and the lactone in II as are found in ψ-santonin.



II III IV

In view of this indicative evidence, it was clear that the most efficient manner to establish the structure of desoxy-ψ-santonin was to convert ψ-santonin to this structure. In this manner, if the products were identical, the structure, complete with stereochemical detail, would be established. The first reaction sequence investigated involved the use of 8-dehydro-ψ-santonin (V), a material readily prepared from ψ-santonin *via* the 8-tosyl derivative.[6]



V VI III

In the ψ-santonin series, it was found that under any hydrogenation conditions the cleavage of the lactone occurred but if Pd–$SrCO_3$ was used as the catalyst the reaction stopped cleanly after one mole of hydrogen uptake. Under such reaction conditions, the double bond which had migrated to the 5,6-position and the carbonyl group at C-1 were not affected. Using these hydrogenation conditions, the dehydro material V should undergo the facile hydrogenolysis reaction to yield the acid VI and this material, in turn, should react only at the 8,9-double bond to yield the dihydrodesoxy acid III. It was found, however, that with V, one mole of hydrogen was absorbed in 5 minutes (assumed to be the hydrogenolysis reaction) but an additional 1.5

(1) For the previous paper in this series see, THIS JOURNAL, **82**, 2232 (1960).

(2) Du Pont Teaching Fellow, 1956–1957.

(3) Dow Fellow, 1953–1954.

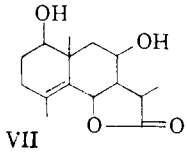
(4) W. G. Dauben and P. D. Hance, THIS JOURNAL, **75**, 3352 (1953).

(5) W. G. Dauben and P. D. Hance, *ibid.*, **77**, 2451 (1955).

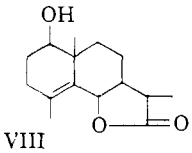
(6) W. G. Dauben and P. D. Hance, *ibid.*, **77**, 606 (1955).

moles of hydrogen was consumed rapidly. From the reaction mixture no crystalline product could be isolated and in view of this over-hydrogenation, it must be assumed that the presence of the 8,9-double bond increases the reactivity of the 5,6-double bond toward hydrogen and that no highly selective hydrogenation can be achieved. It was found that by stopping the reaction when 2 moles of hydrogen had been absorbed and treating the crude reaction mixture with bromine in the presence of sodium carbonate, a very small yield of a bromo lactone could be isolated. This lactone, although possessing a slightly lower optical rotation and melting point than the authentic material IV, nevertheless displayed an infrared spectrum identical to that of IV.

In view of the inadequacies of the above process, hydrogenation conditions which would not affect the lactone were sought. It was found that if the lactone of ψ-santonin (I) was saponified and the alkaline solution of the sodium salt was allowed to hydrogenate in the presence of Pd–$SrCO_3$, only a slow reduction of the carbonyl group occurred and upon acidification of the reaction mixture, the diol VII was obtained. When 8-dehydro-ψ-santonin (V) was hydrogenated under the same conditions

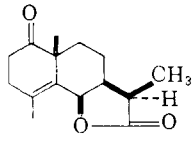


VII

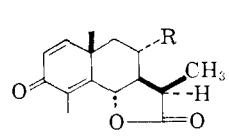


VIII

one mole of hydrogen was absorbed in the course of 20 minutes but there was no change in the reaction rate until about 1.5 moles of hydrogen had been absorbed and finally a total of 2 moles was absorbed. After acidification, about 50% of the reaction product was a neutral material and from this fraction an over-all yield of 8% of alcohol VIII was obtained. When desoxy-ψ-santonin(II) was hydrogenated under the same conditions, one mole of hydrogen was absorbed in 5 hours and after the usual processing, VIII was obtained and was identical in all respects with that prepared by the first route from V. When the hydrogenation of the salt of V was stopped when the rate of the reaction changed (~1.5 moles), desoxy-ψ-santonin (II) was isolated directly in a yield of 38%. These results clearly establish the structure of the new sesquiterpene lactone as II, shown below with complete stereochemical detail, and thus makes ψ-santonin an 8-α-hydroxy derivative of this parent material.



II

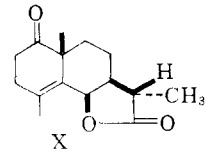


IXa, R = H
IXb, R = OH

It is of biogenetic interest that from various *Artemisia* species, both (−)-α-santonin (IXa) and its 8α-hydroxy derivative, artemisin (IXb), occur together.

During the course of this work, Kawatani and Takeuchi[7] reported the isolation of another new lactone from still another species of *Artemisia*. The compound was called *finitin*, after the species of the plant, and it was reported to have a composition identical with that of desoxy-ψ-santonin. Due to the very small amount of material obtained in the isolation, only the physical and spectral properties and the preparation of a derivative were reported. The spectral properties clearly showed the presence of all of the functional groups of II, but the physical properties established that finitin was not identical with desoxy-ψ-santonin. In view of the great similarity of the spectra, it was suggestive that the two compounds differed only in stereochemical detail. In line with this was the finding of Kawatani and Takeuchi[7] that in the *Artemisia* species which yielded finitin, no (−)-α-santonin was present, only its C-11 epimer, (−)-β-santonin. In view of the discussed biogenetic relationships in these series of sesquiterpenic lactones, it seemed likely that since desoxy-ψ-santonin (II) occurs in plants which yield (−)-α-santonin, then its C-11 epimer should occur in plants yielding (−)-β-santonin. As has been evaluated, in detail, previously,[1] this type of isomerism should make the material which possesses the (−)-α-santonin C-11 configuration less dextrorotatory than its C-11 epimer. Such, indeed, was the case for the two materials, the rotation for deoxy-ψ-santonin being −207° and for finitin being −168°. Furthermore, the magnitude of the rotatory difference was that expected for a C-11 epimeric pair.

On the basis of this suggestive evidence, the conversion of desoxy-ψ-santonin into its C-11 epimer was investigated. It has been reported by Cocker and his co-workers[8] that by heating the lactones of the santonin series with anhydrous potassium carbonate in a hydrocarbon solvent, the product with the stable C-11 configuration will be formed. Since desoxy-ψ-santonin possesses a *cis*-lactone structure, the 11β-configuration should be unstable and should epimerize to the 11α-form.[9] When II was allowed to react with anhydrous potassium carbonate in refluxing tetralin, a new material was obtained which possessed the properties reported for finitin. Through the kindness of Professor Kawatani, a sample of finitin was obtained and direct comparison established the identity of the materials. Thus, finitin is the 11α-methyl isomer of desoxy-ψ-santonin and possesses structure X.[10]



X

Acknowledgment.—We are indebted to Messrs. T. and H. Smith, Edinburgh, for kindly supplying the crude extracts from which desoxy-ψ-santonin was isolated.

(7) T. Kawatani and T. Takeuchi, *J. Pharm. Soc., Japan*, **74**, 793 (1954).

(8) W. Cocker and T. B. H. McMurry, *J. Chem. Soc.*, 4430 (1955), and earlier papers.

(9) For discussion of the lactone stability rule, see refs. 1 and 8.

(10) It is of interest that similar treatment of ψ-santonin[1] yielded only an inseparable mixture of materials. The presence of the 8α-hydroxy group must make the energy difference of the two isomers too small to permit a large excess of one isomer.

Experimental[11]

Isolation of Desoxy-ψ-santonin (II).—A mixture of crude ψ-santonin, kindly supplied by Messrs. T. and H. Smith, was recrystallized from benzene–chloroform and the pure ψ-santonin obtained. The mother liquors were concentrated and the residue (59 g.) was chromatographed on Florex XXS.[12] The material eluted with benzene was essentially pure desoxy-ψ-santonin (18.4 g.) and the crystalline material was recrystallized twice from benzene–heptane; m.p. 101.3–101.9°, $[\alpha]^{25}D$ −207° (*c* 0.68, EtOH).

Anal. Calcd. for $C_{15}H_{20}O_3$ (248.31): C, 72.55; H, 8.12. Found: C, 72.40; H, 8.04.

The semicarbazone was prepared using sodium acetate as the catalyst and recrystallized twice from methanol m.p. 213–216° dec.

Anal. Calcd. for $C_{16}H_{23}O_3N_3$ (305.37): C, 62.93; H, 7.59; N, 13.76. Found: C, 62.97; H, 7.72; N, 13.56.

1-Oxosant-5-enic Acid (III).—Desoxy-ψ-santonin (2.00 g., 8.07 mmoles) was dissolved in 30 ml. of 95% ethanol and 1 g. of 5% Pd–$SrCO_3$ catalyst added. The mixture was hydrogenated until a net hydrogen uptake of one mole was achieved (~5 min.). The catalyst was filtered and the solvent evaporated. The oily residue was dissolved in excess methanol, water added until a turbidity was noticed and the product allowed to crystallize; yield 0.980 g. (46%), m.p. 111.0–112.0°, $[\alpha]^{25}D$ −76° (*c* 2.29, EtOH). An additional 18% of product was obtained by concentration of the mother liquors.

Anal. Calcd. for $C_{15}H_{22}O_3$ (250.33): C, 71.97; H, 8.86. Found: C, 71.89; H, 8.93.

The 2,4-dinitrophenylhydrazone was prepared and recrystallized from ethanol, m.p. 199.0–200.0°.

Anal. Calcd. for $C_{21}H_{26}O_6N_4$ (430.45): C, 58.59; H, 6.09; N, 13.02. Found: C, 58.55; H, 6.07; N, 12.85.

1-Oxo-5-bromosantan-6β,12-olide (IV).—A solution of 0.30 g. (1.2 mmoles) of 1-oxosant-5-enic acid (III) and 0.127 g. of sodium carbonate in 15 ml. of water was cooled in an ice-bath and 0.384 g. of bromine was added dropwise, with vigorous shaking between each addition. After the addition was complete, the mixture was agitated for an additional 10 minutes and then sufficient sodium bisulfite was added to destroy the excess bromine. The ice-cold suspension was filtered and the white solid was dried by drawing air through it. The yield of this crude material was 0.350 g. (89%) m.p. 110.0–111.0°. The analytical sample was prepared by recrystallization from ethanol; m.p. 112.6–113.0°, $[\alpha]^{25}D$ + 27° (*c* 1.20, EtOH).

Anal. Calcd. for $C_{15}H_{21}O_3Br$ (329.24): C, 54.72; H, 6.43. Found: C, 54.56; H, 6.27.

Preparation of Desoxy-ψ-santonin (II) from Bromolactone (IV).—A solution of 0.400 g. (1.22 mmoles) of non-recrystallized bromolactone (m.p. 110–111°) in 10 ml. of collidine and 3 ml. of toluene was heated at 130° for 3 hours under a nitrogen atmosphere, cooled and poured into water. The product was extracted with benzene and the benzene solution was washed with 5% hydrochloric acid until no collidine odor could be detected in the basified extracts. The organic solution then was washed with several portions of sodium bicarbonate solution, dried and the solvent evaporated to yield 0.247 g. of reddish needles. The material was dissolved in a small portion of benzene and chromatographed on Florex XXS. The product was eluted with benzene and recrystallized from benzene–heptane; yield 0.066 g. (22%), m.p. 99.0–100.6°, $[\alpha]^{25}D$ −198° (*c* 0.90, EtOH). The mixed m.p. with authentic desoxy-ψ-santonin showed no depression.

Anal. Calcd. for $C_{15}H_{20}O_3$ (248.31): C, 72.55; H, 8.12. Found: C, 72.40; H, 8.16.

Hydrogenation of 8-Dehydro-ψ-santonin (V). (a) Neutral Solution.—A solution of 0.508 g. (2.03 mmoles) of V in ethanol containing 5% Pd–$SrCO_3$ catalyst was shaken with hydrogen until 2.01 mmoles of the gas had been absorbed. The solvent was evaporated and the residue dissolved in 25 ml. of water containing 0.215 g. of sodium carbonate. The solution was brominated as described above using 0.2 ml. of bromine and the light yellow sticky solid which formed was separated and dissolved in ethyl acetate. Ligroin was added and the solution cooled to −70°. The small amount of solid which formed was recrystallized from ether–ligroin at −70°; yield 36 mg., m.p. 114.0–114.5°, $[\alpha]^{25}D$ +17.5° (*c* 0.638, EtOH). The mixed m.p. with authentic bromolactone IV prepared above was undepressed and the infrared spectra of the two materials were identical.

(b) **Alkaline Solution.**—A mixture of 0.500 g. (2.00 mmoles) of V and 15 ml. of 1% sodium hydroxide solution was heated on a steam-bath for 20 minutes to effect solution, cooled to room temperature and 0.5 g. of 5% Pd–$SrCO_3$ catalyst added. The mixture was hydrogenated until a net hydrogen uptake of 1.92 mmoles had been achieved (~6 hours) and at this point the reaction had essentially ceased. The mixture was filtered, the filtrate acidified and extracted with chloroform. The chloroform solution was washed with sodium bicarbonate and the solvent evaporated; yield 0.206 g. of neutral oil. The residue was recrystallized twice from ethanol–water; yield of 1-hydroxysant-4-en-6β-12-olide (VIII), 0.040 g. (8%), m.p. 105.5–106.5°, $[\alpha]^{25}D$ −44.4° (*c* 1.23, EtOH). This compound showed no mixed m.p. depression with an authentic sample prepared from desoxy-ψ-santonin (see below).

Anal. Calcd. for $C_{15}H_{22}O_3$ (250.33): C, 71.97; H, 8.86. Found: C, 71.72; H, 8.69.

(c) **Alkaline Solution.**—A mixture of 0.492 g. (1.97 mmoles) of V and 15 ml. of 1% sodium hydroxide solution was heated on a steam-bath until solution occurred and 0.5 g. of 5% Pd–$SrCO_3$ catalyst added. The mixture was hydrogenated until the net hydrogen uptake was 1.5 mmoles (~19 min.), the catalyst filtered and the solution acidified to congo red with 10% hydrochloric acid. The aqueous mixture was extracted several times with chloroform and the combined extracts were evaporated; yield 0.474 g. (95%) of an oil. The material was dissolved in benzene and chromatographed on Florex XXS. The fractions eluted with benzene (total of 0.162 g.) were recrystallized twice from benzene–heptane to yield 0.138 g. (28%) of desoxy-ψ-santonin, m.p. 95.0–99.6°, $[\alpha]^{25}D$ −205° (*c* 0.96, EtOH). This material was identical in all respects with the natural product.

Anal. Calcd. for $C_{15}H_{20}O_3$ (248.31): C, 72.55; H, 8.12. Found: C, 72.33; H, 8.02.

1-Hydroxysant-4-en-6β-12-olide (VIII).—A solution of 2.00 g. (8.08 mmoles) of desoxy-ψ-santonin in 60 ml. of freshly prepared 1% sodium hydroxide solution (prepared by warming overnight on a steam-bath under a nitrogen atmosphere) was hydrogenated over 2.0 g. of 5% Pd–$SrCO_3$ catalyst. Approximately 5 hours was required for a one mole uptake of hydrogen. At this point, the catalyst was filtered and the filtrate acidified and extracted with chloroform. The organic solution was washed with sodium bicarbonate solution, dried and the solvent evaporated to yield 1.93 g. of a neutral oil. The material was dissolved in methanol and water added to turbidity; different preparations required different lengths of time for crystallization, but usually only cooling and scratching were needed. The usual yield was about 1.0 g. (50%), m.p. 107.4–108.0°, $[\alpha]^{25}D$ −46° (*c* 1.49, EtOH).

Anal. Calcd. for $C_{15}H_{22}O_3$ (250.33): C, 71.97; H, 8.86. Found: C, 71.99; H, 8.92.

1,8α-Dihydroxysant-4-en-6β,12-olide (VII).—The salt of ψ-santonin in ethanolic sodium hydroxide was dihydrogenated as described above. The crude product was recrystallized from benzene–methanol; yield 0.400 g. from 1.00 g. (39%), m.p. 212.0–213.4°, $[\alpha]^{25}D$ −14.3° (*c* 1.34, EtOH).

Anal. Calcd. for $C_{15}H_{22}O_4$ (266.33): C, 67.64; H, 8.33. Found: C, 67.43; H, 8.37.

Isomerization of Desoxy-ψ-santonin (II) to Finitin (X).—Under a nitrogen atmosphere a solution of 0.5 g. (2.03 mmoles) of desoxy-ψ-santonin in 20 ml. of freshly distilled dry tetralin was refluxed for 6 hours in the presence of 0.5 g. of freshly ignited potassium carbonate. After cooling, the darkened solution was filtered to remove the solids and the solvent evaporated under reduced pressure. Chromatography of the oily residue on 20 g. of alumina (Act. I) gave 0.26 g. of crystalline material from the benzene eluates. The

(11) All analyses were performed by the Microanalytical Laboratory, Department of Chemistry, University of California, Berkeley.

(12) Obtained from The Floridin Co., Tallahassee, Fla.

product was recrystallized three times from benzene–ligroin; m.p. 151–153°, $[\alpha]^{25}D$ −161° (lit.[7] m.p. 153°, $[\alpha]$ −168°). Upon admixture with an authentic sample there was no depression of m.p.

Anal. Calcd. for $C_{15}H_{20}O_3$ (248.31): C, 72.55; H, 8.12. Found: C, 72.77; H, 8.15.

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

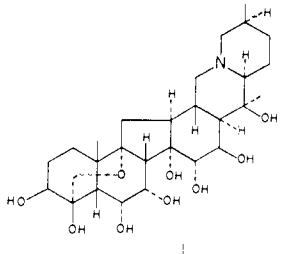
Veratrum Alkaloids. XXXVIII.[1] The Structure and Configuration of Protoverine[2,3]

BY S. MORRIS KUPCHAN, C. IAN AYRES, MOSHE NEEMAN,[4] RUPRECHT H. HENSLER, TADASHI MASAMUNE AND S. RAJAGOPALAN[5]

RECEIVED AUGUST 31, 1959

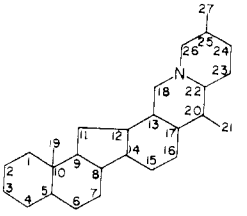
The alkaloid protoverine has been shown to have structure and configuration I. Alkaline isomerization of I leads to isoprotoverine (X) and thence to pseudoprotoverine (XI). Acetic anhydride–pyridine acetylation of I affords a pentaacetate (XII); acetic anhydride–perchloric acid acetylation yields a hexaacetate (XIII). Methanolysis of XIII affords an isopentaacetate (XV) which is oxidized by chromic acid to dehydroprotoverine isopentaacetate (XIV). Alkaline treatment of XIV affords a cross-conjugated diosphenol derivative (VII). Compound I yields an acetonide (XVI) which is acetylated to a triacetate (XVIII). Acid hydrolysis of XVIII yields protoverine triacetate (XXII) which is oxidized by periodate to a cyclopentenone aldehyde (XXIII). Chromic acid oxidation of XVIII affords a dehydroprotoverine acetonide triacetate (XXV) which yields a dehydroprotoverine triacetate (XXVI) on acid hydrolysis. Sodium borohydride reduction of XXV gives a protoverine acetonide diacetate (XXIV). Treatment of isoprotoverine with acetone and hydriodic acid yields a diacetonide (XXVIII). Acetylation of XXVIII gives a diacetate (XXIX). Tosylation of XVI affords a protoverine acetonide tosylate (XXX) which is acetylated to a diacetate (XXXI). Acid hydrolysis of XXXI followed by acetylation yields a tosylate tetraacetate (XXXIII). Proof that protoverine is 6-α-hydroxygermine was obtained by calcium–liquid ammonia reduction of XXV to the known 7-dehydrogermine 14,15-acetonide 3,16-diacetate (XXXIV).

Protoverine, $C_{27}H_{43}O_9N$, is the alkamine present in several polyester alkaloids which occur in *Veratrum* species.[6–10] The structure of protoverine is of particular interest in view of the potent hypotensive action of its ester derivatives[11] and of the use of this antihypertensive action in clinical conditions associated with high blood pressure.[12] In this paper evidence is presented for assignment of structure and configuration I to protoverine.



I

Protoverine was first obtained in amorphous form by Poethke, in 1937, from alkaline hydrolysis of protoveratrine.[6,7] A $C_{28}H_{45}O_{10}N$ formulation was proposed. Jacobs and Craig isolated the alkamine in crystalline form and prepared several crystalline derivatives.[8] On the basis of their analytical study of the base and its derivatives, they assigned the correct $C_{27}H_{43}O_9N$ formulation to protoverine. The latter authors also demonstrated a close structural analogy to cevine and germine by isolating 2-ethyl-5-methylpyridine, cevanthrol and cevanthridine from the products of selenium dehydrogenation of protoveratrine.[13] These results led Jacobs and Pelletier to propose skeletal structure II for protoverine as well as cevine and germine.[14]



II

Protoverine undergoes a series of isomerizations (protoverine → isoprotoverine → pseudoprotoverine)[8,15] which parallels those of zygadenine,[16] veracevine[17,18] and germine.[17,19] The close analogy of the isomerizations to the veracevine-cevagenine-cevine[20] and the germine–isogermine–pseudoger-

(1) Part XXXVII, S. M. Kupchan and A. Afonso, *J. Am. Pharm. Assoc., Sci. Ed.*, **48**, 731 (1959).

(2) The investigations which form the subject of the present paper were first outlined in part in two preliminary communications: *Chemistry & Industry*, 1626 (1958), and THIS JOURNAL, **81**, 4753 (1959).

(3) This investigation was supported by research grants from the National Institutes of Health (H-2275, C1–C3), Pitman–Moore Co., and the Wisconsin Alumni Research Foundation.

(4) On leave from the Technion–Israel Institute of Technology, Haifa, Israel.

(5) Deceased.

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