$[\alpha]^{20}D$ +42°, λ_{max}^{EtOH} 240 mμ, log ε 4.25, $\lambda_{max}^{CS_2}$ 3617 and 1678 cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.45; H, 10.24.

The acetate IIIb was recrystallized from ethyl acetate, whereupon it exhibited m.p. 178–179°, λ_{max}^{EtOH} 240 mμ, log ε 4.25, $\lambda_{max}^{CS_2}$ 1736 and 1674 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.95; H, 9.37.

Δ^4-19-Norpregnene-3,20-dione (19-Norprogesterone) (IIIc).—The above crude 20-alcohol IIIa (0.65 g.) in 15 cc. of glacial acetic acid was treated at 20° dropwise with a solution of 0.15 g. of chromium trioxide in 1 cc. of water and 5 cc. of acetic acid. After 90 minutes at room temperature, the excess reagent was decomposed with methanol and the solution was evaporated to dryness *in vacuo*. The product was extracted with ether, washed with sodium carbonate solution and water, dried, evaporated and crystallized from methanol; yield 0.54 g., m.p. 142–145°, $[\alpha]^{20}D$ +154°. The analytical sample showed m.p. 144–145°, $[\alpha]^{20}D$ +147°, λ_{max}^{EtOH} 240 mμ, log ε 4.24, $\lambda_{max}^{CS_2}$ 1706 and 1674 cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39. Found: C, 80.07; H, 9.28.

The 3,20-bis-dinitrophenylhydrazone was prepared in methanol containing a small amount of concentrated hydrochloric acid and was obtained as dark orange crystals (after recrystallization from chloroform–methanol) with m.p. 278–279°, $\lambda_{max}^{CHCl_3}$ 380 mμ, log ε 4.78.

Anal. Calcd. for $C_{32}H_{36}O_8N_8$: C, 58.17; H, 5.49; N, 16.95. Found: C, 58.28; H, 5.37; N, 16.57.

MEXICO CITY, D. F.

[CONTRIBUTION FROM THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH]

The Veratrine Alkaloids. XXXVII. The Structure of Isorubijervine. Conversion to Solanidine

BY S. W. PELLETIER AND WALTER A. JACOBS

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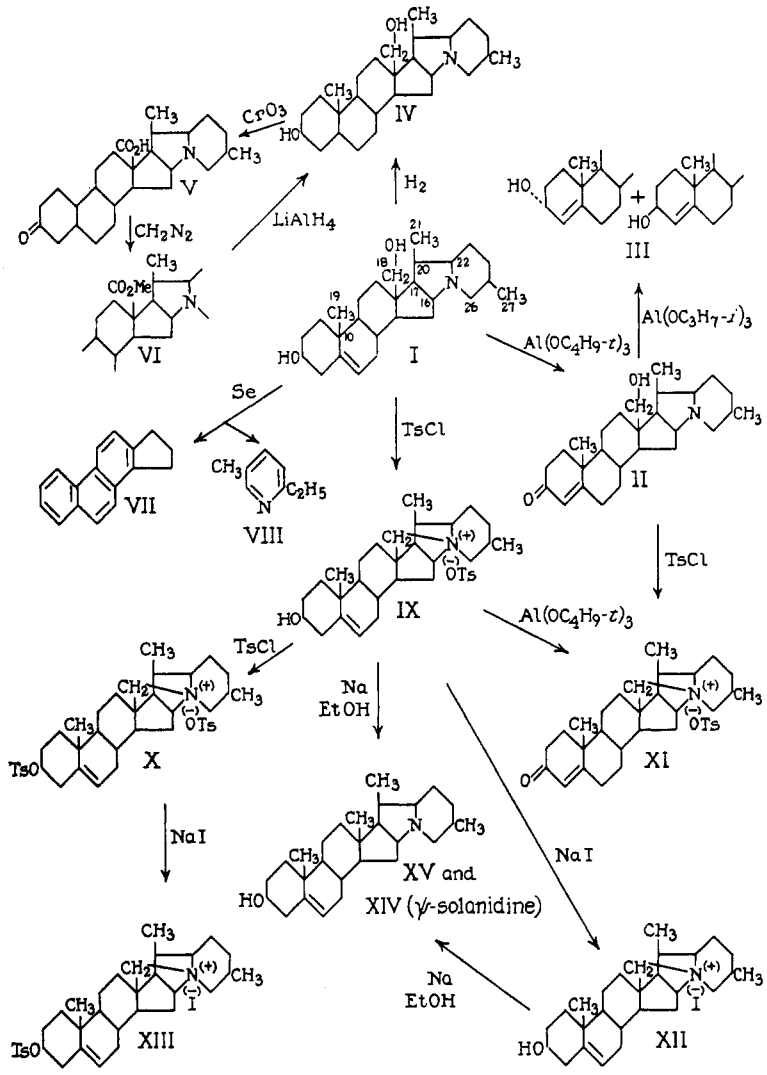
The structure of isorubijervine has been established as a hydroxy-solanidine by conversion to solanidine. Tosylation of isorubijervine gave a unique, quaternary-type monotosylate IX which was converted to a quaternary iodide XII by the action of sodium iodide. Reductive cleavage of either the tosylate or the iodide with sodium in ethanol afforded solanidine (XV) and a new isomeric base designated as **pseudosolanidine (XIV)**. The data at hand confirm the structure originally proposed for isorubijervine, *viz.*, Δ^5-solanidene-3β,18-diol (I).

Isorubijervine, an alkaloid of *Veratrum album* and *Veratrum viride*, first isolated and characterized in this Laboratory,[1,2] has been shown to be a tertiary steroidal base of 3-hydroxy-Δ^5-stenol character. This was supported by its formulation, $C_{27}H_{43}NO_2$, by hydrogenation to a dihydro derivative,[3] by formation of a digitonide,[2,3] and by oxidation to a Δ^4-3-ketone (II), which in turn was reduced to a mixture of epimeric Δ^4-stenols (III).[2] That the non-nitrogenous portion of isorubijervine possesses a normal steroid ring system was given support by the isolation of 1,2-cyclopentenophenanthrene (VII) as a product of its selenium dehydrogenation.[2] Also isolated from the dehydrogenation mixture was the characteristic 2-ethyl-5-methylpyridine (VIII) obtained from other veratrine alkaloids and from the potato base, solanidine.[1,2,4] Such data suggested that isorubijervine, like rubijervine,[5] is a solanidine derivative. The primary character of the second hydroxyl group was shown by oxidation of dihydroisorubijervine (IV) to a keto acid, $C_{27}H_{41}NO_3$ (V), which could be reconverted to dihydroisorubijervine by reduction of the methyl ester VI with lithium aluminum hydride. The resistance of this ester to saponification together with certain other data indicated that this primary hydroxyl group is located on an angular methyl group. The data at hand were best explained by assuming for isorubijervine the structure of Δ^5-solanidene-3β,18-diol (I).[6] This assumed relationship to solanidine has since been confirmed by a direct conversion of isorubijervine to solanidine (Δ^5-solanidene-3β-ol) itself. A preliminary account of this work was outlined in our Communication to the Editor,[7,8] and it is the purpose of this paper to disclose the details of this conversion and to discuss the structure of isorubijervine.

The route originally considered for this conversion involved the preparation of a tosyl ester of the primary hydroxyl group of isorubijervine, followed by replacement of this tosyl group with hydrogen. Treatment of isorubijervine (I) with a slight excess of one equivalent of *p*-toluenesulfonyl chloride in pyridine gave an excellent yield of a monotosylate which in reality is a quaternary salt as discussed below. That the secondary hydroxyl group at carbon 3 was not involved in the formation of this monotosylate was shown by oxidation of the latter with aluminum *t*-butoxide to a Δ^4-3-ketone (XI) which was in all respects identical with the compound formed by the tosylation of Δ^4-isorubijervone-3 (II). This Δ^4-3-ketone was further characterized by the oxime. Treatment of isorubijervine or of its monotosylate with an excess of *p*-toluenesulfonyl chloride yielded a neutral ditosylate (X).

Normal structures for isorubijervine monotosylate and Δ^4-isorubijervone-3 tosylate were first assumed by us.[7] However, an attempt to reduce the monotosylate of isorubijervine to solanidine by boiling for 90 hours in ether with lithium aluminum hydride was unsuccessful. The tosylate was therefore

(1) W. A. Jacobs and L. C. Craig, *J. Biol. Chem.*, **148**, 41 (1943).
(2) W. A. Jacobs and L. C. Craig, *ibid.*, **159**, 617 (1945).
(3) L. C. Craig and W. A. Jacobs, *ibid.*, **149**, 451 (1943).
(4) L. C. Craig and W. A. Jacobs, *J. Biol. Chem.*, **129**, 79 (1939); *ibid.*, **139**, 263 (1948); *ibid.*, **148**, 57 (1943); *Science*, **97**, 122 (1943); V. Prelog and S. Szpilfogel, *Helv. Chim. Acta*, **125**, 1306 (1942).
(5) Y. Sato and W. A. Jacobs, *J. Biol. Chem.*, **179**, 623 (1949).
(6) Y. Sato and W. A. Jacobs, *ibid.*, **191**, 63 (1951).
(7) S. W. Pelletier and W. A. Jacobs, THIS JOURNAL, **74**, 4218 (1952).
(8) While our Communication was in press, a preliminary report by Burn and Rigby (*Chemistry and Industry*, **27**, 668 (1952)) appeared which described the conversion of dihydroisorubijervine to solanidan-3β-ol. An article by Weisenborn and Burn[9] appeared later in which similar methods were used to convert isorubijervine to solanidane and solanidan-3β-ol.

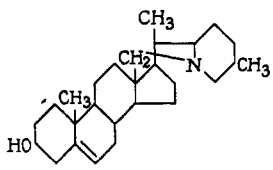


converted with sodium iodide to the monoiodide XII for subsequent reduction. It is interesting to note that treatment of the ditosylate X with sodium iodide resulted in replacement of only one of the tosyl groups to give a monotosyl monoiodide (XIII). Numerous methods for effecting the conversion of isorubijervine monoiodide to solanidine proved unsuccessful. Thus, boiling with coppered zinc in ethanol failed to effect reduction. Equally unsuccessful were aluminum amalgam, hydrogenation with Adams catalyst or palladium-on-calcium carbonate and zinc dust in boiling acetic acid. The reason for this anomalous behavior of isorubijervine monotosylate and monoiodide has since been shown by Weisenborn and Burn[9] and confirmed by us. These substances have abnormal salt-like structures (IX and XII, respectively) and perhaps would be more properly designated as isorubijervinium tosylate and iodide. Since 3-tosylisorubijervine tosylate, Δ^4-isorubijervone-3 tosylate and 3-tosylisorubijervine iodide are also salt-like in character they must be assigned structures X, XI and XIII, respectively.[10]

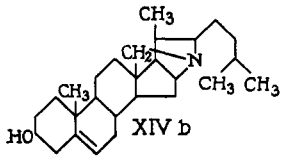
(9) F. Weisenborn and D. Burn, THIS JOURNAL, **75**, 259 (1953).

(10) No attempt has been made to develop a systematic nomenclature for these unique salt-like compounds. Trivial names are used throughout this paper.

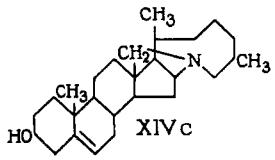
The successful conversion of isorubijervine to solanidine was effected by boiling either isorubijervine monotosylate (IX) or monoiodide (XII) with a large excess of sodium in ethanol. Thus reductive cleavage of the iodide gave a product, m.p. 185–232° which yielded analytical data corresponding to the values calculated for $C_{27}H_{43}NO$. Reductive cleavage of the tosylate likewise gave a similar mixture. When chromatographed on alumina and fractionally crystallized, the mixture yielded two isomeric bases. It was later found that the mixture could be resolved more easily with digitonin. The first component was identified as solanidine (XV) by its analysis, optical rotation, the melting point when mixed with authentic material, by conversion to its acetate, and by comparison of its infrared spectrum with that of solanidine (Fig. 1). The second component is a new base which we have named **pseudosolanidine (XIV)**. This substance melts at 236–237°, shows $[\alpha]^{26}D$ −11.7°, and does not form a digitonide. These facts and the similarity of its infrared spectrum to that of solanidine, suggested at first a structure of the epimeric Δ^5-solanidene-3α-ol. Furthermore catalytic reduction of pseudosolanidine in acetic acid gave a dihydro derivative XVI with constants (m.p. 210–211°, $[\alpha]D$ −33.6°) very close to those reported for solanidan-3α-ol (m.p 211–213°, $[\alpha]D$ −31.9°). However, we have since found that a mixture with solanidan-3α-ol[11] shows a marked depression. This result confirms the interpretation of Weisenborn and Burn that solanidine and this isomer must result from a reductive cleavage of the quaternary iodide.[9] Thus solanidine is formed by a cleavage of the C_{18}–nitrogen bond of IX or XII, and pseudosolanidine (XIV) by a cleavage of the C_{16}–, or perhaps less likely the C_{22}– or C_{26}–nitrogen bond. It follows therefore that pseudosolanidine



XIVa



XIVb



XIVc

(11) V. Prelog and S. Szpilfogel, *Helv. Chim. Acta*, **27**, 390 (1944).

probably has structure XIVa, although XIVb or XIVc are possibilities. It is interesting to note that although pseudosolanidine has a 3β-configuration and a normal sterol skeleton, it does not form an insoluble digitonide under the usual conditions.

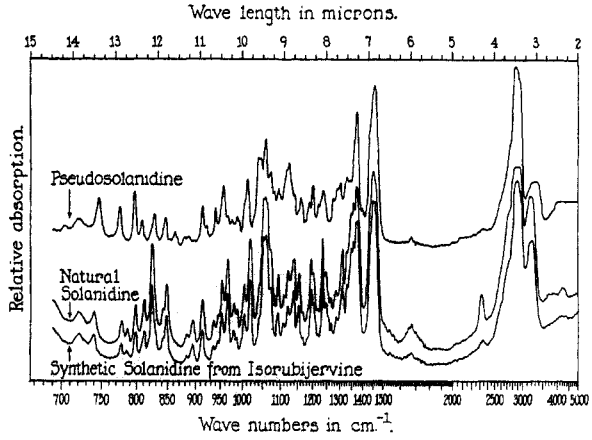


Fig. 1.—Infrared absorption spectra (Nujol mull).

The above conversion of isorubijervine to solanidine demonstrates conclusively that isorubijervine is a hydroxy-solanidine. Since this hydroxyl group is of primary character, only four points of attachment need be considered, *viz.*, C_{18}, C_{19}, C_{21} and C_{27}. Because oxidation of dihydroisorubijervine (IV) gave an acid, the methyl ester VI of which was exceedingly difficult to saponify[6] (a property of tertiary carboxylic esters) only C_{18} or C_{19} can be the site of the primary hydroxyl group. Inasmuch as the resistance of this methyl ester to saponification was much greater than that experienced with derivatives of strophanthidin[6,12] bearing a carbomethoxyl group on carbon atom 10, and since the quaternary tosylate IX must arise by formation of a new carbon–nitrogen bond (C_{19} is not in bonding range of the nitrogen[9]), position 19 is eliminated as the site of the primary hydroxyl group. Isorubijervine must therefore have the structure of Δ⁵-solanidene-3β,18-diol (I) as originally proposed.

Experimental[13]

Isorubijervine Monotosylate (IX).—A solution of 1.0 g. of isorubijervine (m.p. 238–240°) in 15 ml. of dry pyridine was treated at 10° with 500 mg. of *p*-toluenesulfonyl chloride. After standing at 0° for 1 to 3 days the solution had become deep rose in color and some crystalline material had separated. The reaction mixture was poured in a thin stream into a cold, saturated sodium bicarbonate solution. After an hour the flocculent pink precipitate was collected and dried *in vacuo*. When dissolved in a large volume of boiling acetone, the tosylate separated quickly as stout needles; 830 mg., m.p. 270–273° dec. Repeated recrystallization gave material melting at 276–279° dec., $[\alpha]^{30}D$ −36° (*c* 1.5 in abs. EtOH).

Anal. Calcd. for $C_{34}H_{49}NO_4S$: C, 71.92; H, 8.70; S, 5.65. Found: C, 71.95; H, 8.58; S, 5.53.

Concentration of the mother liquor afforded 80 mg. of less pure material melting at 260–265° dec.

When the above monotosyl derivative was recrystallized from methanol–acetone–ether (1:10:10) it separated as rosettes of slender needles which contained methanol. The needles lost solvent and birefringence around 200°, became birefringent above 230° and finally melted at 279–281.5° dec., $[\alpha]^{27}D$ −36.8° (*c* 1.85 abs. EtOH). This compound appeared to be neutral since it was not titratable with perchloric acid in acetic acid[9,14] and gave an instantaneous precipitate of sodium *p*-toluenesulfonate when treated with sodium iodide in acetonitrile.

Anal. Calcd. for $C_{34}H_{49}NO_4S \cdot CH_3OH$: 70.08; H, 8.94. Calcd. for $C_{34}H_{49}NO_4S$: C, 71.92; H, 8.70; S, 5.65. Found (dried at 60°): C, 70.26, 70.25; H, 9.06, 8.60. Found (dried at 150°): C, 71.80; H, 8.58; S, 5.31.

3-Tosylisorubijervine Tosylate (X). A. From Isorubijervine.—A solution of 110 mg. of isorubijervine in 3 ml. of dry pyridine was treated with 120 mg. of *p*-toluenesulfonyl chloride, allowed to stand at 0° for 2 days, and then processed as described for IX. A solution of the crude product in warm acetone was treated with Norit, and concentrated *in vacuo*.[15] White needles separated; 80 mg., 164.5–167.5°. Recrystallization gave material melting at 166–169° and showing $[\alpha]^{26}D$ −38.2° (*c* 2.1 in abs. EtOH). An attempted titration with perchloric acid indicated that this compound is neutral.

Anal. Calcd. for $C_{41}H_{55}NO_6S_2$: C, 68.20; H, 7.68; S, 8.88. Found: C, 68.17; H, 7.79; S, 8.86.

B. From Isorubijervine Monotosylate.—Treatment of 100 mg. of isorubijervine monotosylate in pyridine with 150 mg. of *p*-toluenesulfonyl chloride, and processing the mixture in the usual way yielded a crude ditosylate. Recrystallization from acetone gave 46 mg., m.p. 165–167°, which was identical with that prepared directly from isorubijervine.

Δ⁴-Isorubijervone-3 Tosylate (XI). A. By Oxidation of Isorubijervine Monotosylate.—A suspension of 125 mg. of IX in 6 ml. of benzene was concentrated to 3 ml. to remove water. To the suspension was added 300 mg. of aluminum *t*-butoxide in 4 ml. of dry benzene and 2 ml. of acetone. The mixture was boiled under reflux for 7 hours and then allowed to stand overnight. After addition of aqueous sodium bicarbonate, the mixture was extracted with chloroform, the combined extracts washed with water and evaporated to dryness *in vacuo*. The residue was washed carefully with cold ether to remove acetone-condensation products and then crystallized from acetone–methanol (20:1) to give 32 mg. of slender needles, m.p. 323–328° dec. The mother liquor yielded 14 mg. of m.p. 295–300°. Recrystallization of the 328° variety from acetone–ether yielded long, thin needles of m.p. 327–329° dec. A mixture melting point with authentic Δ⁴-isorubijervone-3 tosylate prepared by tosylation of Δ⁴-isorubijervone-3 gave no depression.

Anal. Calcd. for $C_{34}H_{47}NO_4S$: C, 72.17; H, 8.37; S, 5.67. Found: C, 71.92; H, 8.37; S, 5.62.

B. By Tosylation of Δ⁴-Isorubijervone-3.—One hundred and ten mg. of Δ⁴-isorubijervone-3[2] in 2 ml. of dry pyridine was allowed to react with 70 mg. of *p*-toluenesulfonyl chloride at 25° for 3 days, and the mixture worked up as described for IX. The crude product (135 mg.) when crystallized from methanol–acetone yielded 75 mg., m.p. 324–328° dec. Concentration of the mother liquor gave an additional 45 mg., m.p. 319–327° dec. Recrystallization from acetone–ether gave fine needles, m.p. 327–330° dec., $[\alpha]^{29}D$ +34.5° (*c* 1.02, chf).

Anal. Calcd. for $C_{34}H_{47}NO_4S$: C, 72.17; H, 8.37; S, 5.67. Found: C, 72.20; H, 8.52; S, 5.82.

Oxime.—A solution of hydroxylamine acetate was prepared from 10 mg. of hydroxylamine hydrochloride and 20 mg. of hydrated sodium acetate in 0.5 ml. of methanol. To the decanted solution was added 35 mg. of XI (prepared from IX) in 1 ml. of methanol. After boiling under reflux for 1.75 hours, the solvent was removed *in vacuo* and the

(12) W. A. Jacobs and A. M. Collins, *J. Biol. Chem.*, **65**, 491 (1925).

(13) Melting points are corrected. They were taken on a hot-stage microscope equipped with a polarizer. Finely powdered samples were placed on the stage about 10° below the m.p. and the temperature raised rapidly to within 3° of the m.p. The temperature was then raised 2°/min. M.p.'s were 10 to 15° lower for some compounds when placed on the hot-stage at room temperature.

(14) J. Fritz, "Acid-base Titrations in Nonaqueous Solvents," G. Frederick Smith Chemical Co., Columbus, Ohio, 1952, pp. 13–15.

(15) When the solution was heated or allowed to stand very long, sufficient decomposition occurred to inhibit crystallization of the product and very small yields then resulted. Additional crystalline material could be obtained by reprocessing the resin obtained by evaporating the solution.

residue was treated with 5 ml. of saturated sodium bicarbonate solution. The mixture was extracted with ten 3-ml. portions of chloroform and the combined extracts were washed and evaporated *in vacuo*. The residue was dissolved in acetone–methanol (20:1), clarified, and concentrated to a small volume. The crude oxime, m.p. 300–303° dec., separated as delicate micro-needles. Recrystallization from acetone gave 17 mg. of the same melting point.

Anal. Calcd. for $C_{34}H_{48}N_2O_4S$: C, 70.31; H, 8.33; N, 4.82. Found: C, 70.10; H, 8.38; N, 4.82.

Isorubijervine Monoiodide (XII).—A solution of 700 mg. of isorubijervine monotosylate (IX) in 50 ml. of warm acetonitrile was mixed with a solution of 1.3 g. of sodium iodide in 25 ml. of acetonitrile. Precipitation of sodium *p*-toluenesulfonate occurred immediately. After one-half hour the reaction mixture was diluted with a large volume of a solution of sodium thiosulfate and sodium bicarbonate. The mixture was extracted repeatedly with chloroform, and the washed extract was evaporated *in vacuo*. When the white residue was crystallized from acetone–methanol it gave 627 mg., m.p. 298–307° dec. Recrystallization from methanol–ether yielded delicate needles, m.p. 307–309.5° dec.,[16] $[\alpha]^{28}D$ −46.5°[17] (*c* 1.90 in abs. EtOH). Treatment of an alcoholic solution of this substance with silver nitrate gave an immediate precipitate of silver iodide. The compound also was not titratable with perchloric acid in acetic acid,[9,14] thus indicating a quaternary nitrogen.

Anal. Calcd. for $C_{27}H_{42}INO$: C, 61.94; H, 8.09; I, 24.24. Found: C, 62.00; H, 8.15; I, 24.12.

This compound was also prepared by heating a suspension of IX in acetone with sodium iodide at 105–110° for 20 hours or in boiling diethyl ketone.

Attempts to reduce isorubijervine monoiodide with a zinc–copper couple in boiling ethanol, with aluminum amalgam or with hydrogen and platinum oxide or palladium-on-calcium carbonate were unsuccessful. The material recovered in each case was unchanged iodide.

3-Tosylisorubijervine Iodide (XIII).—A solution of 150 mg. of 3-tosylisorubijervine tosylate (X) in 10 ml. of acetonitrile was treated with 1.0 g. of sodium iodide in 15 ml. of acetonitrile. The reaction mixture was processed as described for isorubijervine monoiodide and the product recrystallized from acetone–ether to give 120 mg. of an iodide, m.p. 180–183° dec. This substance gave a precipitate with alcoholic silver nitrate and could not be titrated against perchloric acid.

Anal. Calcd. for $C_{34}H_{48}INO_3S$: C, 60.25; H, 7.14; I, 18.73. Found: C, 60.17; H, 7.14; I, 19.08.

Reductive Cleavage of Isorubijervine Monoiodide to Solanidine and Pseudosolanidine.—A boiling solution of 170 mg. of XII in 10 ml. of absolute ethanol was treated with 2.0 g. of sodium during a period of 30 minutes. After dilution with 30 ml. of water, the mixture was extracted with eight 15-ml. portions of chloroform. The extract was washed with 10 ml. of water, dried over potassium carbonate and evaporated *in vacuo*. When crystallized from methanol, the residue yielded 120 mg. of white needles which melted at 185–235° and did not contain halogen.

Anal. Calcd. for $C_{27}H_{43}NO$: C, 81.54; H, 10.91. Found: C, 81.12, 80.97; H, 10.60, 10.78.

Since the identification and characterization of the components of this mixture were carried out on material obtained chromatographically, the actual separation procedure employed is described. The mixture was dissolved in 20 ml. of benzene–petroleum ether (2:1) and chromatographed over 10 g. of alumina. This yielded three fractions: A, 31 mg., m.p. 191–218°; B, 57 mg., m.p. 209–238°; and C, 32 mg., m.p. 234–237.5°. Fraction B was rechromatographed in benzene over alumina and gave: B_1, 21 mg., m.p. 209–218.5°; B_2, 12 mg., m.p. 184–238°; B_3, 22 mg., m.p. 234–238°. Fractions A and B_1 were combined, C and B_3 were combined and B_2 was reserved.

Fractional crystallization of A–B_1 (52 mg.) indicated it still contained substantial amounts of the higher melting compound. The following fractions were isolated: a, 15 mg., m.p. 212–218.5°; b, 17.5 mg., m.p. 190–237°; c, 12.5 mg., m.p. 190–200°.

Fraction "a" was recrystallized from methanol to give 10 mg. of solanidine melting at 216.5–218.5° and showing $[\alpha]^{34}D$ −27.1° (*c* 0.54, chf) (reported[11] −27.0 ± 4°). A mixture with authentic solanidine (m.p. 216–218°) melted at 216–218.5°.

Anal. Calcd. for $C_{27}H_{43}NO$: C, 81.54; H, 10.91. Found: C, 81.27; H, 10.95.

The material recovered from the optical determination was recrystallized from acetone to give 4 mg. of fine needles which sublimed above 212° and melted at 216–217.5°. The infrared spectrum of this material (Fig. 1) proved to be identical in all points with that of authentic solanidine which had also been recrystallized from acetone.

Fractional crystallization of B–C (54 mg.) from methanol gave 36 mg. of **pseudosolanidine**, m.p. 233–238°. The mother liquors furnished an additional 10 mg. of material which was obviously a mixture, m.p. 190–232°. Recrystallization of the 36 mg. furnished 20 mg. of apparently pure XIV, m.p. 236–237.3°, $[\alpha]^{34}D$ −12° (*c* 1.5, chf).

Anal. Calcd. for $C_{27}H_{43}NO$: C, 81.54; H, 10.91. Found: C, 81.43; H, 11.12.

The material recovered from the optical determination was recrystallized from acetone to give 11.5 mg. of fine, silky needles melting at 236.0–237.0°. The infrared spectrum of this material (Fig. 1) was very similar to that of solanidine.

Separation of Solanidine and Pseudosolanidine with Digitonin.—When a solution of 4 mg. of the 236–237° material XIV in 0.4 ml. of ethanol was treated with 1 ml. of 1% digitonin solution, no precipitate formed after 19 hours. Under identical conditions, solanidine formed a copious digitonide within five minutes. A more efficient separation of solanidine and pseudosolanidine was therefore effected in the following way.

A solution of 200 mg. of the reduction product in 25 ml. of 95% ethanol was treated with 70 ml. of warm 1% digitonin. After standing one hour the copious precipitate was collected and washed with cold absolute ethanol. The solution (S) was reserved for later use.

Solanidine.—The digitonide was dissolved in 5 ml. of warm pyridine, and the digitonin precipitated with 75 ml. of dry ether. The filtrate was concentrated and evaporated to dryness *in vacuo*. The residue (60 mg.) was recrystallized from methanol to give 52 mg. of solanidine (XV), m.p. 214–217°, $[\alpha]^{28}D$ −26.2° (*c* 1.74, chf).

Anal. Found: C, 81.55; H, 11.12.

Acetylsolanidine.—Fifteen mg. of the above solanidine in pyridine was allowed to react with an excess of acetic anhydride overnight and worked up in the usual manner to give 11 mg. of long, flat blades of the acetate, m.p. 206.5–209.5° (ethanol). A mixture with an authentic sample melted at 207–209.5°. The reported m.p. is 207–209°.[5]

Pseudosolanidine.—The solution (S) was evaporated to dryness *in vacuo* and the residue dissolved in 7 ml. of warm pyridine. After precipitating the digitonin with 125 ml. of ether, the filtrate was concentrated to dryness *in vacuo*. The white residue was crystallized from methanol to give 149 mg. of slender needles, m.p. 226–236°. Since repeated recrystallization from methanol did not appreciably change the melting point, the product was thought to still contain some solanidine. It was therefore dissolved in alcohol (15 ml.) and treated again with 1% digitonin (25 ml.). However, since no insoluble digitonide separated, the reduction product (m.p. 225–236°) was recovered as previously described. When dissolved in a large volume of boiling acetone, a small amount of insoluble material remained. Concentration of the filtrate gave 127 mg. of long, slender needles; m.p. 235.8–236.5°, $[\alpha]^{26}D$ −11.7° (*c* 1.37, chf). Recrystallization did not change the melting point.

Acetylpseudosolanidine.—Treatment of 36 mg. of pseudosolanidine by the usual procedure gave 18 mg. of long, thin blades of the acetate after two recrystallizations from methanol; m.p. 149–150°.

Anal. Calcd. for $C_{29}H_{45}NO_2$: C, 79.22; H, 10.32; sapn. equiv., 439.7. Found: C, 79.12; H, 10.26; sapn. equiv., 448.7.

Reductive Cleavage of Isorubijervine Monotosylate to Solanidine and Pseudosolanidine.—Treatment of 70 mg. of

(16) The m.p. previously reported (294–297° dec.)[7] was obtained when this compound was heated on the hot-stage from 100° to its melting point.

(17) We previously reported $[\alpha]D$ −38°[7]; repeated determinations on freshly crystallized material indicate that −46.5° is the correct value.

IX with a large excess of sodium in boiling absolute ethanol and processing the reaction mixture as described above gave 45 mg. of product, m.p. 190–218°. Separation with digitonin and recrystallization of each component from the appropriate solvent gave 6 mg. of solanidine (m.p. and mixture m.p. was 215.5–218°) and 24 mg. of pseudosolanidine (m.p. was 235.7–236.5°, unchanged when mixed with previous material).

Dihydropseudosolanidine (XVI).—A solution of 22 mg. of XIV in glacial acetic acid was hydrogenated with 16 mg. of platinum oxide catalyst. The absorption was equivalent to 1 mole in excess of the catalyst requirement. After filtration and dilution, addition of potassium carbonate solution caused the separation of a gelatinous mass which was extracted with chloroform. The extract yielded a residue which after two crystallizations from methanol gave 6.5 mg. of XVI melting at 210–211°, $[\alpha]^{33}D$ +33.6° (*c* 0.52, chf). The mother liquor yielded 2.5 mg. of less pure material, m.p. 209–211.5°. The reported constants for solanidin-3α-ol are m.p. 211–213°, $[\alpha]D$ +31.9 ± 4°. An authentic sample of solanidanol-3(α) prepared by a modification of the method of Prelog and Szpilfogel[11] melted at 214.5–216.0°; acetate, 176.0–178.0° (reported 211–213° acetate, 174–176°). A mixture melting point with XV showed a marked depression; m.p. 182–201°. XVI therefore cannot be solanidan-3α-ol.

Infrared Spectra.—Samples were prepared as Nujol mulls and the 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.

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[CONTRIBUTION FROM THE NAGOYA INDUSTRIAL SCIENCE RESEARCH INSTITUTE,* ROKUNO-CHO ATSUTA-KU, AND THE CHEMICAL INSTITUTE, NAGOYA UNIVERSITY**]

Studies on Pteridines.[1] IV. Synthesis of 6- and 7-Hydroxypteridines

BY SADAO MATSUURA,* SABUTO NAWA,* HIROSHI KAKIZAWA** AND YOSHIMASA HIRATA**

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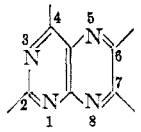
The synthesis, ultraviolet spectra and paper chromatography of several pteridines are described. The present work has been undertaken for the purpose of identifying the structures of pteridines isolated in our laboratory from the eggs of *Bombyx mori* (silk worm)[2] and the scale of carp.[3]

The 6- and 7-hydroxypteridines I have been synthesized by the condensation of 4,5-diamino-



I

pyrimidine derivatives with ethoxalyl (R–CO–CO_2–C_2H_5) derivatives, the formation of the 6- or 7-hydroxy compounds depending mainly on the acidity of the medium and to some extent on the nature of the reagents. In general, weak acidity (*p*H 5) favored the formation of 7-hydroxypteridines, whereas strong acid (2 *N* HCl) favored that of the 6-hydroxypteridines; these results can be interpreted in terms of mono- and bivalent cation formation of the pyrimidine derivatives in weak and strong acid media.[4]

Paper chromatography (Table I) and ultraviolet spectra (Table II), together with several specific reactions such as Al–Hg reduction,[5] MnO_2 oxidation,[2] hydrolysis, decarboxylation, etc., were employed for the characterization of the products.

Comparison of R_f values of closely related pteridines in the two sets of solvents were consistent with the differences in their hydrophilic nature and were utilized in interpreting the nature of the products (*e.g.*, compounds XVIII to XXII).

(1) Previous paper, *Experientia*, **8**, 339 (1952).

(2) To be published.

(3) Y. Hirata and S. Nawa, *Compt. rend. soc. biol.*, **145**, 661 (1951). Recent results will be published in a forthcoming paper.

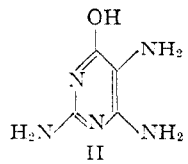
(4) G. B. Elion, G. H. Hitchings and P. B. Russell, THIS JOURNAL, **72**, 78 (1950); H. S. Forrest and J. Walker, *J. Chem. Soc.*, 79 (1949).

(5) Paper V, THIS JOURNAL, **75**, 4450 (1953).

Ultraviolet spectra (Table II) were measured in 0.1 *N* NaOH solutions. All of the compounds belonging to the isoxanthopterin series possessed a maximum at 253–260 mμ (log *E* 3.9–4.2), a shoulder or maximum around 275 mμ (log *E* 3.44–3.72), and a maximum at 340–350 mμ (log *E* 4.0–4.2). Compounds belonging to the xanthopterin series possessed one or two maxima or shoulders around 250–280 mμ (log *E ca.* 4.0) and maximum around 380–400 mμ (log *E ca.* 3.7). Other pteridines also showed curves characteristic of their series and the ultraviolet spectra may serve for identification purposes. The pteridines which have been synthesized are listed in Table I.

In general the crude products were purified by several repetitions of the process of dissolution in dilute alkali, charcoal treatment and acidification with acetic acid.

When 2,4,5-triamino-6-hydroxypyrimidine (II)



II

and ethyl ethoxalylacetate were condensed in mineral media (*p*H 2), a simultaneous hydrolysis and decarboxylation occurred giving a mixture of 6-methylisoxanthopterin (IV) and 7-methylxanthopterin (XXIII), whereas when condensed at *p*H 5, an almost exclusive formation of ethyl isoxanthopteryl-6-acetate took place. The ester was subsequently hydrolyzed with alkali to give isoxanthopteryl-6-acetic acid (VIII). This compound is unstable to acids and is easily decarboxylated to