g. of a mobile sirup which failed to crystallize, b.p. 100° at 0.2 mm., $[\alpha]_D$ 38° (*c* 3.79, methanol at 20°).

Anal. Calcd. for $C_{10}H_{18}O_7$: OMe, 62.0. Found: OMe, 60.5.

When 0.5 g. of the sirup was treated with methanolic ammonia in the refrigerator for two days the solution deposited crystals. Upon removal of gas and solvent, the diamide of 2,3,4-trimethyl-L-araboglutaric acid[13] was obtained, m.p. 233° (recrystallized from methanol), $[\alpha]_D$ 42.6° (*c* 3.5, water at 20°).

Anal. Calcd. for $C_8H_{16}O_5N_2$: OMe, 42.3; N, 12.7. Found: OMe, 42.2; N, 12.2.

(13) E. L. Hirst and G. J. Robertson, *J. Chem. Soc.*, **127**, 362 (1925).

Examination of Fraction II.—Fraction II proved to be a mixture of the compounds identified in fractions I and III. After hydrolysis with *N* sulfuric acid for 2 hours the free sugars were isolated in the usual manner and examined by paper partition chromatography using the previously identified compounds as reference standards. There was no indication of the presence of any substance other than those characterized.

Acknowledgment.—The author is pleased to acknowledge the advice and assistance of E. E. Dickey in the chromatographic separation. He is also indebted to Heinz Seiler who analyzed the compounds reported for their methoxyl content.

APPLETON, WISCONSIN

[CONTRIBUTION FROM RIKER LABORATORIES, INC.]

The Structure of Isorubijervine. Conversion to Solanidane and Solanidane-3β-ol[1]

BY FRANK L. WEISENBORN AND DIANA BURN

RECEIVED JULY 28, 1952

Isorubijervine has been established as a hydroxy derivative of solanidine by conversion to solanidane and solanidane-3β-ol. Treatment of isorubijervine with *p*-toluenesulfonyl chloride led to a unique, salt-like tosyl derivative showing that the primary hydroxyl must be within bonding range of the nitrogen. Carbon 19 was thus eliminated as a site for this hydroxyl.

Only one of the veratrum alkaloids, rubijervine, has been shown to have a steroidal type ring system and to be related to solanidine. This was demonstrated by Sato and Jacobs,[2] who converted rubijervine to solanidine and solanidane-3β-ol.

Isorubijervine, another alkaloid from *Veratrum viride* was also studied by Jacobs and co-workers.[3-6] This substance was found to contain two hydroxyl groups, one of which was secondary and at carbon 3. The other was shown to be of primary character by the oxidation of dihydroisorubijervine to an acid which could be reconverted to dihydroisorubijervine by reduction of the corresponding ester with lithium aluminum hydride. Since the ester was difficult to saponify and since selenium dehydrogenation of isorubijervine yielded 1,2-cyclopentenophenanthrene, isorubijervine was assigned a hydroxysolanidine structure (I) with the primary hydroxyl group at carbon 18. No evidence for a solanidine type ring system was obtained, however. We have now shown that isorubijervine is in fact a derivative of solanidine by conversion to solanidane-3β-ol and solanidane.

Oppenauer oxidation of dihydroisorubijervine (II) yielded solanidane-3-one-18-ol (III) which was then further oxidized to the solanidane-3-one-18-al (IV) using one equivalent of chromic acid. Compound IV could also be obtained, although in lower yield, by the direct oxidation of dihydroisorubijervine with 1.6 equivalents of chromic acid. No ketoaldehyde could be isolated when two equivalents of chromic acid were used. Reduction of solanidane-3-one-18-al (IV) using the Huang-Minlon modification of the Wolff–Kishner method gave an excellent yield of an oxygen-free base identical in all respects with solanidane (V).

A sample of solanidane for comparison was obtained by the modified Wolff–Kishner reduction of solanidane-3,12-dione (prepared from rubijervine by the method of Sato and Jacobs[2]). It is interesting to note that the Huang-Minlon modification of the reduction gave only solanidane, whereas Sato and Jacobs[2] found that reduction of the disemicarbazone by the normal Wolff–Kishner procedure yielded the alcohol, solanidane-3β-ol, as the major product.

In addition, dihydroisorubijervine was converted to solanidane-3β-ol by the following method. Oxidation of dihydroisorubijervine with one equivalent of chromic acid in 95% acetic acid gave solanidane-3β-ol-18-al (VI) in 70% yield. Reduction of VI by the Wolff–Kishner method gave an 89% yield of solanidane-3β-ol (VII). Its identity was confirmed by comparison of its infrared spectrum with that of an authentic sample and by conversion to the monoacetyl derivative and the corresponding 3-ketone.[7]

Solanidane-18-al was prepared in surprisingly good yield (84%) by oxidation of solanidane-18-ol with chromic anhydride. When this aldehyde or solanidane-3β-ol-18-al was treated with ethyl orthoformate in ethanol–sulfuric acid solution, no formation of an enol ether could be detected and the majority of starting material was recovered. Carbon 21 or carbon 27, therefore, would not appear to be the site of the aldehyde group (and thus the primary hydroxyl) since both positions possess an α-hydrogen and thus should form an enol ether.

Another route originally considered for the

(1) Presented before the Division of Medicinal Chemistry at the 122nd Meeting of the A.C.S., Atlantic City, N. J., September, 1952.

(2) Y. Sato and W. A. Jacobs, *J. Biol. Chem.*, **179**, 623 (1949).

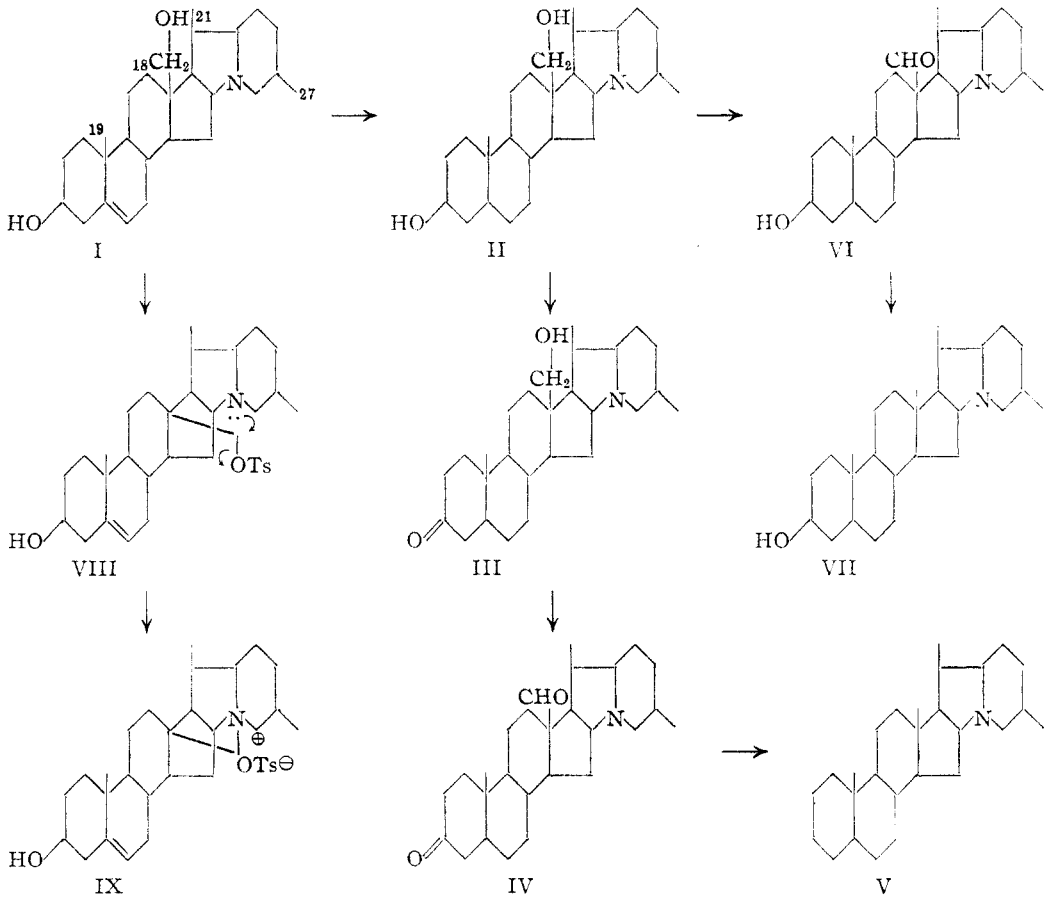
(3) W. A. Jacobs and L. C. Craig, *ibid.*, **148**, 41 (1943).

(4) W. A. Jacobs and L. C. Craig, *ibid.*, **149**, 451 (1943).

(5) W. A. Jacobs and L. C. Craig, *ibid.*, **159**, 617 (1945).

(6) Y. Sato and W. A. Jacobs, *ibid.*, **191**, 63 (1951).

(7) After this manuscript had been prepared for publication, a Communication to the Editor by Rigby and Burn (*Chemistry and Industry*, **27**, 668 (1952)) appeared in which these authors report the conversion of isorubijervine to solanidane-3β-ol by this same method. This portion of our work thus confirms their results.



conversion of isorubijervine to solanidine involved the preparation of the tosyl ester of the primary alcohol of isorubijervine followed by the reduction of this ester with lithium aluminum hydride. Treatment of isorubijervine with one equivalent of *p*-toluenesulfonyl chloride in pyridine did in fact give an excellent yield of a monotosylate. The substance, however, was not basic (could not be titrated with perchloric acid in acetic acid), nor could it be reduced with lithium aluminum hydride. The presence of only one free hydroxyl group was shown by formation of a monoacetate on heating with acetic anhydride. When the tosylate was dissolved in acetonitrile and treated with sodium iodide, precipitation of sodium *p*-toluenesulfonate took place instantaneously and an iodide was obtained. The iodide was also neutral and could not be reduced catalytically with platinum or Raney nickel. From these results, structure IX was derived for the salt-like tosylate. This compound could be formed from the intermediate normal tosyl ester (VIII) by displacement of the *p*-toluenesulfonate ion by the electron pair on the nitrogen, forming a bond with carbon 18. A similar intramolecular alkylation has been studied by Clark, Todd and Zussman.[8]

Δ^4-Isorubijervone also reacted with *p*-toluenesulfonyl chloride to give a similar salt-like compound with comparable properties, showing that the hydroxyl group at carbon 3 is not involved in this remarkable reaction. Further, solanidane-3-one-18-ol (III) was reduced by the Wolff–Kishner method to solanidane-18-ol which on treatment with *p*-toluenesulfonyl chloride also gave a non-basic, salt-like derivative.

These abnormal tosyl derivatives of isorubijervine are easily detected by a study of their infrared spectra since they all show four strong, sharp, very characteristic bands at 8.56, 8.96, 9.71 and 9.94μ (Fig. 1A,B). These bands are characteristic of the *p*-toluenesulfonate ion since they also appear in the spectrum of the *p*-toluenesulfonic acid salt of isorubijervine (Fig. 1C). On the other hand, none of these bands was found in the spectrum of the normal tosylate of solanidane-3β-ol (Fig. 1D). In addition, all the abnormal tosylates showed weak absorption at 3.0μ, indicative of a quaternary ammonium salt.

Since this ionic sulfonate must arise by formation of a new carbon–nitrogen bond, carbon 19 cannot be the site of the primary hydroxyl as it is not within bonding range of the nitrogen. Of the three remaining positions C_{18}, C_{21} or C_{27}, the bond between carbon 18 and the nitrogen involves no strain, whereas a bond involving C_{21} or C_{27} appears to be sterically impossible. Thus isorubijervine must have structure I in which the hydroxyl group occupies the 18-position.

Acknowledgments.—We wish to thank Mr. M. A. Robinson and Mr. C. H. Stimmel of this Laboratory for the determination of physical constants. We are grateful to Professor V. Prelog for taking a

(8) V. M. Clark, A. R. Todd and J. Zussman, *J. Chem. Soc.*, 2952 (1951).

mixed melting point of our solanidane with an authentic sample and for infrared spectra of solanidane and solanidane-3β-ol. We are indebted to Professor L. Briggs for an authentic sample of solanidane-3β-ol.

Experimental[9]

Dihydroisorubijervine (II).—This compound was prepared according to the method of Jacobs and Craig.[4] It crystallized from ethanol in colorless prisms, m.p. 247–249°, $[\alpha]^{24}D$ +38.8° (reported[4] m.p. 241–243°).

Solanidane-3-one-18-ol (III).—Dihydroisorubijervine (685 mg.) was dissolved in 20 ml. of toluene and 4 ml. of cyclohexanone. After a few milliliters of the solution was removed by distillation, 400 mg. of aluminum isopropoxide was added. The mixture was then refluxed for three hours and diluted with 30 ml. of 2 *N* sodium hydroxide. After the toluene and cyclohexanone had been steam distilled off, the solution was cooled, the precipitate filtered and recrystallized from hot acetone. The yield was 630 mg. (90%), m.p. 215–217°, $[\alpha]^{24}D$ +57° (reported[6] m.p. 217–222°).

Solanidane-3-one-18-al (IV).—A solution of chromic anhydride (46.4 mg.) in 30 ml. of 95% acetic acid was added dropwise with stirring to a solution of solanidane-3-one-18-ol (271 mg.) in 80 ml. of acetic acid. After two hours the reaction mixture was worked up as usual to give 230 mg. (85%) of the ketoaldehyde. After crystallization from acetone, the substance melted at 223–224°, $[\alpha]^{24}D$ +65°.

Anal. Calcd. for $C_{27}H_{41}O_2N$: C, 78.78; H, 10.04; equiv. wt., 412. Found: C, 78.95; H, 9.83; equiv. wt., 410.

Solanidane (V).—Hydrazine hydrate (4 ml.) and potassium hydroxide (0.5 g.) were added to a solution of solanidane-3-one-18-al (210 mg.) in 20 ml. of diethylene glycol. The reaction mixture was heated at 100° for one hour after which the temperature was allowed to rise to 195° during the removal of hydrazine and water. After heating at this temperature for four hours, the mixture was worked up in the usual manner to give 193 mg. of product. The solanidane was recrystallized from chloroform–methanol, m.p. 160–161°, $[\alpha]^{24}D$ +31.8° (reported[10] m.p. 161.5–162.5°, $[\alpha]D$ +33.1°).

Anal. Calcd. for $C_{27}H_{41}N$: C, 84.52; H, 11.82. Found: C, 84.92; H, 12.07.

Comparison of the infrared spectrum of this product with that of an authentic sample showed that the compounds were identical. Mixed melting point with an authentic sample of solanidane, kindly carried out by Professor Prelog, showed no depression.

A sample of solanidane for comparison was also prepared starting with rubijervine. The preparation is described below.

Dihydrorubijervine.—This was prepared by the method of Jacobs and Craig.[4] The compound had m.p. 224–226°, $[\alpha]^{24}D$ +59.7° (absolute ethanol). The reported[4] melting point was 222° (uncorrected).

Solanidane-3-12-dione.—Prepared by the method of Sato and Jacobs.[2] The diketone had a melting point, 241.5–243.5°, $[\alpha]^{24}D$ +114° (reported[2] m.p. 242–244°, $[\alpha]D$ +119°).

Solanidane from Solan-3,12-dione.—The Wolff–Kishner reduction of solanidane-3,12-dione by the Huang-Minlon modification gave solanidane, m.p. 163–164°, $[\alpha]^{24}D$ +32.1, in 80% yield, whereas Sato and Jacobs[2] found that the principal product obtained by normal Wolff–Kishner reduction of the disemicarbazone was solanidane-3β-ol.

The solanidane from the above preparation gave no depression in melting point when mixed with the solanidane obtained from isorubijervine. The infrared spectra were also identical.

Lithium Aluminum Hydride Reduction of Solanidane-3-one-18-al.—A solution of 200 mg. of IV in 10 ml. of dry tetrahydrofuran was added dropwise to a vigorously stirred solution of 400 mg. of lithium aluminum hydride in 50 ml. of dry ether and the mixture refluxed for 45 minutes. Five milliliters of water was added followed by 36 ml. of 2 *N* sulfuric acid. The layers were separated and the aqueous portion extracted twice with ether. The aqueous layer was made basic with sodium carbonate solution and extracted several times with chloroform. The combined extracts were dried over magnesium sulfate and evaporated. The product was crystallized from ethanol, m.p. 245–249°, $[\alpha]^{24}D$ +43°. A mixed melting point with dihydroisorubijervine showed no depression.

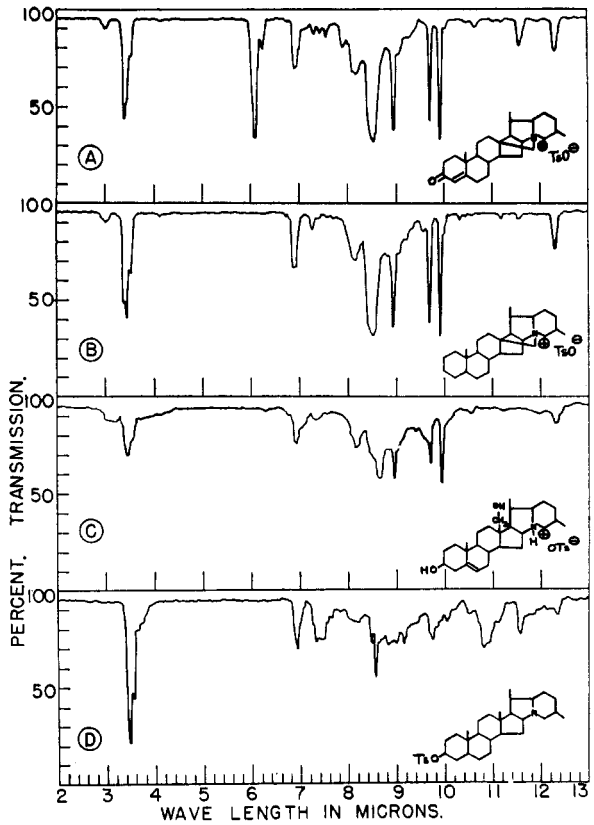


Fig. 1.—Infrared absorption spectra (in chloroform).

Solanidane-3β-ol-18-al (VI).—A solution of chromic anhydride (170 mg.) in 60 ml. of 95% acetic acid was added dropwise with stirring to a solution of dihydroisorubijervine (1.0 g.) in 200 ml. of acetic acid. The solution was stirred for a further four hours (*i.e.*, until all the chromic anhydride had reacted). The acetic acid was then evaporated off and the resultant solid taken up in water and extracted several times with chloroform. The combined extracts were dried over magnesium sulfate and evaporated. The product was crystallized from methanol to give 697 mg. (70%) of solanidane-3β-ol-18-al, m.p. 206–208.5°, $[\alpha]^{24}D$ +51°. (reported[7] m.p. 204.6°, $[\alpha]D$ +45°).

Anal. Calcd. for $C_{27}H_{43}O_2N$: C, 78.40; H, 10.48. Found: C, 78.61; H, 10.52.

Solanidane-3β-ol (VII).—Hydrazine hydrate (3 ml.) and potassium hydroxide (0.5 g.) were added to a solution of 400 mg. of solanidane-3β-ol-18-al in 40 ml. of diethylene glycol. The reaction mixture was heated at 100° for one hour. The temperature was then allowed to rise to 195° during the removal of hydrazine and water. After four hours at 195°, the mixture was poured into water and extracted several times with chloroform. The combined extracts were washed twice with water to remove any diethylene glycol, then dried and concentrated, yielding 345 mg. (89%) of crystalline solid. Recrystallization from chloroform–acetone gave solanidane-3β-ol, m.p. 218–220°, $[\alpha]^{24}D$ +29.5° (reported[10] m.p. 220°, $[\alpha]D$ +28.2°). A mixed melting point with an authentic sample kindly taken by Professor Briggs, showed no depression.

Comparison of the infrared spectrum with that of an authentic sample of solanidane-3β-ol showed that the compounds were identical.

The identity with solanidane-3β-ol was further demonstrated by the preparation of the acetate and the corresponding ketone.

(9) Rotations were taken in chloroform unless otherwise indicated. All melting points are corrected. The microanalyses were carried out by Dr. A. Elek.

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

The acetate of solanidane-3β-ol was prepared by heating the alcohol in acetic anhyride for one hour on the steam-bath. The product crystallized from ethyl acetate, m.p. 191–192°, $[\alpha]^{24}D$ +17.3° (reported[10] m.p. 196°, $[\alpha]D$ +16.5°).

Anal. Calcd. for $C_{29}H_{47}O_2N$: C, 78.86; H, 10.73. Found: C, 78.93; H, 10.69.

Solanidane-3-one was prepared by chromic acid oxidation of solanidane-3β-ol. Crystallization from ethyl acetate gave solanidane-3-one, m.p. 209–211°, $[\alpha]^{24}D$ +45.7 (reported[10] m.p. 210–211°, $[\alpha]D$ +45.8°).

Anal. Calcd. for $C_{27}H_{43}ON$: C, 81.55; H, 10.90. Found: C, 81.86; H, 10.73.

Isorubijervine Monotosylate.—*p*-Toluenesulfonyl chloride (0.690 g., 3.6 millimoles) was added to a solution of isorubijervine (1.490 g., 3.6 millimoles) in 20 ml. of pyridine. The mixture was allowed to stand overnight, concentrated under vacuum, made basic with sodium carbonate solution and extracted with chloroform. The combined extracts were dried over magnesium sulfate and evaporated to dryness to give 2.105 g. (97%) of product which was crystallized from methanol, m.p. 277–281°. The compound appeared to be neutral since it could not be titrated with perchloric acid in acetic acid. The infrared spectrum showed absorption at 3.0μ indicative of a quaternary ammonium salt.

Anal. Calcd. for $C_{34}H_{49}O_4NS$: C, 71.91; H, 8.70. Found: C, 71.60; H, 8.62.

The monoacetate was prepared by heating in acetic anhydride. The product crystallized from methanol–water, m.p. 263–267°.

Anal. Calcd. for $C_{36}H_{51}O_5NS$: C, 70.91; H, 8.43. Found: C, 70.58; H, 8.44.

Isorubijervine Monoiodide.—Two grams of sodium iodide dissolved in 10 ml. of acetonitrile was added to a hot solution of isorubijervine monotosylate (700 mg.) in 21 ml. of acetonitrile. A heavy white precipitate appeared immediately. This precipitate of sodium *p*-toluenesulfonate amounted to 230 mg. (92%). The filtrate was concentrated, diluted with water and extracted with chloroform. The extracts were dried and evaporated yielding 530 mg. (82%) of an iodide. The product was recrystallized from ethanol, m.p. 306–310°. On titration it was found to be non-basic.

Anal. Calcd. for $C_{27}H_{42}ONI$: C, 61.94; H, 8.09. Found: C, 61.86; H, 8.15.

The iodide could not be reduced catalytically with platinum or Raney nickel.

Δ⁴-Isorubijervone.—This was prepared by Oppenauer oxidation as described by Jacobs and Craig.[5] The compound had m.p. 252–255°, $[\alpha]^{24}D$ +99° (reported[5] m.p. 250–255°, $[\alpha]D$ +111° in pyridine).

The monotosylate of this compound was prepared in the same way as that of isorubijervine, m.p. 326–328°. It was also non-basic.

Anal. Calcd. for $C_{34}H_{47}O_4NS$: C, 72.17; H, 8.37. Found: C, 72.00; H, 8.45.

Solanidane-18-ol.—Hydrazine hydrate (15 ml.) and 2 g. of potassium hydroxide were added to a solution of solanidane-3-one-18-ol (III) (0.833 mg.) in 50 ml. of diethylene glycol. The reaction mixture was heated at 100° for one hour and the temperature was then allowed to rise to 195°. The solution was heated at this temperature for a further three hours. It was then worked up in the usual way, to give 800 mg. of product which after recrystallization from ethanol melted at 206–207.5°, $[\alpha]^{24}D$ +38.6°.

Anal. Calcd. for $C_{27}H_{45}ON$: C, 81.14; H, 11.35. Found: C, 81.51; H, 11.20.

Solanidane-18-al.—A solution of 44.4 mg. of chromic anhydride in 20 ml. of 95% acetic acid was added dropwise with stirring to a solution of 250 mg. of solanidane-18-ol in 50 ml. of acetic acid. After the reaction was complete (two hours) the product was isolated in the usual manner (209 mg., 84%), m.p. 179.5–182°, $[\alpha]^{24}D$ +54.2°.

Anal. Calcd. for $C_{27}H_{43}ON$: C, 81.55; H, 10.90. Found: C, 81.29; H, 11.15.

Tosylate of Solanidane-18-ol.—*p*-Toluenesulfonyl chloride (75 mg., 0.395 mm.) was added to a solution of 150 mg. solanidane-18-ol (0.375 mm.) in 5 ml. of pyridine. After standing overnight, the mixture was worked up as described for the tosylate of isorubijervine to give 180 mg. (87%), m.p. 345°.

Anal. Calcd. for $C_{34}H_{51}O_3NS$: C, 73.74; H, 9.29. Found: C, 73.40; H, 9.38.

This compound was found to be non-basic and showed the four characteristic bands in the infrared.

***p*-Toluenesulfonic Acid Salt of Isorubijervine.**—Equimolar quantities of isorubijervine and *p*-toluenesulfonic acid were mixed in ethanol. Concentration of the solution followed by the addition of ether caused precipitation of the salt, m.p. 234–235°.

NOTE ADDED IN PROOF.—Pelletier and Jacobs (THIS JOURNAL, 74, 4218 (1952)) have recently reported the formation of solanidine in addition to an isomeric compound by reduction of the iodo derivative (IX, OTs = I) with sodium and alcohol. These authors, however, were not aware of the quaternary nature of the iodo derivative and assumed that the isomer resulted from epimerization of the C_3 hydroxyl group. Actually, the solanidine was obtained by cleavage of the C_{18}-nitrogen bond, and the isomer is probably formed by cleavage of the C_{16}-nitrogen bond.

LOS ANGELES, CALIFORNIA