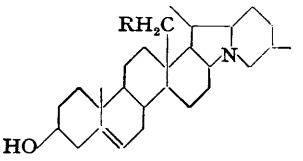
201. *The Skeleton of* iso*Rubijervine.*

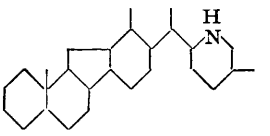
By Derek Burn and W. Rigby.

That *iso*rubijervine has the solanidane skeleton has been proved by conversion of dihydro*iso*rubijervine into solanidan-3β-ol.

So far, two skeletal types have been found among the *Veratrum* alkaloids. Rubijervine has been shown to have a normal steroid structure based on (I), being a hydroxysolanidine (Sato and Jacobs, *J. Biol. Chem.*, 1949, **179**, 623); the other type, (II), is represented by jervine and veratramine (Fried, Wintersteiner, Moore, Iselin, and Klingsberg, *J. Amer. Chem. Soc.*, 1951, **73**, 2970; Tamm and Wintersteiner, *ibid.*, 1952, **74**, 3842).



(I; R = H) (III; R = OH)



(II)

Sato and Jacobs (*J. Biol. Chem.*, 1951, **191**, 63) produced strong evidence in support of their formula (III) for *iso*rubijervine. They showed that the primary alcohol group is in a hindered position and is probably a modified methyl group situated at a bridgehead—the acid resulting from its oxidation has the properties expected for a tertiary, or hindered secondary, carboxylic acid. They adduced reasons for preferring $C_{(18)}$ of a steroid skeleton as the location of this primary alcohol function. However, confirmation of the solanidane skeleton by direct correlation with substances of known structure was still lacking.

We have oxidised the primary alcohol group in dihydro*iso*rubijervine to the corresponding aldehyde, 18(?)-oxosolanidan-3β-ol, and reduced this by the Wolff–Kishner method (Huang-Minlon modification) to solanidan-3β-ol; it follows that *iso*rubijervine has the skeleton proposed by Sato and Jacobs, only the position of the primary hydroxyl remaining in doubt. Shortly after these findings were published in preliminary form (*Chem. and Ind.*, 1952, 668) confirmation of the skeletal structure was given in a note by Pelletier and Jacobs (*J. Amer. Chem. Soc.*, 1952, **74**, 4218) and by Weisenborn and Burn (Abs. Papers, 122nd meeting, Amer. Chem. Soc., 1952, No. 23L) who also give evidence for the primary alcohol groups' being at $C_{(18)}$.

Experimental

M. p.s are corrected. The chloroform used as solvent in measurements of specific rotations was B.P. grade, *i.e.*, containing 1—2% of alcohol.

*iso*Rubijervine was kindly supplied by Dr. H. L. Holmes of Riker Laboratories, Inc., through the courtesy of Dr. D. H. R. Barton; it had m. p. 233—236°, $[\alpha]_D^{25}$ −9·2° (*c*, 1·72 in $CHCl_3$), $[\alpha]_D^{27}$ +9·3° (*c*, 0·96 in 95% EtOH).

*Dihydro*iso*rubijervine.*—*iso*Rubijervine in alcohol containing acetic acid was hydrogenated at atmospheric pressure in the presence of Adams's catalyst. The product, worked up in the usual way, had m. p. 244—248° [Craig and Jacobs, *J. Biol. Chem.*, 1943, **149**, 461, give m. p. 244° (uncorr.)]. Addition of sodium hydroxide to a solution in methyl alcohol of the toluene-*p*-sulphonate gave pure dihydro*iso*rubijervine as prisms, m. p. 252—253°.

*Oxidation of Dihydro*iso*rubijervine.*—(*a*) *With* tert.*-butyl chromate.* A solution of dihydro-*iso*rubijervine in benzene was kept at room temperature for 7—8 days with 1·25 mol. of *tert.*-butyl chromate. Low yields of 18(?)-oxosolanidan-3β-ol were obtained; much dihydro*iso*-rubijervine remained unattacked, results were erratic, and the aldehyde was difficult to purify.

(*b*) *With chromium trioxide.* To dihydro*iso*rubijervine, m. p. 244—248° (0·1 g.), in 90% acetic acid (4 ml.), chromium trioxide (0·016 g.) in 90% acetic acid (1 ml.) was added. The mixture was kept at room temperature until reduction appeared to be complete (*ca.* 12 hr.), and the total bases were isolated in the usual way and chromatographed on acid-washed alumina (5 g.). Elution with benzene gave fairly pure 18(?)-oxosolanidan-3β-ol, m. p. 198—204° (0·05 g.); elution with benzene containing 1% of alcohol then gave a mixture of this with dihydro*iso*-

rubijervine (0·034 g.) which could be resolved by crystallisation from methyl alcohol or by fractional vacuum-sublimation; finally, elution with benzene containing 5% of alcohol gave a small quantity of material, m. p. 265—285°, possibly the keto-acid described by Sato and Jacobs (*loc. cit.*). The crude aldehyde was purified by sublimation at 180° in the vacuum of a diffusion pump, followed by crystallisation from methyl alcohol, 18(?)-*oxosolanidan*-3β-*ol* being obtained as needles, m. p. 204—206°, $[\alpha]_D^{25}$ +45° (*c*, 1·3 in $CHCl_3$) (Found: C, 77·6; H, 10·4. $C_{27}H_{43}O_2N$ requires C, 78·4; H, 10·5%). It gave a 2 : 4-*dinitrophenylhydrazone*, orange needles (from dioxan–methyl alcohol), m. p. 220—223° (Found: C, 65·6; H, 8·2. $C_{33}H_{47}O_6N_5$ requires C, 65·0; H, 7·8%), and a sparingly soluble digitonide.

Solanidan-3β-*ol*.—18(?)-Oxosolanidan-3β-ol (0·19 g.) was refluxed for 1½ hr. with alcohol (5 ml.), diethylene glycol (4 ml.), hydrazine hydrate (100%; 4 ml.), and sodium ethoxide (0·025 g. of Na). A further quantity of sodium ethoxide (0·075 g. of Na) and benzene (5 ml.) were added, volatile solvents were removed, and the residue was kept at 200° for 3 hr. The product was isolated by chloroform-extraction and purified by crystallisation from methyl alcohol and vacuum-sublimation at 170—175°; final recrystallisation from ethyl acetate gave solanidan-3β-ol as needles, m. p. 220·5—221·5°, $[\alpha]_D$ +27° (*c*, 1·1 in $CHCl_3$) (Found: C, 79·5; H, 11·6. Calc. for $C_{27}H_{45}ON$: C, 81·1; H, 11·4%). The m. p.s of this material and of a mixture of it with an authentic specimen of solanidan-3β-ol were identical. For further confirmation of identity, some of the material was acetylated (acetic anhydride–pyridine), to give 3β-acetoxysolanidane, needles (from methyl alcohol), $[\alpha]_D$ +18° (*c*, 1·13 in $CHCl_3$), m. p. 197—199° alone or mixed with an authentic specimen. Oxidation with chromium trioxide–acetic acid yielded solanidan-3-one, needles (from ethyl acetate), m. p. 204—205°, $[\alpha]_D$ +43·5° (*c*, 0·7 in $CHCl_3$).

*Dihydroiso*rubijervine *Toluene*-p-*sulphonate*.—On addition of toluene-*p*-sulphonic acid to an alcoholic solution of dihydro*iso*rubijervine, the *toluene*-p-*sulphonate* crystallised; it formed stout needles (from alcohol–ethyl acetate), m. p. 205—206° if put into the heating bath a few degrees below this temp., but 289—291° if heated from *ca.* 180° (Found: C, 66·7; H, 8·7. $C_{34}H_{53}O_5NS,1\frac{1}{2}H_2O$ requires C, 66·4; H, 9·2%). Addition of sodium hydroxide to a solution in methyl alcohol precipitated pure dihydro*iso*rubijervine, m. p. 252—253°.

The salt was heated under nitrogen from 180° to 240° during 3/4 hr. The residue (m. p. 294—296°) crystallised as stout needles, m. p. 294·5—295·5° (decomp.), from ethyl acetate (Found: C, 67·8; H, 9·1. $C_{34}H_{53}O_5NS,H_2O$ requires C, 67·4; H, 9·15%). Recrystallisation from solvents containing water did not convert it into the starting material, nor did seeding with the latter. Addition of sodium hydroxide to a solution in methyl alcohol precipitated dihydro*iso*-rubijervine, m. p. 250—254°.

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