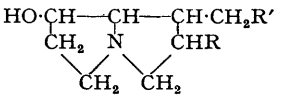
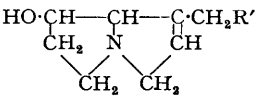
109. *The* Senecio *Alkaloids. Part II. Isatinecine.*

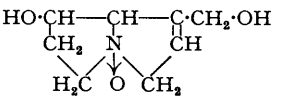
By Ernest C. Leisegang and Frank L. Warren.

Isatinecine, $C_8H_{13}O_3N$, is shown to be retronecine *N*-oxide. Catalytic reduction in the presence of Adams's catalyst gives retronecanol, $C_8H_{15}ON$, and with Raney nickel yields platynecine, $C_8H_{15}O_2N$. Isatinecine is reduced by zinc dust to retronecine, $C_8H_{13}O_2N$, which is oxidised by hydrogen peroxide to isatinecine.

Isatinecine, $C_8H_{13}O_3N$, obtained by hydrolysis of isatidine (Blackie, *Pharm. J.*, 1937, **138**, 1), has two hydrogen atoms less than rosmarinecine for which a constitution (I; R = R′ = OH) was suggested by Richardson and Warren (*J.*, 1943, 452).


(I.)


(II.)


(III.)

Isatidine on reduction absorbed four molecules of hydrogen to give octahydroanhydroisatidine which on hydrolysis gave tetrahydroisatinecine, $C_8H_{17}O_3N$ (de Waal, *Onderstepoort J. Vet. Sci. and Animal Husb.*, 1940, **14**, 433). From this, de Waal concluded that the pyrrolizidine nucleus, common to the other alkaloids of the *Senecio* species, was open, and suggested a 2-butenylpyrroline as the basic structure (*idem, ibid.*, 1941, **16**, 149; *Tydskrif vir Wetenskap en Kuns*, 1941, **1**, 88). All attempts to prepare derivatives to characterise the oxygen atoms failed to give any crystalline product and usually resulted in complete degradation. It was thought that the reduced molecule might be more stable, and reduction experiments were carried out. Catalytic reduction in the presence of Adams's catalyst in alcohol resulted in the absorption of three molecules of hydrogen to give a brown oil which had a strong odour of acetamide and from which a small quantity of crystalline material could be obtained by high-vacuum distillation. When reduction was effected in acid solution, exactly three molecules of hydrogen were taken up to give a colourless oil which sublimed completely in high vacuum to give crystals of retronecanol (I; R = R′ = H), which showed no depression in m. p. on admixture with an authentic specimen obtained by the hydrogenation of retronecine as described by Adams and Rogers (*J. Amer. Chem. Soc.*, 1939, **61**, 2815). That no change had occurred during distillation was established by the preparation of the picrate of the oily hydrogenation product which was identical with that of retronecanol.

The removal of one of the oxygen atoms during hydrogenation could be accounted for by the assumption of a retronecine structure (II; R′ = OH). This concept was supported by the reduction of isatinecine in the presence of Raney nickel, using the conditions of Adams and Rogers (*ibid.*, 1941, **64**, 540) for the reduction of retronecine; two molecules of hydrogen were smoothly absorbed to give a quantitative yield of platynecine (I; R = H, R′ = OH).

The elimination of the other oxygen atom during catalytic reduction could be explained by assuming the presence of either a tertiary amine-oxide grouping or an anionotropic system similar to that in cotarnine. A carbinol-amine grouping would not seem to be present in the free base, as this forms neither a nitromethane condensation product (cf. Hope and Robinson, *J.*, 1911, **99**, 2119) nor *O*-alkyl compounds when heated with alcohols (cf. Blount and Robinson, *J.*, 1932, 2305). To test the assumption of the presence of a tertiary nitrogen-oxide group, isatinecine was treated with zinc dust and dilute sulphuric acid; retronecine (II; R′ = OH) was quantitatively formed (cf. Dunstan, *J.*, 1899, **75**, 796). It would seem therefore that isatinecine is retronecine *N*-oxide (III), a structure which receives support by the ready oxidation with hydrogen peroxide (cf. *idem, ibid.*, p. 1004) of retronecine to isatinecine, obtained as a hygroscopic material but rendered anhydrous by boiling with alcohol (cf. hydrohydrastinene *N*-oxide prepared by Polonovski and Polonovski, *Bull. Soc. chim.*, 1936, **3**, 885).

Isatidine crystallises with two firmly bound molecules of water of crystallisation, a property associated with amine oxides, and attempts to dehydrate it over phosphoric oxide in a vacuum resulted in decomposition (de Waal, *Onderstepoort J. Vet. Sci. and Animal Husb.*, 1939, **12**, 159). Furthermore, both isatidine and isatinecine liberate iodine from potassium iodide in acetic acid on warming, which is a reaction reported by Hasse and Wolffenstein (*Ber.*, 1898, **31**, 1553) for *N*-alkylpiperidine *N*-oxides.

Experimental.

Isatinecine.—(*a*) Isatidine (3·76 g.; 1 mol.) in hot water (20 ml.) was added to barium hydroxide octahydrate (3·6 g.; 1·1 mols.) in water (30 ml.), and the mixture heated on a steam-bath for 2 hours.

Carbon dioxide was then passed into the boiling solution, and the barium carbonate was filtered off and washed with hot water. The combined filtrates were evaporated under reduced pressure at 40°, and the residue extracted with boiling absolute alcohol to leave barium isatinecate. The alcoholic filtrates, evaporated under reduced pressure, gave an almost quantitative yield of isatinecine, m. p. 214—215° (corr.) (decomp.) (Found : C, 55·8; H, 7·88; N, 8·22. Calc. for $C_8H_{13}O_3N$: C, 56·1; H, 7·65; N, 8·18%). de Waal (*Onderstepoort J. Vet. Sci.*, 1940, **14**, 441) gives m. p. 212—215°. The *picrate* crystallised from alcohol in rods, m. p. 145° (corr.) (Found : C, 42·1; H, 4·27. $C_{14}H_{16}O_{10}N_4$ requires C, 42·0; H, 4·03%).

(*b*) Retronecine (0·47 g.; 1 mol.) in alcohol was warmed with 30% hydrogen peroxide solution (0·50 ml.; 1·1 mols.) for 45 minutes. The solution on evaporation gave an oil which solidified on addition of dry acetone. The hygroscopic crystals were washed with dry acetone and dissolved in boiling alcohol (absolute), and the solvent was removed by evaporation. In a vacuum, the oil slowly set to a mass of crystals characteristic of isatinecine, m. p. 214° (corr.) (decomp.).

Retronecanol.—Isatinecine (2·83 g.; 1 mol.), neutralised with 4·6N-sulphuric acid (3·8 ml.) and diluted with water (300 ml.), was shaken with hydrogen and platinum (from 100 mg. of PtO_2). The hydrogen was slowly absorbed and the reaction was complete after 13 hours (observed 1·17 l. at S.T.P. Calc. for $C_8H_{13}O_3N$ for 3 $\equiv$: 1·11 l.). The solution was filtered, excess of barium hydroxide added to the hot filtrate, the excess precipitated by passing carbon dioxide, and the filtered solution evaporated to dryness under reduced pressure. The colourless viscous oil sublimed completely at 45—55°/0·001 mm. to give hygroscopic rhombic crystals, m. p. 92—94° (corr.) (Found : N, 10·0. Calc. for $C_8H_{15}ON$: N, 9·92%), undepressed by mixing with an authentic specimen obtained by hydrogenolysis of retrorsine according to the method of Adams and Rogers (*loc. cit.*). The picrate, from absolute alcohol, had m. p. 211—214° (corr.) (Found : C, 45·5; H, 4·61. Calc. for $C_{14}H_{18}O_8N_4$: C, 45·4; H, 4·90%).

Platynecine.—Isatinecine (4·59 g.) was shaken with hydrogen and Raney nickel (1·0 g., prepared according to the method of Colvert and Adkins, *J. Amer. Chem. Soc.*, 1932, **54**, 4117); the absorption was complete in 13 hours (observed 1·10 l. at S.T.P.; calc. for $C_8H_{13}O_3N$ for 2 $\equiv$: 1·20 l.). The solution was filtered and evaporated under reduced pressure to give a colourless viscous oil which crystallised immediately from acetone. Three crystallisations gave platynecine as colourless needles, m. p. 145—147° (corr.) (Found : N, 8·91. Calc. for $C_8H_{15}O_2N$: N, 8·91%), undepressed on admixture with an authentic specimen (Richardson and Warren, *J.*, 1943, 453). The picrate, from alcohol, had m. p. 183·5—185·5° (corr.). Orechov (*Ber.*, 1935, **68**, 1886) gives platynecine, m. p. 148—149·5°, and picrate, m. p. 184—185°.

Retronecine.—Isatinecine (0·5 g.; 1 mol.) was dissolved in 4·6N-sulphuric acid (10 ml.; 8 mols.) and water (25 ml.), and zinc dust (1·0 g.; 5 atoms) was added slowly. The reaction was completed by heating on a steam-bath until all the zinc had dissolved; powdered barium carbonate was then added in slight excess. The solution was filtered, the precipitate washed with hot alcohol, and the combined filtrates evaporated under reduced pressure. The residual oil crystallised from acetone to give retronecine as prisms, m. p. 121° (corr.) (Found : N, 9·2. Calc. for $C_8H_{13}O_3N$: N, 9·03%), undepressed by an authentic specimen obtained by hydrolysis of retrorsine according to the method of Barger, Seshadri, Watt, and Yabuta (*J.*, 1935, 11) who give m. p. 121—122°.

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NATAL UNIVERSITY COLLEGE,
UNIVERSITY OF SOUTH AFRICA, PIETERMARITZBURG. [*Received, May 18th*, 1948.]