141. *The* Senecio *Alkaloids. Part VII. The Structure of Retrorsine and Isatidine: The Ester Groupings.*

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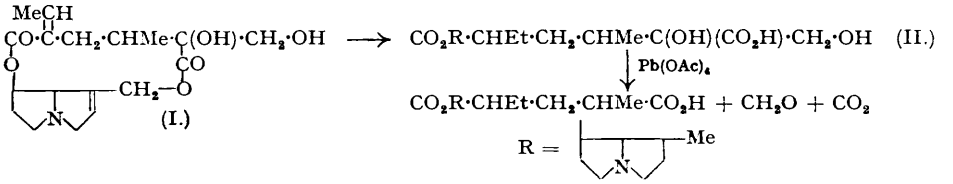
Isatidine is reduced to retronecanyl dihydroisatinecate (dihydroretronecate) (II) which with lead tetra-acetate in aqueous acetic acid gives one mole of carbon dioxide. Thus in isatidine (retrorsine *N*-oxide) and retrorsine (I), the 2-carboxylic group of *cis*-1 : 2-dihydroxy-3-methylhept-5-ene-2 : 5-dicarboxylic acid (isatinecic acid) is esterified by the hydroxymethyl group of isatinecine and retronecine, respectively. The structure of similar *Senecio* alkaloids is indicated.

Isatidine is the ester of isatinecine, which Leisegang and Warren (*J.*, 1949, 486) showed to be retronecine *N*-oxide, with isatinecic acid, which Christie, Kropman, Novellie, and Warren (*J.*, 1949, 1703) gave as *cis*-1 : 2-dihydroxy-3-methylhept-5-ene-2 : 5-dicarboxylic acid. The general structure of isatidine is in conformity with de Waal's observation (*Onderstepoort J. Vet. Sci. Animal Husb.*, 1940, **14**, 445) that catalytic reduction gave octahydroanhydroisatidine, formulated as the dihydroisoatinecic (dihydroretronecic) ester of retronecanol by Christie, Kropman, Leisegang, and Warren (*J.*, 1949, 1700). We have now confirmed the structure of this reduction product by its hydrolysis to retronecanol, characterised as its picrate, and dihydroisatinecic acid, identified as its *p*-phenylphenacyl ester. Hydrogenolysis occurs at the carboxyl group esterified by the hydroxymethyl grouping of isatinecine.

To determine the orientation of the acid in isatidine we treated the reduced isatidine with lead tetra-acetate in acetic acid containing a small quantity of water. Carbon dioxide was immediately evolved as would be expected if the 2-carboxylic grouping were not esterified. The evolution of gas did not take place in anhydrous solvents; but the addition of a little water started the reaction so that the lead tetra-acetate caused fission of the glycol grouping to leave a keto-acid which was attacked by the reagent only in the presence of hydroxyl-forming compounds (cf. Baer, *J. Amer. Chem. Soc.*, 1940, **62**, 1597). Since the quantity of carbon dioxide which dissolves in glacial acetic acid is large and varies considerably with the partial pressure of the gas (cf. Just, *Z. physikal. Chem.*, 1901, **37**, 342), the acetic acid was saturated and the reaction vessel filled with carbon dioxide before mixing the reagents. Only when the importance of this was pointed out by Dr. H. A. E. Mackenzie of these laboratories were we able to obtain quantitative yields of carbon dioxide. No evolution of gas was observed on treating either isatidine or retrosine with lead tetra-acetate under similar conditions.

The reduction of isatidine gave an oily product and hydrolysis of the alkaloid might have occurred during hydrogenation. Continuous ether extraction of the reduction product in hydrochloric acid gave, however, a negligible residue. On the other hand, previous hydrolysis of the reduced isatidine with barium hydroxide followed by continuous ether extraction of the acidified product for the same time gave an 80% yield of dihydroisatinecic acid:



These results lead to the structure of retronecanyl dihydroisatinecate (dihydroretronecate) (II) and hence to retrorsine (I) and isatidine, which Christie, Kropman, Leisegang, and Warren (*loc. cit.*) showed to be retrorsine *N*-oxide.

The " necine " bases so far investigated may be formulated as derivatives of retronecine, *e.g.* platynecine (dihydroretronecine) (Adams and Rogers, *J. Amer. Chem. Soc.*, 1941, **63**, 228) and rosmarinecine (hydroxydihydroretronecine) (Richardson and Warren, *J.*, 1942, 452). In view of the structural similarity of senecic and integerrinecic (*trans*-senecic) acids with isatinecic (hydroxysenecic) and retronecic (*trans*-hydroxysenecic) acids, respectively (Christie, Kropman, Novellie, and Warren, *loc. cit.*; Kropman and Warren, *J.*, 1949, 2852), the orientation of these acids in the complete alkaloids (shown below as derivatives of retronecine and senecic acid) is probably similar.

Senecionine [a]	= retronecine + senecic acid.
Integerrimine [b]	= retronecine + *trans*-senecic acid.
Platyphylline [c,d]	= dihydroretronecine + senecic acid.
Rosmarinine [d]	= hydroxydihydroretronecine + senecic acid.

[a] Barger and Blackie, *J.*, 1936, 743; [b] Manske, *Canad. J. Res.*, 1939, **17**, 1; [c] Orekhov and Tiedebel, *Ber.*, 1935, **68**, 650; with Konovalova, *ibid.*, 1186; [d] de Waal and Tiedt, *Onderstepoort J. Vet. Sci. Animal Husb.*, 1940, **15**, 251; Richardson and Warren (*loc. cit.*).

Experimental.

Retronecanyl Dihydroisatinecate (*Dihydroretronecate*).—Isatidine (4·70 g., 1 mol.) in 0·47N-sulphuric acid (50 ml., 4 mols.) and Adams's catalyst (130 mg.) were shaken with hydrogen at room temperature and 20 atmospheres pressure for 6 hours. The filtered solution was treated with just sufficient 0·4N-barium hydroxide to precipitate the sulphuric acid, and the filtered solution was evaporated under reduced pressure giving retronecanyl dihydroisatinecate as a clear oil which did not crystallise when kept. This product (1·01 g., 1 mol.) was boiled with barium hydroxide octahydrate (1·07 g., 1·2 mols.) in water (20 ml.) for ½ hour, cooled, acidified with hydrochloric acid, and extracted with ether for 6 hours. The ethereal extract gave dihydroisatinecic acid (530 mg., 0·8 mol.), which was characterised as its *p*-phenylphenacyl ester, m. p. 124—127°, undepressed when mixed with an authentic specimen (Christie *et al.*, *J.*, 1949, 1700). The aqueous solution gave retronecanyl picrate, m. p. 205—207° (Barger *et al.*, *J.*, 1935, 11, give m. p. 208°).

Retronecanyl dihydroisatinecate was acidified with hydrochloric acid and extracted under similar conditions. The ether extract gave a negligible residue.

Action of Lead Tetra-acetate on Retronecanyl Dihydroisatinecate.—Glacial acetic acid (10 ml.) was placed in a flask connected to a gas burette containing brine, and dry carbon dioxide swept through to saturate the acetic acid and to displace all the air. An excess of lead tetra-acetate was added and then retronecanyl dihydroisatinecate (280 mg., 1 mol.). No reaction was observed. Without opening the apparatus a small quantity of water was squirted into the mixture whereupon carbon dioxide was evolved (observed: 18·3 ml. at N.T.P. Calc. for $C_{18}H_{31}O_6N$: 18·7 ml.). Isatidine under similar conditions gave no carbon dioxide during 12 hours.

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