601. *The* Senecio *Alkaloids. Part V. The Structure of Senecic Acid.*

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Senecic acid, $C_{10}H_{16}O_5$, is a monohydroxy-dicarboxylic acid containing three *C*-alkyl groups and one ethylenic bond. The hydroxy-group is in the α-position to one carboxylic group and in the δ-position to the other. Light-extinction curves show senecic acid to be an αβ-unsaturated acid, whilst ozonolysis to give acetaldehyde establishes the presence of an ethylidene group.

Senecic acid gave by oxidative degradation β-methyl-lævulic and methylsuccinic acid. Reduction to dihydrosenecic acid, followed by oxidation with, successively, lead tetra-acetate and sodium hypobromite, yields α-methyl-γ-ethylglutaric acid.

Senecic acid is therefore 2-*hydroxy*-3-*methylhept*-5-*ene*-2 : 5-*dicarboxylic acid* (I; X = H). The structure is similar to that found previously by Christie, Kropman, Novellie, and Warren (this vol., p. 1703) for isatinecic and retronecic acid which are thus the *cis*- and *trans*-forms of hydroxysenecic acid (I; X = OH).

SENECIC ACID LACTONE, $C_{10}H_{14}O_4$, was first obtained pure under the name of platynecic acid by Orékhov and Tiedebel (*Ber.*, 1935, **68**, 650). Barger and Blackie (*J.*, 1936, 743) obtained this lactone from the hydrolysis of senecionine and called it " senecic acid," which they stated was an unsaturated lactonic acid (readily reduced to " dihydrosenecic acid," $C_{10}H_{16}O_4$) and contained three *C*-alkyl groups. De Waal (*Onderstepoort J. Vet. Sci. Animal Ind.*, 1940, **15**, 241) obtained " senecic acid " from rosmarinine and showed that it was identical with platynecic acid, an observation later confirmed by Richardson and Warren (*J.*, 1943, 453). Manske (*Canad. J. Res.*, 1939, **17**, 1) pointed out that the unsaturated centre was present as an ethylidene group because acetic acid was obtained by oxidation with alkaline potassium permanganate. Developing the concept of Barger and Blackie (*loc. cit.*) that the

" necic " acids were terpene acids, and assuming that their nitric acid oxidation product was a paraconic acid, Manske (*loc. cit.*) put forward two γ-lactone structures for senecic acid.

$$\begin{tikzcd}
\text{(IV.)}\ \mathrm{CO_2H{\cdot}CH_2{\cdot}CHMe{\cdot}CO_2H} & \mathrm{CO_2H{\cdot}CH_2{\cdot}CHMe{\cdot}COMe}\ \text{(III.)} + \mathrm{CO_2} \arrow[l] \\
 & \mathrm{Me{\cdot}CHO} + \mathrm{CO_2H{\cdot}CO{\cdot}CH_2{\cdot}CHMe{\cdot}CMe(OH){\cdot}CO_2H}\ \text{(II.)} \arrow[u] \\
 & \mathrm{CHMe{:}C(CO_2H){\cdot}CH_2{\cdot}CHMe{\cdot}C(OH)(CO_2H){\cdot}CH_2X}\ \text{(I.)} \arrow[u] \arrow[d] \\
 & \mathrm{CO_2H{\cdot}CHEt{\cdot}CH_2{\cdot}CHMe{\cdot}CMe(OH){\cdot}CO_2H}\ \text{(V.)} \arrow[d] \\
\text{(VII.)}\ \mathrm{CO_2H{\cdot}CHEt{\cdot}CH_2{\cdot}CHMe{\cdot}CO_2H} & \mathrm{CO_2H{\cdot}CHEt{\cdot}CH_2{\cdot}CHMe{\cdot}COMe}\ \text{(VI.)} + \mathrm{CO_2} \arrow[l]
\end{tikzcd}$$

Richardson and Warren (*loc. cit.*) obtained senecic acid as a hydroxy-dicarboxylic acid, $C_{10}H_{16}O_5$, as well as its lactone, and since both showed considerable stability it is reasonable to assume that the hydroxyl group is in the δ-position to one of the carboxyl groups. We have now shown that senecic acid gives a yellow colour with dilute ferric chloride (cf. Mitchell, Weinstock, Snell, Stanbery, and Williams, *J. Amer. Chem. Soc.*, 1940, **62**, 1776; Berg, *Bull. Soc. chim.*, 1894, [iii], **11**, 883) so that the hydroxyl group must be in the α-position with respect to the other carboxyl group.

Since the acetic acid obtained by Manske (*loc. cit.*) might have been derived by the oxidation fission at the hydroxyl group we sought to establish the position of the ethylenoid linkage by ozonolysis. Acetaldehyde, identified by condensation to ethylidenedi-β-naphthol, was obtained as a volatile product, and thus the presence of the ethylidene group was established. Furthermore this grouping exists as an $\alpha\beta$-unsaturated acid in that the ultra-violet extinction curve for senecic acid in water showed $\lambda_{\text{max.}}$ at 215 mμ. with $\varepsilon_{\text{max.}}$ 4140.

These deductions, together with the observations of Barger and Blackie (*loc. cit.*) that senecic acid contains three *C*-alkyl groups, which we have confirmed, fit formula (I; X = H) for senecic acid. To establish this, senecic acid was subjected to stepwise oxidation.

Senecic acid was ozonised, and the fission product, presumably (II), treated with lead tetra-acetate in aqueous solution (cf. Baer, *J. Amer. Chem. Soc.*, 1940, **62**, 1597) whereupon, as expected for an α-hydroxy-acid, carbon dioxide was evolved and β-methyl-lævulic acid (III) was obtained as an oil. With the small quantity available, this acid (III) was not isolated pure. It showed with dinitrobenzoic acid the characteristic violet coloration of methyl ketones, and oxidation with sodium hypobromite gave bromoform and methylsuccinic acid (IV), m. p. 103°, undepressed when mixed with an authentic specimen of the (+)-acid. The available quantity did not permit the measurement of the specific rotation. It is almost certainly dextrorotatory since the methylsuccinic acid, obtained from isatinecic acid which contains the same basic structure as senecic acid (see below), gave a hydrogen strychnine salt, m. p. 186° (Christie, Kropman, Novellie, and Warren, this vol., p. 1703), and has now been shown to have $[\alpha]_D^{19}$ 9·51° (*c*, 1 in water) (cf. Ladenberg, *Ber.*, 1896, **29**, 1254).

Our experience with both the (+)- and the inactive methylsuccinic acid shows that the melting points vary considerably. When crystallisation was slow the high recorded melting points were obtained; but when crystallisation was more rapid the melting point was never above 103° (uncorr.).

Methylsuccinic acid could have been formed under the same conditions from α-methyl-lævulic acid and, to establish conclusively structure (I; X = H) for senecic acid, an additional degradation was carried out. Senecic acid was reduced catalytically to dihydrosenecic acid (V) which was not isolated but was oxidised directly with lead tetra-acetate (cf. Baer, *loc. cit.*) in aqueous solution to give 6-*keto*-5-*methylheptane*-3-*carboxylic acid* (VI), b. p. 120°/0·01 mm. This showed the characteristic reactions of methyl ketones but owing to the small quantity available was not further characterised; on oxidation with sodium hypobromite it gave bromoform and the oily acid (VII) which was characterised as its imide, m. p. 118—119°. This imide showed no depression on admixture with *cis*-α-methyl-γ-ethylglutarimide previously obtained by Christie *et al.* (*loc. cit.*) from the oxidation of dihydroretronecic and dihydroisatinecic acids. A mixture with an authentic specimen of the (±)-imide (m. p. 109—113°) kindly supplied by Dr. H. N. Rydon (*J.*, 1936, 1444) showed an intermediate melting point.

These observations confirm the structure of senecic acid as 2-*hydroxy*-3-*methylhept*-5-*ene*-2 : 5-*dicarboxylic acid* (I; X = H). It bears a close similarity to the structures previously put forward by Christie *et al.* (*loc. cit.*) for isatinecic and retronecic acids which were represented as *cis*- and *trans*-isomers of (I; X = OH). The concept of Barger and Blackie (*loc. cit.*) that the C_{10} acid fission products of the *Senecio* alkaloids were examples of terpene acids is fully justified.

The acid, $C_6H_8O_4$, m. p. 142°, obtained by Barger and Blackie (*loc. cit.*) by oxidation of senecic acid with nitric acid is probably the lactide of dimethylmalic acid, $C_{12}H_{16}O_8$. This oxidation product together with the geometric configuration of senecic acid is at present under investigation in these laboratories.

EXPERIMENTAL.

Senecic Acid.—The material was obtained from *S. adnatus* D.C. by the method previously described (*J.*, 1943, 453). Kuhn–Roth determination was made on senecic acid lactone (Found: CH_3, 22·6. Calc. for $C_{10}H_{14}O_4$: $3CH_3$, 23·3%).

Ozonisation of Senecic Acid.—Senecic acid (1 g.) in ethyl acetate was ozonised at 0°. The viscous ozonide obtained by removal of the solvent was warmed with water in a current of carbon dioxide, and the gas passed into β-naphthol in acetic acid containing a drop of hydrochloric acid. The solution on warming and cooling gave ethylidenedi-β-naphthol, m. p. 173°, undepressed on admixture with authentic specimen.

Methylsuccinic Acid.—Senecic acid (1 g., 1 mol.) was ozonised and decomposed as above and the aqueous solution treated with lead tetra-acetate (6 g., 3 mols.) whereupon carbon dioxide was evolved. The lead was precipitated with sulphuric acid, and the ethereal extract gave β-methyl-lævulic acid as an oil which gave a purple colour with dinitrobenzoic acid and reacted with sodium hydrogen sulphite (as shown by iodometric titration). The oil, dissolved in excess of sodium hydroxide, was treated dropwise at 0° with a slight excess of sodium hypobromite; bromoform separated. The solution was treated with excess of sodium hydrogen sulphite. The ethereal extract gave a solid, which, crystallised from benzene–ether (1 : 1), gave methylsuccinic acid (50 mg.), m. p. 103°, undepressed by an authentic specimen of the (+)-acid.

6-*Keto*-5-*methylheptane*-3-*carboxylic Acid.*—Senecic acid (1 g., 1 mol.) in water was hydrogenated in the presence of Adams's catalyst, 1 mole of hydrogen being smoothly absorbed The filtered solution was treated with lead tetra-acetate (4 g., 2 mols.) and heated on a water-bath; carbon dioxide was evolved during 1 hour (Observed: CO_2, 97·6 ml. at S.T.P. Calc. for $C_{10}H_{18}O_5$: 1 CO_2, 104 ml.) after which sulphuric acid was added. The ethereal extract gave a yellow oil which, distilled 4 times at 120°/0·01 mm., gave 6-*keto*-5-*methylheptane*-3-*carboxylic acid* as a colourless oil (Found: C, 61·9; H, 9·30%; equiv., 171·2, 175·6. $C_9H_{16}O_3$ requires C, 62·8; H, 9·2%; equiv., 172·2). It gave a purple colour with dinitrobenzoic acid.

cis-α-*Methyl*-γ-*ethylglutarimide.*—The foregoing acid (0·7 g.) in water was treated at 0° with excess of sodium hypobromite and allowed to warm to room temperature, whereupon bromoform separated. Excess of sodium hydrogen sulphite was added and the acid solution extracted with ether. The extract gave an oily acid which was treated with acetyl chloride at 100°, and then, after the excess of reagent had been removed, heated at 200° with urea. The product was made alkaline with sodium hydrogen carbonate. The ethereal extract gave a solid, which, crystallised from light petroleum, gave long needles of *cis*-α-methyl-γ-ethylglutarimide, m. p. 118—119°. The m. p. was undepressed when the imide was mixed with the specimen obtained by us from the oxidation of retronecic acid (*loc. cit.*). On admixture with an authentic specimen of the (±)-imide (m. p. 109—113°) kindly supplied by Dr. H. N. Rydon (*J.*, 1936, 1444), it melted at 112—117°. The quantity available did not permit the determination of [α].

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