175. *The* Senecio *Alkaloids. Part XV.* The Structure of Sceleranecic and Sceleratinic Acids and Sceleratine.*

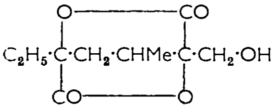
By H. L. DE WAAL, A. WIECHERS, and F. L. WARREN.

Sceleranecic acid is reduced with lithium aluminium hydride to a diglycol which is oxidised to 2,3-dimethyl-lævulic acid which is also formed by direct oxidation of disodium sceleranecate with lead tetra-acetate. These findings lead to a new structure for sceleranecic acid which is in accord also with previous experimental results.

SCELERANECIC ACID, $C_{10}H_{14}O_5$, first isolated by de Waal and Pretorius[1] as the necic acid from sceleratine (retronecyl sceleranecate) was shown to be a monohydroxy-dilactone. It was oxidised by nitric acid to a monocarboxylic acid $C_9H_{11}O_4{\cdot}CO_2H$, m. p. 216°, which with chromic acid gave a monolactone monocarboxylic acid, $C_6H_{11}(-CO_2-){\cdot}CO_2H$, m. p. 100°. The oxidation product was also obtained by oxidation of sceleranecic acid dilactone with potassium permanganate, and, together with formaldehyde and carbon dioxide, by the action of potassium periodate or lead tetra-acetate on dipotassium sceleranecate, which therefore contained the grouping $-C(OH)(CO_2H){\cdot}CH_2{\cdot}OH$.

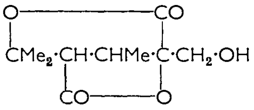
When dipotassium sceleranecate was treated with thionyl chloride there was produced sceleratinic acid, $C_{10}H_{13}ClO_4$, m. p. 208°, whilst a hydroxy-dicarboxylic acid, $C_8H_{13}O(OH)(CO_2H)_2$, m. p. 192°, was obtained by the action of alkali on sceleratinic acid. The formation of this new acid, m. p. 192°, which was shown to be a hydroxy-acid by its conversion into a chloro-acid, $C_8H_{13}ClO(CO_2H)_2$, was attributed by de Waal, Serfontein, and Garbers[2] to the formation of a cyclic ether.

On the basis of these results de Waal *et al.*[2] assigned structure (I) to sceleranecic acid, including the general carbon skeleton advanced for other " necic " acids.[3] Adams and Gianturco[4] reinterpreted the findings of de Waal *et al.* and suggested a glutaric structure (II) to account for only two *C*-methyl groups, although this had been previously corrected to three by de Waal and Crous.[5] At the same time de Waal and van Duuren,[6] on the basis of infrared spectra and the different stability of the two lactone rings, advanced structure (III).



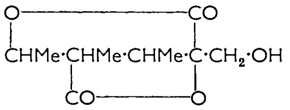
$$\begin{array}{l} O\text{————}CO \\ C_2H_5{\cdot}C{\cdot}CH_2{\cdot}CHMe{\cdot}C{\cdot}CH_2{\cdot}OH \\ CO\text{————}O \end{array}$$

(I)



$$\begin{array}{l} O\text{————}CO \\ CMe_2{\cdot}CH{\cdot}CHMe{\cdot}C{\cdot}CH_2{\cdot}OH \\ CO\text{———}O \end{array}$$

(II)



$$\begin{array}{l} O\text{————}CO \\ CHMe{\cdot}CHMe{\cdot}CHMe{\cdot}C{\cdot}CH_2{\cdot}OH \\ CO\text{————}O \end{array}$$

(III)

Structure (II) seemed unlikely[5] in that acetone could not be detected on chromic acid oxidation and the infrared spectrum of sceleranecic acid showed no doublet due to a *gem*-dimethyl group.[7] In addition, Dreiding models showed that both structures (II) and (III) involved considerable strain.

Sceleranecic acid has now been degraded by a new route. With lithium aluminium hydride it gave a neutral syrupy glycol which did not yield a crystalline benzoate or acetate and was quantitatively oxidised with periodic acid to formaldehyde and 2,3-dimethyl-lævulic acid (VII), identified as its methyl ester. Oxidation of disodium

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* Part XIV, *J.*, 1962, 34. The present paper is also Part XII of de Waal's series (Part XI, *J. Amer. Chem. Soc.*, 1956, **78**, 4464).

[1] de Waal and Pretorius, *Onderstepoort J. Vet. Sci. Animal Ind.*, 1941, **17**, 181.

[2] de Waal, Serfontein, and Garbers, *J.S. African Chem. Inst.*, 1951, **4**, 115.

[3] Christie, Kropman, Novellie, and Warren, *J.*, 1949, 1703.

[4] Adams and Gianturco, *J. Amer. Chem. Soc.*, 1956, **78**, 4458.

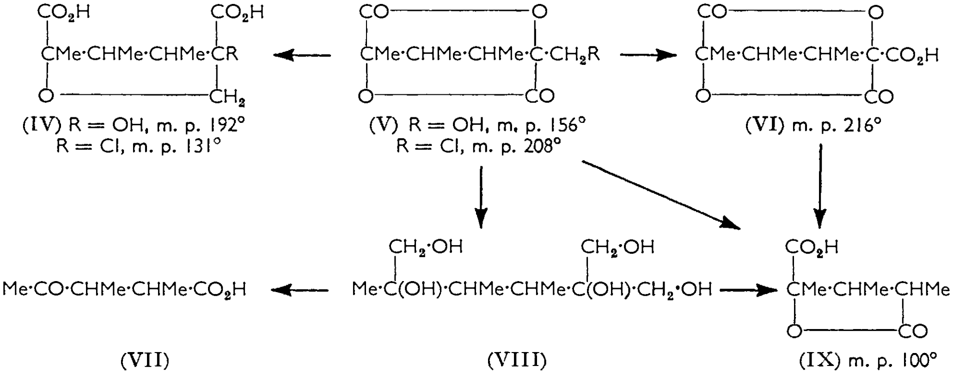
[5] de Waal and Crous, *J. S. African Chem. Inst.*, 1948, **1**, 23.

[6] de Waal and van Duuren, *J. Amer. Chem. Soc.*, 1956, **78**, 4464.

[7] A. D. Cross, " An Introduction to Practical Infrared Spectroscopy," Butterworths Scientific Publns., London, 1960, p. 57.

sceleranecate in glacial acetic acid with lead tetra-acetate gave a mixture of this acid (VII) and the previously reported γ-lactone monocarboxylic acid, m. p. 100°. The oxidation of the 2,3-dimethyl-lævulic acid with sodium hypobromite gave butane-2,3-dicarboxylic acid, m. p. 132—134°, characterised as its 4-bromophenacyl ester, m. p. 186°. The infrared spectrum of the butanedicarboxylic acid in potassium bromide showed a carbonyl stretching at 1715vs with a shoulder at 1730 cm.$^{-1}$, indicative of an active, as distinct from the racemic or *meso*, form.[8] It has not, however, been possible to assign unequivocally the rotation with available material. These results permit formulating sceleranecic acid dilactone as (V; R = OH) and the glycol as (VIII).

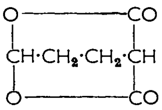
The structure of sceleranecic acid leads directly to the formulation of sceleratinic acid as (V; R = Cl), the oxidation products referred to above as (IX) and (VI), the cyclic ether, m. p. 192°, as (IV; R = OH) and its chloro-derivative, m. p. 131°, as (IV; R = Cl).

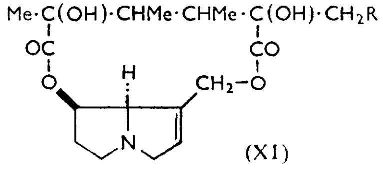

(IV) R = OH, m. p. 192°
R = Cl, m. p. 131°
(V) R = OH, m. p. 156°
R = Cl, m. p. 208°
(VI) m. p. 216°
(VII)
(VIII)
(IX) m. p. 100°

A re-examination of the infrared spectrum of sceleranecic acid in chloroform with maximum resolution showed broad bands at 1795—1764 with possible maxima at 1792 and 1770 cm.$^{-1}$, whilst in potassium bromide there was a band at 1770, with a shoulder at 1787 cm.$^{-1}$. This increased carbonyl frequency has been observed previously in a similar dilactone (X)[9] and other bicyclic[10] and tricyclic[11] δ-lactones and gives convincing support for the new formula for sceleranecic acid (V; R = OH).

The difference in stability of the two δ-lactone rings, one being opened readily at room temperature, and the other only after boiling with an excess of alkali, is of interest. The dilactone must have a boat six-ring structure and once one lactone ring has been opened the molecule may assume the more stable form further stabilised by alkyl substitution.

Further, this structure of sceleranecic acid (V; R = OH) is in better accord with the biosynthetic route[12] than the formulæ previously proposed.


(X)


(XI)

The alkaloid sceleratine was shown by de Waal and Pretorius[1] to be retronecyl sceleranecate and to occur in the plant with retrorsine. The orientation of the acid in the

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[8] Rosenberg and Schotte, *Acta Chem. Scand.*, 1954, **8**, 867; *Arkiv Kemi*, 1954, **7**, 479.
[9] Marvel, Weil, Wakefield, and Fairbanks, *J. Amer. Chem. Soc.*, 1953, **75**, 2326.
[10] Geissman, *Austral. J. Chem.*, 1959, **12**, 247; Ashworth, Whitham, and Whiting, *J.*, 1957, 4633.
[11] Wilder and Winston, *J. Amer. Chem. Soc.*, 1955, **76**, 5598.
[12] Hughes and Warren, *J.*, 1962, 34.

sceleratine is likely to be similar to that of retrorsine,[13] so that sceleratine may be formulated as (XI; R = OH). Further, sceleratinic acid, originally isolated as the free acid from the plant, has recently been isolated as the ester of retronecine,[14] namely, sceleratenyl chloride, which must have structure (XI; R = Cl).

EXPERIMENTAL

M. p.s were taken on the Kofler block. Infrared spectra were obtained for chloroform solutions with Perkin-Elmer model 137-B and model 21 infrared spectrophotometers.

Oxidation of Disodium Sceleranecate by Lead Tetra-acetate.—Sceleranecic acid (V) (4 g.) was hydrolysed with sodium hydroxide (1·6 g.) in water (30 ml.). The solution, concentrated to 10 ml., was added dropwise (1 hr.) to a stirred and ice-cooled solution of lead tetra-acetate (25 g.) in glacial acetic acid (500 ml.) and stirred for 6 hr. The solution, freed from acetic acid under reduced pressure, was cooled in ice, treated with 10% sulphuric acid (40 ml.), and filtered. The filtrate and washings were extracted repeatedly with ether. Distillation of the dried ethereal solution afforded a colourless oil (3·1 g.), which, set aside in a vacuum-desiccator, crystallised. The oily acid crystals gave an immediate positive iodoform (m. p. 118—119°) reaction. The infrared spectrum (in $CHCl_3$) showed bands at 1783 (γ-lactone), 1727 (ketone, carboxyl), and in the range of 2400—2800 cm.$^{-1}$ (carboxyl-OH). Crystallisation of the product from carbon tetrachloride furnished the 1-hydroxy-2,3,4-trimethylglutaric acid lactone, m. p. 99—100°, $\nu_{max.}$ (in $CHCl_3$) 1786 (γ-lactone), 1730 (carboxyl), and in the range of 2400—2800 cm.$^{-1}$ (carboxyl-OH) (Found: C, 55·3; H, 6·8. Calc. for $C_8H_{12}O_4$: C, 55·8; H, 7·0%). Removal of the solvent from the mother-liquors afforded 2,3-dimethyl-lævulic acid, b. p. 115—122°/3—4 mm. (bath), $\nu_{max.}$ (in $CHCl_3$) 1770 (γ-lactone), 1717 (methyl ketone, carboxyl), 1608 (C=C), and in the range of 2400—2800 cm.$^{-1}$ (carboxyl-OH). 4-Hydroxy-2,3-dimethylpentenoic acid lactone was formed to a certain extent when 2,3-dimethyl-lævulic acid was distilled, as was evident from the infrared spectrum and microanalysis.

Disodium sceleranecate was oxidised as above and the crude product (0·86 g.) in ether was treated with ethereal diazomethane. The resulting product (0·9 g.), $\nu_{max.}$ 1779 (γ-lactone), 1739 (ester), and 1718 cm.$^{-1}$ (ketone), was distilled into two fractions. A fraction of b. p. 85—91° (bath temp.)/10 mm. (80 mg.) gave methyl 2,3-dimethyl-lævulic acid, n_D^{20} 1·4278, $\nu_{max.}$ 1736 (ester) and 1718 cm.$^{-1}$ (Ac) (Found: C, 60·2; H, 8·8. Calc. for $C_8H_{14}O_3$: C, 60·7; H, 8·9%). The mixed esters were also separated by Girard's reagent P.

Reduction of Sceleranecic Acid by Lithium Aluminium Hydride.—Sceleranecic acid (3·0 g.) in dry ether (150 ml.) was added dropwise to a stirred suspension of lithium aluminium hydride (1·0 g.) in ether (100 ml.). The mixture was stirred for 3 hr. in the solution, then cooled, and water (100 ml.) was added. The filtered solution was concentrated (50 ml.) under reduced pressure and extracted with ether continuously for 72 hr. Distillation of the dried ethereal extract afforded a colourless syrup (2·12 g.). The infrared spectrum did not show any absorption in the carbonyl region, but showed an intense and broad absorption in the hydroxyl region.

Periodate Oxidation of the Lithium Aluminium Hydride Reduction Product of Sceleranecic Acid.—0·3M-Periodic acid (25 ml.), diluted immediately before use with N-sodium hydrogen carbonate (25 ml.), was added to the lithium aluminium hydride reduction product (0·5 g.) in water and set aside for 17 days. The solution was evaporated to dryness under reduced pressure on a water-bath, water was added, and the evaporation process was repeated. The distillate, collected at 0°, was treated with dimedone (2·1 g.) in water (130 ml.) to give the dimedone derivative of formaldehyde (0·5 g.), m. p. and mixed m. p. with authentic sample, 188—189°.

The evaporated residue was dissolved in water (100 ml.) and extracted with ether. The aqueous solution, cooled to 0° and treated with sulphur dioxide until decolorised, was extracted repeatedly with ether. The dried ethereal solution afforded a colourless oily acid (0·28 g.), which gave an immediate positive iodoform reaction and had $\nu_{max.}$ in the range of 3100—3600 (hydroxyl-OH), 2400—2800 (carboxyl-OH), 1776 (γ-lactone), and 1715 cm.$^{-1}$ (Ac, carboxyl).

The oily acid (0·16 g.) in dry ether (10 ml.) was treated with diazomethane. The product (0·16 g.) gave methyl 2,3-dimethyl-lævulate (90 mg.), b. p. 87—91° (bath-temp.)/11 mm., having b. p., n_D^{20}, analysis, and infrared spectrum identical with product reported above.

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[13] Kropman and Warren, *J.*, 1950, 700.

[14] Gordon-Gray and Warren (unpublished work).

Oxidation of 2,3-*Dimethyl-lævulic Acid by Hypobromite.*—A solution of 2,3-dimethyl-lævulic acid (1·0 g.) in water (10 ml.) was made slightly alkaline, then cooled to 0°, and a sodium hypobromite solution, prepared from sodium hydroxide (3 g.), bromine (5 g.), and water (40 ml.), was added dropwise. After 3 hr. at 0°, the solution was allowed to warm to room temperature, decanted from the bromoform, and extracted with ether. The alkaline layer was acidified with dilute hydrochloric acid to Congo Red and extracted with ether. The ethereal solution gave a solid (0·64 g.) which, recrystallised several times from chloroform, gave butane-2,3-dicarboxylic acid, m. p. 132—134° (preheated to 128°), $\nu_{max.}$ (solid in KBr), 3077s,br, 2632w, 1730sh, 1715vs, 1471s, and 1429s cm.$^{-1}$. The crude butane-2,3-dicarboxylic acid (0·1 g.), m. p. 120—130°, gave the *di-4-bromophenacyl butane-2,3-dicarboxylate* which, recrystallised several times from ethanol, had m. p. 186°, $\nu_{max.}$ (in $CHCl_3$) 1742 (ester) and 1706 cm.$^{-1}$ (aryl ketone) (Found: C, 49·0; H, 3·7. Calc. for $C_{22}H_{20}Br_2O_6$: C, 48·9; H, 3·7%).

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