1333. *The Chemistry of Fungi. Part LI.*[1] *The Absolute Configuration of C-13 in Rosenono- and Rosolo-lactone: Rosololactone*

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Degradation of (+)-5-ethyl-2,5-dimethylcyclohexanone (I) derived from ring c of dihydrorosenonolactone gave (+)-3-ethyl-3-methyladipic acid. The synthesis of this acid has established the absolute configuration of C-13 in rosenono- and rosolo-lactone.

The structures of various degradation products of resololactone have been clarified.

We have previously [2] defined the absolute configuration of rosenonolactone,[3] at all centres except C-13. • This has now been achieved chemically as follows.

Ozonolysis of (+)-5-ethyl-2,5-dimethylcyclohexanone (I), which is a product from the alkaline fission of rosoic acid,[3,4] formed (+)-3-ethyl-3-methyl-6-oxoheptanoic acid (II). Degradation of (II) with sodium hypobromite gave (+)-3-ethyl-3-methyladipic acid (III; R = CO_2H), which has been synthesised. Thus, resolution of (±)-3-ethyl-3-methyl-3-methoxycarbonylpropionic acid (IV; R = H) gave the (+)-isomer (IV; R = H) which was converted into (−)-2-ethyl-2-methylbutane-1,4-diol (III; R = OH) by reduction of the (+)-ester (IV; R = Me). Nucleophilic displacement of the tosyl residues from (III; R = OTs) gave (+)-3-ethyl-3-methyladiponitrile (III; R = CN). This was hydrolysed to (+)-3-ethyl-3-methyladipic acid (III; R = CO_2H) which was identical with the natural acid. Since hydrolysis of (+)-3-ethyl-3-methyl-3-methoxycarbonylpropionic acid gave (+)-2-ethyl-2-methylsuccinic acid, the absolute configuration of which has been defined [5] as in (IV), it follows that the adipic acid has the absolute configuration (III; R = CO_2H). The complete absolute stereochemistry of rosenonolactone is thus defined as (V). Further, since rosolo- and rosenono-lactone have the same configuration [6] at C-13 our work defines the absolute configuration of C-13 in rosololactone.

This definition is in agreement with that of Scott *et al.*[7] From an *X*-ray determination of the relative configuration of 18,19-dibromorosololactone in conjunction with our correlation of rosenono- and rosolo-lactone [6] and our previous definition [2] of the absolute stereochemistry (except C-13) of rosenonolactone these authors ascribed the absolute configuration (VI) to rosololactone. The work of Scott *et al.*[7] also confirmed the position of the hydroxyl residue and defined the α-configuration of the C-8 proton. Our further investigations have shown that the 2-ethyl-2-methylsuccinic acid produced by oxidation of the ketone (I) with nitric acid [6] is optically inactive. This is clearly due to the succinic acid being derived, with approximately equal facility, from carbon atoms 4, 5, 6, and 1 and from 3, 4, 5, and 6 of the cyclohexanone (I).

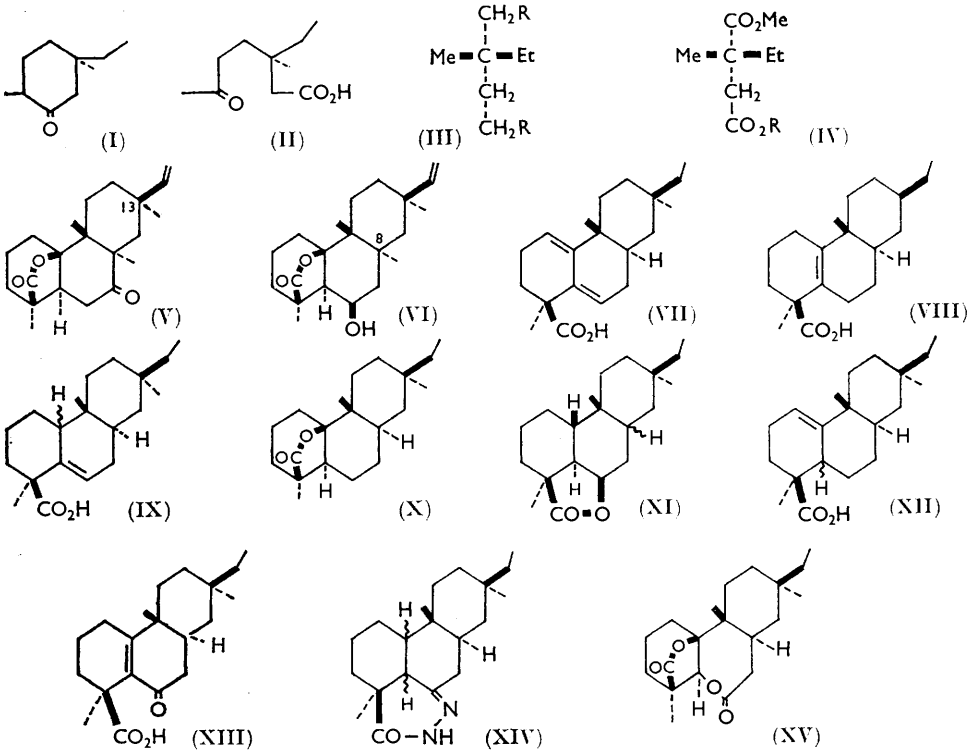
Our investigation, in conjunction with that of Scott *et al.*,[7] provides unequivocal confirmation for the presently accepted absolute configuration of (+)-2-ethyl-2-methylsuccinic acid, derived [5] on the basis of the Fredga rule.

The model synthesis of (±)-3-ethyl-3-methyladipic acid is recorded.

The structures of various degradation products of rosololactone can now be clarified. Thus, we have shown [6] dihydrorosenic acid, which is formed by the action of acidic reagents upon dihydrorosololactone, to be an heteroannular, transoid, dienoic acid. This may now be formulated as roso-1(10),5-dien-16-oic acid (VII), in agreement with the n.m.r. spectrum

[1] Part L, preceding Paper.
[2] W. B. Whalley, B. Green, D. Arigoni, J. J. Britt, and C. Djerassi, *J. Amer. Chem. Soc.*, 1959, **81**, 5520.
[3] Adelaide Harris, A. Robertson, and W. B. Whalley, *J.*, 1958, 1799.
[4] A. Robertson, W. R. Smithies, and E. Tittensor, *J.*, 1949, 879.
[5] J. Porath, *Arkiv. Kemi*, 1951, **3**, 163.
[6] Adelaide Harris, A. Robertson, and W. B. Whalley, *J.*, 1958, 1807.
[7] A. I. Scott, S. A. Sutherland, D. W. Young, I. Guglielmetti, D. Arigoni, and G. A. Sim, *Proc. Chem. Soc.*, 1964, 19.

which exhibits a poorly resolved multiplet at τ 4·1—4·6, equivalent to two protons, *i.e.*, the vinylic protons at C-1 and C-6. Hydrogenation of dihydrorosenic acid (VII) yields a monounsaturated acid, tetrahydrorosenic acid [6] which has the properties of a $\beta\gamma$-unsaturated acid [6] and is isomeric with ros-5(10)-en-16-oic acid (VIII).[1,6] Although tetrahydrorosenic acid and (VIII) are not readily interconvertible, they yield the same allo- and neo-hydroxyrosanoic γ-lactones upon solution in sulphuric acid.[6] The n.m.r. spectrum of methyl tetrahydrorosenate contains a poorly resolved multiplet centred at τ 4·8 (1 proton). Tetrahydrorosenic acid can thus be formulated as (IX), although the alternative (XII) cannot be entirely excluded. The formation of (IX) from (VII) by 1,2- rather than the more usual 1,4-addition is in accord with the relative inaccessibility of the 5,6-double bond in (VII) to the approach of the catalyst.



Whilst it is not possible to define precisely the structures of allo- and neo-hydroxyrosanoic γ-lactone, allo-hydroxyrosanoic γ-lactone (the major product) can confidently be represented by (X). Neo-hydroxyrosanoic γ-lactone could be (XI) or the C-8 epimer of (X). The structures of other transformation products from rosololactone follow without comment. Thus, *e.g.*, dihydrorosonic acid [6] is (XIII) whilst the methoxyl-free product derived by the interaction of hydrazine and methyl tetrahydrorosonate is (XIV), as previously adumbrated.[6]

Oxidation of dihydrorosonolactone by the Baeyer–Villiger process (cf. rosenonolactone [1]) gave the dilactone (XV) which has $\nu_{max.}$ 1786 (γ-lactone) and 1736 (ε-lactone) cm.$^{-1}$. The low yield of (XV) is in keeping with the hindered environment of the C-5 carbonyl group (cf. the analogous behaviour of dihydroisorosenonolactone [1]).

Since dihydrorosonolactone is reduced by sodium borohydride in high yield, to dihydrorosololactone * it may be inferred that the C-6 hydroxyl group in the metabolite is axial, *i.e.*, β-oriented (cf. Scott *et al.*[7]).

* Adelaide Harris, Ph.D. Thesis, Liverpool, 1958.

Experimental

(+)-3-*Ethyl*-3-*methyladipic Acid*.—(*a*) (+)-5-Ethyl-2,5-dimethylcyclohexanone (1·8 g.) was ozonised as described previously.[4] The crude (+)-3-ethyl-3-methyl-6-oxoheptanoic acid was isolated as the semicarbazone (1·3 g.) which was kept with 2N-hydrochloric acid (20 ml.) during 18 hr. After isolation (+)-3-ethyl-3-methyl-6-oxoheptanoic acid was obtained as an oil (0·8 g.). A solution of this keto-acid (0·65 g.) in 2N-sodium hydroxide (3 ml.) was treated at 0° with a solution of bromine (3·3 g.) in 2N-sodium hydroxide (25 ml.). After 2 hr., the mixture was diluted with water (25 ml.), extracted with ether (to remove bromoform), acidified, and exhaustively extracted with ether. Purification of a solution of the crude product in benzene by chromatography on silica, followed by elution with benzene–chloroform (3 : 2) gave (+)-3-*ethyl*-3-*methyladipic acid* which formed needles (0·2 g.), m. p. 80°, having $\nu_{max.}$ 1704 cm.$^{-1}$ (in CCl_4) $[\alpha]_D^{20}$ +5·4° (*c*, 1·22 in $CHCl_3$) [Found: C, 57·6; H, 8·5%; Equiv., 92·5. $C_7H_{14}(CO_2H)_2$ requires C, 57·4; H, 8·6%; Equiv., 94·4].

Distillation of this acid (0·1 g.) with barium oxide (10 mg.) gave (+)-3-ethyl-3-methylcyclopentanone; this was characterised as the *semicarbazone*, prisms, m. p. 174°, from aqueous methanol (Found: N, 22·3. $C_9H_{17}N_3O$ requires N, 22·9%).

(*b*) A solution of (±)-3-ethyl-3-methyl-3-carboxymethoxypropionic acid (97 g.) in methanol (300 ml.) was treated with dehydroabietylamine (162 g.) in methanol (300 ml.). Next day the salt was collected and crystallised five times from methanol to give a salt (40 g.), m. p. 149—151°, whose decomposition yielded (+)-3-*ethyl*-3-*methyl*-3-*carbomethoxypropionic acid*, b. p. 135°/0·1 mm., $[\alpha]_D^{20}$ +8·2° (*c*, 8·5 in alcohol), $[\alpha]_D^{20}$ +8·92° (homogeneous), d_4^{23} 1·096 [Found: C, 54·4; H, 8·1; OMe, 16·7. $C_7H_{11}O_3(OMe)$ requires C, 55·2; H, 8·1; OMe, 17·7%]. Hydrolysis of this ester (1·5 g.) with excess of 20% sodium hydroxide for 45 min. on the steam-bath gave (+)-2-*ethyl*-2-*methylsuccinic acid* (1 g.) which formed needles, m. p. 65—66°, from benzene–light petroleum (b. p. 60—80°), $[\alpha]_D^{20}$ +2·97° (*c*, 6·7 in ($CHCl_3$) (Found: C, 53·0; H, 7·7. $C_7H_{12}O_4$ requires C, 52·5; H, 7·6%). Prepared quantitatively by the use of diazomethane the (+)-*dimethyl ester* had b. p. 100°/20 mm., $[\alpha]_D^{19}$ +6·5° (*c*, 0·7 in methanol) [Found: C, 56·9; H, 8·6; OMe, 31·5. $C_7H_{10}O_2(OMe)_2$ requires C, 57·4; H, 8·6; OMe, 32·9%].

Reduction of this ester (9·5 g.) with lithium aluminium hydride (3·2 g.) in ether (250 ml.) during 1 hr. (reflux)gave (−)-2-ethyl-2-methylbutane-1,4-diol (6·0 g.) as a viscous liquid, b. p. 90°/0·2 mm., $[\alpha]_D^{20}$ −0·60° (*c*, 9·9 in $CHCl_3$). The *di*-p-*nitrobenzoate* formed pale yellow needles, m. p. 154°, from alcohol–ethyl acetate, $[\alpha]_D^{20}$ −1·8° (*c*, 3·3 in $CHCl_3$) (Found: C, 58·6; H, 5·2; N, 7·0. $C_{21}H_{22}N_2O_8$ requires C, 58·6; H, 5·2; N, 6·5%). Prepared from this diol (5 g.) and toluene-*p*-sulphonyl chloride (30 g.) in pyridine (100 ml.) at 0° during 24 hr., the ditosylate formed a viscous liquid (6·8 g.) which decomposed upon attempted distillation (Found: C, 56·5; H, 6·5; S, 14·5. $C_{21}H_{28}O_6S_2$ requires C, 57·3; H, 6·4; S, 14·5%).

A solution of this tosylate (6·8 g.) and potassium cyanide (7·0 g.) in dimethyl sulphoxide (40 ml.) was kept at 120° in nitrogen for 21 hr. After isolation (+)-3-*ethyl*-3-*methyladiponitrile* was obtained as a pale yellow liquid (1·8 g.), b. p. 120°/0·9 mm., $[\alpha]_D^{21}$ +1·3° (*c*, 3·86 in alcohol) (Found: C, 71·9; H, 9·5; N, 18·5. $C_9H_{14}N_2$ requires C, 72·0; H, 9·4; N, 18·7%).

A solution of this dinitrile (1·5 g.) in concentrated hydrochloric acid (50 ml.) and acetic acid (20 ml.) was refluxed for 10 hr. and the solvent then removed *in vacuo*. Extraction of the residue with ether (5 × 20 ml.) gave a viscous oil which was purified from light petroleum (b. p. 40—60°) to give (+)-3-ethyl-3-methyladipic acid (0·8 g.) in needles, m. p. 76—78°, $[\alpha]_D^{20}$ +4·15° (*c*, 5·1 in $CHCl_3$), identical in m. p. and mixed m. p. with the product derived from (*a*) and having a similar plain, positive o.r.d. curve (Found: C, 57·0; H, 8·7. Calc. for $C_9H_{16}O_4$: C, 57·4; H, 8·6%).

(±)-3-*Ethyl*-3-*methyladipic Acid*.—Reduction of (±)-dimethyl 2-ethyl-2-methylsuccinate (1 g.) in refluxing ether (60 ml.) containing lithium aluminium hydride (1 g.) during 2 hr. gave (±)-2-ethyl-2-methylbutane-1,4-diol (0·8 g.) as a viscous oil, b. p. 134—136°/14 mm. The *di*-p-*nitrobenzoate* formed needles, m. p. 148°, from alcohol (Found: C, 58·2; H, 5·2; N, 6·6. $C_{21}H_{22}N_2O_8$ requires C, 58·6; H, 5·2; N, 6·5%).

Prepared from this diol (1 g.) in pyridine (10 ml.) containing toluene-*p*-sulphonyl chloride (4·5 g.) during 24 hr., the di-toluene-*p*-sulphonate formed a viscous liquid (2·8 g.), which decomposed on distillation. Prepared by the interaction of this tosylate (0·5 g.) and potassium cyanide (0·6 g.) in dimethyl sulphoxide (15 ml.) at 120° during 4 hr., (±)-3-*ethyl*-3-*methyladiponitrile* formed a pale yellow liquid (0·1 g.), b. p. 125°/0·1 mm. (Found: N, 19·3. $C_9H_{14}N_2$ requires N, 18·7%). Hydrolysis of this nitrile (0·1 g.) with boiling concentrated hydrochloric

acid (5 ml.) during 8 hr. gave a product which was purified by chromatography from chloroform containing 1% of methanol on silica to yield (±)-*3-ethyl-3-methyladipic acid* (0·05 g.) which formed needles, m. p. 75—76°, from benzene–light petroleum (b. p. 60—80°) (Found: C, 57·4; H, 8·5. $C_9H_{16}O_4$ requires C, 57·4; H, 8·6%).

Distillation of this acid (0·1 g.) with barium hydroxide (5 mg.) at 300° gave impure (±)-3-ethyl-3-methylcyclopentanone which was characterised as the *semicarbazone*, needles, m. p. 171°, from aqueous methanol (Found: C, 58·8; H, 9·1; N, 23·1. $C_9H_{17}N_3O$ requires C, 59·0; H, 9·4; N, 22·9%). The infrared spectrum of this semicarbazone was identical with that of the semicarbazone from the (+)-3-ethyl-3-methylcyclopentanone.

Dilactone from Dihydrosonolactone.—Oxidation of dihydrorosonolactone (0·5 g.) with peroxytrifluoroacetic acid, as described previously,[1] gave a crude product which after purification by chromatography on neutral alumina from benzene–light petroleum (b. p. 60—80°) (1 : 1) gave the *dilactone* (0·15 g.) as needles, m. p. 176°, from light petroleum (b. p. 60—80°), $[\alpha]_D^{19}$ −16·1° (*c*, 4·34 in $CHCl_3$) (Found: C, 72·1; H, 8·8. $C_{20}H_{30}O_4$ requires C, 71·8; H, 9·0%).

Potassium Borohydride Reduction of Dihydrorosonolactone (with Adelaide Harris).—A solution of potassium borohydride (0·3 g.) in water (2 ml.) and 2N-sodium hydroxide (0·1 ml.) was added dropwise to a solution of dihydrorosonolactone (0·6 g.) in the minimum volume of methanol. After 1 hr., the solution was diluted with water and the product purified from aqueous methanol to yield dihydrorosololactone (0·5 g.), identical (m. p., mixed m. p., and infrared spectrum) with an authentic specimen.

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