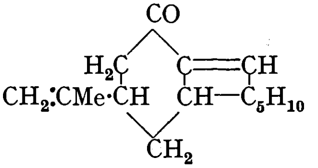
## **15.** *The Constitutions of Eremophilone, Hydroxyeremophilone, and Hydroxydihydroeremophilone. Part III.*

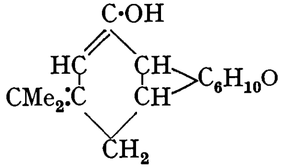
By A. R. Penfold and J. L. Simonsen.

It is shown that the methyl ester of the cyclic acid, $C_{10}H_{18}O_2$, obtained by the reduction of the keto-acid, $C_{10}H_{16}O_3$, an oxidation product of hydroxyeremophilone benzoate, yields on selenium dehydrogenation *o*-xylene. It is suggested that the cyclic acid is 1 : 2-dimethyl*cyclo*hexylacetic acid (VII), which leads to the representations (III), (IV), and (V) for eremophilone, hydroxyeremophilone and hydroxydihydroeremophilone respectively. These sesquiterpene ketones would therefore appear to be exceptions to the " isoprene rule."

In a recent communication (J., 1938, 767) the available evidence relating to the structures of the sesquiterpene ketone, eremophilone, and its congeners, hydroxyeremophilone and hydroxydihydroeremophilone, was summarised and the conclusion was reached that the first two ketones could best be represented by the partial formulæ (I) * and (II).

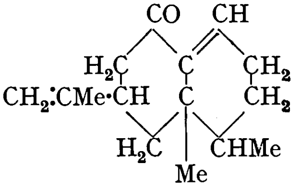
(I.)



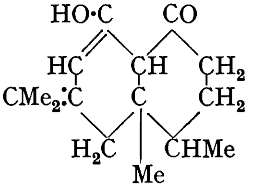


(II.)

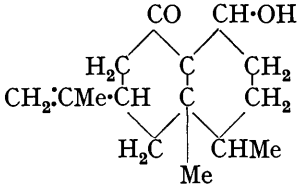
A consideration of the published data led Professor R. Robinson to suggest to us that eremophilone was most probably represented by (III); hydroxyeremophilone would then be (IV) and hydroxydihydroeremophilone (V).



(III.)



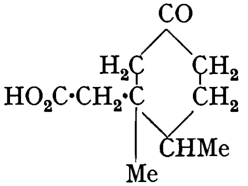
(IV.)

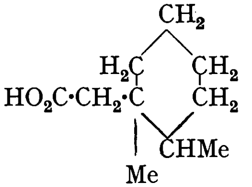


(V.)

This valuable suggestion was obviously capable of simple proof, since, if hydroxyeremophilone was (IV), the keto-acid, $C_{10}H_{16}O_3$, obtained by the ozonolysis of its benzoate (*loc. cit.*, p. 773) would be (VI), yielding on Clemmensen reduction the *cyclo*hexyl acid (VII).

(VI.)





(VII.)

An acid having this structure might be expected to yield on selenium dehydrogenation either *o*-tolylacetic acid or *o*-xylene or a mixture of the two (cf. Ruzicka, *Helv. Chim. Acta*, 1936, **19**, 419). We have now subjected the *methyl* ester of the *cyclo*hexyl acid to the action of selenium at 360° and have obtained in almost theoretical yield a hydrocarbon, b. p. 135—145°, yielding phthalic acid on oxidation with potassium permanganate. The hydrocarbon must therefore have been *o*-xylene and the *cyclo*hexyl acid, (VII), since the only other acid of this composition, assuming no migration of methyl groups, which could on dehydrogenation yield *o*-xylene is 1 : 1-dimethyl*cyclo*hexylacetic acid, with which it has been shown by synthesis (Adamson and Simonsen, J., 1938, 776) not to be identical.

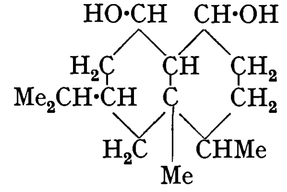
The structures (III), (IV), and (V) now assigned to the three ketones are in full accord with all the available experimental evidence; the only reaction somewhat difficult of

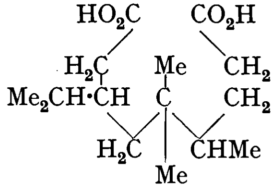
* This formula is incorrect in (XIII) (*loc. cit.*, p. 769).

interpretation and requiring further consideration is that of the oxidation of hydroxyeremophilone with hydrogen peroxide in alkaline solution. It was shown (J., 1932, 2748) that the hydroxy-ketone gave with this reagent a mixture of two stereoisomeric dihydroxy-acids, $C_{15}H_{26}O_6$, which naturally suggested that it was a potential 1 : 2-diketone. This suggestion received further support from the observation (*loc. cit.*, p. 772) that the oil obtained by the hydrolysis of the catalytic hydrogenation product of hydroxyeremophilone benzoate gave on oxidation with hydrogen peroxide a dibasic acid, $C_{15}H_{26}O_4$. We now find that the products from the reduction with sodium and alcohol of either hydroxyeremophilone or of hydroxydihydroeremophilone also yield this acid on oxidation with Criegee's reagent (lead tetra-acetate), a reaction generally assumed to be diagnostic for 1 : 2-glycols.

On the basis of the structure (IV) for hydroxyeremophilone, the glycol would be (VIII), a 1 : 3-glycol; its oxidation with Criegee's reagent must therefore proceed abnormally, the most probable formula for the dibasic acid being (IX).

(VIII.)



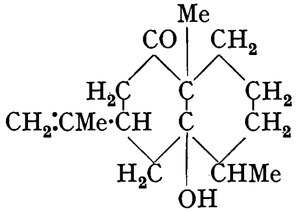


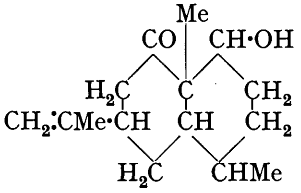
(IX.)

It is well known that substituents in the *peri*-position in the naphthalene nucleus show behaviour similar to that of *o*-substituents; unfortunately, however, no 1 : 8-dihydroxy- or 1-hydroxy-8-keto-decalins have been described and we have no knowledge of their reactions. In our opinion there would appear to be little doubt that eremophilone and the related hydroxy-ketones have the formulæ now suggested, although a rigid proof must await the synthesis and resolution of the two possible *dl*-modifications of (VI) and a study of the 1 : 8-dihydroxydecalins. We propose to extend our investigation in these directions. Until this further evidence is forthcoming it appears to us desirable to defer emendation of the structures assigned previously to the various degradation products of these ketones.

The proposed representation of eremophilone is of importance, since it is not in accord with the so-called " isoprene rule." As has been suggested to us by Professor Robinson, a possible explanation is that eremophilone is formed in Nature from either (X) or (XI) by a molecular rearrangement, the αβ-unsaturated ketone (III) being formed.

(X.)





(XI.)

If the structure now assigned to eremophilone proves to be correct, the implications are somewhat far-reaching. So far as we are aware, in only one case, that of cyperone (Adamson, McQuillin, Robinson, and Simonsen, J., 1937, 1576), has the position of the angle methyl group in a sesquiterpene derivative yielding eudalene on dehydrogenation been rigidly proved. In the selinenes, elemol and eudesmol, it is assumed on the basis of the " isoprene rule." It is obvious that a more rigid proof is now necessary. It is also no longer possible to assume that the " isoprene rule " will apply in the polyterpene series.

## EXPERIMENTAL.

*Dehydrogenation of Methyl* 1 : 2-*Dimethyl*cyclo*hexylacetate* (?).—The *methyl* ester, b. p. 110—112°/19 mm. (Found: C, 71·7; H, 11·2. $C_{11}H_{20}O_2$ requires C, 71·7; H, 10·9%), was prepared by the action of diazomethane on an ethereal solution of the acid (*loc. cit.*, p. 773).

A mixture of the ester (3 g.) and selenium (5 g.) was heated in a sealed tube at 360° for 24 hours. The product was dissolved in ether, the filtered solution washed with aqueous sodium carbonate (*A*) and dried, and the ether removed through an efficient column. The residual oil distilled at 135—145° (1·3 g.), leaving a very small high-boiling residue. Extraction with ether of the acidified sodium carbonate solution (*A*) gave only a trace of a crystalline acid.

The hydrocarbon was suspended in water (150 c.c.), and the mixture heated on the water-bath (mechanical stirring), finely powdered potassium permanganate (7·7 g.) being gradually added. After the oxidation was complete, the manganese dioxide sludge was removed, and the filtrate concentrated, acidified, and extracted with ether. Evaporation of the solvent left phthalic acid, decomp. 201°, without recrystallisation, identified by conversion into the anhydride, m. p. 131°, both alone and in admixture (Found : C, 64·7; H, 3·0. Calc. for $C_8H_4O_3$ : C, 64·8; H, 2·7%).

*Oxidation of Hydroxytetrahydroeremophilol with Lead Tetra-acetate.*—To a solution of hydroxyeremophilone (1·4 g.) in boiling ethyl alcohol (70 c.c.), sodium (7 g.) was added. After completion of the reaction the ethyl alcohol was removed in steam, the glycol dissolved in ether, the solution dried, and the solvent evaporated. The glycol (1·3 g.), which was a viscid oil, was dissolved in acetic acid (10 c.c.) and mixed with an acetic acid solution of lead tetra-acetate (110 c.c.; 0·104N). Oxidation was complete in 48 hours. Addition of water precipitated an oil; this was dissolved in ether and washed with aqueous sodium carbonate, the final washings (*A*) being kept separate. Evaporation of the dried ethereal extract gave an oil (0·8 g.), which reacted readily with Brady's reagent but gave no crystalline derivatives. On oxidation with potassium permanganate in acetone solution it gave the dibasic acid described below.

The final sodium carbonate washings (*A*) gave on acidification an oil which rapidly crystallised in fine needles. The acid (0·3 g.) crystallised from dilute methyl alcohol in needles, m. p. 193—195°, both alone and in admixture with the acid described previously (*loc. cit.*, p. 772) (Found: C, 66·7; H, 9·5. Calc. for $C_{15}H_{26}O_4$ : C, 66·7; H, 9·6%).

Oxidation with lead tetra-acetate in acetic acid solution of the product (0·95 g.) obtained by the reduction of hydroxydihydroeremophilone with sodium and alcohol gave the above-mentioned acid (0·2 g.) together with an aldehyde (0·8 g.), from which a further quantity of the acid was obtained by oxidation with potassium permanganate.

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UNIVERSITY COLLEGE OF NORTH WALES, BANGOR.
THE TECHNOLOGICAL MUSEUM, SYDNEY.

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