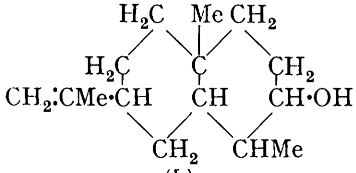
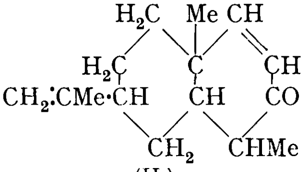
152. *The Constitution of α-Cyperone.*

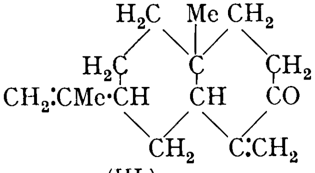
By A. E. BRADFIELD, R. R. PRITCHARD and J. L. SIMONSEN.

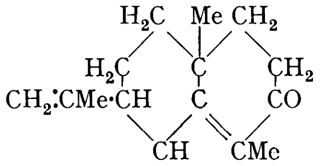
IT was shown by Bradfield, Hegde, Rao, Simonsen, and Gillam (J., 1936, 667) that dihydro-α-cyperol, obtained by the sodium and alcohol reduction of α-cyperone, had the constitution (I). This allows of three alternative structures (II), (III) and (IV) for the parent ketone, and on the evidence then available, the formula (II) was adopted as the most probable.

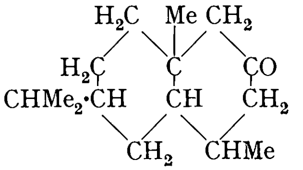
The further study of the apparently anomalous formation of hydroxymethylene-α-cyperone (*loc. cit.*, p. 669) has necessitated a revision of the previous conclusions.


(I.)


(II.)


(III.)

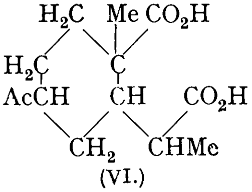
(IV.)


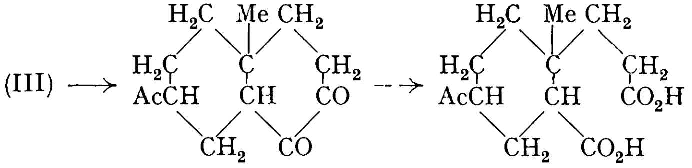

(V.)

By reduction of the hydroxymethylene derivative, followed by dehydrogenation with selenium, a hydrocarbon yielding a picrate, m.p. 102·5—104°, and a *s*-trinitrobenzene derivative, m. p. 116—118°, was obtained. This was not identical with the dimethyl*iso*propylnaphthalene (picrate, m. p. 113—114·5°; *s*-trinitrobenzene derivative, m. p. 141—142°) obtained by dehydrogenation of the product of the action of methylmagnesium iodide on tetrahydroeremophilone. On the basis of the structure (V) assigned to tetrahydroeremophilone by Bradfield, Penfold, and Simonsen (J., 1932, 2744) the latter hydrocarbon was regarded as 1 : 3-dimethyl-7-*iso*propylnaphthalene. The non-identity of the two hydrocarbons was regarded as evidence against the normal formation of a hydroxymethylene derivative and appeared to supply a convincing reason for rejecting (III) and (IV) as representations of α-cyperone, since in both of these there is a methylene group in the 3-position adjacent to the carbonyl group.

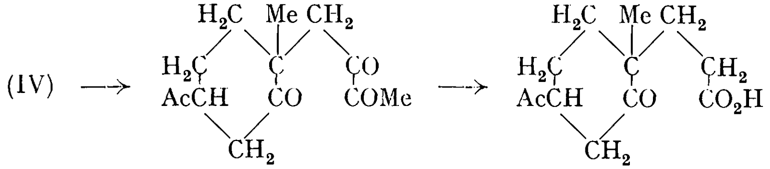
1 : 3-Dimethyl-7-*iso*propylnaphthalene has now been synthesised. Cuminaldehyde was condensed with ethyl α-bromopropionate in the presence of sodium ethoxide, and hydrolysis of the resulting *ester* yielded *cuminyl methyl ketone.* Condensation of this ketone with ethyl bromoacetate, followed by replacement of the hydroxyl group by hydrogen by the usual series of reactions, yielded *ethyl* β-*cuminylbutyrate,* which was cyclised by treatment with sulphuric acid. Treatment of the tetralone with methylmagnesium iodide and dehydrogenation of the product with selenium yielded 1 : 3-dimethyl-7-*iso*propylnaphthalene, the *picrate* and the s-*trinitrobenzene* derivative of which were identical with the corresponding derivatives of the hydrocarbon obtained from the hydroxymethylene-α-cyperone. In consequence, there is now no reason to suppose that the formation of the hydroxymethylene compound has proceeded abnormally and its formation may therefore be taken as a proof that the carbon atom 3 in α-cyperone carries two hydrogen atoms and as providing a cogent argument for the rejection of (II) and for the retention of either (III) or (IV) as the representation of this ketone.

It follows that the interpretation of the oxidative degradation of the ketone requires reconsideration. Ozonolysis of α-cyperone gave formaldehyde and a liquid ketonic acid, to which, on the basis of the analysis of its liquid methyl ester and of the crystalline semicarbazone of the ester, was ascribed the formula $C_{13}H_{20}O_5$ (VI). An acid of the same composition, but of different structure, could, however, be obtained from the ketone (III) by the further oxidation of the primary product (VII) to (VIII) by the hydrogen peroxide formed during the decomposition of the ozonide. On the other

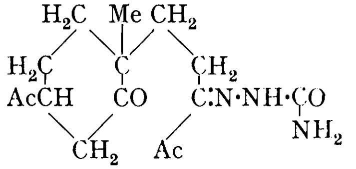

(VI.)

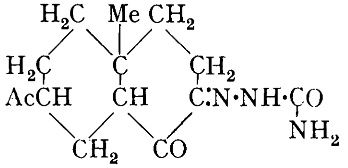

(VII.) (VIII.)

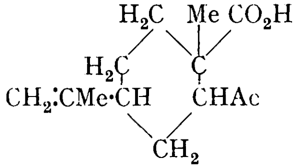
hand, ozonolysis of (IV) would lead to the formation of (IX) as a primary, and the diketonic acid $C_{12}H_{18}O_4$ (X) as a secondary product. The analytical figures previously given (ester : C, 64·3; H, 8·4%; semicarbazone : C, 56·8; H, 7·9%) do not provide a distinction between (VIII) and (X) ($C_{15}H_{24}O_5$ requires C, 63·4; H, 8·5%. $C_{13}H_{20}O_4$ requires C, 65·0; H, 8·3%. $C_{16}H_{27}O_5N_3$ requires C, 56·4; H, 7·9%. $C_{14}H_{23}O_4N_3$ requires C, 56·6; H, 7·7%). Unfortunately a nitrogen determination which would have distinguished the two semicarbazones was not made.

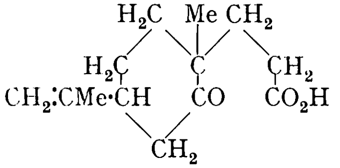

(IV) (IX.) (X.)

We must turn therefore to the product of the ozonolysis of α-cyperone semicarbazone, for which analysis requires the composition $C_{15}H_{23}O_4N_3$, to differentiate between (III) and (IV). This we now regard as having the structure (XI), derived from (IV), since the product (XII) which would be expected from (III) has the composition $C_{14}H_{21}O_3N_3$.

(XI.)



(XII.)

(XIII.)



(XIV.)

It was mentioned (*loc. cit.*, p. 668) that by the action of hydrogen peroxide in alkaline solution on α-cyperone a small yield of a ketonic acid, $C_{13}H_{20}O_3$, was obtained, which, on the basis of (II), was considered to be 6-acetyl-1-methyl-4-*iso*propenyl*cyclo*hexane-1-carboxylic acid (XIII). On the basis of (IV) this acid must now be represented as 1-methyl-4-*iso*propenyl*cyclo*hexan-2-one-1-propionic acid (XIV). It is difficult to derive a keto-acid of the required composition from the alternative formula (III).

In view of the considerations now advanced, we conclude, therefore, that (IV) is the most satisfactory representation of α-cyperone and since β-cyperone semicarbazone gives the same degradation product as α-cyperone semicarbazone, the two ketones must presumably be stereoisomerides, differing in the disposition of the angle methyl and the *iso*propenyl group. It is somewhat remarkable that the interchange between the two forms should take place with such facility.

In advancing this structure for α-cyperone we desire to emphasise the fact that our conclusions are based ultimately on the dehydrogenation of dihydro-α-cyperol to eudalene and on the assumption of an angle methyl group in position 9. We are at present engaged, in collaboration with Professor R. Robinson, in attempting the synthesis of the ketone.

The fact that the product from the action of methylmagnesium iodide on tetrahydroeremophilone does not, on dehydrogenation, yield 1 : 3-dimethyl-7-*iso*propylnaphthalene throws doubt on the structures assigned to eremophilone and its congeners. The constitution of these ketones will be discussed in a future communication.

EXPERIMENTAL.

Ethyl αβ-Epoxy-β-cumyl-α-methylpropionate.—In the course of 3 hours, powdered sodium ethoxide (47 g.) was added, with occasional shaking, to a mixture of cuminaldehyde (100 g.) and ethyl α-bromopropionate (122 g.), cooled in a freezing mixture. After standing overnight, the mixture was warmed on the water-bath for 6 hours. After the addition of ice-water and dilute acetic acid, the product was extracted with ether, the extract washed with water and dried, and the ether removed, leaving an oil, which was twice fractionated. The *ester* (66 g.) boiled at 180—181°/24 mm. (Found : C, 72·4; H, 8·1. $C_{15}H_{20}O_3$ requires C, 72·6; H, 8·1%).

Cuminyl Methyl Ketone.—The above ester (66 g.) was refluxed with methyl-alcoholic potassium hydroxide (potassium hydroxide, 30 g.) for 3 hours. After addition of water and removal of the alcohol by distillation, the solution was acidified and extracted with ether. The acid remaining after evaporation of the ether was heated at 180° for 5 hours. The product was submitted to steam distillation, the ketone passing over, and a brown residue (A) being left in the flask. The ketone was collected in ether, and the extract washed with sodium carbonate solution, removing some cuminic acid, dried, and evaporated. The *ketone* distilled at 137°/22 mm. (Found : C, 81·4; H, 9·0. $C_{12}H_{16}O$ requires C, 81·8; H, 9·1%). The *semicarbazone* crystallised from methyl alcohol in rosettes of prismatic needles, m. p. 142—143° (Found : N, 17·7. $C_{13}H_{19}ON_3$ requires N, 18·0%). The 2 : 4-*dinitrophenylhydrazone* crystallised from alcohol, in which it was very sparingly soluble, in golden leaflets, m. p. 137—138° (Found : N, 15·5. $C_{18}H_{20}O_4N_4$ requires N, 15·7%). The residue (A) crystallised from chloroform, in which it was sparingly soluble, in fine needles, decomp. 170—171°, and was undoubtedly *αβ-dihydroxy-β-cumyl-α-methylpropionic acid* (Found : C, 65·4; H, 7·8. $C_{13}H_{18}O_4$ requires C, 65·5; H, 7·6%).

Ethyl β-Cuminylbutyrate.—A mixture of cuminyl methyl ketone (26 g.), ethyl bromoacetate (22 g.), and zinc (9·7 g.) in dry benzene (250 c.c.) was heated on the water-bath, reaction initiated by the addition of a little methylmagnesium iodide, and the heating continued for 3 hours. The cooled solution was shaken with dilute sulphuric acid until the benzene layer became clear, ether added, and the ethereal solution separated and washed with dilute sulphuric acid, potassium carbonate solution, and water, dried, and evaporated. The residue was fractionated under reduced pressure. The fraction (25·2 g.), b. p. 160—200°/16 mm., which consisted of a mixture of unsaturated ester and hydroxy-compound, was heated with an equal weight of potassium hydrogen sulphate for 8 hours, and the product without further purification was reduced in ethyl-alcoholic solution by hydrogen in the presence of palladium–norit catalyst, yielding the *butyrate*, b. p. 170—174°/18 mm. (Found : C, 78·0; H, 9·7. $C_{16}H_{24}O_2$ requires C, 77·4; H, 9·7%).

3-*Methyl*-7-iso*propyl*-1 : 2 : 3 : 4-*tetral*-1-*one.*—The above ester (18·2 g.) was heated on the water-bath with a mixture of sulphuric acid (135 c.c.) and water (45 c.c.) for 1¼ hours. The cooled solution was poured into water, and the product extracted with ether. The residue after evaporation of the ether was refluxed with alcoholic potassium hydroxide (potassium hydroxide, 10 g.) for 2 hours, the solution poured into water, and the ketone extracted with ether. Removal of the ether left the tetralone as an oil, b. p. 165—173°/17 mm., from which were prepared the *semicarbazone*, which separated from aqueous alcohol in rhombic leaflets, decomp. 180—182° (Found : C, 69·7; H, 8·3. $C_{15}H_{21}ON_3$ requires C, 69·5; H, 8·1%), and the 2 : 4-*dinitrophenylhydrazone*, crystallising from butyl alcohol in orange-red needles, m. p. 235—236° (Found : C, 62·8; H, 5·9. $C_{20}H_{22}O_4N_4$ requires C, 62·8; H, 5·8%).

1 : 3-*Dimethyl*-7-iso*propylnaphthalene.*—The product (7·6 g.) obtained by treatment of 3-methyl-7-*iso*propyl-1 : 2 : 3 : 4-tetral-1-one with methylmagnesium iodide (from methyl iodide 16·3 g., magnesium 2·8 g.) in the usual manner, was heated with selenium (10 g.) at 300° for 24 hours. The oil was dissolved in ether, washed with sodium hydroxide solution, and dried. Removal of the ether left the naphthalene derivative (6·0 g.), b. p. 165—167°/19 mm. The *picrate* crystallised from alcohol in short orange needles, m. p. 102·5—104° (Found : C, 58·9; H, 5·0. $C_{15}H_{18},C_6H_3O_7N_3$ requires C, 59·0; H, 4·9%). The s-*trinitrobenzene* derivative crystallised from ethyl alcohol in yellow needles, m. p. 117—119°, completely molten at 121° (Found : C, 60·8; H, 5·3. $C_{15}H_{18},C_6H_3O_6N_3$ requires C, 61·3; H, 5·1%). The two derivatives were identical (m. p. and mixed m. p.) with the derivatives of the hydrocarbon obtained from hydroxymethylene-α-cyperone.

The description of a picrate, m. p. 113—114·5°, and a *s*-trinitrobenzene derivative, m. p. 141—142°, as derivatives of 1 : 3-dimethyl-7-*iso*propylnaphthalene, previously given (*loc. cit.*), is now withdrawn. In a subsequent communication it will be shown that these substances are derivatives of 1 : 5-dimethyl-7-*iso*propylnaphthalene.

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