# *The Structure of Cyperone. Part II.* The Alkali-catalysed Isomerisation of α-Cyperone and an Autoxidation.*

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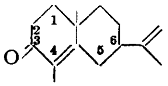
The action of alcoholic alkali on α-cyperone (I), reported to lead to an isomeric ketone, is chiefly to induce autoxidation to the 6-hydroxy-derivative (V) though it may in small part be associated with the presence in natural cyperone of an *iso*propylidene isomer (III).

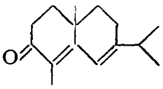
α-Cyperone has been shown to have the structure (I) (Bradfield, Pritchard, and Simonsen, *J.*, 1937, 763; Bradfield, Hegde, Rao, Simonsen, and Gillam, *J.*, 1936, 667). An isomeric ketone obtained from it by acid digestion (Bradfield, Hegde, *et al.*, *loc. cit.*), and regarded on the basis of oxidation experiments as a diastereoisomer arising by inversion at $C_{(6)}$, was later shown (Part I) to consist of a mixture of α-(I) and the structurally isomeric β-cyperone (II).

Acid-catalysed isomerisation of (I) to (II) has well-known analogies and the mechanism is clear. Bradfield, Hegde, *et al.*, however, refer without experimental details to obtaining the isomerised ketone also by alkali digestion of α-cyperone.

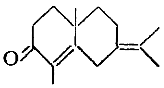
Simonsen and Barton ("The Terpenes," Vol. III, Cambridge Univ. Press, 1952, p. 209) state this was by means of methyl-alcoholic potassium hydroxide. Since alkali should not readily induce isomerisation of (I) and the product reported appeared to be only partially isomerised, we were inclined to infer the presence in α-cyperone of some of the *iso*propylidene isomer (III), which would be expected to pass readily by enolisation into (II) under acid or alkaline conditions.



(I)



(II)



(III)

Evidence was sought in the intensity of absorption at *ca.* 890 cm.$^{-1}$ (*ca.* 11·28 μ) of α-cyperone in comparison with a synthetic specimen (cf. Adamson, McQuillin, Robinson,

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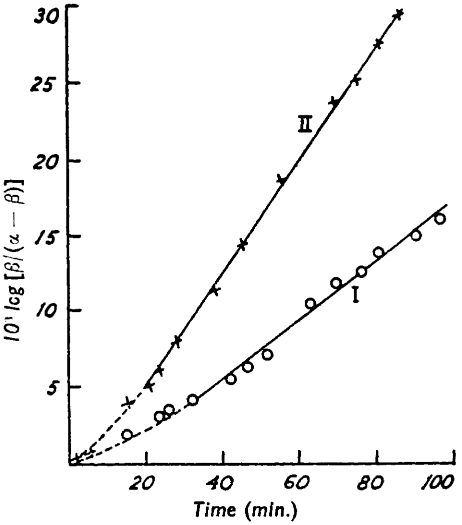
* The paper, *J.*, 1951, 716, is regarded as Part I.

and Simonsen, *J.*, 1937, 1576; and the following paper), and with related compounds. Barnard, Bateman, Harding, Koch, Sheppard, and Sutherland (*J.*, 1950, 915) have indicated that absorption in this region is a sensitive index of the *iso*propenyl group in simpler terpenes. The results (see Table) indicated apparently reduced absorption due to terminal methylene in natural α-cyperone. Its oxime, however, gave a high extinction value in contrast with the consistent group formed by the synthetic and related oximes, " β-cyperone " oxime from natural sources being known from its ultraviolet absorption to be a mixture of (I) and (II) (Part I). The extinction coefficient of *ca.* 170 shown by a number of these substances is in good agreement with the value of 155—160 found by Barnard *et al.* (*loc. cit.*) for substances known to exist in the *iso*propenyl form. These authors moreover also encountered anomalously high absorption in some cases; reduced absorption is, however, probably more significant. The low ε value for the natural ketone may therefore indicate the presence of some of (III) in the natural ketone but the high absorption shown by the oxime renders this conclusion tentative.

ε (*l. mole*$^{-1}$ *cm.*$^{-1}$) *at* ~11·28 μ *in carbon disulphide.*

| | ε | λ (μ) | | ε | λ (μ) |
|---|---|---|---|---|---|
| α-Cyperone, natural .............. | 121 | 11·26 | " β-Cyperone " oxime, natural | 100 | 11·28 |
| ,, synth. .............. | 170 | 11·25 | β-Cyperone oxime, synth. ...... | 0 | — |
| ,, oxime, natural ...... | 207 | 11·28 | (−)-Dihydrocarvoxime ........ | 176 | 11·27 |
| ,, ,, synth. ...... | 171 | 11·28 | | | |

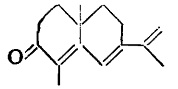


*Rate of apparent isomerisation of natural* (I) *and synthetic α-cyperone* (II) *in* N-*alcoholic potassium hydroxide.*

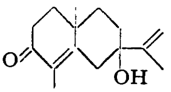
The amount of natural α-cyperone available did not permit close investigation; the small remaining sample was kindly made available by Dr. L. N. Owen and Sir John Simonsen to whom our best thanks are offered. After digestion with hot alcoholic potassium hydroxide this showed increased absorption at 300 mμ, corresponding to the presence of only 3—4% of the conjugated isomer (II): the main absorption at 250 mμ remained essentially unchanged.

In alcoholic alkali at the room temperature, the natural and the synthetic ketone showed progressively increased absorption at 300 mμ which in both cases came to an end at an apparent 20% isomerisation to the fully conjugated isomer. The rate of this change followed an apparently pseudo-unimolecular course but in both cases only after an induction period (see Figure). This was clearly a different phenomenom from the isomerisation, and its kinetics suggested an oxidation. Treibs (*Ber.*, 1931, **64**, 2178, 2545, and later papers) has recorded a number of examples of autoxidation of αβ-unsaturated ketones under alkaline conditions. Indeed, the synthetic ketone (I), after being kept for some days in alcoholic potassium hydroxide at room temperature, was converted into a crystalline hydroxy-ketone $C_{15}H_{22}O_2$ in good yield. This showed infrared absorption bands at 2·85 (OH), 11·28 (terminal $CH_2$:), and 6·05 μ (C:C·CO; confirmed by ultra-violet absorption at 250 mμ, log ε 3·91). On hydrogenation two mols. of hydrogen were absorbed. With acetic anhydride the substance was not dehydrated but gave a liquid acetate. With 2 : 4-dinitrophenylhydrazine, however, in strongly acid solution the elements of water were lost to give a derivative having $\lambda_{max.}$ 420 mμ (log ε 4·58 in $CHCl_3$), which clearly corresponds with the trienone (IV); the 2 : 4-dinitrophenylhydrazone of the dienone (II) gave $\lambda_{max.}$ 404 mμ (log ε 4·57), and that of the monounsaturated ketone (I) gave $\lambda_{max.}$ 386 mμ (log ε 4·39) (in EtOH) (Part I). The wave-length increments are comparable. These results indicate structure (V) or (VI) for the hydroxy-ketone. Neither structure is in complete accord with recovery of the substance unchanged after refluxing with aqueous-alcoholic alkali; under these conditions a hydroxy-ketone (V) should be dehydrated, and (VI) isomerised to the 3 : 5-diketone (cf. Heilbron, Jones, and Spring, *J.*, 1937, 801; Ellis and Petrov, *J.*, 1939, 1078). Structure (V) is preferred since the substance was not oxidised by manganese dioxide, a reagent known to oxidise αβ-unsaturated primary or secondary alcohols (cf. Attenburrow *et al.*, *J.*, 1952, 1094; Amendolla, Rosenkranz, and Sondheimer, *J.*, 1954, 1226).

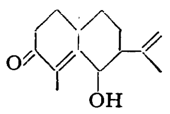
The oxidation therefore appears to follow a somewhat different course from the examples discussed by Treibs (*loc. cit.*). It seems most reasonable to associate oxidation at $C_{(6)}$ with the analogy between the enolic form (VII) present in strongly alkaline solution and the environmentally analogous methylene present in the autoxidisable dienoic acids. The intermediate hydroperoxides are known to be decomposed in alkaline solution to the corresponding hydroxy-derivative (cf. Hock and Gänicke, *Ber.*, 1938, **71**, 1430; Farmer and Sundralingam, *J.*, 1942, 121), leading *via* (X) to (V).



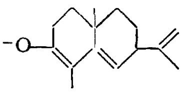
(IV)



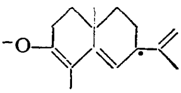
(V)



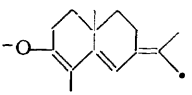
(VI)



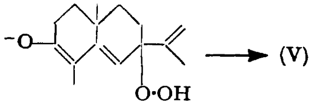
(VII)



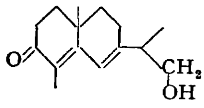
(VIII)



(IX)



(X)



(XI)

The formation of the intermediate radical (VIII) may clearly have a bearing on the alkali-catalysed isomerisation discussed above since the mesomeric form (IX) may lead to (XI), a hydroxy-derivative of the conjugated ketone (II). This interpretation and the generality of the autoxidation reaction in other cases are being examined. The development of conjugation during autoxidation of some unconjugated dienes is, however, already well-known (cf., *e.g.*, Farmer, Koch, and Sutton, *J.*, 1943, 541).

## EXPERIMENTAL

$[\alpha]_D$ are for solutions in $CHCl_3$. Infrared measurements were carried out by Dr. F. B. Strauss, The Dyson Perrins Laboratory, Oxford, whom we thank. The specimens employed were (i) α-cyperone, natural, kindly made available by Dr. L. N. Owen, Imperial College of Science, London, whom we thank, (ii) the oxime of natural α-cyperone, a specimen provided by Sir John Simonsen, (iii) synthetic α-cyperone, $[\alpha]_{5461}$ +210°, and its oxime, prepared by the improved method described in the following paper, (iv) " natural " and synthetic β-cyperone oximes, previously reported (Adamson, McQuillin, Robinson, and Simonsen, *loc. cit.*). The natural ketone had undergone some oxidation and for characterisation a small sample was purified by chromatography on alumina. Elution by light petroleum gave the ketone as a colourless oil, b. p. 85°/0·05 mm., $n_D^{17}$ 1·5292, $[\alpha]_{5461}$ +119·2° (*c* 1·03), $\lambda_{max.}$ 250 mμ (log ε 4·17), λ 300 mμ (log ε 1·55) (Found : C, 82·7; H, 10·4. Calc. for $C_{15}H_{22}O$ : C, 82·6; H, 10·1%).

*Alkali-induced Isomerisation.*—α-Cyperone (natural) (0·1 g., not purified by chromatography) was heated with 10% alcoholic potassium hydroxide (2·5 c.c.) on the steam-bath for 4 hr. Recovered by dilution with water (without acidification) the ketone afforded a colourless oil, b. p. 95°/0·1 mm., $n_D^{20}$ 1·5313, $[\alpha]_{5461}$ +129·5° (*c* 0·29), $\lambda_{max.}$ 251 mμ (log ε 4·11), λ 300 mμ (log ε 3·007).

*Autoxidation of Synthetic α-Cyperone.*—Synthetic α-cyperone (1·5 g.) in alcohol (20 c.c.) was treated with potassium hydroxide (1·5 g.) in water (7 c.c.) and kept loosely corked at room temperature for 9 days. The material recovered by dilution gave on distillation a viscous colourless oil (1·1 g.), b. p. 115—120°/0·1 mm., $n_D^{18}$ 1·5418, which solidified, to give 1 : 2 : 3 : 5 : 6 : 7 : 8 : 9-*octahydro*-6-*hydroxy*-4 : 9-*dimethyl*-3-*oxo*-6-iso*propenylnaphthalene*, m. p. 61°, as prisms from light petroleum, $[\alpha]_{5461}$ +100° (*c*, 1·0), $\lambda_{max.}$ 250 mμ (log ε 3·92) (Found : C, 76·7; H, 9·4. $C_{15}H_{22}O_2$ requires C, 77·0; H, 9·4%). Refluxing for some hours with acetic anhydride and distillation gave an *acetate*, b. p. 100—105°/0·05 mm., $n_D^{17}$ 1·5210 (Found : C, 74·3; H, 9·1. $C_{17}H_{24}O_3$ requires C, 73·9; H, 8·7%). The 2 : 4-*dinitrophenylhydrazone* corresponded with a derivative of the 1 : 2 : 3 : 7 : 8 : 9-hexahydro-ketone and formed very dark red prisms, m. p. 228°, from butanol (Found : C, 64·1; H, 5·8. $C_{21}H_{24}O_4N_4$ requires C, 63·7; H, 6·1%).

In an attempt to isomerise the hydroxy-ketone, 0·1 g. in alcohol (5 c.c.) was treated with potassium hydroxide (0·2 g.) in water (1 c.c.) and refluxed under nitrogen for 2·5 hr. The recovered material, b. p. 115—120°/0·1 mm., crystallised as prisms, m. p. and mixed m. p. 61°, from light petroleum. In the attempted oxidation the hydroxy-ketone (0·2 g.) in benzene (15 c.c.) was refluxed for 5 hr. in the presence of manganese dioxide (1·5 g.) prepared as described by Attenburrow *et al.* (*loc. cit.*). The recovered material crystallised to give unchanged hydroxy-ketone, m. p. and mixed m. p. 59°.

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