The Structure of Cyperone. Part IV. The Synthesis of (Natural) (+)-α-Cyperone, its Enantiomorph, and an Epimer.*

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The structure and configuration (IX) for natural (+)-α-cyperone have been confirmed by synthesis of its (+)- and (−)-form.

It was shown in Part III,* from a comparison with a synthetic ketone (IV), and its derivatives, that (+)-α-cyperone must have the absolute configuration (IX). The synthetic ketone (IV) was obtained by condensation of (—)-dihydrocarvone (I) with diethylmethyl-3-oxopentylammonium iodide. The ketol (II) which formed the principal product and could be dehydrated to give (IV), was accompanied by a mixture of dehydro-ketones regarded as (IV) and (III). The latter should represent (—)-α-cyperone.

A parallel series of products, (VII), (VIII), and (IX) has now been prepared from (+)-dihydrocarvone (VI).

The mixtures of dehydro-ketones (III) and (IV), and (VIII) and (IX), were conveniently separated *via* their oximes, the derivative of (+)-α-cyperone and its enantiomorph being the higher-melting and less soluble. Direct chromatography of the ketones on alumina was relatively ineffective.

The oximes were hydrolysed by oxalic acid in aqueous methanol in the presence of light petroleum. Continuous extraction of the ketone into the second phase largely avoids acid-induced isomerisation and contamination of the product with the corresponding β-cyperones (V) and (X). Any small amount of β-cyperone formed was removed by chromatography and in this way (+)-α-cyperone (IX) and its enantiomorph (III) were obtained in a state of purity. These ketones have been isomerised by sulphuric acid to the corresponding (+)- and (—)-β-cyperones (X) and (V).

With the preparation of the (—)-dehydro-ketone (VIII), following the methods of

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* Part III, *J.*, 1955, 528.

Part III, all the possible isomers in this series have now been obtained. It is suggested that the compounds (IV) and (VIII) may be conveniently referred to as (+)- and (—)-6-*epi*-α-cyperones, and that in systematic nomenclature the 6-alkyl substituent may be designated α and β as in the sterol system.

The infrared and ultraviolet absorption spectra of the synthetic (+)-α-cyperone (IX) were identical with those of the natural ketone, and different from those of the (+)-6-*epi*-ketone (IV) (cf. Figs. 1 and 2). The ultraviolet absorption maximum for the 6-*epi*-cyperones is moved by 3 mμ towards longer wavelengths and the intensity is somewhat reduced relative to the absorption of ketones of the natural series. Steric compression due to the axial *iso*propenyl group, which will raise the energy level of the ground state, would be expected to be relatively less in the excited state of the molecule. The main differences in the infrared spectra are summarised in Table 1 : in the *epi*-series certain additional hydrogen deformation frequencies, probably associated with the 6-hydrogen atom, and additional skeletal vibration frequencies are observed.

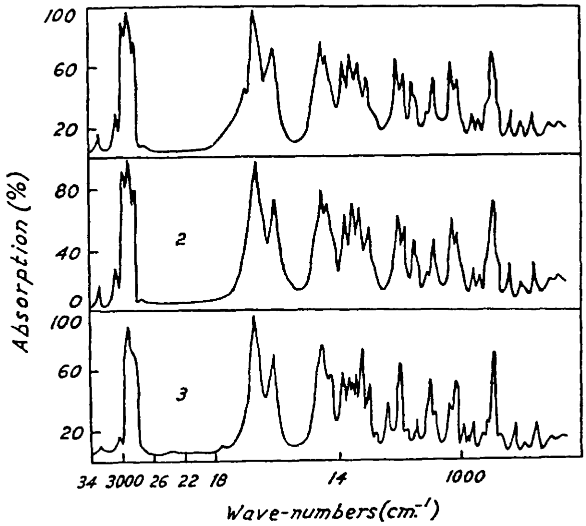


FIG. 1. *Infrared spectra of* (1) *natural* (*C.S. No.* 215) *and* (2) *synthetic* (+)-α-*cyperone* (*C.S. No.* 216) *and* (3) (+)-6-epi-α-*cyperone* (*C.S. No.* 217).*

* Larger copies of these spectra have been deposited with the Chemical Society. Photocopies, price 3*s*. 0*d*. per copy per spectrum, may be obtained on application, quoting the C.S. Nos. to the General Secretary, The Chemical Society, Burlington House, Piccadilly, London, W.1.

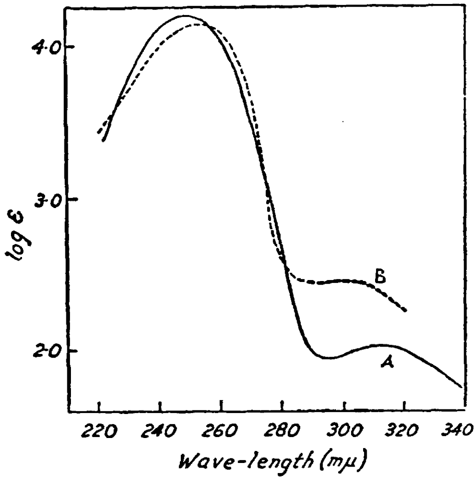


FIG. 2. *Ultraviolet spectra of* (*A*) *natural and synthetic* (+)-α-*cyperone and* (*B*) (+)-6-epi-α-*cyperone.*

The oximes of natural and synthetic (+)-α-cyperone gave identical *X*-ray powder photographs.

The natural and the synthetic ketones are compared in Table 2. The synthetic ketones, and their semicarbazones and 2 : 4-dinitrophenylhydrazones, were chromatographed specimens. The correspondence in physical properties leaves no doubt that natural (+)-α-cyperone has the structure and configuration (IX). The close agreement excludes the possibility of anything beyond minute amounts of any other isomer in the ketone isolated from natural sources and supports this conclusion reached earlier on other grounds (Cardwell and McQuillin, *J.*, 1955, 526). Only two points require comment. The rotation of natural (+)-α-cyperone semicarbazone has been redetermined. Bradfield, Hedge, Rao, Simonsen, and Gillam (*loc. cit.*) give the melting point of the 2 : 4-dinitrophenylhydrazone of the natural ketone as 210°; Barton and Tarlton (*loc. cit.*) give 188—190° for a chromatographed specimen. Our product, m. p. 205°, was homogeneous on chromatography and gave no evidence in the ultraviolet spectrum of the presence of the derivative of β-cyperone. Sharp melting points over a relatively wide range of values are, however, characteristic of a number of 2 : 4-dinitrophenylhydrazones (cf., *e.g.*, Woodward, Sondheimer, Taub, Heusler, and McLamore, *J. Amer. Chem. Soc.*, 1952, **74**, 4226). In solution the different samples show essentially identical properties (rotation and ultraviolet absorption). The difference in melting point must be ascribed to differences in crystal habit.

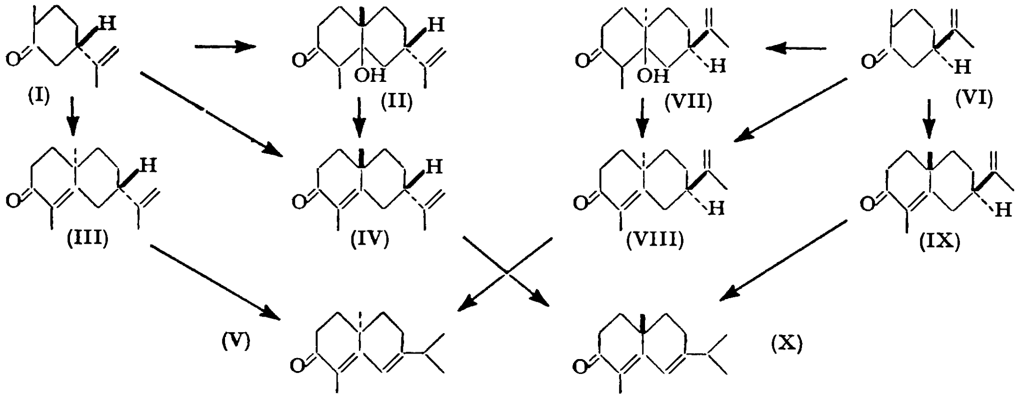


TABLE 1. *Absorption peaks* (*cm.*$^{-1}$).

(+)-α-Cyperone	1351 1322		1181	1106 1083	1007	937	837
(+)-6-*epi*-α-Cyperone	1353 1347 1333 1315	1232		1091 1073	1033	983 973 928 915	819

TABLE 2.

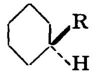
	Natural	Synthetic (+)	Synthetic (−)		Natural	Synthetic (+)	Synthetic (−)
		Ketones				Semicarbazones	
n_D^{17}	1·5292 [b]	1·5294	1·5288	M. p.	215—216° [a]	215—216°	215—216°
$[\alpha]_{5461}$	+119·2° [b]	+115·4°	−115·9°	$[\alpha]_{5461}$	+244°	+231°	−227°
$\lambda_{max.}$ (mμ) [e]	250·0	249·5	249·5	$\lambda_{max.}$ (mμ) [e]	270 [c]	272	—
log ε	4·17	4·21	4·21	log ε	4·32	4·48	—
		Oximes				2 : 4-Dinitrophenylhydrazones	
M. p.	150·5° [a]	150·5°	150·5°	M. p.	210° [a]	205°	205°
$[\alpha]_{5461}$	+134° [a]	+134°	−134°	$[\alpha]_{5461}$	+414° [d]	+387°	−395°
$\lambda_{max.}$ (mμ) [e]	244 [c]	244	—	$\lambda_{max.}$ (mμ) [f]	395 [d]	395	395
log ε	4·25	4·28	—	log ε	4·47	4·46	4·45

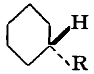
Bradfield, Hegde, Rao, Simonsen, and Gillam, *J.*, 1936, 667. Cf. Part II, *J.*, 1955, 526. [c] Cf. Part I, *J.*, 1951, 716. [d] Barton and Tarlton, *J.*, 1954, 3492. In EtOH. [f] In CHCl$_3$.

The properties of (—)-6-*epi*-α-cyperone (VIII) and of (—)-β-cyperone (V) and their derivatives agreed closely with those for the (+)-enantiomorphs previously reported (cf. Experimental section and Part III).

Mills (*J.*, 1952, 4976) drew attention to the large positive molecular-rotation difference for the epimeric change (XI) ⟶ (XII) in a number of monocyclic terpenes (R = OH, Me, CMe:CH$_2$) containing a strongly polarisable centre. It is of interest that the molecular-rotation difference for the corresponding change, (+)-α-cyperone (IX) ⟶ (+)-6-*epi*-α-cyperone (IV) is in close agreement (cf. Table 3). This is to be expected from the relation of these sesquiterpenes to the simpler examples discussed by Mills, although the polarisable centres are differently located in these cases.

TABLE 3.


(XI)


(XII)

	(XI)	(XII)	Δ
R = CMe:CH$_2$	(+)-α-Cyperone	(+)-6-*epi*-α-Cyperone	+238° *
,, ...	(+)-*cis*-Menth-2-ene	(+)-*trans*-Menth-2-ene	+119
,, ...	(−)-*cis*-Menth-2-ene	(+)-*trans*-Menth-2-ene	+245
R = Me	(−)-*cis*-δ-Pinene	(+)-*trans*-δ-Pinene	+226

* ΔM_{5461}, for the remainder ΔM_D.

It is also of interest that the absolute stereochemistry of (+)-α-cyperone corresponds with that established for (+)-β-eudesmol (Woodward, Fürst, Riniker, Kalvoda, Arigoni, Jeger, and Gold, *J. Amer. Chem. Soc.*, 1954, **76**, 313) and for (−)-α-santonin (Woodward and Yates, *Chem. and Ind.*, 1954, 1391), and that in all these instances the 6-substituent adopts the thermodynamically more stable configuration.

EXPERIMENTAL

Ultraviolet spectra were measured on a Hilger Uvispectrometer. Infrared absorption spectra were measured on a Grubb–Parsons double-beam spectrometer on liquid films of 0·02-mm. thickness. Ultraviolet spectra and $[\alpha]_{5461}$ are for solutions in CHCl$_3$ unless otherwise stated.

Condensation of (+)-*Dihydrocarvone with Diethylmethyl*-3-*oxopentylammonium Iodide*.—(+)-Dihydrocarvone (45 g.) in ether (200 c.c.) was converted into the sodio-derivative by sodamide (12·7 g.) under ether (200 c.c.). Diethylmethyl-3-oxopentylammonium iodide (86 g.) in dry pyridine (90 c.c.) was then added, and the mixture stirred at 0° for 6 hr. and then refluxed for 5½ hr. Water was then added and the ether extract washed free from pyridine and dried. Distillation gave (+)-dihydrocarvone (9 g.), followed by a fraction, b. p. 115—130°/0·2 mm. (42·8 g.), which solidified and by means of light petroleum gave (+)-*decahydro*-10-*hydroxy*-4 : 9-*dimethyl*-3-*oxo*-6β-iso*propenylnaphthalene* (23 g.), m. p. 106°, $[\alpha]_{5461}$ +54° (*c*, 3·0) (Found: C, 76·0; H, 10·1. C$_{15}$H$_{24}$O$_2$ requires C, 76·3; H, 10·2%). Redistillation of the non-crystalline material gave further (+)-ketol (2 g.) and the residue was chromatographed on alumina. Elution with light petroleum (b. p. 60—80°) gave fractions, (*a*) b. p. 104—106°/0·3 mm. (5·35 g.), n_D^{20} 1·5260, $[\alpha]_{5461}$ −10° (*c*, 5·95) (Found: C, 82·5; H, 10·2. Calc. for C$_{15}$H$_{22}$O: C, 82·6; H, 10·1%), (*b*) b. p. 106—108°/0·3 mm. (2·55 g.), n_D^{20} 1·5285, $[\alpha]_{5461}$ −62° (*c*, 5·2) (Found: C, 82·3; H, 10·35%), and (*c*) the (+)-ketol (1 g.), m. p. 105°.

(+)-1 : 2 : 3 : 5 : 6 : 7 : 8 : 9-*Octahydro*-4 : 9-*dimethyl*-3-*oxo*-6β-iso*propenylnaphthalene*.—(i) The combined fractions (*a*) and (*b*) above were converted into the oxime. Repeated crystallisation from methanol gave (+)-α-*cyperone oxime* as needles (2 g.), m. p. and mixed m. p. 150·5°, $[\alpha]_{5461}$ +133·5° (EtOH; *c*, 1·09) (Found: C, 77·5; H, 9·8; N, 6·2. C$_{15}$H$_{23}$ON requires C, 77·25; H, 9·9; N, 6·0%).

(ii) This oxime (1·25 g.) in methanol (55 c.c.), water (25 c.c.), light petroleum (b. p. 60—80°; 20 c.c.) was refluxed for 22 hr. with oxalic acid (3 g.) and 40% aqueous formaldehyde (15 c.c.). Water was added and the light petroleum layer washed and dried. Chromatography of the product on alumina with light petroleum (b. p. 60—80°) gave (+)-α-*cyperone* as a colourless oil, b. p. 96—97°/0·2 mm., n_D^{17} 1·5294, $[\alpha]_{5461}$ +115·4° (*c*, 1·3) (Found: C, 82·7; H, 10·1%). The 2 : 4-dinitrophenylhydrazone formed red needles, m. p. 204°, from ethyl acetate. Chromatography of the product on alumina with benzene–light petroleum (b. p. 40—60°) (1 : 3), and collection of fractions of maximal absorption at 395 mμ gave (+)-α-*cyperone* 2 : 4-*dinitrophenylhydrazone* as scarlet prisms, m. p. and mixed m. p. 205°, from chloroform–di*iso*propyl ether,

$[\alpha]_D$ +387° (*c*, 0·088) (Found: C, 62·9; H, 6·7; N, 13·9. $C_{21}H_{26}O_4N_4$ requires C, 63·3; H, 6·5; N, 14·1%). The *semicarbazone* crystallised as irregular prisms, m. p. and mixed m. p. 215—216°, from methanol, $[\alpha]_{5461}$ +233° (*c*, 1·9). After chromatography on alumina in benzene–chloroform (1 : 3) the semicarbazone was recovered and crystallised as irregular prisms, m. p. 215—216°, from methanol, $[\alpha]_{5461}$ +231° (*c*, 1·47) (Found: C, 70·1; H, 9·2; N, 15·2. $C_{16}H_{25}ON_3$ requires C, 69·8; H, 9·1; N, 15·3%).

(−)-1 : 2 : 3 : 5 : 6 : 7 : 8 : 9-*Octahydro*-4 : 9-*dimethyl*-3-*oxo*-6α-iso*propenylnaphthalene*.—(i) The non-crystalline product (14 g.) from condensation of (−)-dihydrocarvone with diethylmethyl-3-oxopentylammonium iodide (cf. Part III), similarly converted into the oxime and recrystallised as above, gave (−)-α-*cyperone oxime* as needles (2 g.), m. p. 150·5°, $[\alpha]_{5461}$ −133·9° (EtOH, *c*, 1·35) (Found: C, 77·2; H, 9·8; N, 5·8%).

(ii) This oxime (1·1 g.), hydrolysed as above, gave (−)-α-*cyperone*, b. p. 96—98°/0·2 mm., n_D^{17} 1·5288, $[\alpha]_{5461}$ −115·9° (*c*, 1·6) (Found: C, 82·85; H, 10·3%). Its 2 : 4-*dinitrophenylhydrazone*, chromatographed and crystallised as above, formed scarlet prisms, m. p. 205°, $[\alpha]_D$ −395° (*c*, 0·036) (Found: C, 63·3; H, 6·8; N, 13·8%). The *semicarbazone* crystallised as irregular prisms, m. p. 215·5—216·5°, from methanol, $[\alpha]_{5461}$ −227° (*c*, 1·75) (Found: C, 69·9; H, 9·5; N, 15·3%).

(−)-1 : 2 : 3 : 5 : 6 : 7 : 8 : 9-*Octahydro*-4 : 9-*dimethyl*-3-*oxo*-6β-iso*propenylnaphthalene*—(*a*) (+)-Decahydro-10-hydroxy-4 : 9-dimethyl-3-oxo-6β-*iso*propenylnaphthalene (5 g.) in alcoholic potassium hydroxide (10%; 50 c.c.) was refluxed under nitrogen for 8 hr. The mixture was then cooled, diluted, and neutralised with dilute hydrochloric acid. The product, isolated in ether, on distillation gave (−)-1 : 2 : 3 : 5 : 6 : 7 : 8 : 9-*octahydro*-4 : 9-*dimethyl*-3-*oxo*-6β-iso*propenylnaphthalene* as a pale yellow oil, b. p. 102—104°/0·25 mm. (4·3 g.), n_D^{20} 1·5340, $[\alpha]_{5461}$ −225° (*c*, 5·0), $\lambda_{max.}$ 252·5 mμ (log ε 4·16) (EtOH) (Found: C, 82·5; H, 10·2%). The 2 : 4-*dinitrophenylhydrazone* formed red needles, m. p. 202°, from ethyl acetate (Found: C, 63·3; H, 6·1; N, 13·8%). The *oxime* formed flattened needles, m. p. 89·5—90° (from methanol–water), $[\alpha]_{5461}$ −177° (EtOH, *c*, 2·7) [*] (Found: C, 77·1; H, 10·0; N, 6·4%). The *semicarbazone* formed prisms, m. p. 176° (from methanol), $[\alpha]_{5461}$ −267° (*c*, 2·0) (Found: C, 70·0; H, 8·9; N, 15·6%).

(*b*) (+)-Decahydro-10-hydroxy-4 : 9-dimethyl-3-oxo-6β-*iso*propenylnaphthalene (1·5 g.) in ethanol (25 c.c.) was treated with concentrated hydrochloric acid (2·5 c.c.). After 8 days, water was added, and the solution neutralised with sodium hydrogen carbonate. The bulk of the ethanol was removed in a vacuum and the oil extracted with ether. The oil after chromatography on alumina with light petroleum (b. p. 60—80°) gave (−)-1 : 2 : 3 : 5 : 6 : 7 : 8 : 9-octahydro-4 : 9-dimethyl-3-oxo-6β-*iso*propenylnaphthalene, b. p. 98°/0·2 mm. (1 g.), n_D^{20} 1·5337, $[\alpha]_{5461}$ −228° (*c*, 1·2) (Found: C, 82·7; H, 10·3%). This material gave a 2 : 4-dinitrophenylhydrazone, oxime, and semicarbazone identical with those prepared above.

(+)-1 : 2 : 3 : 7 : 8 : 9-*Hexahydro*-4 : 9-*dimethyl*-3-*oxo*-6-iso*propylnaphthalene*.—(+)-α-Cyperone (0·25 g.) was treated with ice-cold sulphuric acid (50% v/v; 3·5 c.c.). After 6 hr. ice and water were added. The oil isolated with ether gave (+)-1 : 2 : 3 : 7 : 8 : 9-hexahydro-4 : 9-dimethyl-3-oxo-6-*iso*propylnaphthalene, b. p. 95°/0·2 mm., n_D^{20} 1·5620, $[\alpha]_{5461}$ +681° (*c*, 2·1), $\lambda_{max.}$ 300·5 mμ (log ε 4·49) (EtOH) (cf. Part III) (Found: C, 82·3; H, 10·35%). The 2 : 4-*dinitrophenylhydrazone* formed plates, m. p. 230—231° (from ethyl acetate), $\lambda_{max.}$ 417 mμ (log ε 4·50) (Found: C, 62·8; H, 6·5; N, 14·5%).

(−)-1 : 2 : 3 : 7 : 8 : 9-*Hexahydro*-4 : 9-*dimethyl*-3-*oxo*-6-iso*propylnaphthalene*.—(*a*) (+)-Decahydro-10-hydroxy-4 : 9-dimethyl-3-oxo-6β-*iso*propenylnaphthalene (1·5 g.) was treated with ice-cold sulphuric acid (50% v/v; 20 c.c.). After 6 hr. ice and water were added. The oil isolated with ether gave (−)-1 : 2 : 3 : 7 : 8 : 9-*hexahydro*-4 : 9-*dimethyl*-3-*oxo*-6-iso*propylnaphthalene* as a pale yellow oil, b. p. 95—98°/0·25 mm. (1·3 g.), n_D^{20} 1·5619, $[\alpha]_{5461}$ −688° (*c*, 2·7), $\lambda_{max.}$ 301 mμ (log ε 4·40) (EtOH) (Found: C, 82·6; H, 10·3%). The 2 : 4-*dinitrophenylhydrazone* formed plates, m. p. 231—232° (from ethyl acetate), $\lambda_{max.}$ 417 mμ (log ε 4·50) (Found: C, 63·4; H, 6·6; N, 13·7%). The *oxime* formed needles, m. p. 139° (from methanol), $[\alpha]_{5461}$ −320° (EtOH *c*, 1·2) (Found: C, 77·1; H, 9·7; N, 5·7%). The *semicarbazone* formed slightly yellow plates (photochromic), m. p. 208° (from methanol), $[\alpha]_{5461}$ −399° (*c*, 1·9) (Found: C, 70·0; H, 9·4; N, 15·05%). (*b*) (−)-α-Cyperone (0·15 g.), treated with ice-cold sulphuric acid (50% v/v; 2 c.c.) and re-isolated after 6 hr. as above, gave (−)-1 : 2 : 3 : 7 : 8 : 9-hexahydro-4 : 9-dimethyl-3-oxo-6-*iso*propylnaphthalene, b. p. 94—96°/0·2 mm., n_D^{20} 1·5622, $[\alpha]_{5461}$ −679° (*c*, 0·7) (Found: C,

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[*] The rotation of the (+)-enantiomorph of this oxime was given in Part III (*loc. cit.*) as +233°. This should read +178°.

82·8; H, 10·2%), characterised as the 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 231° (Found : C, 63·2; H, 6·7; N, 14·1%).

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