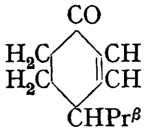
351. *Researches on Phellandrenes. Part III. The Correlation of* l-α-*Phellandrene with* l-4-iso*Propyl*-Δ^2-cyclo*hexen*-1-*one.*

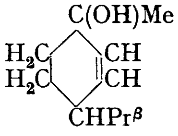
By Alfred S. Galloway, John Dewar, and John Read.

Earlier researches have dealt with the isolation and precise diagnosis of α-phellandrene (J., 1923, **123**, 1657; 1924, **125**, 930), with the establishment of a chemical and stereochemical connexion between *l*-α-phellandrene, *l*-piperitol and *l*-piperitone in *Eucalyptus* oils (J., 1930, 2770), and with a possible mechanism of formation of these substances in nature (*J. Soc. Chem. Ind.*, 1929, **48**, 786; 1935, **54**, 312; *Chem. Reviews*, 1930, **7**, 41).

A second *Eucalyptus* ketone, *l*-4-*iso*propyl-Δ^2-*cyclo*hexen-1-one (I), isolated from the essential oil of *E. cneorifolia* by Cahn, Penfold, and Simonsen (J., 1931, 1366), also bears a striking structural likeness to α-phellandrene (III). It is now shown that this ketone, like *l*-piperitone, is related stereochemically to the *l*-form of α-phellandrene, into which it may be converted by dehydration of the tertiary alcohol, 1-Δ^2-*menthen*-1-*ol* (II), which it yields in reaction with methylmagnesium iodide. Wallach (*Annalen*, 1905, **343**, 30) reported the formation of a small amount of "phellandrene," and some tertiary alcohol, by applying this reagent to *iso*propyl*cyclo*hexenone derived from sabina ketone. The hydrocarbon had a slight dextrorotation and yielded a nitrosite, m. p. 113°, which was almost optically inactive: this result was therefore indeterminate (J., 1923, **123**, 1657). Our specimen of phellandrene was strongly lævorotatory, and readily yielded pure *l*-α-phellandrene α-nitrosite, m. p. 119°, with the characteristic high dextrorotation and pronounced mutarotation.



(I.)



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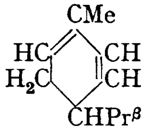

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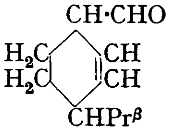

(IV.)

We found that *l*-4-*iso*propyl-Δ^2-*cyclo*hexen-1-one, which has not hitherto been obtained stereochemically pure, could not be purified by means of the semicarbazone, since it underwent partial racemisation during the process. The optically pure ketone, having $[\alpha]_D$ — 119·3° (alcohol), was prepared by oxidising pure 1-4-iso*propyl*-Δ^2-cyclo*hexen*-1-*ol*. This substance was obtained by fractionally crystallising the mixed *p*-nitrobenzoates of the stereoisomeric alcohols which resulted when the crude ketone was reduced by Ponndorf's method.

Wallach (*Annalen*, 1905, **343**, 35) showed that β-phellandrene may be oxidised by free oxygen to *iso*propyl*cyclo*hexenone and by potassium permanganate to the aldehyde (IV), which was afterwards found in certain *Eucalyptus* oils and named cryptal (Penfold, J., 1922, **121**, 266; Penfold and Simonsen, J., 1930, 403). It has been suggested (Penfold and Simonsen, *loc. cit.*, p. 405) that cryptal, and its associates phellandral and cuminaldehyde, may arise biogenetically through the oxidation of α-phellandrene; also that 4-*iso*propyl-Δ^2-*cyclo*hexen-1-one may be an oxidation product of the enolic form of cryptal (Cahn, Penfold, and Simonsen, J., 1931, 1367). The above work of Wallach lends support to the possibility that both *iso*propyl*cyclo*hexenone (cf. Cahn, Penfold, and Simonsen, *loc. cit.*) and cryptal may derive naturally from a closely related precursor, β-phellandrene. This alternative is of particular interest when correlated with observations (Cahn, Penfold, and Simonsen, *loc. cit.*; private communications from Dr. P. A. Berry and Prof. A. K.

Macbeth) indicating that in certain species of *Eucalyptus* the above aldehyde and ketone are produced somewhat capriciously : a variation of the conditions prevailing *in vivo* may thus be the cause of the appearance of *l*-cryptal or the alternative *l*-4-*iso*propyl-Δ^2-*cyclo*hexen-1-one, derived from a common precursor, β-phellandrene, in the same plant at different seasons of the year.

EXPERIMENTAL.

Crude 1-4-iso*Propyl*-Δ^2-cyclo*hexen*-1-*one*.—The crude oil used in this work was sent to us by Dr. P. A. Berry, of Messrs. A. M. Bickford and Sons, Ltd., Adelaide. It came from the last runnings of three large-scale fractional steam distillations of the essential oil of *Eucalyptus cneorifolia* (from material collected in Kangaroo Island during the months of March, April, and May). This liquid, forming 4% (vol.) of the original essential oil, was again fractionally steam distilled. The last runnings (23% vol., $d_{15^\circ}^{15^\circ}$ 0·9622, $[\alpha]_{\mathrm{D}}^{20^\circ}$ −35·01°) were shaken with 5% sodium hydroxide solution to remove australol, and then washed with water. The resulting material was a mobile yellow oil, with $n_{\mathrm{D}}^{18\cdot5^\circ}$ 1·4987, $[\alpha]_{\mathrm{D}}^{20^\circ}$ −35·0° (homogeneous), $[\alpha]_{\mathrm{D}}^{20^\circ}$ −37·3° (*c* 2·0, alcohol) ; it was stated to be free from phellandrene and to contain 22·6% (wt.) of cineole, 40% of aldehydes (including ketone), and also some cymene, terpenes, and sesquiterpenes.

Fractional treatment with sodium bisulphite solution showed the presence in this oil of cuminaldehyde (semicarbazone, m. p. 210—211° ; 2 : 4-dinitrophenylhydrazone, m. p. 238°), *l*-phellandral, and *l*-4-*iso*propyl-Δ^2-*cyclo*hexen-1-one ; but cryptal was not found. The crude ketone was isolated (cf. Penfold, J., 1922, **121**, 266) by shaking the oil (200 c.c.) for about 10 hours at room temperature with a solution of sodium bisulphite (100 g.) in water (300 c.c.). The solid bisulphite compounds of *l*-phellandral and cuminaldehyde (83 g.) were removed. Successive treatment of the aqueous filtrate with sodium carbonate and sodium hydroxide yielded, respectively, a yellow oil (1·5 g., $n_{\mathrm{D}}^{20^\circ}$ 1·4912) which deposited crystals of terpin hydrate after 24 hours, and crude *l*-4-*iso*propyl-Δ^4-*cyclo*hexen-1-one (43·5 g., $n_{\mathrm{D}}^{20^\circ}$ 1·4856). Fractional distillation of the latter yielded a colourless specimen (35 g.) of the purer ketone, b. p. 105—109°/14 mm., $n_{\mathrm{D}}^{19^\circ}$ 1·4852, $\alpha_{\mathrm{D}}^{19^\circ}$ − 63·00° (*l* 1, homogeneous), $[\alpha]_{\mathrm{D}}^{19^\circ}$ − 86·6° (*c* 2·1, alcohol) (Found : C, 77·5; H, 9·6. Calc. : C, 78·2; H, 10·1%). The specimen gradually became yellow, and after several months had $\alpha_{\mathrm{D}}^{19^\circ}$ − 51·25° (*l* 1, homogeneous) ; when it was then heated for 30 minutes on the water-bath with 20% aqueous oxalic acid the value declined to $\alpha_{\mathrm{D}}^{19^\circ}$ −48·9°.

The semicarbazone, made by heating an aqueous alcoholic solution of the purified ketone ($\alpha_{\mathrm{D}}^{19^\circ}$ − 63·00°) with semicarbazide acetate, when recrystallised from aqueous methyl alcohol had m. p. 185—186°, $[\alpha]_{\mathrm{D}}$ − 27·0° (*c* 2·0, chloroform). Two further recrystallisations from ethyl alcohol containing a little chloroform gave a product which was not appreciably affected by renewed crystallisation : m. p. 188°, $[\alpha]_{\mathrm{D}}$ − 20·6°. The ketone regenerated from this semicarbazone by hydrolysis with hot 20% oxalic acid had $n_{\mathrm{D}}^{19^\circ}$ 1·4900, $\alpha_{\mathrm{D}}^{19^\circ}$ − 16·4° (*l* 1, homogeneous), $[\alpha]_{\mathrm{D}}^{19^\circ}$ − 21·6° (*c* 2·0, alcohol). The ketone recovered by hydrolysing the material in the mother-liquors from the recrystallisation of the semicarbazone had $[\alpha]_{\mathrm{D}}$ − 18·4° (*c* 2·0, alcohol). The semicarbazone prepared from the above regenerated ketone, with $\alpha_{\mathrm{D}}^{19^\circ}$ − 16·4°, had $[\alpha]_{\mathrm{D}}$ − 5·9° (*c* 2·0, chloroform).

The 2 : 4-*dinitrophenylhydrazone* crystallised at once when a solution of the purified ketone (0·7 g.) in alcohol (20 c.c.) was added to a filtered solution of 2 : 4-dinitrophenylhydrazine (1 g.) in concentrated sulphuric acid (2 c.c.) and alcohol (15 c.c.). The crude product had m. p. 118—120°. When recrystallised twice from alcohol it formed red flakes, m. p. 129—130°, and the deeply coloured solution in chloroform appeared to be weakly dextrorotatory (Found : C, 56·9; H, 5·6. $C_{15}H_{18}O_4N_4$ requires C, 56·6; H, 5·7%).

The tarry residues from the fractional distillation of the above ketone contained crystalline material, which after treatment on porous plate and recrystallisation from ether–light petroleum had m. p. 145°, $[\alpha]_{\mathrm{D}}$ −105·3° (*c* 2·0, alcohol) : this substance, resulting probably from the oxidation of *l*-phellandral, appeared to be *l*-4-*iso*propyl-Δ^1-*cyclo*hexene-1-carboxylic acid (Found : C, 71·5; H, 9·1. Calc. : C, 71·4; H, 9·5%) (Simonsen, "The Terpenes," 1931, I, 272).

1-4-iso*Propyl*-Δ^2-cyclo*hexen*-1-*ol*.—The above ketone (15 g.), having $n_{\mathrm{D}}^{19^\circ}$ 1·4852, $[\alpha]_{\mathrm{D}}^{19^\circ}$ − 86·6° (*c* 2·1, alcohol), was reduced by the method of Ponndorf (*Z. angew. Chem.*, 1926, **39**, 138) with aluminium *iso*propoxide (6 g.) and dry *iso*propyl alcohol (50 c.c.), the slow constant-volume distillation being continued until acetone was no longer found in the distillate (5 hours). Distillation of the solvent, followed by steam distillation and extraction with ether, gave a mobile oil (14·2 g.) with $n_{\mathrm{D}}^{22^\circ}$ 1·4760. The fraction (12·4 g.) distilling at 98—103°/10 mm. had $n_{\mathrm{D}}^{19^\circ}$ 1·4812,

α_D −49·9° (*l* 1, homogeneous). Treatment with 3 : 5-dinitrobenzoyl chloride in pyridine yielded a crude ester, which, after four recrystallisations from alcohol–ethyl acetate, gave l-4-iso*propyl*-Δ^2-cyclo*hexenyl* 3 : 5-*dinitrobenzoate*, m. p. 115°, $[\alpha]_D$ − 136·5° (*c* 1·3, chloroform) (Found : C, 57·6; H, 5·5. $C_{16}H_{18}O_6N_2$ requires C, 57·5; H, 5·4%). The crude *p*-nitrobenzoate (11·7 g. from 8 g.), after the removal of impurities by acid and alkaline washing and steam distillation, was a brownish, waxy solid, m. p. 56—61°, $[\alpha]_D$ − 33·5° (*c* 2·0, chloroform); five recrystallisations from methyl alcohol yielded pale yellow needles (4·2 g.), m. p. 84°, $[\alpha]_D$ −168·5° (*c* 2·1, chloroform). Since these values were unaffected by further recrystallisation, the substance was regarded as pure l-4-iso*propyl*-Δ^2-cyclo*hexenyl* p-*nitrobenzoate* (Found : C, 66·5; H, 6·3. $C_{16}H_{19}O_4N$ requires C, 66·4; H, 6·6%). The mother-liquors contained a much more soluble ester, which was not isolated : the above data indicate that this was dextrorotatory.

The pure *p*-nitrobenzoate (4 g.) was boiled under reflux for 30 minutes with 5% methyl-alcoholic potassium hydroxide (23 c.c.). l-4-iso*Propyl*-Δ^2-cyclo*hexen*-1-*ol* (1·5 g.), isolated by steam distillation, followed by extraction with ether, had a fragrant smell reminiscent of geraniol: b. p. 97°/8 mm., $n_D^{21°}$ 1·4771, $[\alpha]_D$ − 139·3° (*c* 2·3, alcohol) (Found : C, 77·0; H, 11·5. $C_9H_{16}O$ requires C, 77·1; H, 11·5%).

Pure l-4-iso*Propyl*-Δ^2-cyclo*hexen*-1-*one*.—When the above l-4-*iso*propyl-Δ^2-*cyclo*hexen-1-ol (1·4 g.) was treated with a mixture of potassium dichromate (2 g.) and 15% sulphuric acid (12 g.) at 40°, a black addition compound was formed. This decomposed slowly when raised to 55°, yielding the ketone, which was extracted with ether. Distillation in a vacuum yielded a colourless liquid (1 g.) with the smell of the original ketone; it had b. p. 90°/9 mm., $n_D^{18°}$ 1·4810, $[\alpha]_D$ − 119·3° (*c* 2·0, alcohol). The semicarbazone crystallised from aqueous methyl alcohol in small prisms, m. p. 186°, $[\alpha]_D$ − 23·5° (*c* 1·0, chloroform) (Found : C, 61·8; H, 8·7. Calc. : C, 61·6; H, 8·7%). The 2 : 4-dinitrophenylhydrazone separated from methyl alcohol in red, feathery needles, m. p. 132°, with a dextrorotation in chloroform solution (Found : C, 57·0; H, 5·6. Calc. : C, 56·6; H, 5·7%).

l-Δ^2-*Menthen*-1-*ol*.—Impure *l*-4-*iso*propyl-Δ^2-*cyclo*hexen-1-one (15 g.), b. p. 105—109°/14 mm., $[\alpha]_D^{19°}$ − 86·6° (*c* 2·1, alcohol), was dissolved in dry ether (20 c.c.) and added slowly to an ice-cooled solution of methylmagnesium iodide (prepared from 2·4 g. of magnesium, 100 c.c. of ether, and 14·2 g. of methyl iodide). After remaining overnight in the ice-chest, the mixture was boiled for 10 minutes; it was then poured into ice-water and steam distilled. The resulting ethereal solution was extracted twice with 30% aqueous sodium bisulphite. Distillation of the dried ethereal solution gave a yellow liquid (12·5 g., b. p. 84—88°/10 mm., $n_D^{20°}$ 1·4754); the specimen of l-Δ^2-*menthen*-1-*ol* obtained upon redistillation, as a colourless mobile liquid with a pleasant odour, had b. p. 92°/11 mm., $n_D^{17·5°}$ 1·4758, α_D − 52·8° (*l* 1, homogeneous), $[\alpha]_D$ − 61·2° (*c* 2·2, alcohol). The alcohol did not react readily, and attempts to prepare a *p*-nitro- or a 3 : 5-dinitro-benzoate were unavailing (Found : C, 78·1; H, 11·3. $C_{10}H_{18}O$ requires C, 77·9; H, 11·8%).

The purer ketone described above (15 g.), having $\alpha_D^{19°}$ − 51·3° (*l* 1), when treated with three times the above quantity of the Grignard reagent and heated for 2½ hours on the water-bath, yielded a small preliminary fraction (0·5 g., $n_D^{18°}$ 1·4750), which gave the phellandrene nitrosite reaction, and a main fraction (10·6 g.), b. p. 110—115°/25 mm., $n_D^{18°}$ 1·4743, $\alpha_D^{18°}$ − 45·8° (*l* 1, homogeneous), which did not give the reaction.

l-α-*Phellandrene*.—The above *l*-Δ^2-menthenol (10·5 g.), having $\alpha_D^{18°}$ − 45·8°, was boiled under reflux for 2½ hours with a solution of oxalic acid (30 g.) in water (60 c.c.). The steam-distilled product (6·9 g.) had b. p. 83—86°/32 mm., $n_D^{16°}$ 1·4820, $\alpha_D^{16°}$ − 53·7° (*l* 1, homogeneous), $[\alpha]_D$ − 73·9° (*c* 2·0, alcohol). The crude nitrosite (0·8 g. from 6 g.; J., 1930, 2781) had m. p. 105—107°; after two recrystallisations from chloroform–methyl alcohol this yielded long fine needles, m. p. 119°, $[\alpha]_D$ + 148·5° (*c* 1·0, chloroform, 13 mins.), declining to + 130·0° in 48 mins., and to − 45·8° in 115 hours (J., 1923, **123**, 1665) (Found : C, 56·8; H, 7·6. Calc. : C, 56·6; H, 7·6%).

l-α-Phellandrene, $n_D^{18°}$ 1·4783, $\alpha_D^{18°}$ − 62·7° (*l* 1, homogeneous), was heated with aqueous oxalic acid under the conditions noted in the above dehydration : the recovered material had $n_D^{19°}$ 1·4800, $\alpha_D^{19°}$ − 58·7°.

We are indebted to Dr. P. A. Berry of Adelaide for the crude material used in this investigation, and to the Carnegie Trust for the Universities of Scotland for the award of a Fellowship (A. S. G.) and a Teaching Fellowship (J. D.) to two of us.

THE UNIVERSITY, ST. ANDREWS. [*Received, September 26th*, 1936.]