A Synthesis of (±)-*Phellandral.*

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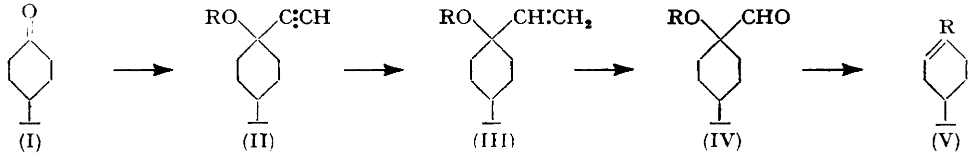
The synthesis of (±)-phellandral from dihydrocryptone has been achieved. Work on 1-vinyl*cyclo*hexanol as a model compound is also described.

THE terpene aldehyde (—)-phellandral occurs with (—)-phellandrene in various eucalyptus oils (Penfold, *J.*, 1922, **121**, 266; Berry, Macbeth, and Swanson, *J.*, 1937, 986), and the (+)-form of both the aldehyde and the hydrocarbon have been isolated from *Phellandrium aquaticum* (*idem, ibid.*, p. 1448). Extensive studies in these laboratories (*J.*, 1939, 1245; 1940, 808; 1946, 145) suggested the structure (V; R = CHO) for phellandral; and this was supported by a synthesis described by Frank, Berry, and Shotwell (*J. Amer. Chem. Soc.*, 1949, **71**, 3890). In this, dihydrocryptone (I) was converted into the acetate of the corresponding cyanohydrin, which by deacetoxylation and hydrolysis of the resultant nitrile (V; R = CN) gave phellandric acid and thence on reduction a low yield of phellandral. The synthesis is thought not to be unambiguous, as a high temperature (575—600°) was required for deacetoxylation, and the nitrile was assumed to have its unsaturation in the position αβ to the cyano-group: and during hydrolysis of the nitrile αβ–βγ shifting of the double bond occurred so that a mixture of the unsaturated acids was obtained. Work on the synthesis of phellandral according to the scheme below (Macbeth, Aust. and N.Z. Assoc. for Advancement of Science, Sydney, August, 1952) was therefore continued, and an unequivocal synthesis of the aldehyde is now presented.

As some difficulty was experienced at the ozonolysis stage (III ⟶ IV), exploratory work was carried out with the readily available 1-vinyl*cyclo*hexanol (Cook and Lawrence, *J.*, 1938, 58). Best results were obtained by using a slight excess of ozone at —75° in ethyl acetate solution, but even under these conditions the ozonide sometimes decomposed before the subsequent hydrogenation, although the yield of hydroxy-aldehyde was not noticeably affected. An improvement in overall yield was effected by ozonisation of 1-vinyl*cyclo*hexyl acetate, obtained by reduction of the corresponding ethynyl compound.



About equal amounts of the acetoxy-acid and acetoxy-aldehyde were obtained, but deacetoxylation of the latter under mild conditions could not be effected. Dehydration of the hydroxy-aldehyde was also difficult, boiling acetic anhydride, for example, giving the acetoxy-aldehyde. *cyclo*Hexene-1-aldehyde, however, was easily derived by decomposition of the 2 : 4-dinitrophenylhydrazones.

In the synthesis of phellandral the condensation of dihydrocryptone with acetylene was best carried out with sodium acetylide in liquid ammonia, and the resultant mixture was separated into the *cis*- and the *trans*-form by fractional crystallisation of the *p*-nitrobenzoates. The configurations were assigned on the basis of the Auwers–Skita rule, the ethynyl and *iso*propyl groups being regarded as similar. The *trans*-acetate was prepared under conditions which do not effect rearrangement (Rupe, Meisner, and Kambli, *Helv. Chim. Acta*, 1928, **11**, 449). Catalytic reduction gave the vinyl compound (III; R = Ac), ozonolysis of which gave a mixture of the acetoxy-acid and acetoxy-aldehyde. The latter resisted attempts at deacetoxylation at temperatures below 300°, but hydrolysis to the hydroxy-aldehyde could be carried out; the latter was more simply obtained by direct ozonolysis of (III; R = H). The hydroxy-aldehyde was very resistant to dehydration to phellandral; *e.g.*, unchanged material was recovered from heating with potassium hydrogen sulphate at 160°, and from hot 10% alcoholic sulphuric acid; and acetic anhydride gave the acetoxy-aldehyde. Phosphorus oxychloride in pyridine effected direct dehydration in rather poor yield, but the most satisfactory method of recovery of phellandral was by the action of 2 : 4-dinitrophenylhydrazine in alcoholic sulphuric acid. Dehydration during the reaction resulted in the formation of the 2 : 4-dinitrophenylhydrazone of phellandral.

Methods for the recovery of ketones have been described using pyruvic acid and hydrobromic acid (Mattox and Kendall, *J. Amer. Chem. Soc.*, 1948, **70**, 882; Djerassi, *ibid.*, 1949, **71**, 1003), or pyruvic acid and sodium acetate (Koechlin, Kritchevsky, and Gallagher, *J. Biol. Chem.*, 1950, **184**, 393). The latter proved ineffective, but the former reacted under relatively mild conditions. Pyruvic acid alone was also satisfactory although a higher temperature was needed. The recovered (±)-phellandral was characterised by its physical constants, by preparation of the semicarbazone and *p*-nitrophenylhydrazone, and by oxidation to phellandric acid.

EXPERIMENTAL

Dihydrocryptone.—This was prepared from cryptone isolated from *Eucalyptus cneorifolia* by reduction in the presence of palladium–charcoal. The product was shaken with disodium sulphite and then with 35% aqueous sodium hydrogen sulphite. From the latter, dihydrocryptone was obtained by decomposition with aqueous sodium carbonate and isolation with ether.

cis- *and* trans-1-*Ethynyl*-4-iso*propyl*cyclo*hexanol*.—(*a*) Potassium *tert.*-pentyloxide, prepared from potassium (5 g.), was treated with dihydrocryptone (17·5 g.), and the solution cooled and added dropwise during 30 min. to a saturated solution of acetylene in ether (50 ml.) at −15°. Acetylene was passed into the mixture for a further 10 min., the product decomposed with ammonium chloride, and the ether separated and washed with 35% sodium hydrogen sulphite and then water. The ethereal residue yielded the mixture of ethynyl compounds, b. p. 68°/0·4 mm.

(*b*) The procedure detailed by Vogel ("Practical Organic Chemistry," 2nd edn., 1951, Longmans, p. 1002) for the preparation of 1-ethynyl*cyclo*hexanol employing sodium acetylide in liquid ammonia was used. The residue left after decomposition with ammonium chloride and evaporation of the ammonia was extracted (Soxhlet) with ether, and the extract washed with water and dilute acid, and evaporated. Distillation gave the mixture, b. p. 83°/3 mm., which partly crystallised, yielding about equal amounts of an oil and the solid trans-*compound*. Crystallisation of the latter from light petroleum (b. p. <40°) gave long needles, m. p. 45° (Found: C, 79·6; H, 11·1. $C_{11}H_{18}O$ requires C, 79·5; H, 10·8%). The trans-*acetate* prepared with boiling acetic anhydride crystallised from light petroleum (b. p. <40°) as large prisms, m. p. 44° (Found: C, 75·4; H, 9·8. $C_{13}H_{20}O_2$ requires C, 75·0; H, 9·6%). The acetate was recovered unchanged after 1 hour's refluxing with 15% aqueous potassium hydroxide but was hydrolysed by 2 hours' refluxing with 20% aqueous methanolic potassium hydroxide. The trans-p-*nitrobenzoate*, prepared by means of the acid chloride in boiling benzene and a trace of pyridine for 6 hr., crystallised from methanol as cream-coloured rhombs, m. p. 82—83° (Found: C, 68·5; H, 6·4; N, 4·5. $C_{18}H_{21}O_4N$ requires C, 68·6; H, 6·7; N, 4·4%), hydrolysed in 2 hr. with 10% methanolic potassium hydroxide. Similar esterification of the liquid portion and fractional crystallisation gave a further crop of the *trans*-derivative and the cis-*ester* in the ratio 3 : 1. Crystallisation of the latter from methanol gave plates, m. p. 120—121° (Found: C, 68·8; H, 6·2; N, 4·6. $C_{18}H_{21}O_4N$ requires C, 68·6; H, 6·7; N, 4·4%). Hydrolysis of this ester with methanolic potassium hydroxide, isolation with ether, and distillation gave cis-1-*ethynyl*-4-iso*propyl*cyclo*hexanol*, b. p. 94°/7 mm., n_D^{25} 1·4720, d_4^{25} 0·9182, $[R_L]_D^{25}$ 50·7 (Calc.: 50·5) (Found: C, 79·3; H, 10·9. $C_{11}H_{18}O$ requires C, 79·5; H, 10·8%).

trans-4-iso*Propyl*-1-*vinyl*cyclo*hexanol*.—The *trans*-ethynyl compound (10 g.) in alcohol (100 ml.) was hydrogenated at room temperature and pressure in the presence of a 10% palladium–calcium carbonate catalyst (1 g.), until 1·35 l. (1 mol.) of hydrogen were absorbed, whereupon reduction slackened noticeably. Temperature control was obtained by using a flask with a sealed-in cooling coil. The catalyst was separated, and the filtrate diluted with water and extracted with ether. Evaporation of the dried extract and distillation of the residue gave an oil, b. p. 79—80°/2 mm., which gradually solidified. Crystallisation from light petroleum (b. p. <40°) gave needles, m. p. 21° (Found: C, 77·7; H, 11·9. Calc. for $C_{11}H_{20}O$: C, 78·6; H, 11·9%). The acetate, prepared similarly from *trans*-4-*iso*propyl-1-vinyl-*cyclo*hexanyl acetate, was obtained as an odourless oil, b. p. 91—92°/2 mm. The p-*nitrobenzoate*, prepared in benzene, crystallised from methanol as cream-coloured needles, m. p. 73° (Found: C, 68·1; H, 7·2; N, 4·6. $C_{18}H_{23}O_4N$ requires C, 68·1; H, 7·3; N, 4·4%). The cis-p-*nitrobenzoate*, obtained by esterification and fractional crystallisation from the partial reduction product of the mixed ethynyl compounds, crystallised from methanol as cream-coloured needles, m. p. 103° (Found: C, 68·3; H, 7·3; N, 4·7%).

Ozonolyses.—The apparatus employed was a ten-tube Towers ozoniser fitted with a flow-meter and calibrated at a rate of 200 c.c. of oxygen per min. Equilibrium was established after 3 hours' operation.

1-*Hydroxy*cyclo*hexanealdehyde*.—1-Vinyl*cyclo*hexanol (12 g.) in ethyl acetate (120 ml.) was cooled to −75° and treated with a 5% excess of ozone. The solution was then hydrogenated by use of a palladium–calcium carbonate catalyst in a flask held at 0° by a cooling coil. Reduction was variable and in some cases was not observed although the same products were obtained in all cases. Evaporation of the ethyl acetate yielded an oil which was washed with 10% sodium carbonate solution (A) and extracted with ether, and the ethereal solution shaken with saturated sodium hydrogen sulphite during 2 days. The precipitate (6·5 g.) was decomposed with 10% sodium carbonate solution, and the resultant oil (3 g.) isolated with ether and combined with a further fraction (1 g.) derived from the bisulphite liquors. After prolonged standing partial crystallisation occurred. Recrystallisation from hexane gave the *aldehyde* as prisms (0·5 g.), m. p. 84° (Found: C, 65·6; H, 9·4. $C_7H_{12}O_2$ requires C, 65·6; H, 9·4%). Attempts to prepare a 2 : 4-dinitrophenylhydrazone (in alcoholic sulphuric acid) resulted in dehydration with formation of the derivative of *cyclo*hexene-1-aldehyde, m. p. 215° alone or mixed with an authentic sample (Heilbron, Jones, Richardson, and Sondheimer, *J.*, 1949, 737). The sodium carbonate washings (A) were made acid and extracted with ether. The ethereal residue crystallised from benzene–hexane to give 1-hydroxy*cyclo*hexanecarboxylic acid, m. p. 108° alone or mixed with an authentic sample (Bucherer, *Ber.*, 1894, **27**, 1231).

1-*Acetoxy*cyclo*hexanealdehyde*.—Similar ozonolysis of 1-acetoxyvinyl*cyclo*hexane (12 g.) yielded 1-*acetoxy*cyclo*hexanecarboxylic acid* (4 g.), which crystallised from hexane in plates, m. p. 103° (Found: C, 58·2; H, 7·4. $C_9H_{14}O_4$ requires C, 58·1; H,7·5%). Alkaline hydrolysis yielded the hydroxy-acid, m. p. and mixed m. p. 108°. The neutral fraction from the ozonolysis was distilled. The fraction, b. p. 80°/2·5 mm. (3 g.), consisted almost entirely of the acetoxy-aldehyde, as shown by the preparation of the 2 : 4-*dinitrophenylhydrazone* in high yield in acetic acid solution. Crystallisation from alcohol–ethyl acetate gave yellow plates, m. p. 158° (Found : C, 51·7; H, 5·2; N, 15·7. $C_{15}H_{18}O_6N_4$ requires C, 51·4; H, 5·1; N, 16·0%). The *semicarbazone* formed needles (from alcohol), m. p. 193° (Found : C, 53·3; H, 7·4; N, 18·9. $C_{10}H_{17}O_3N_3$ requires C, 52·9; H, 7·5; N, 18·5%). Attempted deacetoxylation of the acetoxy-aldehyde by 1 hour's refluxing (bath-temp. 300°) under nitrogen resulted in recovery of the starting material. However, *cyclo*hexene-1-aldehyde was obtained as its 2 : 4-dinitrophenylhydrazone from attempts to prepare the derivative from the acetoxy-aldehyde in alcoholic solution with sulphuric acid. Similar ozonolysis of 1-acetoxy-4-*iso*propyl-1-vinyl*cyclo*hexane (9 g.) gave the *acetoxy-acid* (4 g.), which crystallised from hexane as prisms, m. p. 107° (Found : C, 63·3; H, 8·5. $C_{12}H_{20}O_4$ requires C, 63·2; H, 8·8%). The neutral fraction (3·0 g.) consisted mainly of the acetoxy-aldehyde. The 2 : 4-*dinitrophenylhydrazone*, prepared in acetic acid, crystallised from alcohol–ethyl acetate in yellow needles, m. p. 202—204° (Found : C, 55·0; H, 6·2; N, 14·0. $C_{18}H_{24}O_6N_4$ requires C, 55·1; H, 6·1; N, 14·3%). The *semicarbazone* crystallised from ethyl acetate as needles, m. p. 198° (Found : C, 58·4; H, 8·6; N, 15·8. $C_{13}H_{23}O_3N_3$ requires C, 58·0; H, 8·6; N, 15·6%). All attempts to eliminate elements of acetic acid from the acetoxy-aldehyde failed, although preparation of the 2 : 4-dinitrophenylhydrazone in the presence of alcoholic sulphuric acid yielded the derivative of phellandral.

1-*Hydroxy*-4-iso*propyl*cyclo*hexanealdehyde*.—Ozonolysis of the corresponding vinyl compound (10 g.) gave an *acid* fraction (0·5 g.) which formed a sparingly soluble sodium salt and crystallised from benzene–hexane as plates, m. p. 105°, alone or mixed with a sample derived from the acetate (Found : C, 64·6; H, 9·8. $C_{10}H_{18}O_3$ requires C, 64·5; H, 9·7%). The neutral portion was shaken with saturated sodium hydrogen sulphite solution and left overnight. The precipitate was separated and decomposed with boiling 10% sodium carbonate solution. Isolation with ether gave a viscous oil which partly crystallised. Adherent oil was removed by solution in light petroleum (b. p. <40°) and filtration of the residue. Slow evaporation of the filtrate yielded further crops. Crystallisation from aqueous alcohol gave a micro-crystalline *aldehyde* (2·4 g.). The m. p. varied from 70° to 150°. Different samples showed the same analysis [Found : C, 70·5; H, 10·4%; *M* (Rast), 160. $C_{10}H_{18}O_2$ requires C, 70·6; H, 10·6%; *M*, 170]. The 2 : 4-*dinitrophenylhydrazone*, prepared in methyl alcohol containing 2% of sulphuric acid, crystallised from benzene–methanol as yellow needles, m. p. 184° (Found : C, 56·4; H, 6·6; N, 15·6. $C_{16}H_{22}O_5N_4$ requires C, 54·9; H, 6·3; N, 16·0%). This 2 : 4-dinitrophenylhydrazone underwent dehydration in hot alcoholic solution containing sulphuric acid (10%), yielding (±)-phellandral 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 198° (Found : C, 57·9; H, 5·9; N, 16·8. Calc. for $C_{16}H_{20}O_4N_4$: C, 57·9; H, 6·0; N, 16·9%). The hydroxy-aldehyde was recovered as the acetate after 2 hours' refluxing with acetic acid or acetic anhydride, and unchanged after 1 hour's boiling with 10% alcoholic sulphuric acid or heating for the same period with potassium hydrogen sulphate at 160°.

(±)-*Phellandral*.—(*a*) Direct formation of phellandral from the hydroxy-aldehyde (0·3 g.) was effected in low yield on treatment with redistilled phosphorus oxychloride (0·2 g.) at room temperature for 24 hr. Decomposition with ice and isolation with ether gave an oil, one half of which yielded the 2 : 4-dinitrophenylhydrazone (0·08 g.), m. p. and mixed m. p. 198°. The other portion was identified as its semicarbazone, m. p. and mixed m. p. 200°.

(*b*) Phellandral 2 : 4-dinitrophenylhydrazone (1 g.), derived from the hydroxy-aldehyde as above, was recovered unchanged after 48 hr. at room temperature in acetone (200 ml.) and hydrochloric acid (10 ml.). The 2 : 4-dinitrophenylhydrazone (0·5 g.) was also undecomposed after 3 hours' refluxing in chloroform (15 ml.) containing acetic acid (9 ml.), sodium acetate (0·23 g.), pyruvic acid (9 ml.), and water (3 ml.), during which period pyruvic acid (3 ml.) and water (2 ml.) were added in three portions. Recovery of (±)-phellandral from the phenylhydrazone was, however, effected by acting on it (5 g.) in chloroform (100 ml.) with pyruvic acid (100 ml.; B.D.H.) and hydrochloric acid in acetic acid (5 ml.; 4N) under reflux in nitrogen for 10 min. Dilution with water and chloroform and washing the latter with aqueous potassium carbonate gave on evaporation an oil which had b. p. 70°/1 mm. (1·4 g.), n_D^{15} 1·4880, n_D^{20} 1·4898, d_4^{15} 0·9430. This was identified as (±)-phellandral by preparation of its 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 198°, and its *p*-nitrophenylhydrazone, m. p. and mixed m. p. 163—164° (Found : C, 66·9; H, 7·8; N, 14·7. Calc. for $C_{16}H_{21}O_2N_3$: C, 66·9; H, 7·4, N; 14·6%). The semicarbazone had m. p. and mixed m. p. 200° (Found :

C, 63·6; H, 9·2; N, 19·7. Calc. for $C_{11}H_{19}ON_3$: C, 63·2; H, 9·2; N, 20·1%). Oxidation with silver oxide (Burger and Macbeth, *loc. cit.*) yielded (±)-phellandric acid, m. p. and mixed m. p. 143—144°. Phellandral (0·8 g.) was also recovered in about 85% yield from its dinitrophenylhydrazone (2 g.) by heating it in pyruvic acid (50 ml.; B.D.H.) at 100° in nitrogen for 4 hr. and isolation with chloroform.

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