81. *Reactions of αβ-Unsaturated Cyclic Aldehydes and Ketones. Part VII. Alcohols derived from Phellandral.*

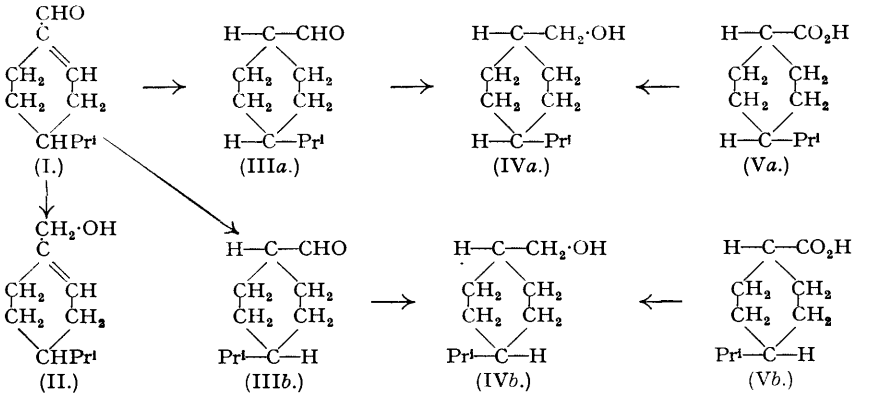
By J. P. E. Human, A. Killen Macbeth, and H. J. Rodda.

Phellandrol (4-*iso*propyl*cyclo*hex-1-enyl-1-carbinol) has been prepared by the Ponndorf reduction of phellandral, and characteristic derivatives are described. Dihydrophellandral and dihydrophellandrols have also been prepared, and the epimeric forms identified by their relationship to the 4-*iso*propyl*cyclo*hexyl-1-carbinols and corresponding carboxylic acids.

The study of alcohols related to simple carbonyl compounds isolated from natural products was undertaken some time ago with a view to the later identification of the alcohols in the essential oils themselves. In previous papers cumyl alcohol (*J.*, 1938, 1825) and the alcohols related to cryptone, 4-*iso*propyl*cyclo*hex-2-en-1-one (*J.*, 1938, 1820; 1939, 264, 518, 1531; 1948, 996), were described; and the reduction products of phellandral have now been examined.

The structure of phellandral has been established (*J.*, 1940, 808; 1946, 145) as 4-*iso*propyl-*cyclo*hex-1-en-1-aldehyde (I). Reduction by aluminium *iso*propoxide gives a crude alcohol from which, on repeated crystallisation of the *p*-nitrobenzoate and hydrolysis, pure phellandrol (II) is isolated in a yield approaching 50% of the crude material. The *p*-nitrobenzoate was found to be the best derivative for purification, although in the earlier experiments the hydrogen phthalate was used with fair success. In some of the Ponndorf reductions a higher-boiling fraction was isolated which was considered to be *diphellandryl ether*.

Phellandrol has b. p. 114°/5 mm., 122°/7 mm.; $\alpha_D^{24°}$ −99·5° (homogeneous; $l = 1$ dm.); $d_{30°}^{30°}$ 0·9311; $d_{4°}^{30°}$ 0·9252; $n_D^{20°}$ 1·4826. It gives a p-*nitrobenzoate*, a 3 : 5-*dinitrobenzoate*, a *phenylurethane*, and an *α-naphthylurethane*.



Dihydrophellandral was prepared by the catalytic hydrogenation of phellandral, using palladised charcoal. It can exist in two epimeric forms (III*a* and *b*), and two semicarbazones were readily isolated by fractional crystallisation. Cooke and Macbeth (*J.*, 1939, 1245) prepared and characterised the 4-*iso*propyl*cyclo*hexan-1-carboxylic acids (V*a* and *b*) and related carbinols (IV*a* and *b*) by hydrogenation of cuminic acid, and reduction of the epimeric esters of the hexahydrocuminic acids. These substances are therefore available for determining the configurations of the dihydrophellandrals and dihydrophellandrols. The dihydrophellandral samples regenerated from the two semicarbazones were both found to give *trans*-hexahydrocuminic acid (V*b*) on oxidation, and the semicarbazones would therefore appear to be derived from the same epimeric form of the aldehyde. The less soluble derivative, trans-4-iso*propyl*cyclo*hexen*-1-*aldehyde* α-*semicarbazone*, has m. p. 173°, and the more soluble β-*semicarbazone* melts at 139°. Dihydrophellandral was further characterised by a p-*nitrophenylhydrazone*, mustard-coloured needles, melting at 161°.

Samples of dihydrophellandrol were derived in three ways, namely, (*a*) the Ponndorf reduction of dihydrophellandral, (*b*) the hydrogenation of dihydrophellandral using platinum oxide (Adams) as catalyst, and (*c*) catalytic hydrogenation in the presence of Raney nickel. In all cases mixtures of the epimeric alcohols were obtained, the *cis*-form being identified by the *p*-nitrobenzoate (m. p. 54—55°) and the 3 : 5-dinitrobenzoate (m. p. 72°), whilst the presence of the *trans*-form was detected by the characteristic curved laths of the 3 : 5-dinitrobenzoate (m. p. 95°). It would thus appear that the isolation of *trans*-dihydrophellandral from both

of the semicarbazones described above is probably due either to the removal of a more soluble *cis*-derivative during the crystallisations of the semicarbazones, or to the transmutation of a labile *cis*- to a more stable *trans*-form during the hydrolysis.

Experimental.

Ponndorf Reduction of Phellandral.—The phellandral used in the reductions was part of a supply obtained in a large-scale separation from *E. cneorifolia*, and had α_D −133° (homogeneous; $l = 1$ dm.). In a typical reduction a solution of redistilled aluminium *iso*propoxide in dry *iso*propyl alcohol (200 c.c. of M; 1·2 equivs.) was placed in a flask attached to a metre-long column packed with glass beads, and fitted with a reflux divider. A further quantity of solvent (100 c.c.) was added, and after the flask and contents had been heated in a bath at 160° the aldehyde (75 g.), in dry *iso*propyl alcohol (85 c.c.), was run in through a funnel fitted with a calcium chloride tube, at such a rate that steady boiling was maintained. Using a high reflux ratio acetone was slowly distilled off until (6 hours) the distillate was acetone free. Most of the *iso*propyl alcohol was then removed under reduced pressure through a short bead column, and the residue was cooled, light petroleum (200 c.c.; b. p. 50—80°) was added, followed by crushed ice (300 g.), and then sulphuric acid was added slowly (50 c.c., 10N; 2·6 equivs.). The light petroleum layer was separated, the acid layer washed again with the same solvent, and the total extract washed successively with water, sodium carbonate solution, and water (twice). After drying ($MgSO_4$), the solvent was removed, leaving crude phellandrol (75 g.).

The crude phellandrol may be converted into the *p*-nitrobenzoate for purification by repeated crystallisation, but it is better to carry out a preliminary purification by fractional distillation through a well-lagged, short, bead column. A main fraction (almost 65%) boiling at 94—97°/2·0 mm. was collected, and converted into the *p*-nitrobenzoate. In a typical experiment the phellandrol (25 g.) was placed in a 500 c.c. flask fitted with a mechanical stirrer and protected from moisture. Dry benzene (35 c.c.) and excess pyridine (40 c.c.) were added, and a solution of *p*-nitrobenzoyl chloride (30 g.) in warm, dry benzene (65 c.c.) was run in during half-an-hour, the mixture being cooled to about 25° when necessary. After being left for 12 hours the solution was acidified (hydrochloric acid, 33%, 40 c.c.; water 350 c.c.) to remove pyridine, the benzene layer was collected, and successively washed with water, 10% sodium carbonate solution, and water. After the benzene had been removed by steam distillation the residual oil crystallised on cooling, and the nitrobenzoate was dried on a porous tile, and recrystallised from light petroleum and finally from methanol–water. *Phellandryl* p-*nitrobenzoate* had m. p. 67°, $[\alpha]_D^{16°}$ −56·6° (*c*, 6·2, in chloroform) (Found: N, 4·6%. $C_{17}H_{21}O_4N$ requires N, 4·5%).

In a typical hydrolysis of the *p*-nitrobenzoate, the ester (20 g.) was dissolved in methanol (100 c.c.) containing potassium hydroxide (4·1 g.) and water (5 c.c.). After being heated under reflux on the steam-bath for an hour, about half of the methyl alcohol was removed under reduced pressure, the residue was steam-distilled, and the distillate extracted with light petroleum. After the solution had been dried ($MgSO_4$) and the solvent removed, pure phellandrol distilled (b. p. 114°/5 mm.), and had the following constants: $\alpha_D^{20°}$ −99·95° (homogeneous; $l = 1$ dm.); $\alpha_D^{24°}$ −99·45° (homogeneous; $l = 1$ dm.); $d_{30°}^{30°}$ 0·9311; $d_{4°}^{30°}$ 0·9252; $n_D^{20°}$ 1·4826.

Phellandryl hydrogen phthalate. Phellandrol [18 g., $\alpha_D^{24°}$ −99·3 (homogeneous; $l = 1$ dm.)], phthalic anhydride (18 g.), and pyridine (60 c.c.) were heated with stirring for 6 hours at 60°. The resulting mixture was poured into sulphuric acid (10%, 600 c.c.), and extracted with ether. To the extract, mixed with crushed ice, about 90% of the theoretical amount of ice-cold sodium hydroxide solution was added with vigorous stirring, and the solution thereafter made alkaline with sodium carbonate. After the aqueous layer had been washed with ether it was acidified, and extracted with chloroform. A fine suspension of phthalic acid separated from the dried extract on standing, and after the solution had been centrifuged and the solvent removed the residual syrup crystallised on seeding. Yield 90%. Recrystallisation from light petroleum (40—60°) gave *phellandryl hydrogen phthalate* (11 g.) having m. p. 74°, $[\alpha]_D^{28°}$ −54·4 (*c*, 1·5, in chloroform) (Found: C, 71·45; H, 7·25. $C_{18}H_{22}O_4$ requires C, 71·45; H, 7·35%).

Phellandryl N-lævo*Menthylphthalamate.* A sample of phellandryl hydrogen phthalate (11 g.) was converted into the acid chloride by adding pyridine (2·95 g.) to a dry ethereal solution followed by the gradual addition of thionyl chloride (2·65 c.c.). The resultant mixture was treated with *lævo*menthylamine (6·62 c.c.) in pyridine (2·95 c.c.), and the crude *lævo*menthylphthalamate was obtained in over 80% yield. After recrystallisation from light petroleum (b. p. 60—90°) *phellandryl* N-lævo*menthylphthalamate* had m. p. 120° and $[\alpha]_D^{25°}$ −71·8° (Found: N, 3·25. $C_{28}H_{41}O_3N$ requires N, 3·2%). Hydrolysis of the menthylphthalamate by 10% methyl-alcoholic potassium hydroxide gave a sample of phellandrol (83% yield) after two distillations which had the same physical constants as the original alcohol.

To characterise phellandrol the following derivatives were also prepared. *Phellandryl phenylurethane*, recrystallised from light petroleum (60—90°), had m. p. 79°, $[\alpha]_D^{16°}$ −60·1° (*c*, 4·0, in chloroform) (Found: N, 5·2. $C_{17}H_{23}O_2N$ requires N, 5·15%). *Phellandryl* α-*naphthylurethane*, recrystallised from light petroleum, had m. p. 69·5°, $[\alpha]_D^{16°}$ −52·6° (*c*, 3·9, in chloroform) (Found: N, 4·4. $C_{21}H_{25}O_2N$ requires N, 4·35%). *Phellandryl* 3 : 5-*dinitrobenzoate* had m. p. 57·5°, $[\alpha]_D^{15°}$ −49·8° (*c*, 4·5, in chloroform) (Found: N, 8·15. $C_{17}H_{20}O_6N_2$ requires N, 8·05%).

Diphellandryl Ether.—In some of the Ponndorf reductions of phellandrol a higher-boiling component was isolated which appeared to be *diphellandryl ether*. In a typical case, after the reduction of phellandrol (90 g.) by the action of aluminium (6 g.) in *iso*propyl alcohol (300 c.c.) steam-distillation left a considerable amount of yellow polymerised product in the flask, and the distillate was extracted with ether. The extract, after being washed with sodium hydrogen sulphite solution (35%) and water, was dried (Na_2SO_4) and gave, on removal of the solvent, a first fraction (21 g.) boiling below 100°/1 mm., $n_D^{17°}$ 1·492. The residue, when transferred to a small flask and distilled over the open flame, gave a fraction, b. p. 170—180°/1 mm. It had $d_{19°}^{19°}$ 0·9351; $d_{4°}^{19°}$ 0·9337; $n_D^{19°}$ 1·4986 and $[\alpha]_D$ −71·4° (homogeneous) (Found: C, 82·9; H, 11·6%. $C_{20}H_{34}O$ requires C, 82·7; H, 11·8%). The compound was unsaturated, and absorbed bromine readily, but no crystalline derivative could be isolated.

Dihydrophellandral.—Phellandral was hydrogenated to dihydrophellandral in the presence of palladised charcoal, and the reduction has been carried out both at atmospheric pressure and in a high-pressure bomb with an initial pressure of 70 atmospheres of hydrogen. In both cases an appreciable amount of higher-boiling by-product was formed. For purification an ethereal extract of the crude dihydrophellandral was shaken with concentrated sodium hydrogen sulphite solution (35%). The dihydrophellandral quickly formed a hydrogen sulphite compound which was filtered off within a few minutes (the higher-boiling impurity slowly forms a hydrogen sulphite compound on standing). The washed hydrogen sulphite cake was decomposed by steam-distillation with sodium carbonate, and the dihydrophellandral, extracted by ether from the distillate, had b. p. 57—59°/1 mm. when fractionated under reduced pressure.

Dihydrophellandral formed two *semicarbazones* which were separated by repeated fractional crystallisation from alcohol. The major product separated as feathery pearly crystals having m. p. 173° (Found : C, 62·7; H, 10·0; N, 20·0. $C_{11}H_{21}ON_3$ requires C, 62·6; H, 9·95; N, 19·9%). The more soluble component required more rigid purification, and was finally obtained as small granular crystals having m. p. 139° (Found : C, 62·65; H, 10·2; N, 20·0%).

In each case dihydrophellandral was regenerated from the semicarbazone (17 g.) by steam-distillation with dilute sulphuric acid (200 c.c., 10%). The aldehyde was extracted from the distillate with ether, dried ($MgSO_4$), and distilled, b. p. 61·5°/1·5 mm., n_D 1·4572 (yield, 8 g.). In both cases the recovered aldehyde gave, on oxidation, *trans*-hexahydrocuminic acid so that the two semicarbazones are apparently derived from *trans*-dihydrophellandral. The oxidation was conveniently carried out by dissolving the aldehyde (1·8 g.) in alcohol (60 c.c.), and adding a solution of silver nitrate (5·4 g.) in water (20 c.c.). Sodium hydroxide solution (100 c.c., N/2) was gradually added with shaking during ½ hour, and after further mechanical shaking the mixture was left overnight. After the precipitated silver had been removed, and washed, the filtrate was saturated with carbon dioxide, the alcohol distilled off, and the residue concentrated to about 100 c.c. On cooling and being acidified *trans*-hexahydrocuminic acid was precipitated, which gave a *p*-chlorophenacyl ester, m. p. 97·5°, which was not depressed on admixture with an authentic sample (Cooke and Macbeth, *loc. cit.*).

Although the semicarbazones provide evidence of the presence of *trans*-dihydrophellandral alone, the aldehyde must be a mixture of the epimeric forms as the alcohol obtained on reduction gave derivatives of both *cis*- and *trans*-forms. Dihydrophellandral was further characterised as the p-*nitrophenylhydrazone*, fine mustard-coloured needles, m. p. 161°, after crystallisation from methanol (Found : C, 66·3; H, 8·2; N, 14·4. $C_{16}H_{23}O_2N_3$ requires C, 66·4; H, 8·0; N, 14·5%).

Dihydrophellandrol.—(1) Dihydrophellandral (41 g.) was converted into the alcohol on Ponndorf reduction using aluminium foil (4 g.) dissolved in *iso*propyl alcohol (200 c.c.). After working up dihydrophellandrol (30 g.) was obtained, having b. p. 98°/1 mm. and $n_D^{20°}$ 1·4692. The alcohol consisted mainly of *cis*-4-*iso*propyl*cyclo*hexyl-1-carbinol as it gives a *p*-nitrobenzoate, m. p. 54—55° (Found : C, 66·7; H, 7·7; N, 4·6. Calc. for $C_{17}H_{23}O_4N$: C, 66·8; H, 7·6; N, 4·6%), and an α-naphthylurethane, m. p. 78° (Found : C, 77·65; H, 8·2; N, 4·35. Calc. for $C_{21}H_{27}O_2N$: C, 77·5; H, 8·35; N, 4·3%), which are identical with the *cis*-derivatives previously described (Cooke and Macbeth, *loc. cit.*). (The m. p. of the α-naphthylurethane was previously wrongly recorded.) The 3 : 5-dinitrobenzoate, m. p. 71—72°, is also derived from the *cis*-epimer, but some of the characteristic curved laths, m. p. 95°, of the *trans*-ester were also isolated.

(2) A sample of phellandral (20 g.) was hydrogenated in alcoholic solution (40 c.c.) containing Adams platinum oxide catalyst (0·3 g.), the initial hydrogen pressure of 820 lb. per sq. in. gradually falling during 2 hours to a final value of 520 lb. per sq. in. The product was poured into water and extracted with ether. The ether solution was washed with hydrogen sulphite solution to remove traces of aldehyde (2—3 g. of hydrogen sulphite compound) and subsequently worked up giving a sample (12 g.) of dihydrophellandrol which had b. p. 90—93°/0·5 mm. The alcohol consisted of both the *cis*- and the *trans*-form, the former being identified as the *p*-nitrobenzoate, m. p. 54—55°, the latter being isolated as the curved laths of the 3 : 5-dinitrobenzoate, m. p. 95°.

(3) Hydrogenation of phellandral in the presence of Raney nickel also gave a mixed dihydrophellandrol from which the same two derivatives were isolated.

We are indebted to the Commonwealth Research Fund which enabled two of us (H. J. R. and J. P. E. H.) to take part in this work.

JOHNSON CHEMICAL LABORATORIES,
UNIVERSITY OF ADELAIDE.

[*Received, May 13th,* 1948.]