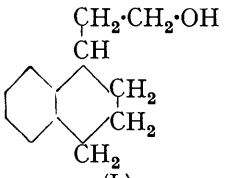
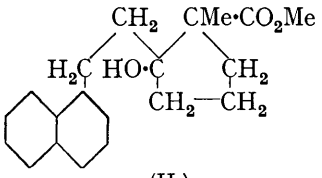
363. *Experiments on the Synthesis of Substances Related to the Sterols. Part VI.*

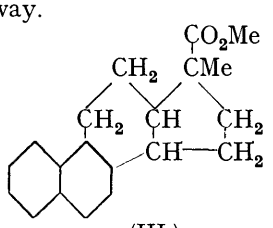
By Robert Robinson and James Walker.

This communication deals with exploratory work of a somewhat varied nature on the construction of molecular species required as intermediates or models for syntheses in the sterol (sex-hormone) group.

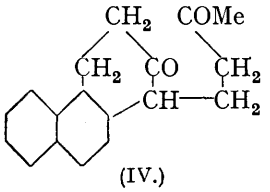
Continuation of the work described in Part V (this vol., p. 1414) was abandoned when it was found that the condensation of *p*-methoxyphenylsuccinic anhydride with veratrole was by no means so smooth a process as that of phenylsuccinic anhydride. We then considered applications of the Diels–Alder reaction * and, in view of the fact that *as.*-diphenylethylene (but not styrene) reacts as a conjugated diene with maleic anhydride (Wagner-Jauregg, *Annalen*, 1931, **491**, 1), studied the interaction of α-vinylnaphthalene and maleic anhydride —no addition occurred. It was then proposed to study the reactions of the conjugated vinyldihydronaphthalene (similar experiments have recently been described by Cohen, this vol., p. 429). The Bouveault–Blanc reduction of ethyl 3 : 4-dihydro-1-naphthyl acetate (v. Braun, Gruber, and Kirschbaum, *Ber.*, 1922, **55**, 3672; cf. Schroeter, Zadek, and Hoffmann, *Ber.*, 1925, **58**, 713) afforded, however, β-*tetrahydro*-1-*naphthylethyl alcohol* (I), and vinyldihydronaphthalene could not be obtained in this way.

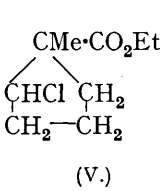

(I.)

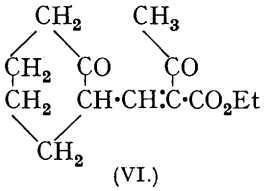

(II.)

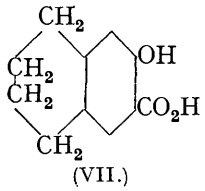

(III.)

The *ester* (II) was synthesised for dehydration to (III) [from which (IV) might be accessible and thence the angle-methyl ketone group of œstrone by successive pinacol and pinacolin formation], but this could not be accomplished. An interesting parallel is the failure of Dobson, Ferns, and Perkin (J., 1909, **95**, 2017) to remove the elements of hydrogen chloride from (V), even on boiling with diethylaniline (compare, however, the following communication).


(IV.)


(V.)


(VI.)


(VII.)

Alkylation of ethyl *cyclo*pentanonecarboxylate by means of methyl sulphate affords some *O*-methyl ether. The formation of a Grignard reagent from β-naphthylethyl chloride, as from the bromide (Harper, Kon, and Ruzicka, J., 1934, 127), involves the production of dinaphthylbutane as a by-product. This is not mentioned by Cook and Hewett, who employed naphthylmagnesium chloride (J., 1933, 1107), but in our case it rendered the purification of (II) a matter of great difficulty.

In connexion with our scheme for the use of the pinacol–pinacolin rearrangement as a stage in an œstrone synthesis, we have attempted to exploit condensation reactions of 2-formyl*cyclo*hexanone. When this substance was converted into crude methoxymethyl-

* Dr. A. R. Todd made some early experiments in this direction in collaboration with one of us. For example, he found that methyl-Δ^1-*cyclo*hexen-3-one would not form an adduct with butadiene or with hexatriene. The latter experiment represented a somewhat ambitious attempt to build up a reduced chrysene skeleton with two angle-methyl groups in one operation.

ene*cyclo*hexanone and condensed with ethyl sodioacetoacetate, an intermediate (probably VI) was formed in poor yield. On further treatment with boiling alcoholic sodium ethoxide, condensation and hydrolysis occurred and 6-hydroxytetralin-7-carboxylic acid (VII) was obtained. The acid has been previously prepared from 6-hydroxytetralin by means of the Kolbe reaction (Schroeter, *Annalen*, 1922, **426**, 147; D.R.-P., 357,663). In view of the theories of Mills and Nixon (J., 1930, 2510), the orientation of the substitution in this case must be regarded as exceptional, but the present synthesis confirms the structure put forward by Schroeter.

The aromatic nucleus of 2-methylchroman (Baker and Walker, this vol., p. 646) could not be reduced catalytically; and other possible avenues of approach to the desired 1 : 5-diketones of the *cyclo*hexane series are being explored.

Experimental.

β-*Tetrahydro*-1-*naphthylethyl Alcohol*.—Ethyl 3 : 4-dihydro-1-naphthylacetate has been obtained in improved yields. Zinc filings (23 g.) were added to a mixture of ethyl bromoacetate (40 c.c.), α-tetralone (45 c.c.), and dry benzene (240 c.c.). Eventually there were isolated 43 g., b. p. 170—175°/13 mm.; $n_D^{11°}$ 1·5592 (v. Braun, Gruber, and Kirschbaum cite a 50% yield, b. p. 183—184°/16 mm.). The condensation of α-tetralone with ethyl cyanoacetate or with cyanoacetic acid could not be effected under any of the standard conditions.

A solution of ethyl dihydronaphthylacetate (37 g.) in anhydrous alcohol (150 c.c.) was added as quickly as possible to sodium (25 g.) in a flask heated in an oil-bath at 160°. Solution of the sodium was completed by the addition of alcohol, aqueous alcohol and water, and after removal of the alcohol in steam the product was collected (24 g.) by means of ether. The colourless oil (20 g. or 68%), b. p. 158—160°/11 mm., solidified on cooling, but could not be crystallised (Found: C, 81·4; H, 8·9. $C_{12}H_{16}O$ requires C, 81·8; H, 9·1%).

Methyl 2-β-1′-*Naphthylethyl*-1-*methyl*cyclo*pentan*-2-*ol*-1-*carboxylate* (II).—(a) The preparation of β-1-naphthylethyl alcohol (Ruzicka, Ehmann, Goldberg, and Hösli, *Helv. Chim. Acta*, 1933, **16**, 833; Haworth and Mavin, J., 1933, 1014; Cook and Hewett, *ibid.*, p. 1107) has been improved. 1-Bromonaphthalene (200 g., b. p. 144—145°/18 mm., free from naphthalene and tribromonaphthalene) was used for the preparation of a Grignard solution (24 g. of magnesium, 400 c.c. of dry ether, and 400 c.c. of benzene) in an apparatus provided with a mercury-sealed stirrer. Ethylene oxide (50 g.), dissolved in ether (200 c.c.), was introduced at — 10° and the product was isolated after 12 hours; b. p. 176—180°/15 mm. (124 g. or 75%).

(b) A mixture of the alcohol (124 g.), hydrobromic acid (160 c. c. of constant b. p.), and sulphuric acid (50 c.c.) was refluxed for 16 hours. The product (142 g.) had b. p. 174—178°/11 mm., $n_D^{14·5°}$ 1·6422. In the preparation of the chloride, the details given by Cook and Hewett (*loc. cit.*) were followed, but chloroform was used as diluent.

(c) The ethyl esterification of adipic acid by the method of van Rysselberge (*Bull. Acad. roy. Belg.*, 1926, **12**, 171) works well on a 300 g. scale; b. p. 124°/11 mm., $n_D^{17°}$ 1·4277 (yield, 92%), and the details given by this author for the preparation of ethyl *cyclo*pentanonecarboxylate were followed except that the treatment with cold aqueous potassium hydroxide was found to be unnecessary (yield, 75%; lit., 66—68%).

(d) Methylation of ethyl *cyclo*pentanonecarboxylate by the method of Cornubert and Borrel (*Bull. Soc. chim.*, 1930, **47**, 304) was found to be quite unreliable, as rupture of the *cyclo*pentane ring occurred to a large extent (cf. also Kon, J., 1933, 1085). The following method gave satisfactory results. Sodium (23 g.) was powdered under toluene, and dry benzene (100 c.c.) added. To the cold suspension, a solution of ethyl *cyclo*pentanonecarboxylate (156 g.) in dry benzene (200 c.c.) was carefully added, and the mixture refluxed for 1·5—2 hours. The solid part of the cooled product was broken up, methyl iodide (94 c.c.) added, and the mixture kept at room temperature until the reaction was completed. On working up, a colourless oil (126 g. or 74%), b. p. 105—106°/14 mm., $n_D^{16°}$ 1·4479, was isolated.

(e) Owing to the large amounts of ethyl methyl*cyclo*pentanonecarboxylate required, an attempt was made to effect an economy by using methyl sulphate in place of methyl iodide. Ethyl *cyclo*pentanonecarboxylate (30 g.) was converted into the sodio-derivative as described above (4·4 g. of sodium); when the reaction was complete, methyl sulphate (20 c.c.) was added, and the mixture maintained at 100° for 5 hours. The product, worked up as usual, was a colourless oil (21 g.), b. p. 104—105°/14 mm., $n_D^{10°}$ 1·4565.

The methyl-alcoholic solution decolorised bromine instantly, and estimation of alkoxyl

content (kindly carried out by Mr. J. D. Rose), allowing for the ester group, indicated *O*-methylation to the extent of 27·3%.

(f) The condensation of β-1-naphthylethyl bromide with ethyl methyl*cyclo*pentanonecarboxylate was repeated several times with consistent results. To the cooled solution of a Grignard reagent prepared from naphthylethyl bromide (100 g.) (the chloride also was used with similar results), magnesium (10 g.), and dry ether (600 c.c.), a solution of ethyl methyl*cyclo*pentanonecarboxylate (73 g.) in dry ether (100 c.c.) was added with stirring, and the mixture kept for 17 hours. The product was isolated in the normal way after addition of ammonium chloride solution; a somewhat viscous oil (72 g.), b. p. 175—230°/0·4 mm., $n_D^{14°}$ 1·5470, was obtained. Further fractionation gave (I) 175°/0·5 mm. (8·5 g.), (II) 175—200°/0·5 mm. (14·3 g.), (III) 200—220°/0·5 mm. (mainly 210—215°/0·5 mm.) (31·5 g.), (IV) 220—230°/0·4 mm. (10·8 g.).

Fraction (II) gave analytical figures which showed it to consist of an impure condensation product of the keto-ester itself (Found: C, 70·9; H, 7·6%). Fraction (III) gave analytical figures approximating to the theoretical for the required product (Found, in samples from two different preparations: C, 76·1, 76·2; H, 8·0, 7·6. $C_{21}H_{26}O_3$ requires C, 77·3; H, 8·0%). Fraction (IV) partly crystallised when kept in the ice-chest, but inoculation of fraction (III) with fraction (IV) did not induce crystallisation. Fraction (IV) gave a picrate, m. p. 172—173° (not crystallised), with alcoholic picric acid (Harper, Kon, and Ruzicka, *loc. cit.*, record m. p. 174° for αδ-di-1-naphthylbutane dipicrate). The still residue solidified and after crystallisation from acetone had m. p. 101° (Harper, Kon, and Ruzicka, *loc. cit.*, record m. p. 102° for αδ-di-1-naphthylbutane).

Fractions (III) and (IV) were united (42 g.) and refluxed for 8 hours with 10% methyl-alcoholic potassium hydroxide (80 c.c.). The product was poured into water, acidified, and extracted with ether. The extract was washed several times with sodium carbonate solution, dried, and fractionated, crude dinaphthylbutane (9·7 g.) being obtained. The sodium carbonate washings, on acidification, extraction with ether, and fractionation of the dried extract, yielded a light brown, viscous acid (28 g.). This was treated with an ethereal solution of diazomethane (from 25 g. of nitrosomethylurea), and after 30 minutes the excess was decomposed with a few drops of glacial acetic acid and the product was fractionated. A fairly mobile, yellow oil (23 g.) was obtained, b. p. 206—214°/0·4 mm., $n_D^{15°}$ 1·5565, $n_D^{20°}$ 1·5540 (Found: C, 77·0; H, 7·9. $C_{20}H_{24}O_3$ requires C, 76·9; H, 7·7%).

In order to characterise the substance this *methyl* ester (0·5 g.) was mixed with aqueous methylamine (7 c.c. of 33%); after a few days the *methylamide* crystallised. On recrystallisation from benzene–light petroleum (b. p. 80—100°) (1 : 1), very fine, colourless needles were obtained, m. p. 100° (Found: C, 77·2; H, 8·2; N, 4·5. $C_{20}H_{25}O_2N$ requires C, 77·2; H, 8·0; N, 4·5%).

(g) The dehydration of this methyl ester was attempted with sulphuric acid at 0° (cf. Bogert, *Science*, 1933, **77**, 289; Bogert and Davidson, *J. Amer. Chem. Soc.*, 1934, **56**, 185; Bogert, Davidson, and Apfelbaum, *ibid.*, p. 959), with anhydrous formic acid at 100° (Wallach, *Annalen*, 1896, **291**, 361; 1907, **356**, 243), with potassium hydrogen sulphate at 185°, with thionyl chloride and pyridine (also quinoline) (cf. Darzens, *Compt. rend.*, 1911, **152**, 1601), with phosphoryl chloride in boiling benzene solution, with phosphoric oxide in toluene solution at 100°, and finally with phosphorus pentachloride followed by alcoholic potassium hydroxide. In most cases the unchanged ester was recovered, but some unsaturated product was obtained in the experiments with phosphoryl chloride and with phosphorus pentachloride and alkali.

*Methylation of Hydroxymethylene*cyclo*hexanone.*—Methylation under the conditions used by Bishop, Claisen, and Sinclair (*Annalen*, 1894, **281**, 366) for the preparation of ethers of hydroxymethylenecamphor led almost entirely to *C*-methylation, accompanied by hydrolysis with the production of 2-methyl*cyclo*hexanone, b. p. 60—66°/17 mm., $n_D^{18°}$ 1·4538 (cf. Sen and Mondal, *J. Indian Chem. Soc.*, 1928, **5**, 609). There was a small fraction (less than 10%) distilling to 110°/16 mm., $n_D^{18°}$ 1·4883, which gave an intense violet ferric reaction, apparently due to hydrolysis (Found: MeO, 7·1%).

Methylation with methyl sulphate and caustic alkali gave a product containing the desired *O*-methyl ether. Hydroxymethylene*cyclo*hexanone (21 g.) was dissolved in an aqueous solution of potassium hydroxide (9·3 g. in 150 c.c.), and methyl sulphate (15·8 c.c.) added to the cold solution, which was shaken mechanically for 12 hours and then extracted with ether. The extract was rapidly washed once with 2% sodium hydroxide solution (100 c.c.), dried over sodium sulphate, and fractionated; a colourless mobile oil (12·3 g.) distilled at 75—80°/13 mm., $n_D^{18°}$ 1·4854. This compound rapidly decomposed, turning green within a few minutes and dark

green after 1—2 hours (Found in two different specimens : MeO, 12·9, 11·9. $C_8H_{12}O_2$ requires MeO, 22·7%).

*Condensation of Crude Methoxymethylene*cyclo*hexanone with Ethyl Acetoacetate.*—The product from the above-described methylation experiment was added to a solution of ethyl acetoacetate (13 g.) in absolute alcoholic sodium ethoxide (2·3 g. of sodium in 60 c.c.). A solid slowly separated at room temperature and after 2 days the mixture was acidified with acetic acid and mixed with ether and water. The ethereal solution was washed twice with 10% sodium hydroxide solution, dried, and fractionated, yielding a viscous oil (5·2 g.), which gave no immediate colour with ferric chloride but slowly developed a brown-violet coloration. This material (1·2 g.) was dissolved in alcoholic sodium ethoxide (0·2 g. of sodium in 5 c.c.), kept for 30 minutes in the cold, and heated on the steam-bath for 2 hours; a solid then separated. Water and ether were added and the separated aqueous layer was acidified and extracted with ether. The extract was dried over sodium sulphate and evaporated, yielding a brown oil (0·9 g.), which crystallised on complete removal of the solvent. Recrystallisation from 20% acetic acid (norit) gave long, narrow, rectangular plates, m. p. 178° (Found : C, 68·9; H, 6·2. Calc. for $C_{11}H_{12}O_3$: C, 68·8; H, 6·2%). The compound gave a violet ferric reaction indistinguishable from that given by salicylic acid; 6-hydroxytetralin-7-carboxylic acid (*loc. cit.*) is stated to have m. p. 177—178°.

The authors thank the Carnegie Trust for the Universities of Scotland for a Fellowship awarded to one of them.

Dyson Perrins Laboratory, Oxford University. [*Received, August 1st,* 1935.]