206. Cannabis Indica. *Part IV. The Synthesis of Some Tetrahydrodibenzopyran Derivatives.*

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A general method for the synthesis of 2 : 2-dimethyl-3′ : 4′ : 5′ : 6′-tetrahydrodibenzopyrans by the action of excess of methylmagnesium iodide on 3 : 4-*cyclo*hexenocoumarins is described. The compounds prepared include 6″-*hydroxy*-2 : 2 : 5′-*trimethyl*-4″-n-*amyl*-3′ : 4′ : 5′ : 6′-*tetrahydrodibenzopyran* (V), which may be a tetrahydrocannabinol (cf. Part II, this vol., p. 649). Several of the synthetic substances have been tested on rabbits by the Gayer hashish test, but all were inactive at a dosage of 5 mg./kg. None of the compounds prepared gave a positive Beam test (red-violet colour with alcoholic potash). Although hydroxy-3 : 4-*cyclo*hexenocoumarins could be prepared from quinol and from resorcinol derivatives, no such compounds could be synthesised from derivatives of catechol.

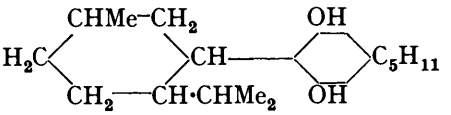
In Part III (preceding paper) the application of the Bamberger reaction to the synthesis of dibenzopyrans related to cannabinol was described. This type of reaction has obvious limitations and, amongst others, methods have been investigated which involve the synthesis of partially hydrogenated dibenzopyrans which could subsequently be dehydrogenated to give cannabinol types. The use of such methods has an added advantage in that they might be applied to the synthesis of other constituents of *Cannabis* resin. Cannabidiol, a constituent of American (Adams, Hunt, and Clark, *J. Amer. Chem. Soc.*, 1940, **62**, 196) and of Egyptian hashish (Jacob and Todd, *Nature*, 1940, **145**, 350; this vol., p. 649), is a doubly unsaturated derivative of menthylolivetol (I) (Adams, Hunt, and Clark, *loc. cit.*, p. 735); the exact location of the double bonds is not certain, although it is known that neither can be conjugated with the aromatic nucleus (Jacob and Todd, this vol., p. 649). Re-examination of the spectrum of cannabidiol by Dr. A. E. Gillam of this Department has shown it to possess a strong absorption band in the neighbourhood of 2300 A. (ε *ca.* 10,000), which suggests the presence of a conjugated system in which one double bond is exocyclic. On the grounds of common occurrence it is probable that the orientation of substituents in cannabidiol and cannabinol is the same, *i.e.*, that the latter is simply a dibenzopyran derivative formed by cyclisation and dehydrogenation of the former. Cannabol, which has been obtained in very small amount from Indian hashish (Jacob and Todd, *Nature*, 1940, **145**, 350), may be a cyclised isomer of cannabidiol and the general properties of the *Cannabis* resins suggest that they may contain complex mixtures of compounds related to these three individuals but differing from each other in degree of unsaturation and location of double bonds.

The present communication describes a series of experiments designed to test the validity of the synthetic methods and to pave the way for the synthesis of cannabinol. The first step was the condensation of cyclic β-ketonic esters with dihydric phenols to give derivatives of 3 : 4-*cyclo*hexenocoumarin (II). Several coumarins of this type have already been described: Dieckmann (*Annalen*, 1907, **317**, 27) prepared 7-hydroxy-3 : 4-*cyclo*hexenocoumarin from ethyl *cyclo*hexanone-2-carboxylate and resorcinol and Ahmad and Desai (*Chem. Abstr.*, 1938, 4562, 9066) synthesised in analogous fashion 7-hydroxy-5′-methyl-3 : 4-*cyclo*hexenocoumarin from resorcinol and the coumarins (III; $R_1 = H$, $R_2 = Me$) and (III; $R_1 = R_2 = Me$) from orcinol. We prepared the above compounds by the normal v. Pechmann procedure, using concentrated sulphuric acid as condensing agent. The products had the properties recorded by the above workers, save that 7-hydroxy-5′-methyl-3 : 4-*cyclo*hexenocoumarin had m. p. 199—200°, whereas Ahmad and Desai (*loc. cit.*, 9066) give m. p. 142°; possibly this figure is a misprint. The orientation of these compounds is confirmed by the fact that the resorcinol products give no coloration with 2 : 6-dichloroquinonechloroimide and the orcinol products having the *p*-position to the hydroxyl group unsubstituted give a blue colour with this reagent (indophenol test; cf. Gibbs, *J. Biol. Chem.*, 1927, **72**, 649). With quinol as phenolic component in the *cyclo*hexenocoumarin synthesis, 6-*hydroxy*-3 : 4-cyclo*hexenocoumarin* and 6-*hydroxy*-5′-*methyl*-3 : 4-cyclo*hexenocoumarin* were obtained, although the yields were poor. With catechol, guaiacol, or vanillic acid, no coumarin formation could be detected.

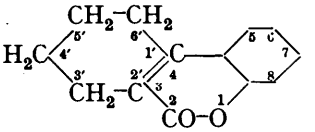
When the acetates of the various *cyclo*hexenocoumarins were treated in anisole solution with an excess of methylmagnesium iodide, they yielded directly the corresponding hydroxylated derivatives of 2 : 2-dimethyl-3′ : 4′ : 5′ : 6′-tetrahydrodibenzopyran (IV). No intermediate products were isolated. The individual compounds were colourless crystalline solids which were characterised as acetates.

The successful outcome of these model experiments led to their extension to the synthesis of 6″-*hydroxy*-2 : 2 : 5′-*trimethyl*-4″-n-*amyl*-3′ : 4′ : 5′ : 6′-*tetrahydrodibenzopyran* (V). Olivetol (5-*n*-amylresorcinol) condensed smoothly with ethyl 1-methyl*cyclo*hexan-3-one-4-carboxylate to give 5-*hydroxy*-5′-*methyl*-7-n-*amyl*-3 : 4-cyclo*hexenocoumarin* (III; R_1=Me, $R_2 = C_5H_{11}$); the *acetate* of this product, treated with methylmagnesium iodide, afforded (V) as a viscous resin which has not yet been crystallised. It may be noted that (V) is probably a tetrahydrocannabinol (cf. Jacob and Todd, this vol., p. 649) and experiments are now in progress on its dehydrogenation with the object of achieving the synthesis of cannabinol itself. Absorption spectrum measurements carried out on the synthetic

tetrahydrodibenzopyran derivatives described afford additional evidence for the view that cannabinol, which has a single maximum at 2850 A., cannot be a derivative of 4''- or 5''-hydroxydibenzopyran (cf. Jacob and Todd, *loc. cit.*). Of the compounds examined, only those bearing a hydroxyl in position 6'' showed a single absorption maximum; 4''- and 5''-hydroxy-compounds showed two maxima. Several of these synthetic tetrahydrodibenzopyrans have been tested on rabbits by the Gayer test by Prof. A. D. Macdonald of this University, to whom we are deeply indebted. At a dose level of 5 mg. per kg. body weight the following compounds were completely inactive: 4''-hydroxy-2 : 2-dimethyl-3' : 4' : 5' : 6'-tetrahydrodibenzopyran and its acetate, 4''-hydroxy-2 : 2 : 5'-trimethyl-3' : 4' : 5' : 6'-tetrahydrodibenzopyran and 6''-hydroxy-2 : 2 : 5' : 4''-tetramethyl-3' : 4' : 5' : 6'-tetrahydrodibenzopyran. Tests on (V) are not yet complete.



(I.)



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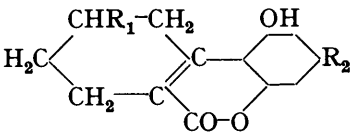

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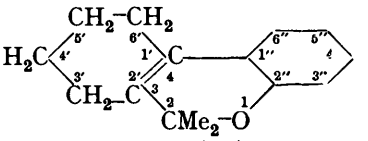

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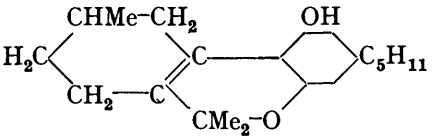

(V.)

Experimental.

6-*Hydroxy*-3 : 4-cyclo*hexenocoumarin.* Concentrated sulphuric acid (80 g.) was slowly added to a suspension of quinol (30 g.) in ethyl *cyclo*hexanone-2-carboxylate (34 g.). The dark red mixture was then warmed gently to bring all the solid into solution, left at room temperature for 24 hours, and poured on ice. The red sticky precipitate was recrystallised several times from alcohol (charcoal). The *product* (6 g.) formed very pale yellow prisms, m. p. 239—240° (Found: C, 71·6; H, 5·7. $C_{13}H_{12}O_3$ requires C, 72·2; H, 5·5%).

6-*Hydroxy*-5'-*methyl*-3 : 4-cyclo*hexenocoumarin*, obtained in small yield (0·25 g.) by the condensation of quinol (5·2 g.) with ethyl 1-methyl*cyclo*hexan-3-one-4-carboxylate (9·2 g.) in presence of concentrated sulphuric acid (21 g.) as above, and recrystallised from aqueous alcohol, formed almost colourless needles, m. p. 246° (Found: C, 73·2; H, 6·3. $C_{14}H_{14}O_3$ requires C, 73·1; H, 6·1%).

7-Hydroxy-5'-methyl-3 : 4-*cyclo*hexenocoumarin, prepared in analogous fashion from resorcinol and ethyl 1-methyl*cyclo*hexan-3-one-4-carboxylate, crystallised from alcohol in pale yellow diamond-shaped plates, m. p. 199—200° (Found: C, 72·9; H, 6·1; *M*, 227. Calc. for $C_{14}H_{14}O_3$: C, 73·1; H, 6·1%; *M*, 230). Its yellowish alkaline solution showed a strong blue fluorescence.

The indophenol test for all three compounds was negative.

5-*Hydroxy*-5'-*methyl*-7-n-*amyl*-3 : 4-cyclo*hexenocoumarin.*—Olivetol monohydrate (1·05 g.) condensed smoothly with ethyl 1-methyl*cyclo*hexan-3-one-4-carboxylate (0·96 g.) in presence of concentrated sulphuric acid (2·5 c.c.). The product (1·6 g.) crystallised from aqueous alcohol in colourless needles, m. p. 177° (Found: C, 75·7; H, 8·3. $C_{19}H_{24}O_3$ requires C, 76·0; H, 8·0%). The *substance* showed a yellow colour in alkaline solution. As the indophenol test is normally carried out under weakly alkaline conditions, the effect of this yellow colour was to produce a blue-green solution with 2 : 6-dichloroquinonechloroimide; subsequent addition of a little acid caused the solution to turn pure blue and the substance having the blue colour could be extracted with amyl alcohol. A similar state of affairs was noticed with the corresponding 7-methyl analogue derived from orcinol.

Acetoxy-3 : 4-cyclo*hexenocoumarins*.—The following acetoxy-compounds were prepared by refluxing the corresponding hydroxy*cyclo*hexenocoumarins with acetic anhydride in presence of pyridine and were crystallised from alcohol: 7-*Acetoxy*-3 : 4-cyclo*hexenocoumarin*, long colourless needles, m. p. 185—186° (Found: C, 69·7; H, 5·5. $C_{15}H_{14}O_4$ requires C, 69·8; H, 5·4%); 7-*acetoxy*-5′-*methyl*-3 : 4-cyclo*hexenocoumarin*, colourless prisms, m. p. 132° (Found: C, 70·4; H, 6·1. $C_{16}H_{16}O_4$ requires C, 70·6; H, 5·9%); 6-*acetoxy*-3 : 4-cyclo*hexenocoumarin*, colourless needles, m. p. 139—140° (Found: C, 69·8; H, 5·7. $C_{15}H_{14}O_4$ requires C, 69·8; H, 5·4%); 5-*acetoxy*-7-*methyl*-3 : 4-cyclo*hexenocoumarin*, colourless needles, m. p. 124° (Found: C, 70·4; H, 6·2. $C_{16}H_{16}O_4$ requires C, 70·6; H, 5·9%); 5-*acetoxy*-5′-*methyl*-7-n-*amyl*-3 : 4-cyclo*hexenocoumarin*, colourless prisms, m. p. 82—83° (Found: C, 73·6; H, 7·8. $C_{21}H_{26}O_4$ requires C, 73·7; H, 7·6%).

4″-*Hydroxy*-2 : 2-*dimethyl*-3′ : 4′ : 5′ : 6′-*tetrahydrodibenzopyran*.—A solution of 7-acetoxy-3 : 4-*cyclo*hexenocoumarin (28 g.) in dry anisole (600 c.c.) was added slowly at room temperature to a solution of methylmagnesium iodide (from 100 g. of methyl iodide and 17 g. of magnesium) in anisole. The mixture was heated on the steam-bath for 8 hours, cooled, and decomposed with ice and dilute sulphuric acid, and the anisole removed by steam-distillation. The residue was extracted with ether, and the reddish extract washed with aqueous sodium bicarbonate, sodium bisulphate, and finally with water, dried over anhydrous sodium sulphate, and evaporated. The solid thus obtained was recrystallised several times from benzene and formed colourless prisms (14 g.), m. p. 135° (Found: C, 78·5; H, 8·0. $C_{15}H_{18}O_2$ requires C, 78·3; H, 7·8%). Absorption maxima in alcohol, 2760 A. (ε, 7250) and 3050 A. (ε, 6900). The *substance* gave no coloration with alcoholic potash or with 2 : 6-dichloroquinonechloroimide. On warming with acetic anhydride in pyridine solution the *acetate* was obtained; it separated from alcohol in colourless prisms, m. p. 66° (Found: C, 75·0; H, 7·4. $C_{17}H_{20}O_3$ requires C, 75·0; H, 7·3%). In alcoholic solution the acetate had absorption maxima at 2680 A. (ε, 6240) and 3050 A. (ε, 6780).

4″-*Hydroxy*-2 : 2 : 5′-*trimethyl*-3′ : 4′ : 5′ : 6′-*tetrahydrodibenzopyran*.—Prepared, as described above, from 7-acetoxy-5′-methyl-3 : 4-*cyclo*hexenocoumarin and methylmagnesium iodide, the crude product, a red semi-solid resin, was distilled at 0·025 mm. At 154° a yellowish oil came over and quickly solidified. Recrystallised from ether–light petroleum (b. p. 40—60°), it formed colourless leaflets, m. p. 144—145° (Found: C, 78·5; H, 8·4. $C_{16}H_{20}O_2$ requires C, 78·7; H, 8·2%). The *substance* gave no coloration with alcoholic potash and the indophenol test was negative. In alcoholic solution it showed absorption maxima at 2760 A. (ε, 7950) and 3050 A. (ε, 7730). The *acetate*, prepared by warming with acetic anhydride in pyridine solution, was a faintly yellowish oil distilling at 160—165° (bath temp.)/0·05 mm. (Found: C, 75·3; H, 8·0. $C_{18}H_{22}O_3$ requires C, 75·5; H, 7·7%); it solidified after several days and then recrystallised from alcohol in colourless prisms, m. p. 58°.

5″-*Hydroxy*-2 : 2-*dimethyl*-3′ : 4′ : 5′ : 6′-*tetrahydrodibenzopyran*.—Prepared from 6-acetoxy-3 : 4-*cyclo*hexenocoumarin and methylmagnesium iodide, the crude product was a viscous oil, which yielded a pale yellow solid at 150°/0·02 mm. The latter crystallised from light petroleum (b. p. 60—80°) in colourless needles, m. p. 130° (Found: C, 78·3; H, 8·2. $C_{15}H_{18}O_2$ requires C, 78·3; H, 7·8%). Yield, 60%. The *product* gave no coloration with either alcoholic potash or 2 : 6-dichloroquinonechloroimide. Absorption maxima in alcohol, 2640 A. (ε, 5550) and 3280 A. (ε, 5150).

6″-*Hydroxy*-2 : 2 : 4″-*trimethyl*-3′ : 4′ : 5′ : 6′-*tetrahydrodibenzopyran*.—Prepared as above from 5-acetoxy-7-methyl-3 : 4-*cyclo*hexenocoumarin, the crude product, recrystallised from benzene or light petroleum (b. p. 60—80°), formed fine colourless plates, m. p. 138° (Found: C, 78·3; H, 8·4. $C_{16}H_{20}O_2$ requires C, 78·7; H, 8·2%). Yield, 60%. The *substance* dissolved in alkali to a colourless solution and gave a blue colour with 2 : 6-dichloroquinonechloroimide. In alcoholic solution it had an absorption maximum at 2790 A. (ε, 10370). The *acetate*, prepared in the usual manner, separated from alcohol in colourless octahedra, m. p. 107—108° (Found: C, 75·2; H, 8·0. $C_{18}H_{22}O_3$ requires C, 75·5; H, 7·7%).

6″-*Hydroxy*-2 : 2 : 5′ : 4″-*tetramethyl*-3′ : 4′ : 5′ : 6′-*tetrahydrodibenzopyran*.—The crude product from the reaction between methylmagnesium iodide and 5-acetoxy-5′ : 7-dimethyl-3 : 4-*cyclo*hexenocoumarin was recrystallised once from benzene and twice from light petroleum (b. p. 60—80°); colourless plates, m. p. 112—113°, were obtained (Found: C, 79·2; H, 8·7. $C_{17}H_{22}O_2$ requires C, 79·1; H, 8·5%). The *substance* dissolved in alkali to a colourless solution and gave a blue colour in the indophenol test. In alcoholic solution it had an absorption maximum at 2790 A. (ε, 10,980). Its *acetate* formed colourless feathery needles, m. p. 124° (Found: C, 76·0; H, 8·2. $C_{19}H_{24}O_3$ requires C, 76·0; H, 8·0%).

6″-*Hydroxy*-2 : 2 : 5′-*trimethyl*-4″-n-*amyl*-3′ : 4′ : 5′ : 6′-*tetrahydrodibenzopyran* (V).—Prepared in analogous fashion from the acetate of (III; R_1 = Me, R_2 = C_5H_{11}), the product was

a thick purplish resin, which distilled at 165—175° (bath temp.)/0·02 mm. (Found : C, 80·9; H, 10·2. $C_{21}H_{30}O_2$ requires C, 80·2; H, 9·6%). The *substance*, which was still slightly coloured, has not yet been crystallised. It gave a blue coloration with 2 : 6-dichloroquinonechloroimide, but no colour with alcoholic potash; it was insoluble in aqueous sodium hydroxide. In alcoholic solution the substance showed an absorption maximum at 2755 A. (ε, 11,130).

(*Note added in proof.*) Since this paper was submitted we have successfully dehydrogenated the acetyl derivative of (V) with palladised charcoal. The deacetylated product, 6''-hydroxy-2 : 2 : 5'-trimethyl-4''-*n*-amyldibenzopyran, was identified as cannabinol by conversion into its *p*-nitrobenzoate, m. p. 163—164°, undepressed on admixture with an authentic specimen (m. p. 162—163°) prepared from natural cannabinol. Full details of these experiments will be published separately.

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