264. Cannabis Indica. *Part V. The Synthesis of Cannabinol.*

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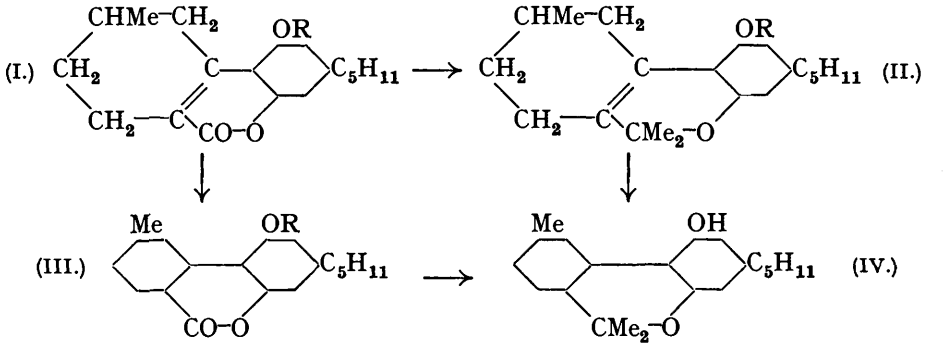
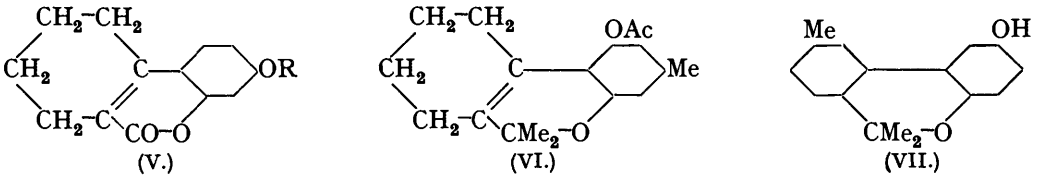
A series of experiments on the dehydrogenation of derivatives of 3 : 4-*cyclo*hexenocoumarin and of 2 : 2-dimethyl-3′ : 4′ : 5′ : 6′-tetrahydrodibenzopyran have been carried out. By methods derived from these, 6″-*hydroxy*-2 : 2 : 5′-*trimethyl*-4″-n-*amyldibenzopyran* (IV) has been synthesised by two routes from compounds described in Part IV (this vol., p. 1121). The identity of the product with cannabinol, a constituent of Indian and Egyptian hashish, was confirmed by comparison of its acetate and *p*-nitrobenzoate with the corresponding esters of the natural material.

In previous papers of this series evidence has been presented for the view that cannabinol, a constituent of *Cannabis indica* resin first isolated by Wood, Spivey, and Easterfield (J., 1896, **69**, 539; 1899, **75**, 20), is 6″-*hydroxy*-2 : 2 : 5′-*trimethyl*-4″-n-*amyldibenzopyran* (IV). The evidence was derived from the degradative work of Cahn (J., 1930, 986; 1931, 630; 1932, 1342; 1933, 1400) and Bergel (*Annalen*, 1930, **482**, 55; 1932, **493**, 250), from colour reactions, from a consideration of cannabidiol which accompanies it in Egyptian hashish and whose structure has been elucidated in its main features by Adams and his collaborators (*J. Amer. Chem. Soc.*, 1940, **62**, 196, 732, 735, 1770), and finally from absorption spectrum measurements on synthetic dibenzopyran and tetrahydrodibenzopyran derivatives (Parts III and IV; this vol., pp. 1118, 1121). A final decision as to the correctness of this view could only be obtained by a complete synthesis of (IV). In Part IV (*loc. cit.*) a general method was described for the synthesis of derivatives of 2 : 2-dimethyl-3′ : 4′ : 5′ : 6′-tetrahydrodibenzopyran by the action of excess of methylmagnesium iodide on 3 : 4-*cyclo*hexenocoumarins, and by its use 6″-hydroxy-2 : 2 : 5′-trimethyl-4″-*n*-amyl-3′ : 4′ : 5′ : 6′-tetrahydrodibenzopyran (II; R = H) was prepared from 5-acetoxy-5′-methyl-7-*n*-amyl-3 : 4-*cyclo*hexenocoumarin (I; R = Ac). As was noted briefly in the same communication, we have successfully converted (II; R = H) into cannabinol and it is the purpose of this paper to record the experiments involved.

Since a synthesis of cannabinol, to be of any value, must leave no doubt as to the

structure of the final product, a dehydrogenating agent was sought which would effect the final stage under the mildest possible conditions. The desirability of dehydrogenating (II) or the *cyclo*hexenocoumarin (I) from which it was prepared was also considered, since it might have been expected that the coumarin would be less liable to disruption and the resulting 3 : 4-benzocoumarin (III) could subsequently be converted into (IV) by a Grignard reaction. These points were first investigated by model experiments on substances of analogous structure derived from more accessible materials than olivetol, which is necessary for the synthesis of (I).





7-Acetoxy-3 : 4-*cyclo*hexenocoumarin (V ; R = Ac) underwent dehydrogenation and partial deacetylation when heated at 300—310° with palladised charcoal; the crude product yielded, on saponification, 7-*hydroxy*-3 : 4-*benzocoumarin*. Selenium also effected dehydrogenation but was less satisfactory, and this reagent could also be used to dehydrogenate 7-hydroxy-3 : 4-*cyclo*hexenocoumarin (V; R = H) directly. The same product was also obtained by dehydrogenation of *ethyl* 2′ : 4′-*dimethoxyphenyl*-Δ^1-cyclo*hexene*-2-*carboxylate* with sulphur or selenium, followed by demethylation and hydrolysis of the product with hydrobromic acid. It was also found that 6″-acetoxy-2 : 2 : 4″-trimethyl-3′ : 4′ : 5′ : 6′-tetrahydrodibenzopyran (VI) could be dehydrogenated by heating for a short time with palladised charcoal, yielding the corresponding dibenzopyran. In the case of the compounds mentioned above, chloroanil proved ineffective as a dehydrogenating agent.

In the light of experience gained in the above model experiments 6″-acetoxy-2 : 2 : 5′-trimethyl-4″-*n*-amyl-3′ : 4′ : 5′ : 6′-tetrahydrodibenzopyran (II; R = Ac) was dehydrogenated with palladised charcoal. The hydrolysed product, 6″-*hydroxy*-2 : 2 : 5′-*trimethyl*-4″-n-*amyldibenzopyran* (IV), was an almost colourless resin having all the properties of cannabinol. The same product was obtained by the following alternative route : (I; R = Ac) was dehydrogenated with palladised charcoal, and the product hydrolysed, giving 5-*hydroxy*-5′-*methyl*-7-n-*amyl*-3 : 4-*benzocoumarin* (III ; R = H), which on acetylation and treatment with methylmagnesium iodide furnished (IV). The synthetic product was identified with natural cannabinol by preparation of its acetate and *p*-nitrobenzoate, which were identical with the corresponding derivatives prepared from the natural material.

In order to demonstrate that no rearrangements occur during the dehydrogenation processes used in the synthesis, we also dehydrogenated 5″-*acetoxy*-2 : 2 : 5′-*trimethyl*-3′ : 4′ : 5′ : 6′-*tetrahydrodibenzopyran* in the same way. The hydrolysed product was identical with 5″-hydroxy-2 : 2 : 5′-trimethyldibenzopyran (VII) (m. p. and mixed m. p.) prepared by an unambiguous synthetic route which did not involve dehydrogenation (Part III ; *loc. cit.*).

Experimental.

2′ : 4′-Dimethoxyphenyl-Δ¹-cyclohexene-2-carboxylic Acid and its Ethyl Ester.—7-Hydroxy-3 : 4-*cyclo*hexenocoumarin (V; R = H) (27 g.) was refluxed with aqueous sodium hydroxide (120 c.c. of 15%) for 1½ hours, methyl sulphate (30 c.c.) then slowly added, and heating continued for a further 2 hours, small quantities of methyl sulphate and alkali being added from time to time. The alkaline solution was cooled and acidified, and the *product* recrystallised from alcohol, giving colourless octahedral crystals (24 g.), m. p. 153—154° (Found: C, 68·8; H, 7·2. $C_{15}H_{18}O_4$ requires C, 68·7; H, 6·9%).

The acid (7 g.) was refluxed for 6 hours with alcoholic hydrogen chloride (78 c.c. of 2%), the alcohol removed, and the residue taken up in ether. After being washed with sodium carbonate and water, the extract was dried and evaporated, and the residual oil distilled. The *ester* came over at 130—140°/0·04 mm. as a colourless syrup, which set to a mass of needles, m. p. 48° (Found: C, 70·5; H, 8·0. $C_{17}H_{22}O_4$ requires C, 70·5; H, 7·6%).

7-Hydroxy-3 : 4-benzocoumarin.—This compound was prepared by the following methods in the course of model experiments.

(a) *From ethyl 2′ : 4′-dimethoxyphenyl-Δ¹-cyclohexene-2-carboxylate.* The ester (1·8 g.) was heated with sulphur (0·4 g.) at *ca.* 300° for 4 hours. The mixture was extracted with ether, and the extracted material distilled. The main fraction, b. p. 160—170°/0·004 mm., was refluxed with concentrated hydrobromic acid (15 c.c. of 48%) during 2 hours; the mixture was made alkaline, filtered, and again acidified. *7-Hydroxy-3 : 4-benzocoumarin* separated and was recrystallised from alcohol, forming colourless needles (0·7 g.), m. p. 233° (Found: C, 73·3, 73·4; H, 4·0, 3·8. $C_{13}H_8O_3$ requires C, 73·6; H, 3·8%). Using selenium in place of sulphur and heating at 300—320° for 24 hours, an analogous experiment yielded the same product (m. p. and mixed m. p.); the yield was slightly lower (0·5 g. from 2 g. of the ester).

(b) *From 7-acetoxy-3 : 4-cyclohexenocoumarin* (V; R = Ac). The acetoxy-compound (0·5 g.) was heated with palladised charcoal (0·25 g.) at 300—310° during 7 hours, an odour of acetic acid being observed. The product, hydrolysed with alcoholic potassium hydroxide (5%) and worked up in the usual way, yielded 7-hydroxy-3 : 4-benzocoumarin in colourless needles (0·3 g.), m. p. 233°, undepressed on admixture with material prepared by route (a). Dehydrogenation with selenium at 300—320° for 24 hours gave the same product (0·9 g. from 2 g. of the acetate).

(c) *From 7-hydroxy-3 : 4-cyclohexenocoumarin* (V; R = H). The coumarin (10 g.) was heated with selenium (8 g.) at 300—320° during 36 hours. The product (6 g.), crystallised from alcohol, had m. p. 233°, undepressed on admixture with 7-hydroxy-3 : 4-benzocoumarin prepared by either of the above methods.

6″-Hydroxy-2 : 2 : 4″-trimethyldibenzopyran.—6″-Acetoxy-2 : 2 : 4″-trimethyl-3′ : 4′ : 5′ : 6′-tetrahydrobenzopyran (VI) (0·2 g.) was heated with palladised charcoal (0·1 g.) at 300—310° till gas evolution ceased (*ca.* 30 mins. Gas evolved, 35·5 c.c. Calc. for $2H_2$, 39 c.c.). The product was extracted with ether and hydrolysed with alcoholic potassium hydroxide. The *dibenzopyran* crystallised from ether–light petroleum in colourless needles, m. p. 164° (Found: C, 79·6; H, 7·8. $C_{16}H_{16}O_2$ requires C, 80·0; H, 6·7%). The yield was almost quantitative.

5-Hydroxy-5′-methyl-7-n-amyl-3 : 4-benzocoumarin (III; R = H).—5-Acetoxy-5′-methyl-7-*n*-amyl-3 : 4-*cyclo*hexenocoumarin (II; R = Ac) (0·7 g.) was heated with palladised charcoal (0·4 g.) at 300—310° for 30 mins. (gas evolved, 100 c.c. Calc. for $2H_2$, 98 c.c.), and the mixture worked up as before. The hydrolysed *product* crystallised from ether–light petroleum in colourless needles, m. p. 187° (Found: C, 77·2; H, 7·0. $C_{19}H_{20}O_3$ requires C, 77·0; H, 6·8%). The *acetate* (III; R = Ac), prepared by heating with acetic anhydride in pyridine, formed colourless needles (from alcohol), m. p. 98° (Found: C, 74·8; H, 6·8. $C_{21}H_{22}O_4$ requires C, 74·6; H, 6·5%).

6″-Hydroxy-2 : 2 : 5′-trimethyl-4″-n-amyldibenzopyran (Cannabinol) (IV).—*Method I.* Acetylation of 6″-hydroxy-2 : 2 : 5′-trimethyl-4″-*n*-amyl-3′ : 4′ : 5′ : 6′-tetrahydrodibenzopyran (II; R = H) gave the *acetate* (II; R = Ac) as a yellowish resin distilling fairly constantly at 140—145°/10^{-3} mm. (Found: C, 76·9; H, 9·3. $C_{23}H_{32}O_3$ requires C, 77·5; H, 9·0%). This product (0·5 g.) was heated for 30 mins. at 300—310° with palladised charcoal (0·25 g.) (gas evolved, 62 c.c. Calc. for $2H_2$, 67 c.c.). The product, hydrolysed as before, gave a reddish resin, which was distilled. The main fraction (0·3 g.), a faintly yellow resin, distilled at 160—165°/10^{-2} mm. This material showed the same colour reactions as cannabinol isolated from hashish. For identification a portion (0·16 g.) was refluxed in pyridine solution with *p*-nitrobenzoyl chloride (0·23 g.) during 3 hours. The *p*-nitrobenzoate crystallised from alcohol in faintly yellow needles, m. p. 163—164° undepressed on admixture with authentic cannabinol *p*-nitrobenzoate

(m. p. 162—163°) (Found: C, 73·4; H, 6·6; N, 3·3. Calc. for $C_{28}H_{29}O_5N$: C, 73·2; H, 6·3; N, 3·1%).

In the distillation of the crude synthetic cannabinol a very small amount of a reddish oil, b. p. 190—210°/10^{-3} mm., was obtained. Unlike cannabinol, this by-product gave a reddish-violet colour with alcoholic potassium hydroxide; it has not been further investigated.

Method II. A solution of 5-acetoxy-5'-methyl-7-*n*-amyl-3 : 4-benzocoumarin (III; R = Ac) (0·5 g.) in dry anisole (20 c.c.) was added slowly to a solution of methylmagnesium iodide (from 4 g. of methyl iodide and 0·5 g. of magnesium) in anisole. The mixture was heated on the steam-bath for 4 hours, cooled, and decomposed with ice and dilute sulphuric acid, and the anisole removed by steam-distillation. The residue was extracted with ether, washed with aqueous sodium bicarbonate, sodium bisulphite, and then water, dried over sodium sulphate, and evaporated. The product distilled at 140—145°/10^{-3} mm. as an almost colourless resin (0·4 g.) having the properties of cannabinol (Found: C, 81·3; H, 8·2. Calc. for $C_{21}H_{26}O_2$: C, 81·3; H, 8·4%).

In alcoholic solution the synthetic material showed an absorption maximum at 2840 A. (ε, 17,000) and a minimum at 2510 A.; natural cannabinol has a maximum at 2850 A. (ε, 16,790) and a minimum at 2500 A. (Jacob and Todd, this vol., p. 649).

Acetylation of the synthetic product with acetic anhydride in pyridine solution gave the acetate, which crystallised from alcohol in colourless prisms, m. p. 75—76° (Found: C, 78·4; H, 8·3. Calc. for $C_{23}H_{28}O_3$: C, 78·4; H, 8·0%). The acetate was indistinguishable in properties from an authentic specimen of cannabinol acetate (m. p. 75°) prepared from hashish, and a mixed m. p. showed no depression.

5''-Hydroxy-2 : 2 : 5'-trimethyl-3' : 4' : 5' : 6'-tetrahydrodibenzopyran.—6-Hydroxy-5'-methyl-3 : 4-*cyclo*hexenocoumarin (Part IV; *loc. cit.*) was acetylated, and the acetate treated with excess of methylmagnesium iodide in anisole solution in the usual manner. The *product* was a yellowish resin distilling at 130—135°/10^{-2} mm. (Found: C, 78·9; H, 8·5. $C_{16}H_{20}O_2$ requires C, 78·7; H, 8·2%).

5''-Hydroxy-2 : 2 : 5'-trimethyldibenzopyran (VII).—The above tetrahydro-compound was heated with acetic anhydride in pyridine solution, and the crude acetate dehydrogenated with palladised charcoal at 300—310°. The product was hydrolysed and worked up as usual, (VII) being obtained in colourless needles, m. p. 118°. A mixed m. p. with an authentic specimen (m. p. 118°) prepared as described in Part III (*loc. cit.*) showed no depression.

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