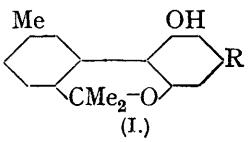
31. Cannabis Indica. *Part VI. The Condensation of Pulegone with Alkyl Resorcinols. A New Synthesis of Cannabinol and of a Product with Hashish Activity.*

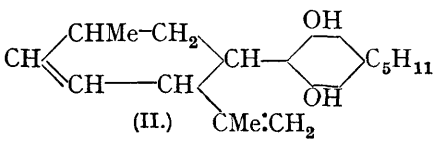
By R. Ghosh, A. R. Todd, and D. C. Wright.

The condensation of terpene derivatives with orcinol and olivetol has been studied in connection with suggestions made as to the biogenesis of certain constituents of *Cannabis* resins (Part II, Jacob and Todd, J., 1940, 649). Crude pulegol, prepared by reduction of pulegone, when heated with orcinol in presence of zinc chloride, yielded, as expected, a hexahydrodibenzopyran derivative. Pulegone itself condensed with orcinol in presence of formic acid to give a product which appeared to be a mixture of isomerides, including (VI; R = Me); dehydrogenation of the product yielded *6″-hydroxy-2 : 2 : 5′ : 4″-tetramethyldibenzopyran* (I; R = Me), identified by comparison of its p-*nitrobenzoate* with that of a specimen prepared by dehydrogenating (VI; R = Me). Pulegone and olivetol condensed similarly to give a product with the composition of a tetrahydrocannabinol. This product had about half the hashish activity shown by a pure specimen of the tetrahydrocannabinol (VI; R = C_5H_{11}) (Gayer test) and is probably a mixture of this substance with some isomeride in which the ethenoid linkage is not conjugated with the aromatic ring. Dehydrogenation of the pulegone–olivetol condensation product yielded cannabinol, identified as its *p*-nitrobenzoate.

Of the substances hitherto isolated from *Cannabis* resin, cannabinol has been shown by synthesis to be 6″-hydroxy-2 : 2 : 5′-trimethyl-4″-*n*-amyldibenzopyran (I; R = C_5H_{11}) (Adams, Baker, and Wearn, *J. Amer. Chem. Soc.*, 1940, **62**, 2204; Ghosh, Todd, and Wilkinson, Parts IV and V, J., 1940, 1121, 1393), and cannabidiol is believed to have structure (II), in which the position of the cyclic ethylenic linkage has not been rigidly established (Adams, Loewe, Pease, Cain, Wearn, Baker, and Wolff, *J. Amer. Chem. Soc.*, 1940, **62**, 2566). It has been suggested (Part II; *loc. cit.*) that these compounds might arise in the plant by condensation of a terpene derivative with olivetol. The initial product of such a condensation might be cannabidiol, from which, by cyclisation, a tetrahydrocannabinol could be produced; dehydrogenation of the cyclised material would give cannabinol. It has been shown by Adams, Pease, Cain, and Clark (*J. Amer. Chem. Soc.*, 1940, **62**, 2402) that cannabidiol can be cyclised, yielding, according to conditions, one or more tetrahydrocannabinols which exhibit the characteristic pharmacological properties of the hemp drugs when tested on dogs. As these products can be dehydrogenated to cannabinol, it is clear that part, at any rate, of this hypothetical scheme of biogenesis is capable of realisation in the laboratory. The observation is of added interest since it seems probable that the activity of the hemp drugs may be due, in part at least, to the presence in them of one or more tetrahydrocannabinols. For some time we have been studying the possibility of synthesising cannabinol by direct condensation of terpene derivatives with olivetol, followed by dehydrogenation. Such a synthetic process would be attractive not merely in connection with the above scheme but also because the inter-



(I.)



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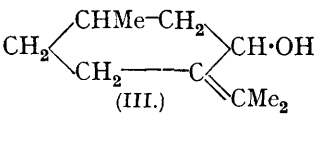

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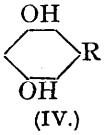

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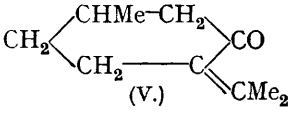

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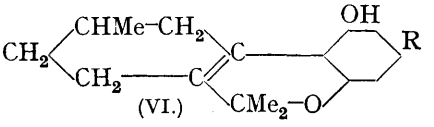

(VI.)

mediate, partially hydrogenated cannabinols formed in the synthesis might, if an optically active terpene derivative were used, themselves be at once optically and pharmacologically

active like the cyclised isomerides of cannabidiol. The fact that the synthesis of cannabinol has been achieved in this way warrants the publication of our results at this stage.

In the vitamin E group α-tocopherol has been synthesised by several methods, including the condensation of phytol with ψ-cumoquinol (Bergel, Copping, Jacob, Todd, and Work, J., 1938, 1382). By analogy it was to be expected that pulegol (III) would condense with olivetol (IV; R = C_5H_{11}) to give a hexahydrocannabinol. The preparation of pulegol from pulegone by reduction with aluminium *iso*propoxide has been described by Doeuvre and Perret (*Bull. Soc. chim.*, 1935, **2**, 298), who record rather poor yields. In our hands the method of these authors gave rise to a mixture containing in addition to pulegol a considerable proportion of doubly unsaturated compounds, since it showed selective light absorption in the neighbourhood of 2350 A. No better results were achieved by reduction of pulegone with aluminium *iso*propoxide in *iso*butyl alcohol, following the procedure used by Malcolm and Read (J., 1939, 1037) for the reduction of Δ^4-menthen-3-one. When the crude pulegol obtained by either of these methods was heated in decalin solution with orcinol (IV; R = Me) in presence of anhydrous zinc chloride, condensation occurred and a thick, yellowish, alkali-insoluble oil was produced, which distilled at a fairly constant temperature and appeared from analysis and properties to consist essentially of the expected 6''-*hydroxy*-2 : 2 : 5' : 4''-*tetramethyl*-1' : 2' : 3' : 4' : 5' : 6'-*hexahydrodibenzopyran*. The condensation was, however, unsatisfactory in so far as one of the starting materials was of doubtful composition, and attention was directed to the condensation of the readily accessible pulegone (V) with resorcinol derivatives. As far as we are aware the condensation of αβ-unsaturated ketones with phenols to produce chromens has not been hitherto reported, but by analogy with the well-known Doebner–v. Miller synthesis of quinoline derivatives it might be expected that the condensation of (V) with (IV) would yield a tetrahydrodibenzopyran derivative (VI). It was indeed observed that, on heating pulegone with orcinol in presence of formic acid (98—99%) and subsequently hydrolysing the product to remove any formyl groups introduced, a thick alkali-insoluble oil was obtained, which distilled at a more or less constant temperature and was then colourless; several samples were analysed and had the composition of the expected product (VI; R = Me). That this material had the tetrahydrodibenzopyran structure was demonstrated by dehydrogenation with palladised charcoal; 2 mols. of hydrogen were evolved and 6''-*hydroxy*-2 : 2 : 5' : 4''-*tetramethyldibenzopyran* (I; R = Me) was produced. The identity of this product was established by comparison of its p-*nitrobenzoate* with the corresponding ester of the product obtained by dehydrogenating authentic 6''-hydroxy-2 : 2 : 5' : 4''-tetramethyl-3' : 4' : 5' : 6'-tetrahydrodibenzopyran (VI; R = Me) (Part IV; *loc. cit.*).

The products from different pulegone–orcinol condensations showed absorption spectra closely similar to one another and to that of (VI; R = Me) as regards the position of the maximum, but the intensity of light absorption varied. In general the intensity was only about half that shown by a pure specimen of (VI; R = Me), although in one case a fraction was obtained showing an intensity of a similar order. Moreover (VI; R = Me) is a crystalline solid (Part IV, *loc. cit.*; Adams, Pease, Cain, Clark, Wolff, and Wearn, *J. Amer. Chem. Soc.*, 1940, **62**, 2245), and in no case could the pulegone–orcinol products be crystallised. The most probable explanation of these facts is that the condensation product is not homogeneous but contains in addition to (VI; R = Me) an isomeric substance in which the ethenoid linkage is not conjugated with the aromatic ring. The view that (VI; R = Me) is present in the condensation products is strongly supported by absorption spectrum measurements; in compounds where there is no ethenoid linkage conjugated with an aromatic ring (*e.g.*, in cannabidiol or in the pulegol–orcinol condensation product) the intensity of absorption is very low (ε, 1000—2000), whereas when there is such a linkage, as in (VI; R = Me), the intensity is much greater (ε *ca.* 10,000). Only the presence of (VI; R = Me) or the somewhat unlikely isomeride with the double bond in the 1' : 6'-position could account for the observed intensity. Further investigation will be required before any more definite statements can be made as to the structure of the accompanying material.

Olivetol (IV; R = C_5H_{11}) underwent condensation with pulegone in presence of formic acid under conditions similar to those used in the case of orcinol. The product, a slightly

yellowish oil, had the composition of a tetrahydrocannabinol. In accordance with such a structure the oil, on being heated to 300° with palladised charcoal, evolved 2 mols. of hydrogen and gave a colourless resin with the composition and reactions of cannabinol (I; R = C_5H_{11}); the product was identified by conversion into its crystalline *p*-nitrobenzoate, whose m. p. was undepressed on admixture with authentic cannabinol *p*-nitrobenzoate. It may be mentioned in passing that, although cannabinol has been obtained in crystalline form by Adams and his collaborators, no specimen, synthetic or natural, has so far crystallised in our laboratories; there is, however, no doubt as to the identity of the materials handled by both groups of workers, since they give derivatives with identical properties. The pulegone–olivetol condensation product resembled the pulegone–orcinol product in that its absorption spectrum showed a single band similar to but only about half as intense as that shown by the tetrahydrocannabinol (VI; R = C_5H_{11}); similar views are held regarding its composition.

In Part IV (*loc. cit.*) the synthesis of (VI; R = C_5H_{11}) was described and it was mentioned that pharmacological investigations on it were then incomplete. The results of tests by Prof. A. D. Macdonald have shown that the substance exhibits hashish activity in the Gayer test on rabbits at a dose of 1 mg./kg.; it has thus activity similar in degree to that of a distilled Indian hemp resin. Details of the pharmacological examination of this and other synthetic substances will be reported elsewhere. The activity of the same compound in dogs has been reported in the interim by Adams, Loewe, Pease, Cain, Wearn, Baker, and Wolff (*loc. cit.*). The pulegone–olivetol condensation product, which had little or no optical activity, was pharmacologically active in the Gayer test at a dose of 2·5 mg./kg. and inactive at 1 mg./kg., *i.e.*, it had about half the activity of a pure specimen of (VI; R = C_5H_{11}). Since the spectroscopic evidence suggests that only about half of the product is (VI; R = C_5H_{11}), it would appear that the remainder has little or no hashish activity.

It is clear that the procedure above described opens up a new route to the synthesis of substances which may show hashish activity. The synthetic method also affords some support for the hypothetical scheme suggested for the biogenesis of *Cannabis* constituents; in this connexion a knowledge of the composition of the terpene fraction obtained in the distillation of hemp resin would be of the greatest interest.

Experimental.

Condensation of Pulegol with Orcinol.—Crude pulegol (20 g.), obtained from pulegone by the method of Doeuvre and Perret (*loc. cit.*), orcinol monohydrate (10 g.), powdered anhydrous zinc chloride (20 g.), and decalin (200 c.c.) were heated together at 130—140° during 2 hours. After cooling, the decalin solution was decanted, diluted with ether, washed several times with aqueous sodium hydroxide (10%), dried, and evaporated, first under atmospheric pressure, then in a vacuum to remove decalin and unchanged pulegol. The residue distilled fairly steadily at 140—150° (bath temp.)/10^{-2} mm., very little material boiling outside this range. The product, a yellowish viscous oil, gave a blue colour with 2 : 6-dichlorobenzoquinonechloroimide, and from its analysis appeared to be the expected *6″-hydroxy-2 : 2 : 5′ : 4″-tetramethyl-1′ : 2′ : 3′ : 4′ : 5′ : 6′-hexahydrodibenzopyran* [Found: C, 79·2, 79·2; H, 9·6, 9·5; active H (Zerewitinoff), 0·40. $C_{17}H_{24}O_2$ requires C, 78·5; H, 9·3; 1 active H, 0·38%]. *Light absorption in alcohol:* Max. 2800 A. (ε 1300); min. 2670 A. It gave no coloration with alcoholic potassium hydroxide.

Condensation of Pulegone with Orcinol.—A mixture of pulegone (5 c.c.), orcinol monohydrate (5·5 g.), and formic acid (30 c.c. of 98—99%) was refluxed for 3½ hours. The resulting brownish solution was evaporated on the water-bath under reduced pressure, the residue made alkaline, and the excess of pulegone removed by steam-distillation. The viscous oil obtained from the distillation residue by ether extraction was hydrolysed by refluxing for 1½ hours with methyl-alcoholic potassium hydroxide (25 c.c. of 4%). After removal of most of the methyl alcohol by distillation the mixture was cooled, diluted with water, and extracted with ether. The extract was dried over sodium sulphate and evaporated; the residue distilled at 150° (bath temp.)/2 × 10^{-3} mm. as a colourless viscous oil which could not be crystallised (Found: C, 78·9; H, 8·8. $C_{17}H_{22}O_2$ requires C, 79·1; H, 8·5%). *Light absorption in alcohol:* Max. *ca.* 2750 A. (ε *ca.* 5000); min. 2500 A. There was no evidence of separation into distinct fractions

by distillation or chromatographic analysis; arbitrarily selected fractions all had the same composition and differed but little in intensity of light absorption. In one instance, however, a product was obtained showing a maximum at 2770 A. of intensity ε 9620 (Found: C, 78·8; H, 9·0%) [(VI; R = Me) has max. 2790 A. (ε 10,980); min. 2500 A.]. The condensation products obtained in all the experiments gave a blue colour with 2 : 6-dichlorobenzoquinonechloroimide but gave no coloration with alcoholic potassium hydroxide.

6″-Hydroxy-2 : 2 : 5′ : 4″-tetramethyldibenzopyran (I; R = Me) (This experiment was carried out by Mr. P. B. Russell, B.Sc., to whom our thanks are due).—6″-Acetoxy-2 : 2 : 5′ : 4″-tetramethyl-3′ : 4′ : 5′ : 6′-tetrahydrodibenzopyran (VI; R = Me) (0·5 g.) (Part IV, *loc. cit.*) was heated with palladised charcoal (0·2 g.) at 300—320° until evolution of hydrogen ceased (hydrogen evolved, 73 c.c. Calc. for $2H_2$, 75 c.c.). The product was extracted from the charcoal with ether, the acetyl group removed by hydrolysis with methyl-alcoholic potassium hydroxide, and the *dibenzopyran* (I; R = Me) distilled at 152° (bath temp.)/10^{-3} mm. It was obtained as a colourless viscous oil which showed a tendency to crystallise on long standing (Found: C, 79·8; H, 7·2. $C_{17}H_{18}O_2$ requires C, 80·3; H, 7·1%). *Light absorption in alcohol:* Max. 2820 A. (ε 14,740); min. 2500 A. On refluxing in pyridine solution with *p*-nitrobenzoyl chloride a p-*nitrobenzoate* was obtained, which crystallised from alcohol in pale yellow needles, m. p. 215—216° (Found: N, 3·7. $C_{24}H_{21}O_5N$ requires N, 3·5%).

Dehydrogenation of the Pulegone–Orcinol Condensation Product.—The distilled condensation product (0·23 g.) was heated with palladised charcoal (0·11 g.) at 300—320° for *ca.* 1 hour until evolution of hydrogen ceased (hydrogen evolved, 39 c.c. Calc. for $2H_2$, 40 c.c.). The product was extracted from the charcoal with ether and distilled, coming over as a colourless viscous oil at 150—160° (bath temp.)/10^{-3} mm. (Found: C, 80·0; H, 7·3. Calc. for $C_{17}H_{18}O_2$: C, 80·3; H, 7·1%). In accordance with experience of analogous cases (cf. Part V; *loc. cit.*) it was observed that the dehydrogenation proceeded more smoothly and rapidly when the acetate of the pulegone–orcinol condensation product was employed. The identity of the dehydrogenation product with 6″-hydroxy-2 : 2 : 5′ : 4″-tetramethyldibenzopyran was confirmed by preparation of its *p*-nitrobenzoate, which crystallised from alcohol in pale yellow needles, m. p. 215—216°, undepressed by the specimen described above.

Condensation of Pulegone with Olivetol.—Pulegone (1·5 c.c.), olivetol monohydrate (1 g.), and formic acid (7 c.c. of 98—99%) were refluxed for 3 hours, and the product isolated as before. The colourless viscous oil obtained distilled at 170° (bath temp.)/10^{-3} mm. [Found: C, 80·3; H, 9·5; active H (Zerewitinoff), 0·31. $C_{21}H_{30}O_2$ requires C, 80·3; H, 9·6; 1 active H, 0·31%]. *Light absorption in alcohol:* Max. 2760 A. (ε, 6200); min. 2500 A. [(VI; R = C_5H_{11}) has max. 2755 A. (ε, 11,130); min. 2490 A.]. The material gave a blue colour with 2 : 6-dichlorobenzoquinonechloroimide but gave no coloration with alcoholic potassium hydroxide. It appeared to have an insignificant lævorotation in acetone solution and was pharmacologically active in the Gayer test on rabbits.

Dehydrogenation of the Pulegone–Olivetol Condensation Product to Cannabinol.—The condensation product (0·37 g.) was dehydrogenated by heating at 300—320° with palladised charcoal (0·2 g.) in the usual manner (hydrogen evolved, 51 c.c. Calc. for $2H_2$, 53 c.c.). The product, which distilled as a slightly yellowish resin at 160—170° (bath temp.)/10^{-2} mm., showed the colour reactions of cannabinol. It was identified by heating with *p*-nitrobenzoyl chloride in pyridine solution, giving a *p*-nitrobenzoate, m. p. 160—162°, undepressed by authentic cannabinol *p*-nitrobenzoate (m. p. 162—163°).

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