## 31. Cannabis Indica. *Part IX. The Isolation of* 3′ : 4′ : 5′ : 6′-*Tetrahydrodibenzopyran Derivatives from Pulegone–Orcinol and Pulegone–Olivetol Condensation Products. Synthesis of* d-*Tetrahydrocannabinol.*

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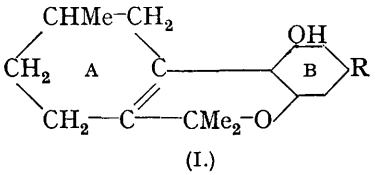
Extension of the work described in Part VI (J., 1941, 137) has led to the isolation from the pulegone–orcinol condensation product of 6″-hydroxy-2 : 2 : 5′ : 4″-tetramethyl-3′ : 4′ : 5′ : 6′-tetrahydrodibenzopyran (I; R = Me) as its crystalline acetate. The isolated phenol is dextrorotatory, but partial racemisation must have occurred at some stage, since the rotation is much lower than that of the pure *d*-form of (I; R = Me), whose synthesis is described. The nature of the resin accompanying (I; R = Me) in the condensation product remains to be determined. In the same way a dextrorotatory tetrahydrocannabinol (I; R = *n*-$C_5H_{11}$) has been isolated as an *l*-menthoxyacetate from the pulegone–olivetol product. For purposes of comparison *d*-tetrahydrocannabinol (I; R = *n*-$C_5H_{11}$) has been synthesised; it shows much less hashish activity in rabbits than does the racemic form.

The view that some of the typical constituents of *Cannabis* resin might arise in nature by the condensation of terpene derivatives with dihydric phenols was expressed in earlier communications from these laboratories (Jacob and Todd, *Nature*, 1940, **145**, 350; J., 1940, 649) and investigations were then initiated with the object of realising such condensations in the laboratory. Condensations of pulegone with orcinol and with olivetol have already been reported (Part VI; Ghosh, Todd, and Wright, J., 1941, 137). These gave rise to resins which, on evidence derived from analysis, measurements of absorption spectra, behaviour on dehydrogenation, and, in the case of the olivetol product, pharmacological activity, were considered to be mixtures containing in each case about 50% of the expected tetrahydrodibenzopyran derivatives (I; R = Me) and (I; R = *n*-$C_5H_{11}$). Since the publication of these results Adams, Smith,

and Loewe (*J. Amer. Chem. Soc.*, 1941, **63**, 1973) have described very similar condensations and their results may be regarded as, in the main, confirmatory. The main difference between their results and our own is the pronounced *dextro*-rotation of their pulegone–olivetol product. This discrepancy may have been due to a variable amount of racemisation during our condensation or to some error in our original determination; at any rate, in subsequent experiments we have found the pulegone–olivetol product to show an optical activity similar in degree to that reported by these authors. The publication by Adams and his co-workers on this subject, however, makes it desirable for us to record some further results at this stage.

Definite proof of the correctness of our view as to the nature of one of the pulegone–orcinol products has been obtained by the isolation, from the acetylated resin, of 6″-acetoxy-2 : 2 : 5′ : 4″-tetramethyl-3′ : 4′ : 5′ : 6′-tetrahydrodibenzopyran. The identity of this substance, which has a pronounced *dextro*-rotation, was established by mixed m. p. determinations with an authentic specimen of the racemic modification (Ghosh, Todd, and Wilkinson, J., 1940, 1121) and by its hydrolysis to (I; R = Me). The product (I; R = Me) isolated in this way had $[\alpha]_D^{20°}$ approx. + 42° in successive preparations. That partial racemisation had occurred during the condensation was proved by synthesis of pure *d*-6″-hydroxy-2 : 2 : 5′ : 4″-tetramethyl-3′ : 4′ : 5′ : 6′-tetrahydrodibenzopyran (I; R = Me) in the following way. *d*-Methyl*cyclo*hexan-3-one, prepared from pulegone by heating with water under pressure (Wallach, *Annalen*, 1896, **289**, 340), was converted by the glyoxylic ester route into ethyl 1-methyl*cyclo*hexan-3-one-4-carboxylate. From this product, presumably containing a mixture of stereoisomers, *d*-5-hydroxy-5′ : 7-dimethyl-3 : 4-*cyclo*hexenocoumarin was obtained by condensation with orcinol in presence of sulphuric acid, and from it (I; R = Me) was prepared by a Grignard reaction; it had $[\alpha]_D^{20°}$ = + 161°.



(I.)

After separation of the acetate of (I; R = Me) from the acetylated pulegone–orcinol condensation product the residual resin was hydrolysed. Neither the resin so obtained nor any derivative of it has yet been crystallised. It has a definite *dextro*-rotation and analysis shows that it has the same composition as (I; R = Me). In alcoholic solution it shows selective light absorption at 2780 A. similar to, but a good deal less intense than, that shown by (I; R = Me). The possibility of its containing a double bond conjugated with an aromatic nucleus cannot be entirely excluded on this evidence, since there are indications of fairly intense absorption in the region of 2300 A.; this absorption band is more clearly evident in the acetylated resin. It may be mentioned that all the 3′ : 4′ : 5′ : 6′-tetrahydrodibenzopyrans so far examined by us show strong light absorption between 2000 and 2300 A.; as a rule we have not recorded the intensity of absorption in this region, as it is difficult to measure accurately with the apparatus at our disposal and variation in intensity and location with different substituents is more easily followed in the maxima at higher wave-lengths. In Part VI (*loc. cit.*) it was suggested that the pulegone–orcinol condensation product might contain in addition to (I; R = Me) an isomer in which the double bond in ring A was not conjugated with the aromatic nucleus. The implied migration of a double bond during reaction has been criticised by Adams, Smith, and Loewe (*loc. cit.*) on the ground that it is without precedent; such criticism appears to us ill-considered in view of the numerous cases of deconjugation recorded in the literature, *e.g.*, the isomerisation of α-phellandrene to a mixture of α- and γ-terpinenes by means of sulphuric or phosphoric acid (Wallach, *Annalen*, 1887, **239**, 44; Carter, Smith, and Read, *J. Soc. Chem. Ind.*, 1925, **44**, 543). That the material accompanying (I; R = Me) should differ only in the location of a double bond now seems to us less probable, since not only does the crude pulegone–orcinol product give on catalytic dehydrogenation a poor yield of 6″-hydroxy-2 : 2 : 5′ : 4″-tetramethyldibenzopyran, but the residue after removal of (I; R = Me) gives on similar treatment a resin from which no crystalline product has been isolated. Several hypothetical structures, including some with angular alkyl groups, might be advanced for the resin, but no convincing evidence can at present be adduced in support of any one. Further investigation of this material is in hand; products rather similar in properties have also been obtained by condensing resorcinol derivatives with other terpene derivatives, *e.g.*, limonene and α-terpineol.

The isolation of (I; R = Me) from the pulegone–orcinol product made it practically certain that the pulegone–olivetol product must contain the tetrahydrocannabinol (I; R = *n*-$C_5H_{11}$). The lack of any crystalline derivative of (I; R = *n*-$C_5H_{11}$) at first hampered isolation efforts, but this difficulty was removed when it was discovered, in the course of some experiments on optical resolution, that synthetic racemic tetrahydrocannabinol (I; R = *n*-$C_5H_{11}$) yields a crystalline ester on treatment with *l*-menthoxyacetyl chloride. The product from the racemic phenol had m. p. 56—57°, whereas that from pure *d*-tetrahydrocannabinol (I; R = *n*-$C_5H_{11}$) synthesised from *d*-methyl*cyclo*hexan-3-one in a similar fashion to the

*d*-form of (I; R = Me), had m. p. 76—77°. Accordingly the distilled pulegone–olivetol product was esterified by means of *l*-menthoxyacetyl chloride, and the esterified material after purification by chromatographic analysis crystallised in part from alcohol. The crude crystalline product had m. p. 66—68°, raised by admixture with d-*tetrahydrocannabinol* l-*menthoxyacetate*. Presumably the pulegone–olivetol product contained partially racemised tetrahydrocannabinol, leading to the production of a mixture of *l*-menthoxyacetates. This mixture apparently underwent separation on further recrystallisation, since it yielded finally a product, m. p. 76°, undepressed on admixture with *d*-tetrahydrocannabinol *l*-menthoxyacetate and having an optical rotation only a little less than that of the latter. As regards the nature of the material accompanying tetrahydrocannabinol in the pulegone–olivetol product little further can be said than that it resembles closely the unidentified pulegone–orcinol product.

In the Gayer test on rabbits synthetic *d*-tetrahydrocannabinol (I; R = $n$-$C_5H_{11}$) appeared to show no activity in doses less than 6—8 mg./kg., *i.e.*, it was only $\frac{1}{6}$—$\frac{1}{8}$ as potent as the racemic modification. The pure *l*-form has not yet been obtained, but from these results it may be inferred that it should be 11—15 times as active as the *d*-form. Purified active fractions of hashish are lævorotatory, as also are the tetrahydrocannabinols obtained by cyclisation of cannabidiol (Adams, Pease, Cain, and Clark, *J. Amer. Chem. Soc.*, 1940, **62**, 2402). Another point of interest emerging from pharmacological tests by Professor A. D. Macdonald and Mr. G. Woolfe is that the acetate of tetrahydrocannabinol exhibits the hashish activity of the free phenol; it may be first hydrolysed in the animal, however, since the action is slow in developing and is very prolonged.

## Experimental.

*Pulegone–Orcinol Condensation Products.*—The condensation of pulegone with orcinol, carried out as described by Ghosh, Todd, and Wright (*loc. cit.*), gave a pale yellow resin distilling at 155—160° (bath temp.)/$10^{-1}$ mm., $[\alpha]_D^{22°}$ + 47·1° (*c* = 0·956 in chloroform). Light absorption in alcohol: max. 2720 A.; ε, 3520. This resin was acetylated by heating with acetic anhydride in pyridine solution. The product distilled at 150—152°/$10^{-1}$ mm. and had $[\alpha]_D^{22°}$ + 33·8° (*c* = 1·670 in chloroform). An alcoholic solution of this material slowly deposited colourless prisms (4 g.), m. p. 123° after recrystallisation from alcohol, $[\alpha]_D^{21°}$ + 30·4° (*c* = 2·076 in chloroform). Light absorption in alcohol: maxima at 3050 A. (ε, 4425), 2670 A. (ε, 7605) and 2250 A. (ε, 23,100). A mixed m. p. with *dl*-6″-acetoxy-2 : 2′ : 5′ : 4″-tetramethyl-3′ : 4′ : 5′ : 6′-tetrahydrodibenzopyran [m. p. 124°; absorption maxima in alcohol 3050 A. (ε, 4680), 2670 A. (ε, 7550), and 2250 A. (ε, 24,000)] showed no depression. In a second pulegone–orcinol condensation the crude acetylated resin had $[\alpha]_D^{23°}$ + 40·0° (*c* = 1·474 in chloroform), and the isolated crystalline acetate $[\alpha]_D^{22°}$ + 30·6° (*c* = 1·270 in chloroform). Hydrolysis of this crystalline acetate gave (I; R = Me), m. p. 112°, $[\alpha]_D^{19°}$ + 42·7° (*c* = 2·273 in chloroform). Light absorption in alcohol: maxima at 2780 A. (ε, 8,930) and 2290 A. (ε, 24,000). A mixed m. p. with the synthetic *dl*-modification of (I; R = Me) [m. p. 113°; absorption maxima in alcohol: 2780 A. (ε, 10,600) and 2300 A. (ε, 25,500)] showed no depression.

The non-crystalline portion (16 g.) of the acetylated pulegone–orcinol product (20 g.) had $[\alpha]_D^{20°}$ + 23·2° (*c* = 4·866 in chloroform) and in alcoholic solution it showed maxima at 2650 A. (ε, 3680) and 2330 A. (ε, 8700). Hydrolysis with alcoholic potassium hydroxide yielded a colourless resin, $[\alpha]_D^{18°}$ + 36·8° (*c* = 1·276 in chloroform), which defied all efforts at crystallisation (Found: C, 79·0; H, 9·0. $C_{17}H_{22}O_2$ requires C, 79·1; H, 8·5%). On catalytic hydrogenation ($PtO_2$) 79·5 mg. absorbed 6·8 c.c. of hydrogen (calculated absorption for $C_{17}H_{22}O_2$ taking up 1 mol. of hydrogen, 6·8 c.c.). In a second preparation the non-crystalline portion of the acetylated resin had a higher dextrorotation, $[\alpha]_D^{22°}$ + 36·8° (*c* = 2·092 in chloroform).

d-*Methyl*cyclo*hexan*-3-*one*.—Pulegone (125 g.) and water (100 g.) were heated at 250° in an autoclave for 2 hours (Wallach, *loc. cit.*). The oil was separated, dried, and distilled, yielding *d*-methyl*cyclo*hexan-3-one (48 g.), b. p. 168—170°, $[\alpha]_D^{19·5°}$ + 7·9° (*c* = 5·928 in alcohol). The alternative method of preparation from pulegone with sulphuric acid (Zelinsky, *Ber.*, 1897, **30**, 1532) was found to be unsatisfactory.

d-5-*Hydroxy*-5′ : 7-*dimethyl*-3 : 4-cyclo*hexenocoumarin*.—Ethyl 1-methyl*cyclo*hexan-3-one-4-carboxylate ($[\alpha]_D^{19°}$ + 79·2°), prepared from *d*-methyl*cyclo*hexan-3-one, was condensed with orcinol in presence of concentrated sulphuric acid in the normal manner. The coumarin formed colourless needles, m. p. 252—253°, $[\alpha]_D^{19°}$ + 168·3° (*c* = 0·974 in alcohol). The corresponding *dl*-coumarin has m. p. 260° (Ahmad and Desai, *Chem. Abstr.*, 1938, 9066) and a mixture of the two melted at 253—255°.

d-6″-*Hydroxy*-2 : 2 : 5′ : 4″-*tetramethyl*-3′ : 4′ : 5′ : 6′-*tetrahydrodibenzopyran* (I; R = Me).—Prepared from the above coumarin by the method of Ghosh, Todd, and Wilkinson (*loc. cit.*), the *product* crystallised from light petroleum in colourless plates, m. p. 104—105°, $[\alpha]_D^{19·7°}$ + 161° (*c* = 1·684 in chloroform) (Found: C, 78·8; H, 8·4. $C_{17}H_{22}O_2$ requires C, 79·1; H, 8·5%). In alcoholic solution it showed absorption maxima at 2785 A. (ε, 10,600) and 2300 A. (ε, 25,500). The corresponding racemic compound has m. p. 113° and a mixed m. p. of the two was 106—110°.

d-5-*Hydroxy*-5′-*methyl*-7-n-*amyl*-3 : 4-cyclo*hexenocoumarin*.—Prepared as above from optically active ethyl 1-methyl*cyclo*hexan-3-one-4-carboxylate and olivetol, the coumarin had a rather indefinite m. p. 145—

148°; $[\alpha]_D^{24°}$ + 130·3° (*c* = 2·34 in chloroform). The corresponding racemate has m. p. 177° (Ghosh, Todd, and Wilkinson, *loc. cit.*). The *acetate* had m. p. 76—77° and $[\alpha]_D^{22°}$ + 132·9° (*c* = 0·948 in chloroform) (Found: C, 73·8; H, 7·8. $C_{21}H_{26}O_4$ requires C, 73·7; H, 7·6%). The mixed m. p. with the racemic acetate (m. p. 82—83°) was 78—79°.

d-*Tetrahydrocannabinol* (I; R = *n*-$C_5H_{11}$).—Prepared by the action of methylmagnesium iodide on the above acetoxycoumarin, the *product* was a purplish resin distilling at 160° (bath temp.)/$10^{-3}$ mm. (Found: C, 79·8; H, 9·6. $C_{21}H_{30}O_2$ requires C, 80·2; H, 9·5%). It had $[\alpha]_D^{20°}$ + 134·8° (*c* = 0·331 in chloroform) and in alcoholic solution had absorption maxima at 2750 A. (ε, 11,500) and 2290 A. (ε, 25,120).

*d*-Tetrahydrocannabinol *l*-menthoxyacetate, prepared from *d*-tetrahydrocannabinol by heating with *l*-menthoxyacetyl chloride (Read and Grubb, *J. Soc. Chem. Ind.*, 1932, **51**, 330T) in pyridine solution, crystallised from 95% alcohol in colourless needles, m. p. 76—77°. It had $[\alpha]_D^{25°}$ + 62·16° (*c* = 0·708 in chloroform) and in alcoholic solution showed absorption maxima at 3050 A. (ε, 5500), 2690 A. (ε, 8160), and 2260 A. (ε, 23,000).

l-*Menthoxyacetate of* dl-*Tetrahydrocannabinol.*—Menthoxyacetylation of racemic (I; R = *n*-$C_5H_{11}$) gave an *ester* crystallising from 95% alcohol in colourless needles, m. p. 56—57° (Found: C, 77·5; H, 9·8. $C_{33}H_{50}O_4$ requires C, 77·6; H, 9·8%). It had $[\alpha]_D^{17·5°}$ — 53·7° (*c* = 0·670 in chloroform) and its absorption spectrum in alcohol showed maxima at 3050 A. (ε, 5360) and 2700 A. (ε, 8330). The mixed m. p. with *d*-tetrahydrocannabinol *l*-menthoxyacetate (m. p. 76—77°) was 68—72°.

*Pulegone–Olivetol Condensation Products.*—Repetition of the pulegone–olivetol condensation as described by Ghosh, Todd, and Wright (*loc. cit.*) gave products which, contrary to the statement made in that communication, had a pronounced dextrorotation. The following account refers to the product from one such condensation, a pale yellow resin distilling at 160—170° (bath temp.)/6 × $10^{-3}$ mm.; it had $[\alpha]_D^{21°}$ + 62·7° (*c* = 2·976 in chloroform). After three further distillations the main fraction, b. p. 140—142° (bath temp.)/1·5 × $10^{-5}$ mm., had $[\alpha]_D^{21°}$ + 76·5° (*c* = 2·104 in alcohol). In agreement with earlier observations this material showed an absorption maximum in alcohol at 2780 A. (ε, 5340). A portion of the resin (450 mg.) was refluxed with *l*-menthoxyacetyl chloride in pyridine and the product, a reddish viscous oil, was dissolved in light petroleum and adsorbed on a column of activated aluminium oxide (2 cm. × 20 cm.; Birmingham Electric Co., Ltd.). When the column was washed with light petroleum (250 c.c., b. p. 40—60°) and the washings were evaporated, a colourless resin (*ca.* 300 mg.) was obtained which on dissolution in a small amount of alcohol and standing in the ice-chest for 24 hours deposited a crystalline menthoxyacetate, m. p. 66—68°. After three recrystallisations from alcohol this product was obtained in colourless needles (80 mg.), m. p. 76°, undepressed on admixture with *d*-tetrahydrocannabinol *l*-menthoxyacetate (m. p. 76—77°) (Found: C, 77·5; H, 10·0. Calc. for $C_{33}H_{50}O_4$: C, 77·6; H, 9·8%). It had $[\alpha]_D^{24°}$ + 51·9° (*c* = 0·616 in chloroform) and in alcoholic solution showed absorption maxima at 3050 A. (ε, 5360) and 2710 A. (ε, 8460). Hydrolysis of this ester gave a tetrahydrocannabinol having $[\alpha]_D^{22·4°}$ + 118·4° (*c* = 1·09 in chloroform).

The mother-liquor from the original crystallisation yielded on evaporation a colourless resin (*ca.* 200 mg.), $[\alpha]_D^{23·4°}$ — 31·4° (*c* = 2 506 in chloroform). On hydrolysis a dextrorotatory resin was obtained, b. p. 155° (bath temp.)/3·8 × $10^{-4}$ mm., $[\alpha]_D^{22°}$ + 59·2° (*c* = 1·39 in alcohol), closely resembling the original pulegone–olivetol product in its light absorption (ε, 5055 at 2760 A.). By eluting with benzene the material remaining on the adsorbent after the above-mentioned chromatogram had been washed with light petroleum, a product was obtained, which was hydrolysed to a pale yellow resin, $[\alpha]_D^{22°}$ + 22·2° (*c* = 1·17 in alcohol), with a rather similar absorption spectrum (ε, 3050 at 2790 A.).

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