36. Cannabis Indica. *Part VII. The Relation between Chemical Constitution and Hashish Activity.*

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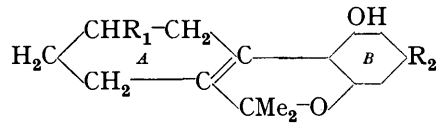
In view of the hashish activity shown by the synthetic tetrahydrocannabinol (I; $R_1 = Me$, $R_2 = C_5H_{11}$) in dogs and rabbits a number of structurally related compounds have been synthesised by the general method previously described (Part IV; J., 1940, 1121) and tested pharmacologically. The bearing of the results so far obtained on the general question of chemical constitution and hashish activity is discussed.

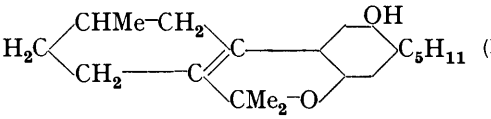
In Part IV (Ghosh, Todd, and Wilkinson, J., 1940, 1121) a general method was described for the synthesis of 3′ : 4′ : 5′ : 6′-tetrahydrodibenzopyran derivatives by the action of Grignard reagents on 3 : 4-*cyclo*hexenocoumarins and a number of such compounds were thus synthesised, including the tetrahydrocannabinol (I; $R_1 = Me$, $R_2 = C_5H_{11}$). As has been mentioned in Part VI (this vol., p. 137), the latter substance shows hashish activity in rabbits (Gayer test), and its activity in the dog test has been recorded by Adams, Loewe, Pease, Cain, Wearn, Baker, and Wolff (*J. Amer. Chem. Soc.*, 1940, **62**, 2566), who synthesised it independently by a very similar method. It was clearly a matter of great interest to examine a series of compounds related to (I; $R_1 = Me$, $R_2 = C_5H_{11}$) in the hope of ascertaining the structural features essential to the exhibition of hashish activity. Several of the 3′ : 4′ : 5′ : 6′-tetrahydrodibenzopyrans prepared in the course of model experiments (Part IV; *loc. cit.*) were tested pharmacologically on rabbits and found uniformly inactive by intravenous injection in acetone solution at a dose of 5 mg./kg. of body weight, a dose which is much in excess of the active dose of an ordinary distilled Indian hemp resin. The substances thus examined were 4″-hydroxy-2 : 2-di-

methyl-3′ : 4′ : 5′ : 6′-tetrahydrodibenzopyran, 4″-hydroxy-2 : 2 : 5′-trimethyl-3′ : 4′ : 5′ : 6′-tetrahydrodibenzopyran, the corresponding acetoxy-compounds, and (I; $R_1 = R_2 = Me$).

In preliminary extension of this work we have now synthesised and tested pharmacologically the following compounds: 6″-*hydroxy*-2 : 2-*dimethyl*-4″-n-*amyl*-3′ : 4′ : 5′ : 6′-*tetrahydrodibenzopyran* (*tetrahydronorcannabinol*) (I; $R_1 = H$, $R_2 = C_5H_{11}$), 5″-*hydroxy*-2 : 2 : 5′-*trimethyl*-4″-n-*amyl*-3′ : 4′ : 5′ : 6′-*tetrahydrodibenzopyran* (II), 5-*hydroxy*-2 : 2 : 4-*trimethyl*-7-n-*amyl*-Δ^3-*chromen* (III; $R = C_5H_{11}$), and 5-*hydroxy*-2 : 2-*dimethyl*-7-n-*amyl*-3 : 4-cyclo*penteno*-Δ^3-*chromen* (IV; $R = C_5H_{11}$). Each of these compounds was prepared by the action of excess of methylmagnesium iodide on the corresponding coumarin synthesised by the v. Pechmann method. The biological test results are in the table. 5-*Hydroxy*-2 : 2 : 4 : 7-*tetramethyl*-Δ^3-*chromen* (III; R = Me) and 5-*hydroxy*-2 : 2 : 7-*trimethyl*-3 : 4-cyclo*penteno*-Δ^3-*chromen* (IV; R = Me) were also synthesised in preliminary experiments; (III; R = Me) was not tested pharmacologically.

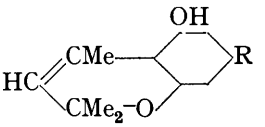
(I.)

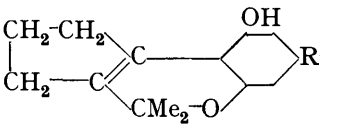




(II.)

(III.)





(IV.)

Substance.	Dose (mg./kg.).	Activity.
Tetrahydrocannabinol ..... (I; $R_1 = Me$, $R_2 = C_5H_{11}$)	1	+
"Tetrahydrocannabinol —165°"	0·3	+
,, ,,	0·1	—
Hexahydrocannabinol	5	+
,, ,, ...	1	—

	Dose (mg./kg.).	Activity.
Tetrahydronorcannabinol (I; $R_1 = H$, $R_2 = C_5H_{11}$)	5	+
(II)	20	—
(I; $R_1 = R_2 = Me$)	20	—
(III; $R = C_5H_{11}$)	15	—
(IV; $R = C_5H_{11}$)	30	—
(IV; R = Me)	20	—

There has been in the past some disagreement as to the comparability of the various biological tests for *Cannabis* preparations and it was therefore desirable to compare the results of Adams, Loewe, Pease, Cain, Wearn, Baker, and Wolff (*loc. cit.*) on the dog with those obtained by us on the rabbit. The American workers assessed the activity of various materials by comparison with a fraction of distilled "red oil" from American hemp to which was ascribed unit potency. Since our results could not be expressed in the same terms, we prepared "tetrahydrocannabinol, $[\alpha]_D^{22\cdot5°} = -165°$," by cyclisation of cannabidiol as described by Adams, Pease, Cain, and Clark (*J. Amer. Chem. Soc.*, 1940, **62**, 2402) and tested it on rabbits. The results of our tests are, like those in the dog test, only very roughly quantitative and a more accurate assay method is desirable. Nevertheless it can be seen from the table that the cyclised cannabidiol has an activity markedly greater than that of the synthetic tetrahydrocannabinol (I; $R_1 = Me$, $R_2 = C_5H_{11}$). The ratio of the activities of these two compounds in the dog test ($2\cdot15 \pm 0\cdot66/0\cdot20 \pm 0\cdot07$) (Adams, Loewe, Pease, Cain, Wearn, Baker, and Wolff, *loc. cit.*) is higher than in the rabbit test, where it is of the order 5/1. Bearing in mind the very pronounced variation in the response of experimental animals to *Cannabis*, it may be said that the results are qualitatively similar and it would appear likely that the dog and rabbit tests will give comparable results in assessing the hashish activity of synthetic compounds. The few observations which we have made in the dog confirm this impression. Indeed we have so far no reason to doubt that the Gayer response in the rabbit and ataxia in the dog are produced by the same principle, and that this principle can be assayed by either test.

The results recorded in this paper are of too preliminary a nature to warrant any sweeping conclusions as to the structural features necessary for hashish activity, but certain points emerge from them. The activity shown by tetrahydronorcannabinol (I; $R_1 = H$, $R_2 = C_5H_{11}$) and by hexahydrocannabinol, prepared by catalytic hydrogenation of

synthetic tetrahydrocannabinol (I; R = Me, $R_2 = C_5H_{11}$), although less than that shown by (I; R_1 = Me, $R_2 = C_5H_{11}$), indicates that the presence of an alkyl group or a double bond in ring *A* of partly reduced dibenzopyran derivatives is not of primary importance. The orientation of the hydroxyl group (cf. II) and the nature of the side chain in ring *B* (cf. I; $R_1 = R_2$ = Me) seem to be very important. A reduction in the size of ring *A* as in (IV; R = C_5H_{11}) or its complete removal as in (III; R = C_5H_{11}) seems to destroy or at any rate greatly reduce activity. A curious observation made with (IV; R = C_5H_{11}) was that in isolated cases it seemed to show a considerable degree of toxicity. It may be recalled that attention was drawn in Part I (Work, Bergel, and Todd, *Biochem. J.*, 1939, **33**, 123) to the toxic effect of cannabinol in rabbits. In further tests we have been unable to confirm the high degree of toxicity there recorded. We are at a loss to account for this fact, unless it is to be attributed to an unusual degree of sensitivity shown by the strain of animals used in the original experiments.

In the course of experiments carried out in the hope of isomerising synthetic tetrahydrocannabinol (I; R_1 = Me, $R_2 = C_5H_{11}$) by double-bond migration it was observed that irradiation of a sample in ethereal solution with ultra-violet light during 48 hours caused a considerable diminution in hashish activity, although there was little change in absorption spectrum. The nature of the product remains to be determined, but the result may be significant in view of the frequently reported deterioration, also noted by us, of *Cannabis* preparations on keeping.

Experimental.

6-Hydroxy-5'-methyl-7-n-amyl-3 : 4-cyclohexenocoumarin.—*n*-Amylquinol (1·57 g.), prepared by demethylation of its dimethyl ether (Ghosh, Pascall, and Todd, J., 1940, 1118), was suspended in ethyl 1-methyl*cyclo*hexan-3-one-4-carboxylate (1·7 g.), and concentrated sulphuric acid (3 c.c.) gradually added. After 24 hours the solution was poured on ice, and the precipitate collected. Recrystallised from alcohol, the *product* formed pale yellow plates, m. p. 188° (Found : C, 76·4; H, 8·0. $C_{19}H_{24}O_3$ requires C, 76·0; H, 8·0%). On heating with acetic anhydride in pyridine solution the *acetate* was obtained; it crystallised from alcohol in colourless needles, m. p. 119—120° (Found : C, 73·5; H, 7·7. $C_{21}H_{26}O_4$ requires C, 73·7; H, 7·6%).

5''-Hydroxy-2 : 2 : 5'-trimethyl-4''-n-amyl-3' : 4' : 5' : 6'-tetrahydrodibenzopyran (II), prepared from the above acetoxy-coumarin (0·25 g.) by treatment with methylmagnesium iodide (from 0·25 g. of magnesium) in anisole solution, was obtained as a pale yellow resin distilling at 150—160° (bath temp.)/10^{-3} mm. (Found : C, 79·7; H, 9·4. $C_{21}H_{30}O_2$ requires C, 80·2; H, 9·5%). *Light absorption in alcohol :* Maxima at 3280 A. (ε, 5,680) and 2670 A. (ε, 6,190). The *acetate*, prepared in the usual manner, was a pale yellow resin distilling at 150° (bath temp.)/10^{-3} mm. (Found : C, 77·3; H, 8·7. $C_{23}H_{32}O_3$ requires C, 77·5; H, 9·0%).

5-Hydroxy-7-n-amyl-3 : 4-cyclohexenocoumarin.—Condensation of olivetol monohydrate with ethyl *cyclo*hexanone-2-carboxylate in presence of concentrated sulphuric acid gave a *product* crystallising from alcohol in colourless needles, m. p. 180° (Found : C, 75·4; H, 7·9. $C_{18}H_{22}O_2$ requires C, 75·5; H, 7·7%). The *acetate* crystallised from alcohol in colourless plates, m. p. 80° (Found : C, 73·2; H, 7·6. $C_{20}H_{24}O_4$ requires C, 73·1; H, 7·3%).

6''-Hydroxy-2 : 2-dimethyl-4''-n-amyl-3' : 4' : 5' : 6'-tetrahydrodibenzopyran (*Tetrahydronorcannabinol*) (I; R_1 = H, $R_2 = C_5H_{11}$).—The above acetoxycoumarin was treated with excess of methylmagnesium iodide in anisole solution. The *product*, a pale yellow resin, distilled fairly steadily at 158—165° (bath temp.)/10^{-3} mm. (Found : C, 79·1; H, 9·4. $C_{20}H_{28}O_2$ requires C, 80·0; H, 9·4%). *Light absorption in alcohol :* Max. 2740 A. (ε, 10,100).

5-Hydroxy-2 : 2 : 4 : 7-tetramethyl-Δ³-chromen (III; R = Me).—5-Acetoxy-4 : 7-dimethylcoumarin (v. Pechmann, *Ber.*, 1884, **17**, 2188) was treated with excess of methylmagnesium iodide. On being worked up in the usual way, the *chromen* was obtained as a yellowish resin distilling at 115—120° (bath temp.)/10^{-3} mm., which slowly solidified. Recrystallised from light petroleum, it formed colourless needles, m. p. 97° (Found : C, 75·9; H, 7·8. $C_{13}H_{16}O_2$ requires C, 76·5; H, 7·9%). *Light absorption in alcohol :* Max. 2750 A. (ε, 8500).

5-Hydroxy-4-methyl-7-n-amylcoumarin, prepared in the usual manner from ethyl acetoacetate and olivetol monohydrate in presence of concentrated sulphuric acid, formed colourless prisms, m. p. 185°, from alcohol (Found : C, 73·5; H, 7·4. $C_{15}H_{18}O_3$ requires C, 73·2; H, 7·3%). The corresponding *acetate* crystallised from alcohol in needles, m. p. 97° (Found : C, 70·7; H, 6·9. $C_{17}H_{20}O_4$ requires C, 70·8; H, 6·9%).

5-Hydroxy-2 : 2 : 4-trimethyl-7-n-amyl-Δ³-chromen (III; R = C_5H_{11}).—Prepared by the

action of excess of methylmagnesium iodide on the above acetate in anisole solution, the *product* was a yellowish resin, b. p. 140—150° (bath temp.)/10^{-1} mm. (Found: C, 78·7; H, 9·6. $C_{17}H_{24}O_2$ requires C, 78·5; H, 9·4%).

5-*Hydroxy*-7-*methyl*-3 : 4-cyclo*pentenocoumarin*, prepared as above from ethyl *cyclo*pentanone-2-carboxylate (15·6 g.) and orcinol monohydrate (14·2 g.) in presence of concentrated sulphuric acid (2 g.), formed colourless needles, m. p. 254°, from alcohol (Found: C, 72·2; H, 5·4. $C_{13}H_{12}O_3$ requires C, 72·2; H, 5·6%). The *acetate* crystallised from alcohol in needles, m. p. 131° (Found: C, 69·6; H, 5·4. $C_{15}H_{14}O_4$ requires C, 69·8; H, 5·4%).

5-*Hydroxy*-2 : 2 : 7-*trimethyl*-3 : 4-cyclo*penteno*-Δ^3-*chromen* (IV; R = Me).—Treatment of the above acetate with excess of methylmagnesium iodide in the normal manner gave a pale yellow resin distilling at 140—150° (bath temp.)/10^{-1} mm. (Found: C, 77·9; H, 8·1. $C_{15}H_{18}O_2$ requires C, 78·3; H, 7·8%). *Light absorption in alcohol:* Max. 2760 A. (ε, 6440).

5-*Hydroxy*-7-n-*amyl*-3 : 4-cyclo*pentenocoumarin*, prepared as above from ethyl *cyclo*pentanone-2-carboxylate and olivetol monohydrate in presence of concentrated sulphuric acid, formed colourless prisms, m. p. 176°, from alcohol (Found: C, 74·8; H, 7·5. $C_{17}H_{20}O_3$ requires C, 74·9; H, 7·4%). The *acetate* crystallised from alcohol in needles, m. p. 65—66° (Found: C, 72·5; H, 6·9. $C_{19}H_{22}O_4$ requires C, 72·6; H, 7·0%).

5-*Hydroxy*-2 : 2-*dimethyl*-7-n-*amyl*-3 : 4-cyclo*penteno*-Δ^3-*chromen* (IV; R = C_5H_{11}).—Prepared by the action of excess of methylmagnesium iodide on the above acetate, the *substance* distilled at 135—140° (bath temp.)/10^{-3} mm. as a pale yellow resin which crystallised on standing. Recrystallised from light petroleum, it formed colourless needles, m. p. 78° (Found: C, 79·8; H, 9·1. $C_{19}H_{26}O_2$ requires C, 79·7; H, 9·1%). *Light absorption in alcohol:* Max. 2790 A. (ε, 11,100).

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