147. Cannabis Indica. *Part VIII. Further Analogues of Tetrahydrocannabinol.*

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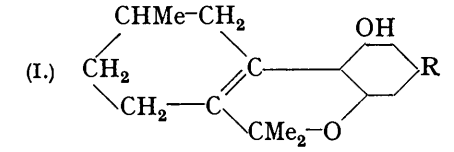
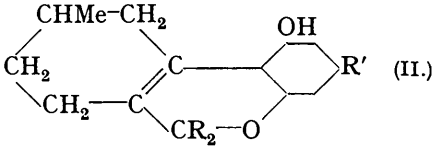
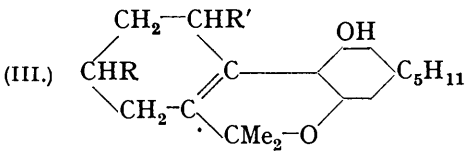
The survey initiated in Part VII of the effect of structural modification on hashish activity in the tetrahydrocannabinol group has been extended by the synthesis and testing of a further series of analogues. These include substances of type (I) in which R is varied from ethyl to octyl in the *n*-alkyl series and in which R = *iso*amyl and *iso*hexyl. Both (I; R = *n*-C_6H_{13}) and (I; R = *n*-C_7H_{15}) are considerably more active in the Gayer test than tetrahydrocannabinol itself, but the *iso*amyl and *iso*hexyl analogues have negligible activity. Other analogues prepared included compounds belonging to types (II), (III), and (IV) as well as a substance (I; R = OH). With the exception of one compound of type (III) none of them showed marked activity.

In Part VII (Russell, Todd, Wilkinson, Macdonald, and Woolfe, this vol., p. 169) we reported some results of a preliminary investigation into the relation between chemical constitution and hashish activity as manifested in the Gayer test on rabbits. The compounds synthesised and examined pharmacologically were analogues of tetrahydrocannabinol (I; R = *n*-C_5H_{11}), and although their number was not large certain tentative conclusions could be drawn as to the important structural features of the tetrahydrocannabinol molecule. In continuation of this work we have since prepared a further series of analogues, using the general synthetic method for tetrahydrodibenzopyran derivatives described by Ghosh, Todd, and Wilkinson (J., 1940, 1121), and tested them pharmacologically on rabbits. These new compounds include (1) analogues of type (I) in which R is varied in size from methyl to octyl inclusive in the *n*-alkyl series and from amyl to hexyl in the *iso*alkyl series; (2) analogues in which the methyl groups on the heterocyclic ring of (I) are replaced by ethyl, *n*-propyl or *n*-butyl groups; (3) isomers of tetrahydrocannabinol (I; R = *n*-C_5H_{11}) in which the location of the methyl group in ring *A* is varied; (4) 5-hydroxy-2 : 2 : 4-trimethyl-3-*n*-butyl-7-*n*-amyl-Δ^3-chromen (IV;

R = *n*-C_5H_{11}), isomeric with tetrahydrocannabinol, and the corresponding *substance* (IV; R = Me), and (5) an *analogue* (I; R = OH) containing two hydroxyl groups on ring *B*.







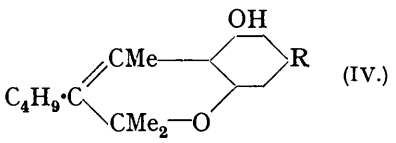


TABLE I.

Substance.	Dose (mg./kg.).	Activity.	Substance.	Dose (mg./kg.).	Activity.
Tetrahydrocannabiol	1	+	II; R = Et; R' = *n*-C_5H_{11}	20	—
I; R = Me	20	—	II; R = *n*-C_3H_7; R' = Me	15	—
I; R = Et	15	—	II; R = *n*-C_4H_9; R' = Me	20	—
I; R = *n*-C_3H_7	20	—	III; R = H; R' = Me	1	+
I; R = *n*-C_4H_9	1	+	III; R = Me; R' = H	20	—
I; R = *n*-C_6H_{13}	0·1	+	IV; R = Me	20	—
I; R = *n*-C_7H_{15}	0·1	+	IV; R = *n*-C_5H_{11}.....	10	—
I; R = *n*-C_8H_{17}	1	+	I; R = OH	15	—
I; R = *iso*-C_5H_{11}	15	—			
I; R = *iso*-C_6H_{13}	15	—			

When these compounds were tested biologically (see Table I), the remarkable observation was made that in analogues of type (I) hashish activity as assayed by the Gayer test increased from the *n*-butyl compound and was much greater in the case of the *n*-hexyl and *n*-heptyl compounds than in tetrahydrocannabinol itself; the *iso*amyl and *iso*hexyl analogues, on the contrary, showed no appreciable activity, at any rate in doses 15 times greater than the active dose of tetrahydrocannabinol itself. The preparation of further analogues of this type containing still longer *n*-alkyl chains, although envisaged, was not pursued in view of the publication by Adams and his collaborators of several papers (*J. Amer. Chem. Soc.*, **1941**, **63**, 1971, 1973, 1977) which we have recently received, and in which many of the compounds above mentioned are described. In them the *n*-octyl analogue is reported to have an activity in the dog test rather less than that of tetrahydrocannabinol itself; this result has been roughly confirmed as regards the Gayer test by Mr. R. E. Davies in this laboratory, who synthesised the *n*-octyl analogue by our standard method, and found its activity to be comparable with that of tetrahydrocannabinol. In view of our obvious prior interest in *Cannabis* it is regrettable that in one of these papers (p. 1971) Adams and his co-workers should have complained on priority grounds of our working in this field. Where two groups of workers arrive independently and well-nigh simultaneously at the same results in one field of research, arguments as to priority have little force, and are, in our view, futile. We must, however, point out that the claim of the American workers to priority in the synthesis of tetrahydrocannabinol finds no justification in the dates of the relevant published papers.

As regards the other analogues of tetrahydrocannabinol those of types (II) and (IV) and the compound (I; R = OH) seem to have negligible activity. Alteration in the position of the methyl group in ring *A* has apparently a variable effect on activity. For instance, in the Gayer test, (III; R = H; R' = Me) appeared to be of the same order as tetrahydrocannabinol itself and (III; R = Me, R' = H) appeared to have little or no effect. This result is rather surprising, since in the dog test these two compounds are reported to be approximately $\frac{1}{4}$ and $\frac{1}{3}$ as active as tetrahydrocannabinol (Adams *et al.*, *loc. cit.*, p. 1973). Details of the compounds prepared are given in the experimental section. Where substances have also been described by Adams *et al.* (*loc. cit.*) we have refrained from entering analytical data and record for purposes of comparison only the

b. p. and light absorption, save in the case of (I; R = *n*-C_3H_7), where the compound was obtained by us in crystalline form with m. p. different from that reported by the American workers. It will be noted that where the same compounds have been examined pharmacologically by ourselves and by the American workers, the relative activities of individual compounds are as a rule only very roughly comparable. For instance, on our results the activity of (I; R = *n*-C_6H_{13}) is considerably more than 1·82 times that of tetrahydrocannabinol (I; R = C_5H_{11}) itself. It must be again emphasised that the Gayer test in our hands, using a small number of rabbits, is only very roughly quantitative; it is impossible by its use to express the ratio between the activities of two compounds to two significant places of decimals as is done by Adams and his co-workers (*loc. cit.*), measuring degree of ataxia in dogs. Nevertheless the difference between our ratio and that of the American workers in the case of, say, tetrahydrocannabinol and the analogue (I; R = *n*-C_6H_{13}) is large. If significant, this difference would suggest that the effects measured in the two tests are different in type, although both are characteristic of hashish activity. Alternatively, of course, the difference in the test results might be due to a difference in the grading of the responses as elicited in dogs on the one hand and rabbits on the other. No definite conclusions can be drawn in the absence of much more extended pharmacological study, but these possibilities must be borne in mind. It should be mentioned finally that for ordinary purposes we do not test synthetic substances pharmacologically in doses of more than 15—20 mg. per kg. of body-weight; this, of course, explains the apparent discrepancy between our report on the inactivity of certain compounds, *e.g.* (I; R = Me) (Part IV; *loc. cit.*), and the positive results of Adams and his co-workers, who probably test in much higher doses; feeble activities of this nature are of some theoretical interest but are unlikely to have any practical significance.

Experimental.

Analogues of Type (I) *in which* R *is varied.*—The procedure used throughout was that of Ghosh, Todd, and Wilkinson (Part IV; *loc. cit.*). The appropriate resorcinol derivative was condensed with ethyl 1-methyl*cyclo*hexan-3-one-4-carboxylate in presence of sulphuric acid to give a 3 : 4-*cyclo*hexenocoumarin, which as such or after preliminary acetylation was converted into the required tetrahydrodibenzopyran by treatment with excess of methylmagnesium iodide. In general, preliminary acetylation of the coumarin derivative led to cleaner products. Of the compounds prepared, those in which R is ethyl, *iso*amyl, and *iso*hexyl have not previously been described; for the others, the properties agreed in the main with those described by Adams *et al.* (*loc. cit.*, p. 1971), save that (I; R = *n*-C_3H_7) was obtained as a crystalline solid differing in m. p. from the product described by these workers.

*5-Hydroxy-5′-methyl-7-ethyl-*3 : 4-cyclo*hexenocoumarin*, obtained by means of 5-ethylresorcinol, formed colourless needles, m. p. 204—205° (Found: C, 74·0; H, 7·1. $C_{16}H_{18}O_3$ requires C, 74·5; H, 7·0%). With methylmagnesium iodide it gave *6″-hydroxy-*2 : 2 : *5′-trimethyl-4″-ethyl-*3′ : 4′ : 5′ : 6′-*tetrahydrodibenzopyran* (I; R = Et), a yellowish resin, b. p. 155°/0·1 mm. (bath temp.) (Found: C, 79·3; H, 8·6. $C_{18}H_{24}O_2$ requires C, 79·4; H, 8·8%). On standing, the resin crystallised and then separated from light petroleum in colourless needles, m. p. 100—101°. Light absorption in alcohol: Max. 2760 A., ε 11,400. This compound is mentioned by Adams *et al.* (*loc. cit.*, p. 1973) but no description of it is given.

(I; R = *n*-C_3H_7). The product distilled at 160—165°/0·1 mm. (bath temp.) as a reddish oil which subsequently crystallised; recrystallised from light petroleum, it formed colourless plates, m. p. 92—93° (Found: C, 79·7; H, 9·2. Calc. for $C_{19}H_{26}O_2$: C, 79·7; H, 9·2%). Light absorption in alcohol: Max. 2750 A., ε 10,950. Adams *et al.* (*loc. cit.*, p. 1972) give m. p. 145—146°.

(I; R = *n*-C_4H_9). Yellowish resin, b. p. 180°/0·1 mm. (bath temp.). Light absorption in alcohol: Max. 2760 A., ε 11,400.

(I; R = *n*-C_6H_{13}). Purplish resin, b. p. 175°/0·1 mm. (bath temp.). Light absorption in alcohol: Max. 2760 A., ε 12,700.

(I; R = *n*-C_7H_{15}). Yellowish resin distilling at 190—192°/0·1 mm. (bath temp.). Light absorption in alcohol: Max. 2795 A., ε 12,550.

*5-Hydroxy-5′-methyl-*7-iso*amyl-*3 : 4-cyclo*hexenocoumarin*, prepared from 5-*iso*amylresorcinol (Found: C, 76·3; H, 8·0. $C_{19}H_{24}O_3$ requires C, 76·0; H, 8·0%), and its *acetate* (Found:

C, 73·5; H, 7·4. $C_{21}H_{26}O_4$ requires C, 73·7; H, 7·6%) separated from alcohol in colourless needles, m. p. 200—201° and 98—99°, respectively. The latter with methylmagnesium iodide gave 6″-*hydroxy*-2 : 2 : 5′-*trimethyl*-4″-iso*amyl*-3′ : 4′ : 5′ : 6′-*tetrahydrodibenzopyran* (I; R = *iso*-C_5H_{11}), a yellowish resin, b. p. 170°/0·1 mm. (bath temp.) (Found : C, 80·0; H, 9·2. $C_{21}H_{30}O_2$ requires C, 80·2; H, 9·6%). The product slowly solidified and then crystallised from light petroleum in colourless needles, m. p. 56—57°. Light absorption in alcohol : Max. 2785 A., ε 10,267.

5-*Hydroxy*-5′-*methyl*-7-iso*hexyl*-3 : 4-cyclo*hexenocoumarin*, prepared from 5-*iso*hexylresorcinol, formed colourless needles, m. p. 177—180°, from alcohol (Found : C, 76·9; H, 8·1. $C_{20}H_{28}O_3$ requires C, 76·5; H, 8·3%). With methylmagnesium iodide it gave 6″-*hydroxy*-2 : 2 : 5′-*trimethyl*-4″-iso*hexyl*-3′ : 4′ : 5′ : 6′-*tetrahydrodibenzopyran* (I; R = *iso*-C_6H_{13}), a yellowish resin, b. p. 203°/1 mm. (bath temp.) (Found : C, 80·2; H, 9·6. $C_{22}H_{32}O_2$ requires C, 80·5; H, 9·8%). Light absorption in alcohol : Max. 2760 A., ε 10,900.

Analogues of Type (II).—These were prepared by the action of the appropriate alkylmagnesium halide on the corresponding tetrahydro*cyclo*hexenocoumarin acetate.

(II; R = Et, R′ = *n*-C_5H_{11}), already described by Adams *et al.* (*loc. cit.*, p. 1973), was a yellowish resin, b. p. 180—190°/0·1 mm. (bath temp.). Light absorption in alcohol : Max. 2790 A., ε 9500.

6″-*Hydroxy*-5′ : 4″-*dimethyl*-2 : 2-*di*-n-*propyl*-3′ : 4′ : 5′ : 6′-*tetrahydrodibenzopyran* (II; R = *n*-C_3H_7, R′ = Me), an isomer of tetrahydrocannabinol, was a yellowish resin, b. p. 165°/0·1 mm. (bath temp.) (Found : C, 79·8; H, 9·5. $C_{21}H_{30}O_2$ requires C, 80·2; H, 9·6%). Light absorption in alcohol : Max. 2790 A., ε 8300.

6″-*Hydroxy*-5′ : 4″-*dimethyl*-2 : 2-*di*-n-*butyl*-3′ : 4′ : 5′ : 6′-*tetrahydrodibenzopyran* (II; R = *n*-C_4H_9, R′ = Me) was a yellowish resin, b. p. 170—175°/0·1 mm. (bath temp.) (Found : C, 80·5; H, 9·6. $C_{23}H_{34}O_2$ requires C, 80·7; H, 9·9%). Light absorption in alcohol : Max. 2815 A., ε 10,260.

Isomers of Tetrahydrocannabinol (I; R = *n*-C_5H_{11}) *in which the Location of the Methyl Group in Ring* A *is varied.*—The following two compounds, also described by Adams *et al.* (*loc. cit.*, p. 1973), were prepared by the standard procedure starting respectively with ethyl 1-methyl*cyclo*hexan-2-one-3-carboxylate and ethyl 1-methyl*cyclo*hexan-4-one-5-carboxylate.

(III; R = H, R′ = Me), a yellowish resin, b. p. 165°/0·1 mm. (bath temp.). Light absorption in alcohol : Max. 2750 A., ε 11,230.

(III; R = Me, R′ = H), a purplish resin, b. p. 170—180°/0·01 mm. (bath temp.). Light absorption in alcohol : Max. 2740 A., ε 11,000.

4″ : 6″-*Dihydroxy*-2 : 2 : 5′-*trimethyl*-3′ : 4′ : 5′ : 6′-*tetrahydrodibenzopyran* (I; R = OH).—Prepared in the normal manner by the action of methylmagnesium iodide on 5 : 7-dihydroxy-5′-methyl-3 : 4-*cyclo*hexenocoumarin (Ahmad and Desai, *Proc. Indian Acad. Sci.*, 1938, **8**, *A*, 1), the *substance* distilled as a reddish-yellow resin at 200°/0·1 mm. (bath temp.) (Found : C, 73·6; H, 7·8. $C_{16}H_{20}O_3$ requires C, 73·8; H, 7·7%). Light absorption in alcohol : Max. 2750 A., ε 11,150).

5-*Hydroxy*-2 : 2 : 4 : 7-*tetramethyl*-3-n-*butyl*-Δ^3-*chromen* (IV; R = Me).—Contrary to the experience of Adams *et al.* (*loc. cit.*, p. 1977) no difficulty was experienced in condensing orcinol with ethyl *n*-butylacetoacetate in presence of sulphuric acid. The resulting coumarin crystallised from alcohol in colourless needles, m. p. 192° (Adams *et al.* give m. p. 191—195°) (Found : C, 73·2; H, 7·2. Calc. for $C_{15}H_{18}O_3$: C, 73·2; H, 7·3%). The corresponding *acetate* separated from alcohol in colourless needles, m. p. 93° (Found : C, 70·5; H, 7·2. $C_{17}H_{20}O_4$ requires C, 70·8; H, 6·9%). The *chromen*, prepared by treating the coumarin acetate with methylmagnesium iodide, was a purplish resin, b. p. 160—170°/0·1 mm. (bath temp.) (Found : C, 78·3; H, 9·3. $C_{17}H_{24}O_2$ requires C, 78·5; H, 9·2%). Light absorption in alcohol : Max. 2720 A., ε 9850.

(IV; R = *n*-C_5H_{11}). The chromen was a purplish resin, b. p. 170—180°/0·1 mm. (bath temp.). Light absorption in alcohol : Max. 2740 A., ε 10,500.

The authors are indebted to Messrs. Roche Products, Ltd., for grants and to Dr. H. Rinderknecht of that firm for assistance in the preparation of some of the compounds described.

THE UNIVERSITY OF MANCHESTER. [*Received, October 20th,* 1941.]