79. *Cannabis Indica. Part XII. Some Analogues and a Water-soluble Derivative of Tetrahydrocannabinol.*

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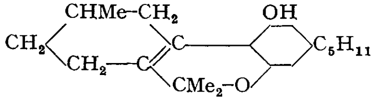
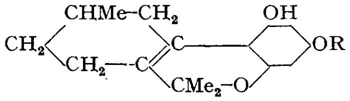
Four analogues of tetrahydrocannabinol (I) in which the *n*-amyl group is replaced by *n*-alkoxy-groups have been prepared. Of these, only (II; R = *n*-C_6H_{13}) appeared to show hashish activity in rabbits. Disodium tetrahydrocannabinyl phosphate, a water-soluble material, has also been prepared. It showed no activity when tested on rabbits by the Gayer method.

In previous papers (Russell, Todd, Wilkinson, Macdonald, and Woolfe, J., 1941, 169, 826) we described the preparation of a variety of analogues of tetrahydrocannabinol (I), using the general synthetic method of Ghosh, Todd, and Wilkinson (J., 1940, 1121), and reported the results of their pharmacological examination for hashish activity, using the Gayer test on rabbits. Among the synthetic analogues those in which the size of the alkyl substituent in the aromatic ring varied from methyl to octyl proved perhaps the most interesting from the standpoint of the relation between hashish activity and chemical constitution, activity in the *n*-alkyl series rising to a maximum in the hexyl and heptyl analogues, both of which were considerably more potent than (I). The same series of analogues was also prepared by Adams, Loewe, Zelinek, and Wolff (*J. Amer. Chem. Soc.*, 1941, **63**, 1971) and examined pharmacologically by the dog ataxia method; by this test the *n*-hexyl analogue clearly represented the peak of activity. Differences of this type in the relative potencies of various compounds reported by the American workers and ourselves are almost certainly due to the different biological tests employed. The striking gradation of activity observed in this series of compounds caused us to include in our investigations an examination of analogues of type (II) in which the *n*-amyl group of tetrahydrocannabinol (I) is replaced by *n*-alkoxy-groups of varying size. We prepared in all four compounds of type (II) in which R = *n*-C_4H_9, -C_5H_{11}, -C_6H_{13}, -C_7H_{15}, and we wish to place our results on record. The compounds described were prepared by condensation of 4″ : 6″-dihydroxy-2 : 2 : 5′-trimethyl-3′ : 4′ : 5′ : 6′-tetrahydrodibenzopyran (Ghosh, Todd, and Wilkinson, *loc. cit.*) with the appropriate alkyl bromide in presence of alcoholic sodium ethoxide. Under the conditions employed, only the 4″-hydroxyl was alkylated, since the products, viscous amber-coloured oils, gave an intense blue coloration with 2 : 6-dichloroquinonechloroimide, indicating the presence in them of a phenolic hydroxyl group, the *p*-position to which was unsubstituted. When tested on rabbits by the Gayer method, *6″-hydroxy-4″-*n*-hexyloxy-2 : 2 : 5′-trimethyl-3′ : 4′ : 5′ : 6′-tetrahydrodibenzopyran* (II; R = *n*-C_6H_{13}) appeared to show feeble activity in doses between 10 and 20 mg./kg., but none of the other substances showed any activity in doses up to 20 mg./kg.

(I.)





(II.)

In view of possible clinical application of synthetic hashish-active substances, it seemed of interest to prepare a water-soluble derivative of tetrahydrocannabinol. To this end, following a model experiment on the readily accessible 6″-hydroxy-2 : 2 : 5′ : 4″-tetramethyl-3′ : 4′ : 5′ : 6′-tetrahydrodibenzopyran (Ghosh, Todd, and Wilkinson, *loc. cit.*), tetrahydrocannabinol (I) was brought into reaction with phosphoryl chloride in pyridine solution, and the resulting O-*dichlorophosphoryltetrahydrocannabinol* converted into the readily soluble disodium tetrahydrocannabinyl phosphate. The product showed no apparent hashish activity in rabbits (Gayer test) in a dose of 20 mg./kg. This finding was unexpected, since it had already been observed that the acetate of tetrahydrocannabinol is active in the Gayer test, although it is slower in action than tetrahydrocannabinol itself (Leaf, Todd, and Wilkinson, J., 1942, 185). The only reasonable explanation would appear to be a greater resistance of the phosphate to hydrolysis.

EXPERIMENTAL.

*6″-Hydroxy-4″-*n*-hexyloxy-2 : 2 : 5′-trimethyl-3′ : 4′ : 5′ : 6′-tetrahydrodibenzopyran* (II; R = *n*-C_6H_{13}).—To alcoholic sodium ethoxide (0·23 g. of sodium in 22 c.c. of absolute alcohol), 4″ : 6″-dihydroxy-2 : 2 : 5′-trimethyl-3′ : 4′ : 5′ : 6′-tetrahydrodibenzopyran (II; R = H) (2·6 g.) and *n*-hexyl bromide (2·15 g.) were added, and the mixture heated in a sealed tube in a boiling water-bath for 15 hours. The liquid was filtered and evaporated, and the residue taken up in ether, washed with dilute hydrochloric acid, sodium bicarbonate solution and water, and dried over anhydrous sodium sulphate. After removal of the ether the product (2·2 g.) distilled at 205—209° (bath temp.)/0·2 mm. as a viscous amber-coloured oil (Found: C, 76·9; H, 9·5. $C_{22}H_{32}O_3$ requires C, 76·8; H, 9·3%).

The following compounds were prepared in similar fashion: *6″-Hydroxy-4″-*n*-butoxy-2 : 2 : 5′-trimethyl-3′ : 4′ : 5′ : 6′-tetrahydrodibenzopyran* (II; R = *n*-C_4H_9); distilled at 185—189° (bath temp.)/0·01 mm. (Found: C, 75·9; H, 9·2. $C_{20}H_{28}O_3$ requires C, 76·0; H, 8·9%). *6″-Hydroxy-4″-*n*-amyloxy-2 : 2 : 5′-trimethyl-3′ : 4′ : 5′ : 6′-tetrahydrodibenzopyran* (II; R = *n*-C_5H_{11}); distilled at 205—210° (bath temp.)/0·1 mm. (Found: C, 77·0; H, 9·6. $C_{21}H_{30}O_3$ requires C, 76·4; H, 9·1%). *6″-Hydroxy-4″-*n*-heptyloxy-2 : 2 : 5′-trimethyl-3′ : 4′ : 5′ : 6′-tetrahydrodibenzopyran* (II; R = *n*-C_7H_{15}); distilled at 210—215° (bath temp.)/0·15 mm. (Found: C, 77·0; H, 9·5. $C_{23}H_{34}O_3$ requires C, 77·1; H, 9·5%).

*6″-*O*-Dichlorophosphoryl-2 : 2 : 5′ : 4″-tetramethyl-3′ : 4′ : 5′ : 6′-tetrahydrodibenzopyran.*—To 6″-hydroxy-2 : 2 : 5′ : 4″-tetramethyl-3′ : 4′ : 5′ : 6′-tetrahydrodibenzopyran (0·7 g.), dissolved in dry pyridine (2·5 c.c.) and cooled in ice, phosphoryl chloride (0·6 g.) was added. After several hours the mixture was refluxed for 30 mins., cooled, and extracted twice with dry benzene. The extract was evaporated under reduced pressure to remove solvents, and again after addition of more dry benzene. The residue was distilled, giving a colourless oil (0·6 g.) at 170° (bath temp.)/0·15 mm. (Found : C, 53·6, 55·0; H, 6·2, 6·3; Cl, 18·3. $C_{17}H_{21}O_3Cl_2P$ requires C, 54·3; H, 5·6; Cl, 18·9%).

The *dichlorophosphoryl* derivative (0·55 g.) in ethereal solution was shaken with water for 3 hours; titration then showed that 99% had been converted into the corresponding acid. The ethereal solution was washed with water, dried, and evaporated, and the viscous residue treated with alcoholic sodium hydroxide (2 mols.). The corresponding *disodium phosphate* was obtained as a white hygroscopic powder by precipitation with dry ether (Found : C, 49·0; H, 6·2. $C_{17}H_{21}O_5PNa_2,2H_2O$ requires C, 48·8; H, 6·0%).

O-*Dichlorophosphoryltetrahydrocannabinol*.—Prepared in similar fashion from tetrahydrocannabinol (I), the *product* was a colourless oil distilling at 185° (bath temp.)/0·1 mm. (Found : C, 57·5; H, 6·9; Cl, 16·5. $C_{21}H_{29}O_3Cl_2P$ requires C, 58·5; H, 6·7; Cl, 16·5%). The corresponding disodium phosphate, a white hygroscopic powder, was prepared by the method described above; in this case hydrolysis of the dichlorophosphoryl derivative was slower. After 3 days' standing in the refrigerator 50% of the phosphoryl compound was hydrolysed. A further 3 hours of shaking with fresh water were necessary for completion of the hydrolysis.

Tetrahydrocannabinyl Phosphate.—The above sodium salt was dissolved in water, the solution acidified with hydrochloric acid, and the *phosphate* extracted with ether. Removal of the ether left a viscous oil, which was dried in a vacuum at 50° (Found : C, 64·0; H, 7·9. $C_{21}H_{31}O_5P$ requires C, 64·0; H, 7·9%).

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