[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Structure of Cannabidiol. VI. Isomerization of Cannabidiol to Tetrahydrocannabinol, a Physiologically Active Product. Conversion of Cannabidiol to Cannabinol[1]

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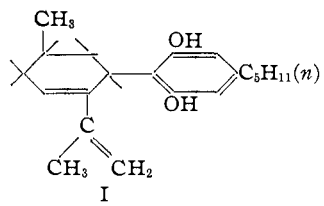
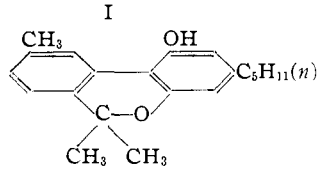
Previous investigations on cannabidiol[1] have indicated that it has the structure shown in I, with doubt merely as to the position of the double bond in the left-hand ring. Synthesis has demonstrated cannabinol to have structure II.



I

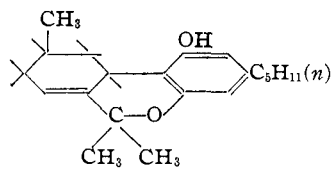


II

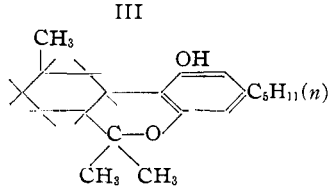
Cannabidiol has now been subjected to a variety of reagents which cause the characteristic purple color it gives with 5% ethanolic potassium hydroxide (Beam test) to disappear. It has been found that a mixture of pyridine hydrochloride and cannabidiol when heated at a temperature considerably below that at which it is cleaved to olivetol and *p*-cymene[2] yields a colorless, very viscous oil which does not exhibit the Beam test. This oil contains chlorine until it is distilled in high vacuum, after which it is chlorine-free. The analysis of the chlorine-free material indicates it has the same molecular formula as cannabidiol, a Zerewitinoff determination proves the presence of one hydroxyl group and by quantitative reduction one double bond is shown to be present. Fractions of the product through high-vacuum distillation varied in specific rotation, dependent on the exact details of preparation as well as on the mode of distillation. The material thus obtained is consequently not a pure substance.

The structure of cannabidiol is such that the loss of an hydroxyl group and a double bond by treatment with pyridine hydrochloride is readily understandable. This reagent isomerizes *o*-allyl phenols to substituted dihydrobenzofurans.[3] Perhaps by a similar mechanism, first addition of hydrogen chloride and then elimination involving the hydroxyl hydrogen, cannabidiol isomerizes to a pyran, tetrahydrocannabinol (III). The hydrogenated product, hexahydrocannabinol, will have structure IV.

The remaining double bond in III is apparently



III



IV

very susceptible to addition so that after the pyran ring is closed, it adds hydrogen chloride. Although the position of this double bond is uncertain it is of no significance so far as discussion of what probably happens during the reaction. This double bond may add hydrogen chloride in two ways, thus yielding two chlorine derivatives, probably with one predominating over the other. It is also possible, however, for each to exist in more than one stereochemical form. This mixture of chlorides dehydrohalogenates on distillation and it is obvious that each chloride can theoretically give two olefinic compounds depending on the hydrogen selected for elimination as hydrogen chloride. The fact that more than one tetrahydrocannabinol is obtained thus becomes explicable.

Confirmation of the presence of a pyran ring in the isomerized cannabidiol was obtained by dehydrogenation of the product. By means of sulfur, the left-hand ring was aromatized and the substance obtained was cannabinol (II) as shown by mixed melting point with an authentic sample

(1) For previous paper in this series see Adams, Wolff, Cain and Clark, THIS JOURNAL, **62**, 2215 (1940).

(2) Adams, Hunt and Clark, *ibid.*, **62**, 735 (1940).

(3) Claisen and co-workers, *Ber.*, **58**, 275 (1925); **59**, 2344 (1926); *Ann.*, **401**, 26 (1903); **418**, 76 (1919); **442**, 230 (1925).

and comparison of derivatives. Since the pyran structure in cannabinol has been proved by synthesis, the presence of the pyran ring in isomerized cannabidiol is established. This experiment is interesting also in that it suggests that in the hemp plant, cannabinol may be formed by an analogous mechanism; the precursor cannabidiol isomerizes to a tetrahydrocannabinol which in turn is oxidized to cannabinol.[4]

The isomerization of cannabidiol occurs with many other reagents, and can be very conveniently followed experimentally by the gradual disappearance of the Beam test. Hydrogen chloride in ether and a mixture of a substantial amount of hydrochloric acid and ethanol act rapidly. In both these cases, the primary products contain chlorine and, after distillation, the chlorine-free products do not give a tetrahydrocannabinol of constant rotation. Sulfamic acid, ethanolic phosphoric acid or zinc chloride is also effective in introducing the pyran ring.

After a rather extensive study, a very convenient method of cannabidiol isomerization was found which consists in refluxing an ethanolic solution of cannabidiol containing 0.1 mole equivalent of hydrogen chloride in the form of hydrochloric acid for about eight hours. The addition of hydrogen chloride to the ring double bond of the isomerized product must then be reduced to a minimum, not only because the hydrogen chloride is very dilute but also because it is present in amounts sufficient only to react with 10% of the tetrahydrocannabinol even if it added quantitatively. Actually as much hydrogen chloride can be recovered after the reaction is complete as can be obtained from a blank run of ethanolic hydrogen chloride treated in a similar manner, thus indicating that addition of hydrogen chloride to the tetrahydrocannabinol is essentially nil. The possibility that even this very dilute hydrogen chloride solution may cause a shifting of the double bond in the tetrahydrocannabinol or interconversion of stereoisomers cannot be disregarded. By such treatment cannabidiol gives a tetrahydrocannabinol of fairly constant specific rotation, $[\alpha]^{34}D - 165 \pm 7°$, indicating it to be a substance that is very nearly homogeneous.

The use of phosphoric acid for isomerization under carefully regulated conditions resulted in a tetrahydrocannabinol of essentially the same specific rotation. No crystalline derivative of this isomerized material has been isolated as yet. The evidence is that it is a tetrahydrocannabinol which contains small amounts of one or more very closely related isomers or stereoisomers.

Upon heating cannabidiol with pyridine hydrochloride under specified conditions, cannabidiol gives a tetrahydrocannabinol of fairly constant rotation $[\alpha]^{34}D - 240 \pm 10°$. In a single experiment with sulfamic acid, the same product of high rotation resulted.

When the tetrahydrocannabinol is reduced, regardless of its initial rotation, a hexahydrocannabinol (IV) is formed which has a constant specific rotation $[\alpha]^{27}D - 70°$. This indicates that the difference in the rotation of the tetrahydrocannabinols is due probably to the difference in the position of the double bond, and the variability in rotation of any particular product depends on the relative amounts of the tetrahydrocannabinol isomers present.

Of great importance is the observation that the tetrahydrocannabinols by isomerization of cannabidiol, whether the specific rotation of the sample is fairly constant or whether it varies widely upon fractionation, have a marihuana activity many times that of the purified red oil used as a raw material. Since cannabidiol was shown by us in previous work to be physiologically inactive and this has been confirmed by repetition of the tests with crystalline material, one or more active products are obviously being synthesized. Moreover, the hexahydrocannabinol, apparently a homogeneous product, obtained by reduction of the double bond in the tetrahydrocannabinol is also physiologically active.

The evidence from these experiments is that there are at least two tetrahydrocannabinols and probably more which are physiologically active and that the double bond in the left-hand ring is not essential for marihuana activity. It thus appears likely that the marihuana activity in red oil is due to one or more of these or to analogous substances. Hence the crystalline physiologically active compound, recently reported by Haagen-Smit[5] and isolated from red oil will probably be found to possess a structure of this kind.

Experimental

Isomerization of Cannabidiol; Formation of Tetrahydrocannabinols

A. By Hydrogen Chloride in Ethanol.—A solution of 3.14 g. (0.01 mole) of cannabidiol (m. p. 66–67°) in 100 cc.

(4) Jacob and Todd, *J. Chem. Soc.*, 649 (1940).

(5) Haagen-Smit, Wawra, Koepfli, Alles, Feigen and Prater, *Science*, **91**, 602 (1940).

of absolute ethanol containing 0.001 mole of hydrogen chloride (added as *M* ethanolic hydrochloric acid) was refluxed on a steam-bath for eight hours. At the end of this time the Beam test (purple color with 5% ethanolic potassium hydroxide) had become negative. The reaction mixture was poured into water and the product extracted with ether. The ether extract was washed with water, dilute aqueous sodium bicarbonate and again with water. After drying and evaporating the ether, the residue was distilled; colorless, highly viscous oil, b. p. 188–190° (2.5 mm.), 158–160° (0.05 mm.), $n^{20}D$ 1.5432. Six fractions of the distillate were collected, the specific rotation values of each being essentially the same.

Rotation. 0.0297 g. made up to 5 cc. with 95% ethanol at 27° gave αD −1.90°; *l*, 2; $[\alpha]^{27}D$ −160°. Zerewitinoff: 0.246 g. gave 16.0 cc. of methane (S. T. P.). Calculated for one OH, 17.5 cc. of methane.

Anal. Calcd. for $C_{21}H_{30}O_2$; C, 80.21; H, 9.62. Found: C, 79.90; H, 9.52.

The reaction product in a run similar to that described was washed carefully with water and the hydrogen chloride was titrated. About 72% of the hydrogen chloride originally added was found. However, if the same concentration of hydrogen chloride in ethanol without any cannabidiol is treated in exactly the same manner, only 75% recovery was obtained. Thus it is fair to conclude that essentially no hydrogen chloride is being added to the tetrahydrocannabinol.

After the initial experiments in which, regardless of the method of isomerization, it was found the product boiled the same, an all-glass high vacuum apparatus was used with no attempt to determine the temperature of distillation except by the control of the bath temperature.

It was found that varying the quantities of reactants, although in the same proportion, sometimes gave a product with a specific rotation varying as much as 7° from the above value.

Using a larger proportion of hydrochloric acid up to 1.5 moles per mole of cannabidiol caused addition of hydrogen chloride to the double bond but distillation of the product resulted in the loss of hydrogen chloride and a chlorine-free material. It had the same b. p. as previously recorded but the specific rotation of various fractions varied widely. Thus, in several typical runs the following values for successive fractions were obtained. A. 1 mole of hydrogen chloride and 1 mole of cannabidiol refluxed for five hours gave fractions $[\alpha]^{30}D$ −146°, −191°, −223°. B. 1.5 moles of hydrogen chloride and 1 mole of cannabidiol refluxed for seven hours gave fractions $[\alpha]^{28}D$ −163°, −174°, −215°. C. 0.75 mole of hydrogen chloride and 1 mole of cannabidiol refluxed for 2.75 hours gave fractions $[\alpha]^{27}D$ −207°, −219°, −235°, −234°.

B. By Hydrogen Chloride in Ether.—A solution of 3.1 g. of cannabidiol (m. p. 66–67°) was prepared in 50 cc. of dry ether which had been saturated previously with dry hydrogen chloride at 0°. The solution was allowed to stand for four hours at 0°, then poured onto ice. The ether layer was separated, washed with aqueous sodium bicarbonate and water, dried and distilled. The remaining oil which contained chlorine was heated with 10 cc. of quinoline for two hours at 185–190°. After cooling, the reaction mixture was poured into cold 10% sulfuric acid. The product was extracted with ether and the ether solution washed with dilute sulfuric acid, with aqueous sodium bicarbonate then water. The cyclization resulted in a substance with the same boiling point as that previously reported. Four fractions gave variable rotations: $[\alpha]^{29}D$ −166°, −180°, −188°, −191°.

C. By Pyridine Hydrochloride.—A mixture of 6 g. of dry pyridine hydrochloride and 3 g. of cannabidiol (m. p. 66–67°) was heated at 125° for one hour. The Beam test (purple color with 5% ethanolic potassium hydroxide) had entirely disappeared after a relatively short time. The product was washed with water to free from pyridine hydrochloride, extracted with ether and the ether solution washed with water. After evaporation of the solvent, the product was distilled in high vacuum, whereupon hydrogen chloride was evolved. The distillate was a highly viscous, colorless oil with a b. p. approximately the same as that reported in the experiments using hydrochloric acid in ethanol for cyclization. Upon separating into six fractions, the specific rotations were as follows: $[\alpha]^{32}D$ −235°, −236°, −235°, −241°, −244°, −249°.

Rotation. (Fraction 1) 0.0314 g. made up to 5 cc. with 95% ethanol at 32° gave αD −2.95°; *l*, 2; $[\alpha]^{32}D$ −235°.

D. By Phosphoric Acid.—A mixture of 3 g. of cannabidiol (m. p. 66–67°), 150 cc. of ethanol and 50 cc. of sirupy phosphoric acid (85%) was refluxed for thirty-five minutes which resulted in a negative Beam test. It was poured into water and the product extracted with ether. Six fractions were collected in distillation, all of which gave essentially the same specific rotation, $[\alpha]^{26}D$ −160°. This product appears, therefore, to be the same as that prepared by the very dilute ethanolic hydrochloric acid method A.

Rotation. (Fraction 3) 0.0481 g. made up to 5 cc. with 95% ethanol at 26° gave αD −1.54°; *l*, 1; $[\alpha]^{26}D$ −160°.

If the reaction mixture was refluxed for two hours instead of thirty-five minutes with the proportions 3 g. of cannabidiol, 55 cc. of ethanol, 20 cc. of sirupy phosphoric acid (85%), a product was obtained which gave fractions with specific rotations varying from −188° to −199°. Upon refluxing one of these fractions for twelve hours with ethanol and phosphoric acid, the product gave a specific rotation of −179°.

It is obvious that changes are taking place in the molecule by the treatment just described. It may consist in shifting of the double bond or interchange of stereoisomers or both.

E. Sulfamic Acid; Zinc Chloride.—The experiments on the isomerization of cannabidiol with sulfamic acid or zinc chloride are in the preliminary stage. It may be mentioned here, however, that upon heating with these reagents, the Beam test rapidly disappeared. From one sulfamic acid experiment at 125° (0.5 g. of cannabidiol, 1 g. of sulfamic acid), the product gave a specific rotation of −250°.

Dehydrogenation of Tetrahydrocannabinol to Cannabinol.—A mixture of 2.82 g. of tetrahydrocannabinol ($[\alpha]^{32}D$ −167°) and 0.58 g. of sulfur in a side-neck test-tube was heated at 240–250° until evolution of hydrogen sulfide had ceased (about twenty minutes). After cooling to 180–190°, the product was distilled *in vacuo* onto a cold finger. The resulting material was taken up in about 25 cc. of petroleum ether (b. p. 30–60°) the solution cooled and scratched. About 0.5 g. of crude cannabinol was

thus obtained. On further purification from the same solvent, it gave white crystals, m. p. 75–76° (cor.) identical in all respects with an authentic sample of cannabinol.

Anal. Calcd. for $C_{21}H_{26}O_2$: C, 81.21; H, 8.45. Found: C, 81.48; H, 8.66.

The cannabinol thus obtained was converted into the *p*-nitrobenzoate by the procedure previously described.[6] It had a melting point of 165–166° (cor.) and showed no melting point depression when mixed with an authentic sample of cannabinol *p*-nitrobenzoate.

Hexahydrocannabinol by Reduction of Tetrahydrocannabinol.—A solution of 3.14 g. of tetrahydrocannabinol ($[\alpha]^{27}D$ −160°) which had been distilled in high vacuum in an all-glass apparatus, in 50 cc. of glacial acetic acid was reduced with hydrogen at room temperature, using 0.1 g. of platinum oxide. Hydrogen corresponding to 0.96 mole per mole of tetrahydrocannabinol was absorbed in about four hours, after which hydrogenation continued to proceed but at a very much slower rate. After absorption of one mole equivalent of hydrogen, the solution was filtered and the acetic acid removed *in vacuo*. The hexahydrocannabinol formed a colorless, highly viscous resin, b. p. 153–155° (0.1 mm.) (bath temp. 180–185°), $n^{20}D$ 1.5348.

Rotation. 0.0252 g. made up to 5 cc. with 95% ethanol at 27° gave αD −0.71°; *l*, 2; $[\alpha]^{27}D$ −70°.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.69; H, 10.19. Found: C, 79.35; H, 10.43.

It was found that regardless of the initial rotation of the tetrahydrocannabinol used, the hexahydro product always had essentially the same specific rotation.

(6) Adams, Baker and Wearn, THIS JOURNAL, **62**, 2204 (1940).

Summary

By a variety of reagents cannabidiol loses one hydroxyl and a double bond and is isomerized to tetrahydrocannabinol. The structure of this latter product was determined by dehydrogenation to cannabinol.

The tetrahydrocannabinol varies in rotation depending upon the mode of formation. A product of fairly constant rotation $[\alpha]^{34}D$ −165 ± 7° was obtained by the use of very dilute ethanolic hydrochloric acid or ethanolic sirupy phosphoric acid under regulated conditions; by use of pyridine hydrochloride or sulfamic acid, a product $[\alpha]^{34}D$ −240 ± 10°. The difference in rotation is due probably to the difference in the position of the double bond in the tetrahydrocannabinol.

Regardless of the specific rotation of the tetrahydrocannabinol, it absorbs one mole of hydrogen upon reduction with formation of a hexahydrocannabinol of constant rotation $[\alpha]^{27}D$ −70°.

The tetrahydrocannabinol preparations showed marihuana activity many times that of the purified red oil used for isolation of cannabidiol. The hexahydrocannabinol is also active. The inactivity of cannabidiol by tests on crystalline material, has been confirmed.

URBANA, ILLINOIS RECEIVED JULY 23, 1940

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Structure of Cannabidiol. VII. A Method of Synthesis of a Tetrahydrocannabinol which Possesses Marihuana Activity[1]

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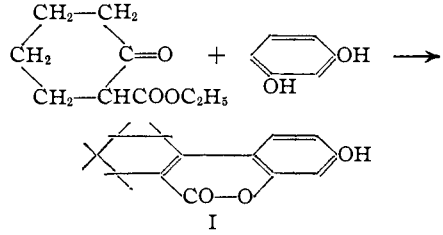
Ahmad and Desai[2] have reported that ethyl cyclohexanone-2-carboxylate condenses with resorcinol and with orcinol in the presence of phosphorous oxychloride to yield partially reduced dibenzopyrones I and II. The pyrone (II) was



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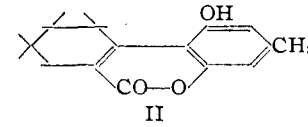
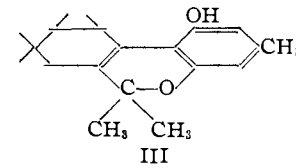


II

prepared and treated with excess methylmagnesium iodide. It is thus readily converted to the corresponding pyran (III).



III

These results have an important bearing upon the cannabidiol problem, for cannabidiol isomer-

(1) For previous paper in this series see Adams, Pease, Cain and Clark, THIS JOURNAL, **62**, 2402 (1940).

(2) Ahmad and Desai, *J. Univ. Bombay*, **6**, Pt. II, 89 (1937).