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

Structure of Cannabidiol. III. Reduction and Cleavage

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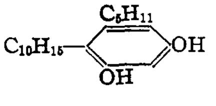
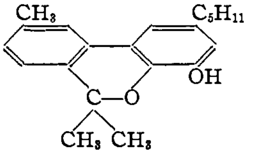
On the basis of absorption spectra,[2] cannabidiol (I) appears to be a resorcinol and not a catechol derivative as was first assumed after a consideration of the structure proposed by Cahn[3] for the closely related compound cannabinol (II).



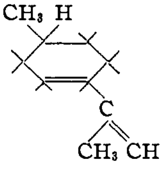
I



II

The C_5H_{11}-group previously has been shown to be normal. New chemical evidence is now submitted to demonstrate that cannabidiol is a resorcinol derivative. Information also has been discovered pertaining to the position of the amyl group in the resorcinol nucleus and to the chemical characteristics and the mode of attachment of the $C_{10}H_{15}$-grouping.

Earlier experiments on catalytic reduction of cannabidiol were variable and hence unsatisfactory for quantitative deductions. These results probably were due primarily to the fact that the cannabidiol used contained traces either of 3,5-dinitrobenzamide or ethyl 3,5-dinitrobenzoate. When pure, cannabidiol reduces rapidly in glacial acetic acid with platinum oxide catalyst and hydrogen at room temperature and 2–3 atm. pressure. Two moles of hydrogen are absorbed before the reduction stops. The product has all of the characteristic color reactions of the original molecule and contains two active hydrogens. It was concluded, therefore, that the amylresorcinol nucleus remained unaffected, and that the reduction had occurred in the $C_{10}H_{15}$-residue with the establishment of the presence therein of two double bonds. In view of the rapidity of hydrogenation under mild conditions, it appears unlikely that the unsaturation consists of one double bond and a three-, four- or five-membered ring such as was suggested as a possibility in the first paper in this series. With these facts in hand and keeping in mind the cannabinol formula, the $C_{10}H_{15}$-group may be postulated as a menthyl residue containing two double bonds (III) which have been assigned the positions indicated fortuitously.



III

The tetrahydrocannabidiol is an essentially colorless, viscous, optically active oil. No crystalline derivatives have as yet been isolated. The product probably is not a pure individual, for reduction of two double bonds in an optically active nucleus is likely to lead to diastereoisomeric tetrahydro derivatives.

Dehydrogenation of cannabidiol was also attempted. The product was optically inactive and analyzed satisfactorily for a biphenyl molecule. No solid derivatives, however, were obtained. In view of the possibility of disproportionation and the small amounts of material taken, these experiments may be used merely as a further indication of the presence of a menthyl group containing two double bonds, which may dehydrogenate, possibly with rearrangement, to a cymyl group. The description of these experiments will be postponed to a later paper.

A reaction of cannabidiol which proved to be very informative was its pyrolytic cleavage with pyridine hydrochloride. When heated to 210–230° for three hours, a mixture of cannabidiol and pyridine hydrochloride decomposes and cymene distils. Cymene was proven beyond a doubt by its analysis, physical and chemical properties. Isolation of cymene confirms the previous evidence that the $C_{10}H_{15}$-residue is a menthyl containing two double bonds. From the residual mixture after pyrolysis, was isolated olivetol, 1,3-dihydroxy-5-*n*-amylbenzene, proved by comparison of it and its *bis*-3,5-dinitrobenzoate with au-

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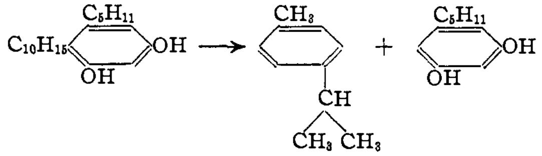
(1) An abstract of a thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy in chemistry. Solvay Process Company Fellow, 1939–1940.

(2) (a) Adams, Cain and Wolff, THIS JOURNAL, **62**, 732 (1940); (b) for first paper in this series see Adams, Hunt and Clark, *ibid.*, **62**, 196 (1940).

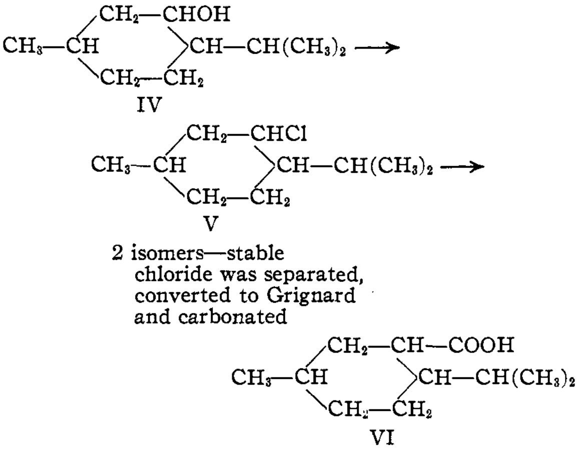
(3) Cahn, *J. Chem. Soc.*, 986 (1930); 630 (1931); 1342 (1932); 1400 (1933).

thentic samples of these products. The equation may be written as follows



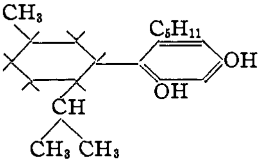
The isolation of olivetol establishes the orientation of the two hydroxyls and the *n*-amyl groups in cannabidiol. The mechanism of this cleavage is not clear and the limited quantity of cannabidiol available excluded further study. It may consist in the primary addition of hydrogen chloride, the hydrogen sufficing to complete the olivetol molecule and the chlorine forming $C_{10}H_{15}Cl$. This latter then is dehydrohalogenated to an olefin linkage which with the other two already present conjugate to a benzene system. On the other hand, the pyridine hydrochloride may function merely as a catalyst in the cleavage. The olivetol then would be formed by removal of a hydrogen from a carbon adjacent to that to which it is attached in the $C_{10}H_{15}$–residue. A new double bond simultaneously would be introduced in the $C_{10}H_{15}$–group thus leading to the completed molecule $C_{10}H_{14}$. Sulfamic acid in place of pyridine hydrochloride gave traces of cymene but the cleavage reaction did not appear to take place readily under these conditions.

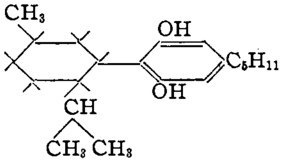
Numerous experiments on the oxidation of cannabidiol to obtain one of the two possible olivetol carboxylic acids and thus to establish the position of the $C_{10}H_{15}$–group were unsuccessful. However, oxidation of the tetrahydrocannabidiol gave evidence as to the carbon of the dihydrocymyl residue (III) which was attached to the olivetol. Permanganate in acetone oxidation resulted in a mixture from which sodium bicarbonate solution extracted organic acids. It was obvious by the odor that caproic acid and possibly other low molecular weight aliphatic acids were present. This mixture was converted into the corresponding acid chlorides and then to the anilides. By crystallizing the anilides from benzene a single pure substance was isolated with a melting point of 152–152.5°. Analysis showed $C_{17}H_{25}ON$ and thus the molecule coincided with that of a menthanecarboxylic acid anilide $C_{10}H_{19}CONHC_6H_5$. Of the various theoretically-possible menthane carboxylic acids, one is described, the anilide of which melts at about the same point as that obtained in the above oxidation experiment.[4] This was synthesized by Kurssanow's method. It proved by mixed melting point to be identical with the cannabidiol product. Since the synthetic acid was prepared from *l*-menthol (IV–VI), the configuration of one or more of the asymmetric carbons in tetrahydrocannabidiol probably is similar to the corresponding asymmetric carbons in *l*-menthol



It would appear likely that this acid is the same as that obtained by Bergel[5] from oxidation of reduced red oil. He reported that the anilide of his acid melted at 148.5° (uncor.) but did not identify it. The analyses for this product averaged quite close to the calculated for menthane carboxylic acid anilide (Calcd.: C, 78.72; H, 9.72; N, 5.40. Found: C, 78.56; H, 9.68; N, 6.05).

Significant is the fact that isolation of menthane carboxylic acid anilide establishes the linkage of the $C_{10}H_{15}$–group to the olivetol residue as on the carbon adjacent to that holding the isopropyl group. Consequently, tetrahydrocannabidiol may be formulated as VII or VIII.


VII


VIII

Cannabidiol then must be considered as one of these two molecules with two double bonds in the left-hand cycle, the positions of which are now being investigated.

[4] Kurssanow, *J. Russ. Phys.-Chem. Soc.*, **46**, 815 (1914); *C. A.*, **9**, 1751 (1915).

[5] Bergel, *Ann.*, **482**, 72 (1930).

Experimental

Cleavage of Cannabidiol to Cymene and Olivetol.—A mixture of 10 g. of cannabidiol and 12 g. of pyridine hydrochloride was heated for three hours at 210–230°. During the heating a liquid distilled. It was taken up in a little ether, extracted with dilute hydrochloric acid and then with water. After drying with anhydrous magnesium sulfate, the ether was removed by distillation and the product distilled. It boiled very sharply at 176° (cor.) (745 mm.); n^{20}_D 1.4900; d^{20}_4 0.8561; yield 2.6 g.

Anal. Calcd. for $C_{10}H_{14}$: C, 89.53; H, 10.51. Found: C, 89.55; H, 10.50.

The same constants were found for an authentic sample of *p*-cymene.

The residue in the reaction flask was treated with a little water and extracted several times with ether. The ether layer was separated, washed with dilute hydrochloric acid and then extracted twice with 10% aqueous sodium hydroxide. The aqueous extracts were acidified with hydrochloric acid and extracted several times with ether. After drying the ether layer with anhydrous magnesium sulfate, the ether was removed and the product distilled. It boiled at 170–175° (2 mm.); yield 3.2 g. The oil was warmed with water and on cooling a white crystalline material, m. p. 41°, was obtained. The crystalline product showed no melting point depression when mixed with an authentic sample of olivetol hydrate, 1,3-dihydroxy-5-*n*-amylbenzene hydrate. Upon drying the hydrate at 50° (2 mm.), anhydrous olivetol was obtained.

Anal. Calcd. for $C_{11}H_{16}O_2 \cdot H_2O$: C, 66.64; H, 9.15. Found: C, 66.69; H, 8.98.

For further identification of the olivetol from the cleavage reaction, it was converted to the *bis*-3,5-dinitrobenzoate by the use of 3,5-dinitrobenzoyl chloride and pyridine. The product was purified from ethanol or ether; white crystals, m. p. 127–128° (cor.).

Anal. Calcd. for $C_{25}H_{20}O_{12}N_4$: C, 52.90; H, 3.54; N, 9.84. Found: C, 52.87, 52.98; H, 3.59, 3.87; N, 10.08.

An identical product was obtained in a similar manner from synthetic olivetol.

Tetrahydrocannabidiol.—A solution of 4.86 g. of cannabidiol in 150 cc. of glacial acetic acid was reduced with hydrogen at 2–3 atm. pressure at room temperature using 0.1 g. of platinum oxide. Hydrogen corresponding to 2.06 moles per mole of cannabidiol was absorbed in fifteen minutes, after which no pressure change was noted in an additional thirty minutes.

The acetic acid was removed *in vacuo* and the tetrahydrocannabidiol, a pale yellowish highly viscous resin, was distilled, b. p. 188–190° (2.5 mm.) (bath temperature 200–215°, n^{20}_D 1.5298; yield 4.05 g.).

Rotation. 0.0582 g. made up to 5 cc. with 95% ethanol at 25° gave α_D −0.33; l, 1; $[\alpha]^{25}_D$ −28°.

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.18; H, 10.76. Found: C, 78.97; H, 10.52.

Oxidation of Tetrahydrocannabidiol.—To a solution of 2.75 g. of tetrahydrocannabidiol in 100 cc. of acetone was added over a three-hour period a solution of 9.5 g. of potassium permanganate in 500 cc. of acetone at room temperature. During the first ninety minutes of addition, reaction was instantaneous. The flask became warm. The reaction was much slower during the latter part of the addition and unreacted permanganate remained an hour after addition was complete.

The mixture was made slightly acid and the manganese dioxide and excess permanganate were destroyed with sodium bisulfite. After dilution with 500 cc. of water, most of the acetone was removed by distillation. It was then extracted with ether and the ether in turn extracted with aqueous sodium bicarbonate. The bicarbonate layer was acidified and extracted with ether. After removal of the ether the crude bicarbonate-soluble portion amounted to 0.87 g. and the bicarbonate-insoluble, 1.52 g.

The bicarbonate-soluble material, which had an odor of lower fatty acids, was treated with 1.6 g. of thionyl chloride and refluxed overnight on a steam cone. The excess thionyl chloride was evaporated, the resulting mixture dissolved in 10 cc. of benzene, and 4 g. of aniline added. Solid material separated at once. The mixture was heated on the steam cone for two hours, poured into dilute hydrochloric acid solution and extracted with benzene. A product gradually crystallized and was purified by further crystallization from benzene; white crystals, m. p. 152–152.5° (cor.).

Anal. Calcd. for $C_{17}H_{25}ON$: C, 78.72; H, 9.72; N, 5.40. Found: C, 78.79; H, 9.81; N, 5.37.

A mixed melting point with the anilide of *p*-menthane carboxylic acid prepared by the method of Kurssanow[4] showed no depression.

Summary

Cleavage of cannabidiol with pyridine hydrochloride resulted in formation of *p*-cymene and olivetol, demonstrating that cannabidiol probably is a dihydrocymyl group attached to an olivetol residue.

Reduction of cannabidiol resulted in the rapid absorption of two moles of hydrogen with formation of a tetrahydro derivative which showed the same color reactions as cannabidiol. From this experiment it was deduced that the olivetol nucleus was unattacked and confirmed the fact that two double bonds were present in the $C_{10}H_{15}$– grouping.

Oxidation of tetrahydrocannabidiol led to the isolation of a menthane carboxylic acid identical with that which previously has been synthesized from *l*-menthol. The linkage of the $C_{10}H_{15}$–residue thus is established as on the carbon adjacent to that holding the isopropyl group.

Evidence is presented that cannabidiol is a dihydrocymyl olivetol.

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