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

Structure of Cannabidiol. II. Absorption Spectra Compared with those of Various Dihydric Phenols

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The isolation of a new substance, cannabidiol, from the red oil of Minnesota wild hemp was recently described.[1] It proved to be an optically active, resinous, dihydric phenol from which two crystalline derivatives, the *bis*-3,5-dinitrobenzoate and the *bis*-*m*-nitrobenzenesulfonate, could be obtained. A pure dimethyl ether also was prepared. Oxidation of cannabidiol with formation of *n*-caproic acid indicated the likelihood of the presence of an *n*-amyl group in the phenolic nucleus.

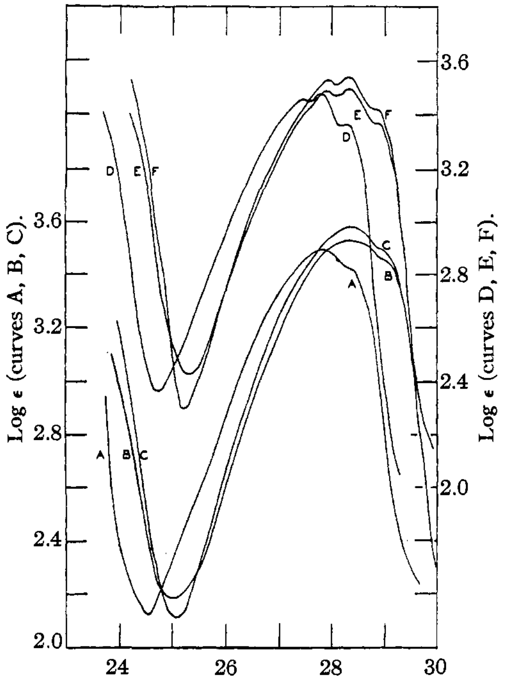
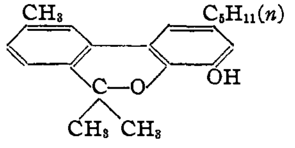
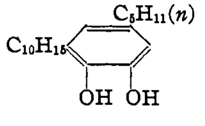


Fig. 1.—A, Catechol; B, 4-methylcatechol; C, 4-*n*-amylcatechol; D, catechol dimethyl ether; E, 4-methylcatechol dimethyl ether; F, 4-*n*-amylcatechol dimethyl ether.

The analyses of cannabidiol and its derivatives revealed the probable formula as $C_{21}H_{30}O_2$, whose similarity to that of cannabinol, $C_{21}H_{26}O_2$, is striking. With the structure of cannabinol (I) satisfactorily established,[2] except for the positions of the hydroxyl and *n*-amyl groups, an analogous structure for cannabidiol might be anticipated, since these two natural products come from essentially the same source.



I



II

Consequently, a tentative formula (II) for cannabidiol was suggested with the postulation that the $C_{10}H_{15}$-group was probably a menthyl residue containing two double bonds.

Information concerning the orientation of the two hydroxyls in the cannabidiol molecule is not readily obtained chemically but through absorption spectra the relationship should be possible to determine. With this end in view a comparison has been made of the ultraviolet absorption spectra of cannabidiol and cannabidiol dimethyl ether with those of catechol, 4-methylcatechol and 4-*n*-amylcatechol and their dimethyl ethers, and with those of resorcinol, 5-methylresorcinol and 5-*n*-amylresorcinol and the corresponding dimethyl ethers.

From Fig. 1 it is apparent that the catechols have one broad peak and one that is much narrower. The introduction of alkyl groups into the catechol molecule in the 4-position causes a shift of the peaks of the spectra toward longer wave lengths with a simultaneous increase in the extinction coefficients at these wave lengths. The dimethyl ethers of these compounds show spectra having three distinct peaks and the variations with introduction of the alkyl groups are similar to those in the unmethylated compounds.

In Fig. 2 are given the spectra of resorcinol and its derivatives. They all show two distinct peaks of about the same breadth. In marked contrast to the catechol derivatives, the introduction of alkyl groups in the 5-position causes a slight shift in the peaks of the spectra toward lower wave lengths and the molecular extinction coefficients at these wave lengths are decreased. The same

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[1] Adams, Hunt and Clark, THIS JOURNAL, **62**, 196 (1940).

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

general effects are found in the spectra of the dimethyl ethers.

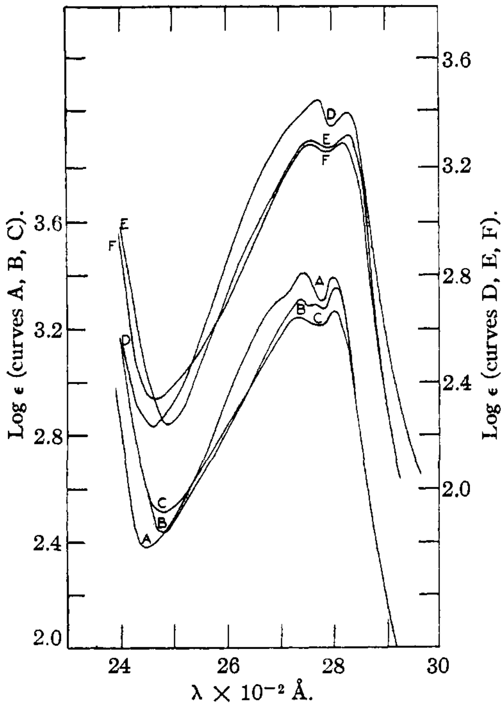


Fig. 2.—A, Resorcinol dimethyl ether; B, 5-methylresorcinol dimethyl ether; C, 5-*n*-amylresorcinol dimethyl ether; D, resorcinol; E, 5-methylresorcinol; F, 5-*n*-amylresorcinol.

A comparison of the spectra of cannabidiol, 5-*n*-amylresorcinol and 4-*n*-amylcatechol shows the striking similarity of the curves of cannabidiol and 5-*n*-amylresorcinol. The peaks in the curve for cannabidiol are shifted toward lower wave lengths and lower extinction coefficients, as was shown to be the effect on the spectra of resorcinol when alkyl groups are introduced. The dimethyl ethers of these three compounds give spectra similarly related.

Confirmation of the deduction that cannabidiol probably is a resorcinol derivative was obtained by infrared absorption spectra (Fig. 4). These were kindly carried out for us by Dr. W. H. Rodebush and Mr. G. W. McMillan of this Laboratory, to whom we are deeply indebted. The spectra of cannabidiol and 5-*n*-amylresorcinol have only single peaks at essentially the same wave length, while that of 4-*n*-amylcatechol shows two distinct peaks at different wave lengths from those shown in the other two spectra.

On the basis of these results, structure II for cannabidiol must be incorrect; it may now be assigned structure III which represents the molecule as a resorcinol derivative. The location of the

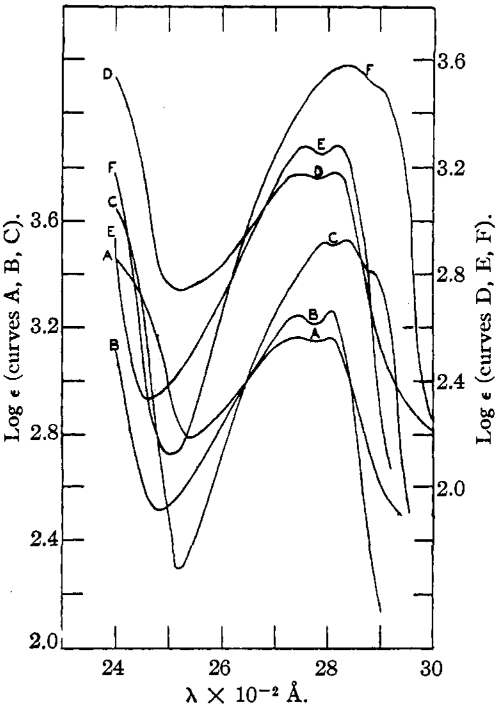


Fig. 3.—A, Cannabidiol dimethyl ether; B, 5-*n*-amylresorcinol dimethyl ether; C, 4-*n*-amylcatechol dimethyl ether; D, cannabidiol; E, 5-*n*-amylresorcinol; F, 4-*n*-amylcatechol.

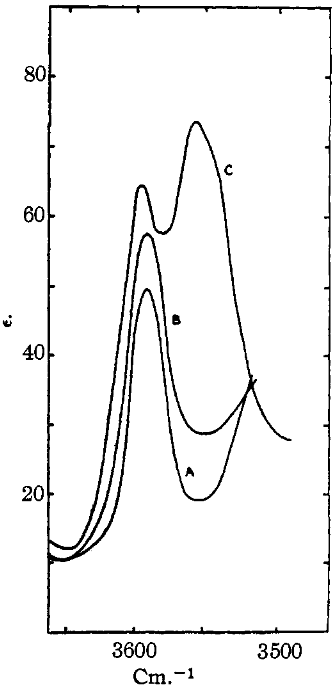
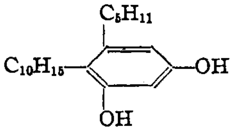


Fig. 4.—A, Cannabidiol; B, 5-*n*-amylresorcinol; C, 5-*n*-amylcatechol.



III

$C_{10}H_{15}$-radical and of the *n*-amyl group in relation to the hydroxyl groups in structure III is purely arbitrary.

Attempts to determine the presence of a resorcinol or catechol orientation of hydroxyls in cannabidiol by means of a variety of color reactions such as have been used in the past for testing for resorcinol, catechol, and red oil, proved negative. No satisfactory correlation was apparent between the color reactions of cannabidiol and 5-*n*-amylresorcinol nor between cannabidiol and 5-*n*-amylcatechol.

Experimental

A Bausch and Lomb medium quartz spectrograph and a Moll type recording densitometer were used for the ultraviolet absorption spectra of solutions of the compounds in ether. The infrared absorption spectra were taken of carbon tetrachloride solutions.

Cannabidiol and cannabidiol dimethyl ether were prepared as previously described.[1]

1,2-Dimethoxy-4-methylbenzene.—This was prepared by the Clemmensen reduction of veratric aldehyde as described by King and l'Ecuyer.[3] The product used boiled at 112° (20 mm.); m. p. 23° (cor.); $n^{25}\text{D}$ 1.5250.

1,2-Dihydroxy-4-methylbenzene (4-Methylcatechol).—A mixture of 9 g. of 1,2-dimethoxy-4-methylbenzene and 37 cc. of 48% hydrobromic acid was refluxed for six hours. Water was added followed by sodium bicarbonate until neutral. The compound was ether extracted, the ether solution in turn extracted with 10% aqueous sodium hydroxide, and the alkaline solution which became deeply colored was acidified immediately with dil. sulfuric acid. Subsequent extraction with ether and evaporation of the solvent gave a product which had a b. p. 141–143° (20 mm.). This liquid solidified and was crystallized from a mixture of benzene and petroleum ether (b. p. 40–60°), m. p. 65–66°. Finally it was redistilled before determining the absorption spectra; yield 4.5 g.

1,2-Dihydroxy-4-*n*-pentanoylbenzene.—This was prepared by a method previously described.[4] The observed m. p. 99–100° (cor.) differed slightly from that given by the above authors.[4]

1,2-Dihydroxy-4-*n*-amylbenzene (4-*n*-Amylcatechol).—Miller, Hartung, Rock and Crossley report only a 40% yield by the Clemmensen reduction of 1,2-dihydroxy-4-*n*-pentanoylbenzene, but a 90% yield by a palladium-hydrogen reduction. It has been found that the Clemmensen reduction of the ketone by the modification of Martin[5] gave a 72% yield; b. p. 153–155° (4–5 mm.); $n^{20}\text{D}$ 1.5258. The product crystallized in rosets on cooling in ice.

1,2-Dimethoxy-4-*n*-amylbenzene (4-*n*-Amylcatechol Dimethyl Ether).—To a mixture of a solution of 3.6 g. of 4-*n*-amylcatechol in 100 cc. of methanol and 6 g. of dimethyl sulfate was added slowly a 10% ethanolic sodium hydroxide solution until the reaction remained neutral. Another 6 g. of dimethyl sulfate was introduced and the procedure repeated. Most of the color in the solution had disappeared when methylation was complete. The mixture was extracted with ether and the ether solution was washed with aqueous alkali; b. p. 124–126° (4–5 mm.); $n^{20}\text{D}$ 1.5084; d^{20}_4 0.9856.

Anal. Calcd. for $C_{13}H_{20}O_2$: C, 75.00; H, 9.62. Found: C, 75.29; H, 9.85.

The resorcinol and orcinol used were purified grades of commercial products. The methyl ethers were prepared in the usual way.

Olivetol dimethyl ether and olivetol were made by the method of Asahina,[6] though more recently the procedure of Suter and Weston[7] for the preparation of these compounds proved to be more satisfactory.

Summary

The ultraviolet and infrared absorption spectra of cannabidiol resemble closely that of olivetol, 1,3-dihydroxy-5-*n*-amylbenzene, and do not resemble that of 4-*n*-amylcatechol. It therefore was concluded that cannabidiol is a resorcinol derivative.

A comparison of the absorption spectra of resorcinol with its 5-methyl and 5-*n*-amyl derivatives indicates that introduction of the alkyl groups causes a slight shift in the peaks toward lower wave lengths and the molecular extinction coefficients at these wave lengths are decreased.

A comparison of catechol and its 4-methyl and 4-*n*-amyl derivatives indicates that introduction of the alkyl groups causes a shift in the peaks toward longer wave lengths and an increase in the extinction coefficients at these wave lengths.

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(3) King and l'Ecuyer, *J. Chem. Soc.*, 427 (1937).

(4) Miller, Hartung, Rock and Crossley, THIS JOURNAL, **60**, 7 (1938).

(5) Martin, *ibid.*, **58**, 1438 (1936).

(6) Asahina, *Ber.*, **69B**, 1643 (1936).

(7) Suter and Weston, THIS JOURNAL, **61**, 232 (1939).