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

Structure of Cannabinol. I. Preparation of an Isomer, 3-Hydroxy-1-*n*-amyl-6,6,9-trimethyl-6-dibenzopyran

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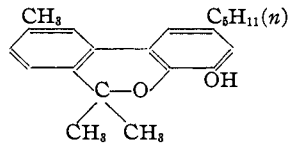
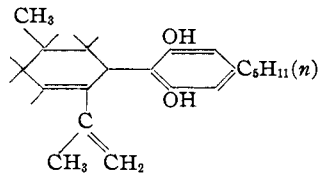
Cannabinol was isolated in 1899 by Wood, Spivey and Easterfield[2] from the red oil from *Cannabis* indica. Crystalline cannabinol acetate served as an intermediate for its separation from the other closely related products in the crude material. Hydrolysis of the ester gave the pure cannabinol, an amber liquid or resin, b. p. 263–264° (20 mm.). Just recently[7d] cannabinol has been isolated from the red oil of Minnesota wild hemp extract through its 3,5-dinitrophenyl urethan. For the first time, cannabinol was obtained as a crystalline solid, m. p. 75–76°. The major contribution to the structure of this product was made by Cahn,[3] supplementing the investigations of Wood, Spivey and Easterfield,[2,4] and supplemented by those of Bergel.[5] Since an excellent discussion of the pertinent chemical work on cannabinol has appeared already,[6] it is necessary merely to present here the formula (I) proposed by Cahn. The structure of the left-hand portion of the molecule was established satisfactorily but no evidence was submitted by which to place the hydroxyl and *n*-amyl groups in the right-hand benzene ring.

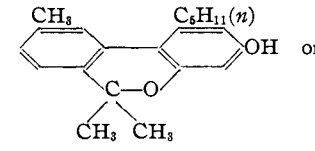


I

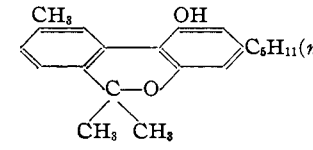


II

The isolation of cannabidiol, $C_{21}H_{30}O_2$ (II, provisional as to double bonds in left-hand portion and position of linkage to right-hand portion), from red oil has been reported[7] and the similarity in its formula and in some of its reactions to cannabinol, $C_{21}H_{26}O_2$, has been observed. Cannabinol and cannabidiol are natural products obtained from essentially the same source. Structural relationships would, therefore, be expected. On this basis it seemed likely that the orientation of the oxygens to each other and of the oxygens to the amyl group might be the same in both molecules. Since cannabidiol was shown to contain an olivetol residue, this same residue might be anticipated in cannabinol which then would have one of the two possible structures (III or IV) instead of that proposed by Cahn (I).[3] These



III



IV

structures would conform very satisfactorily with the observation of Cahn that two nitro groups can be introduced quite readily into the hydroxylated ring of cannabinol.[3]

If one of these structures were established for cannabinol, the inference could be drawn that the doubly unsaturated menthyl residue, $C_{10}H_{15}$–, in cannabidiol (II) was attached similarly. This would be important evidence in regard to whether the $C_{10}H_{15}$– group is linked between the hydroxyls or between an hydroxyl and amyl group in cannabidiol.

(1a) An abstract of a thesis submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry.

(1b) Solvay Process Fellow, 1939-1940.

(2) Wood, Spivey and Easterfield, *J. Chem. Soc.*, **75**, 20 (1899). See also Dunston and Henry, *Proc. Chem. Soc.*, **14**, 44 (1898).

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

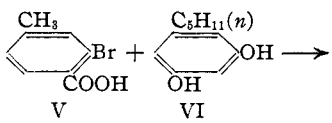
(4) Wood, Spivey and Easterfield, *ibid.*, **69**, 539 (1896).

(5) Bergel, *Ann.*, **482**, 55 (1930); Bergel and Vögele, *ibid.*, **493**, 250 (1932).

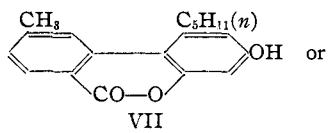
(6) Blatt, *J. Washington Acad. Sci.*, **28**, 465 (1938).

(7) (a) Adams, Hunt and Clark, THIS JOURNAL, **62**, 196, 735 (1940); (b) Adams, Cain and Wolff, *ibid.*, **62**, 732 (1940); (c) Jacob and Todd, *Nature*, **145**, 350 (1940); (d) Adams, Pease and Clark, THIS JOURNAL, **62**, 2194 (1940).

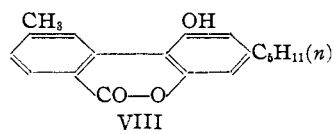
The synthesis of structure III or IV has been completed. Olivetol (VI) was condensed with 4-methyl-2-bromobenzoic acid (V) by means of dilute aqueous alkali and aqueous copper sulfate to give the bicyclic lactone (VII or VIII). The reaction of *o*-bromobenzoic acid and resorcinol to give an analogous lactone was described by Hurtley,[8] who reported about a 65% yield. Before proceeding with the condensation just described, type reactions were carried out; *o*-bromobenzoic



V VI



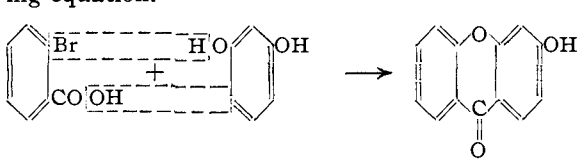
VII



VIII

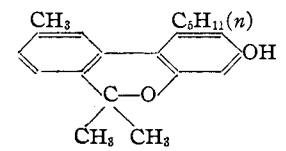
acid with resorcinol and orcinol; 4-methyl-2-bromobenzoic acid with resorcinol and orcinol. The presence of an alkyl group in the resorcinol molecule or in the *o*-bromobenzoic acid reduced the yield of the condensation reaction to approximately 25%, but in each case the product was isolated and purified easily.

Hurtley did not prove the structure of the reported lactone formed in this reaction. The only other possible, though not probable, compound which could result from the elimination of hydrogen bromide and water would be a xanthone. Thus, *o*-bromobenzoic acid and resorcinol might yield 3-hydroxyxanthone according to the following equation.

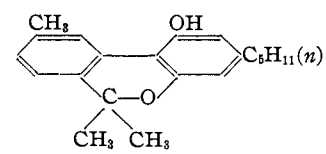


The melting point of 3-hydroxyxanthone prepared by an unequivocal method as reported by Atkinson and Heilbron[9] is 246°; for the product from *o*-bromobenzoic acid and resorcinol, 247°. These constants are very close together but the methyl ether of the xanthone has a melting point of 128° and the acetate a melting point of 157°, whereas the ether of the product in hand has a melting point of 143°, and the acetate 177°. Xanthones react with only one molecule of Grignard reagent whereas pyrones react with two. As many of the condensation products described in this investigation were converted readily by excess Grignard to dimethyl derivatives with replacement of an oxygen, there exists little doubt that pyrones have been formed.

The lactone (VII or VIII) with excess methylmagnesium iodide in benzene solution resulted in formation of a trimethyldibenzopyran (IX or X). The final product (IX or X) was a low-melting crystalline solid, m. p. 83°, obviously not cannabinol, and formed an acetate, *p*-nitrobenzoate and *m*-nitrobenzene sulfonate with melting points differing widely from the corresponding derivatives of cannabinol.



IX



X

TABLE I

CONSTANTS OF CANNABINOL AND ITS DERIVATIVES COMPARED WITH THE SYNTHETIC PRODUCT

	M. p., °C. (cor.)			
		Acetate	*p*-Nitrobenzoate	*m*-Nitrobenzene sulfonate
Cannabinol[7d]	75–76	76–77	165–166	127-129
1 - *n* - Amyl - 3-hydroxy - 6,6,9-trimethyl - 6 - dibenzopyran (IX)	83	62	92	118

Whether the synthetic compound in hand is IX or X must await the preparation of one or the other by an unequivocal method. Evidence to be published in a subsequent communication points to IX as the correct formula for this substance.

Experimental

3-Hydroxy-6-dibenzopyrone.—From 5 g. of *o*-bromobenzoic acid, 5 g. of resorcinol, 2 g. of sodium hydroxide in 50 cc. of water and 2 cc. of 10% aqueous copper sulfate according to the directions of Hurtley,[8] the product was obtained and purified from glacial acetic acid or ethanol: white crystals, m. p. 247° (cor.); yield 2.8 g. (52%). Hurtley[8] reported a 66% yield of product, m. p. 232°.

(8) Hurtley, *J. Chem. Soc.*, 1870 (1929).

(9) Atkinson and Heilbron, *ibid.*, 2688 (1926).

3-Methoxy-6-dibenzopyrone.—To a solution of 2.1 g. of 3-hydroxy-6-dibenzopyrone in 50 cc. of acetone was added 1.4 g. of methyl iodide and 5 g. of finely pulverized anhydrous potassium carbonate. After refluxing for five to six hours, the reaction mixture was cooled and diluted with water. The precipitated material was recrystallized from ethanol; white crystals, m. p. 143° (cor.) (Hurtley[8] reported m. p. 141°).

3-Acetoxy-6-dibenzopyrone.—A solution of 1 g. of 3-hydroxy-6-dibenzopyrone in 15 cc. of acetic anhydride was refluxed for three hours and then cooled. The product separated and was purified from ethanol; white crystals, m. p. 177° (cor.).

Anal. Calcd. for $C_{15}H_{10}O_4$: C, 70.85; H, 3.97. Found: C, 71.06; H, 4.16.

3-Hydroxy-6,6-dimethyl-6-dibenzopyran.—To a solution of a Grignard reagent prepared from 8 g. of magnesium and 48 g. of methyl iodide in 200 cc. of dry ether was added, with stirring, 10 g. of 3-hydroxy-6-dibenzopyrone suspended in 300 cc. of benzene. The ether was distilled from the mixture, which then was refluxed for eighteen hours. After cooling, it was poured slowly, with stirring, into chopped ice and 35 cc. of concentrated sulfuric acid. Complete decomposition was assured by vigorous stirring and the solid product suspended in the aqueous benzene mixture then was filtered, washed with dilute acid, sodium bisulfite and water. It then was dissolved in about 400 cc. of hot benzene and the benzene evaporated to dryness on a steam-bath. This procedure served to dehydrate to the pyran any undehydrated product. The residual substance thus obtained was purified by crystallization from 50% acetic acid: white crystals, m. p. 128° (cor.); yield 4.3 g. (40%).

Anal. Calcd. for $C_{15}H_{14}O_2$: C, 79.61; H, 6.24. Found: C, 79.53; H, 6.33.

3-Acetoxy-6,6-dimethyl-6-dibenzopyran.—A mixture of 2 g. of 3-hydroxy-6,6-dimethyl-6-dibenzopyran and 10 cc. of acetic anhydride was refluxed for five hours. It was decomposed with 50 cc. of water and extracted with ether. The product was purified by crystallization from methanol; white crystals, m. p. 96° (cor.).

Anal. Calcd. for $C_{17}H_{16}O_3$: C, 76.09; H, 6.02. Found: C, 76.27; H, 6.34.

This product, on hydrolysis with aqueous sodium hydroxide, gave 3-hydroxy-6,6-dimethyl-6-dibenzopyran.

3-Hydroxy-1-methyl-6-dibenzopyrone.—From 8.3 g. of *o*-bromobenzoic acid, 4 g. of orcinol, 75 cc. of *N* aqueous sodium hydroxide, and 2 cc. of 10% aqueous copper sulfate, 2 g. (27%) of condensation product was obtained. The procedure followed was that described for 3-hydroxy-6-dibenzopyrone except that heating for five hours was required; white crystals from glacial acetic acid or ethanol, m. p. 313° (bloc Maquenne).

Anal. Calcd. for $C_{14}H_{10}O_3$: C, 74.30; H, 4.49. Found: C, 74.30; H, 4.65.

3-Acetoxy-1-methyl-6-dibenzopyrone.—The product separated from solution on cooling, after refluxing 1 g. of 3-hydroxy-1-methyl-6-dibenzopyrone with 15 cc. of acetic anhydride for eight hours. Purified from methanol, it formed white crystals, softening at 143°, m. p. 150° (cor.).

Anal. Calcd. for $C_{16}H_{12}O_4$: C, 71.61; H, 4.52. Found: C, 71.32; H, 4.90.

3-Hydroxy-1,6,6-trimethyl-6-dibenzopyran.—The procedure used in this preparation was the same as that for 3-hydroxy-6,6-dimethyl-6-dibenzopyrone. However, the product was soluble in cold benzene. Consequently, the benzene layer, after acid decomposition, merely was evaporated to dryness on a steam-bath. From 5.3 g. of magnesium, 31 g. of methyl iodide, 200 cc. of dry ether, 7 g. of 3-hydroxy-1-methyl-6-dibenzopyrone and 250 cc. of benzene, 5.5 g. (75%) of the pyran was obtained; white crystals from 50% acetic acid, m. p. 144° (cor.).

Anal. Calcd. for $C_{16}H_{16}O_2$: C, 79.97; H, 6.72. Found: C, 80.24; H, 7.06.

3-Acetoxy-1,6,6-trimethyl-6-dibenzopyran.—The reaction mixture, after boiling 1 g. of 3-hydroxy-1,6,6-trimethyl-6-dibenzopyran with 20 cc. of acetic anhydride and 2 g. of anhydrous sodium acetate for seven hours, was decomposed with water and extracted with ether. The ether solution, after washing with 10% aqueous sodium hydroxide, was distilled and the product crystallized from methanol or petroleum ether (b. p. 60–110°); white crystals, m. p. 85° (cor.).

Anal. Calcd. for $C_{18}H_{18}O_2$: C, 76.59; H, 6.43. Found: C, 76.92; H, 6.67.

3-Hydroxy-9-methyl-6-dibenzopyrone.—This was prepared in the same manner as 3-hydroxy-6-dibenzopyrone. From 1 g. of 4-methyl-2-bromobenzoic acid, 0.4 g. of sodium hydroxide in 10 cc. of water, and 1 g. of resorcinol, 0.36 g. (34%) of product was obtained. It was purified by crystallization from *n*-pentanol; white needles, m. p. 263–264° (cor.).

Anal. Calcd. for $C_{14}H_{10}O_3$: C, 74.33; H, 4.46. Found: C, 74.59; H, 4.62.

3-Acetoxy-9-methyl-6-dibenzopyrone.—A mixture of 0.9 g. of 3-hydroxy-9-methyl-6-dibenzopyrone and 10 cc. of acetic anhydride was refluxed for three hours. The product separated on cooling and was purified by crystallization from glacial acetic acid; white needles, m. p. 172–173° (cor.).

Anal. Calcd. for $C_{15}H_{12}O_4$: C, 71.63; H, 4.51. Found: C, 71.57; H, 4.59.

3-Hydroxy-1,9-dimethyl-6-dibenzopyrone.—This was prepared in a manner similar to the 3-hydroxy-6-dibenzopyrone. From 5 g. of 4-methyl-2-bromobenzoic acid, 5 g. of orcinol, and 2 g. of sodium hydroxide in 50 cc. of water was obtained 1.3 g. (24%) of product. It was purified by crystallization from *n*-pentanol or glacial acetic acid; flat white needles, m. p. 311° (bloc Maquenne).

Anal. Calcd. for $C_{15}H_{12}O_3$: C, 74.98; H, 5.04. Found: C, 75.11; H, 5.24.

3-Acetoxy-1,9-dimethyl-6-dibenzopyrone.—Prepared in the same way as the previous acetoxy pyrone, the product was purified from glacial acetic acid; white needles, m. p. 175–176° (cor.).

Anal. Calcd. for $C_{17}H_{14}O_4$: C, 72.33; H, 5.00. Found: C, 72.07; H, 5.09.

3-Hydroxy-1-*n*-amyl-9-methyl-6-dibenzopyrone (VII).—To 4.6 g. of olivetol[10] was added a hot solution

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

composed of 70 cc. of *N* aqueous sodium hydroxide and 7.6 g. of 4-methyl-2-bromobenzoic acid. The mixture was boiled for a few seconds and 2 cc. of 10% aqueous copper sulfate was added with efficient stirring. Heating was maintained for five hours on a steam-bath. The crystalline material which separated was filtered and purified by crystallization from methanol or from glacial acetic acid: white crystals, m. p. 206° (cor.); yield 1.8 g. (25%).

Anal. Calcd. for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 77.19; H, 7.00.

3 - Acetoxy - 1 - *n* - amyl - 9 - methyl - 6 - dibenzopyrone.—A mixture of 0.1 g. of 3-hydroxy-1-*n*-amyl-9-methyl-6-dibenzopyrone and 5 cc. of acetic anhydride was refluxed for five hours. Upon cooling in an ice–salt mixture, the product separated. It was purified from methanol; white crystals, m. p. 126°.

Anal. Calcd. for $C_{21}H_{22}O_4$: C, 74.50; H, 6.56. Found: C, 74.30; H, 6.66.

3 - Hydroxy - 1 - *n* - amyl - 6,6,9 - trimethyl - 6 - dibenzopyran (IX).—The procedure employed was that for the 3-hydroxy-1,6,6-trimethyl-6-dibenzopyran. The product was soluble in cold benzene. The benzene solution, from the reaction of 8.1 g. of magnesium, 48 g. of methyl iodide, 200 cc. of dry ether, 8.3 g. of 3-hydroxy-1-*n*-amyl-9-methyl-6-dibenzopyrone and 300 cc. of benzene, was evaporated and the residue distilled, b. p. 197–199° (2.5 mm.) (bath temperature 247–260°). This product crystallizes slowly on standing. It was recrystallized from petroleum ether (b. p. 40–60°); white crystals, m. p. 83° (cor.).

Anal. Calcd. for $C_{21}H_{26}O_2$: C, 81.25; H, 8.44. Found: C, 80.94; H, 8.45.

The product is insoluble in 10% aqueous sodium hydroxide, gives no color with ethanolic ferric chloride and no alkaline Beam test.

3 - Acetoxy - 1 - *n* - amyl - 6,6,9 - trimethyl - 6 - dibenzopyran.—A mixture of 0.5 g. of 3-hydroxy-1-*n*-amyl-6,6,9-trimethyl-6-dibenzopyran and 10 cc. of acetic anhydride was refluxed for two hours, decomposed with water and extracted with ether. The product was purified from methanol; white crystals, m. p. 62° (cor.).

Anal. Calcd. for $C_{23}H_{28}O_3$: C, 78.37; H, 8.00. Found: C, 78.11; H, 8.22.

3 - *p* - Nitrobenzoxy - 1 - *n* - amyl - 6,6,9 - trimethyl-6-dibenzopyran.—To a solution of 0.6 g. of 3-hydroxy-1-*n*-amyl-6,6,9-trimethyl-6-dibenzopyran in 15 cc. of dry pyridine, was added 0.36 g. of *p*-nitrobenzoyl chloride and the mixture heated on a steam-bath overnight. Upon pouring into dilute sulfuric acid–ice mixture, the product separated. It was purified from ethanol; light yellow crystals, m. p. 92° (cor.).

Anal. Calcd. for $C_{28}H_{29}O_5N$: C, 73.17; H, 6.37. Found: C, 73.16; H, 6.40.

3 - *m* - Nitrobenzenesulfonoxy - 1 - *n* - amyl - 6,6,9 - trimethyl-6-dibenzopyran.—A mixture of 0.47 g. of 3-hydroxy-1-*n*-amyl-6,6,9-trimethyl-6-dibenzopyran, 0.37 g. of *m*-nitrobenzenesulfonyl chloride and 10 cc. of dry pyridine was warmed for two and one-half hours on a steam-bath. After addition of 50 cc. of ethanol to the cooled reaction mixture, scratching caused separation of a crystalline product. Purified from ethanol it formed light yellow crystals, m. p. 118° (cor.).

Anal. Calcd. for $C_{27}H_{29}O_6NS$: C, 65.40; H, 5.90. Found: C, 65.55; H, 5.89.

Summary

The preparation of 3-hydroxy-1-*n*-amyl-6,6,9-trimethyl-6-dibenzopyran is described. Olivetol was condensed with 4-methyl-2-bromobenzoic acid to give 3-hydroxy-1-*n*-amyl-9-methyl-6-dibenzopyrone. The pyrone was converted to the corresponding pyran by treatment with excess methylmagnesium iodide.

The product was not identical with cannabinol. Its derivatives were different from the corresponding cannabinol derivatives.

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