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

Structure of Cannabinol. II. Synthesis of Two New Isomers, 3-Hydroxy-4-*n*-amyl- and 3-Hydroxy-2-*n*-amyl 6,6,9-Trimethyl-6-dibenzopyrans[1]

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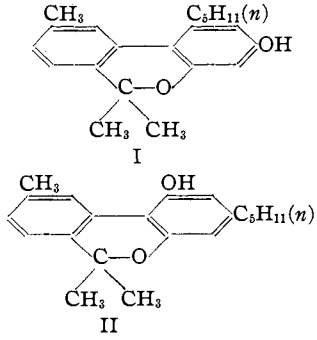
Cannabinol was postulated in a previous paper as a resorcinol derivative possessing either structure I or II with the latter being favored. Condensation of 4-methyl-2-bromobenzoic acid and



olivetol yielded a pyrone which, by means of methylmagnesium iodide, gave a pyran (I or II). The product was not cannabinol. An investigation, therefore, was started to find unequivocal methods for obtaining these two products. In the meantime, advantage was taken of the simple procedure used in preparing I or II, to synthesize two other compounds of cannabinol-like structure (VIII and IX). Although these latter molecules were resorcinol derivatives, the possibility that either was cannabinol seemed slight in view of the evidence previously discussed[1] and in view of the fact that these molecules would not be expected, like cannabinol, to dinitrate readily in the right-hand ring. Neither compound VIII nor IX was cannabinol. The constants of these compounds compared with those of cannabinol are given in Table I.

The dibenzopyran structure for cannabinol suggested by Cahn now has been supported by comparing the absorption spectra of the acetates of cannabinol and the two synthetic isomers (I or II and VIII). The similarity of the spectra (Fig. 1),

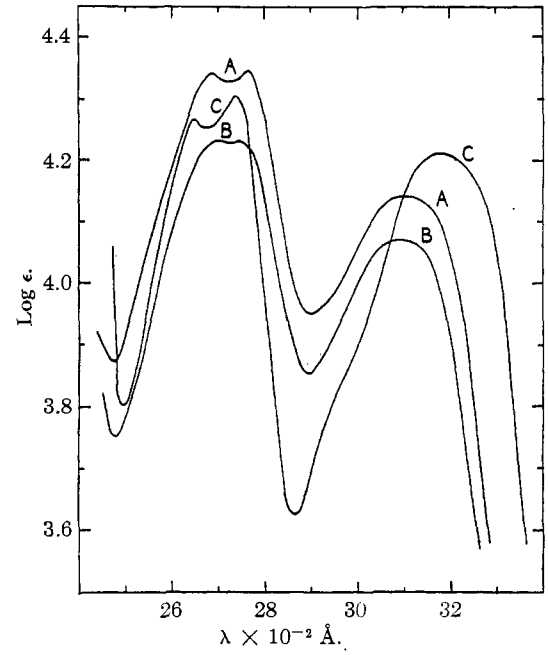


Fig. 1.—A, Cannabinol acetate; B, 3-acetoxy-1-*n*-amyl-6,6,9-trimethyl-6-dibenzopyran (acetate of I) or 1-acetoxy-3-*n*-amyl-6,6,9-trimethyl-6-dibenzopyran (acetate of II); C, 3-acetoxy-2-*n*-amyl-6,6,9-trimethyl-6-dibenzopyran (acetate of VIII).

especially between the acetates of cannabinol and I or II, is striking, indicating that the basic nuclei of all are most likely the same. These spectra may have no significance so far as indicating the relative positions of the acetoxy and *n*-amyl

TABLE I

COMPARISON OF CONSTANTS OF CANNABINOL AND SYNTHETIC PRODUCTS

	M. p., °C. (cor.)				
		Acetate	*p*-Nitrobenzoate	*p*-Aminobenzoate	*m*-Nitrobenzene sulfonate
Cannabinol	75–76[a]	76–77[a]	165–166[a]	149–150[b]	127–129[a]
3-Hydroxy-4-*n*-amyl-6,6,9-trimethyl-6-dibenzopyran (IX)	87.5–88.5	...	120–121	165.5–166.5	122–123
3-Hydroxy-2-*n*-amyl-6,6,9-trimethyl-6-dibenzopyran (VIII)	86–88	68–69	...	...	100–101

[a] Adams, Pease and Clark, THIS JOURNAL, **62**, 2194 (1940). [b] Work, Bergel and Todd, *Biochem. J.*, **33**, 124 (1939).

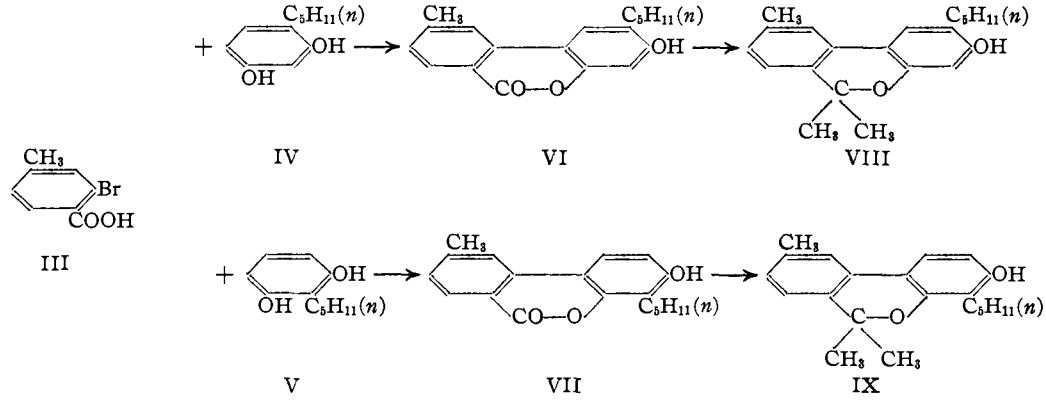
(1) For previous paper see Adams, Pease, Clark and Baker, THIS JOURNAL, **62**, 2197 (1940).

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

groups, though curves A and B are so much alike that it is inviting to postulate the 1,3,5-relationship of the two oxygens and *n*-amyl groups in each.

The cannabinol acetate was furnished by Dr. A. R. Todd of the University of Manchester, England, to whom we are deeply indebted.

To synthesize these isomers, 4-methyl-2-bromobenzoic acid (III) was condensed with 4-*n*-amylresorcinol (IV) and with 2-*n*-amylresorcinol (V).



In each case, the reactions proceeded smoothly with formation of the pyrones (VI and VII). Although 4-*n*-amylresorcinol may condense theoretically in two ways, only a single product was obtained. Since 4-alkylresorcinols generally condense merely in the 6-position, structure VI has been postulated as probably the correct one. With 2-*n*-amylresorcinol only one pyrone is possible.

The pyrones (VI and VII) were converted readily by means of methylmagnesium iodide to the corresponding pyrans (VIII and IX).

Experimental

The synthesis of 2-*n*-amylresorcinol was accomplished by means of a modification of the method of Robertson and Subramaniam[3] for the synthesis of 2-isoamylresorcinol.

4-Methyl-7-hydroxycoumarin.—Resorcinol was condensed with acetoacetic ester by the method of Russell.[4]

4-Methyl-7-*n*-valeroxycoumarin.—To a solution of 48 g. of 4-methyl-7-hydroxycoumarin in 120 cc. of dry pyridine was added 39 g. of *n*-valeryl chloride. After refluxing for thirty minutes, the mixture was poured into ice water and the resulting solid removed by filtration. Recrystallization from alcohol gave 60 g. of white needles, m. p. 75–76° (cor.).

Anal. Calcd. for $C_{15}H_{16}O_4$: C, 69.20; H, 6.20. Found: C, 69.16; H, 6.42.

4-Methyl-7-hydroxy-8-*n*-valerylcoumarin.—An intimate mixture of 59 g. of 4-methyl-7-*n*-valeroxycoumarin and 147.5 g. of anhydrous aluminum chloride was placed in a 500-cc. round-bottomed flask connected to a drying tube. The flask and contents were placed in an oil-bath at 80° and heated to 150° during one hour. The reaction mixture was cooled, treated with ice and dilute hydrochloric acid and finally warmed on the steam-bath for one hour. After cooling and filtering, the resulting solid was crystallized from ethanol, yield 40 g. The product formed pale yellow needles, m. p. 98–103° (cor.). Numerous recrystallizations failed to change the melting point.

Anal. Calcd. for $C_{15}H_{16}O_4$: C, 69.20; H, 6.20. Found: C, 69.38; H, 6.23.

2,6-Dihydroxyvalerophenone.—The dissolved air was removed from 250 cc. of a 16% aqueous sodium hydroxide solution by a stream of nitrogen, after which 34 g. of 4-methyl-7-hydroxy-8-*n*-valerylcoumarin was added. The solution was refluxed for four hours, cooled, and acidified with dilute hydrochloric acid, the stream of nitrogen continuing until after the solution was acid. The precipitated solid was removed by filtration and recrystallized from a mixture of benzene and petroleum ether; yellow needles, m. p. 85–86° (cor.), yield 22.5 g.

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.28; H, 7.34.

2-*n*-Amylresorcinol (V).—A mixture of 300 g. of amalgamated zinc and 250 cc. of 18% hydrochloric acid was warmed on the steam-bath until vigorous evolution of hydrogen took place. A solution of 20 g. of 2,6-dihydroxyvalerophenone in 250 cc. of ethanol was added and the mixture refluxed on the steam-bath for one hour. The solution was cooled, decanted from the unreacted zinc and extracted with ether. The ether extract was washed with sodium bicarbonate followed by water and dried. After removal of the ether, the residue was distilled under reduced pressure. The colorless oil thus obtained crystallized on cooling and scratching. Upon recrystallization from a mixture of benzene and petroleum ether (b. p. 40–60°), 14 g. of white needles was obtained, m. p. 55–56° (cor.).

Anal. Calcd. for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.47; H, 9.10.

A similar reduction, using concentrated hydrochloric acid and no alcohol, resulted in elimination of the valeroyl group and regeneration of resorcinol.

3-Hydroxy-4-*n*-amyl-9-methyl-6-dibenzopyrone

(3) Robertson and Subramaniam, *J. Chem. Soc.*, 278 (1937).
(4) Russell, THIS JOURNAL, **62**, 1441 (1940).

(VII).—A hot solution of 7.6 g. of 2-bromo-4-methylbenzoic acid in 70 cc. of 1 *N* aqueous sodium hydroxide was added to 4.6 g. of 2-*n*-amylresorcinol. The solution was heated to boiling and 2 cc. of 10% aqueous copper sulfate was added. The mixture was heated for five hours on the steam-bath and filtered hot. The precipitate was crystallized from glacial acetic acid followed by recrystallization from methanol. The yield was 1.6 g. of white needles, m. p. 238–239° (cor.) with decomposition.

Anal. Calcd. for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 76.94; H, 6.83.

3 - Hydroxy - 4 - *n* - amyl - 6,6,9 - trimethyl - 6 - dibenzopyran (IX).—The Grignard reagent was prepared from 1.6 g. of magnesium and 9.8 g. of methyl iodide in 40 cc. of dry ether. A suspension of 1.7 g. of 3-hydroxy-4-*n*-amyl-9-methyl-6-dibenzopyrone in 60 cc. of dry benzene was added and the ether distilled off. After refluxing for eighteen hours, the mixture was decomposed with ice and dilute hydrochloric acid. The benzene layer was separated, washed with sodium bicarbonate solution and dried. To ensure closing of the pyran ring, the benzene solution was placed in a Soxhlet extractor containing anhydrous magnesium sulfate in the thimble and the extractor operated for five hours. The benzene finally was evaporated off, leaving an oil which crystallized upon the addition of petroleum ether (b. p. 40–60°) and scratching. Recrystallization from petroleum ether (b. p. 40–60°) gave 1.3 g. of white plates, m. p. 87.5–88.5° (cor.).

Anal. Calcd. for $C_{21}H_{26}O_2$: C, 81.25; H, 8.44. Found: C, 81.31; H, 8.57.

The acetate could not be obtained crystalline.

3 - *p* - Nitrobenzoxy - 4 - *n* - amyl - 6,6,9 - trimethyl - 6-dibenzopyran.—To 0.3 g. of 3-hydroxy-4-*n*-amyl-6,6,9-trimethyl-6-dibenzopyran in 7 cc. of dry pyridine was added 0.18 g. of *p*-nitrobenzoyl chloride and the mixture heated on the steam-bath overnight, after which it was poured into ice and dilute sulfuric acid. The resulting oil was taken up in ether and the ether evaporated. The product crystallized from ethanol in yellow needles, m. p. 120–121° (cor.).

Anal. Calcd. for $C_{28}H_{29}O_5N$: C, 73.19; H, 6.36. Found: C, 72.98; H, 6.29.

3 - *p* - Aminobenzoxy - 4 - *n* - amyl - 6,6,9 - trimethyl-6-dibenzopyran.—A solution of 0.15 g. of the *p*-nitrobenzoxy compound in 75 cc. of ethanol was reduced with 0.05 g. of platinum oxide and hydrogen by shaking at 2–3 atm. pressure for one hour. The solid resulting from evaporation of the ethanol was recrystallized from methanol. The product formed white needles, m. p. 165.5–166.5° (cor.).

Anal. Calcd. for $C_{28}H_{31}O_3N$: C, 78.30; H, 7.28. Found: C, 78.13; H, 7.17.

3 - *m* - Nitrobenzenesulfonoxy - 4 - *n* - amyl - 6,6,9 - trimethyl-6-dibenzopyran.—A solution of 0.2 g. of 3-hydroxy-4-*n*-amyl-6,6,9-trimethyl-6-dibenzopyran in 5 cc. of dry pyridine was treated with 0.16 g. of *m*-nitrobenzenesulfonyl chloride and warmed on the steam-bath for two hours. The mixture was poured into water and the resulting oil taken up in ether. Evaporation of the ether left a residue which crystallized from ethanol in white needles, m. p. 122.5–123° (cor.).

Anal. Calcd. for $C_{27}H_{29}O_6NS$: C, 65.44; H, 5.90. Found: C, 65.68; H, 5.89.

3 - Hydroxy - 2 - *n* - amyl - 9 - methyl - 6 - dibenzopyrone (VI).—4-*n*-Valeroresorcinol was prepared from *n*-valeric acid, resorcinol and zinc chloride in 76% yield. Clemmensen reduction gave an 85% yield of 4-amylresorcinol.[5]

To a boiling solution of 11 g. of 4-methyl-2-bromobenzoic acid and 16 g. of 4-*n*-amylresorcinol in 100 cc. of a 4% aqueous sodium hydroxide solution was added 4 cc. of 10% aqueous copper sulfate solution. In a few minutes the product separated. It was removed by filtration and purified by recrystallization from acetic acid: white needles, m. p. 226° (cor.); yield 7.5 g. or 46%.

Anal. Calcd. for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 77.05; H, 6.99.

3 - Hydroxy - 2 - *n* - amyl - 6,6,9 - trimethyl - 6 - dibenzopyran (VIII).—To a solution of the Grignard reagent from 24 cc. of methyl iodide and 10 g. of magnesium in 100 cc. of dry ether was added a suspension of 6.9 g. of 3-hydroxy-2-*n*-amyl-9-methyl-6-dibenzopyrone in 150 cc. of dry benzene. The solution was refluxed for fifteen hours and then poured on iced hydrochloric acid. The organic layer was separated and the aqueous layer extracted once with benzene. The combined extracts were washed with dilute sodium bisulfite, dilute sodium bicarbonate and finally water. The benzene was distilled until dry and then refluxed for four and one-half hours in a Soxhlet apparatus containing about 20 g. of anhydrous magnesium sulfate in the thimble. The benzene was then evaporated and the residue distilled *in vacuo*, b. p. 193–196° (2.5 mm.). The distillate soon solidified and was further purified by recrystallization from petroleum ether (b. p. 30–60°): white prisms, m. p. 86–88° (cor.); yield 6.0 g. (85%).

Anal. Calcd. for $C_{21}H_{26}O_2$: C, 81.25; H, 8.44. Found: C, 80.98; H, 8.53.

3 - Acetoxy - 2 - *n* - amyl - 6,6,9 - trimethyl - 6 - dibenzopyran.—A solution of 0.8 g. of 3-hydroxy-2-*n*-amyl-6,6,9-trimethyl-6-dibenzopyran in 15 cc. of acetic anhydride was refluxed for two and one-half hours. This was poured into hot water, cooled in an ice-bath and the water decanted from the separated gum. The acetate was dissolved in ethanol from which it readily crystallized. It was further purified by recrystallization from ethanol; white crystals, m. p. 68–69° (cor.).

Anal. Calcd. for $C_{23}H_{28}O_3$: C, 78.37; H, 8.01. Found: C, 78.75; H, 8.17.

3 - *m* - Nitrobenzenesulfonoxy - 2 - *n* - amyl - 6,6,9-trimethyl-6-dibenzopyran.—A solution of 0.37 g. of *m*-nitrobenzenesulfonyl chloride and 0.47 g. of 3-hydroxy-2-*n*-amyl-6,6,9-trimethyl-6-dibenzopyran in 10 cc. of dry pyridine was heated under reflux on the steam-bath for forty-four hours. The solution was diluted with ether, washed with dilute hydrochloric acid and then with dilute sodium hydroxide. The ether was evaporated and the residue crystallized and recrystallized from ethanol; yellow needles, m. p. 100–101° (cor.).

Anal. Calcd. for $C_{27}H_{29}O_6NS$: C, 65.40; H, 5.90 Found: C, 65.34; H, 5.83.

(5) Dohme, Cox and Miller, THIS JOURNAL, **48**, 1688 (1926).

The *p*-nitrobenzoate of 3-hydroxy-2-*n*-amyl-6,6,9-trimethyl-6-dibenzopyran could not be obtained crystalline.

Summary

Two new isomeric cannabinols have been prepared by condensing 4-methyl-2-bromobenzoic acid with 4-*n*-amylresorcinol and 2-*n*-amylresorcinol followed by conversion of the pyrones obtained to pyrans.

URBANA, ILLINOIS RECEIVED MAY 20, 1940

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

Structure of Cannabinol. III. Synthesis of Cannabinol, 1-Hydroxy-3-*n*-amyl-6,6,9-trimethyl-6-dibenzopyran[1]

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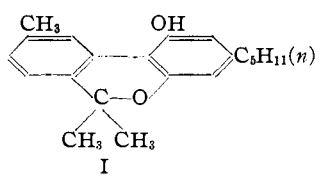
The synthesis of 1-hydroxy-3-*n*-amyl-6,6,9-trimethyl-6-dibenzopyran (I), the previously postulated formula for cannabinol,[1a] has now been accomplished by an unequivocal method. It proved to be cannabinol and its derivatives were identical with those obtained from cannabinol. These results also establish with certainty that the product obtained by the condensation of 4-methyl-2-bromobenzoic acid and olivetol followed by conversion of the pyrone to the pyran must have structure II.[1a]



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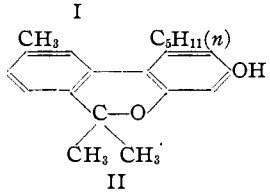
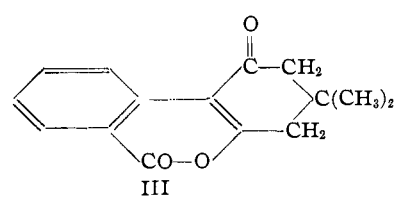


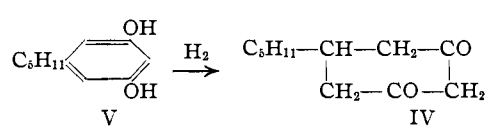
II

o-Bromobenzoic acid was shown by Hurtley[3] to condense readily in the presence of alkali and copper salts with certain active methylene compounds such as acetylacetone, malonic ester and acetoacetic ester as well as with resorcinol. This last reaction was applied in previous papers[1] for preparing certain cannabinol isomers. It now has been found that Hurtley's method is applicable equally well to alicyclic molecules containing active methylenes. Thus *o*-bromobenzoic acid condensed readily with methone in the presence of sodium ethylate and cupric acetate to give an 80% yield of the pyrone (III), 1-keto-3,3-dimethyl-1,2,3,4-tetrahydro-6-dibenzopyrone.

The reaction then was applied to 5-*n*-amyl-1,3-cyclohexanedione (IV). This compound is dihydroolivetol and was obtained by catalytic reduction of olivetol (V) in alkaline solution according to the method used previously for the reduction of many 4-alkylresorcinols,[4] and also by a series of reactions from *n*-hexaldehyde.



III



V IV

The condensation of 5-*n*-amyl-1,3-cyclohexanedione (IV) with 4-methyl-2-bromobenzoic acid could be carried out either in aqueous alkali in the presence of copper sulfate or in ethanolic sodium ethylate in the presence of cupric acetate with the formation of a good yield of the pyrone, 1-keto-3-*n*-amyl-9-methyl-1,2,3,4-tetrahydro-6-dibenzopyrone (VI). It will be noticed that the cyclohexanedione reacted in its enolic form and also that it is symmetrical, thus making possible only a single course for the condensation reaction.

(1) For previous papers see (a) Adams, Pease and Clark, THIS JOURNAL, **62**, 2194 (1940); (b) Adams, Pease, Clark and Baker, *ibid.*, **62**, 2197 (1940); (c) Adams, Cain and Baker, *ibid.*, **62**, 2201 (1940).

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

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

(4) Hoffman and LaRoche, British Patent 767,619 (*C. A.*, **29**, 482 (1935)); French Patent 783,715 (*C. A.*, **29**, 8008 (1935)).