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

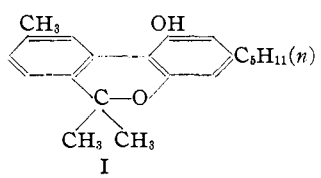
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

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

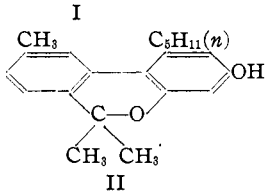
BY ROGER ADAMS, B. R. BAKER,[2] AND R. B. WEARN[2]

IN COLLABORATION WITH THE TREASURY DEPARTMENT, NARCOTICS LABORATORY, WASHINGTON, D. C.

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]



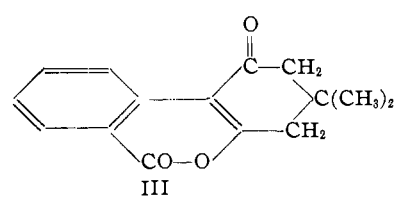
I



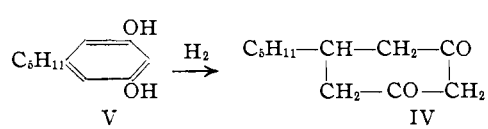
II

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

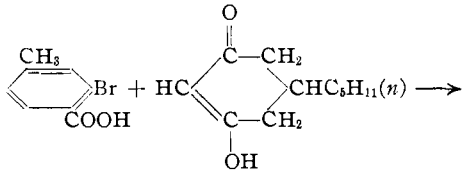
The condensation of 5-*n*-amyl-1,3-cyclohexanedione (IV) with 4-methyl-2-bromobenzoic acid could be carried out either in aqueous alkali in the presence of copper sulfate or in ethanolic sodium ethylate in the presence of cupric acetate with the formation of a good yield of the pyrone, 1-keto-3-*n*-amyl-9-methyl-1,2,3,4-tetrahydro-6-dibenzopyrone (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.

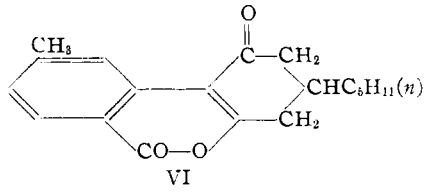
(1) For previous papers see (a) Adams, Pease and Clark, THIS JOURNAL, **62**, 2194 (1940); (b) Adams, Pease, Clark and Baker, *ibid.*, **62**, 2197 (1940); (c) Adams, Cain and Baker, *ibid.*, **62**, 2201 (1940).

(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).

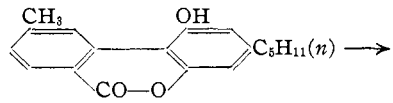
(4) Hoffman and LaRoche, British Patent 767,619 (*C. A.*, **29**, 482 (1935)); French Patent 783,715 (*C. A.*, **29**, 8008 (1935)).



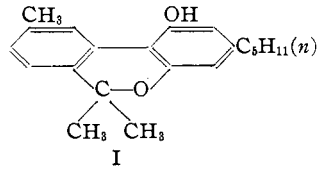


VI

The product VI was dehydrogenated with sulfur to give 1-hydroxy-3-*n*-amyl-9-methyl-6-dibenzopyrone (VII) which was different in properties from its isomer obtained by direct condensation of olivetol and 4-methyl-2-bromobenzoic acid.[1a]



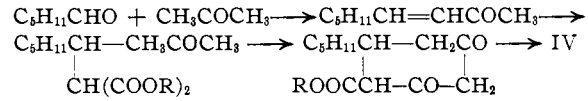
VII



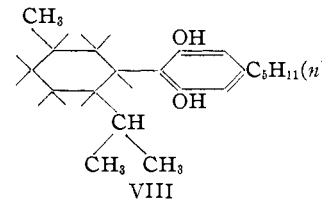
I

Conversion of the dibenzopyrone (VII) to the pyran (I) proceeded smoothly with methylmagnesium iodide. The product proved to be cannabinol as demonstrated by its properties and the melting points of its derivatives, the acetate, *p*-nitrobenzoate, and *m*-nitrobenzene sulfonate. Mixed melting points of the acetate and *p*-nitrobenzoate with the corresponding derivatives of cannabinol, kindly furnished by Dr. A. R. Todd of the University of Manchester, as well as with these same derivatives and the *m*-nitrobenzene sulfonate prepared in this Laboratory[1a] showed no depression.

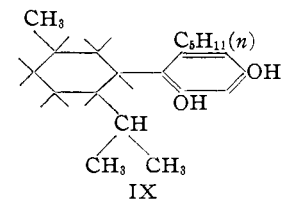
A second method for the preparation of the intermediate 5-*n*-amyl-1,3-cyclohexanedione (IV) was also successful. It consisted in condensation of *n*-hexaldehyde with acetone to hexylidene acetone. Malonic ester was then added to the double bond. By means of sodium ethylate the malonic ester addition product was cyclized, then saponified with aqueous potassium hydroxide, finally acidified and heated. This resulted in the conversion of the ester to the acid and loss of carbon dioxide with formation of the desired substance, 5-amyl-1,3-cyclohexanedione. The product was identical with that obtained by the reduction of olivetol. In the initial experiments using *n*-hexaldehyde which was from a commercial source, the final product was obtained in very low yield and it was difficult to crystallize, m. p. 104–105°. It was found later that the commercial aldehyde, though it boiled fairly constant, contained among other impurities a substantial amount of diethylacetaldehyde and it was a derivative of this substance which was isolated. To confirm this, pure diethylacetaldehyde was carried through the same series of reactions and the product, m. p. 104–105°, mentioned above resulted. The conversion of this compound to the corresponding isomeric cannabinol had been completed before the structure of the hexanedione was known.



It is seen that, as anticipated, cannabinol has a structure similar to cannabidiol[5] in that it is an olivetol derivative. The position of the linkage between the doubly unsaturated menthyl residue and the olivetol residue in cannabidiol has been in doubt in respect as to whether it occurs between the two hydroxyls or between an hydroxyl and the *n*-amyl group. In a previous paper[6] it was deduced from the comparison of the absorption spectrum of tetrahydrocannabidiol dimethyl ether and the spectra of certain analogous synthetic compounds of unequivocal constitution that tetrahydrocannabidiol probably had the linkage between the hydroxyls. It would be represented by structure VIII of the two alternative structures VIII and IX. The establishment of the struc-



VIII



IX

(5) Adams, Hunt and Clark, THIS JOURNAL, **62**, 196, 735 (1940); Adams, Cain and Wolff, *ibid.*, **62**, 732 (1940).

(6) Adams, Wolff and Cain, *ibid.*, **62**, 1770 (1940).

ture of cannabinol as I offers confirmatory and convincing evidence that the linkage in cannabidiol is also between the two hydroxyls.

Experimental

1 - Keto - 3,3 - dimethyl - 1,2,3,4 - tetrahydro - 6 - dibenzopyrone (III).—To a solution of 1.15 g. of sodium in 25 cc. of absolute ethanol was added 5 g. of *o*-bromobenzoic acid, 3.5 g. of methone and 0.1 g. of cupric acetate. After refluxing for five hours, the solution was poured into water, the crystalline precipitate collected and washed. The filtrate was acidified, extracted with chloroform and the latter washed with dilute aqueous sodium carbonate. The residue from evaporation of the chloroform was combined with the precipitate from the original reaction mixture and recrystallized from 50% ethanol or a mixture of benzene and petroleum ether (b. p. 60–110°); white prisms, m. p. 145–146° (cor.). The product gave no color with ferric chloride.

Anal. Calcd. for $C_{15}H_{14}O_3$: C, 74.35; H, 5.82. Found: C, 74.35; H, 5.87.

5 - *n* - Amyl - 1,3 - cyclohexanedione (Dihydroolivetol) (IV).—A solution of 9.5 g. of 1,3-dihydroxy-5-*n*-amylbenzene (olivetol) in 60 cc. of *N* sodium hydroxide and 70 cc. of water was reduced with hydrogen at an initial pressure of 2800 pounds and at 125° in the presence of a half teaspoonful of Raney nickel as a catalyst. One mole of hydrogen was absorbed in about one minute and further shaking did not increase the quantity of hydrogen used. The filtered solution was acidified and the product crystallized immediately. It was purified by recrystallization from petroleum ether (b. p. 60–110°); white leaflets, m. p. 70–71° (cor.); yield 6.5–7 g. (70–75%).

Anal. Calcd. for $C_{11}H_{18}O_2$: C, 72.49; H, 9.94. Found: C, 72.40; H, 10.10.

The 5-*n*-amyl-1,3-cyclohexanedione also was prepared by another method from *n*-hexaldehyde.

A mixture of 100 g. of synthetic *n*-hexaldehyde,[7] 335 cc. of water, 106 cc. of 10% aqueous sodium hydroxide and 140 cc. of acetone was stirred vigorously at room temperature for twenty-four hours. The organic layer was separated and washed with 2% hydrochloric acid. After drying over anhydrous magnesium sulfate, the product was distilled through a carborundum packed column. The fraction, b. p. 102–105° (32 mm.), $n^{18}D$ 1.4490, was collected as pure hexylidene acetone, weight 52 g. A lower fraction of 5 g. was discarded but a higher fraction of 28 g., b. p. 124–125° (32 mm.), was collected. Since this last product contained an hydroxyl group, it was assumed to be the aldol which had not dehydrated. Consequently, it was redistilled from 0.5 g. of anhydrous phosphoric acid. Water came over, then 13 g. of hexylidene acetone; total yield 65 g. (46%).

To a solution of 2.07 g. of sodium in 54 cc. of absolute ethanol (dried with magnesium methylate) was added 18 cc. of malonic ester and 20 g. of hexylidene acetone. The mixture was refluxed for two hours, after which a solution of 14.7 g. of potassium hydroxide in 67 cc. of water was added and refluxing continued for five more hours. At the end of this time, the mixture was diluted with one volume of water. An insoluble oil separated and was removed by extraction with benzene. The aqueous layer was acidified with excess of hydrochloric acid and refluxed for thirty minutes. The organic layer which separated was extracted with ether. Upon evaporation of the dried ether solution, the product was obtained and purified by crystallization from petroleum ether (b. p. 60–110°): white plates, m. p. 69–71°; yield 7.5 g. (29%). It was identical with dihydroolivetol prepared by the reduction of olivetol.

1 - Keto - 3 - *n* - amyl - 9 - methyl - 1,2,3,4 - tetrahydro-6-dibenzopyrone (VI).—To a solution of 0.7 g. of sodium in 20 cc. of absolute ethanol was added 2.7 g. of 5-*n*-amyl-1,3-cyclohexanedione, 3.7 g. of 4-methyl-2-bromobenzoic acid and about 0.2 g. of cupric acetate. After refluxing for five hours, the solution was poured into three volumes of water and acidified. The exact time of refluxing had an important bearing on the yield. The product was extracted with chloroform, the solution washed with dilute aqueous sodium bicarbonate, and the chloroform evaporated. The product was purified by crystallization from methanol; white needles, m. p. 95–96° (cor.), yield 3.5 g. (78%).

Anal. Calcd. for $C_{19}H_{22}O_3$: C, 76.46; H, 7.43. Found: C, 76.56; H, 7.64.

1 - Hydroxy - 3 - *n* - amyl - 9 - methyl - 6 - dibenzopyrone (VII).—An intimate mixture of 10.4 g. of 1-keto-3-*n*-amyl-9-methyl-1,2,3,4-tetrahydro-6-dibenzopyrone and 1.13 g. of sulfur was heated in a two-bulbed distilling flask in a bath at 250° for twenty-five minutes with occasional mixing. The product was distilled at 3 mm. using a low free flame. The distillate crystallized and was purified by recrystallization from toluene or acetic acid; white needles, m. p. 186° (cor.), yield 3.5 g. (34%). By evaporation to dryness of the filtrates and crystallization of the residue from ethanol, 4.5 g. (43%) of starting material was recovered.

Anal. Calcd. for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 76.72; H, 6.75.

1 - Hydroxy - 3 - *n* - amyl - 6,6,9 - trimethyl - 6 - dibenzopyran (Cannabinol) (I).—To a solution of the Grignard reagent from 8 cc. of methyl iodide and 3.3 g. of magnesium in 30 cc. of dry ether was added a suspension of 3.6 g. of 1-hydroxy-3-*n*-amyl-9-methyl-6-dibenzopyrone in 50 cc. of dry benzene. After refluxing for twenty hours the solution was poured into iced ammonium chloride solution, the organic layer separated and the aqueous layer extracted once with benzene. The combined benzene extracts were washed with dilute sodium bisulfite solution, then with water and distilled until dry. It was then refluxed for four hours in a Soxhlet apparatus containing anhydrous magnesium sulfate in the thimble. The benzene was evaporated, the residue dissolved in 60 cc. of petroleum ether (b. p. 60–110°), three drops of 48% hydrobromic acid added and the solution boiled on a hot-plate for fifteen minutes to be certain the dehydration was complete. Petroleum ether was added from time to time to keep the volume essentially constant. Upon cooling in an ice-bath and inoculating with a crystal of cannabinol, the product crystallized upon scratching the sides of the flask. It was purified by recrystallization from petroleum ether (b. p. 60–110°) with the aid of norit, yield, 2.8 g. (75%). The product was purified further by sublimation at 4 mm. with a bath temperature of 180–190° followed by recrystal-

(7) "Organic Syntheses," **16**, 41 (1936).

lization from petroleum ether (b. p. 60–110°); white leaflets, m. p. 76–77° (cor.). A mixed melting point with cannabinol isolated from red oil gave no depression.

Anal. Calcd. for $C_{21}H_{26}O_2$: C, 81.25; H, 8.44. Found: C, 81.33; H, 8.26.

1 - Acetoxy - 3 - *n* - amyl - 6,6,9 - trimethyl - 6 - dibenzopyrone.—A solution of 0.2 g. of crystalline cannabinol in 5 cc. of acetic anhydride was refluxed for two hours, then poured into hot water. A small amount was removed on a spatula and suspended in a little ethanol, when it immediately solidified. The aqueous suspension was seeded and the crystalline product that formed was collected on a filter. It was purified by recrystallization from ethanol; white needles, m. p. 75–76° (cor.). This compound gave no depression in melting point when mixed with cannabinol acetate.

Anal. Calcd. for $C_{23}H_{28}O_3$: C, 78.37; H, 8.01. Found: C, 78.27; H, 7.95.

1 - *p* - Nitrobenzoxy - 3 - *n* - amyl - 6,6,9 - trimethyl - 6-dibenzopyran.—A solution of 0.2 g. of crystalline cannabinol, 0.3 g. of *p*-nitrobenzoyl chloride and 6 cc. of dry pyridine was refluxed for four hours. The solution was poured on iced hydrochloric acid and the solid product collected on a filter. It was washed with dilute alkali, then water and finally purified by recrystallization from ethanol with the aid of norit; yellow needles, m. p. 165–166° (cor.). This compound gave no depression in melting point when mixed with cannabinol *p*-nitrobenzoate.

Anal. Calcd. for $C_{28}H_{29}O_5N$: C, 73.17; H, 6.36; N, 3.05. Found: C, 72.96; H, 6.60; N, 3.18.

1 - *m* - Nitrobenzenesulfonoxy - 3 - *n* - amyl - 6,6,9-trimethyl-6-dibenzopyran.—A solution of 0.2 g. of crystalline cannabinol and 0.16 g. of *m*-nitrobenzenesulfonyl chloride in 0.7 cc. of pyridine was heated on a steam-bath for two and one-half hours. Upon addition of 10 cc. of ethanol the product crystallized and was purified from benzene–ethanol; yellow prisms, m. p. 127–129° (cor.). This compound gave no depression in melting point when mixed with cannabinol *m*-nitrobenzene sulfonate.

Anal. Calcd. for $C_{27}H_{29}O_6NS$: N, 2.8. Found: N, 2.9.

5 - Diethylmethyl - 1,3 - cyclohexanedione.—Diethylacetaldehyde was converted to 5-ethyl-3-heptene-2-one by the method previously described.[8]

To a solution of 2 g. of sodium in 40 cc. of absolute ethanol was added 13.5 cc. of diethylmalonate and 15 g. of 5-ethyl-3-heptene-2-one. The mixture was refluxed for two hours, then a solution of 11 g. of potassium hydroxide in 50 cc. of water was added and refluxing continued for an additional five hours. After dilution with an equal volume of water, the solution was washed with benzene, then acidified with hydrochloric acid and refluxed for thirty minutes. Upon cooling to room temperature, crystals of 5-diethylmethyl-1,3-hexanedione separated. It was purified by recrystallization from benzene–petroleum ether (b. p. 60–110°); white leaflets, m. p. 104–105° (cor.).

Anal. Calcd. for $C_{11}H_{18}O_2$: C, 72.49; H, 9.94. Found: C, 72.40; H, 10.10.

(8) Carbide and Carbon Company, British Patent 446,084; *C. A.*, **30**, 6758 (1936).

1 - Keto - 3 - diethylmethyl - 9 - methyl - 1,2,3,4 - tetrahydro-6-dibenzopyrone.—Prepared in a similar manner to the 3-*n*-amyl compound using 5-diethylmethyl-1,3-cyclohexanedione, it formed from ethanol white crystals, m. p. 111–112° (cor.).

Anal. Calcd. for $C_{19}H_{22}O_3$: C, 76.46; H, 7.43. Found: C, 76.41; H, 7.34.

1 - Hydroxy - 3 - diethylmethyl - 9 - methyl - 6 - dibenzopyrone.—By sulfur dehydrogenation of the previously described compound, the product was obtained and purified by crystallization from toluene; white leaflets, m. p. 217–218° (cor.).

Anal. Calcd. for $C_{19}H_{20}O_3$: C, 76.97; H, 6.88. Found: C, 76.89; H, 6.80.

1 - Acetoxy - 3 - diethylmethyl - 9 - methyl - 6 - dibenzopyrone.—From methanol, white needles, m. p. 128–130° (cor.).

Anal. Calcd. for $C_{21}H_{22}O_4$: C, 74.51; H, 6.56. Found: C, 74.24; H, 6.71.

1 - Hydroxy - 3 - diethylmethyl - 6,6,9 - trimethyl - 6-dibenzopyran.—Treatment of the pyrone with methylmagnesium iodide gave the product; white prisms from petroleum ether (b. p. 60–110°), m. p. 133–134 (cor.).

Anal. Calcd. for $C_{21}H_{26}O_2$: C, 81.25; H, 8.44. Found: C, 81.04; H, 8.49.

1 - Acetoxy - 3 - diethylmethyl - 6,6,9 - trimethyl - 6-dibenzopyran.—The product was purified from ethanol; white leaflets, m. p. 103° (cor.).

Anal. Calcd. for $C_{23}H_{28}O_3$: C, 78.37; H, 8.01. Found: C, 78.59, 78.46; H, 8.18, 8.11.

1 - *p* - Nitrobenzoxy - 3 - diethylmethyl - 6,6,9 - trimethyl-6-dibenzopyran.—This product formed from ethanol, yellow crystals, m. p. 171° (cor.).

Anal. Calcd. for $C_{28}H_{29}O_5N$: C, 73.17; H, 6.36; N, 3.05. Found: C, 73.15; H, 6.39; N, 3.11.

Summary

Cannabinol has been shown to be 1-hydroxy-3-*n*-amyl-6,6,9-trimethyl-6-dibenzopyran by synthesis. The procedure for preparation was to condense 4-methyl-2-bromobenzoic acid with dihydroolivetol, dehydrogenate the product to the pyrone and finally to convert it to the pyran by means of methylmagnesium iodide.

Dihydroolivetol was made by the catalytic reduction of olivetol and through a series of reactions starting with *n*-hexaldehyde.

The derivatives of the synthetic cannabinol agree in all respects with the corresponding derivatives of natural cannabinol.

An isomer of cannabinol, 1-hydroxy-3-diethylmethyl-6,6,9-trimethyl-6-dibenzopyran has also been prepared by a similar procedure.

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