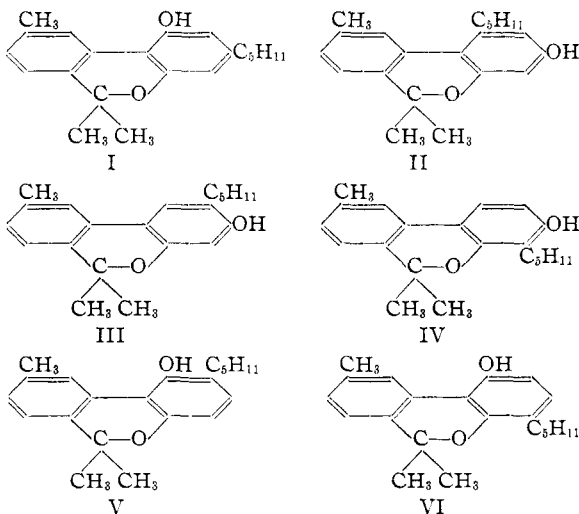


[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Structure of Cannabinol. IV. Synthesis of Two Additional Isomers Containing a Resorcinol Residue¹BY ROGER ADAMS AND B. R. BAKER²

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There are six possible cannabinoids (I–VI), with the oxygens in the right-hand ring linked *meta* to each other. The compounds I–IV have been



synthesized and described in previous papers.¹ Of these, compound I proved to be identical with natural cannabinol.^{1c} It was produced by the condensation of 4-methyl-2-bromobenzoic acid with dihydroolivetol, followed by dehydrogenation and conversion of the resulting pyrone to the pyran. The success of this procedure opened the way to a method of synthesis of the remaining isomers (V and VI), which are now described. This work was begun before cannabinol had been synthesized. It was carried through to completion not so much because of its significance in relation to the cannabinol problem but because of the novel transformations observed in this investigation.

4-*n*-Amylresorcinol was reduced catalytically to the corresponding dihydro compound³ which can enolize in two ways (VII and VIII). Consequently, it was not surprising that in the condensation with 4-methyl-2-bromobenzoic acid, two

compounds were formed (IX and X) one with m. p. 65–66°, the other, m. p. 97–99°. These could be separated by their difference in solubility in solvents; the lower-melting was less soluble in petroleum ether, the higher-melting, less soluble in methanol. However, a more convenient method of separation through derivatives will be described later. Either isomer could be converted to a mixture of the two isomers by dissolving in methanolic alkali followed by acidification. Evidence is presented below that the compound, m. p. 97–99°, has formula IX and the compound, m. p. 65–66°, formula X.

The product, m. p. 97–99°, could be dehydrogenated by means of sulfur or bromine and quinoline to a pyrone (XI), m. p. 176–177°; the product, m. p. 65–66°, was dehydrogenated successfully only by means of bromine and quinoline to give a pyrone (XII), m. p. 182–183°.

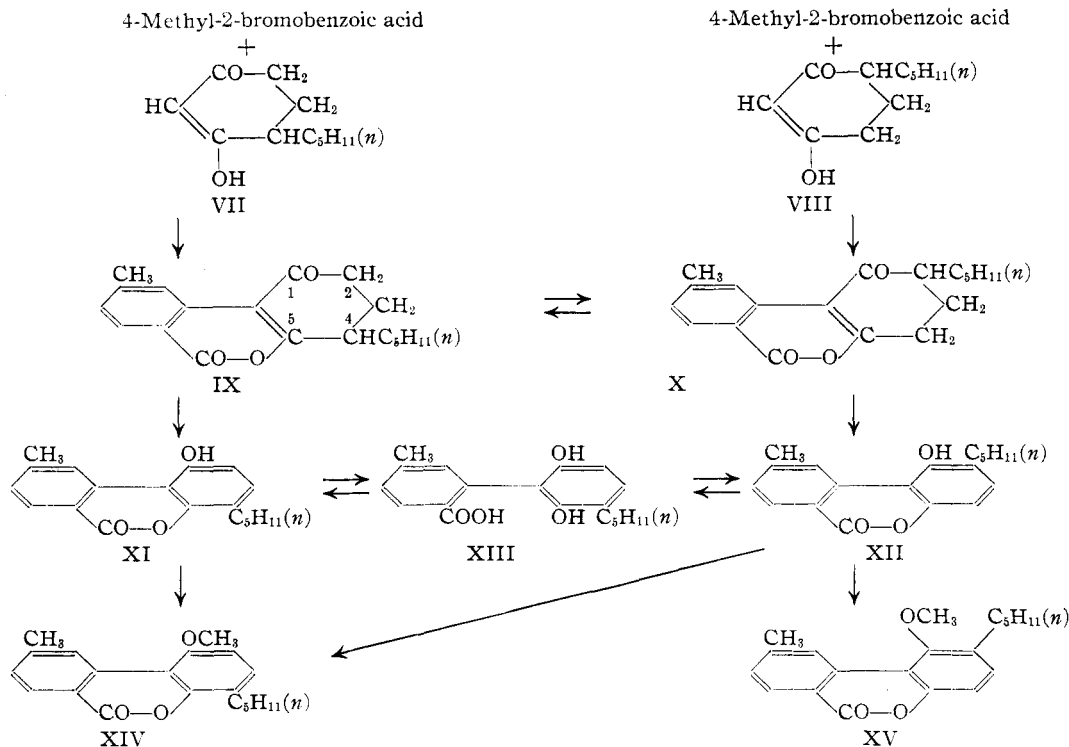
The pyrones XI and XII upon methylation with sodium methylate in methanol and dimethyl sulfate gave the same monomethyl ether, m. p. 96°. It must be concluded, therefore, that both lactones in this methylation reaction first must have opened to the same hydroxy acid (XIII), following which the hydroxyl group more favorably situated was methylated and then lactone formation again took place. The hydroxyl in compound XIII with only one ortho group unquestionably would be the first to methylate and, as a consequence, the resulting pyrone methyl ether must be assigned structure XIV.

Methylation of the two pyrones XI and XII by means of dimethyl sulfate in acetone with anhydrous potassium carbonate avoided the intermediate hydrolysis of the pyrone to the hydroxy acid and, consequently, each pyrone gave a characteristic methyl ether. The lower-melting pyrone, m. p. 176–177°, gave the same monomethyl ether (XIV), m. p. 96°, by both methylation procedures. Consequently, this establishes structure XI for this pyrone, and structure IX for its ketone precursor. By the acetone–anhydrous potassium carbonate method from the pyrone, m. p. 182–183°, the monomethyl ether was obtained as a

(1) For previous papers see (a) Adams, Pease, Clark and Baker, *THIS JOURNAL*, **62**, 2197 (1940); (b) Adams, Cain and Baker, *ibid.*, **62**, 2201 (1940); (c) Adams, Baker and Wearn, *ibid.*, **62**, 2204 (1940).

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

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



crystalline solid, m. p. 45°; it must have structure XV, the corresponding pyrone structure XII, and its ketone precursor, structure X.

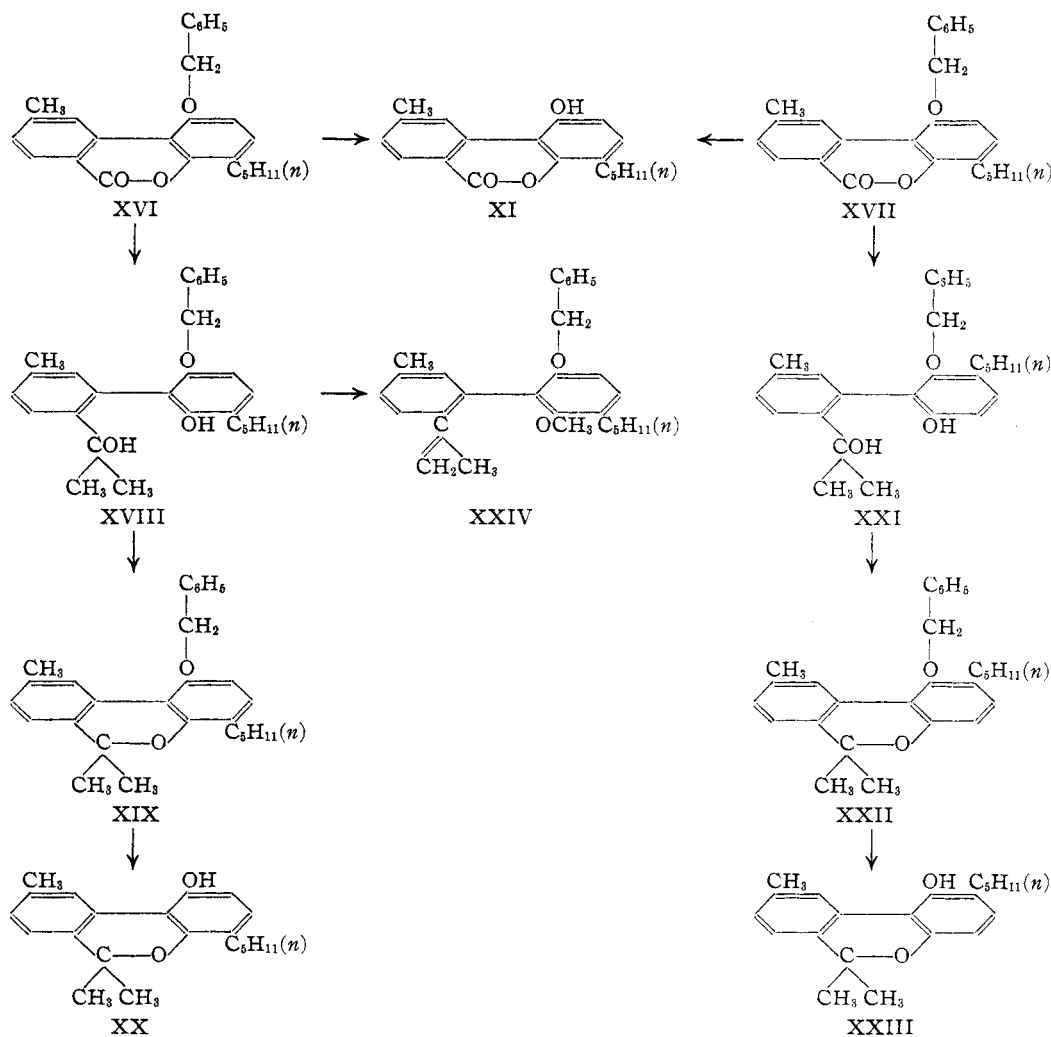
This assignment of structures is supported by the fact that a compound of structure IX should dehydrogenate more readily than one of structure X. The higher-melting keto compound (IX) readily dehydrogenated with sulfur while the lower-melting (X) did not react under similar conditions. The mechanism probably involves the removal of two hydrogens in the 3,4-positions (IX) followed by enolization or *vice versa*. One secondary hydrogen and one tertiary hydrogen (IX) would be removed more easily than two secondary hydrogens (X). Moreover, the bromine and quinoline method, though this served to dehydrogenate both compounds IX and X, reacted more smoothly and gave better yields with the lower-melting isomer (X) as might be anticipated; the tertiary hydrogen alpha to the ketone (IX) would be replaced more readily than a secondary hydrogen (X) and the resulting tertiary halide would lose hydrogen halide more readily.

The benzyl ethers of the two pyrones XI and XII also were studied. Using benzyl chloride in acetone and anhydrous potassium carbonate, XI gave an ether (XVI), m. p. 121°, and XII an

ether (XVII), m. p. 86°. Both, upon hydrolysis with hydrochloric acid in acetic acid, gave the same pyrone (XI). Thus, in acid solution the lactone ring can open and close to the more stable configuration. The two pyrones XI and XII upon benzylation with sodium methylate in methanol gave the same benzyl ether, that derived from the pyrone XI. These results parallel those on methylation.

As the ketones (IX and X) were separated only with difficulty by solubility methods, advantage was taken of the facts about the ethers just described, to devise a method for separating the corresponding pyrones. A mixture of IX and X obtained in the initial condensation of 4-methyl-2-bromobenzoic acid and dihydro-4-*n*-amylresorcinol, was dehydrogenated by the bromine-quinoline method to the mixture of pyrones XI and XII. The pyrone XII, m. p. 182–183°, was much less soluble in methyl ethyl ketone than its isomer, so could readily be separated and purified. The filtrate consisting of a mixture of both pyrones was benzylated by the sodium methylate-benzyl chloride method which gave only the benzyl ether (XVI) of the pyrone XI. This could be hydrolyzed to the corresponding unalkylated pyrone XI.

The conversion of the pyrones XI and XII di-



rectly to pyrans by means of methylmagnesium iodide presented the difficulty of obtaining with certainty a pyran of unequivocal structure from each, since the mechanism of conversion of a pyrone to a pyran undoubtedly involves an intermediate phenolic alcohol which subsequently dehydrates, and in this case may do so in one or two ways. The benzyl ethers, therefore, were employed. The benzylated pyrone (XVI) readily reacted with the Grignard reagent, and the intermediate phenolic alcohol (XVIII) dehydrated smoothly to the benzylated pyran (XIX). Methylation of the phenolic alcohol (XVIII) resulted in formation of the phenol ether with simultaneous dehydration of the alcohol to give compound XXIV. The corresponding methylated pyrone (XIV) in a similar manner gave an intermediate phenolic alcohol which dehydrated to the methylated pyran.

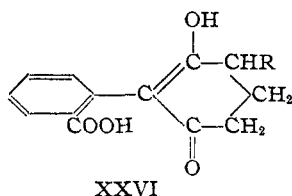
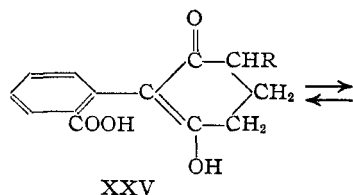
The benzyl ether with hydrochloric acid in acetic acid, and the methyl ether with hydrobromic acid in acetic acid were dealkylated to 1-hydroxy-4-*n*-amyl-6,6,9-trimethyl-6-dibenzopyran (XX), an isomer of cannabinol. This was a solid, m. p. 62–63°, and its derivatives all melted at points different from the corresponding derivatives of cannabinol.

The other benzylated pyrone (XVII), however, gave with methylmagnesium iodide a phenolic alcohol (XXI) which did not dehydrate merely by refluxing a benzene solution. It was necessary to add a few drops of aqueous hydrobromic acid to the benzene solution to obtain the pyran XXII. The phenolic alcohol (XXI) upon arylation with *p*-nitrobenzoyl chloride gave the *p*-nitrobenzoate of the phenol group and at the same time the alcohol was dehydrated to an isopropenyl group. The corresponding methylated py-

rone also gave a relatively stable crystalline phenolic alcohol which by the same procedure used for the benzyl ether dehydrated to a methylated pyran which was an oil.

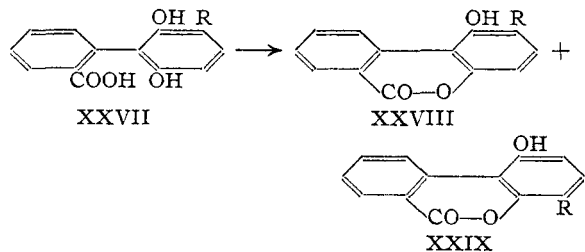
The hydrolysis of the benzyl ether (XXII) and the corresponding methyl ether gave 1-hydroxy-2-*n*-amyl-6,6,9-trimethyl-6-dibenzopyran (XXIII) which was isolated as an oil. Its *p*-nitrobenzoate was a crystalline solid with a melting point different from that of cannabinol *p*-nitrobenzoate.

These experiments demonstrate some interesting facts in regard to isomerism and tautomerism in molecules of the type studied. Compounds illustrated in general form by structures XXV and XXVI exist in equilibrium with each other for



lactonization results in the formation of two lactones, either of which in pure form is converted by dissolving in alkali and acidification to a mixture of the two; from this it may be deduced that probably any substituted 1,3-cyclohexanedione capable theoretically of enolizing in two ways actually does so in solution.

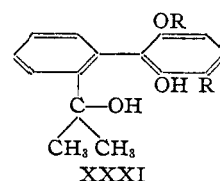
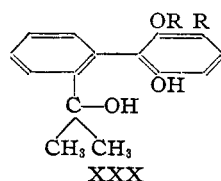
Free rotation between the two cyclic residues is established in compound XXVII, for treatment



of either pure lactone of structure XXVIII or XXIX with aqueous sodium hydroxide followed by acidification results in a mixture of the two. Moreover, the two lactones XXVIII and XXIX, after treatment with methanolic alkali to give the sodium salt of the acid XXVII followed by

methylation, yield the same monomethyl ether lactone (XXIX). Also by debenzoylation of the two benzyl ethers of compounds XXVIII and XXIX with hydrochloric acid, the same hydroxy pyrone (XXIX) results.

The introduction of a third ring, either pyrone or pyran, into such molecules as these, occurs preferably with the hydroxyl adjacent to the alkyl group. This was shown by the tendency of a molecule (XXVII) to give primarily a pyrone derived from XXIX, and also by the relative stability to dehydration of the phenolic alcohols XXX and XXXI. Compound XXX is much less easily dehydrated than compound XXXI.



Experimental

4-*n*-Amyldihydroresorcinol (VII or VIII).—A solution of 18 g. of 4-*n*-amylresorcinol and 4 g. of sodium hydroxide in 120 cc. of water was reduced with hydrogen at an initial pressure of 2800 lb. (190 atm.) at 125° in the presence of one-quarter teaspoon of Raney nickel. The hydrogenation stopped when one molecule of hydrogen had been absorbed (fifteen to twenty minutes). The filtered solution was acidified and the product extracted with benzene. After concentration of the extract to 30 cc., the product was crystallized by the addition of 80 cc. of petroleum ether (b. p. 60–110°) and cooling in an ice-bath. The product was purified by recrystallization from petroleum ether (b. p. 60–110°); white prisms, m. p. 67°; yield 13 g. (72%).

Anal. Calcd. for $C_{11}H_{18}O_2$: C, 72.49; H, 9.94. Found: C, 72.73; H, 10.20.

1-Keto-4-*n*-amyl-9-methyl-1,2,3,4-tetrahydro-6-dibenzopyrone (IX) and 1-Keto-2-*n*-amyl-9-methyl-1,2,3,4-tetrahydro-6-dibenzopyrone (X).—To a solution of 7 g. of sodium in 300 cc. of absolute ethanol was added 29 g. of 4-*n*-amylidihydroresorcinol, 31 g. of 4-methyl-2-bromobenzoic acid and 1 g. of cupric acetate. The solution was refluxed on the steam-bath for fifteen hours, then poured into three volumes of water and acidified. The separated oil was extracted with two 100 cc. portions of chloroform, washed with dilute sodium carbonate and evaporated. The residue was dissolved in 150 cc. of methanol and the product allowed to crystallize at room temperature. The product which separated (A) amounted to 8.5 g. (20%); two crystallizations from methanol gave fine white needles, m. p. 97–99° (cor.).

Anal. Calcd. for $C_{19}H_{22}O_8$: C, 76.46; H, 7.43. Found: C, 76.61; H, 7.57.

The filtrate from A was concentrated to 100 cc. and a second crop (B) obtained by cooling in an ice-bath, yield 14.5 g. (33%). It was purified by recrystallization from

petroleum ether (b. p. 60–110°); fine white needles, m. p. 65–66° (cor.).

Anal. Calcd. for $C_{19}H_{20}O_3$: C, 76.46; H, 7.43. Found: C, 76.72; H, 7.59.

If merely a mixture of isomers was obtained by evaporation of the original methanol solution to 100 cc. and by cooling in an ice-bath, a yield of 75–78% was obtained.

When A or B was dissolved in methanolic alkali and acidified, a mixture of the two keto lactones was obtained.

1 - Hydroxy - 4 - *n* - amyl - 9 - methyl - 6 - dibenzopyrone (XI).—A. An intimate mixture of 7.8 g. of 1-keto-4-*n*-amyl-9-methyl-1,2,3,4-tetrahydro-6-dibenzopyrone (m. p. 97–99°) and 0.86 g. of sulfur was heated at 250–255° for one hour in a two-bulbed distilling flask with frequent stirring. The product was then distilled at 2 mm. pressure. It was crystallized from ethanol with the aid of Norit: white plates, m. p. 176–177° (cor.); yield 4.5 g. (53%).

B. A solution of 2 g. of 1-keto-4-*n*-amyl-9-methyl-1,2,3,4-tetrahydro-6-dibenzopyrone and 0.35 cc. of bromine in 20 cc. of chloroform was allowed to stand at room temperature protected from moisture until the bromine had all reacted (about four hours). The solvent was evaporated and the residue heated with 10 cc. of quinoline at 200° for one hour. The cooled solution was poured into dilute hydrochloric acid and the precipitate recrystallized from ethanol, m. p. 176–177° (cor.); yield 0.55 g. (27%).

Anal. Calcd. for $C_{19}H_{20}O_3$: C, 76.97; H, 6.80. Found: C, 76.70; H, 6.44.

This pyrone on dissolving in aqueous alkali and acidification gives a low-melting product, undoubtedly a mixture of the 2-*n*-amyl and 4-*n*-amyl pyrones.

1 - Hydroxy - 2 - *n* - amyl - 9 - methyl - 6 - dibenzopyrone (XII).—A procedure similar to that described in B under the dehydrogenation of 1-keto-4-*n*-amyl-9-methyl-1,2,3,4-tetrahydro-6-dibenzopyrone, was used. A solution of 9.3 g. of 1-keto-2-*n*-amyl-9-methyl-1,2,3,4-tetrahydro-6-dibenzopyrone (m. p. 65–66°) and 1.63 cc. of bromine in 75 cc. of chloroform was allowed to stand, protected from moisture, for five hours. Evaporation of the solvent and heating with 45 cc. of quinoline at 200° for one hour was followed by pouring the cooled solution into dilute hydrochloric acid and extraction with chloroform. The product was purified from methyl ethyl ketone; white plates, m. p. 182–183° (cor.); yield 5.1 g. (55%).

Anal. Calcd. for $C_{19}H_{20}O_3$: C, 76.97; H, 6.80. Found: C, 77.22; H, 6.88.

A mixed melting point of the 1-hydroxy-4-*n*-amyl and the 1-hydroxy-2-*n*-amyl derivatives just described gave a value below 155°. This pyrone on dissolving in aqueous alkali and acidification gives a low-melting product, undoubtedly a mixture of the 2-*n*-amyl and 4-*n*-amyl pyrones.

2 - (α - Methyl - α - hydroxyethyl) - 5 - methyl - 2',6'-dihydroxy - 3' - *n* - amylbiphenyl.—This compound was prepared in 80% yield from 1-hydroxy-2-*n*-amyl-9-methyl-6-dibenzopyrone following the same procedure as was used for preparing the 2-(α-methyl-α-hydroxyethyl)-5-methyl-2'-methoxy-3'-*n*-amyl-6'-hydroxybiphenyl given later. It was purified from petroleum ether (b. p. 60–110°); white prisms, m. p. 103–104° (cor.).

Anal. Calcd. for $C_{21}H_{20}O_3$: C, 76.80; H, 8.56. Found: C, 77.03; H, 8.74.

The substance was soluble in dilute aqueous sodium hydroxide but insoluble in aqueous sodium bicarbonate. It gave a cherry red color which gradually changed to brown, when treated with 5% ethanolic sodium hydroxide.

1 - Methoxy - 4 - *n* - amyl - 9 - methyl - 6 - dibenzopyrone (XIV).—A. To a solution of 3 g. of 1-hydroxy-4-*n*-amyl-9-methyl-6-dibenzopyrone (m. p. 176–177°) in 30 cc. of *N* sodium methylate and 100 cc. of methanol was added 5.4 g. of dimethyl sulfate. The solution was refluxed until acid to litmus (about three minutes), then 2.8 cc. of dimethyl sulfate and 30 cc. of sodium methylate were added, and the solution again refluxed until acidic. This was repeated once more with similar amounts. Finally, 30 cc. of *N* sodium methylate was added and the mixture concentrated to a paste on a steam-bath. Water was added and the gummy product separated and crystallized from methanol: white needles, m. p. 96° (cor.); yield 2.3 g. (75%).

1-Hydroxy-2-*n*-amyl-9-methyl-6-dibenzopyrone (m. p. 182–183°) upon methylation by the same procedure gave the same product, m. p. 96°.

B. A mixture of 1.3 g. of 1-hydroxy-4-*n*-amyl-9-methyl-6-dibenzopyrone, 1.5 cc. of dimethyl sulfate, 7 g. of anhydrous potassium carbonate and 50 cc. of reagent acetone was refluxed on a steam-bath for four hours. The filtered solution was evaporated to dryness and the residue crystallized from methanol: white needles, m. p. 96°, identical with the product obtained in part A; yield 0.9 g. (65%).

Anal. Calcd. for $C_{20}H_{22}O_3$: C, 77.40; H, 7.13. Found: C, 77.18; H, 7.31.

1 - Methoxy - 2 - *n* - amyl - 9 - methyl - 6 - dibenzopyrone (XV).—A mixture of 3.25 g. of 1-hydroxy-2-*n*-amyl-9-methyl-6-dibenzopyrone (m. p. 182–183°), 7 cc. of methyl iodide, 13 g. of anhydrous potassium carbonate and 75 cc. of reagent acetone was refluxed on a water-bath for five hours. The filtered solution was evaporated to dryness, the residue dissolved in ether, the ether solution washed with water and then with dilute aqueous sodium bisulfite. The ether was evaporated and the residue after standing several hours crystallized. It was purified by recrystallization from 40 cc. of methanol. A second crop was obtained on concentration of the filtrate. When less solvent was used the product separated as an oil. It formed white needles, m. p. 45–46° (cor.); yield 2.5 g. (75%).

Anal. Calcd. for $C_{20}H_{22}O_3$: C, 77.40; H, 7.13. Found: C, 77.81; H, 7.28.

1 - Benzyloxy - 4 - *n* - amyl - 9 - methyl - 6 - dibenzopyrone (XVI).—A. A solution of 2.1 g. of 1-hydroxy-4-*n*-amyl-9-methyl-6-dibenzopyrone (m. p. 176–177°), 1.4 cc. of benzyl chloride, 10 cc. of *N* sodium methylate in methanol and 40 cc. of methanol was refluxed for three hours. The hot solution was decanted from the sodium chloride and, upon cooling, the product separated. It was purified by crystallization from methanol: white needles, m. p. 121–121.5° (cor.); yield 1.6 g. (60%).

1-Hydroxy-2-*n*-amyl-9-methyl-6-dibenzopyrone (m. p. 182–183°) by a similar procedure gave the same benzyloxy compound, m. p. 121–121.5°.

B. A mixture of 0.2 g. of 1-hydroxy-4-*n*-amyl-9-methyl-6-dibenzopyrone (m. p. 176–177°), 0.2 cc. of benzyl chloride, 1 g. of anhydrous potassium carbonate and 5 cc. of reagent acetone was refluxed on a steam-bath for two

hours. The filtered solution was evaporated to dryness and the product crystallized from methanol: white needles, m. p. 120–121° (cor.); yield 0.17 g. (65%). This was identical with the product formed by procedure A.

Anal. Calcd. for $C_{26}H_{26}O_3$: C, 80.79; H, 6.78. Found: C, 80.90; H, 6.98.

When 0.25 g. of this compound was refluxed for five hours with 1 cc. of concentrated hydrochloric acid and 10 cc. of acetic acid, 1-hydroxy-4-*n*-amyl-9-methyl-6-dibenzopyrone crystallized from the mixture on cooling, m. p. 176–177°.

1 - Benzenesulfonyloxy - 4 - *n* - amyl - 9 - methyl - 6 - dibenzopyrone.—A solution of 0.2 g. of 1-hydroxy-4-*n*-amyl-9-methyl-6-dibenzopyrone (m. p. 176–177°) and 0.2 cc. of benzenesulfonyl chloride in 3 cc. of pyridine was refluxed for four hours. The solution was poured into dilute hydrochloric acid. The oil which separated soon solidified and was purified by crystallization from ethanol; white needles, m. p. 103–104° (cor.).

Anal. Calcd. for $C_{26}H_{24}O_2S$: C, 68.77; H, 5.53. Found: C, 69.14; H, 5.95.

1 - Benzenesulfonyloxy - 2 - *n* - amyl - 9 - methyl - 6 - dibenzopyrone.—This was prepared in the same manner as the corresponding 1-benzenesulfonyloxy-4-*n*-amyl derivative. The product was purified by recrystallization from ethanol; white needles, m. p. 139° (cor.).

Anal. Calcd. for $C_{26}H_{24}O_2S$: C, 68.77; H, 5.53. Found: C, 68.88; H, 5.52.

Bromine-Quinoline Dehydrogenation of Mixed 1-Keto-4-*n*-amyl- and 1-Keto-2-*n*-amyl-9-methyl-1,2,3,4-tetrahydro-6-dibenzopyrones.—A mixture of 7.4 g. of the two keto lactones (IX and X) and 1.4 cc. of bromine in 50 cc. of chloroform was allowed to stand at room temperature for five hours or refluxed gently for half an hour until all the bromine had reacted. The solvent was evaporated and the residue heated with 30 cc. of quinoline at 200° for one hour. The cooled solution was poured into dilute hydrochloric acid; after one hour, the dark solid mass was removed by filtration and crystallized from 35 cc. of methyl ethyl ketone. The 1-hydroxy-2-*n*-amyl-9-methyl-6-dibenzopyrone crystallized and was purified from the same solvent, m. p. 182–183° (cor.); yield 2.7 g. (37%).

The filtrates were evaporated to dryness on the steam-bath and refluxed for two hours with 5 cc. of benzyl chloride and 60 cc. of 0.5 *N* sodium methylate. The hot solution was decanted from the sodium chloride and the 1-benzyloxy-4-*n*-amyl-9-methyl-6-dibenzopyrone separated on cooling, m. p. 120–121° (cor.); yield 2.2 g. (23%).

1-Methoxy-4-*n*-amyl-6,6,9-trimethyl-6-dibenzopyran.—To a solution of the Grignard reagent from 8 cc. of methyl iodide, 3.3 g. of magnesium and 30 cc. of dry ether, was added 2.1 g. of 1-methoxy-4-*n*-amyl-9-methyl-6-dibenzopyrone in 50 cc. of dry benzene. After refluxing for sixteen hours, the solution was poured into ice and hydrochloric acid. The organic layer was separated and the aqueous layer extracted once with benzene. The combined extracts were washed with aqueous sodium hydroxide and water and then were refluxed for three hours in a Soxhlet apparatus containing anhydrous magnesium sulfate in the thimble. The benzene was evaporated and the residue crystallized from methanol: white leaflets, m. p. 75–76° (cor.); yield 1.85 g. (84%).

Anal. Calcd. for $C_{22}H_{28}O_2$: C, 81.45; H, 8.67. Found: C, 81.71; H, 9.00.

1 - Benzyloxy - 4 - *n* - amyl - 6,6,9 - trimethyl - 6 - dibenzopyran (XIX).—The procedure was exactly the same as that described for the methoxy compound. From the Grignard reagent from 3 cc. of methyl iodide, 1.3 g. of magnesium in 15 cc. of dry ether, and 1 g. of 1-benzyloxy-4-*n*-amyl-9-methyl-6-dibenzopyrone (m. p. 121°) suspended in 30 cc. of dry ether was obtained 0.90 g. (86%) of pyran; white leaflets from ethanol, m. p. 74–75° (cor.).

Anal. Calcd. for $C_{25}H_{32}O_2$: C, 83.96; H, 8.05. Found: C, 83.84; H, 8.23.

2 - (α - Methyl - α - hydroxyethyl) - 5 - methyl - 2' - hydroxy - 3' - *n* - amyl - 6' - benzyloxybiphenyl (XVIII).—This compound was prepared by the procedure described for the 1-benzyloxy-4-*n*-amyl-6,6,9-trimethyl-6-dibenzopyran except that the benzene extracts after the Grignard reaction was carried out were evaporated to dryness by means of a stream of air. The crystalline residue was recrystallized from petroleum ether (b. p. 60–110°): white leaflets, m. p. 73–74° (cor.); yield, 85%.

Anal. Calcd. for $C_{28}H_{34}O_3$: C, 80.34; H, 8.18. Found: C, 80.11; H, 8.33.

2 - Isopropenyl - 5 - methyl - 2' - methoxy - 3' - *n* - amyl - 6' - benzyloxybiphenyl XXIV.—To a solution of 12.5 g. of 2-(α -methyl- α -hydroxyethyl)-5-methyl-2'-hydroxy-3'-*n*-amyl-6'-benzyloxybiphenyl in 75 cc. of methanol and 15 cc. of dimethyl sulfate was added 10% methanolic potassium hydroxide until the solution was permanently basic to litmus paper. This was repeated with a 10-cc. portion and a 5-cc. portion of dimethyl sulfate, then refluxed for fifteen minutes. The solution was poured into water and the crystalline precipitate removed by filtration. It was purified by recrystallization from acetone: white prisms, m. p. 76–77° (cor.); yield 7 g. (54%).

Anal. Calcd. for $C_{28}H_{34}O_2$: C, 84.02; H, 8.23. Found: C, 84.13; H, 8.21.

1 - Hydroxy - 4 - *n* - amyl - 6,6,9 - trimethyl - 6 - dibenzopyran (XX).—A. A solution of 1.44 g. of 1-benzyloxy-4-*n*-amyl-6,6,9-trimethyl-6-dibenzopyran in 35 cc. of acetic acid and 5 cc. of concentrated hydrochloric acid was refluxed for ninety minutes. The cooled solution was diluted with water and extracted with benzene. The benzene was steam distilled to remove volatile matter and the aqueous residual suspension extracted with benzene. The product was distilled, b. p. 205–210° (4 mm.) after which it crystallized and was purified by recrystallization from petroleum ether (b. p. 30–60°): white hexagonal plates, m. p. 62–63° (cor.); yield 0.88 g. (82%).

B. A mixture of 1 cc. of acetic acid saturated with hydrogen bromide, 2 cc. of acetic acid, 0.5 cc. of 48% aqueous hydrobromic acid and 0.2 g. of 1-methoxy-4-*n*-amyl-6,6,9-trimethyl-6-dibenzopyran was refluxed for three and one-half hours; the mixture became homogeneous at the end of two hours. After dilution with water, the product was extracted with benzene. The product, after evaporation of the benzene, crystallized from petroleum ether (b. p. 30–60°) upon chilling in ice and hydrochloric acid. When pure it melted at 62–63° (cor.) and was identical with that obtained in A.

Anal. Calcd. for $C_{21}H_{20}O_2$: C, 81.24; H, 8.45. Found: C, 81.27; H, 8.71.

1 - Acetoxy - 4 - *n* - amyl - 6,6,9 - trimethyl - 6 - dibenzopyran.—By refluxing the hydroxy compound with excess acetic anhydride for two hours, destroying excess of reagent with hot water and cooling, the acetate was obtained. If seeded, it crystallized. To obtain seed, a separate run was extracted with ether, washed and evaporated. The residue was dissolved in methanol and allowed to stand for two weeks in a refrigerator with occasional scratching.

The product was purified by recrystallization from ethanol; white leaflets, m. p. 72–73° (cor.).

Anal. Calcd. for $C_{28}H_{30}O_3$: C, 78.37; H, 8.01. Found: C, 78.03; H, 8.07.

1 - *p* - Nitrobenzoxy - 4 - *n* - amyl - 6,6,9 - trimethyl - 6 - dibenzopyran.—A mixture of 0.11 g. of the hydroxy compound, 0.07 g. of *p*-nitrobenzoyl chloride and 3 cc. of pyridine was refluxed for four hours and then allowed to stand at room temperature for thirty-six hours. Upon pouring into dilute hydrochloric acid, the ester crystallized and was extracted with ether. The product was purified by recrystallization from ethanol; yellow crystals, m. p. 144° (cor.).

Anal. Calcd. for $C_{28}H_{29}O_3N$: C, 73.17; H, 6.36. Found: C, 73.23; H, 6.30.

1 - Benzyloxy - 2 - *n* - amyl - 9 - methyl - 6 - dibenzopyrone (XVII).—A mixture of 1.8 g. of 1-hydroxy-2-*n*-amyl-9-methyl-6-dibenzopyrone, 1.8 cc. of benzyl chloride, 9 g. of anhydrous potassium carbonate and 50 cc. of reagent acetone was refluxed for two and one-half hours. The filtered solution was evaporated to dryness and the residue purified by crystallization from methanol: white felted needles, m. p. 86° (cor.), yield 1.5 g. (62%).

Anal. Calcd. for $C_{26}H_{26}O_3$: C, 80.79; H, 6.78. Found: C, 80.65; H, 6.91.

2-(α -Methyl- α -hydroxyethyl)-5-methyl-2'-hydroxy-5'-*n*-amyl-6'-benzyloxybiphenyl (XXI).—To a solution of Grignard reagent from 6 cc. of methyl iodide and 2.5 g. of magnesium in 30 cc. of dry ether was added 1.5 g. of 1-benzyloxy-2-*n*-amyl-9-methyl-6-dibenzopyrone in 30 cc. of benzene. After refluxing for fourteen hours, the solution was poured into iced ammonium chloride. The organic layer was separated and the aqueous layer extracted with benzene. The benzene extracts were washed, and the benzene evaporated. The residue was crystallized from petroleum ether (b. p. 60–110°): white felted needles, m. p. 106.5–107.5° (cor.); yield 1.2 g. (74%). The compound was soluble in ethanolic but insoluble in aqueous alkali.

Anal. Calcd. for $C_{28}H_{34}O_3$: C, 80.34; H, 8.18. Found: C, 80.62; H, 8.43.

1 - Benzyloxy - 2 - *n* - amyl - 6,6,9 - trimethyl - 6 - dibenzopyran (XXII).—A solution of 0.8 g. of the phenolic alcohol just described in 40 cc. of benzene containing three drops of 48% hydrobromic acid was refluxed for four hours in a Soxhlet apparatus containing anhydrous magnesium sulfate in the thimble. The benzene was evaporated and the residue purified by recrystallization from ethanol: blunt white needles, m. p. 67–68° (cor.); yield 0.45 g. (60%).

Anal. Calcd. for $C_{28}H_{30}O_2$: C, 83.96; H, 8.05. Found: C, 84.13; H, 7.68.

This product could be made also directly from the pyrone without isolation of the intermediate phenolic carbinol.

2 - Isopropenyl - 5 - methyl - 2' - *p* - nitrobenzoxy - 5' - *n*-amyl-6'-benzyloxybiphenyl.—A solution of 0.2 g. of 2-(α -methyl- α -hydroxyethyl)-5-methyl-2'-hydroxy-5'-*n*-amyl-6'-benzyloxybiphenyl and 0.25 g. of *p*-nitrobenzoyl chloride in 6 cc. of pyridine was refluxed for four hours. The solution was poured into dilute hydrochloric acid and the product extracted with ether. The product was purified by crystallization from ethanol; light yellow needles, m. p. 100–101° (cor.). Apparently aroylation was accompanied by dehydration of the carbinol.

Anal. Calcd. for $C_{35}H_{35}NO_3$: C, 76.48; H, 6.41; N, 2.55. Found: C, 76.47, 76.44; H, 6.54, 6.54; N, 2.68, 2.69.

2 - (α - Methyl - α - hydroxyethyl) - 5 - methyl - 2' - methoxy - 3' - *n* - amyl - 6' - hydroxybiphenyl.—This was prepared in exactly the same manner as the corresponding benzyloxy compound. From 2.6 cc. of methyl iodide, 1.1 g. of magnesium, and 1.36 g. of pyrone was obtained 1.20 g. (80%) of phenolic alcohol. It was purified from petroleum ether (b. p. 60–110°); white needles, m. p. 102–103° (cor.).

Anal. Calcd. for $C_{22}H_{30}O_3$: C, 79.49; H, 9.06. Found: C, 79.44; H, 9.14.

1 - Methoxy - 2 - *n* - amyl - 6,6,9 - trimethyl - 6 - dibenzopyran.—To a solution of 1.1 g. of 2-(α -methyl- α -hydroxyethyl)-5-methyl-2'-methoxy-3'-*n*-amyl-6'-hydroxybiphenyl in 50 cc. of petroleum ether (b. p. 60–110°) was added two drops of 48% aqueous hydrobromic acid. The mixture was then boiled gently on a hot-plate for forty minutes. Petroleum ether was added from time to time to maintain the volume at about 35–50 cc. The cooled solution was washed with 15 cc. of 1 *N* sodium methylate in methanol. The methanol was extracted with four 15-cc. portions of petroleum ether, the combined petroleum ether extracts washed with water and the solvent evaporated. The residue distilled as a colorless liquid, b. p. 182° (3 mm.); yield 0.6 g. (58%).

Anal. Calcd. for $C_{22}H_{28}O_2$: C, 81.45; H, 8.67. Found: C, 81.31; H, 8.87.

1 - Hydroxy - 2 - *n* - amyl - 6,6,9 - trimethyl - 6 - dibenzopyran (XXIII).—A. A mixture of 0.5 g. of 1-methoxy-2-*n*-amyl-6,6,9-trimethyl-6-dibenzopyran, 6 cc. of acetic acid, 1.5 cc. of 48% aqueous hydrobromic acid and 3 cc. of acetic acid saturated with hydrogen bromide was refluxed for three and one-half hours. At the end of about two hours the mixture became homogeneous. The cooled solution was diluted with water and the product extracted with petroleum ether. The petroleum ether was washed with water, dilute aqueous sodium hydroxide, then extracted with two 15-cc. portions of 10% methanolic potassium hydroxide. The methanol solution, after being washed with 25 cc. of petroleum ether, was diluted with water and acidified. The separated oil was taken up in petroleum ether, the solvent evaporated and the residue distilled: viscous yellow liquid, b. p. 203–205° (3 mm.); yield 0.39 g. (82%). It was not obtained crystalline.

Anal. Calcd. for $C_{21}H_{26}O_2$: C, 81.24; H, 8.45. Found: C, 80.89; H, 8.59.

B. A mixture of 1.4 g. of 1-benzyloxy-2-*n*-amyl-6,6,9-trimethyl-6-dibenzopyran, 20 cc. of acetic acid and 3 cc. of concentrated hydrochloric acid was refluxed for three and one-half hours. At the end of the first and second hours, 2-cc. portions of concentrated hydrochloric acid were added. The solution was diluted with water, extracted with ether, the ether washed with water and then evaporated. The residue was steam distilled to remove volatile matter and the insoluble, non-volatile material taken up in petroleum ether. The latter was washed with water, evaporated and the residue distilled: viscous yellow liquid, b. p. 203–206° (3 mm.); yield 0.7 g. (64%).

1 - *p* - Nitrobenzoxy - 2 - *n* - amyl - 6,6,9 - trimethyl - 6 - dibenzopyran.—This product was prepared from the corresponding hydroxy compound from methods A and B just described by the procedure followed for *p*-nitrobenzoxylation of the 4-*n*-amyl derivative; yellow crystals from ethanol, m. p. 129–130° (cor.).

Anal. Calcd. for $C_{28}H_{29}O_5N$: C, 73.17; H, 6.36. Found: C, 73.06; H, 6.44.

Summary

Two isomeric cannabinols have been prepared, 1-hydroxy-4-*n*-amyl-6,6,9-trimethyl-6-dibenzopyran and 1-hydroxy-2-*n*-amyl-6,6,9-trimethyl-6-dibenzopyran. These compounds were synthe-

sized through the condensation of 4-methyl-2-bromobenzoic acid with 4-*n*-amyl-dihydroresorcinol. The two isomeric lactones thus obtained were separated and dehydrogenated to the corresponding dibenzopyrones. Each dibenzopyrone was alkylated by a method which avoided as an intermediate the hydroxy acid, and then treated with methylmagnesium iodide to form the corresponding pyrans. The alkylated pyrans were then dealkylated to the cannabinol isomers.

It has been demonstrated experimentally that 4-alkyl-1,3-cyclohexanedione enolizes in two ways; that ring closure of a 2-carboxyl-2',6'-dihydroxy-5-alkylbiphenyl to a pyrone is preferably through the 6'-hydroxyl; that the dehydration of the phenolic alcohols to the pyrans of such molecules as 2-(α -methyl- α -hydroxyethyl)-2'-hydroxy-6'-alkoxy-5'-alkylbiphenyl and 2-(α -methyl- α -hydroxyethyl)-2'-hydroxyl-3'-alkyl-6'-alkoxybiphenyl takes place much more readily in the latter than in the former.

URBANA, ILLINOIS

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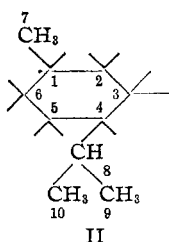
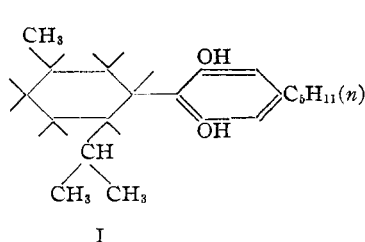
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Structure of Cannabidiol. V.¹ Position of the Alicyclic Double Bonds

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The evidence submitted in previous communications¹ establishes for tetrahydrocannabidiol structure I. No attempt was made to determine the relative configuration of the asymmetric carbon



atoms. As tetrahydrocannabidiol was made by catalytic reduction of cannabidiol with absorption

of four atoms of hydrogen, this latter compound must have two double bonds in the left-hand residue (II). The possible combinations of two double bonds in such a radical (II) are very numerous (twenty or more) and merely the configurations for the two double bonds 6,1 and 3,4 or 1,2 and 3,4 are immediately excluded since the resulting structures would not allow the presence of optical activity in the molecule (cannabidiol $[\alpha]^{25}_D -125^\circ$). The cleavage of cannabidiol by pyrolysis with pyridine hydrochloride to *p*-cymene and olivetol is carried out under such conditions that, regardless of the mechanism involved, the double bonds in the molecule, wherever they may be placed, probably would migrate to complete the benzene nucleus.

It has been found that the possibility of either double bond being in positions 2,3 or 3,4 (structure II) is eliminated. This was accomplished by comparison of the absorption spectra of cannabidiol dimethyl ether and dihydrocannabidiol di-

(1) For previous papers see (a) Adams, Hunt and Clark, *THIS JOURNAL*, **62**, 196 (1940); (b) Adams, Cain and Wolff, *ibid.*, **62**, 732 (1940); (c) Adams, Hunt, and Clark, *ibid.*, **62**, 735 (1940); (d) Adams, Wolff, Cain and Clark, *ibid.*, **62**, 2215 (1940); (e) Adams, Pease and Clark, *ibid.*, **62**, 2194 (1940); (f) Adams, Baker, and Wearn, *ibid.*, **62**, 2204 (1940).

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