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

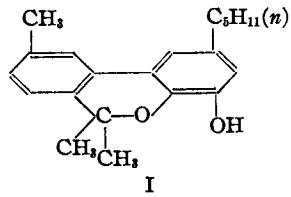
Structure of Cannabidiol, a Product Isolated from the Marihuana Extract of Minnesota Wild Hemp. I

BY ROGER ADAMS, MADISON HUNT, AND J. H. CLARK[1]

(IN COLLABORATION WITH THE TREASURY DEPARTMENT, NARCOTICS LABORATORY, WASHINGTON, D. C., AND DR. S. LOEWE, DEPT. OF PHARMACOLOGY, CORNELL UNIVERSITY MEDICAL COLLEGE)

Marihuana is the term commonly used in the United States to represent those portions of the *Cannabis sativa* or hemp plant which are capable of inducing somatic and psychic changes in humans. It is also familiarly known as hashish, bhang, charas, and ganja. The activity of an extract of the plant is found to vary widely, and to be dependent on the source of the hemp. Previous investigators, for the most part, have studied the resin obtained by working up hashish of Indian origin from the variety of hemp known as *Cannabis indica*. In this investigation, Minnesota wild hemp, cut after flowering had begun and before the seed had "set" in the female tops, was used as a raw material. It was extracted with ethanol and the so-called "red oil" containing the active principle or principles was obtained by distillation under diminished pressure.

Numerous investigators have studied the active red oil from *Cannabis sativa* and *indica* but only a single pure substance other than nonacosane has yet been isolated from the mixture of products present. This was called cannabinol by Wood, Spivey and Easterfield,[2] and was purified through its crystalline acetate. They assigned the formula $C_{21}H_{26}O_2$. This formula was confirmed and the constitution investigated by Cahn,[3] who proposed structure I in which the positions of the hydroxyl and *n*-amyl groups are uncertain.



I

Cannabinol is very toxic but has no marihuana activity. A knowledge of the structure of this compound is significant, however, due to the fact that the active red oil, even though derived from various sources, gives an analysis not substantially different from that of pure cannabinol.

When the red oil from Minnesota hemp was treated to isolate cannabinol according to methods previously suggested, no crystalline cannabinol acetate[3] or *p*-nitrobenzoate[4] could be isolated. Since the red oil contained substances with phenolic groups as shown by qualitative tests, other reagents for phenols were studied. This resulted in observing that a crystalline 3,5-dinitrobenzoyl derivative could be isolated in yields which corresponded to about 33% of the purified red oil used. Analysis indicated this derivative to be a *bis*-3,5-dinitrobenzoate of a dihydric phenol of the formula $C_{21}H_{30}O_2$ or $C_{21}H_{32}O_2$, the analysis not allowing distinction between them. It was readily purified. Upon ammonolysis of the purified *bis*-3,5-dinitrobenzoate by means of ammonia in toluene, the isolation of a pure compound was accomplished. It proved to have one of the two empirical formulas suggested above and has been given the name cannabidiol. It has none of the physiological activity typical of marihuana. The product is optically active, $[\alpha]_D$ −119°, and gives a very strong alkaline Beam test somewhat different from and more intense than that exhibited by purified red oil. Numerous other color tests applied to cannabidiol and purified red oil are given in Table I. It is obvious that the colors given by the red oil are dependent in part on substances other than cannabidiol.

By comparison with the formula of cannabinol, it is obvious that cannabidiol contains merely four or six more hydrogen atoms. The presence of two hydroxyls, presumably phenolic, is shown by the *bis*-3,5-dinitrobenzoate derivative and further was confirmed by the preparation of a crystalline *bis*-*m*-nitrobenzene sulfonate, a dimethyl ether, and a Zerewitinoff determination.

Methylation by means of repeated treatments with excess methyl iodide in acetone and potas-

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

(2) Wood, Spivey and Easterfield, *J. Chem. Soc.*, **69**, 539 (1896); **75**, 20 (1899).

(3) Cahn, *ibid.*, 986 (1930); 630 (1931); 1342 (1932); 1400 (1933). See also Bergel, *Ann.*, **482**, 55 (1930); **493**, 250 (1932). An excellent review of the literature dealing with the chemical constituents of *Cannabis sativa* is given in an article by Blatt, *J. Wash. Acad. Sci.*, **28**, 465 (1938).

(4) Work, Bergel and Todd, *Biochem. J.*, **33**, 123 (1939).

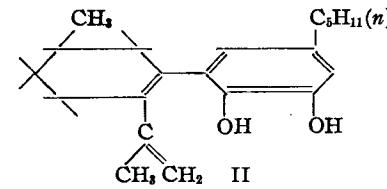
TABLE I

COLOR REACTIONS OF CANNABIDIOL AND OF PURIFIED RED OIL

Test	Red oil	Cannabidiol	References
Beam test 5% ethanolic KOH	Reddish violet, yellowish brown on acidification	Deep violet, yellow on acidification	*C. A.*, **6**, 1952 (1912). Wellcome, *Trop Res. Labs. Khortoum*, 4th Rept. (B), 25.
Duquenois test acetaldehyde, vanillin–HCl	Opaque blue after several minutes	Clear pale blue, deepening on standing	*J. Egypt. Med. Assoc.*, **21**, 224 (1938) [*C. A.*, **32**, 5993 (1938)].
Ghamrawy test *p*-dimethylaminobenzaldehyde	Deep red; on dilution with water changes to deep purple	Bright red; on dilution with water changes to bluish green	*J. Egypt. Med. Assoc.*, **20**, 193 (1937) [*C. A.*, **32**, 4724 (1938)].
Ethanolic $FeCl_3$	No color	No color	*Pharm. Acta Helv.*, **1**, 210 (1926) [*C. A.*, **21**, 2050 (1927)].
Millon's reagent	Red and precipitate in cold	Red and precipitate in cold	Same
Ammoniacal $AgNO_3$	Reduces slightly in cold, readily when hot	Very slight reduction in cold, slow reduction when hot	Same
Fehling's soln.	Reduces* slowly in cold, readily when hot	Reduces very slowly when hot, no reduction in cold	Same
Formaldehyde–H_2SO_4	Dark brown	Very deep red	*The Analyst*, **36**, 540 (1911).[a]
Opianic acid–H_2SO_4	Bright red changing to brown	Bright red	*Ber.*, **20**, 874 (1887).[a]
Alloxan–H_2SO_4	Deep red changing to brown	Bright red	*Chem. Zentr.*, **73**, I, 631 (1902).[a]
Acetic acid	No color	No color	*Pharm. Acta Helv.*, **1**, 210 (1926).
H_2SO_4	Brown	Pale orange, fading to pale yellow	Same
Acetic anh.–H_2SO_4	Brown	Light brown	Same
$CHCl_3$–H_2SO_4	Brown in acid layer	Brilliant brown red in acid layer	Same
$Ca(OCl)_2$	Yellowish red	No reaction	*Ann.*, **68**, 95 (1848).[a]
$CHCl_3$–10% aq. KOH	Dark red in aqueous layer	Red in aqueous layer	*Z. anal. Chem.*, **56**, 286 (1917).[a]
$NaNO_3$–dil. H_2SO_4	No reaction	No reaction	*Ber.*, **7**, 248 (1874).[a]

* Tests have not previously been used on red oil. References are to the description of the tests on simply polyhydroxy benzenes.

sium carbonate resulted finally in formation of a dimethyl ether. Oxidation with permanganate in acetone gave *n*-caproic acid, which represents strong evidence for an *n*-amyl group in a phenolic ring. From these few facts alone, it may be concluded that one-half of the molecule of cannabidiol probably corresponds to the right-hand half of cannabinol (I). However, both hydroxyls are free in the cannabidiol so that the possibility of a pyran ring such as exists in cannabinol is excluded. On the assumption that the cannabidiol resembles cannabinol in entirety, the other half of the cannabidiol molecule may be postulated as a partially hydrogenated methylisopropylbenzene nucleus. Thus, formula II expresses satisfactorily the available experimental facts.



II

If the correct formula is $C_{21}H_{30}O_2$ (II), then two double bonds or the equivalent must be present. The positions assigned them in II are essentially fortuitous as no sound evidence has yet been revealed whereby to place them. The possibility of one double bond and a three-, four-, or five-membered ring, such as occurs in many terpenes, is not excluded. On the other hand, if the formula of cannabidiol is $C_{21}H_{32}O_2$, only one double bond in the left-hand ring can be present. The analyses of cannabidiol and its derivatives, the esters and ether, do not make possible a definite conclusion about the formula though $C_{21}H_{30}O_2$ agrees somewhat more uniformly with the analyses and, therefore, appears the more likely. Hydrogenation experiments, which should lead to the detection of one or two double bonds, have as yet proven indecisive. It is hoped, however, that a

careful reduction study now under way may clarify the question of unsaturation.

Red oil probably contains other products closely related to cannabinol or cannabidiol in structure, such as partially hydrogenated cannabinols, isomers of cannabidiol, or molecules like cannabidiol with less unsaturation. A large number of closely related compounds is possible. The active marihuana principle or principles may be among this group of substances. On the other hand, the possibility of the presence in red oil of a very potent active compound, entirely unrelated structurally to cannabinol or cannabidiol, is not excluded.

Experimental

The hemp used in these experiments grew wild in Minnesota during the season of 1938. It was cut in August, after flowering had begun but before seed had "set" in the female tops. It was stored for six weeks in a room where a fan assured circulation of air in order to dry it completely. No molding occurred. The material was then beaten and shaken to remove the coarse stems which amounted to about one-third of the total dry weight. The stems were discarded and the relatively fine material that remained was extracted with 95% ethanol in the manner described below.

Four 20-gallon (75-liter) crocks, each holding approximately 23 lb. (10 kg.) of material, were set up in series for countercurrent extraction. Each crock held approximately 61 liters of solvent of which about 41 liters were withdrawn at each transfer, the remainder being retained by the hemp. Once the process had become uniform in operation, the extract received from crock no. 4 at each transfer reached a concentration of approximately 2 g. per 100 cc. Transfers were made once or twice a day as conditions warranted. The most concentrated extract thus obtained was passed to a concentrator where most of the solvent was "flashed off" under vacuum. It was never heated above 50°. The evaporation was carried out at about 30°. The concentrated solution contained in this case 23.1 g. of solids per 100 cc. and 1 cc. was equivalent to 4.13 g. of hemp extracted. The operations just described were carried out by Dr. John R. Matchett and his assistants in the Narcotics Laboratory of the Treasury Department, Washington, D. C. They kindly furnished us with a generous supply of ethanol extract.

The red oil from these extracts was obtained as follows. Into a 1-liter Claisen flask, with a wide short neck, filled with glass wool was poured ethanolic extract until two-thirds full. The bath temperature was raised gradually from 90–140° while the pressure was diminished slightly. The ethanol distillate was discarded and the flask again filled to two-thirds capacity. This process was repeated until a maximum of 1600 cc. of extract had been added and all the ethanol was distilled. The temperature was then gradually raised to 200° and when distillation of the last traces of ethanol ceased, the bath was lowered to 180° and the pressure gradually reduced to 30 mm. Great care was necessary to prevent the liquid from foaming over. The temperature was gradually raised to 200° (30 mm.) until distillation ceased. The bath was then cooled to 170° and the pressure reduced to 2–5 mm. The residual product was then distilled. Considerable care was necessary to keep the bath at the lowest temperature at which the oil distilled regularly since there was a particular tendency to foam when the superheating was excessive. The material distilled between 100–220° (3 mm.) with the bath temperature at 170–310°; yield 180–200 g.

This crude red oil was dissolved in 500 cc. of petroleum ether (b. p. 30–60°) and extracted twice with water. The aqueous extract was saved and worked up for water-soluble materials. The petroleum ether layer was distilled and the residue fractionated through a good column with an outside heating unit. The first fraction boiled at 115–150° (2 mm.) (bath temperature 190–210°); yield, 70–80 g. The second fraction boiled at 150–175° (2 mm.) (bath temperature 215–225°); yield 25–35 g. The residual material in the flask was removed while still hot by dissolving in ethanol and filtering from the glass wool. The ethanol was removed and the product distilled from a 250-cc. flask, b. p. 175–195° (2 mm.) (bath temperature 220–270°); yield 90–110 g. This last material was considered as purified red oil.

Cannabidiol *bis*-3,5-Dinitrobenzoate.—A solution of 50 g. of purified red oil, b. p. 175–195° (2 mm.), in 200 cc. of dry pyridine was poured rapidly with shaking and cooling on 85 g. of 3,5-dinitrobenzoyl chloride. The mixture was heated on a steam cone for two hours with occasional shaking and was then poured into ice and hydrochloric acid (200 cc. of concentrated hydrochloric acid, 500 cc. of ice). It was filtered or decanted and the insoluble material was washed several times with dilute hydrochloric acid. The residue was dissolved in 600 cc. of benzene and filtered. The insoluble material consisted mainly of 3,5-dinitrobenzoic acid.

The benzene solution was washed with dilute hydrochloric acid, then with aqueous sodium bicarbonate and finally with water. Considerable trouble was encountered with emulsions which broke with difficulty. The benzene was evaporated and the residue was dissolved in 500 cc. of dry ether. This solution was treated with norit (20 g.), filtered, and then concentrated to 300 cc. On cooling in an ice–salt mixture with constant stirring, crystallization set in. After one hour, the product was filtered and washed with cold dry ether. It was purified by recrystallizing from 800 cc. of a mixture of methanol and methyl acetate (2:1); white rods, m. p. 106–107° (corr.).

Anal. Calcd. for $C_{21}H_{28}(OCOC_6H_3(NO_2)_2)_2$: C, 59.82; H, 4.88; N, 7.97. Calcd. for $C_{21}H_{30}(OCOC_6H_3(NO_2)_2)_2$: C, 59.64; H, 5.15; N, 7.95. Found: C, 59.74; H, 5.00; N, 7.96. *Rotation.* 0.057 g. made up to 5 cc. with acetone at 27° gave α_D −1.73°; *l*, 2; $[\alpha]^{27}D$ −76°.

Cannabidiol.—A solution of 50 g. of cannabidiol *bis*-3,5-dinitrobenzoate in 100 cc. of toluene was placed in the glass liner of a high pressure bomb. The mixture was cooled by dry-ice and about 100 cc. of liquid ammonia passed into it. The liner was then placed in the bomb and the cover quickly fastened. The bomb was allowed to stand for five hours at room temperature. At the end of that time the excess ammonia was allowed to escape and the product, which had set to a solid mass, was digested with 400 cc.

of petroleum ether (b. p. 60–110°). The solid 3,5-dinitrobenzamide was filtered and washed with two 50-cc. portions of petroleum ether. Filtrate and washings were combined and extracted six times with 150-cc. portions of boiling water to remove the last traces of 3,5-dinitrobenzamide. The petroleum ether was then evaporated and the residue distilled, b. p. 187–190° (2 mm.) (bath temperature 220°), d^{40}_4 1.040; $n^{20}D$ 1.5404. Cannabidiol is a pale yellow resin; yield 17–19 g.

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Calcd. for $C_{21}H_{32}O_2$: C, 79.69; H, 10.19. Found: C, 80.08, 80.29; H, 9.87, 9.41. *Rotation.* 0.0378 g. made up to 5 cc. with 95% ethanol at 28° gave α_D −0.90°; *l*, 1; $[\alpha]^{28}D$ −119°.

A Zerewitinoff determination showed two active hydrogens.

Cannabidiol is soluble in all common organic solvents, ether, benzene, ethanol, methanol, chloroform, and petroleum ether, but insoluble in water and 10% hot or cold aqueous sodium hydroxide.

That no rearrangement or deep-seated decomposition had taken place by this method of hydrolysis was demonstrated by the fact that the product readily could be reconverted in essentially quantitative yields to the same *bis*-3,5-dinitrobenzoate.

Cannabidiol *bis*-*m*-Nitrobenzene Sulfonate.—To a solution of 0.2 g. of cannabidiol in 5 cc. of dry pyridine, 0.35 g. of *m*-nitrobenzene sulfonyl chloride was added. The mixture was warmed on a steam cone for one hour and was then poured into ice and hydrochloric acid. The product was filtered, washed with dilute hydrochloric acid, aqueous sodium bicarbonate and then with water. It was purified by recrystallization from ethanol: white rods, m. p. 119–120° (corr.); yield 0.17 g. This same derivative could be obtained directly from purified red oil.

Anal. Calcd. for $C_{21}H_{26}(OSO_2C_6H_4NO_2)_2$: C, 57.87; H, 5.30; N, 4.09. Calcd. for $C_{21}H_{30}(OSO_2C_6H_4NO_2)_2$: C, 57.70; H, 5.58; N, 4.08. Found: C, 57.72; H, 5.49; N, 4.39.

Cannabidiol Dimethyl Ether.—A solution of 11.25 g. of cannabidiol in 75 cc. of acetone was refluxed for four hours with 12 g. of methyl iodide and 15 g. of anhydrous potassium carbonate. A deep purple color present at the beginning of the reaction had changed to a pale yellow at the end of this time.

The potassium carbonate was filtered, washed with ether, and the filtrate and washings combined. The solution becomes cloudy due to the precipitation of salts dissolved in the acetone. About 300 cc. more of ether was added and the mixture extracted with water. The solvent was then removed and the product distilled. Five cuts of approximately equal volume were taken since temperature changes were not significant. The refractive indices of these fractions ranged from 1.5330 to 1.5372, indicating that some reaction had taken place but that the product was not homogeneous.

The distillate was dissolved again in acetone, treated with excess methyl iodide and potassium carbonate and refluxed for periods of ten, twelve, forty-eight, and sixty hours. After each treatment the progress of the reaction was followed by the refractive index as described above. At the end of a total of one hundred and thirty-four hours of refluxing the refractive index of the main portion of the distillate was found to have reached a constant value. The material thus obtained was a pale yellow oil, much less viscous than cannabidiol; b. p. 175–177° (3 mm.) (bath temperature 200°); yield 3.3 g.; $n^{20}D$ 1.5254; d^{20}_4 0.9823.

Anal. Calcd. for $C_{21}H_{26}(OCH_3)_2$: C, 80.65; H, 10.01; OCH_3, 18.12. Calcd. for $C_{21}H_{30}(OCH_3)_2$: C, 80.17; H, 10.53; OCH_3, 18.02. Found: C, 80.52; H, 10.08; OCH_3, 18.2. *Rotation.* 0.0535 g. made up to 5 cc. with 95% ethanol at 28° gave α_D −1.42°; *l*, 1; $[\alpha]^{26}D$ −133°.

Cannabidiol dimethyl ether is insoluble in water, difficultly soluble in cold 95% ethanol, and readily soluble in petroleum ether, acetone, and ether.

An attempt was made to prepare the monomethyl ether by refluxing cannabidiol in acetone solution for eight hours with over twice the theoretical amounts of methyl iodide and potassium carbonate. The product was worked up as described above and carefully fractionated. That portion of the distillate which seemed, on the basis of refractive indices, to be homogeneous was found to give a very satisfactory value for methoxyl content, but a consistently poor value for carbon. The material was a clear viscous oil, b. p. 177–179° (2 mm.) (bath temperature 200–210°); $n^{20}D$ 1.5311.

Anal. Calcd. for $C_{21}H_{29}O(OCH_3)$: C, 80.44; H, 9.82; OCH_3, 9.45. Calcd. for $C_{21}H_{31}O(OCH_3)$: C, 79.94; H, 10.37; OCH_3, 9.39. Found: C, 79.67, 79.50; H, 9.65, 9.79; OCH_3, 9.41. *Rotation.* 0.0455 g. made up to 5 cc. with 95% ethanol at 26° gave α_D −2.14; *l*, 2; $[\alpha]^{26}D$ −118°.

Oxidation of Cannabidiol.—To a solution of 5 g. of cannabidiol in 25 cc. of acetone was added a saturated solution of 8 g. of potassium permanganate in 50% aqueous acetone and 5 g. of sodium bicarbonate. The mixture was heated for thirty minutes on a steam-bath. Ethanol was added to remove the last traces of the permanganate, the mixture filtered and acidified with hydrochloric acid. The acid solution was extracted with ether and the ether solution in turn extracted with aqueous sodium bicarbonate.

The aqueous sodium bicarbonate solution was acidified with hydrochloric acid and extracted with ether. The ether solution was dried over anhydrous magnesium sulfate, the solvent removed and the product distilled. It boiled at 200–203° (750 mm.) and weighed 1.15 g. (64% based on one molecule of *n*-caproic acid per molecule of cannabidiol). The anilide was prepared for identification purposes, m. p. 95–96°, and proved to be identical with an authentic sample of *n*-caproanilide.

Summary

A new compound, cannabidiol, present in the purified red oil of *Cannabis sativa* has been isolated through the *bis*-3,5-dinitrobenzoate. This diester is a crystalline, easily purified compound. Ammonolysis of it gives cannabidiol which has the formula $C_{21}H_{30}O_2$ or $C_{21}H_{32}O_2$, the former probably being the correct one.

Cannabidiol is oxidized to *n*-caproic acid, methylated with difficulty to a dimethyl ether and

converted to a *bis-m*-nitrobenzenesulfonate. It is concluded that this substance is closely related to cannabinol in structure. Half the molecule is probably a dihydroxy *n*-amylphenyl, the other half probably an unsaturated alicylic nucleus.

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Structure of Cannabidiol. XII. Isomerization to Tetrahydrocannabinols[1]

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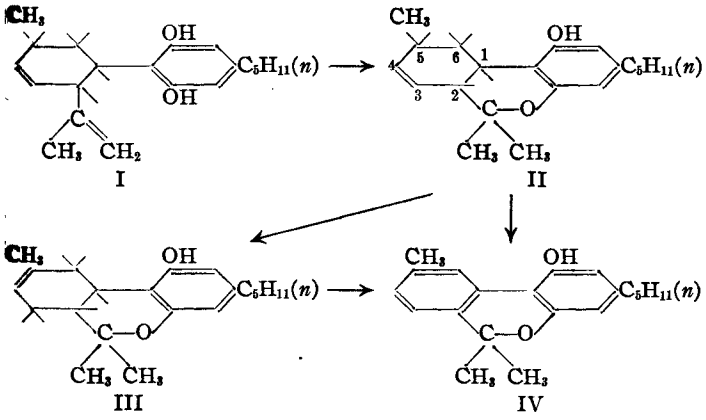
Crystalline cannabidiol (I) isomerizes readily in the presence of a number of acidic reagents to give a tetrahydrocannabinol (II or III).[3] The general structure of the latter was established by dehydrogenation to cannabinol (IV), a product



which was synthesized by two unequivocal methods. Dependent upon the conditions used, the tetrahydrocannabinol obtained had a specific rotation which was reported as α_D $-160 \pm 10°$ or α_D $-240 \pm 10°$. The results in preparing these forms were variable. Even though carefully controlled, successive experiments often gave products with different rotations.

The study of the isomerization of cannabidiol has been continued. It has now been found that very dilute ethanolic hydrochloric acid will convert cannabidiol to a tetrahydrocannabinol α_D $-130 \pm 5°$. An excellent new reagent for converting cannabidiol to high-rotating tetrahydrocannabinol α_D $-265 \pm 5°$ has been discovered in *p*-toluenesulfonic acid which is used in benzene solution and refluxed with the cannabidiol for one to two hours or longer. A drop of sulfuric acid (100%) in cyclohexane acts similarly. On the other hand, trichloroacetic, anhydrous oxalic, picric, 3,5-dinitrobenzoic, 87% formic, glacial acetic and maleic acids failed to isomerize cannabidiol, at least more than partially, in ten to twenty hours of boiling in benzene solution.

Unlike the previous conversions, these forms could be duplicated at will and it is believed that each represents an essentially pure product. It was reported previously that the reagents which convert cannabidiol to the high-rotating tetrahydrocannabinol also convert a low-rotating tetrahydrocannabinol to the same form. However, further experimentation has demonstrated that it is never possible to obtain by this latter conversion a product which has a rotation of α_D $-265 \pm 5°$. The maximum rotation ordinarily is within the range α_D -200 to $-225°$. This is true also of the tetrahydrocannabinol α_D $-130 \pm 5°$ described for the first time in this communication. The explanation of the discrepancy still is being sought but the reduction experiments lead to the belief that it may be accounted for possibly by the difficulty of complete conversion to a single product after the pyran ring once has been established. Upon reduction of a tetrahydrocannabinol of any rotation between α_D $-130°$ and $-270°$, there is always formed a homogeneous hexahydro product of constant rotation α_D $-70°$. The shifting of the nuclear double bond in the cannabidiol may take place simultaneously with or preceding the cyclization to the pyran.

It was suggested earlier[4] that since the reduction of tetrahydrocannabinols of varying rotation gave a hexahydrocannabinol of the same rotation, the difference in the rotation of the low- and high-rotating forms was due, probably, to the shifting of the double bond in the left-hand ring. The position of the double bond in the lower-rotating isomer was assigned that shown in II, since it was produced the more easily and since the evidence favors that position for the nuclear double bond in cannabidiol (I). The terminal double bond in cannabidiol was definitely established; the other

(1) For previous paper see Adams, Cain and Loewe, THIS JOURNAL, **63**, 1977 (1941).

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

(3) Adams, Pease, Cain and Clark, THIS JOURNAL, **62**, 2402 (1940).

(4) Adams, Loewe, Pease, Cain, Wearn, Baker and Wolff, *ibid.*, **62** 2566 (1940).

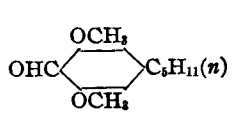
double bond was assigned the 3,4-position partly on the basis of absorption spectra.[5] These eliminated the possibility of a double bond conjugated with the benzene ring and rendered unlikely a conjugated system of double bonds in the left-hand ring. Failure of cannabidiol dimethyl ether to react with maleic anhydride confirmed this latter fact. The shift of a double bond in the 2,3- or 5,6-position of tetrahydrocannabinol by acidic reagents would, expectedly, take place to the 1,2- or 6,1-position, but experiments demonstrated that the product of reaction did not have a double bond conjugated to the benzene ring. The 3,4-position (II) for the double bond is, therefore, selected as the most likely for the low-rotating isomer, α_D −130°, and the 4,5-position (III) for the high-rotating form, α_D −265°.

Indication of a shift of a double bond in the tetrahydrocannabinols has been obtained through the observation that the tetrahydrocannabinol α_D −130° adds hydrogen chloride from an ether solution and gives an addition product (an oil) too unstable to purify, but undecomposed on shaking with dilute aqueous sodium bicarbonate. Upon distillation it loses hydrogen chloride with generation of a product α_D −203°. Attempts to replace the chlorine atom in the addition product by other groups failed.

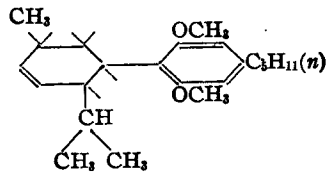
It appears that the product α_D −160°, which varies so in rotation with minor changes in conditions of preparation, may be a mixture of the isomers α_D −130° and α_D −265°. No further experimental evidence is available to support this assumption. Various attempts to separate the form α_D −160° by chromatographic absorption into the lowest- and highest-rotating forms were unsuccessful. Similarly, the product α_D −225° to −240° is probably a mixture.

Further study was made of the position of the double bond in the left-hand ring of cannabidiol. Cannabidiol dimethyl ether was ozonized. After decomposing the ozonide in warm water, methone was added and the formaldehyde derivative isolated. This verified the terminal double bond previously determined by a color reaction. The other product or products were aldehydic oils which gave no solid derivatives and which oxidized to unidentifiable acids.

In one experiment, when the ozonide was decomposed with chromic acid in acetic acid, an oily product was obtained from which a small amount of a crystalline dinitrophenylhydrazone was isolated. This was derived from an aldehyde or ketone of formula $C_{14}H_{20}O_3$ which, probably, is the aldehyde of olivetol dimethyl ether (V).



V



VI

Dihydrocannabidiol dimethyl ether (VI) also was studied with care. The usual reagents which add hydroxyls to the double bond, such as hydrogen peroxide in the presence of osmium tetroxide and monoperphthalic acid, failed to give solid glycol products. These latter on oxidation with lead tetraacetate or periodic acid gave only oils from which no solid derivatives could be isolated.

In an attempt to cause a shift in the double bond in the left-hand ring similar to that which occurred under the same conditions with low-rotating tetrahydrocannabinol, dihydrocannabidiol dimethyl ether was heated in benzene solution with *p*-toluenesulfonic acid. A change in rotation of the molecule was expected. Instead, a cleavage took place analogous to that which occurred when cannabidiol was heated with pyridine hydrochloride[6] to a relatively high temperature. The reaction mixture, upon distillation, yielded olivetol dimethyl ether and an undistillable residue which, probably, was a polymer of the initially formed menthadiene. Further study of this reaction may make possible the isolation of a monomer in which the position of the ring double bonds may be determined.

Attempts to crystallize any of the tetrahydrocannabinols have not succeeded. No reagents were discovered which gave solid derivatives from the form α_D −265° that could be purified. Among these may be mentioned the *p*-phenylazobenzoate, acetate, *p*-nitrobenzoate, *p*-aminobenzoate, 3,5-dinitrobenzoate, 3,5-dinitrophenylurethan, diphenyl carbamate, picrate, succinate half ester, allophanate, methyl ether, acetic acid ether and 2,4-dinitrophenyl ether. In addition condensation products with diazotized *p*-nitraniline, naphthionic acid, β-naphthylamine and 2,4,6-trinitraniline were intractable substances, as were the nitration and nitrosation products. The same was true of the products obtained by treatment

(5) Adams, Wolff, Cain and Clark, THIS JOURNAL, **62**, 2215 (1940).

(6) Adams, Hunt and Clark, *ibid.*, **62**, 735 (1940).

with mercuric acetate, bromine in acetic acid, thiocyanogen and phenylazide, one or more of which it was hoped would add to the double bond with formation of crystalline derivatives.

Ozonization of cannabidiol dimethyl ether obviously attacked not merely the double bonds but also the aromatic ring and actually in one experiment, when excess of ozone was used, caproic acid was isolated.

The ultraviolet absorption spectra of the tetrahydrocannabinols of various rotations showed no significant differences from each other or, peculiarly enough, from the spectrum of cannabidiol (see figure). They differ markedly from the absorption spectrum of the tetrahydrocannabinol with the double bond conjugated to the benzene ring, and thus it is established that the double bonds in the tetrahydrocannabinols obtained by isomerization of cannabidiol do not have the double bond conjugated to the aromatic nucleus.[7]

The tetrahydrocannabinol α_D −130° is physiologically active and not much less potent in its marihuana effect on dogs than higher-rotating forms. It has now been definitely established by clinical experiments that these substances (the form α_D −265° was actually used) have the same activity in humans as red oil or a crude hemp extract. The method of pharmacological testing by Dr. S. Loewe involving "Bioassay by Approximation" evaluating motor incoördination of dogs may, therefore, be considered a satisfactory criterion for determining whether a substance will have marihuana-like activity in humans.

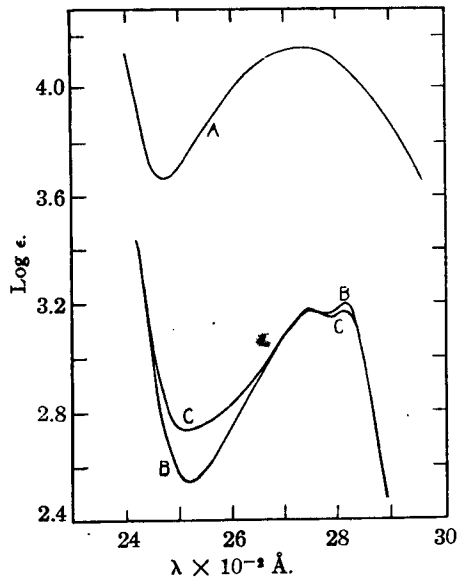


Fig. 1.—A, Synthetic tetrahydrocannabinol in ether. Ghosh, Todd and Wilkinson, *J. Chem. Soc.*, 1121 (1940), report log ε = 4.046 at 2755 Å. in ethanol. B, Tetrahydrocannabinol prepared by isomerization of cannabidiol. The spectra of the low- and high-rotating forms were so nearly identical that they are shown here as one curve. C, Cannabidiol.

Experimental

Isomerization of Cannabidiol with *p*-Toluenesulfonic Acid.—A solntion of 0.19 g. of *p*-toluenesulfonic acid monohydrate and 3.14 g. of crystalline cannabidiol in 100 cc. of dry benzene was refluxed for one and one-half hours. At the end of that time the alkaline Beam test was negative. The benzene solntion was extracted twice with 5% aqueous bicarbonate solution and twice with water. The benzene was evaporated and the residue distilled under reduced pressure. Four fractions were collected, b. p. 169–172° (0.03 mm.), having essentially the same rotation, $[\alpha]^{29}D$ −264 to −270°, and weighing 2.32 g. *Rotation.* 0.0694 g. made up to 5 cc. with 95% ethanol at 29° gave α_D −3.70°; *l*, 1; $[\alpha]^{29}D$ −267°.

Isomerization of Cannabidiol with Sulfuric Acid.—To a solution of 1.94 g. of crystalline cannabidiol in 35 cc. of cyclohexane (free from unsaturated material) was added one drop of 100% sulfuric acid. The mixture was refluxed for one hour, at the end of which time the alkaline Beam test was negative. The solution was decanted from the sulfuric acid, washed twice with aqueous 5% bicarbonate solution and twice with water, and evaporated. The residue was distilled under reduced pressure. Three fractions were collected, b. p. 165–170° (0.1 mm.), $[\alpha]^{29}D$ −259 to −269°, weight 1.51 g. *Rotation.* 0.0381 g. made up to 5 cc. with acetone at 29° gave α_D −2.10°; *l*, 1; $[\alpha]^{29}D$ −264°.

Other relatively strong organic acids were ineffective in catalyzing the isomerization of cannabidiol in boiling benzene. One-tenth mole of acid per mole of cannabidiol was used in each case. The acids and lengths of time of refluxing were as follows: trichloroacetic twenty hours, 87% formic eleven hours, anhydrous oxalic fourteen hours, picric twenty-three hours, 3,5-dinitrobenzoic twenty-five hours, maleic twelve hours. At the end of each treatment the alkaline Beam test was positive. Finally, treatment with *p*-toluenesulfonic acid converted the cannabidiol to tetrahydrocannabinol of rotation $[\alpha]^{28}D$ −266 to −270°.

Preparation of Tetrahydrocannabinol, α_D −130 ± 5°.—A solution of 3.14 g. (0.01 mole) of cannabidiol in 100 cc. of absolute ethanol containing 0.0005 mole of hydrogen chloride (added as 0.5 *M* ethanolic hydrochloric acid) was refluxed on the steam-bath for eleven hours. At the end of this time the alkaline Beam test had become negative. The reaction mixture was poured into cold water and the product extracted with ether. The ether extract was washed with dilute aqueous sodium bicarbonate solution followed by water. The residue remaining upon drying and evaporating the ether was distilled; colorless, highly viscous liquid, b. p. 157–160° (0.05 mm.), $n^{20}D$ 1.5425. Five fractions of the distillate were collected, the specific rotation values of each being essentially the same. *Rotation.* 0.0645 g. made up to 5 cc. with 95% ethanol at 26° gave α_D −3.37°; *l*, 2; $[\alpha]^{26}D$ −130°.

(7) Adams and Baker, THIS JOURNAL, **62**, 2405 (1940).

Isomerization of Low-Rotating to High-Rotating Tetrahydrocannabinol.—A solution of 0.054 g. of *p*-toluenesulfonic acid monohydrate in 25 cc. of benzene was warmed on the steam-bath until the acid dissolved. To this warm solution was added 0.92 g. of tetrahydrocannabinol $[\alpha]^{26}D$ −130° and the mixture refluxed for two and one-half hours. The benzene solution was washed with water, dilute aqueous sodium bicarbonate and again with water. The residue remaining upon evaporation of the benzene was distilled onto a cold finger condenser. Three fractions were taken, the specific rotation values being $[\alpha]^{24}D$ −183, −201 and −223°. *Rotation.* (Fraction 3) 0.0692 g. made up to 5 cc. with 95% ethanol at 24° gave αD −3.09°; *l*, 1; $[\alpha]^{24}D$ −223°.

Addition of Hydrogen Chloride to Tetrahydrocannabinol, αD −130°.—A solution of 1.0 g. of tetrahydrocannabinol $[\alpha]^{27}D$ −130° in 75 cc. of dry ether was cooled to 0° and saturated with dry hydrogen chloride. A calcium chloride drying tube was placed in the mouth of the flask and the flask and contents were allowed to stand at 0° overnight. The ether and hydrogen chloride were evaporated at room temperature by a stream of dry air. The residue was dissolved in 100 cc. of ether and the resulting solution washed several times with dilute aqueous sodium bicarbonate followed by water. The ether solution was dried with Drierite and the ether evaporated by a stream of dry air. To remove the last traces of ether the residue was warmed to 80° while the pressure was reduced to 17 mm. The residue was a clear red resin which gave a strong test for chloride ion when an ethanolic solution was tested with ethanolic silver nitrate solution. *Rotation.* 0.0250 g. made up to 5 cc. with 95% ethanol at 26° gave αD −0.82°; *l*, 2; $[\alpha]^{26}D$ −82°.

The material was distilled with bath temperature at 185° and 0.05 mm. pressure. A trap containing solid potassium hydroxide was placed between the flask and the pump. After the distillation was complete the potassium hydroxide was dissolved in water, acidified with nitric acid and tested for chloride ion. A heavy precipitate of silver chloride indicated that hydrogen chloride had been evolved during the distillation. Three fractions of distillate were collected, having specific rotations of −196, −197 and −203°, respectively. *Rotation.* (Fraction 3) 0.0333 g. made up to 5 cc. with 95% ethanol at 26° gave αD −2.70°; *l*, 1; $[\alpha]^{26}D$ −203°.

Hexahydrocannabinol from Tetrahydrocannabinol, αD −130°.—A solution of 1.411 g. of tetrahydrocannabinol, $[\alpha]^{26}D$ −133°, in glacial acetic acid was reduced with hydrogen and platinum oxide as previously described.[3] Four fractions of distillate were collected having essentially the same specific rotation which checked with that reported for hexahydrocannabinol prepared by reduction of higher-rotating tetrahydrocannabinols. *Rotation.* (Fraction 3) 0.0312 g. made up to 5 cc. with 95% ethanol at 26° gave αD −0.91°; *l*, 2; $[\alpha]^{26}D$ −73°.

Attempted Shift of the Double Bond in Dihydrocannabidiol Dimethyl Ether.—To a solution of 0.07 g. of *p*-toluenesulfonic acid monohydrate in 35 cc. of dry benzene was added 1.28 g. of dihydrocannabidiol dimethyl ether ($n^{20}D$ 1.5185) and the mixture refluxed for four hours. The benzene solution was washed with water, dilute aqueous sodium bicarbonate and again with water. After evaporation of the benzene the residue was distilled, b. p. 100–103° (0.05 mm.). A light brown resin remaining in the flask would not distil even though the bath temperature was raised to 225°. By the lack of optical activity, index of refraction ($n^{28}D$ 1.5062) and the analysis, the distillate was shown to be olivetol dimethyl ether.

Anal. Calcd. for $C_{13}H_{20}O_3$: C, 74.93; H, 9.68. Found: C, 75.47; H, 9.75.

Ozonization of Cannabidiol Dimethyl Ether and Isolation of a Derivative of Formaldehyde.—A solution of 0.04 g. of cannabidiol dimethyl ether in 5 cc. of glacial acetic acid was ozonized for ten minutes with 2.5% ozone. It was then poured into warm water and allowed to stand for thirty minutes. The solution was neutralized with dilute aqueous sodium hydroxide and 0.1 g. of methone in 2 cc. of ethanol was added. When the solution was cooled there was obtained 0.022 g. of crystalline product; m. p. 189–191°. This corresponded to a 67% yield for 1 mole of formaldehyde. A sample of the derivative was prepared from formalin; m. p. 190–191°; mixed melting point of the two was 190–191°.

Ozonization of Cannabidiol Dimethyl Ether Followed by Cleavage with Chromic Acid.—A solution of 1.75 g. of cannabidiol dimethyl ether in 30 cc. of glacial acetic acid was ozonized at room temperature for eighty-four minutes. Two and one-half per cent. ozone, at the rate of 0.000183 mole per minute, was used. This was about 150% of the theoretical amount for two double bonds. A solution of 0.8 g. of chromic oxide (80% of theoretical for 3 atoms of oxygen) in acetic acid was dropped slowly into the ozonide solution with stirring. About 25 cc. of water was added and the mixture warmed at 50–60° for thirty minutes. It was then poured into an excess of water and the oily product extracted with a little benzene. Two extractions with aqueous 5% sodium bicarbonate solution followed by acidification gave only a small amount of acidic product. The semicarbazone, 2,4-dinitrophenylhydrazone, and *p*-bromophenacyl ester derivatives were made but none was a solid. The neutral benzene solution that had been extracted was evaporated, taken up in 20 cc. of acetic acid, and again oxidized by 0.8 g. of chromic oxide in 20 cc. of water. After the solution had been warmed on the steam cone overnight most of the solvent was evaporated and excess water was added. When the oily product was taken up in benzene and extracted with 5% aqueous sodium hydroxide, about 0.15 g. of an acidic oil was obtained but attempts to form solid derivatives failed.

The neutral benzene solution from the above extraction was evaporated and derivatives were made on the residual oil. A 2,4-dinitrophenylhydrazone, sparingly soluble in alcohol, was obtained. It crystallized well from a mixture of acetone and alcohol in orange needles, m. p. 228–230°.

Anal. Calcd. for $C_{20}H_{24}O_6N_4$: C, 57.68; H, 5.94; N, 13.45. Found: C, 57.84, 57.76, 57.90; H, 5.60, 6.22, 5.86; N, 13.21, 13.36.

Reaction of Cannabidiol with 8% Ozone—Isolation of *n*-Caproic Acid.—In this experiment 8% ozone flowing at the rate of 0.0008 mole per minute was used in large excess. A solution of 4 g. of cannabidiol in 100 cc. of glacial acetic acid was ozonized for eight hours. An equal volume of water was added and the solution was refluxed overnight. The solution was cooled and potassium permanganate

added until the excess permanganate color remained for a few minutes, with the object of destroying oxalic acid and oxidizing any aldehydes to acids. Excess permanganate was destroyed by the addition of a little sodium bisulfite and the manganese dioxide was removed by filtration. The solution was then steam distilled. From the residnal solution only an intractable tar was obtained. The steam distillate was neutralized with sodium hydroxide and evaporated to dryness. The salt was then acidified and the solution extracted with ether and distilled. After the acetic acid had been removed a small amount of oily acid remained. It was converted into a crystalline *p*-bromophenacyl ester, m. p. 63°.

A mixed melting point with the *p*-bromophenacyl ester of *n*-caproic acid showed no depression.

This compound was obtained by the same procedure when cannabidiol dimethyl ether was treated with 150% of the theoretical amount of 8% ozone. The residue from steam distillation was again an intractable tar. Apparently this concentration of ozone was attacking the aromatic ring.

Summary

1. New procedures for isomerizing cannabidiol have resulted in synthesizing two tetrahydrocannabinols, α_D −130° and α_D −265°, of essentially constant rotation. Previously obtained tetrahydrocannabinols are assumed to be mixtures.

2. Additional evidence for shifting of the double bond in conversion of the low-rotating to a higher-rotating tetrahydrocannabinol is presented. The low-rotating form adds hydrogen chloride and loses it on distillation to give a higher-rotating form.

3. The form α_D −130° reduces to a hexahydrocannabinol of identical rotation with that obtained by reduction of higher-rotating forms.

4. The form α_D −130° has about the same marihuana activity as the higher-rotating forms. Clinical tests have demonstrated the tetrahydrocannabinols (the form used was α_D −265°) to have exactly the same physiological activity in humans as crude hemp extract.

5. Dihydrocannabidiol dimethyl ether, when heated with *p*-toluenesulfonic acid in benzene, cleaves to olivetol dimethyl ether and an undistillable compound, presumably a polymer of menthadiene.

URBANA, ILLINOIS RECEIVED JUNE 5, 1941

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS, IN COLLABORATION WITH THE TREASURY DEPARTMENT, NARCOTICS LABORATORY, WASHINGTON, D. C.]

Isolation of Cannabinol, Cannabidiol and Quebrachitol from Red Oil of Minnesota Wild Hemp

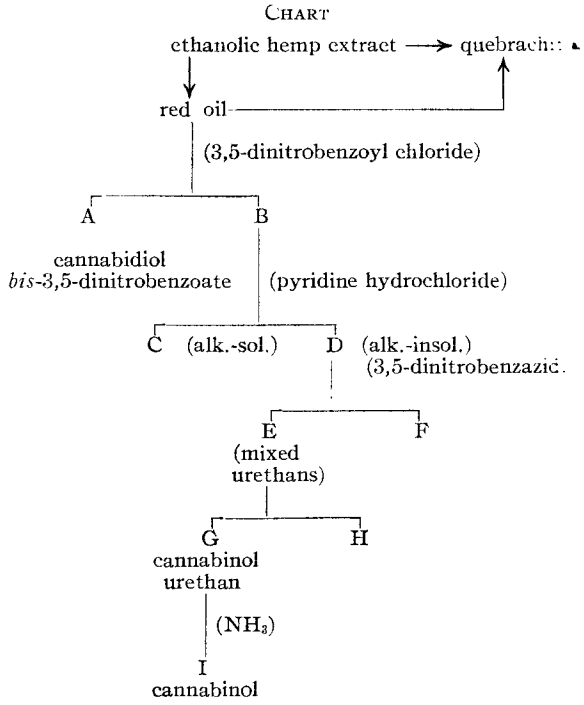
BY ROGER ADAMS, D. C. PEASE AND J. H. CLARK[1]

The isolation of cannabidiol through its *bis*-3,5-dinitrobenzoate from the marihuana red oil of Minnesota wild hemp was described previously.[2] Since that time it has also been isolated from North African charas by Todd.[3] The procedure for obtaining cannabidiol through the ester has now been improved to the point where 45–50% of the purified red oil can be shown to be cannabidiol.

The changes consist mainly in a preliminary steam distillation, followed by a careful high vacuum distillation, which greatly facilitates isolation of a pure product, followed by prompt conversion to the *bis*-dinitrobenzoate. The details are given in the experimental part. The cannabidiol, through ammonolysis of the ester, has now been obtained in crystalline form as long, white rods from petroleum ether, m. p. 66–67°, $[\alpha]^{27}D$ −125°. It was described previously[2] as an oil, b. p. 187–190° (2 mm.), $[\alpha]^{28}D$ −119°.

Advantage has been taken of the chemical properties of cannabidiol to attempt a chemical method of separation of various constituents of red oil. Red oil was first treated for removal of cannabidiol as previously described.[2a] The filtrate from the cannabidiol *bis*-3,5-dinitrobenzoate was ammonolyzed to decompose any esters present and the residual oil (B) distilled. It was then pyrolyzed with pyridine hydrochloride at about 75–100 mm. pressure and 225–230° to convert any cannabidiol still present to cymene and olivetol.[2c] The cymene distilled and the mixture was then extracted with cold aqueous alkali. This removed about 10–15% of product (C). The alkali-insoluble portion (D) was distilled *in vacuo* and then treated in petroleum ether solution with 3,5-dinitrobenzazide.[4] Upon refluxing, a copious precipitate of urethans separated (E). The solid was crystallized from benzene, during which process a considerable loss occurred, possibly indicating the presence of a more soluble urethan (F The less soluble urethan (G), $C_{21}H_{25}O{\cdot}OCONHC_6H_3(NO_2)_2$, after purification, was decomposed with ethanolic ammonia. The dinitrophenyl urea was insoluble and thus removed. The oil obtained by evaporation of the solvent (I) was distilled *in vacuo* and proved to have the boiling point of cannabinol. Upon cooling and scratching, the oil solidified and was recrystallized readily from petroleum ether. This product was indeed cannabinol, isolated for the first time in a crystalline state. It formed plates that were apparently monoclinic pseudohexagonal in form, m. p. 75–76°. Its derivatives proved to be identical with those from cannabinol previously obtained as an oil. The constants of pure crystalline cannabinol and derivatives made from it are given in Table I.

CHART



If any cannabidiol was carried over through this process without decomposition, it did not interfere with the crystallization of the dinitrophenyl urethan of the cannabinol present.

If purified red oil was pyrolyzed directly with pyridine hydrochloride to destroy the cannabidiol

(1) 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.

(2) (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).

(3) Jacob and Todd, *Nature*, **145**, 350 (1940).

(4) Sah and Ma, *J. Chinese Chem. Soc.*, **2**, 41, 162 (1934).

TABLE I

CONSTANTS OF CANNABINOL AND DERIVATIVES[5]

	M. p., °C. (cor.)	Previously recorded M. p., °C.
Cannabinol	75–76	...
p-Nitrobenzoate	165–166	160[6]
m-Nitrobenzene sulfonate	127–129	125–126[7]
Acetate	76–77	75[8]

the product could also be separated into alkali-soluble and alkali-insoluble fractions. The removal of cannabinol from the alkali-insoluble fraction as the dinitrophenyl urethan was not as clean-cut as when cannabidiol was first removed from red oil.

In the isolation of pure red oil from crude ethanolic hemp extract, several distillations are necessary. Whenever the red oil was fractionated there deposited in the upper part of the Widmer column a small amount of crystalline material. This proved to be water-soluble. It was found that this same substance could be extracted from a petroleum ether solution of crude red oil by means of water and was also present in the aqueous layer after steam distillation of the hemp extract. It proved to be quebrachitol, the monomethyl ether of *l*-inositol, as shown by its physical and chemical properties and analysis, as well as by the characteristics of its pentaacetate.

The other fractions (C, F and H) in the schematic procedure just described for separating various products from red oil are being investigated. A somewhat similar method is being applied to "purified red oil" omitting the removal of cannabidiol as the 3,5-dinitrobenzoate. Attempts are under way to separate chemically the products from Indian charas following the procedure described.

Experimental

Purified Red Oil.—The ethanol from 4 liters of ethanolic hemp extracts[2a] (25% solids) was removed by distillation. The residue was subjected to steam distillation to remove terpenes; after the collection of about 8 liters of distillate, the distillation was assumed to be complete. The water-insoluble residue was separated from the water, dissolved in petroleum ether (b. p. 30–60°) and the solution extracted three times with water. After evaporation of the solvent, the oil was distilled, b. p. 70–160° (5×10^{-3} mm.), with the temperature of the still varying from 180–250°. Care was taken in this and subsequent distillations to stop the distillation the moment gases appeared through the apparatus, indicating decomposition. About 300 g. of crude red oil resulted. This was dissolved in petroleum ether, washed with water, the solvent removed and again distilled through a heated carborundum-filled column (35 cm. long with outside diameter of column 23 mm. and of side-arm 12 mm.). Two fractions, about 30 g. each, were separated, one b. p. 70–130°, the second b. p. 130–150° (5×10^{-3} mm.) from which solid material crystallized on cooling (probably nonacosane). When all of the distillate from which solid crystallized had been removed, the fractionating column was replaced by a still head with side-arm of 15 mm. diameter and the material, b. p. 148–160° (5×10^{-3} mm.) (still temp. 180–230°), was collected. It was a clear, light red viscous oil weighing 200 g. and will be designated as "purified red oil."

Cannabidiol *bis*-3,5-Dinitrobenzoate.—Immediately after the purified red oil had been distilled, a solution of 185 g. in 300 cc. of pyridine cooled to 0° was combined with a solution of 250 g. of 3,5-dinitrobenzoyl chloride in 400 cc. of warm pyridine which was then cooled to 0° before the addition. The mixture was well stirred and the lumps broken up while standing in ice for thirty minutes. It was then warmed on a steam-bath for thirty minutes with stirring to disintegrate all lumps. The temperature of the mixture rose to about 60° and its color deepened somewhat. The reaction mixture was then treated immediately with ice and 10% sulfuric acid. The ester was taken up in benzene, washed with 5% sulfuric acid, then aqueous sodium bicarbonate. The benzene was completely removed on a water-bath and ether was added in volume about equal to that of the product. On standing and seeding, crystalline cannabidiol *bis*-3,5-dinitrobenzoate separated and was increased in amount by cooling in an ice–salt-bath; yield of dry crude ester, 195 g. (47%). The procedure for purification and melting point have been given in another communication.[2a]

Crystalline Cannabidiol.—A few drops of cannabidiol, prepared from purified *bis*-dinitrobenzoate as described previously,[2a] was allowed to stand for several weeks spread in a thin layer on glass, after which time it crystallized spontaneously. Using the seed crystals obtained in this way oily cannabidiol was crystallized readily. Recrystallization from petroleum ether (b. p. 30–60°) gave long white rods, m. p. 66–67° (cor.).

Rotation. 0.0665 g. made up to 5 cc. with 95% ethanol at 27° gave α_D −1.66°; *l*, 1; $[\alpha]^{27}_D$ −125°.

Crystalline cannabidiol was converted to the *bis*-3,5-dinitrobenzoate which was identical in melting point and mixed melting point with that obtained from the oily form.

3,5-Dinitrophenyl Urethan of Cannabinol from Red Oil.—The filtrates from the crude precipitate of cannabidiol-*bis*-3,5-dinitrobenzoate were evaporated to free from solvent and dissolved in toluene. The solution was then allowed to stand with liquid ammonia in a bomb for eight hours. The dinitrobenzamide which separated was filtered, the toluene distilled, the residue taken up in petroleum ether (b. p. 60–110°) and extracted with hot water. The material in the petroleum ether distilled in a

(5) Samples of cannabinol acetate and *p*-nitrobenzoate were submitted to us by Dr. A. R. Todd of the University of Manchester to whom we desire to express our thanks. Mixed melting points of his products and those prepared in this research showed no depression. Melting points previously reported by Todd for his compounds obviously had not been corrected values as these were found actually to be slightly above the ones reported and slightly lower than the corrected values of our compounds.

(6) Work, Bergel and Todd, *Biochem. J.*, **33**, 124 (1939).

(7) Cahn, *J. Chem. Soc.*, 1347 (1932).

(8) Wood, Spivey and Easterfield, *J. Chem. Soc.*, **75**, 20 (1899).

high vacuum at essentially the same point as purified red oil. It contained some nonacosane, ethyl 3,5-dinitrobenzoate and ethyl 3-amino-5-nitrobenzoate. Most of these impurities could be removed by taking up first in methanol and then in petroleum ether (b. p. 30–60°), followed by cooling and filtering in each case. The ethyl 3-amino-5-nitrobenzoate could be removed completely by extracting the petroleum ether solution with cold 20% hydrochloric acid. The oil then was redistilled in a high vacuum.

A mixture of 20 g. of the oil just described and 30 g. of dry pyridine hydrochloride was heated under 75–100 mm. pressure at 225–230° (bath temp.) for three hours. Provision was made to retain distillable substances in a dry-ice trap. A small amount of material, presumably *p*-cymene, was thus collected. The cooled reaction mixture was taken up in benzene and the benzene solution washed with water, twice with cold 10% aqueous sodium hydroxide, 5% hydrochloric acid, and finally with aqueous bicarbonate. The sodium hydroxide extract was retained for isolation of alkali-soluble products. The oil remaining in the benzene was then distilled, giving a light amber oil weighing 11 g. It gave no alkaline Beam test.

To a solution of 20 g. of the alkali-insoluble oil, obtained from the pyridine hydrochloride pyrolysis, in 300 cc. of petroleum ether (b. p. 60–110°) was added 18 g. of 3,5-dinitrobenzazide.[9] The reaction mixture was then heated to reflux for thirty minutes to one hour. At the end of this time, a light yellow solid had separated (about 20–25 g.). After cooling, it was filtered and recrystallized five times from benzene; yield 5 g., m. p. 220–222° with decomposition. The urethan was also obtained by condensation of crystalline cannabinol with 3,5-dinitrobenzazide. Two crystallizations gave a pure compound; light yellow needles, m. p. 221–222° with decomposition.

Anal. Calcd. for $C_{28}H_{29}O_7N_3$: C, 64.71; H, 5.63. Found: C, 65.05; H, 5.80.

Cannabinol.—A mixture of 7.5 g. of the 3,5-dinitrophenyl urethan of cannabinol (m. p. 220–222°) in 200 cc. of 95% ethanol and 12 g. of liquid ammonia was allowed to stand. As ammonolysis proceeded, the urethan went into solution and the solute became clear. After standing for three to four hours with occasional shaking, the ethanol was distilled. The residue was extracted with petroleum ether (b. p. 60–110°), the petroleum ether extract washed several times with hot water and the solvent evaporated. The product was completely soluble in petroleum ether (b. p. 30–60°). It was then distilled, b. p. 185° (0.05 mm.) (bath temp. 225–240°); yield 3 g. On scratching the distillate, the oil solidified and was purified by recrystallization from petroleum ether (b. p. 30–60°); plates that were apparently monoclinic pseudohexagonal in form, m. p. 75–76° (cor.).

(9) The product was prepared as described by Sah and Ma[4] except that the azide was allowed to crystallize from the acetic acid instead of precipitating with water. In this way a purer product was obtained, m. p. 100–103° (cor.) with decomposition. Sah reported 87–89°.

Anal. Calcd. for $C_{21}H_{36}O_2$: C, 81.21; H, 8.45. Found: C, 81.44; H, 8.53.

Isolation of Quebrachitol (*l*-Inositol Monomethyl Ether).—The aqueous layer obtained after the steam distillation of the ethanolic hemp extract described above was partially defecated with basic lead acetate. The excess lead was removed by the addition of sulfuric acid, followed by hydrogen sulfide to remove the last traces. The water was evaporated and the thick brown oil obtained was distilled at a pressure of 2 mm. The product, a dark red oil, distilled slowly at a temperature of 190–220°. The distillate was dissolved in water, treated once with norit, and most of the water evaporated. Ethanol and acetone were added until the solution became cloudy. After two or three days a crystalline solid separated and was recrystallized from *n*-propanol; white granular crystals, m. p. 192–193° (cor.).

Anal. Calcd. for $C_7H_{14}O_6$: C, 43.30; H, 7.27. Found: C, 43.17; H, 7.18. *Rotation.* 0.2280 g. made up to 5 cc. with water at 25° gave α_D −3.67°; *l*, 1; $[\alpha]^{25}_D$ −80.5°.

The melting point and rotation of the compound agree quite closely with the values reported previously for quebrachitol.[10]

A small additional amount of quebrachitol was isolated from the extraction with water of a petroleum ether solution of red oil after the first vacuum distillation. It was also obtained from the water extraction step in the preparation of red oil by the method described previously.[2b]

Quebrachitol Pentaacetate.—Prepared as previously described[11] it formed white crystals from chloroform; m. p. 96–97° (cor.). Contardi reported m. p. 91°.

Anal. Calcd. for $C_{17}H_{24}O_{11}$: C, 50.49; H, 5.98. Found: C, 50.30; H, 5.81. *Rotation.* 0.2072 g. made up to 5 cc. with chloroform at 29° gave α_D −2.08°; *l*, 2; α^{29}_D −25.1°.

Summary

1. Crystalline cannabidiol has been described for the first time.

2. A procedure for isolating cannabinol from red oil of Minnesota wild hemp is given. It was isolated through the 3,5-dinitrophenyl urethan from cannabidiol-free red oil. Cannabinol was obtained crystalline.

3. From red oil by distillation or by water extraction of crude red oil, or from the aqueous layer after steam distillation of the hemp extract, quebrachitol was isolated.

URBANA, ILLINOIS RECEIVED MAY 20, 1940

(10) De Jong, *Rec. trav. chim.*, **25**, 48 (1906), m. p. 190–191°, $[\alpha]^{21}_D$ −80.2°; Clark, THIS JOURNAL, **58**, 1009 (1936), m. p. 192–193° (cor.), $[\alpha]^{26}_D$ −81.2°; Bourquelot and Hérissey, *Compt. rend.*, **168**, 414 (1918), m. p. 190°, $[\alpha]_D$ −80.6°; Tanret, *ibid.*, **109**, 908 (1889) m. p. 186–187°.

(11) Contardi, *Ann. chim. applicata*, **14**, 281 (1924); *C. A.*, **19**, 1135 (1925).

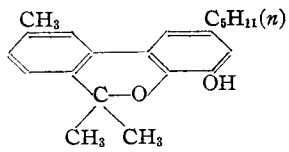
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

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

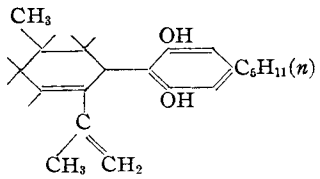
BY ROGER ADAMS, D. C. PEASE, J. H. CLARK[1a,b] AND B. R. BAKER[1a]

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

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.

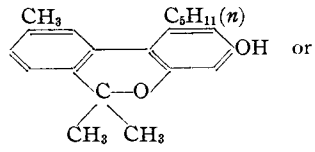


I

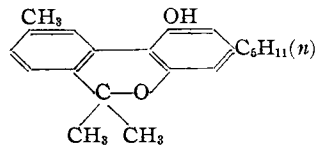


II

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); 1933).

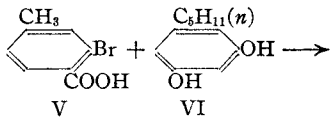
4) Wood, Spivey and Easterfield, *ibid.*, **69**, 539 (1896).

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

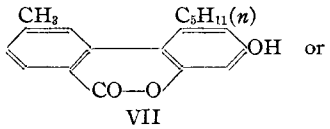
6) Blatt, *J. Washington Acad. Sci.*, **28**, 465 (1938).

(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).

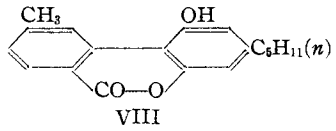
The synthesis of structure III or IV has been completed. Olivetol (VI) was condensed with 4-methyl-2-bromobenzoic acid (V) by means of dilute aqueous alkali and aqueous copper sulfate to give the bicyclic lactone (VII or VIII). The reaction of *o*-bromobenzoic acid and resorcinol to give an analogous 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



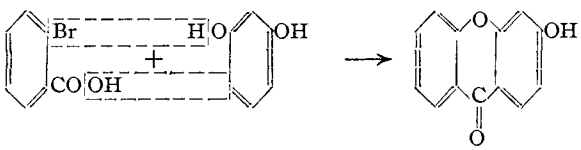
VII



VIII

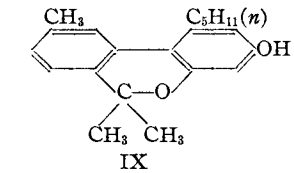
acid with resorcinol and orcinol; 4-methyl-2-bromobenzoic acid with resorcinol and orcinol. The presence of an alkyl group in the resorcinol molecule or in the *o*-bromobenzoic acid reduced the yield of the condensation reaction to approximately 25%, but in each case the product was isolated and purified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

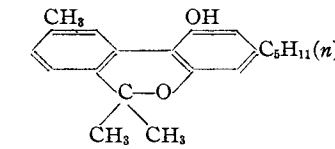


The melting point of 3-hydroxyxanthone prepared by an unequivocal method as reported by Atkinson and Heilbron[9] is 246°; for the product from *o*-bromobenzoic acid and resorcinol, 247°. These constants are very close together but the methyl ether of the xanthone has a melting point of 128° and the acetate 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 2-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 $C_{16}H_{12}O_4$: 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, 6.36. 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 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.

URBANA, ILLINOIS RECEIVED MAY 20, 1940

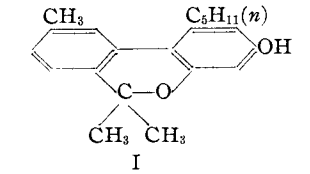
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

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]

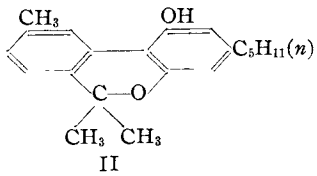
BY ROGER ADAMS, C. K. CAIN AND B. R. BAKER[2]

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

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



I



II

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),

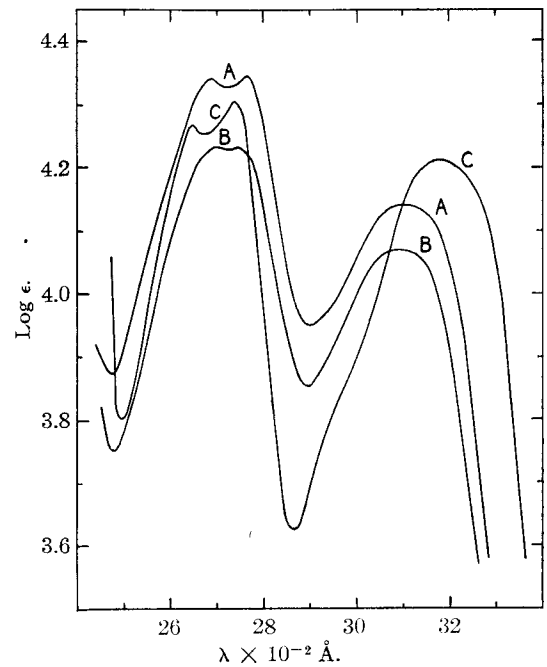


Fig. 1.—A, Cannabinol acetate; B, 3-acetoxy-1-*n*-amyl-6,6,9-trimethyl-6-dibenzopyran (acetate of I) or 1-acetoxy-3-*n*-amyl-6,6,9-trimethyl-6-dibenzopyran (acetate of II); C, 3-acetoxy-2-*n*-amyl-6,6,9-trimethyl-6-dibenzopyran (acetate of VIII).

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).

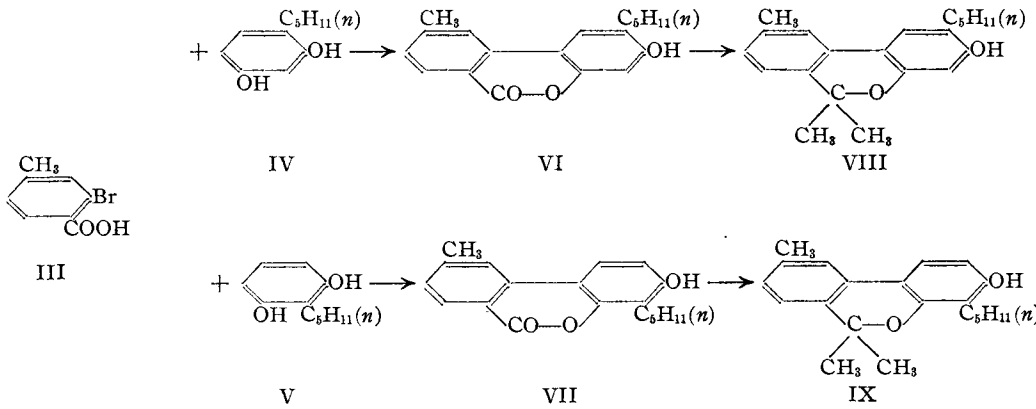
(1) For previous paper see Adams, Pease, Clark and Baker, THIS JOURNAL, **62**, 2197 (1940).

(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 $C_{21}H_{28}O_2$: 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

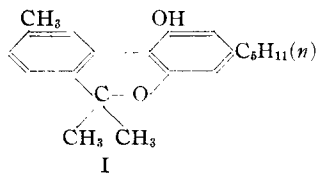
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

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

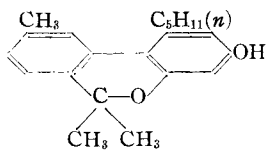
BY ROGER ADAMS, B. R. BAKER,[2] AND R. B. WEARN[2]

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]



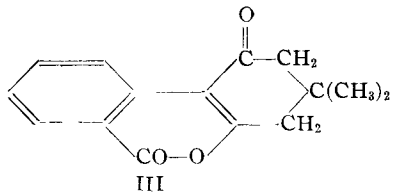
I



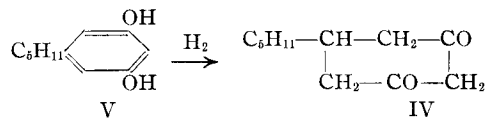
II

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

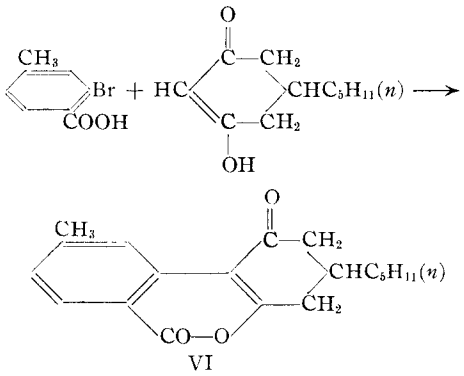
The condensation of 5-*n*-amyl-1,3-cyclohexanedione (IV) with 4-methyl-2-bromobenzoic acid could be carried out either in aqueous alkali in the presence of copper sulfate or in ethanolic sodium ethylate in the presence of cupric acetate with the formation of a good yield of the pyrone, 1-keto-3-*n*-amyl-9-methyl-1,2,3,4-tetrahydro-6-dibenzopyrone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

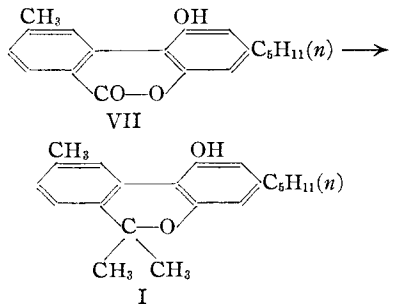
(3) Hurtley, *J. Chem. Soc.*, 1870 (1929).

(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]

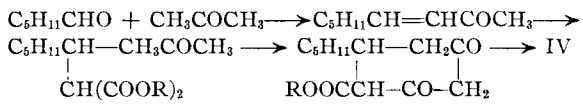


VII

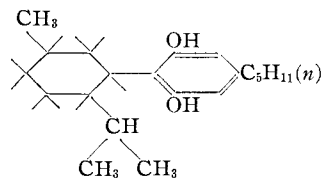
I

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.

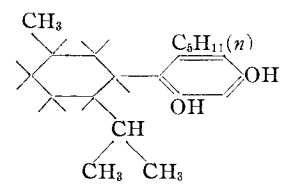
A second method for the preparation of the intermediate 5-*n*-amyl-1,3-cyclohexanedione (IV) was also successful. It consisted in condensation of *n*-hexaldehyde with acetone to hexylidene acetone. Malonic ester was then added to the double bond. By means of sodium ethylate the malonic ester addition 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 structure 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.



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.

URBANA, ILLINOIS RECEIVED MAY 20, 1940

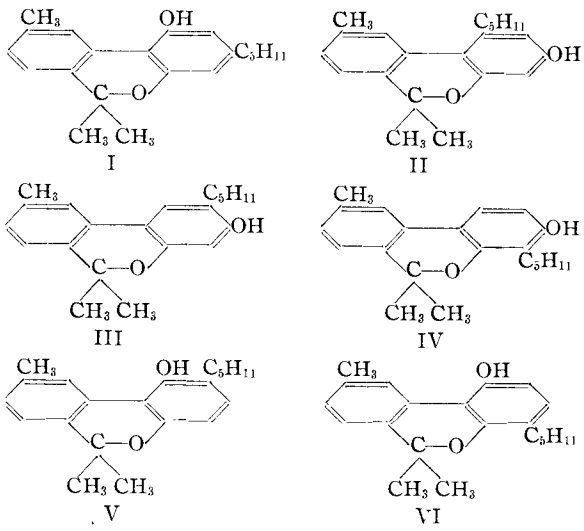
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Structure of Cannabinol. IV. Synthesis of Two Additional Isomers Containing a Resorcinol Residue[1]

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

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

There are six possible cannabinols (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 compound[3] 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°.

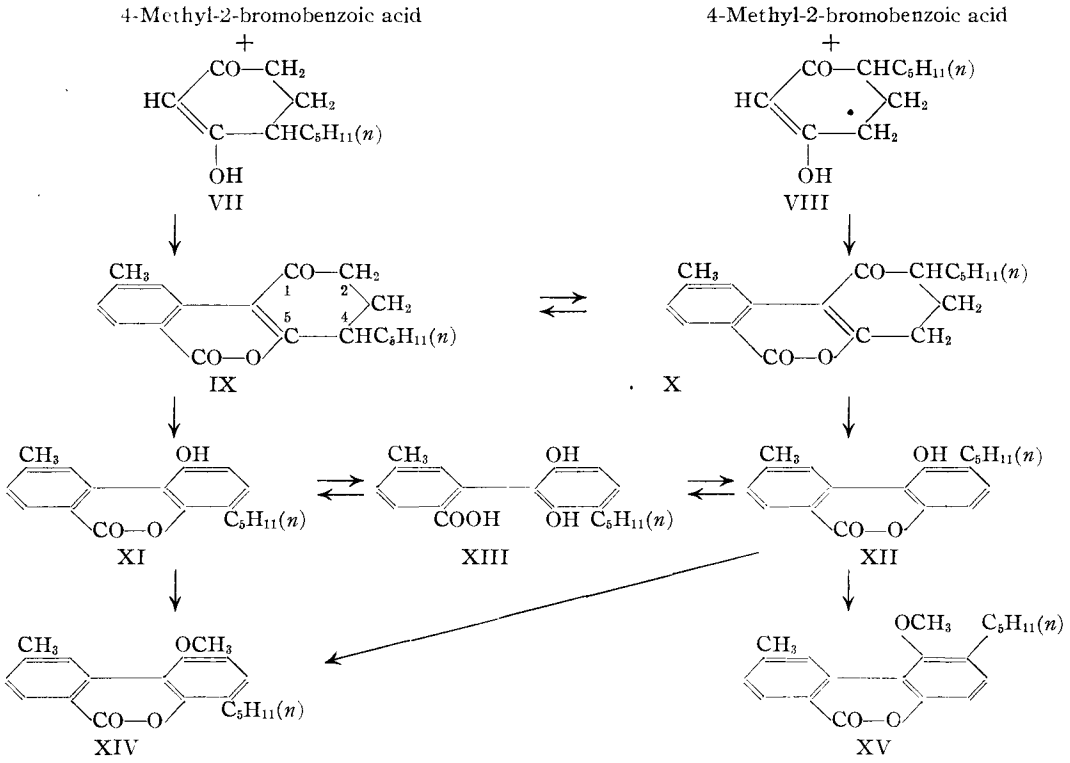
The pyrones XI and XII upon methylation with sodium methylate in methanol and dimethyl sulfate gave the same monomethyl ether, m. p. 96°. It must be concluded, therefore, that both lactones in this methylation reaction first must have opened to the same hydroxy acid (XIII), following which the hydroxyl 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)).



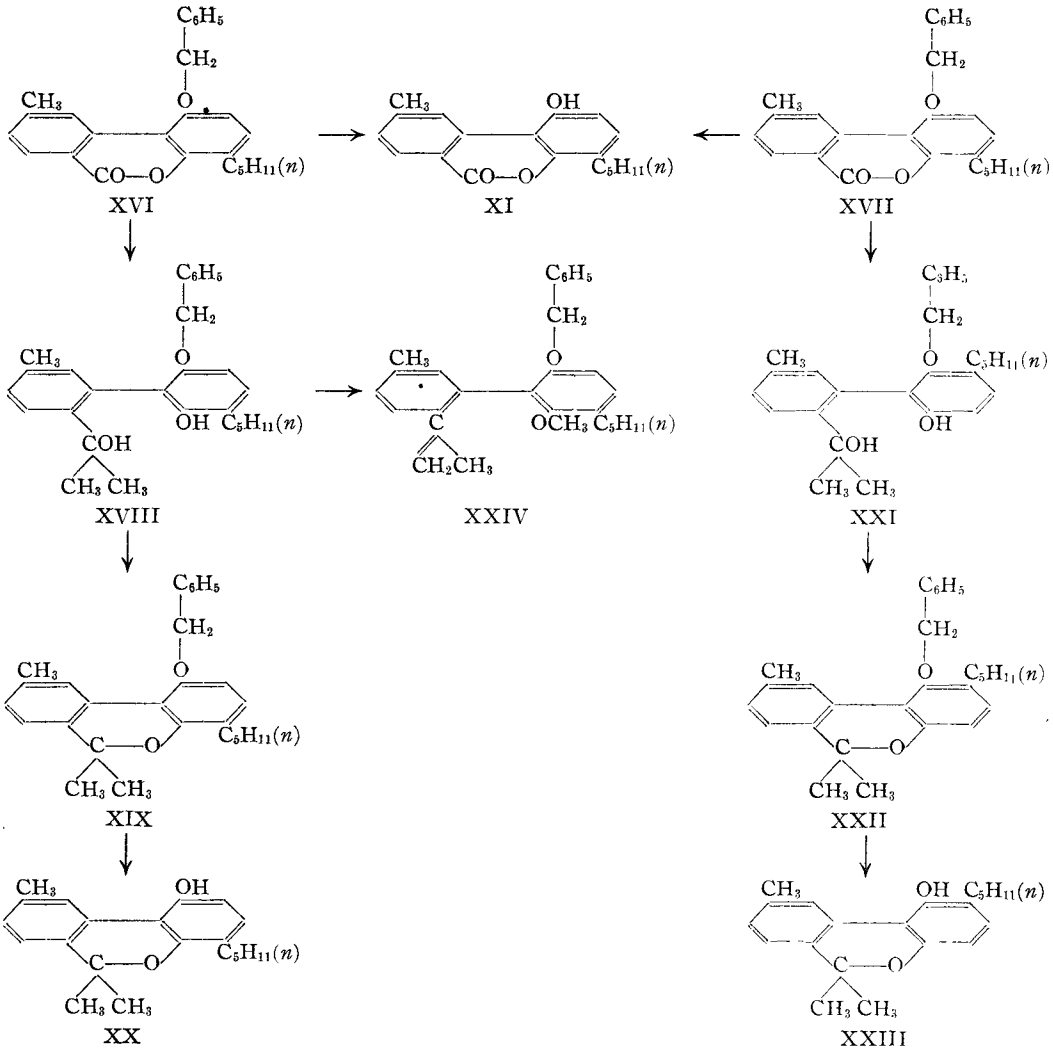
crystalline solid, m. p. 45°; it must have structure XV, the corresponding pyrone structure XII, and its ketone precursor, structure X.

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.

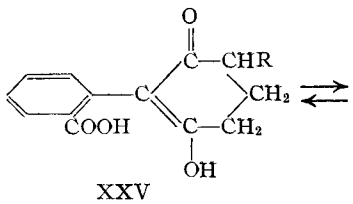
The benzyl ether with hydrochloric acid in acetic acid, and the methyl ether with hydrobromic acid in acetic acid were dealkylated to 1-hydroxy-4-*n*-amyl-6,6,9-trimethyl-6-dibenzopyran (XX), an isomer of cannabinol. This was a solid, m. p. 62–63°, and its derivatives all melted at points different from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

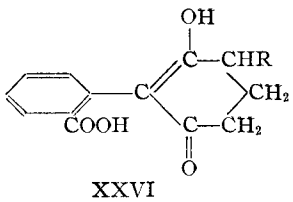
rone also gave a relatively stable crystalline phenolic alcohol which by the same procedure used for the benzyl ether dehydrated to a methylated pyran which was an oil.

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



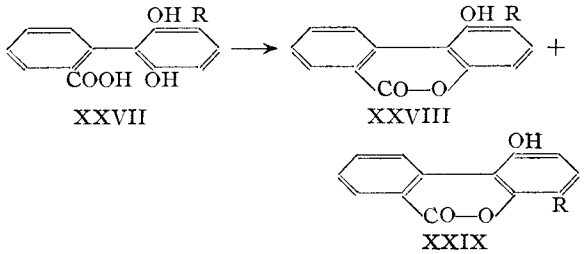
XXV



XXVI

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.

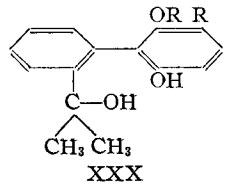
Free rotation between the two cyclic residues is established in compound XXVII, for treatment



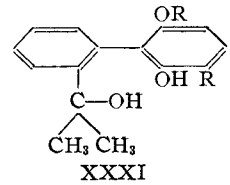
XXVII XXVIII XXIX

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 debenzylation 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.



XXX



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*-amyldihydroresorcinol, 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 $C_{19}H_{22}O_3$: 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 $C_{19}H_{22}O_3$: 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 $C_{21}H_{26}O_3$: 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 $C_{25}H_{24}O_3S$: 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 $C_{25}H_{24}O_3S$: 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 $C_{35}H_{32}O_2$: 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 $C_{29}H_{34}O_2$: 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 $C_{21}H_{26}O_2$: 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 $C_{23}H_{28}O_3$: 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 $C_{28}H_{29}O_5N$: 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 $C_{28}H_{32}O_2$: 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 $C_{35}H_{35}NO_5$: C, 76.48; H, 6.41; N, 2.55. Found: C, 76.47, 76.44; H, 6.54, 6.54; N, 2.68, 2.6.

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*-nitrobenzoylation 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 synthesized through the condensation of 4-methyl-2-bromobenzoic acid with 4-*n*-amyldihydroresorcinol. 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 RECEIVED JUNE 17, 1940

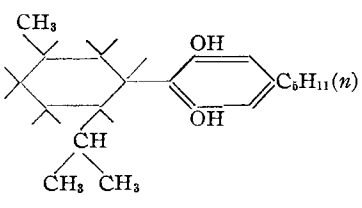
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

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

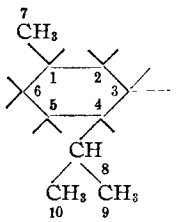
BY ROGER ADAMS, HANS WOLFF, C. K. CAIN AND J. H. CLARK[2]

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

The evidence submitted in previous communications[1] establishes for tetrahydrocannabidiol structure I. No attempt was made to determine the relative configuration of the asymmetric carbon



I



II

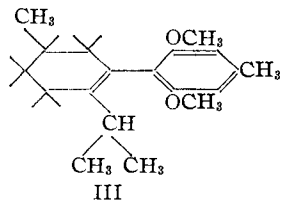
atoms. As tetrahydrocannabidiol was made by catalytic reduction of cannabidiol with absorption of four atoms of hydrogen, this latter compound must have two double bonds in the left-hand residue (II). The possible combinations of two double bonds in such a radical (II) are very numerous (twenty or more) 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 $[\alpha]^{28}D$ −125°). 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-

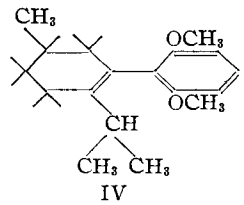
(1) For previous papers see (a) Adams, Hunt and Clark, THIS JOURNAL, **62**, 196 (1940); (b) Adams, Cain and Wolff, *ibid.*, **62**, 732 (1940); (c) Adams, Hunt, and Clark, *ibid.*, **62**, 735 (1940); (d) Adams, Wolff, Cain and Clark, *ibid.*, **62**, 2215 (1940); (e) Adams, Pease and Clark, *ibid.*,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

methyl ether with various synthetic molecules of essentially unequivocal constitution. Thus, the compounds III and IV prepared by condensation of 2-lithium resorcinol dimethyl ether or 2-lithium



III



IV

orcinol dimethyl ether with menthone, followed by dehydration, must have the structures assigned or with the double bonds in the 2,3 positions; the former position for the double bond on general principles seems to be the more likely. The absorption spectra of compounds III and IV and those of the dimethyl ethers of cannabidiol and dihydrocannabidiol are compared in Fig. 1.

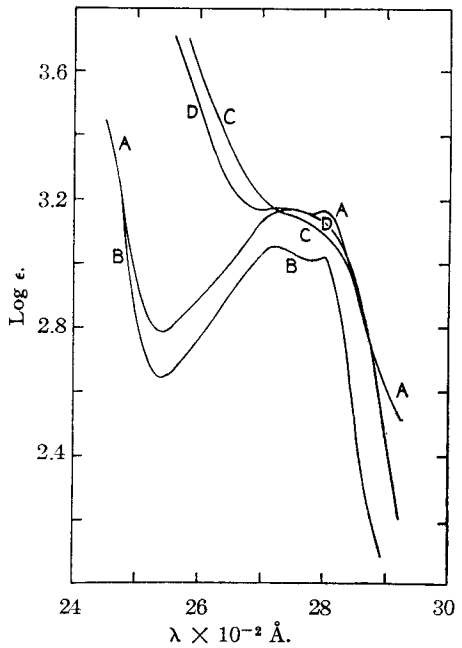


Fig. 1.—A, Cannabidiol dimethyl ether; B, dihydrocannabidiol dimethyl ether; C, 2-(3′-menthen-3′,4′-yl)-1,3-dimethoxy-5-methylbenzene (III); D, 2-(3′-menthen-3′,4′-yl)-1,3-dimethoxybenzene (IV).

It will be noticed that the absorption spectra of the synthetic compounds are entirely different from those of the natural products. Since it is certain that the synthetic compounds contain a double bond (either 2,3 or 3,4) conjugated to the resorcinol residue, it may be concluded that this conjugation may be the cause of the radical difference between their spectra and those of the cannabidiol derivatives. If such is the case double bonds 2,3 or 3,4 (structure II) which would be conjugated to the olivetol residue in cannabidiol could not be present.

This assumption has now been confirmed experimentally. 2-Lithium resorcinol dimethyl ether and 2-lithium orcinol dimethyl ether were condensed with pulegone (V) to give dienes through dehydration of the intermediate tertiary alcohols. The structure of the primary addition product in the case of orcinol dimethyl ether is VI, which by dehydration leads to the introduction of a second double bond (VII). The corresponding product from resorcinol dimethyl ether presumably will have structure VIII. In both compounds VII and VIII the new double bonds must be in the 2,3 positions, unless by chance shifting of the original double bond in pulegone has occurred during the reaction and the second double bond would then probably conjugate with it. The absorption spectra of compounds VII and VIII (Fig. 2) resemble closely those of the synthetic substances III and IV (compare with Fig. 1) which contain only one double bond conjugated to the benzene nucleus. Compounds VII

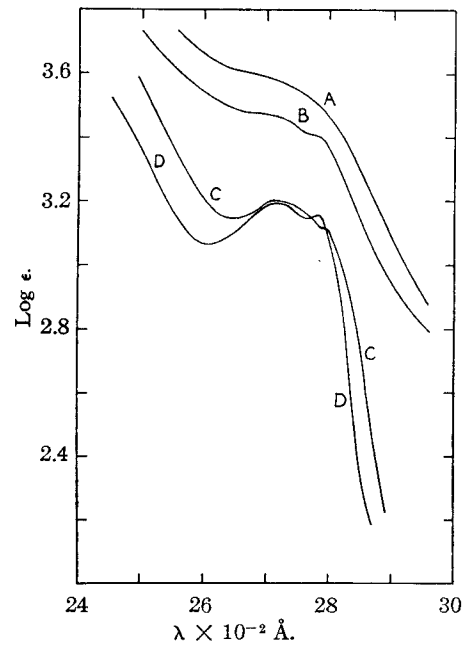
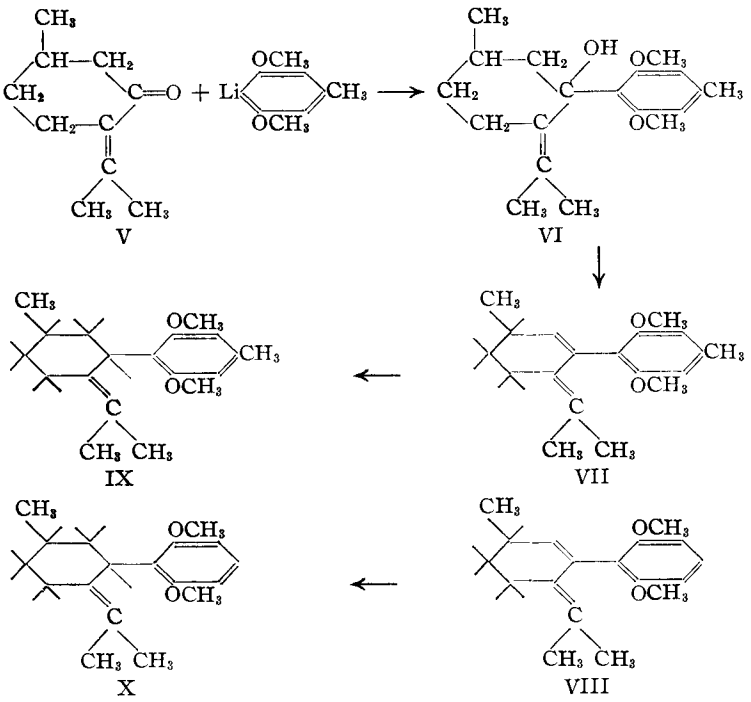


Fig. 2.—A, 2-(2′-Isopropylidene-5′-methyl-2′,3′,4′,5′-tetrahydrophenyl)-orcinol dimethyl ether (VII); B, 2-(2′-isopropylidene-5′-methyl-2′,3′,4′,5′-tetrahydrophenyl)-resorcinol dimethyl ether (VIII); C, 2-(2′-isopropylidene-5′-methylcyclohexyl)-orcinol dimethyl ether (IX); D, 2-(2′-isopropylidene-5′-methylcyclohexyl-resorcinol dimethyl ether (X).



and VIII were then partially reduced. The first molecule of hydrogen was much more rapidly absorbed than the second and the absorption could be stopped readily so as to isolate the molecules with only one double bond whose structures are postulated as IX and X. It was assumed that the 2,3 double bonds which are only trisubstituted would be the first attacked. The absorption spectra of the resulting compounds IX and X (Fig. 2) proved to be strikingly similar to those of cannabidiol dimethyl ether and dihydrocannabidiol dimethyl ether; they were so different from those of the corresponding unreduced synthetics (VII and VIII) or the compounds III and IV, that the only logical deduction is the absence of the conjugation to the benzene ring in IX or X and also in the cannabidiol derivatives. Apparently, the loss of one double bond through hydrogenation in the cannabidiol dimethyl ether molecule has little effect upon the absorption spectrum. The assumption that one of the double bonds in cannabidiol is in the 4,8 position merely because of the spectra similarities of dihydrocannabidiol dimethyl ether and the synthetic dihydropulegone derivatives, is not justified.

A study of cannabidiol and its derivatives has indicated the presence of a methylene group. Doeuvre[3] reports that methylene groups may be determined quantitatively by ozonization, followed by decomposition and colorimetric determination with the Grosse–Bohle reagent of the formaldehyde evolved. Doeuvre's experiments could not be repeated on a quantitative basis; in fact, it is questionable whether theoretically one molecule of formaldehyde always may be expected from such a molecule. If Briner's[4] views on the decomposition of ozonized double bonds is accepted, then the amount of formaldehyde liberated from a molecule containing a methylene group will be dependent upon the substituents present and other factors. The procedure of Doeuvre with minor modifications described in the experimental part appears entirely satisfactory as a qualitative method of detection of a methylene group. The results of the comparison of a variety of compounds are shown in Table I.

TABLE I

COMPARISON OF COLOR INTENSITIES PRODUCED BY OZONIZED COMPOUNDS AND AN EQUIMOLAR QUANTITY OF FORMALDEHYDE AS 100

Formaldehyde	100
Eugenyl cinnamate	63
Cannabidiol	49
Cannabidiol dimethyl ether	41
Dihydrocannabidiol dimethyl ether	0
Tetrahydrocannabidiol dimethyl ether	0

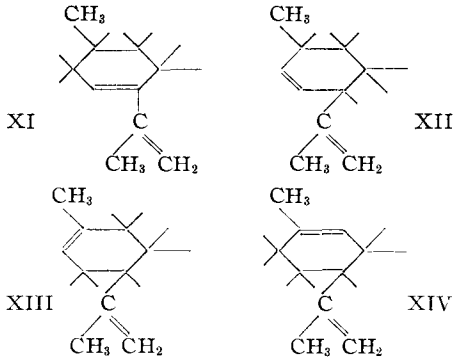
These experiments lead to the conclusion that in cannabidiol a methylene group is present, which is assigned to the 8,9 or 8,10 positions (II) on the basis of the fact that by various acidic reagents it is possible to convert cannabidiol to a pyran derivative with consequent elimination of one of the hydroxyl groups and one double bond; the resulting molecule, tetrahydrocannabinol, containing the second double bond no longer gives a test for a methylene group. The formation of a pyran excludes the possibility of a methylene in the 1,7 positions. A detailed discussion of the transformation of cannabidiol to tetrahydrocannabinol and a description of its interesting properties and chemical reactions will be the subject of the next paper in this series.

With these facts available the structure of can-

(3) Doeuvre, *Bull. soc. chim.*, [5] **3**, 612 (1936); *ibid.*, **45**, 146 (1929).

(4) Briner and de Nemitz, *Helv. Chim. Acta*, **21**, 748 (1938); Briner and Frank, *ibid.*, **22**, 587 (1938); Briner, *ibid.*, **22**, 591 (1939).

nabidiol is limited to one of four; the left-hand rings are shown in formulas XI–XIV.



Experimental

Cannabidiol dimethyl ether and tetrahydrocannabidiol dimethyl ether were prepared as described in previous work.[1d] The dihydrocannabidiol dimethyl ether is described here for the first time.

Dihydrocannabidiol Dimethyl Ether.—A solution of 6.78 g. of cannabidiol dimethyl ether in 50 cc. of 95% ethanol was reduced at atmospheric pressure in a quantitative hydrogenation machine using platinum oxide catalyst. Hydrogen was absorbed corresponding to 1.02 moles per mole of starting material. The catalyst was filtered, the solvent evaporated, and the dihydrocannabidiol dimethyl ether, a colorless viscous oil, was distilled, b. p. 158–161° (2 mm.) (bath temperature 175°), $n^{20}D$ 1.5188; yield 5.53 g.

Anal. Calcd. for $C_{21}H_{30}(OCH_3)_2$: C, 80.17; H, 10.53; OCH_3, 18.02. Found: C, 80.40; H, 10.55; OCH_3, 18.38. *Rotation.* 0.0587 g. made up to 5 cc. with 95% ethanol at 28° gave α_D −1.56°; *l*, 1; $[\alpha]^{28}D$ −133°.

The condensation of lithium orcinol dimethyl ether and lithium resorcinol dimethyl ether with menthone to give carbinols which were dehydrated to the corresponding unsaturated compounds (III and IV) was described in a previous paper.[1d] The condensation with pulegone is given below.

2 - (2′ - Isopropylidene - 5′ - methyl - 2′,3′,4′,5′ - tetrahydrophenyl)-resorcinol Dimethyl Ether (VIII).—To butyllithium prepared from 2.5 g. of lithium and 20.5 g. of *n*-butyl chloride, 20 g. of resorcinol dimethyl ether was introduced. The reaction was carried out under nitrogen in the apparatus previously described.[1d] After shaking for three hours, 25 g. of pulegone in 50 cc. of dry ether was added and fifteen minutes later the mixture was decomposed with ice water. The two layers were separated, the water layer extracted with ether and the combined ether extracts washed with water containing 3 cc. of glacial acetic acid and then with pure water. After drying over anhydrous magnesium sulfate, the ether was evaporated and the oily residue distilled. The mixture of the carbinol and the dehydrated compound distilled at 138–180° (1 mm.). It was found impossible to isolate the pure carbinol from the mixture and, therefore, the whole distillate was treated with approximately 2 g. of fused potassium acid sulfate at 140°. Dehydration of the carbinol occurred readily. After heating for one hour, the product was taken up in ether, filtered and the ether dried: colorless oil, b. p. 138–141° (1 mm.); yield 7 g. Solution in methanol followed by dropwise addition of water, prolonged cooling in a salt–ice-bath and scratching caused crystals to deposit (about 2 g.). After three recrystallizations from 90% methanol, purity was obtained, m. p. 75–76° (cor.). From the combined mother liquors, more crystalline material could be obtained by redistillation and crystallization as described.

Anal. Calcd. for $C_{18}H_{24}O_2$: C, 79.36; H, 8.88. Found: C, 79.12; H, 8.82. *Rotation.* 0.0355 g. made up to 5 cc. with 95% ethanol at 27° gave α_D +0.40; *l*, 1; $[\alpha]^{27}D$ +56°.

2 - (2′ - Isopropylidene - 5′ - methylcyclohexyl) - resorcinol Dimethyl Ether (X).—The reduction of 2-(2′-isopropylidene - 5′ - methyl - 2′,3′,4′,5′ - tetrahydrophenyl)-resorcinol dimethyl ether was carried out with platinum oxide catalyst in 95% ethanol at atmospheric pressure, in which case only 1 mole of hydrogen could be introduced. In glacial acetic acid, under similar conditions, the reduction occurred much more rapidly but if not stopped after introduction of 1 mole of hydrogen it continued to reduce.

To a solution of 0.272 g. of the diene in 50 cc. of 95% ethanol, 30 mg. of previously reduced platinum oxide was added and the reduction carried out at atmospheric pressure. After three hours no more hydrogen was absorbed (1.08 mole). After evaporation of the solvent, the remaining oil was dissolved in ethanol and water added dropwise under cooling in a salt–ice-bath until crystallization occurred; white crystals, m. p. 53–54° (cor.).

Reduction in glacial acetic acid solution yielded the same compound when hydrogenation was stopped after 1 mole of hydrogen was absorbed (about twenty minutes). On further reduction a second mole of hydrogen could be introduced but no crystalline product could be obtained.

Anal. Calcd. for $C_{18}H_{26}O_2$: C, 78.77; H, 9.55. Found: C, 78.93; H, 9.51. *Rotation.* 0.0350 g. made up to 5 cc. with 95% ethanol at 32° gave α_D +0.42°; *l*, 1; $[\alpha]^{32}D$ +60°.

Determination of Methylene Groups.—The procedure used was a modification of that of Doeuvre.[3] A solution of 10^{-4} mole of the compound in 5 cc. of a 3:2 mixture of ethyl acetate and acetic acid was treated for ten minutes with ozone (about 1.5–2%) at −20° and 0.5 cc. was then added to a solution of fuchsin-aldehyde reagent. The excess sulfur dioxide present in the reagent brought about reductive cleavage of the ozonide and the resulting formaldehyde gave a color with the reagent. Addition of hydrochloric acid desensitized the reagent to aldehydes other than formaldehyde. The color was compared with that produced by the ozonization of eugenyl cinnamate, which is known to contain a methylene group, and also with the color produced by an equimolar amount of standard formaldehyde. Quantitative comparisons were obtained through the use of a colorimeter (see Table I).

The ethyl acetate used in the ozonization solvent was refluxed over phosphorus pentoxide before use and the acetic acid distilled from chromic acid (2 g. per 100 g. of acetic acid). The fuchsin–aldehyde reagent was prepared by dissolving 0.5 g. of fuchsin in 500 cc. of water, filtering any undissolved material, and passing in sulfur dioxide until the solution was practically colorless. Excess sulfur di-

oxide was then removed by evacuating the vessel by means of the water pump for thirty minutes. The solution to which the ozonized solution was added was made up of 30 cc. of the above fuchsin reagent, 15 cc. of hydrochloric acid (sp. gr. 1.12; 100 cc. of concentrated hydrochloric acid diluted with 70 cc. of distilled water), and 45 cc. of water. Readings were taken after three to six hours, the time usually required for full development of the color.

2-(2'-Isopropylidene-5'-methyl-2',3',4',5'-tetrahydrophenyl)-orcinol Dimethyl Ether (VII).—This compound was prepared in a manner similar to the corresponding resorcinol dimethyl ether derivative; white crystals, m. p. 81–82° (cor.).

Anal. Calcd. for $C_{19}H_{26}O_2$: C, 79.60; H, 9.16. Found: C, 79.70; H, 9.16. *Rotation.* 0.0325 g. made up to 5 cc. with 95% ethanol at 27° gave α_D +0.24°; *l*, 1; $[\alpha]^{27}D$ +37°.

2-(2'-Isopropylidene-5'-methylcyclohexyl)-orcinol Dimethyl Ether (IX).—The reduction of 0.286 g. of the diene was carried out in 30 cc. of glacial acetic acid with platinum oxide catalyst and stopped after introduction of 1 mole of hydrogen. The solvent was evaporated *in vacuo* and the product recrystallized from ethanol; m. p. 114–115° (cor.).

Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.09; H, 9.79. Found: C, 79.13; H, 9.57. *Rotation.* 0.0309 g. made up to 5 cc. with 95% ethanol at 30° gave α_D +0.27°; *l*, 1; $[\alpha]^{30}D$ +44°.

Summary

Experimental evidence is submitted which limits the positions of the two double bonds in cannabidiol to one of the four following combinations, 8,9 and 4,5, 8,9 and 5,6, 8,9 and 6,7 or 8,9 and 1,2.

Comparison of the absorption spectra of cannabidiol dimethyl ether with various synthetics of unequivocal constitution which had one double bond conjugated with the benzene residue, showed a marked difference. Two analogous synthetic compounds with a double bond not conjugated to the benzene residue, gave absorption spectra very similar to cannabidiol dimethyl ether. Exclusion of double bonds in the 2,3 or 3,4 positions was thus deduced.

Formation of formaldehyde by decomposition of ozonized cannabidiol dimethyl ether indicated presence of a methylene group. Ease of isomerization of cannabidiol to tetrahydrocannabinol, a molecule with one hydroxyl and one double bond eliminated and no methylene group, excludes the possibility of a 1,7 double bond and proves the presence of an 8,9 double bond.

URBANA, ILLINOIS RECEIVED JUNE 26, 1940

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MICHIGAN]

Phenanthrene Derivatives. X. Acetylation of 4-Methylphenanthrene

BY W. E. BACHMANN AND R. O. EDGERTON[1]

As part of a program concerned with the study of the orienting effect of the methyl group in the methylphenanthrenes, we have investigated the Friedel–Crafts reaction of 4-methylphenanthrene with acetyl chloride. In this reaction 4-methylphenanthrene yielded a mixture of acetyl derivatives from which two crystalline compounds were isolated fairly easily. One of these, isolated to the extent of 50%, proved to be 1-acetyl-4-methylphenanthrene (I); the other, isolated in about 15% yield, was shown to be 3-acetyl-5-methylphenanthrene (II), the 6-acetyl derivative of 4-methylphenanthrene.

The formation of 3-acetyl-5-methylphenanthrene corresponds to the reaction of phenanthrene itself, which yields chiefly the 3-derivative and some of the 2-isomer in a similar reaction. In the substituted ring, however, the methyl group exerts its para-directing influence, and judging from the proportions of the isomers its influence is the strongest operating in this reaction.

The structures of the acetyl derivatives were determined by reducing them to 1-ethyl-4-methylphenanthrene and 3-ethyl-5-methylphenanthrene, respectively, the structures of the hydrocarbons being definitely established by synthesis. In the synthesis of 1-ethyl-4-methylphenanthrene, β-(1-naphthyl)-butyric acid (III) was converted to γ-(1-naphthyl)-valeric acid (IV) by means of the Arndt–Eistert reaction. This acid was cyclized through its acid chloride to 1-keto-4-methyl-1,2,3,4-tetrahydrophenanthrene (V). Proof of the structure of this new cyclic ketone was obtained by converting it to 1,4-dimethylphenanthrene through reaction with methylmagnesium iodide and subsequent dehydration and dehydrogenation of the carbinol. Furthermore, the ketone was reduced to 4-methyl-1,2,3,4-tetrahydrophenanthrene, which was dehydrogenated smoothly by

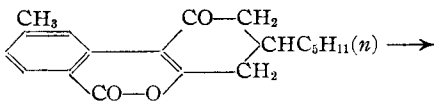
[1] From part of the Ph.D. dissertation of R. O. Edgerton.

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

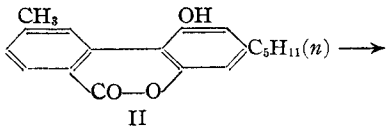
Structure of Cannabinol. V. A Second Method of Synthesis of Cannabinol[1]

BY ROGER ADAMS AND B. R. BAKER

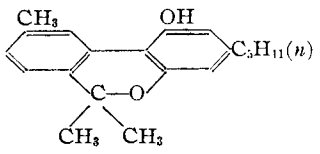
Cannabinol was shown to be 1-hydroxy-3-*n*-amyl-6,6,9-trimethyl-6-dibenzopyran (III) by a synthesis[2] involving (1) the condensation of 4-methyl-2-bromobenzoic acid with dihydroolivetol to 1-keto-3-*n*-amyl-9-methyl-1,2,3,4-tetrahydro-6-dibenzopyrone (I), (2) dehydrogenation of I to 1-hydroxy-3-*n*-amyl-9-methyl-6-dibenzopyrone (II), (3) conversion of II by means of methylmagnesium iodide to cannabinol (III).



I

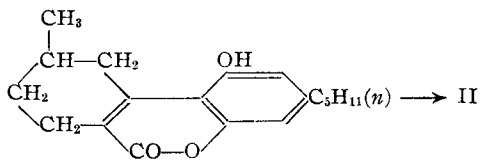


II



III

A second method for synthesizing cannabinol has now been devised. Ethyl 5-methylcyclohexanone-2-carboxylate was condensed with olivetol in the presence of phosphorous oxychloride[3] to give 1-hydroxy-3-*n*-amyl-9-methyl-7,8,9,10-tetrahydro-6-dibenzopyrone (IV). This last compound was dehydrogenated with ease in the presence of sulfur to give the pyrone (II), identical in all respects with the substance previously described. Since this latter is converted with methylmagnesium iodide to cannabinol (III), a second course for the synthesis of cannabinol, new except for the last step, becomes available. The dehydrogenation reaction in this new procedure gives better yields than in the process previously described.



IV

(1) For previous paper in this series, see Adams and Baker, THIS JOURNAL, **62**, 2208 (1940).

(2) Adams, Baker and Wearn, *ibid.*, **62**, 2204 (1940).

(3) Adams and Baker, *ibid.*, **62**, 2405 (1940).

Experimental

1 - Hydroxy - 3 - *n* - amyl - 9 - methyl - 7,8,9,10 - tetrahydro-6-dibenzopyrone.—A solution of 4.5 g. of olivetol (5-*n*-amylresorcinol), 6 g. of ethyl 5-methylcyclohexanone-2-carboxylate and 4.6 cc. of phosphorous oxychloride in 25 cc. of dry benzene protected from moisture was refluxed for three hours in an all-glass apparatus on the steam-bath. The solution rapidly turned deep red. It was washed with dilute aqueous sodium bicarbonate, which caused the benzene layer to become green, then with water. After evaporation of the benzene, the residue was purified by recrystallization from ethyl acetate; white needles, m. p. 180–181° (cor.); yield 4.3 g. (57%).

Anal. Calcd. for $C_{19}H_{24}O_3$: C, 75.97; H, 8.03. Found: C, 76.16; H, 8.00.

1 - Acetoxy - 3 - *n* - amyl - 9 - methyl - 7,8,9,10 - tetrahydro-6-dibenzopyrone.—A solution of 0.2 g. of the above compound and 0.1 g. of fused sodium acetate in 2 cc. of acetic anhydride was refluxed for two hours. The solution was poured into water, a small amount of the separated oil removed on a spatula and suspended in a little methanol. Crystals immediately formed which were used to seed the aqueous suspension. The product was purified by recrystallization from methanol, white needles, m. p. 82.5–84° (cor.).

Anal. Calcd. for $C_{21}H_{26}O_4$: C, 73.66; H, 7.63. Found: C, 73.50; H, 7.80.

1 - Hydroxy - 3 - *n* - amyl - 9 - methyl - 6 - dibenzopyrone.—A mixture of 0.60 g. of 1-hydroxy-3-*n*-amyl-9-methyl-7,8,9,10-tetrahydro-6-dibenzopyrone and 0.13 g. of sulfur was heated in a sidearm test-tube at 255–260° for ten minutes with occasional mixing. A cold finger was inserted and the product sublimed at 230–240° (3 mm.). It was recrystallized from toluene, then acetic acid, white needles, m. p. 184–185° (cor.); yield 0.36 g. (61%). A mixed melting point of this product and that with the same structure prepared in another way[2] gave no depression.

Summary

A second method of synthesis of cannabinol has been devised. It consists in the condensation of ethyl 5-methylcyclohexanone-2-carboxylate with olivetol in the presence of phosphorous oxychloride to give 1-hydroxy-3-*n*-amyl-9-methyl-7,8,9,-10-tetrahydro-6-dibenzopyrone. Dehydrogenation of this product with sulfur gives 1-hydroxy-3-*n*-amyl-9-methyl-6-dibenzopyrone which has been shown previously to give cannabinol when treated with methylmagnesium iodide.

URBANA, ILLINOIS RECEIVED JULY 25, 1940

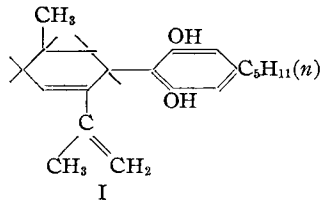
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Structure of Cannabidiol. VI. Isomerization of Cannabidiol to Tetrahydrocannabinol, a Physiologically Active Product. Conversion of Cannabidiol to Cannabinol[1]

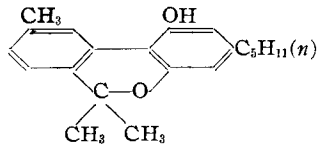
BY ROGER ADAMS, D. C. PEASE, C. K. CAIN AND J. H. CLARK

IN COLLABORATION WITH THE TREASURY DEPARTMENT, NARCOTICS LABORATORY, WASHINGTON, D. C., AND DR. S. LOEWE AT THE PHARMACOLOGICAL DEPARTMENT, CORNELL UNIVERSITY MEDICAL SCHOOL

Previous investigations on cannabidiol[1] have indicated that it has the structure shown in I, with doubt merely as to the position of the double bond in the left-hand ring. Synthesis has demonstrated cannabinol to have structure II.



I

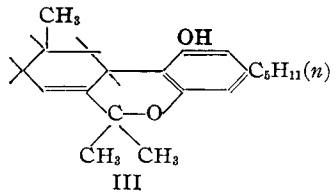


II

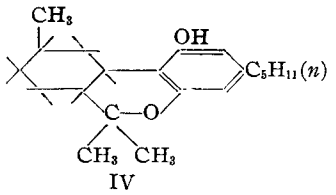
Cannabidiol has now been subjected to a variety of reagents which cause the characteristic purple color it gives with 5% ethanolic potassium hydroxide (Beam test) to disappear. It has been found that a mixture of pyridine hydrochloride and cannabidiol when heated at a temperature considerably below that at which it is cleaved to olivetol and *p*-cymene[2] yields a colorless, very viscous oil which does not exhibit the Beam test. This oil contains chlorine until it is distilled in high vacuum, after which it is chlorine-free. The analysis of the chlorine-free material indicates it has the same molecular formula as cannabidiol, a Zerewitinoff determination proves the presence of one hydroxyl group and by quantitative reduction one double bond is shown to be present. Fractions of the product through high-vacuum distillation varied in specific rotation, dependent on the exact details of preparation as well as on the mode of distillation. The material thus obtained is consequently not a pure substance.

The structure of cannabidiol is such that the loss of an hydroxyl group and a double bond by treatment with pyridine hydrochloride is readily understandable. This reagent isomerizes *o*-allyl phenols to substituted dihydrobenzofurans.[3] Perhaps by a similar mechanism, first addition of hydrogen chloride and then elimination involving the hydroxyl hydrogen, cannabidiol isomerizes to a pyran, tetrahydrocannabinol (III). The hydrogenated product, hexahydrocannabinol, will have structure IV.

The remaining double bond in III is apparently



III



IV

very susceptible to addition so that after the pyran ring is closed, it adds hydrogen chloride. Although the position of this double bond is uncertain it is of no significance so far as discussion of what probably happens during the reaction. This double bond may add hydrogen chloride in two ways, thus yielding two chlorine derivatives, probably with one predominating over the other. It is also possible, however, for each to exist in more than one stereochemical form. This mixture of chlorides dehydrohalogenates on distillation and it is obvious that each chloride can theoretically give two olefinic compounds depending on the hydrogen selected for elimination as hydrogen chloride. The fact that more than one tetrahydrocannabinol is obtained thus becomes explicable.

Confirmation of the presence of a pyran ring in the isomerized cannabidiol was obtained by dehydrogenation of the product. By means of sulfur, the left-hand ring was aromatized and the substance obtained was cannabinol (II) as shown by mixed melting point with an authentic sample

(1) For previous paper in this series see Adams, Wolff, Cain and Clark, THIS JOURNAL, **62**, 2215 (1940).

(2) Adams, Hunt and Clark, *ibid.*, **62**, 735 (1940).

(3) Claisen and co-workers, *Ber.*, **58**, 275 (1925); **59**, 2344 (1926); *Ann.*, **401**, 26 (1903); **418**, 76 (1919); **442**, 230 (1925).

and comparison of derivatives. Since the pyran structure in cannabinol has been proved by synthesis, the presence of the pyran ring in isomerized cannabidiol is established. This experiment is interesting also in that it suggests that in the hemp plant, cannabinol may be formed by an analogous mechanism; the precursor cannabidiol isomerizes to a tetrahydrocannabinol which in turn is oxidized to cannabinol.[4]

The isomerization of cannabidiol occurs with many other reagents, and can be very conveniently followed experimentally by the gradual disappearance of the Beam test. Hydrogen chloride in ether and a mixture of a substantial amount of hydrochloric acid and ethanol act rapidly. In both these cases, the primary products contain chlorine and, after distillation, the chlorine-free products do not give a tetrahydrocannabinol of constant rotation. Sulfamic acid, ethanolic phosphoric acid or zinc chloride is also effective in introducing the pyran ring.

After a rather extensive study, a very convenient method of cannabidiol isomerization was found which consists in refluxing an ethanolic solution of cannabidiol containing 0.1 mole equivalent of hydrogen chloride in the form of hydrochloric acid for about eight hours. The addition of hydrogen chloride to the ring double bond of the isomerized product must then be reduced to a minimum, not only because the hydrogen chloride is very dilute but also because it is present in amounts sufficient only to react with 10% of the tetrahydrocannabinol even if it added quantitatively. Actually as much hydrogen chloride can be recovered after the reaction is complete as can be obtained from a blank run of ethanolic hydrogen chloride treated in a similar manner, thus indicating that addition of hydrogen chloride to the tetrahydrocannabinol is essentially nil. The possibility that even this very dilute hydrogen chloride solution may cause a shifting of the double bond in the tetrahydrocannabinol or interconversion of stereoisomers cannot be disregarded. By such treatment cannabidiol gives a tetrahydrocannabinol of fairly constant specific rotation, $[\alpha]^{34}D - 165 \pm 7°$, indicating it to be a substance that is very nearly homogeneous.

The use of phosphoric acid for isomerization under carefully regulated conditions resulted in a tetrahydrocannabinol of essentially the same specific rotation. No crystalline derivative of this isomerized material has been isolated as yet. The evidence is that it is a tetrahydrocannabinol which contains small amounts of one or more very closely related isomers or stereoisomers.

Upon heating cannabidiol with pyridine hydrochloride under specified conditions, cannabidiol gives a tetrahydrocannabinol of fairly constant rotation $[\alpha]^{34}D - 240 \pm 10°$. In a single experiment with sulfamic acid, the same product of high rotation resulted.

When the tetrahydrocannabinol is reduced, regardless of its initial rotation, a hexahydrocannabinol (IV) is formed which has a constant specific rotation $[\alpha]^{27}D - 70°$. This indicates that the difference in the rotation of the tetrahydrocannabinols is due probably to the difference in the position of the double bond, and the variability in rotation of any particular product depends on the relative amounts of the tetrahydrocannabinol isomers present.

Of great importance is the observation that the tetrahydrocannabinols by isomerization of cannabidiol, whether the specific rotation of the sample is fairly constant or whether it varies widely upon fractionation, have a marihuana activity many times that of the purified red oil used as a raw material. Since cannabidiol was shown by us in previous work to be physiologically inactive and this has been confirmed by repetition of the tests with crystalline material, one or more active products are obviously being synthesized. Moreover, the hexahydrocannabinol, apparently a homogeneous product, obtained by reduction of the double bond in the tetrahydrocannabinol is also physiologically active.

The evidence from these experiments is that there are at least two tetrahydrocannabinols and probably more which are physiologically active and that the double bond in the left-hand ring is not essential for marihuana activity. It thus appears likely that the marihuana activity in red oil is due to one or more of these or to analogous substances. Hence the crystalline physiologically active compound, recently reported by Haagen-Smit[5] and isolated from red oil will probably be found to possess a structure of this kind.

Experimental

Isomerization of Cannabidiol; Formation of Tetrahydrocannabinols

A. By Hydrogen Chloride in Ethanol.—A solution of 3.14 g. (0.01 mole) of cannabidiol (m. p. 66–67°) in 100 cc.

(4) Jacob and Todd, *J. Chem. Soc.*, 649 (1940).

(5) Haagen-Smit, Wawra, Koepfli, Alles, Feigen and Prater, *Science*, **91**, 602 (1940).

of absolute ethanol containing 0.001 mole of hydrogen chloride (added as *M* ethanolic hydrochloric acid) was refluxed on a steam-bath for eight hours. At the end of this time the Beam test (purple color with 5% ethanolic potassium hydroxide) had become negative. The reaction mixture was poured into water and the product extracted with ether. The ether extract was washed with water, dilute aqueous sodium bicarbonate and again with water. After drying and evaporating the ether, the residue was distilled; colorless, highly viscous oil, b. p. 188–190° (2.5 mm.), 158–160° (0.05 mm.), $n^{20}D$ 1.5432. Six fractions of the distillate were collected, the specific rotation values of each being essentially the same.

Rotation. 0.0297 g. made up to 5 cc. with 95% ethanol at 27° gave αD −1.90°; *l*, 2; $[\alpha]^{27}D$ −160°. Zerewitinoff: 0.246 g. gave 16.0 cc. of methane (S. T. P.). Calculated for one OH, 17.5 cc. of methane.

Anal. Calcd. for $C_{21}H_{30}O_2$; C, 80.21; H, 9.62. Found: C, 79.90; H, 9.52.

The reaction product in a run similar to that described was washed carefully with water and the hydrogen chloride was titrated. About 72% of the hydrogen chloride originally added was found. However, if the same concentration of hydrogen chloride in ethanol without any cannabidiol is treated in exactly the same manner, only 75% recovery was obtained. Thus it is fair to conclude that essentially no hydrogen chloride is being added to the tetrahydrocannabinol.

After the initial experiments in which, regardless of the method of isomerization, it was found the product boiled the same, an all-glass high vacuum apparatus was used with no attempt to determine the temperature of distillation except by the control of the bath temperature.

It was found that varying the quantities of reactants, although in the same proportion, sometimes gave a product with a specific rotation varying as much as 7° from the above value.

Using a larger proportion of hydrochloric acid up to 1.5 moles per mole of cannabidiol caused addition of hydrogen chloride to the double bond but distillation of the product resulted in the loss of hydrogen chloride and a chlorine-free material. It had the same b. p. as previously recorded but the specific rotation of various fractions varied widely. Thus, in several typical runs the following values for successive fractions were obtained. A. 1 mole of hydrogen chloride and 1 mole of cannabidiol refluxed for five hours gave fractions $[\alpha]^{30}D$ −146°, −191°, −223°. B. 1.5 moles of hydrogen chloride and 1 mole of cannabidiol refluxed for seven hours gave fractions $[\alpha]^{28}D$ −163°, −174°, −215°. C. 0.75 mole of hydrogen chloride and 1 mole of cannabidiol refluxed for 2.75 hours gave fractions $[\alpha]^{27}D$ −207°, −219°, −235°, −234°.

B. By Hydrogen Chloride in Ether.—A solution of 3.1 g. of cannabidiol (m. p. 66–67°) was prepared in 50 cc. of dry ether which had been saturated previously with dry hydrogen chloride at 0°. The solution was allowed to stand for four hours at 0°, then poured onto ice. The ether layer was separated, washed with aqueous sodium bicarbonate and water, dried and distilled. The remaining oil which contained chlorine was heated with 10 cc. of quinoline for two hours at 185–190°. After cooling, the reaction mixture was poured into cold 10% sulfuric acid. The product was extracted with ether and the ether solution washed with dilute sulfuric acid, with aqueous sodium bicarbonate then water. The cyclization resulted in a substance with the same boiling point as that previously reported. Four fractions gave variable rotations: $[\alpha]^{29}D$ −166°, −180°, −188°, −191°.

C. By Pyridine Hydrochloride.—A mixture of 6 g. of dry pyridine hydrochloride and 3 g. of cannabidiol (m. p. 66–67°) was heated at 125° for one hour. The Beam test (purple color with 5% ethanolic potassium hydroxide) had entirely disappeared after a relatively short time. The product was washed with water to free from pyridine hydrochloride, extracted with ether and the ether solution washed with water. After evaporation of the solvent, the product was distilled in high vacuum, whereupon hydrogen chloride was evolved. The distillate was a highly viscous, colorless oil with a b. p. approximately the same as that reported in the experiments using hydrochloric acid in ethanol for cyclization. Upon separating into six fractions, the specific rotations were as follows: $[\alpha]^{32}D$ −235°, −236°, −235°, −241°, −244°, −249°.

Rotation. (Fraction 1) 0.0314 g. made up to 5 cc. with 95% ethanol at 32° gave αD −2.95°; *l*, 2; $[\alpha]^{32}D$ −235°.

D. By Phosphoric Acid.—A mixture of 3 g. of cannabidiol (m. p. 66–67°), 150 cc. of ethanol and 50 cc. of sirupy phosphoric acid (85%) was refluxed for thirty-five minutes which resulted in a negative Beam test. It was poured into water and the product extracted with ether. Six fractions were collected in distillation, all of which gave essentially the same specific rotation, $[\alpha]^{26}D$ −160°. This product appears, therefore, to be the same as that prepared by the very dilute ethanolic hydrochloric acid method A.

Rotation. (Fraction 3) 0.0481 g. made up to 5 cc. with 95% ethanol at 26° gave αD −1.54°; *l*, 1; $[\alpha]^{26}D$ −160°.

If the reaction mixture was refluxed for two hours instead of thirty-five minutes with the proportions 3 g. of cannabidiol, 55 cc. of ethanol, 20 cc. of sirupy phosphoric acid (85%), a product was obtained which gave fractions with specific rotations varying from −188° to −199°. Upon refluxing one of these fractions for twelve hours with ethanol and phosphoric acid, the product gave a specific rotation of −179°.

It is obvious that changes are taking place in the molecule by the treatment just described. It may consist in shifting of the double bond or interchange of stereoisomers or both.

E. Sulfamic Acid; Zinc Chloride.—The experiments on the isomerization of cannabidiol with sulfamic acid or zinc chloride are in the preliminary stage. It may be mentioned here, however, that upon heating with these reagents, the Beam test rapidly disappeared. From one sulfamic acid experiment at 125° (0.5 g. of cannabidiol, 1 g. of sulfamic acid), the product gave a specific rotation of −250°.

Dehydrogenation of Tetrahydrocannabinol to Cannabinol.—A mixture of 2.82 g. of tetrahydrocannabinol ($[\alpha]^{32}D$ −167°) and 0.58 g. of sulfur in a side-neck test-tube was heated at 240–250° until evolution of hydrogen sulfide had ceased (about twenty minutes). After cooling to 180–190°, the product was distilled *in vacuo* onto a cold finger. The resulting material was taken up in about 25 cc. of petroleum ether (b. p. 30–60°) the solution cooled and scratched. About 0.5 g. of crude cannabinol was

thus obtained. On further purification from the same solvent, it gave white crystals, m. p. 75–76° (cor.) identical in all respects with an authentic sample of cannabinol.

Anal. Calcd. for $C_{21}H_{26}O_2$: C, 81.21; H, 8.45. Found: C, 81.48; H, 8.66.

The cannabinol thus obtained was converted into the *p*-nitrobenzoate by the procedure previously described.[6] It had a melting point of 165–166° (cor.) and showed no melting point depression when mixed with an authentic sample of cannabinol *p*-nitrobenzoate.

Hexahydrocannabinol by Reduction of Tetrahydrocannabinol.—A solution of 3.14 g. of tetrahydrocannabinol ($[\alpha]^{27}D$ −160°) which had been distilled in high vacuum in an all-glass apparatus, in 50 cc. of glacial acetic acid was reduced with hydrogen at room temperature, using 0.1 g. of platinum oxide. Hydrogen corresponding to 0.96 mole per mole of tetrahydrocannabinol was absorbed in about four hours, after which hydrogenation continued to proceed but at a very much slower rate. After absorption of one mole equivalent of hydrogen, the solution was filtered and the acetic acid removed *in vacuo*. The hexahydrocannabinol formed a colorless, highly viscous resin, b. p. 153–155° (0.1 mm.) (bath temp. 180–185°), $n^{26}D$ 1.5348.

Rotation. 0.0252 g. made up to 5 cc. with 95% ethanol at 27° gave αD −0.71°; *l*, 2; $[\alpha]^{27}D$ −70°.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.69; H, 10.19. Found: C, 79.35; H, 10.43.

It was found that regardless of the initial rotation of the tetrahydrocannabinol used, the hexahydro product always had essentially the same specific rotation.

(6) Adams, Baker and Wearn, THIS JOURNAL, **62**, 2204 (1940).

Summary

By a variety of reagents cannabidiol loses one hydroxyl and a double bond and is isomerized to tetrahydrocannabinol. The structure of this latter product was determined by dehydrogenation to cannabinol.

The tetrahydrocannabinol varies in rotation depending upon the mode of formation. A product of fairly constant rotation $[\alpha]^{34}D$ −165 ± 7° was obtained by the use of very dilute ethanolic hydrochloric acid or ethanolic sirupy phosphoric acid under regulated conditions; by use of pyridine hydrochloride or sulfamic acid, a product $[\alpha]^{34}D$ −240 ± 10°. The difference in rotation is due probably to the difference in the position of the double bond in the tetrahydrocannabinol.

Regardless of the specific rotation of the tetrahydrocannabinol, it absorbs one mole of hydrogen upon reduction with formation of a hexahydrocannabinol of constant rotation $[\alpha]^{27}D$ −70°.

The tetrahydrocannabinol preparations showed marihuana activity many times that of the purified red oil used for isolation of cannabidiol. The hexahydrocannabinol is also active. The inactivity of cannabidiol by tests on crystalline material, has been confirmed.

URBANA, ILLINOIS RECEIVED JULY 23, 1940

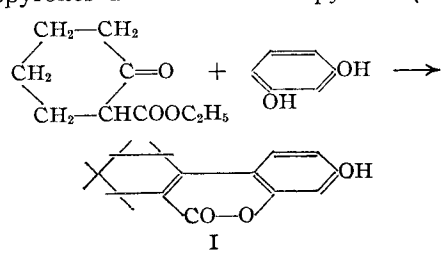
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Structure of Cannabidiol. VII. A Method of Synthesis of a Tetrahydrocannabinol which Possesses Marihuana Activity[1]

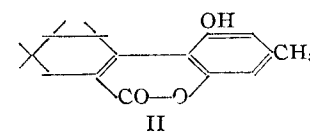
BY ROGER ADAMS AND B. R. BAKER

IN COLLABORATION WITH THE TREASURY DEPARTMENT, NARCOTICS LABORATORY, WASHINGTON, D. C., AND DR. S. LOEWE AT THE PHARMACOLOGICAL DEPARTMENT, CORNELL UNIVERSITY MEDICAL SCHOOL

Ahmad and Desai[2] have reported that ethyl cyclohexanone-2-carboxylate condenses with resorcinol and with orcinol in the presence of phosphorous oxychloride to yield partially reduced dibenzopyrones I and II. The pyrone (II) was

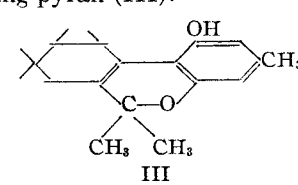


I



II

prepared and treated with excess methylmagnesium iodide. It is thus readily converted to the corresponding pyran (III).

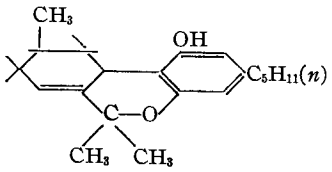


III

These results have an important bearing upon the cannabidiol problem, for cannabidiol isomer-

(1) For previous paper in this series see Adams, Pease, Cain and Clark, THIS JOURNAL, **62**, 2402 (1940).

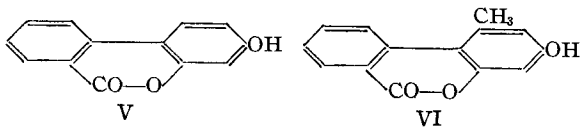
(2) Ahmad and Desai, *J. Univ. Bombay*, **6**, Pt. II, 89 (1937).



IV

izes[1] in the presence of various reagents to a tetrahydrocannabinol (IV) (position of the double bond in the left-hand ring is doubtful) which has a potent marihuana activity. A direct synthesis of this and analogous substances is, therefore, highly desirable. Desai's procedure which results in compound II coupled with the conversion to the pyran (III) offers a satisfactory type reaction for this purpose if the structure II assigned the ethyl cyclohexanone-2-carboxylate and orcinol condensation product is correct.

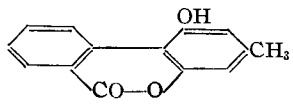
Desai formulates the resorcinol condensation product with the linkage of the two rings in the 4-position (I) and the orcinol derivative with the linkage in the 2-position between the oxygens. These experiments are in contrast to the condensation of *o*-bromobenzoic acid with resorcinol or orcinol in the presence of alkali and copper salts to give pyrones in which the linkage between the rings is in both cases in the 4-position (V and VI).[3]



V VI

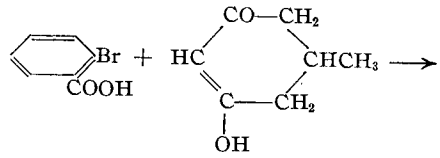
Confirmation that the compound from ethyl cyclohexanone-2-carboxylate and orcinol has structure II is, therefore, necessary.

Structure II has been demonstrated by two methods to be correct. The product from ethyl cyclohexanone-2-carboxylate and orcinol (II) was dehydrogenated to the corresponding dibenzopyrone (VII). This substance proved not to be identical with dibenzopyrone (VI) prepared by condensation of *o*-bromobenzoic acid and orcinol, the constitution of which is unequivocal. The only alternative structure to VI is VII for the dehydrogenated compound. The second method

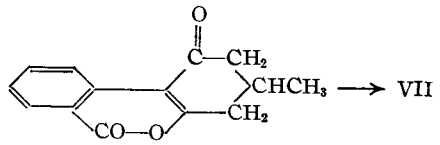


VII

consisted in a direct synthesis of structure VII by a procedure which leaves no doubt in regard to the arrangement of the atoms. *o*-Bromobenzoic acid and dihydroörcinol (5-methyl-1,3-cyclohexanedione) (VIII) were condensed,[3] whereby the linkage of the two rings must be between the two oxygens. The dehydrogenation product of the 1-keto-3-methyl-1,2,3,4-tetrahydro-6-dibenzopyrone (IX) thus formed was identical with the dehydrogenated ethyl cyclohexanone-2-carboxylate and orcinol compound (VII). The structures of



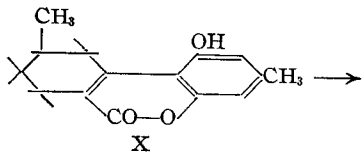
VIII



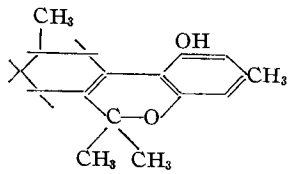
IX

the various products prepared by Desai[2,4] and his associates are thus established. Moreover, the structure of the pyran (III) as 1-hydroxy-3,6,6-trimethyl-7,8,9,10-tetrahydro-6-dibenzopyran is also clarified.

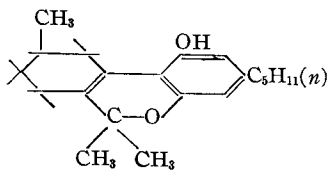
By the use of ethyl 5-methylcyclohexanone-2-carboxylate in place of ethyl cyclohexanone-2-carboxylate with orcinol, the product must have the structure shown in X and the corresponding



X



XI



XII

pyran must be XI, both of which were synthesized. It is, therefore, obvious that by condensing ethyl 5-methylcyclohexanone-2-carboxylate with olivetol, followed by methylmagnesium io-

(3) Adams, Pease, Clark and Baker, THIS JOURNAL, **62**, 2197 (1940); Adams, Baker and Wearn, *ibid.*, **62**, 2204 (1940).

(4) Desai, *Proc. Indian Acad. Sci.*, **8A**, 1, 12 (1938).

dide, it is possible to prepare the tetrahydrocannabinol (XII) with the double bond conjugated to the benzene ring. This substance proved to be a colorless viscous oil and tests showed it to have a marihuana activity.

It is thus established that the double bond in tetrahydrocannabinol does not have to be in any fixed position in the left-hand ring and that optical activity is unnecessary in order to have a substance of marihuana activity. The potency of the various molecules varies widely and the synthetic is much less active than the tetrahydrocannabinols from cannabidiol. The relative physiological activity will be discussed in a subsequent paper.

The method of synthesis just described is being applied to the formation of analogs and homologs of tetrahydrocannabinol.

Experimental

1 - Hydroxy - 3 - methyl - 7,8,9,10 - tetrahydro - 6 - dibenzopyrone (II).—A solution of 6.2 g. of orcinol, 11 g. of ethyl cyclohexanone-2-carboxylate and 4.6 cc. of phosphorous oxychloride in 45 cc. of dry benzene was refluxed for three hours on the steam-bath in an all-glass apparatus protected from moisture. The solution rapidly turned deep red and at the end of one hour a crystalline precipitate began to separate. Two volumes of water were added, the mixture well shaken to destroy the phosphorous oxychloride and then cooled. Most of the product crystallized and was obtained by filtration of the benzene–water mixture. Additional product resulted by separation and evaporation of the benzene layer. It was purified by recrystallization from ethanol; white crystals, m. p. 243–245° (cor.), yield 7.6 g. (66%).

Ahmad and Desai[2] reported a melting point of 242–243°.

The use of sulfuric acid instead of phosphorous oxychloride in benzene gives a much inferior yield (35%).

1 - Hydroxy - 3,6,6 - trimethyl - 7,8,9,10 - tetrahydro - 6-dibenzopyran (III).—To a solution of the Grignard reagent from 2.6 g. of magnesium and 6 cc. of methyl iodide in 30 cc. of dry ether was added a suspension of 1.5 g. of 1-hydroxy-3-methyl-7,8,9,10-tetrahydro-6-dibenzopyrone in 50 cc. of dry benzene. After being refluxed for twelve hours, the solution was poured onto iced ammonium chloride solution. The organic layer was separated and the aqueous layer extracted once with benzene. The combined benzene solutions were washed successively with water, dilute aqueous sodium bicarbonate and water. The benzene was evaporated and the residue suspended in 75 cc. of boiling petroleum ether (b. p. 60–110°). Upon the addition of three drops of 48% aqueous hydrobromic acid the oil dissolved immediately with vigorous boiling. The solution was boiled on a hot-plate for thirty minutes maintaining the volume at 50–75 cc. by the addition of more solvent as necessary. After decantation from a small amount of insoluble material, the solution was cooled and the container scratched, whereby the product crystallized. It was purified by sublimation at 170–180° (3 mm.), then recrystallized from petroleum ether (b. p. 60–110°); white prisms, m. p. 136–138° (cor.); yield 1.0 g. (63%).

Anal. Calcd. for $C_{16}H_{20}O_2$: C, 78.66; H, 8.23. Found: C, 78.98; H, 8.58.

It gave no color with 5% ethanolic potassium hydroxide.

1 - Keto - 3 - methyl - 1,2,3,4 - tetrahydro - 6 - dibenzopyrone (IX).—To a solution of 0.34 g. of sodium in 10 cc. of absolute ethanol was added 0.85 g. of 5-methyl-1,3-cyclohexanedione (dihydroörcinol), 1.61 g. of *o*-bromobenzoic acid and 0.05 g. of cupric acetate. After refluxing for five hours, the solution was diluted with three volumes of water, acidified and extracted with chloroform. The chloroform solution was washed with dilute aqueous sodium bicarbonate and then evaporated. The crystalline residue was purified by recrystallization from ethanol; white needles, m. p. 148–150° (cor.); yield 1.08 g. (71%).

Anal. Calcd. for $C_{14}H_{12}O_3$: C, 73.65; H, 5.31. Found: C, 73.85; H, 5.53.

1-Hydroxy-3-methyl-6-dibenzopyrone (VII).—A. A mixture of 1.0 g. of 1-hydroxy-3-methyl-7,8,9,10-tetrahydro-6-dibenzopyrone (II) and 0.29 g. of sulfur was heated at 255–260° with occasional mixing for twenty minutes. Upon cooling, the product crystallized. It was dissolved in a minimum amount of methyl ethyl ketone, an equal volume of toluene was added and the solution concentrated until crystallization commenced. Upon cooling 0.82 g. (83%) of product resulted. It was purified further by sublimation at 3 mm. (bath temp. 225°) and then recrystallized from ethanol; white prisms, m. p. 249–251° (cor.).

B. A mixture of 0.82 g. of 1-keto-3-methyl-1,2,3,4-tetrahydro-6-dibenzopyrone and 0.12 g. of sulfur was heated at 255–260° in a sidearm test-tube for fifteen minutes. A cold finger was inserted and the product sublimed at 225° (3 mm.). It was recrystallized by using the same procedure described under A; white prisms, m. p. 249–251° (cor.), yield 0.37 g. (45%). A mixed melting point showed it to be identical with the substance obtained in A.

Anal. Calcd. for $C_{14}H_{10}O_3$: C, 74.31; H, 4.47. Found: C, 74.30; H, 4.81.

1-Acetoxy-3-methyl-6-dibenzopyrone.—A solution of 0.10 g. of 1-hydroxy-3-methyl-6-dibenzopyrone and 0.05 g. of fused sodium acetate in 2 cc. of acetic anhydride was refluxed for two hours. The solution was poured into water, the product collected on a filter and recrystallized from methanol; white crystals, m. p. 144–146° (cor.). The same product was obtained by acetylation of the product made by method B just described.

Anal. Calcd. for $C_{16}H_{12}O_4$: C, 71.62; H, 4.51. Found: C, 71.88; H, 4.75.

1 - Acetoxy - 3 - methyl - 7,8,9,10 - tetrahydro - 6 - dibenzopyrone.—This was prepared from 1-hydroxy-3-methyl-7,8,9,10-tetrahydro-6-dibenzopyrone in the same manner as 1-acetoxy-3-methyl-6-dibenzopyrone; white needles from methanol, m. p. 126–127° (cor.); yield 93%.

Anal. Calcd. for $C_{16}H_{16}O_4$: C, 70.56; H, 5.92. Found: C, 70.90; H, 5.97.

When this compound was dehydrogenated with sulfur partial deacetylation also took place. By hydrolysis of the mixture with ethanolic hydrochloric acid, 1-hydroxy-3 methyl-6-dibenzopyrone was obtained, m. p. 249–251°

(cor.). Reacetylation of the mixture gave the corresponding acetate, m. p. 144–146° (cor.).

1 - Hydroxy - 3,9 - dimethyl - 7,8,9,10 - tetrahydro - 6-dibenzopyrone, X.—This compound was prepared in essentially the same manner as 1-hydroxy-3-methyl-7,8,9,10-tetrahydro-6-dibenzopyrone. From 6.2 g. of orcinol, 12 g. of ethyl 5-methylcyclohexanone-2-carboxylate, 4.6 cc. of phosphorous oxychloride in 50 cc. of dry benzene was obtained 7.5 g. (62%) of product, m. p. 262–263° (cor.). Chowdry and Desai[4] report a melting point of 260°.

1 - Hydroxy - 3,6,6,9 - tetramethyl - 7,8,9,10 - tetrahydro-6-dibenzopyran (XI).—This compound was prepared in the same manner as 1-hydroxy-3,6,6-trimethyl-7,8,9,10-tetrahydro-6-dibenzopyran. From 5.2 g. of magnesium, 12 cc. of methyl iodide and 4.5 g. of 1-hydroxy-3,9-dimethyl-7,8,9,10-tetrahydro-6-dibenzopyrone was obtained 3.7 g. (77%) of the pyran. It was purified by recrystallization from petroleum ether (b. p. 60–110°); white crystals, m. p. 115.5–116° (cor.).

Anal. Calcd. for $C_{17}H_{22}O_2$: C, 79.04; H, 8.57. Found: C, 78.98; H, 8.75.

1 - Hydroxy - 3 - *n* - amyl - 6,6,9 - trimethyl - 7,8,9,10-tetrahydro-6-dibenzopyran (Tetrahydrocannabinol) XII.—Prepared from 1-hydroxy-3-*n*-amyl-9-methyl-6-dibenzopyrone[5] and methylmagnesium iodide, (9 g. of magnesium, 22.5 g. of methyl iodide, and 9 g. of 1-hydroxy-3-*n*-amyl-9-methyl-7,8,9,10-tetrahydro-6-dibenzopyrone) the product was obtained as a colorless, viscous oil, b. p. 191–192° (1 mm.); $n^{20}D$ 1.5549; yield 7.3 g. (78%).

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.20; H, 9.62. Found: C, 80.12; H, 9.57.

(5) Adams and Baker, THIS JOURNAL, **62**, 2401 (1940).

Summary

The compound prepared by Desai by condensing ethyl cyclohexanone-2-carboxylate with orcinol has been proved to be 1-hydroxy-3-methyl-7,8,9,10-tetrahydro-6-dibenzopyrone. This was accomplished by dehydrogenation and identification of the 1-hydroxy-3-methyl-6-dibenzopyrone obtained by two methods. The first was by comparing it with a sample of 1-methyl-3-hydroxy-6-dibenzopyrone with which it was not identical. The second was by synthesizing it from *o*-bromobenzoic acid and dihydroörcinol followed by dehydrogenation.

The 1-hydroxy-3-methyl-7,8,9,10-tetrahydro-6-dibenzopyrone with methyl magnesium iodide gives the corresponding pyran, 1-hydroxy-3,6,6-trimethyl - 7,8,9,10 - tetrahydro - 6 - dibenzopyran. By using ethyl 5-methylcyclohexanone-2-carboxylate in place of ethyl cyclohexanone-2-carboxylate, the compound, 1-hydroxy-3,6,6,9-tetramethyl-7,8,9,10-tetrahydro-6-dibenzopyran is produced.

By condensing ethyl 5-methylcyclohexanone-2-carboxylate and olivetol followed by methylmagnesium iodide, a synthetic tetrahydrocannabinol was formed which had marihuana activity.

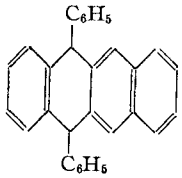
URBANA, ILLINOIS RECEIVED JULY 23, 1940

[COMMUNICATION FROM THE KODAK RESEARCH LABORATORIES]

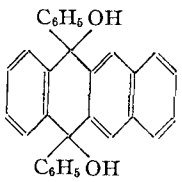
Action of Phenylmagnesium Bromide on Anthraquinones. II

BY C. F. H. ALLEN AND ALAN BELL

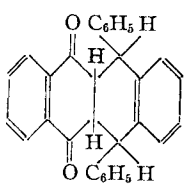
Some time ago, in a paper dealing with the synthesis of rubrene, Dufraisse and Horclois[1] treated naphthacenequinone with phenylmagnesium bromide in toluene, and obtained the diol II formed by 1,2-addition in a yield of 50%. They also obtained some of the 5,12-diphenylnaphthacene I, a very little of the 1,4-addition product III, and recovered a little quinone.



I



II



III

(1) Dufraisse and Horclois, *Bull. soc. chim.*, (5) **3**, 1894 (1936).

About the same time, Allen and Gilman[2] observed that when *n*-butyl ether was used as a solvent the same reagents gave none of the diol, but a considerable amount (20%) of the mixed stereoisomeric tetrahydro ketones III. Though not mentioned in that paper, the hydrocarbon I later was secured from the more soluble products in a yield of 25%. The discrepancy between the two papers led us to look into the reaction in more detail; it seemed *a priori* that the difference in results probably could be traced to differences in operating conditions. The results of this further investigation are described in this paper.

Before this particular instance was taken up, simple anthraquinones were used, to learn the optimum conditions for securing high yields of the

(2) Allen and Gilman, THIS JOURNAL, **58**, 937 (1936).