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°), $n^{20}D$ 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

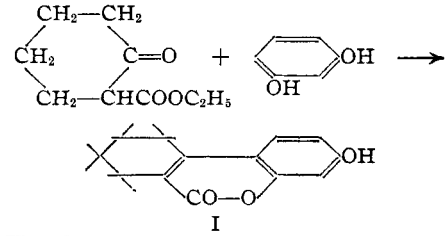
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

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

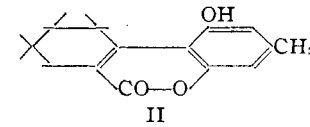
BY ROGER ADAMS AND B. R. BAKER

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

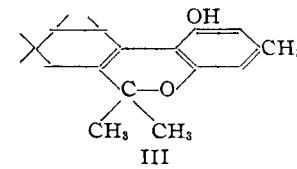


I



II

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

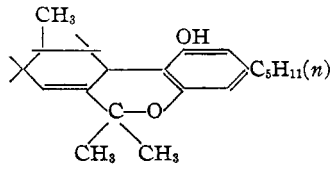


III

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).

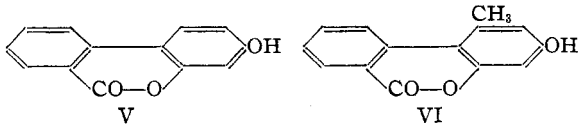
(2) Ahmad and Desai, *J. Univ. Bombay*, **6**, Pt. II, 89 (1937).



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.

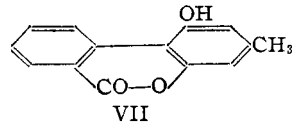
Desai formulates the resorcinol condensation product with the linkage of the two rings in the 4-position (I) and the orcinol derivative with the linkage in the 2-position between the oxygens. These experiments are in contrast to the condensation of *o*-bromobenzoic acid with resorcinol or orcinol in 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

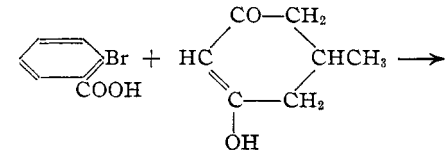
Confirmation that the compound from ethyl cyclohexanone-2-carboxylate and orcinol has structure II is, therefore, necessary.

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

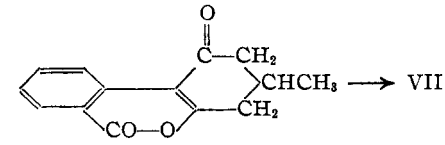


VII

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



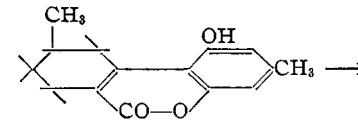
VIII



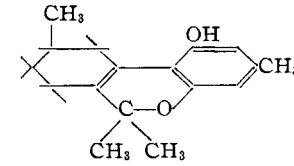
IX

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.

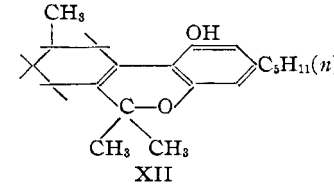
By the use of ethyl 5-methylcyclohexanone-2-carboxylate in place of ethyl cyclohexanone-2-carboxylate with orcinol, the product must have the structure shown in X and the corresponding



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.

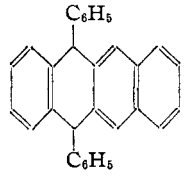
URBANA, ILLINOIS RECEIVED JULY 23, 1940

[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.



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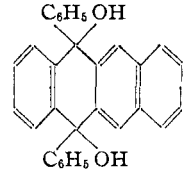
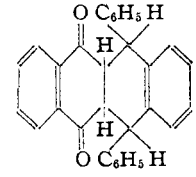


II



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).