lidified on standing and was recrystallized from petroleum ether (b. p. 60–110°); colorless crystals, m. p. 61–62° (cor.).

*Anal.* Calcd. for $C_{14}H_{22}O_2$: C, 75.67; H, 10.00. Found: C, 75.60; H, 9.96.

**1-Hydroxy-3-*n*-alkyl-9-methyl-6-dibenzopyrones.**—They were all prepared by the procedure described below for the *n*-heptyl derivative.

A mixture of 7.6 g. of 1,3-dihydroxy-5-*n*-heptylbenzene, 6.6 g. of ethyl 5-methylcyclohexanone-2-carboxylate, and 5.8 g. of phosphorus oxychloride in 60 cc. of dry benzene was refluxed for five to six hours. After pouring the cooled reaction product into aqueous sodium bicarbonate, crystalline material separated; yield, 6 g. Another 1.1 g. was obtained on concentration of the mother liquor.

**1-Hydroxy-3-*n*-alkyl-6,6,9-trimethyl-7,8,9,10-tetrahydro-6-dibenzopyrans.**—The procedure employed in the preparation of analogous compounds described in previous papers was used. In many cases the reactions were complete in nine hours. The decomposition of the Grignard reaction mixture was carried out with ammonium chloride and dilute sulfuric acid.

## Summary

Synthesis of a series of homologs of a tetrahydrocannabinol with the double bond conjugated to the benzene ring has been completed. These are 1-hydroxy-3-*n*-alkyl-6,6,9-trimethyl-7,8,9,10-tetrahydro-6-dibenzopyrans.

The methyl, ethyl, *n*-propyl, *n*-butyl, *n*-hexyl, *n*-heptyl and *n*-octyl were compared with the *n*-amyl for marihuana potency. The effectiveness of the methyl was low; it increased to a maximum with the *n*-hexyl and again fell off in the higher homologs.

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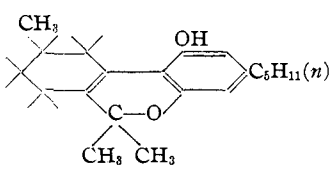
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS, AND FROM THE DEPARTMENT OF PHARMACOLOGY, CORNELL UNIVERSITY MEDICAL COLLEGE]

# Tetrahydrocannabinol Homologs and Analogs with Marihuana Activity. X[1]

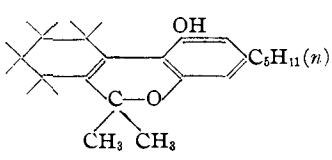
BY ROGER ADAMS, C. M. SMITH AND S. LOEWE

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

A comparison of the change in pharmacological activity upon substitution of the *n*-amyl group in synthetic tetrahydrocannabinol (I) by various other alkyl groups was reported in a previous paper.[1]




I

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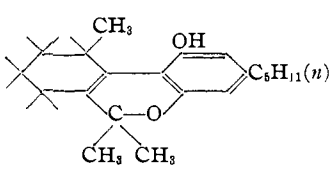


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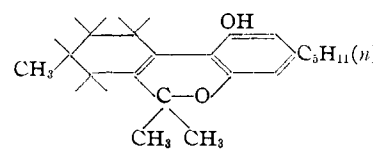
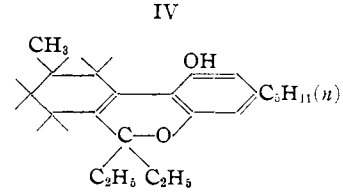
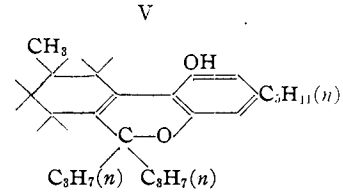



IV




V




VI

Other modifications in the molecule have now been made. They are represented in formula II where the methyl group in the left-hand ring has been eliminated; in formulas III and IV where the methyl group has been shifted to a position *para* and *ortho* to the linkage to the benzene ring; and in formulas V and VI where the two methyl

(1) For previous paper see Adams, Loewe, Jelinek and Wolff, THIS JOURNAL, **63**, 1971 (1941).

groups of the pyran ring have been replaced first by ethyl and second by *n*-propyl groups.

The five new compounds II, III, IV, V and VI were compared in activity with compound I as a standard. The results obtained are shown in Table I.

TABLE I

BIOASSAY OF ANALOGS OF TETRAHYDROCANNABINOL

| Compound | Expts. | Marihuana potency |
|---|---|---|
| I | 20 | 1.00 (standard) |
| II | 4 | 0.126 ±0.05 |
| III | 6 | .25 ±0.05 |
| IV | 6 | .137 ±0.01 |
| V | 8 | .12 ±0.024 |
| VI | 5 | .04 ±0.01 |

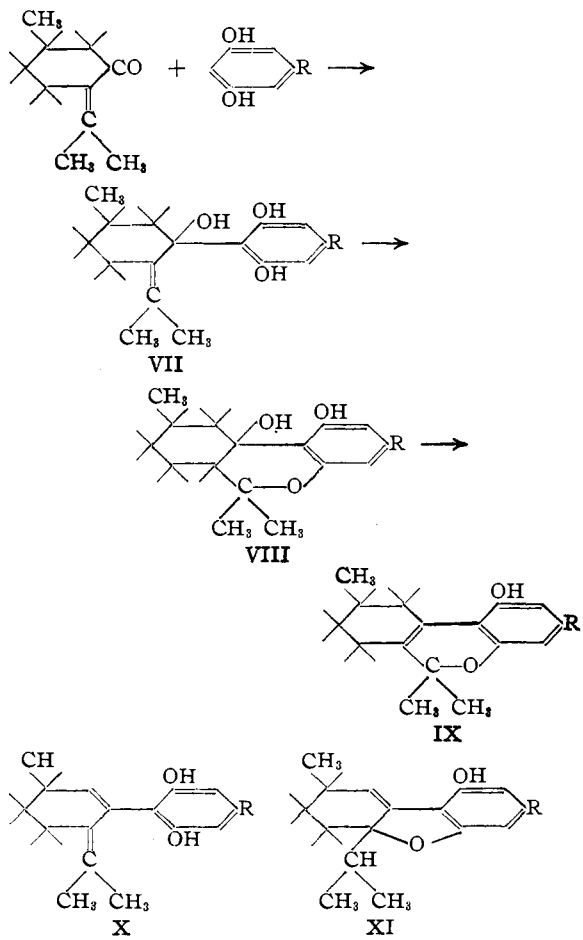
It is thus seen that such minor modifications of structure I as have been introduced reduce materially the marihuana potency.

Compounds II, III, IV, V and VI were made by the general procedure described in a previous paper[1,2] for synthesis of compound I. Ethyl cyclohexanone-2-carboxylate, ethyl 4-methylcyclohexanone-2-carboxylate or ethyl 6-methylcyclohexanone-2-carboxylate were condensed with olivetol and the resulting pyrones converted to the pyrans by means of excess methylmagnesium iodide. Compounds II, III and IV were obtained thus. For compounds V and VI ethyl 5-methylcyclohexanone-2-carboxylate was condensed with olivetol and the resulting pyrone treated with excess ethylmagnesium bromide or excess *n*-propylmagnesium bromide.

Ghosh, Todd and Wright[3] report obtaining a condensation product from olivetol and pulegone in the presence of formic acid which analyzed for a tetrahydrocannabinol. These authors concluded from the absorption spectrum that the product was not homogeneous and probably consisted of a mixture of isomers, one with the double bond conjugated and the other with the double bond not conjugated with the benzene ring.

The condensation of olivetol and pulegone has been under study in this Laboratory also. Our observations do not coincide entirely with those of Ghosh, Todd and Wright. They describe the product as having an insignificant *levo* rotation in acetone solution and a marihuana potency about 40% of that of pure compound I. The condensation in this investigation was carried out not with formic acid but with phosphorus oxychloride in benzene solution. Under these conditions the reaction takes place smoothly and an optically active tetrahydrocannabinol is obtained. The exact rotation was found to be dependent on the amount of phosphorus oxychloride used as a condensing agent; the more reagent, the lower the rotation of the product. Identical effects were observed in both orcinol and olivetol condensations with pulegone. Apparently a change takes place in the molecule during or subsequent to the initial condensation when excess reagent is present.

The formation of a tetrahydrocannabinol may be explained by the following mechanism (VII–IX). It is also possible, however, that compound




X, an intermediate that might be formed by dehydration of VII, could cyclize and rearrange to IX. The final product in this reaction analyzed correctly for a tetrahydrocannabinol. However, the absorption spectrum of the pulegone–olivetol product had two peaks, one (Max. $\epsilon$ = 8650 at 2740 Å.) and a second ($\epsilon$ = 7820 at 2600 Å.)

(2) Adams and Baker, THIS JOURNAL, **62**, 2405 (1940).
(3) Ghosh, Todd and Wright, *J. Chem. Soc.*, 137 (1941).

whereas the absorption spectrum of compound I showed a single peak (Max $\epsilon$ = 14,200 at 2740 Å.). It is thus obvious that impurities are present just as Ghosh, Todd and Wright found in their preparation. The migration of the conjugated double bond to an unconjugated position as suggested by Ghosh, Todd and Wright seems without precedent. The possibility that the isomeric compound has a structure analogous to IX but with the pyran ring linked between the hydroxyl and *n*-amyl groups cannot be excluded; another is a molecule with structure XI, where $R$ = *n*-amyl, which is less stable stereochemically, however, than IX. In spite of the indication of impurities in the product as deduced from the absorption spectrum, the marihuana activity was demonstrated to be essentially the same as that of pure compound I. From eleven experiments on a high-rotating fraction the results indicated a potency 1.04 ± 0.37. As a consequence a more careful study of this product and method of synthesis is warranted.

## Experimental

**1-Hydroxy-3-*n*-amyl-9-methyl-7,8,9,10-tetrahydro-6-dibenzopyrone.**—This product was made by the general procedure of Adams and Baker[2] except for minor details. It was found advantageous in forming the pyrone to use exact molar quantities of olivetol and ethyl 5-methylcyclohexanone-2-carboxylate and an amount of phosphorus oxychloride sufficient to correspond to the removal of three moles of water or ethanol. From 24 g. of ethyl 5-methylcyclohexanone-2-carboxylate and 24 g. of olivetol refluxed in 180 cc. of benzene with 16 g. of phosphorus oxychloride for seven hours was obtained 29.8 g. (74.5%) of crude product. After one crystallization from methanol the product was used for conversion to the pyran.

**1-Hydroxy-3-*n*-amyl-8-methyl-7,8,9,10-tetrahydro-6-dibenzopyrone.**—A mixture of 6 g. of olivetol and 6 g. of ethyl 4-methylcyclohexanone-2-carboxylate and 4.8 g. of phosphorus oxychloride in 55 cc. of dry benzene was refluxed for four hours and then poured into excess aqueous sodium bicarbonate. After cooling, washing with water and benzene, the crude product weighed 7.6 g. (76%). After purification from methanol, it formed white crystals, m. p. 169–169.5° (cor.).

*Anal.* Calcd. for $C_{19}H_{24}O_3$: C, 75.97; H, 8.03. Found: C, 75.90; H, 8.24.

**1-Hydroxy-3-*n*-amyl-10-methyl-7,8,9,10-tetrahydro-6-dibenzopyrone.**—A mixture of 2 g. of ethyl 6-methylcyclohexanone-2-carboxylate, 2 g. of olivetol and 1.75 g. of phosphorus oxychloride in 5 cc. of benzene and 15 cc. of toluene was refluxed for twelve hours. It was poured into saturated aqueous sodium carbonate and boiled till the solvent was removed. After cooling, the product was cooled and washed with benzene. From a mixture of methanol and isopropanol, it formed white crystals, m. p. 194–194.5° (cor.).

*Anal.* Calcd. for $C_{19}H_{24}O_3$: C, 75.97; H, 8.03. Found: C, 76.05; H, 8.33.

**1-Hydroxy-3-*n*-amyl-7,8,9,10-tetrahydro-6-dibenzopyrone.**—Following the procedure just described, olivetol and ethyl cyclohexanone-2-carboxylate were condensed. The product was obtained in 81.5% yield. It was purified from benzene; white crystals, m. p. 183–183.5°.

*Anal.* Calcd. for $C_{18}H_{22}O_3$: C, 75.45; H, 7.76. Found: C, 75.85; H, 7.93.

**1-Hydroxy-3-*n*-amyl-6,6-dimethyl-7,8,9,10-tetrahydro-6-dibenzopyran (II).**—The crude product made by the action of methylmagnesium iodide on the corresponding pyrone, was refluxed in ethanol for three hours with a mixture of activated Darco and Norit. This served to remove a small amount of blue-green by-product. A straw-colored viscous oil, b. p. 175–180° (0.02 mm.), bath 195–200° resulted; $n^{20}D$ 1.5643. The yield was 6 g. (71.5%).

*Anal.* Calcd. for $C_{20}H_{28}O_2$: C, 80.00; H, 9.40. Found: C, 80.23; H, 9.48.

**1-Hydroxy-3-*n*-amyl-6,6-diethyl-9-methyl-7,8,9,10-tetrahydro-6-dibenzopyran (V).**—Ethylmagnesium bromide was used in place of methylmagnesium iodide with the proper pyrone. The product was greenish and the color could not be removed with Darco and Norit, b. p. 185–195° (0.02 mm.) bath 200–210°; $n^{20}D$ 1.5538; yield, 6.3 g. (77%).

*Anal.* Calcd. for $C_{23}H_{34}O_2$: C, 80.70; H, 10.02. Found: C, 80.16; H, 9.83.

**1-Hydroxy-3-*n*-amyl-6,6-di-*n*-propyl-9-methyl-7,8,9,10-tetrahydro-6-dibenzopyran (VI).**—By an anologous procedure using *n*-propyl bromide, the product was obtained. It formed a red resin, b. p. 200–204° (2 mm.), bath 225–230°; $n^{20}D$ 1.5475. The yield was 77.5%.

*Anal.* Calcd. for $C_{25}H_{38}O_2$: C, 81.00; H, 10.34. Found: C, 80.56; H, 10.03.

**1-Hydroxy-3-*n*-amyl-6,6,8-trimethyl-7,8,9,10-tetrahydro-6-dibenzopyran (IV).**—The procedure described by Adams and Baker[2] was used. It was found advantageous to dissolve the pyrones in a mixture of three parts of dry benzene and one part of dry di-*n*-butyl ether before adding to the Grignard reagent. A straw-colored viscous oil was obtained, b. p. 175–180° (0.02 mm.), bath 195–200°; $n^{20}D$ 1.5567. On standing it solidified and was purified by recrystallization from glacial acetic acid; white crystals, m. p. 72–73° (cor.). The yield was 80%.

*Anal.* Calcd. for $C_{21}H_{30}O_2$: C, 80.20; H, 9.62. Found: C, 79.59; H, 9.59.

**1-Hydroxy-3-*n*-amyl-6,6,10-trimethyl-7,8,9,10-tetrahydro-6-dibenzopyran (III).**—The pyrone and methylmagnesium iodide were reacted in ether, benzene added, the ether distilled off and the mixture refluxed for twelve hours. Decomposed in the usual way and decolorized in ethanol with Darco-norit, the product was a viscous oil, b. p. 181–185° (0.5–1.0 mm.), $n^{20}D$ 1.5585; yield, 1.87 g. (71%).

*Anal.* Calcd. for $C_{21}H_{30}O_2$: C, 80.20; H, 9.62. Found: C, 80.38; H, 9.58.

**Pulegone–Orcinol Condensation Product.**—A mixture of 3.1 g. (1.01 moles) of pulegone ($\alpha^{32}D$ +24.3°), 2.5 g. of orcinol (1.00 mole), 0.98 g. of phosphorus oxychloride (0.33

mole) and 20 cc. of dry benzene was refluxed for four hours. It was poured into an excess of aqueous sodium bicarbonate and warmed on a steam-bath until the phosphorus derivatives were decomposed. After cooling, the benzene layer was separated and the aqueous layer extracted with a mixture of benzene and ether. The two solutions were combined, extracted with 2% aqueous sodium hydroxide and the solvent removed. The product was distilled, discarding the forerun; light-yellow resin, b. p. 170–180° (0.5 mm.), bath 202–215°; yield, 3.2 g. (50.5%). The product was separated into four fractions (1) to 170°, (2) 170–172°, (3) 172–175°, (4) 175–180°. The specific rotations were as follows: (1) $\alpha^{31}D$ +86.2°, (2) +90.4°, (3) +88.3°, (4) +83.5°.

*Anal.* Calcd. for $C_{17}H_{22}O_2$: C, 79.04; H, 8.57. Found: C, 78.71; H, 8.80. *Rotation.* (Fraction 2) 0.115 g. made up to 5 cc. with ethanol at 31° gave $\alpha D$ 2.08; *l*, 1; $\alpha^{31}D$ +90.4°.

Two other runs were made using the same quantities of pulegone and orcinol but varying merely the amount of phosphorus oxychloride. The experiment using 0.47 mole of reagent gave 41% yield; four fractions gave the following rotations (1) $\alpha^{31}D$ +78.1°, (2) +82.9°, (3) +84.8°, (4) +81.6°. The other using 0.99 mole of phosphorus oxychloride gave 33% yield; three fractions gave the following rotations (1) $\alpha^{31}D$ +76.9°, (2) +66.0°, (3) +70.5°.

**Pulegone–Olivetol Condensation Product.**—Equimolar quantities of olivetol, pulegone ($\alpha^{32}D$ + 24.3°) and three-tenths of a mole of phosphorus oxychloride were refluxed in benzene solution for four hours and then worked up in the usual way. From 6 g. of olivetol, 5 g. of pulegone and 1.5 g. of phosphorus oxychloride, was obtained 4.4 g. (42.7%) of product boiling at 190–200° (2 mm.). This was separated into three fractions (1) 190–195°, (2) 195–197° and (3) 197–200°; over-all bath temperature 225–233°. A forerun and residue were discarded. The specific rotations and indices of refraction of the fractions were as follows (1) $\alpha^{32}D$ +72.0°, $n^{20}D$ 1.5509; (2) +77.0°, $n^{20}D$ 1.5519; (3) +73.0, $n^{20}D$ 1.5529. The index of refraction of tetrahydrocannabinol (I) has been found to vary somewhat in different samples, $n^{20}D$ 1.5550–1.5564.

*Anal.* Calcd. for $C_{21}H_{30}O_2$: C, 80.20; H, 9.62. Found: C, 80.34; H, 9.74. *Rotation.* (Middle fraction) 0.195 g. made up to 5 cc. with ethanol at 32° gave $\alpha D$ +3.00°; *l*, 1; $\alpha^{32}D$ +77.0°.

Two other condensations similar to the above were carried out, using fifty-three hundredths mole (four hours of refluxing) and seventy-six hundredths mole of phosphorus oxychloride (six hours of refluxing). The yields in both experiments were about 60% but the quality of the products was presumably inferior, if this can be judged from specific rotations. The former experiment yielded two fractions $\alpha^{25}D$ +70.4° and +70.0°, the latter $\alpha^{25}D$ +53.1° and +48.1°.

## Summary

1. Analogs of tetrahydrocannabinol have been synthesized by the general procedure of condensing ethyl cyclohexanone-2-carboxylate or its derivatives with olivetol to form the pyrones from which pyrans were formed by means of excess Grignard reagent. In this way 1-hydroxy-3-*n*-amyl - 6,6,8 - trimethyl - 7,8,9,10 - tetrahydro - 6-dibenzopyran, 1 - hydroxy - 3 - *n* - amyl - 6,6,10-trimethyl - 7,8,9,10 - tetrahydro - 6 - dibenzopyran, 1 - hydroxy - 3 - *n* - amyl - 6,6 - dimethyl-7,8,9,10-tetrahydro-6-dibenzopyran, 1-hydroxy-3 - *n* - amyl - 6,6 - diethyl - 9 - methyl - 7,8,9,10-tetrahydro-6-dibenzopyran and 1-hydroxy-3-*n*-amyl - 6,6 - di - *n* - propyl - 9 - methyl - 7,8,9,10-tetrahydro-6-dibenzopyran were prepared.

All showed marihuana activity much less than that of the tetrahydrocannabinol used as a standard.

2. Pulegone and orcinol or olivetol were condensed by means of phosphorus oxychloride. The product from olivetol was optically active, analyzed for a tetrahydrocannabinol and had a potency essentially the same as pure tetrahydrocannabinol made by another series of reactions and described in a communication published last year.

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