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

Tetrahydrocannabinol Homologs with Marihuana Activity. IX[1]

BY ROGER ADAMS, S. LOEWE, CHARLES JELINEK AND HANS WOLFF

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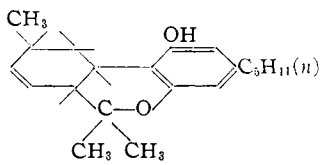
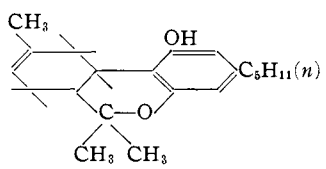
In a previous paper it was reported that the tetrahydrocannabinols (I and II) produced by isomerizing cannabidiol were very potent in marihuana activity[1,2] and one or the other or both probably represented at least part of the active material in the red oil of hemp.

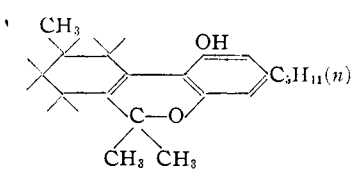


I



II

A synthetic tetrahydrocannabinol (III) with the double bond conjugated to the benzene ring was prepared[3] and was demonstrated to have marihuana activity. It was much less effective than the tetrahydrocannabinols from cannabidiol but nevertheless about as effective as "purified red oil" from hemp.[4] This same optically inactive tetrahydrocannabinol (III) was described about the same time by Ghosh, Todd and Wilkinson[5] in the report of an investigation on the synthesis of cannabinol, but no pharmacological tests on the product were reported.

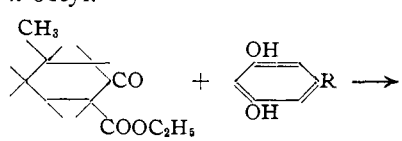


III

In a recent article by Ghosh, Todd and Wright[6] these authors describe the testing of the product III and have confirmed the pharmacological activity as published by us last year. By the Gayer test similar results were obtained as by the ataxia test used by us, the "Bioassay by Approximation" evaluating motor incoördination of dogs. They also report in this most recent article the condensation of pulegone and olivetol to give a product reported as a mixture of tetrahydrocannabinols, which showed about 40% of the physiological activity of the pure compound (III).

The determination of the exact structure of cannabinol, the isolation and determination of the structure of cannabidiol, the formation of tetrahydrocannabinols from cannabidiol and by synthesis—from which followed the discovery of the marihuana activity of these latter products in the Department of Pharmacology at Cornell University Medical College—were demonstrated originally in the University of Illinois Laboratories. It was assumed that the discovery and publication especially of this last observation would allow us a certain priority in the study of synthetic analogs and homologs of the tetrahydrocannabinols without competition. The appearance of the paper just published by Ghosh, Todd and Wright[6] and particularly the announcement of another by the same authors on the relationship of constitution and hashish activity leads us to immediate publication of some of the results accumulated during the past year before they are complete in as great detail as had been hoped.

The establishment of the activity of compound III led us first to the study of homologous substances in which the *n*-amyl group was substituted by other groups. Condensations of ethyl 5-methylcyclohexanone-2-carboxylate were, therefore, carried out with 1,3-dihydroxy-5-alkylbenzenes (IV) in which the alkyl group was methyl, *n*-propyl, *n*-butyl, *n*-hexyl, *n*-heptyl and *n*-octyl.



IV

(1) For previous paper see Adams, Loewe, Pease, Cain, Wearn, Baker and Wolff, THIS JOURNAL, **62**, 2566 (1940).

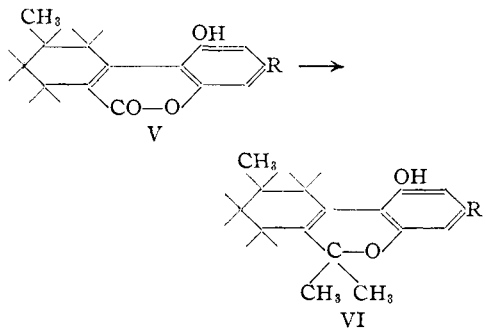
(2) Adams, Pease, Cain and Clark, *ibid.*, **62**, 2402 (1940); see also Adams, *Science*, **92**, 115 (1940).

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

(4) Adams, Hunt and Clark, *ibid.*, **62**, 196 (1940).

(5) Ghosh, Todd and Wilkinson, *J. Chem. Soc.*, 1121 (1940).

(6) Ghosh, Todd and Wright, *ibid.*, 137 (1941).



V

VI

Subsequent treatment of the pyrones (V) with excess methylmagnesium iodide yielded the homologous tetrahydrocannabinols (VI). The activity of these compounds in comparison with the *n*-amyl derivative was determined and is shown in Table I.

TABLE I

BIOASSAY OF HOMOLOGS OF TETRAHYDROCANNABINOL

Compound III R = *n*-alkyl	Expts.	Marihuana potency
CH_3	2	Below 0.2 but still effective
C_3H_7	2	0.40 ± 0.08
C_4H_9	4	0.37 ± 0.12
C_5H_{11}	20	1.00 (standard)
C_6H_{13}	7	1.82 ± 0.18
C_7H_{15}	10	1.05 ± .15
C_8H_{17}	7	0.66 ± .12

The *n*-amyl derivative was used as a standard in these experiments. Its potency has been tested very carefully on twenty dogs and its effectiveness is rated as 0.23 ± 0.02 as compared with the general standard, a sample of high potency red oil obtained by careful molecular fractionation of a purified red oil.[1] It may be mentioned that this value is just about one-tenth that of the optically active higher-rotating tetrahydrocannabinols produced by isomerization of cannabidiol.

On the basis of the *n*-amyl homolog as 1, it may be seen that the activity, which is very low for the methyl derivative and low for both the propyl and butyl, rises to a maximum in the *n*-hexyl and then falls off again. The results are striking in that the *n*-hexyl derivative exceeds the potency of the *n*-amyl standard by better than 50% and that the *n*-heptyl homolog is approximately as effective as the standard. The methyl derivative was reported by Ghosh, Todd and Wilkinson to be inactive but our results indicate it to be active though only slightly so.

The probability is that with various sized alkyl groups, the relative activities will be similar in the series in which the double bond is not conjugated to the benzene ring.

Experimental

1,3-Dihydroxy-5-*n*-alkylbenzenes.—These were prepared by the general method of Suter and Weston,[7] though it was found possible to improve upon the reported yields. Only the 1,3-dihydroxy-5-*n*-octylbenzene had not been described by these authors.

1,3-Dihydroxy-5-*n*-octylbenzene.—The 1,3-dimethoxy-5-octophenone (b. p. 180° at 2 mm., m. p. 36–37°) was converted by the Wolff–Kishner reduction to 1,3-dimethoxy-5-*n*-octylbenzene; colorless oil, b. p. 164–168° (4 mm.); $n^{20}D$ 1.4995.

Anal. Calcd. for $C_{16}H_{26}O_2$: C, 76.80; H, 10.48. Found: C, 77.09; H, 10.63.

TABLE II

1-HYDROXY-3-*n*-ALKYL-9-METHYL-7,8,9,10-TETRAHYDRO-6-DIBENZOPYRONES

3-*n*-Alkyl group	M. p., (cor.), °C.	Solvent for crystallization	Yield, %	Empirical formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
Propyl	233–235	Methanol	55.3	$C_{17}H_{20}O_2$	75.00	7.35	75.03	7.48
Butyl	199–200	Ethyl acetate	59	$C_{18}H_{22}O_3$	75.48	7.76	75.65	7.95
Hexyl	173–174	Ethyl acetate	51.6	$C_{20}H_{26}O_3$	76.38	8.34	76.34	8.48
Heptyl	172–173	Methanol	58.7	$C_{21}H_{28}O_3$	76.78	8.59	76.53	8.53
Octyl	165–167	Methanol	58.8	$C_{22}H_{30}O_3$	77.19	8.77	77.47	8.72

TABLE III

1-HYDROXY-3-*n*-ALKYL-6,6,9-TRIMETHYL-7,8,9,10-TETRAHYDRO-6-DIBENZOPYRANS

3-*n*-Alkyl group	B. p., °C.	Mm.	$n^{20}D$	Yield, %	Empirical formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
Propyl	185[a]	2	1.5680	85.6	$C_{19}H_{26}O_2$	79.66	9.15	79.38	9.32
Butyl	178–180	1	1.5595	80	$C_{20}H_{28}O_2$	79.94	9.40	79.87	9.50
Hexyl	190–192	1	1.5504	80.7	$C_{22}H_{32}O_2$	80.42	9.84	80.78	9.73
Heptyl	225–228	0.05	1.5490	70	$C_{23}H_{34}O_2$	80.63	10.02	80.64	9.86
Octyl	215–220	.01	1.5440	93.2	$C_{24}H_{36}O_2$	80.85	10.16	80.88	10.13

[a] The product crystallized on standing; from petroleum ether (b. p. 30–60°) white crystals, m. p. 145–146° (cor.).

Upon demethylation, 1,3-dihydroxy-5-*n*-octylbenzene was obtained; colorless oil, b. p. 195–197 (2 mm.). It so-

(7) Suter and Weston, THIS JOURNAL, **61**, 232 (1939).

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]

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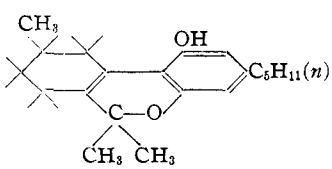
A comparison of the change in pharmacological activity upon substitution of the *n*-amyl group in synthetic tetrahydrocannabinol (I) by various other alkyl groups was reported in a previous paper.[1]



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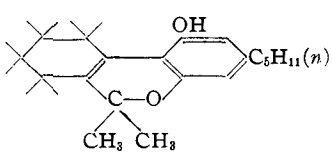

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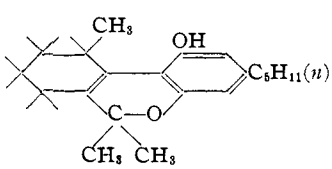
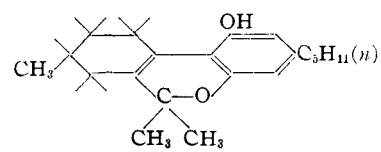


III



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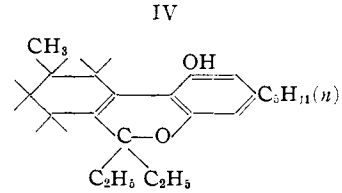
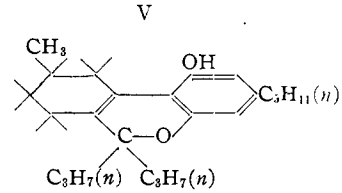


V



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).