mild conditions. Catalytic hydrogenation of the unacetylated compounds VC and VIC caused reduction of the α-keto group to methylene whereas the double bond and the α-amino and α-sulfo group remained intact.

NUTLEY, NEW JERSEY RECEIVED JULY 2, 1947

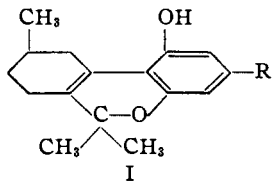
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS, AND THE SCHOOL OF MEDICINE, UNIVERSITY OF UTAH]

Tetrahydrocannabinol Homologs. XVII.[1]

BY ROGER ADAMS, BEN F. AYCOCK, JR., AND S. LOEWE

Modification of the 3-alkyl substituent of the synthetic tetrahydrocannabinol molecule (I) has resulted in the production of compounds of varying marihuana activity. Such compounds containing a 1′-methylalkyl side-chain have been shown to possess greatly enhanced activity compared to their *n*-alkyl analogs, and the most potent compound previously synthesized, the homolog with a 1′-methylheptyl group, has an activity greater than that of natural tetrahydrocannabinol.[1] Two additional members of the series, the 1′-methyloctyl and the 1′-methylnonyl, have now been synthesized.

The effect of distance from the aromatic ring of a substituent methyl in the 3-alkyl group has been investigated by the synthesis and testing of compounds with the 2′-, 3′- and 4′-methylpentyl groups in the 3-position. In Table I are included for comparison the pharmacological activities of these compounds, the 1′-methyloctyl and 1′-methylnonyl homologs and certain closely related compounds.



I

Inspection of Table I leads to several interesting conclusions. The 1′-methyloctyl homolog (no. 5) has an activity double that of the next lower member (no. 4) and over four times that of natural tetrahydrocannabinol (no. 14); thus it becomes the most potent substance ever tested. As a result of the unusual duration of action of the next higher homolog (no. 6) it is impossible to say where the peak of activity in this series occurs. The 1′-methylnonyl compound is only slightly soluble in propylene glycol and therefore was injected as an emulsion. This fact may account for the prolonged action exhibited by this substance.

It is also apparent that substitution of the alkyl group in the position in the side-chain next to the ring has a much greater effect than in a more distant position, the activity falling from 3.7 in the 1′-methylpentyl to 1.14 in the 4′-methylpentyl. Furthermore, the order of activity of the various isomeric hexyl side chains studied shows that all except the 1′-methylpentyl have a lower potency than the *n*-hexyl, the activities falling in the order: 1′-methylpentyl > *n*-hexyl > 1′-ethylbutyl > 2′-methylpentyl > 3′-methylpentyl > 4′-methylpentyl (isohexyl). It is significant that although the isohexyl homolog was reported to have negligible activity[7] by the Gayer test,[8] its potency, according to the dog ataxia test, is even greater than that of the standard.

TABLE I

PHARMACOLOGICAL ACTIVITY OF TETRAHYDROCANNABINOL HOMOLOGS

	3-Substituent	No. of expts.	Potency
1	-C_6H_{11}-*n*	20	1.00 standard
2	-C_6H_{13}-*n*[2]	7	1.82 ± 0.18 (max. in *n*-series)
3	-C_6H_{17}-*n*[2]	7	0.66 ± 0.12
4	-$CH(CH_3)C_6H_{13}$[1]	10	16.4 ± 3.67
5	-$CH(CH_3)C_7H_{15}$	19	32.6 ± 3.02[3]
6	-$CH(CH_3)C_8H_{17}$	7	2.08 ± 1.49[3,4]
7	-$CH(CH_3)C_4H_9$[1]	8	3.17 ± 0.33
8	-$CH_2CH(CH_3)C_3H_7$	7	1.58 ± 0.41[3]
9	-$CH_2CH_2CH(CH_3)C_2H_5$	10	1.26 ± 0.18[3]
10	-$CH_2CH_2CH_2CH(CH_3)_2$	4	1.14 ± 0.10[3]
11	-$CH(C_2H_5)C_3H_7$[1]	11	1.67 ± 0.33
12	Natural tetrahydrocannabinol acetate (from charas)[5]	5	14.6 ± 1.05
13	Natural tetrahydrocannabinol by hydrolysis of 12[5]	15	7.8 ± 0.47
14	Tetrahydrocannabinol from cannabidiol[6]	20	7.3 ± 0.89

The methods of preparation of these homologs are essentially those of Adams and Baker,[9] and

(1) For previous paper see Adams, Chen and Loewe, THIS JOURNAL, **67**, 1534 (1945).

(2) Adams, Loewe, Jelinek and Wolff, *ibid.*, **68**, 1971 (1941).

(3) The values for these compounds were calculated in the basis of standard error values. Miller and Tainter, *Proc. Soc. Exper. Biol. and Med.*, **57**, 261 (1944); Loewe, in press.

(4) Values for No. 6 are incommensurable, since this substance has at least five times the duration of action of its congeners in doses of equal intensity of peak effect.

(5) Wollner, Matchett, Levine and Loewe, THIS JOURNAL, **64**, 26 (1942).

(6) Adams, Loewe, Smith and McPhee, *ibid.*, **64**, 694 (1942).

(7) Russell, Todd, Wilkinson, MacDonald and Woolf, *J. Chem. Soc.*, 826 (1941).

(8) For a discussion of the Gayer test and the dog ataxia test used in these studies, see S. Loewe, *J. Pharm. Exper. Therap.*, **84**, 78 (1945), and "The Marihuana Problem in the City of New York," The Jacques Cattell Press, Lancaster, Pa., 1944, p. 175.

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

TABLE II

3,5-DIMETHOXYPHENYL ALKYL KETONES

Alkyl group	Yield, %	B. p. °C.	B. p. Mm.	Empirical formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
—C_7H_{15}-n[2]	60	155	0.5					
—C_8H_{17}-n	77	180	1.0	$C_{17}H_{26}O_3$	73.36	9.42	73.32	9.47
—$CH(CH_3)CH_2CH_2CH_3$	61	150	1.0	$C_{14}H_{20}O_3$	71.16	8.96	71.26	8.89
—$CH_2CH(CH_3)CH_2CH_3$	60	150	1.0	$C_{14}H_{20}O_3$	71.16	8.96	71.42	8.75
—$CH_2CH_2CH(CH_3)_2$	81	135	0.5	$C_{14}H_{20}O_3$	71.16	8.96	71.24	8.60

TABLE III

3,5-DIMETHOXYPHENYL OLEFINS

R = 3,5-Dimethoxyphenyl	Yield, %	B. p. °C.	B. p. Mm.	$n^{20}D$	Empirical formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
R—$C(CH_3)$=$CH(CH_2)_5CH_3$	87	148	1.0	1.5201	$C_{17}H_{26}O_2$	77.81	9.99	77.87	10.22
R—$C(CH_3)$=$CH(CH_2)_6CH_3$	80	175	1.5	1.5143	$C_{18}H_{28}O_2$	78.21	10.21	78.44	10.49

TABLE IV

3,5-DIMETHOXYPHENYL ALKANES

R = 3,5-Dimethoxyphenyl	Yield, %	B. p. °C.	B. p. Mm.	$n^{20}D$	Empirical formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
R—$CH(CH_3)(CH_2)_6CH_3$	73	137	0.5	1.4970	$C_{17}H_{28}O_2$	77.22	10.67	77.17	10.83
R—$CH(CH_3)(CH_2)_7CH_3$	85	160	1.0	1.4898	$C_{18}H_{30}O_2$	77.64	10.86	78.13	11.25
R—$CH_2CH(CH_3)CH_2CH_2CH_3$	72	126	1.0	1.5034	$C_{14}H_{22}O_2$	75.63	9.98	75.68	10.19
R—$CH_2CH_2CH(CH_3)CH_2CH_3$	78	132	1.0	1.5043	$C_{14}H_{22}O_2$	75.63	9.98	75.72	10.12
R—$CH_2CH_2CH_2CH(CH_3)_2$	78	106	0.5	1.4993	$C_{14}H_{22}O_2$	75.63	9.98	75.98	10.10

TABLE V

3,5-DIHYDROXYPHENYL ALKANES (5-ALKYLRESORCINOLS)

R = 3,5-Dihydroxyphenyl	Yield, %	B. p. °C.	B. p. Mm.	Empirical formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
R—$CH(CH_3)(CH_2)_6CH_3$	78	160	0.5	$C_{15}H_{24}O_2$	76.22	10.24	76.04	10.31
R—$CH(CH_3)(CH_2)_7CH_3$	74	138	1.0	$C_{16}H_{26}O_2$	76.75	10.47	76.62	10.64
R—$CH_2CH(CH_3)CH_2CH_2CH_3$	84	159	1.0	$C_{12}H_{18}O_2$	74.19	9.34	74.19	9.43
R—$CH_2C_2CH(CH_3)CH_2CH_3$	72	159	1.0	$C_{12}H_{18}O_2$	74.19	9.34	74.43	9.55
R—$CH_2CH_2CH_2CH(CH_3)_2$	74	125	0.5	$C_{12}H_{18}O_2$	74.19	9.34	74.05	9.52

TABLE VI

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

Alkyl group	Yield, %	M. p. (cor.), °C.	Solvent for recrystallizing	Empirical formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
—$CH(CH_3)(CH_2)_6CH_3$	38[10]	138	Ethanol–water	$C_{23}H_{32}O_3$	77.49	9.05	77.18	9.24
—$CH(CH_3)(CH_2)_7CH_3$	41[10]	125	Ethanol–water	$C_{24}H_{34}O_3$	77.80	9.25	77.53	9.29
—$CH_2CH(CH_3)CH_2CH_2CH_3$	60	194	Ethanol–water	$C_{20}H_{26}O_3$	76.40	8.34	76.28	8.55
—$CH_2CH_2CH(CH_3)CH_2CH_3$	72	157	Ethanol–water	$C_{20}H_{26}O_3$	76.40	8.34	76.24	8.44
—$CH_2CH_2CH_2CH(CH_3)_2$	73[11]	176.5	Ethanol–water	$C_{20}H_{26}O_3$	76.40	8.34	76.55	8.43

TABLE VII

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

Alkyl groups	Yield, %	B. p. °C.	B. p. Mm.	Empirical formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
—$CH(CH_3)(CH_2)_6CH_3$	59	220	1.0	$C_{25}H_{38}O_2$	81.03	10.34	80.84	10.35
—$CH(CH_3)(CH_2)_7CH_3$	66	183	0.001	$C_{26}H_{40}O_2$	81.19	10.48	80.98	10.37
—$CH_2CH(CH_3)CH_2CH_2CH_3$	72	165	.01	$C_{22}H_{32}O_2$	80.43	9.82	80.37	9.99
—$CH_2CH_2CH(CH_3)CH_2CH_3$	61	180	.1	$C_{22}H_{32}O_2$	80.43	9.82	80.49	10.02
—$CH_2CH_2CH_2CH(CH_3)_2$	72[11]	165	.02	$C_{22}H_{32}O_2$	80.43	9.82	80.44	9.94

(10) These pyrones were prepared by the method of Adams and Baker.[8] The yield would unquestionably have been better if the procedure of Adams, Chen and Loewe had been followed as in the synthesis of the other pyrones.

(11) This pyrone was previously prepared[7] and reported to have a melting point of 177–180°, and the corresponding pyran b. p. 203° (1 mm.) (bath temperature).

Adams, Chen and Loewe.[1] The method of reducing the 3,5-dimethoxyphenyl alkyl ketones to the corresponding methylene compounds by hydrogenation over copper chromite catalyst at 250° and 5000 pounds pressure was found prefer-

able in many respects to the Wolff–Kishner procedure.

Experimental

All compounds prepared are described in Tables II–VII.

3,5-Dimethoxyphenyl Alkyl Ketones.—These ketones were prepared in the usual way[12] in ethyl ether without the addition of dibutyl ether.

3,5-Dimethoxyphenyl Olefins.—The olefins were prepared by the procedure of Adams, Chen and Loewe.[1]

3,5-Dimethoxyphenyl Alkanes.—The two 1′-methylalkyl derivatives were obtained by catalytic reduction of the ketones at high temperature and pressure in the presence of copper chromite as a catalyst. A typical conversion of a ketone to the correponding methylene compound is the preparation of $RCH_2CH_2CH(CH_3)CH_2CH_3$, where R = 3,5-dimethoxyphenyl. A mixture of 18.5 g. of $RCOCH_2CH(CH_3)CH_2CH_3$ and 3 g. of copper chromite catalyst was heated at 260° under an initial pressure of hydrogen (before heating was begun) of 3100 pounds. The hydrogen uptake reached the theoretical in seven hours. After cooling the bomb was opened, and the product rinsed out with ethanol, filtered and distilled. The yield of product was 13.5 g. (78%).

5-Alkylresorcinols.—The cleavage of the ethers was carried out as previously described.[1]

1-Hydroxy-3-alkyl-9-methyl-7,8,9,10-tetrahydro-6-dibenzopyrones.—The condensation of the resorcinols with 5-methyl-2-carbethoxycyclohexanone was effected according to the method of Adams, Chen and Loewe.[1]

1-Hydroxy-3-alkyl-6,6,9-trimethyl-7,8,9,10-tetrahydro-6-dibenzopyrans.—The conversion of the pyrones to pyrans utilized the conventional treatment with 12 moles of methylmagnesium iodide.[9]

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

Summary

1. Two new tetrahydrocannabinol homologs with the groups —$CH(CH_3)(CH_2)_6CH_3$ and —$CH(CH_3)(CH_2)_7CH_3$ in the 3- position have been synthesized.

2. The activity of the 1′-methyloctyl homolog is 32. This is the most potent substance ever tested, having an activity over four times that of natural tetrahydrocannabinol. The 1′-methylnonyl, presumably because of decreased solubility, has a potency of only 2.08 but the duration of peak effect is five times that of its congeners.

3. Three isomeric methylpentyl groups have also been introduced into the 3- position, namely, —$CH_2CH(CH_3)CH_2CH_2CH_3$, —$CH_2CH_2CH(CH_3)CH_2CH_3$ and —$CH_2CH_2CH_2CH(CH_3)_2$.

4. The activities of these isomers varies inversely as the distance of the methyl group from the ring.

URBANA, ILLINOIS RECEIVED JUNE 7, 1947

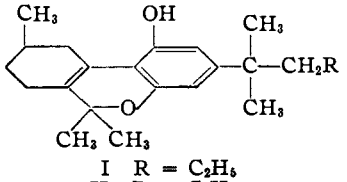
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS, AND THE SCHOOL OF MEDICINE UNIVERSITY OF UTAH]

Tetrahydrocannabinol Homologs with Doubly Branched Alkyl Groups in the 3-Position. XVIII[1]

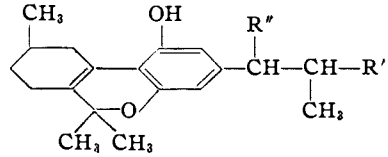
BY ROGER ADAMS, SCOTT MACKENZIE, JR., AND S. LOEWE

In synthetic tetrahydrocannabinols with *n*-alkyl groups or alkyl groups with a methyl substituent next to the ring in the 3-position the marihuana potency reaches a maximum of peak activity as the chain is lengthened. The significant increase in activity resulting from the introduction of a methyl group in the 1′-position of the 3-alkyl group stimulated a study of the activity of homologs having more highly branched side-chains in the 3-position.

Five pyrans have now been prepared, two of which, (I) and (II), have two methyl groups on the 1′-carbon of the side-chains in the 3-position. The other three, (III), (IV) and (V), have two alkyl groups, one on the 1′-carbon and the other on the 2′-carbon of the side-chain.



I R = C_2H_5
II R = C_5H_{11}



III R′ = C_2H_5; R″ = CH_3
IV R′ = CH_3; R″ = C_2H_5
V R′ = C_5H_{11}; R″ = CH_3

All products were tested by a procedure described previously. Activities of these compounds and certain isomers are listed for comparison in Table I.

Examination of Table I reveals the extreme variation in potency induced by changes in the structure of the 3-alkyl substituent. Branching of the side-chains not only increases activity but also requires larger groups to attain the maximum of peak effect (compare nos. 3 and 8). It is not surprising that the compound having the 1′,1′-dimethylbutyl side-chain in the 3-position is the most potent of the hexyl series of compounds. The substances with the 1′,1-dimethylalkyl substitution have activities comparable to the corresponding monomethyl derivatives, and the activity is much higher in the compound with a straight chain of seven carbon atoms than with

(1) For previous paper see Adams, Aycock and Loewe, THIS JOURNAL, 70, 662 (1948).