brecht for the preparation of acetylated α- and β-phenylglycosides has been improved.

2. A method has been described for the rearrangement of tetraacetyl-β-phenylglucoside to tetraacetyl-α-phenylglucoside.

3. A method has been described for the transformation of tetraacetyl-α-methylglucoside and other acetylated glycosides to the corresponding acetylated phenylglycosides.

4. α-Phenyl-D-xyloside, triacetyl-α-phenyl-D-xyloside and α-*o*-nitrophenyl-D-glucoside have been described. New data are reported for a number of other phenylglycosides.

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

Tetrahydrocannabinol Homologs and Analogs with Marihuana Activity. XIII[1]

BY ROGER ADAMS, S. LOEWE, C. M. SMITH AND W. D. MCPHEE

The series of homologs of tetrahydrocannabinol (I), in which the 3-*n*-amyl group is replaced by other groups, has been found to exhibit a maximum activity in the *n*-hexyl compound.[2] The corresponding hexahydrocannabinol and its homologs have been prepared and the marihuana potencies determined. This series also exhibits a potency maximum in the 3-*n*-hexyl compound and with the exception of the *n*-hexyl and the *n*-butyl derivatives the potencies are all lower than those of the corresponding tetrahydro compounds. The potencies of the homologs of tetrahydrocannabinol and the activities of other products are shown in Table I to allow comparison. The high potencies of the optically active tetrahydrocannabinols obtained by isomerization of cannabidiol contrast strikingly with the very low potencies of crude hemp extracts.

TABLE I

BIOASSAY OF HOMOLOGS OF TETRAHYDROCANNABINOL AND OF HEXAHYDROCANNABINOL

3-*n*-Alkyl group Compound I	Potency: Tetrahydro	Potency: Hexahydro
Methyl	0.16 ± 0.03	
Propyl	.40 ± .30	0.26 ± 0.04
Butyl	.37 ± .12	.37 ± .06
Amyl	1.00 (standard)	.51 ± .08
Hexyl	1.82 ± .40	1.86 ± .37
Heptyl	1.05 ± .15	0.83 ± .13
Octyl	0.66 ± .13	.24 ± .06

Tetrahydrocannabinol $[\alpha]^{27}D$	Parke, Davis and Company Fluid Extract	0.060
−265° 7.3 ± 0.89	American Fluid Extracts	
−260° 7.8 ± .78	thirty to forty different	
−240° 7.6 ± 1.1	samples varied in potency	.003–0.130
−165° 9.3 ± 2.9		
−160° 8.23 ± 2.17		
−126° 6.5 ± 0.65	Majority varied	.019– .052
Hexahydrocannabinol	Purified red oil	1.24
−70° 3.0 ± 0.43	Highly purified red oil (Matchett)	4.33

Todd and co-workers[2b] have just published a description of the synthesis and physiological action by the Gayer test of a series of homologs of tetrahydrocannabinol (I) with the amyl group replaced by various alkyl groups. Many of this series had been synthesized previously by us and the marihuana action determined by the dog-ataxia test.[2a] The difference between the ratio of our tests and those of Todd is large. In this connection reference may be made to the extensive results of Loewe described briefly in the Harvey Lecture (February 19, 1942). He has demonstrated that even when applying the "Bioassay by Approximation" procedure with the Gayer test, the intra-individual and inter-individual variations in sensitivity of rabbits is enormous, so that the values of potency by this method are not suitable for anything but qualitative purposes. The Gayer potencies do not parallel the dog-ataxia potencies of the same preparations. On the other hand, the relative potencies of the various products as determined by the dog-ataxia tests parallel to a surprising degree the potencies observed in human subjects. The relative doses of several of the compounds eliciting a similar action in individual dogs elicited the equivalent degree of response in humans. The equated doses administered to the same individual human gave the same intensity of effect, and this result was observed in a large number of subjects.

An attempt has been made in this Laboratory[3] and by Ghosh, Todd and Wright[4] to synthesize an optically active isomer of the tetrahydrocannabinol from cannabidiol by condensing pulegone and olivetol. An optically active resin closely resembling the desired tetrahydrocannabinol in physical properties was obtained. The product obviously was not pure since its absorption spectrum exhibited two peaks in contrast to the one peak of the tetrahydrocannabinol from cannabidiol. The height of the identical peak was only six-tenths that for the pure compound. The initial measurement of the potency of this material made with a few dogs was reported as 1.04 ± 0.37, but further investigation has resulted in a value of 0.58 ± 0.12. It is interesting to note that the ratio of the potencies of the tetrahydrocannabinols made by the two methods parallels the ratio of the heights of the comparable absorption peaks.

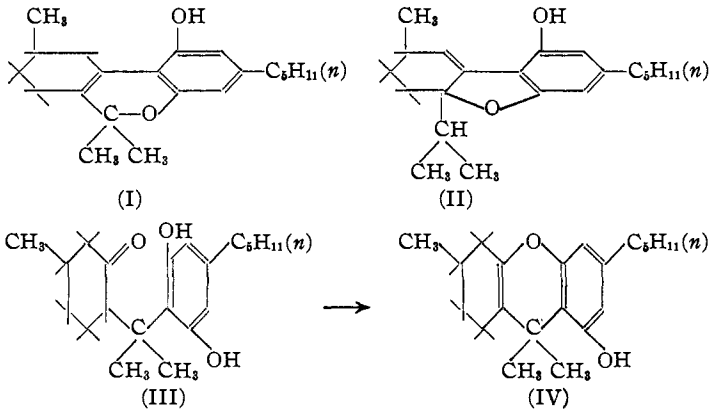
A tentative mechanism for the formation of a tetrahydrocannabinol structure (I) has been ad-

(1) For previous paper see Adams, Cain, McPhee and Wearn, THIS JOURNAL, **63**, 2209 (1941).

(2) (a) Adams, Loewe, Jelinek and Wolff, *ibid.*, **63**, 1971 (1941); (b) see also Russell, Todd, Wilkinson, MacDonald and Woolfe, *J. Chem. Soc.*, 826 (1941).

(3) Adams, Smith and Loewe, THIS JOURNAL, **63**, 1973 (1941).

(4) Ghosh, Todd and Wright, *J. Chem. Soc.*, 137 (1941).



vanced,[3] and it has been pointed out that the presence of a compound with a structure analogous to I but with the pyran ring linked between the hydroxyl and *n*-amyl groups is entirely possible. Also, the formation of a tetrahydrodibenzofuran of type shown in structure II could not be ruled out.

There exists an alternative mode of reaction between pulegone and olivetol which involves the addition of the hydrogen atom between the hydroxyls in olivetol to the double bond in the pulegone, with the formation of an intermediate of type III. By enolization and dehydration a tetrahydroxanthane (IV) would result. An analogous addition has been shown by Robinson and Wallker[5] to be the exclusive reaction in the case of the initial condensation of resorcinol with anisylideneacetophenone and with benzylidene-*p*-methoxyacetophenone in the presence of hydrogen chloride and chloranil.

In the case at hand, however, no decision can as yet be made between the two structural possibilities. It might be thought that the peak due to the impurity would be much lower than that due to tetrahydrocannabinol if this impurity had the tetrahydroxanthane structure, but this may be masked by the strong absorption of the tetrahydrocannabinol in that region. At any rate, it is known definitely that part of the material is tetrahydrocannabinol, since Ghosh, Todd and Wright[4] have obtained cannabinol-*p*-nitrobenzoate by dehydrogenation of this material with palladium charcoal followed by treatment with *p*-nitrobenzoyl chloride. The fact that 96% of the theoretical hydrogen is evolved indicates that the predominant substances present have a tetrahydrobenzene ring in their molecules. The tetrahydrodibenzofuran structure (II) has a tertiary carbon atom at the point of attachment of the isopropyl group and the oxygen bridge and, therefore, a rearrangement and dehydrogenation would be necessary in order to obtain cannabinol.

The fact that the pulegone–olivetol condensation product possesses considerable marihuana activity is of interest quite apart from the objection that this material is not pure and that its composition may vary widely depending on the conditions and reagents used in the condensation. Accordingly, the series of pulegone–5-*n*-alkylresorcinol condensation products, *n*-propyl through *n*-nonyl, have been prepared under the same conditions used for the pulegone–olivetol condensation.[3] The potencies of these products show an interesting displacement of maximum potency to the *n*-octylresorcinol member and at the same time a broadening of the region of high potencies to include the *n*-hexyl, *n*-heptyl, *n*-octyl members. Also the *n*-heptyl and *n*-octyl products exceed in potency the corresponding synthetic tetrahydrocannabinol homologs; in the case of the *n*-octyl product this increment amounts to one hundred per cent. Whether these unexpected results have been influenced by the optical activity or by the presence of varying amounts of impurities in the individual members of the series has not been determined.

By reduction of the pulegone–5-*n*-alkylresorcinol products, *n*-propyl through *n*-octyl inclusive, a series of substances was obtained whose potencies were uniformly lower than those of the parent substances. The broad region of maximum potency was maintained but was displaced to include the reduced *n*-amyl, *n*-hexyl, and *n*-heptyl products. The potency of the reduced *n*-heptyl product was the same as that of the corresponding homolog of hexahydrocannabinol.

The potencies of these various pulegone condensation products and derivatives are in Table II.

TABLE II

PULEGONE CONDENSATION PRODUCTS

5-*n*-Alkylresorcinol	Pulegone–5-*n*-alkylresorcinol condensation product	Reduced condensation product
Propyl	0.24	0.20
Butyl	.25 ± 0.10	.15
Amyl	.58 ± .12	.64 ± 0.10
Hexyl	1.22 ± .12	.78 ± .22
Heptyl	1.15 ± .15	.83 ± 1.7
Octyl	1.37 ± .25	.25
Nonyl	0.20	

(5) Robinson and Wallker, *J. Chem. Soc.*, 1435 (1934).

TABLE III

5-*n*-ALKYLRESORCINOL–PULEGONE CONDENSATION PRODUCTS

n-Alkyl	B. p. °C.	Mm.	α_D	$n^{20}D$	Yield, %	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
Propyl	160–163	0.3	+94 to +78	1.5523–1.5569[a]	61	$C_{19}H_{26}O_2$	79.66	9.15	79.45	9.26
Butyl	147–150	0.08	+71 to +80	1.5556–1.5568	57	$C_{20}H_{28}O_2$	79.96	9.40	80.30	9.53
Amyl	190–200	2.0	+72 to +77	1.5509–1.5529	43	$C_{21}H_{30}O_2$	80.20	9.62	80.34	9.74
Hexyl	180–186	0.3	+61 to +79	1.5419–1.5464	65	$C_{22}H_{32}O_2$	80.41	9.82	80.33	9.87
Heptyl	184–186	.15	+54 to +79	1.5423–1.5446	57	$C_{23}H_{34}O_2$	80.70	10.03	80.55	10.07
Octyl	177–182	.04	+50 to +80	1.5335–1.5395	52	$C_{24}H_{36}O_2$	80.84	10.18	80.94	10.37
Nonyl	190–200	.01	+55 to +68	1.5303–1.5346	30	$C_{25}H_{38}O_2$	81.02	10.34	80.83	10.26

[a] The temperature used in this instance was 34°.

TABLE IV

REDUCED 5-*n*-ALKYLRESORCINOL–PULEGONE CONDENSATION PRODUCTS

n-Alkyl Group	B. p. °C.	Mm.	α_D	$n^{20}D$	Yield, %	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
Propyl[b]	161–165	0.3	+14 to +24	1.5069–1.5408	81	$C_{19}H_{28}O_2$	79.11	9.79	78.57	9.92
Butyl[b]	173–176	.06	+16 to +18	1.5300–1.5392	61	$C_{20}H_{30}O_2$	79.42	10.00	79.07	10.25
Amyl[a]	179–183	.5	+ 2 to + 9	1.5374–1.5409	93	$C_{21}H_{32}O_2$	79.69	10.19	79.70	10.31
Hexyl[b]	183–186	.3	+ 6 to + 9	1.5192–1.5373	89	$C_{22}H_{34}O_2$	79.93	10.38	80.14	10.30
Heptyl[b]	187–193	.3	+ 7 to +10	1.5188–1.5304	82	$C_{23}H_{36}O_2$	80.17	10.54	80.14	10.78
Octyl[b]	206–210	.1	+ 7 to + 8	1.5120–1.5260	97	$C_{24}H_{38}O_2$	80.39	10.68	80.29	10.91

[a] Reduction with platinum oxide, low pressure. [b] Reduction with Raney nickel, high pressure.

TABLE V

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

n-Alkyl Group	B. p. °C.	Mm.	$n^{20}D$	Yield, %	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
Propyl[b]	158–160	0.3	1.5429–1.5444	80	$C_{19}H_{28}O_2$	79.11	9.79	78.78	9.85
								78.71	9.68
Butyl[a]	165–167	0.5	1.5263–1.5412	88	$C_{20}H_{30}O_2$	79.42	10.00	79.56	10.21
Amyl[a]	212	2	1.5349	80	$C_{21}H_{32}O_2$	79.69	10.19	79.75	10.08
Hexyl[a]	200–209	3.0	1.5319–1.5372	84	$C_{22}H_{34}O_2$	79.93	10.38	80.19	10.35
Heptyl[b]	186–187	0.3	1.5214–1.5299	82	$C_{23}H_{36}O_2$	80.17	10.54	80.15	10.88
Octyl[b]	187–197	0.2	1.5196–1.5300	80	$C_{24}H_{38}O_2$	80.39	10.68	80.48	10.90

[a] Reduction with platinum oxide, low pressure. [b] Reduction with Raney nickel, high pressure.

Experimental

The following compounds have been prepared by the general procedure of Suter and Weston.[6]

3,5-Dimethoxyphenyl-*n*-octyl Ketone.—This was prepared by the action of excess *n*-octylmagnesium bromide on 3,5-dimethoxybenzamide, 76% yield, b. p. 150–156° (0.03 mm.) (bath 185–191°), m. p. 35.5–36°.

Anal. Calcd. for $C_{17}H_{26}O_3$: C, 73.33; H, 9.42. Found: C, 73.39; H, 9.37.

3,5-Dimethoxy-*n*-nonylbenzene.—3,5-Dimethoxyphenyl-*n*-octyl ketone was converted to 3,5-dimethoxy-*n*-nonyl benzene by the Wolff–Kishner reduction in 85% yield; b. p. 138–143° (0.1 mm.) (bath 163–165°), $n^{20}D$ 1.4968.

Anal. Calcd. for $C_{17}H_{28}O_2$: C, 77.21; H, 10.68. Found: C, 77.55; H, 10.68.

5-*n*-Nonylresorcinol.—Demethylation of 3,5-dimethoxy-*n*-nonylbenzene with hydrobromic acid and acetic acid gave 5-*n*-nonylresorcinol in 92.5% yield; colorless waxy leaflets from methanol, m. p. 64–65°. Vacuum sublimation twice repeated raised the melting point to 72°.

Anal. Calcd. for $C_{15}H_{24}O_2$: C, 76.21; H, 10.24. Found: C, 76.29; H, 10.61.

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

The pulegone–5-*n*-alkylresorcinol condensations were run in exactly the same manner, and with the same molar ratios of reactants and solvent as was the pulegone–olivetol condensation,[3] namely, equimolar quantities of pulegone and 5-*n*-alkylresorcinol and 0.3 mole of phosphorus oxychloride in dry benzene (100 cc. per 0.1 mole of pulegone), were refluxed for four hours. The reaction mixture was poured into excess saturated aqueous sodium bicarbonate and unchanged alkylresorcinol was removed by extraction with dilute aqueous sodium hydroxide. The washed and dried benzene solution was then evaporated and the residue distilled under reduced pressure. Several fractions were collected and the index of refraction and rotation determined for each. The variability of the constants of the individual fractions is indicated in the table (III). The center fraction was selected for analysis.

The homologs of tetrahydrocannabinol were prepared according to Adams, Loewe, Jelinek and Wolff.[2]

The reduction of the pulegone-5-*n*-alkylresorcinol products and the tetrahydrocannabinol homologs was carried out by one of two methods: (a) by means of platinum oxide catalyst in glacial acetic acid at room temperature and ordinary pressure, or (b) with Raney nickel in absolute ethanol at 75–100° and 35–50 atmospheres. The ma-

terials were reduced by method (a) if possible, but most of the products needed the more drastic conditions of method (b). The only substance in which hydrogenation of the aromatic ring interfered seriously was the pulegone–5-*n*-propylresorcinol product, the fractions of which varied from an oily consistency to a very tacky resin. Each product was fractionated and the constants determined on each fraction. The variability of the constants of the fractions is shown in the tables (IV and V). The center fraction was selected for analysis.

Summary

1. The series of homologs of hexahydrocannabinol of 1-hydroxy-3-*n*-amyl-6,6,9-trimethyl-(7a, 7, 8, 9, 10, 10a)-hexahydro-6-dibenzopyran have been prepared where the 3-*n*-amyl group has been replaced by other *n*-alkyl groups, *n*-propyl through *n*-octyl, inclusive.

The potencies of these compounds, with the exception of the *n*-butyl and *n*-hexyl homologs, are lower than those of the corresponding tetrahydrocannabinol homologs.

2. The series of pulegone–5-*n*-alkylresorcinol condensation products, *n*-propylresorcinol through *n*-nonylresorcinol, have been prepared and their marihuana potencies determined. A revised value for the potency of the previously reported pulegone–olivetol product is given. Maximum potency occurs in the *n*-octyl condensation product in this series, the region of high potency is broadened to include the *n*-hexyl, *n*-heptyl, and *n*-octyl members, and in the case of these latter two members their potencies exceed those of the corresponding tetrahydrocannabinol analogs made in an unequivocal manner.

3. The series of dihydro reduction products of the members of series 2, with the exception of the *n*-nonyl derivative, have been prepared and their marihuana potencies determined. With the exception of the *n*-amyl member their potencies are all significantly lower than the corresponding members of series 2.

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF STANFORD UNIVERSITY]

Halogen Addition to Ethylene Derivatives. I. Bromine Additions in the Presence of Bromide Ions

BY KENZIE NOZAKI[1] AND RICHARD A. OGG, JR.

Many workers have noticed that the addition reactions of halogens to ethylene derivatives may be greatly affected by the addition of halide ions to the reaction mixtures. Williams[2] and more recently Robertson and co-workers[3] have reported that hydrogen bromide catalyzed the addition of bromine to several unsaturated compounds. However, others[4] have observed that the addition of halide ions to reaction mixtures caused a retardation in the rate of halogen addition. A study of the existing data showed that all of the workers, whether reporting catalysis or inhibition, found that in the presence of a considerable concentration of halide ions, the reactions were approximately of first order with respect to total halogen concentration and of first order with respect to the ethylene derivative concentration. Thus it appeared probable that all of the addition reactions followed a similar course when the halide ion concentration was high. The purpose of the present investigation was to make a study of several such reactions in order to obtain information concerning the reaction mechanism. Because of their convenience for kinetic measurements, bromine additions to several ethylene derivatives were studied, using glacial acetic acid as the solvent.

The Equilibrium Constant for the Dissociation of Potassium Tribromide.—Before empirical rate expressions could be formulated for the reactions under investigation, it was necessary to determine the equilibrium constant for the dissociation of tribromide ion into bromine and bromide ion. This was determined by observing the increase in solubility of potassium bromide in glacial acetic acid accompanying the addition of bromine to solvent. The increase was assumed to be due to tribromide formation. The studies were carried out in solutions whose ionic strength was made up

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(2) Williams and James, *J. Chem. Soc.*, 343 (1928).

(3) Robertson, Clare, McNaught and Paul, *ibid.*, 335 (1937).

(4) (a) Bartlett and Tarbell, THIS JOURNAL, **58**, 466 (1936); (b) James and Sudborough, *J. Chem. Soc.*, 1037 (1907); (c) Berthoud and Mosset, *J. Phys. Chem.*, **38**, 271 (1936).