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

New Analogs of Tetrahydrocannabinol. XIX

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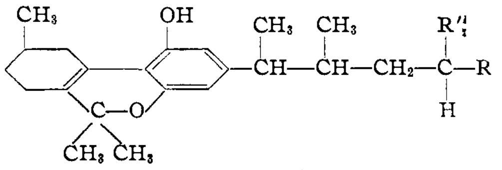
Previous workers[1] have shown that the marihuana activity of "conjugated tetrahydrocannabinol" analogs in which other alkyl groups replace the *n*-amyl group in the 3-position and the alicyclic double bond is conjugated with those of the benzene ring, varies markedly with the structure of the alkyl group, increasing with the number of methyl groups placed on an *n*-alkyl side-chain and decreasing as a methyl group is placed further from the ring. Within any series differing only in the length of an *n*-alkyl group, the activity reaches a maximum value and again declines, although results reported here and previously indicate that the compound with one additional methylene group may have an extended period of high activity. It was thought desirable to determine whether the extremely active 1′,2′-dimethylheptyl homolog represented the most active member of the 1′,2′-dimethylalkyl series in order to aid in further generalizations concerning maxima of activity, and to attempt the preparation of other highly-branched homologs.

Three new pyrans have been prepared, the 1′,2′-dimethylhexyl (I), the 1′,2′-dimethyloctyl (II), and the 1′,2′,4′-trimethylhexyl (III) compounds.



I, R = C_2H_5, R′ = H
II, R = C_4H_9, R′ = H
III, R = C_2H_5, R′ = CH_3

The data in Table I indicate that where the maximum of a branched chain series has been determined, it occurs at a total of nine carbons in the side-chain, as compared to six for the 3-*n*-alkyl series.

The pyrans (I) and (II) were made by the general methods described by previous workers, with relatively slight modification. A large excess of the secondary Grignard reagent was used to prepare the 3,5-dimethoxyphenyl alkyl ketones,[2,3] which were best purified by the use of Girard's reagent—T,[4] and subsequent distillation. The carbinols obtained by treatment of the ketones with methylmagnesium iodide, were best dehydrated by distillation with a catalytic amount of *p*-toluenesulfonic acid. Reduction of the alkenes with copper chromite and hydrogen was slow and the catalyst often seemed to be poisoned after some time. The use of Raney nickel catalyst is extremely effective in promoting reduction, but samples prepared using this catalyst are reported[5] to differ in some properties from those prepared by copper chromite reduction. It was possible to determine the extent of reduction readily by the ultraviolet spectra, the unsaturated compounds having a characteristic high absorption in the 247 mμ region (Fig. 1). The demethylation and formation of the pyran were accomplished as previously described.

TABLE I
PHARMACOLOGICAL ACTIVITY OF TETRAHYDROCANNABINOL HOMOLOGS

	3-Substituent	No. of expts.	Potency[a]
1	$-C_5H_{11}$-*n*	20	1.00 standard
2	$-C_6H_{13}$-*n*	7	1.82 ± 0.18
3	$-C_7H_{15}$-*n*	10	1.05 ± 0.15
4	$-CH(CH_3)C_6H_{13}$	10	16.4 ± 3.67
5	$-CH(CH_3)C_7H_{15}$	19	32.6 ± 3.02
6	$-CH(CH_3)C_8H_{17}$	7	2.08 ± 1.49[b]
7	$-CH(CH_3)CH(CH_3)C_4H_9$	6	39 ± 8[c]
8	$-CH(CH_3)CH(CH_3)C_5H_{11}$	18	512 ± 72.6
9	$-CH(CH_3)CH(CH_3)C_6H_{13}$	5	19 ± 3.5[b,c]
10	$-CH(CH_3)CH(CH_3)CH_2CH(CH_3)C_2H_5$	9	36 ± 9.5
11	Natural tetrahydrocannabinol acetate (from charas)	5	14.6[d]

[a] See preceding papers in this series. [b] Values not comparable, as duration of effect much longer for doses of equal intensity of peak effect. [c] Preliminary values of activity. [d] Wollner, Matchett, Levine and Loewe, THIS JOURNAL, **64**, 26 (1942).

The route to the 1′,2′,4′-trimethylhexyl analog (III) involved the reactions outlined below

$$ArCOOH \xrightarrow{LiAlH_4} ArCH_2OH \xrightarrow[2.\ NaCN]{1.\ SOCl_2}$$

IV

$$ArCH_2CN \xrightarrow[NaOC_2H_5]{(C_2H_5O)_2CO} ArCH(COOC_2H_5)CN \xrightarrow[NaOR]{CH_3I}$$

V VI

$$ArC(CH_3)(COOC_2H_5)CN \xrightarrow{KOH}$$

VII

$$ArCH(CH_3)CN \xrightarrow{R'MgBr} ArCH(CH_3)COR' \xrightarrow{CH_3MgI}$$

VIII IX

$$ArCH(CH_3)C(OH)CH_3)R' \xrightarrow[2.\ H_2/Ni]{1.\ Dehyd.}$$

X

$$ArCH(CH_3)CH(CH_3)R'$$

Ar = 3,5-dimethoxyphenyl-
R = C_2H_5–, $(CH_3)_2CH$–
R′ = $C_2H_5CH(CH_3)CH_2$–

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(1) For previous paper, see Adams, MacKenzie and Loewe, THIS JOURNAL, **70**, 664 (1948).

(2) Adams, Aycock and Loewe, *ibid.*, **70**, 662 (1948).

(3) Suter and Weston, *ibid.*, **61**, 232 (1939).

(4) Girard and Sandulesco, *Helv. Chim. Acta*, **19**, 1095 (1936).

(5) Karl M. Beck, private communication.

Lithium aluminum hydride reduction[6] of the rather ether-insoluble 3,5-dimethoxybenzoic acid to the benzyl alcohol was accomplished in yields consistently over 90% by a slight modification of the procedure recommended for ether-soluble acids. The alternative extraction procedure offers no advantage in this case. The alcohol (IV) was converted to the nitrile as described previously,[1] in general without purification of the intermediate benzyl chloride. The carbethoxylation[7] of the arylacetonitrile and subsequent methylation and saponification were thought to be a better route to (VIII) than the use of sodium amide and methyl iodide[8] which may cause dimethylation, and requires chemical purification to remove unalkylated starting material.[9] Methylation of ethyl 3,5-dimethoxyphenylcyanoacetate (VI) by means of sodium ethoxide and methyl iodide was accompanied by extensive decarbethoxylation. It is obvious that (VI) will exist largely as its conjugate base in the basic solution employed for the methylation, and so would be protected against attack by an alkoxide anion, as compared to α-carbethoxy-3,5-dimethoxyhydratroponitrile (VII). In agreement with this, the lower-boiling fraction of the product of methylation corresponded in analysis to 3,5-dimethoxyhydratroponitrile. A search of the literature revealed other instances of similar behavior, but in general the compounds studied were vinylcyanoacetic esters, in which the decarbethoxylation was accompanied by a shift of the double bond to a conjugated position.[10] It is advisable to use sodium isopropoxide as the catalyst if the cyanoacetic ester (VI) is desired.[11]

The carbinol (X) was dehydrated by the Tschugaeff method,[12] to preclude the possibility of rearrangement by the alternative acid-catalyzed dehydration. The resulting alkene was reduced to nearly pure alkane (XI) by two treatments with Raney nickel and hydrogen, and was converted to the pyrone and pyran in the usual way.

Attempts to prepare a 1′,2′,3′-trimethylalkyl "conjugated tetrahydrocannabinol" have as yet been uniformly unsuccessful. An attempt to use the method by which compounds I and II were prepared was frustrated by the low yield obtained in the preparation of the Grignard reagent from 3-methyl-2-bromoöctane.[13] Treatment of 2-pentanylmagnesium bromide with α-3,5-dimethoxyphenethyl methyl ketone (IX, R′ = CH_3) gave a mixture of alcohols in which the reduction product of the starting ketone seemed to predominate.

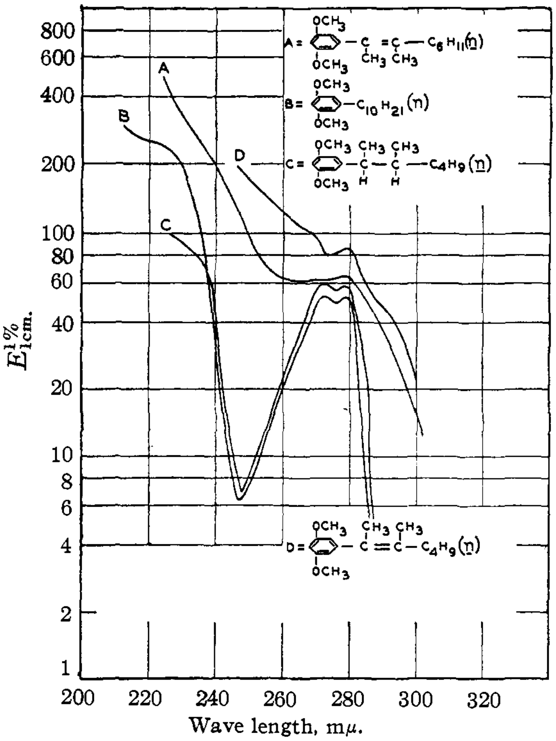

Fig. 1.—Absorption spectra in 95% ethanol of some resorcinol dimethyl ethers.

The reaction sequence below was used to prepare compound XV, where Ar = 3,5-dimethoxyphenyl.

$$\underset{\text{XII}}{\text{ArCOCH}_3} + \text{BrCH(CH}_3\text{)COOC}_2\text{H}_5 \xrightarrow{\text{Zn}}$$

$$\underset{\text{XIII}}{\text{ArC(OH)(CH}_3\text{)CH(CH}_3\text{)COOC}_2\text{H}_5} \xrightarrow{\text{HCl}}$$

$$\underset{\text{XIV}}{\text{ArC(CH}_3\text{)=C(CH}_3\text{)COOC}_2\text{H}_5} \xrightarrow[\substack{2.\ \text{NaOH (aq.)}\\ 3.\ \text{Na-Hg}}]{1.\ \text{H}_2\text{/Pt}}$$

$$\underset{\text{XV}}{\text{ArCH(CH}_3\text{)CH(CH}_3\text{)COOH}}$$

It was hoped that the acid (XV) could be converted to the acid chloride, which might give the propyl ketone upon treatment with propylcadmium. 3,5-Dimethoxyacetophenone (XII) was prepared by treating 3,5-dimethoxybenzamide with methylmagnesium iodide. The carbinol (XIII) could not be "dehydroxylated" with a palladium-on-charcoal catalyst under conditions which caused benzyl alcohol to be reduced to toluene. Dehydration yielded the ester (XIV) which, however, absorbed only slightly over 50% of the calculated quantity of hydrogen upon reduction with platinum oxide. and hydrogen at a pressure of three atmospheres. Tests revealed that the catalyst was not poisoned.[14] A small amount of

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[6] Nystrom and Brown, THIS JOURNAL, **69**, 2548 (1948).

[7] Wallingford, Jones and Homeyer, *ibid.*, **64**, 576 (1942).

[8] Bodroux and Taboury, *Compt. rend.*, **150**, 531 (1910).

[9] (a) V. Meyer, *Ann.*, **250**, 118 (1889); (b) Wideqvist, *Svensk. Kem. Tid.*, **55**, 125 (1943); (c) Crawford, THIS JOURNAL, **56**, 139 (1934).

[10] Osman and Cope, THIS JOURNAL, **66**, 881 (1944); Ingold and Thorpe, *J. Chem. Soc.*, **115**, 143 (1919).

[11] Cope and Hancock, THIS JOURNAL, **60**, 2903 (1938).

[12] Tschugaeff, *Ber.*, **32**, 3332 (1889).

[13] A yield of 18% was found by titration which might have allowed otherwise unnoticeably small amounts of impurity to exert a large effect on the product.

[14] Riegel, *et al.*, THIS JOURNAL, **70**, 1073 (1948), describes similar difficulties in a synthesis of their acid (II).

TABLE II

5-SUBSTITUTED RESORCINOL DIMETHYL ETHERS

R = 3,5-Dimethoxyphenyl	Yield, %	B. p.[a] °C.	Mm.	$n^{20}D$	Empirical formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
$RCOCH(CH_3)C_4H_9$	62	124	0.4	1.5177	$C_{15}H_{22}O_3$	71.97	8.86	72.27	9.04
$RCOCH(CH_3)C_6H_{13}$	63	156–158	.1	1.5118	$C_{17}H_{26}O_3$	73.34	9.42	73.50	9.76
$RCH(CN)COCH_3$	81	65.5–66.8[b,c]			$C_{12}H_{13}O_3N$	65.73	5.98[d]	65.60	5.97
RCH_2COCH_3	34	103–117	.17	Semicarbazone:	$C_{12}H_{17}O_3N_3$	57.35	6.82	57.48	6.91[e]
$RC(CH_3){=}C(CH_3)C_4H_9$	89	120–130	.55	1.5180	$C_{14}H_{24}O_2$	77.37	9.74	77.51 77.70	10.23 10.04
$RC(CH_3){=}C(CH_3)C_6H_{13}$	89	129	.08	1.5118	$C_{18}H_{28}O_2$	78.21	10.21	78.40	10.01
$RCH(CH_3)CH(CH_3)C_4H_9$	76	126–134	.27	1.5030	$C_{16}H_{26}O_2$	76.76	10.47	76.97	10.46
$RCH(CH_3)CH(CH_3)C_6H_{13}$	86	141–150	.05	1.5000	$C_{18}H_{30}O_2$	77.62	10.86	77.82	10.71
$RCH(CH_3)CH(CH_3)CH_2CH(CH_3)C_2H_5$	55[f]	136	.07	1.4995	$C_{17}H_{28}O_2$	77.22	10.67	77.15	10.70
$RCH(CH_3)CH(CH_3)COOC_2H_5$		150	2.8	1.5067	$C_{15}H_{22}O_4$	67.64	8.33	67.77	8.42
$RCH(CH_3)CH(CH_3)COOH$	52	75[b,g]			$C_{13}H_{18}O_4$	65.53	7.61	65.67	7.52
$RCH(OH)C_4H_9$	89	132	0.35	1.5195	$C_{13}H_{20}O_3$	69.61	8.99	69.62	9.15

[a] Boiling points are not corrected. [b] Melting point. [c] Recrystallized from isopropyl ether. [d] N: Calcd., 6.39. Found: 6.56. [e] M. p. 134.5–135.3° from ethanol–water. [f] Yield based on ketone (IX). [g] From petroleum ether (b. p. 60–70°). Crystallized only after several months.

TABLE III

3,5-DIHYDROXYPHENYL ALKANES

R = 3,5-Dihydroxyphenyl	Yield, %	B. p. °C.	Mm.	Empirical formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
$RCH(CH_3)CH(CH_3)C_4H_9$	94	146–155	0.6	$C_{14}H_{22}O_2$	75.63	9.98	75.29 75.29	10.14 10.17
$RCH(CH_3)CH(CH_3)C_6H_{13}$	90	150	.05	$C_{16}H_{26}O_2$	76.75	10.47	76.66	10.30
$RCH(CH_3)CH(CH_3)CH_2CH(CH_3)C_2H_5$	92	165–176	.2	$C_{15}H_{24}O_2$	76.22	10.24	76.43	10.38

TABLE IV

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

3-Substituent	Yield, %	M. p., °C. (cor.)[a]	Empirical formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
$-CH(CH_3)CH(CH_3)C_4H_9$	36	135.5–137.5	$C_{22}H_{30}O_3$	77.15	8.83	77.20	9.01
$-CH(CH_3)CH(CH_3)C_6H_{11}$	54	131.2–132	$C_{24}H_{34}O_3$	77.79	9.25	77.75	9.34
$-CH(CH_3)CH(CH_3)CH_2CH(CH_3)C_2H_5$	46	144–145.2[b]	$C_{23}H_{32}O_3$	77.49	9.05	77.62	9.26

[a] Recrystallized from ethanol–water by adding water to faint turbidity at about 50°. [b] Washed in benzene with 5% aqueous sodium hydroxide before crystallization. Nearly all of the unreacted resorcinol could be recovered.

TABLE V

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

3-Substituent	Yield, %	B. p. °C.	Mm.	Empirical formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
$-CH(CH_3)CH(CH_3)C_4H_9$	54	180	0.05	$C_{24}H_{36}O_2$	80.84	10.18	81.04	10.07
$-CH(CH_3)CH(CH_3)C_6H_{13}$	88	195–210	.7[a]	$C_{26}H_{40}O_2$	81.20	10.49	81.35	10.57
$-CH(CH_3)CH(CH_3)CH_2CH(CH_3)C_2H_5$	64	198–210	.35[a]	$C_{25}H_{38}O_2$	81.03	10.34	80.67 80.47	10.26 10.36

[a] Distilled in flask with short, wide side-arm.

the desired saturated compound, ethyl 2-methyl-3-(3,5-dimethoxyphenyl)-butyrate, could be isolated by repeated distillation of the mixture produced by this reduction. Saponification of the "reduced ester" mixture was accompanied by the production of some 3,5-dimethoxyacetophenone, presumably by a "reverse aldolization" of the unsaturated ester. A sodium amalgam reduction and several distillations of the mixture of acids formed by the saponification removed most of the unsaturated acid.

The crude acid chloride, produced by treating XV with thionyl chloride, was allowed to react with a solution of *n*-propylcadmium in benzene.[15] The product was found to be a mixture from which none of the pure ketone has as yet been obtained.

Certain other compounds were prepared in connection with exploratory studies. 3,5-Dimethoxyphenylbutylcarbinol was made by a lithium aluminum hydride reduction[16] of the valerophenone. 3,5-Dihydroxyphenylbutylcarbinol was obtained by a slight modification of the same procedure.

α-3,5-Dimethoxyphenylacetoacetonitrile was prepared in excellent yield by a method adapted from that designed for the unmethoxylated compound.[17] The yield of 3,5-dimethoxyphenylacetone obtained by hydrolysis was low.

The authors are indebted to J. C. Brantley and

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[15] Cason, THIS JOURNAL, 68, 2078 (1946).

[16] Nystrom and Brown, *ibid.*, 69, 1197 (1947).

[17] Julian, *et al.*, "Organic Syntheses," Coll. Vol. 2, John Wiley and Sons, Inc., New York, N. Y., 1943, pp. 487, 391.

Dorothy D. Brantley for determining the ultraviolet absorption spectra and to Mrs. Agatha R. Johnson for determining the infrared absorption spectra.

Experimental

In Tables II–V are given the constants of the intermediates and products formed by procedures described in previous papers[1] or in detail in the literature cited in the text.

3,5-Dimethoxybenzyl Alcohol.—A suspension of 91 g. of 3,5-dimethoxybenzoic acid in 1.5 l. of ether was added, as rapidly as the vigorous boiling of the solution would allow, to a solution of 24 g. of lithium aluminum hydride (94%) in 1.5 l. of anhydrous ether in a flask equipped with an efficient Hershberg stirrer, a wide-bore stopcock, and a condenser. The solution was refluxed for fifty minutes after the addition was completed, and the flask was cooled in ice while 150 ml. of water was added, *the first few milliliters with extreme caution.* An iced solution of 100 ml. of concentrated sulfuric acid in 2 l. of water was then added slowly, and the ethereal layer was separated, washed with dilute acid, aqueous sodium bicarbonate, and water, and dried over magnesium sulfate. Distillation of the tan-colored oil obtained by removal of the ether, collecting all that distilled up to 170° (0.6 mm.), gave 76 g. (93% when corrected for 2.5 g. of acid recovered from the bicarbonate extract) of product, m. p. 46°. The previously reported melting point was 47–48°.

Ethyl 3,5-Dimethoxyphenylcyanoacetate.—A mixture of 18.6 g. of 3,5-dimethoxyphenylacetonitrile[1] and 130 ml. of freshly-distilled ethyl carbonate was placed in a 3-necked flask bearing a Hershberg stirrer, a dropping funnel, and a heated column about 1.5 cm. in diameter, packed with glass helices for 20 cm. of its length. A solution of 2.9 g. of sodium in 46 ml. of absolute ethanol (dried with magnesium ethoxide or calcium hydride) was added, the system was evacuated to about 200 mm., and the ethanol was distilled off by warming the flask to 80–90°. When the temperature at the still-head rose rapidly from about 47° to about 70° and "schlieren" appeared in the distillate, the tan solution was poured into 600 ml. of ice-water, and extracted with 150 ml. of ether. The ethereal layer was extracted with three 150-ml. portions of water which had been made slightly basic with sodium hydroxide solution. The combined aqueous phases were brought to a *p*H of 5 with acetic acid and ether-extracted twice. The ether extracts were dried over magnesium sulfate and distilled. A yield of 23.5 g. (89%) of apparently homogeneous distillate was obtained, b. p. 165° (0.35 mm.), n^{20}_{D} 1.5164.

Anal. Calcd. for $C_{13}H_{15}O_4N$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.72; H, 6.20; N, 5.82.

The substance may be extracted from an ethereal solution by an aqueous bicarbonate solution.

α-Carbethoxy-3,5-dimethoxyhydratroponitrile.—A mixture of 100 ml. of isopropanol, which had been stored over calcium hydride and 7.5 g. of sodium was heated under reflux until all of the latter had dissolved and then was allowed to cool. A solution of 74 g. of ethyl 3,5-dimethoxyphenylcyanoacetate in 100 ml. of anhydrous isopropanol was added to the hard mass, and then 70 g. of methyl iodide. The solution began to reflux vigorously. After ten minutes, another 70 g. of methyl iodide was added. When the spontaneous boiling had subsided, the reaction mixture was heated on a steam-cone until all of the alkoxide had dissolved, and for ten minutes more, with stirring when it become possible.

The alcoholic solution was poured into 2 l. of ice-water and partitioned between ether and aqueous sodium bicarbonate to remove any of the starting ester. Drying the ethereal solution over magnesium sulfate was followed by removal of the solvent and distillation of the residue, collecting all that distilled at 130–150° (0.55 mm.). A yield of 71 g. (91%) was obtained. A sample was obtained for analysis by repeated distillation of the mixture obtained by an analogous methylation in which sodium ethoxide had been used as catalyst. It had n^{20}_{D} 1.5109.

Anal. Calcd. for $C_{14}H_{17}O_4N$: C, 63.86; H, 6.51; N, 5.32. Found: C, 64.46, 64.38; H, 6.37, 6.50; N, 6.43, 5.39.

3,5-Dimethoxyhydratroponitrile.[9b]—A solution of 36 g. of potassium hydroxide pellets in 300 ml. of 95% ethanol was added to 71 g. of the substituted cyanoacetic ester prepared above. The mixture was allowed to remain at room temperature for three hours with occasional shaking, filtered to remove the potassium carbonate, made neutral with a little concentrated hydrochloric acid, and dried over magnesium sulfate. Removal of the solvent and distillation of the residue gave 52 g. (100%) of an apparently homogenous liquid distilling at 128–134° (0.8 mm.), n^{20}_{D} 1.5240.

Anal. Calcd. for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.33. Found: C, 69.28; H, 6.91; N, 7.56.

3,5-Dimethoxyhydratropic Acid.—A solution of 30 g. of sodium hydroxide and 4 g. of 3,5-dimethoxyhydratroponitrile in 40 g. of water was heated under reflux for four and one-half hours. An oil precipitated upon acidification, and was caused to crystallize by means of a seed crystal obtained by rubbing a little of the oil with low-boiling petroleum ether. Recrystallization from 500 ml. of petroleum ether (b. p. 60–70°) gave 2.5 g. (57%) of product. A sample recrystallized twice more had a m. p. 52–52.5°.

Anal. Calcd. for $C_{11}H_{14}O_4$: C, 62.84; H, 6.71. Found: C, 62.80; H, 6.78.

2-(3,5-Dimethoxyphenyl)-5-methyl-3-heptanone.—To the Grignard reagent prepared from 98.5 g. of 2-methyl-1-bromobutane and 16 g. of magnesium turnings in 1 l. of ether, was added 41.5 g. of 3,5-dimethoxyhydratroponitrile in 200 ml. of ether. After having been heated under reflux for fifty-four hours, the reaction mixture was poured into 1 l. of ice-water containing 160 ml. of concentrated hydrochloric acid. The ethereal layer was separated and washed with two 400-ml. portions of cold, 4 *N* hydrochloric acid, and the aqueous layers were combined and heated on a steam-cone for six hours. The ethereal solution was washed with an aqueous sodium bicarbonate solution and dried over magnesium sulfate. The residue which remained after removal of the ether was treated with 30 g. of Girard's reagent-T in the usual way, and the ketonic fraction so produced was combined with the solution obtained by ether-extracting the acidified "ketimine" fraction above. Distillation, collecting the distillate at 128–132° (0.25 mm.), gave 30 g. (52%) of a nearly colorless oil, n^{20}_{D} 1.5050.

Anal. Calcd. for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.68; H, 9.11.

2-(3,5-Dimethoxyphenyl)-3,5-dimethyl-2-heptene.—A mixture of 32 g. of 2-(3,5-dimethoxyphenyl)-5-methyl-3-heptanone and a solution of two equivalents of methylmagnesium iodide was heated under reflux for four hours, and decomposed with a saturated aqueous ammonium chloride solution. After the ether had been removed, 100 ml. of benzene was added and distilled off, first at atmospheric pressure and finally *in vacuo*. The carbinol was dehydrated substantially as described for 2-methyl-2-(3,5-dimethoxyphenyl)-3-pentanol.[1] The potassium was powdered in 50 ml. of butyl ether by means of a Hershberg stirrer, and the appropriate amount of absolute ethyl ether was then added. Two equivalents of methyl iodide was added at a later point to insure the destruction of any remaining potassium and to hasten the formation of the methyl thioester, and the solution was refluxed for only three hours before filtration. The product was worked up as previously described and amounted to 24.5 g. (81%), b. p. 115–127° (0.2 mm.), n^{20}_{D} 1.5110. Reduction was accomplished with Raney nickel by two treatments at 130–150° and 2500 pounds of hydrogen pressure.

3-Methyl-2-octanol—This alcohol was prepared from 2-bromoheptane and acetaldehyde in 60% yield, by modifying a published procedure[18] for a similar reaction. It was converted to its succinic acid half-ester by replacing the substituted phthalic anhydride with succinic anhydride in the procedure of Fessler and Shriner.[19] The crude ester could neither be crystallized nor distilled. It was, therefore, dissolved in a slight excess of a 10% aqueous sodium hydroxide solution, ether extracted to remove neutral substances, and heated under reflux for four hours after increasing the concentration of the sodium hydroxide solution to 20%. Ether extraction, followed by drying and distillation, gave the alcohol, b. p. 85–87° (7 mm.), n^{20}_D 1.4330. It gave a positive iodoform test. This compound has been reported, b. p. 75° (15 mm.), n^{27}_D 1.437.[20]

Anal. Calcd. for $C_9H_{20}O$: C, 74.93; H, 13.98. Found: C, 75.66; H, 14.36.

3-Methyl-2-bromoöctane.—The halide was prepared by treatment of the alcohol prepared above with 1.1 moles of phosphorus tribromide following a procedure used to prepare 2-bromoöctane.[21] Distillation yielded 86% of a colorless liquid, b. p. 53° (1.7 mm.), n^{20}_D 1.4579.

Anal. Calcd. for $C_9H_{19}Br$: C, 52.18; H, 9.24. Found: C, 52.36; H, 9.37.

3,5-Dimethoxyacetophenone.—This ketone was prepared by adding 110 g. of powdered 3,5-dimethoxybenzamide to a five-fold excess of methylmagnesium iodide, and refluxing the mixture for sixteen hours. The decomposition was effected by adding the reaction product to a slurry of 1.2 l. of concentrated hydrochloric acid and an equal amount of ice, and allowing the mixture to remain for sixteen hours with occasional shaking. Extraction with ether, and distillation of the dark oil after removal of the solvent, gave 66 g., b. p. 115–128° (0.3 mm.), which solidified on being stored in a refrigerator. After having been washed with a little low-boiling petroleum ether to remove oily material, 63 g. (57%) was obtained. Recrystallization from petroleum ether gave a product, m. p. 43°. An alternative route is reported[22] to have given a 15% over-all yield, m. p. 43°.

Ethyl 2-Methyl-3-hydroxy-3-(3,5-dimethoxyphenyl)-butyrate.—The procedure described[23] for the non-methoxylated compound was applied to 16 g. of zinc, 33 g. of 3,5-dimethoxyacetophenone, and 40 g. of ethyl α-bromopropionate, with an increase in the amount of acid used for the decomposition to correspond to the larger amount of zinc relative to ketone used. Fractionation of the crude product gave 2 g. distilling at 110–143° (0.45 mm.) and 46.5 g. (90%) distilling at 140–150° (0.45 mm.). One additional distillation was used to prepare a sample for analysis, n^{20}_D 1.5092.

Anal. Calcd. for $C_{15}H_{22}O_5$: C, 63.81; H, 7.86. Found: C, 63.85; H, 7.99.

Dehydration of the hydroxy ester was accomplished by heating it in a stream of anhydrous hydrogen chloride first on a steam-cone for three hours[24] and then at a bath temperature of 170° for ten minutes more. Careful distillation at 145–165° (0.6 mm.) gave 77 g. (93%) of an intensely yellow liquid, n^{20}_D 1.5163. No chlorine or hydroxyl or ketonic groups could be detected in this product by chemical tests or infrared absorption.

3,5-Dihydroxyphenylbutylcarbinol.—A solution of 10 g. of 3,5-dihydroxyphenyl butyl ketone in 100 ml. of absolute ether was added dropwise, with efficient stirring, to a solution of 2.75 g. of lithium aluminum hydride in 180 ml. of absolute ether. A thick white paste immediately precipitated, accompanied by the vigorous evolution of a hydrogen–ether mixture. Another 100 ml. of ether was added, and the mixture was heated on a steam-cone and stirred for two and one-half hours more. It was decomposed, washed, and dried as described above in the preparation of dimethoxybenzyl alcohol. Addition of a few milliliters of petroleum ether (b. p. 60–70°) to the oil remaining after the removal of the ether caused it to solidify. The yield was 9 g., m. p. 137°. The solid, which was extremely soluble in ethanol and rather insoluble in benzene, was best recrystallized from about 400 ml. of a 15% solution of absolute ethanol in benzene, with a recovery of about 65%. Two recrystallizations gave a pure product, m. p. 144.5°.

Anal. Calcd. for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.19; H, 8.44.

α,3,5-Dimethoxyphenethyl Methyl Ketone.—This ketone was prepared analogously to 2-(3,5-dimethoxyphenyl)-5-methyl-3-heptanone. Use of benzene as solvent resulted in the isolation of some of the desired product, accompanied by larger amounts of alkali-soluble, presumably phenolic, ketones. The product was found to crystallize slowly when the combined ketonic fractions were diluted with a little petroleum ether and scratched. The solid was recrystallized from petroleum ether (b.p. 60–70°), from which it deposited very slowly as stubby blocks, m. p. 62.5°. It gave a positive iodoform test.

Anal. Calcd. for $C_{12}H_{16}O_2$: C, 69.20; H, 7.74. Found: C, 69.45; H, 7.75.

A semicarbazone was prepared and recrystallized from ethanol–water, m. p. 174.8–175.3°.

Anal. Calcd. for $C_{13}H_{19}O_3N_3$: C, 58.85; H, 7.22. Found: C, 59.11; H, 7.26.

3,5-Diacetoxyphenyl Butyl Ketone.—The acetylation[25] of 15.3 g. of 3,5-dihydroxyphenyl butyl ketone gave a liquid diacetate which was taken up in benzene, filtered, and distilled. The yield was 17 g. (78%), b. p. 146–153° (0.15 mm.), n^{20}_D 1.5097.

Anal. Calcd. for $C_{15}H_{18}O_5$: C, 64.73; H, 6.52. Found: C, 64.87; H, 6.68.

Summary

1. Three new conjugated analogs of tetrahydrocannabinol have been prepared. These are 1-hydroxy-3-alkyl-6,6,9-trimethyl-7,8,9,10-tetrahydro-6-dibenzopyrans in which the alkyl groups are 1,2-dimethylhexyl, 1,2-dimethyloctyl, and 1,2,4-trimethylhexyl. The preparation of the 5 alkylresorcinol dimethyl ethers and the corresponding resorcinols required in these, and for other projected syntheses, is discussed.

2. The 1,2-dimethylhexyl and 1,2-dimethyloctyl derivatives have a lower marihuana potency than the 1,2-dimethylheptyl homolog previously prepared. The introduction of a third methyl group, as illustrated by the 1,2,4-trimethylhexyl derivative, does not appear to enhance the physiological activity.

URBANA, ILLINOIS

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