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]

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

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

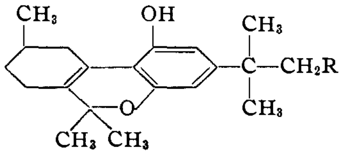
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS, AND THE SCHOOL OF MEDICINE UNIVERSITY OF UTAH]

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

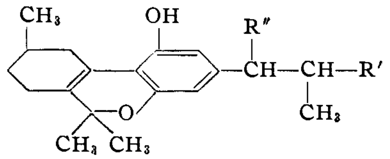
BY ROGER ADAMS, SCOTT MACKENZIE, JR., AND S. LOEWE

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

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

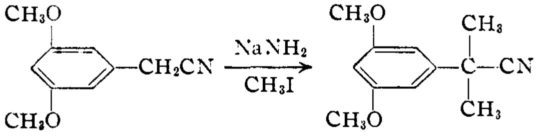
TABLE I

PHARMACOLOGICAL ACTIVITY OF TETRAHYDROCANNABINOL HOMOLOGS

	3-Substituent	No. of expts.	Potency
1	$-C_5H_{11}-n$[2]	20	1.00 Standard
2	Natural tetrahydrocannabinol from cannabidiol[3]	20	7.3 ± 0.89
Hexyl Isomers			
3	$-C_6H_{13}-n$[2]	7	1.82 ± 0.18 (max. in *n*-series)
4	$-CH(CH_3)C_4H_9$[4]	8	3.17 ± 0.33
5	$-CH(C_2H_5)CH(CH_3)CH_3$	6	3.40 ± 1.10
6	$-CH(CH_3)CH(CH_3)C_2H_5$	4	3.80 ± 0.32
7	$-C(CH_3)_2C_3H_7$	5	4.18 ± 0.34
Nonyl Isomers			
8	$-CH(CH_3)C_7H_{15}$[1]	19	32.6 ± 3.02 (max. in *s*-series)
9	$-CH(CH_3)CH(CH_3)C_5H_{11}$	18	512 ± 72.6
10	$-C(CH_3)_2C_6H_{13}$	5	21.8 ± 1.91

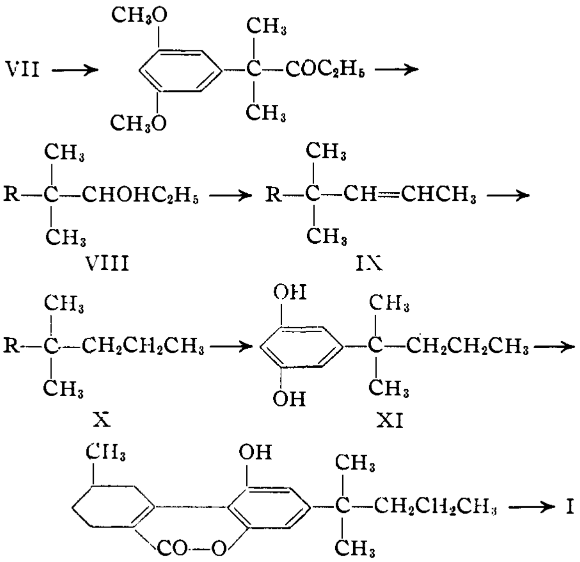
one of four carbon atoms. Although the 1′,2′-dimethylalkyl derivative with a total of six carbon atoms present in the side-chain is about equal in potency to the 1′,1′-dimethylalkyl derivative, the isomeric 1′,2′-dimethylalkyl analog with seven carbon atoms in the straight chain exceeds in activity the corresponding 1′,1′-isomer, and indeed has a value of 512. This is about sixteen times as potent as the most active homolog previously synthesized and seventy times the potency of natural tetrahydrocannabinol. The new order of the marihuana activity of the compound having the 1′,2′-dimethylheptyl side-chain makes generalization difficult at this time.

The 1′,1′-dimethylalkylpyrans were synthesized from 3,5-dimethoxybenzaldehyde. The aldehyde, first prepared by Mauthner[5] by the Rosenmund reduction, was obtained from the acid by the method described by McFadyen and Stevens[6] through 3,5-dimethoxybenzoyl-*p*-toluenesulfonylhydrazide. The aldehyde was hydrogenated in the presence of platinum oxide catalyst and the resulting benzyl alcohol was converted through the corresponding chloride and nitrile (VI) to 2-(3,5-dimethoxyphenyl)-2-methylpropionitrile (VII).



VI VII

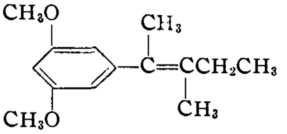
Both pyrans with two carbons on the 1′-carbon atom in the side-chains were prepared from this nitrile (VII) by the scheme shown below for the hexyl compound (VII–XII).



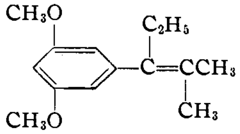
VIII IX X XI XII

The nitrile (VII) was converted by the action of ethylmagnesium bromide to the corresponding ketone which with hydrogen and copper chromite catalyst was reduced to the carbinol (VIII). Attempted dehydration of VIII by acidic reagents always resulted in rearrangement; the olefins thus formed were isolated, reduced and condensed to the pyrones, the structures of which were demonstrated by synthesis using unequivocal methods. The xanthate method of dehydration described by Tschugaeff[7] produced the unrearranged olefin (IX). This was reduced, demethylated, converted to the pyrone (XII), then to the pyran by the procedure previously described.[4,8]

Although Tschugaeff's assertion that no rearrangement occurs when alcohols are dehydrated by the xanthate method was further substantiated by Whitmore,[9] the structure of the tertiary olefin was more conclusively established. Dehydration of the pentanol (VIII) with acidic reagents would lead to the formation of either of two rearrangement products, (XIII) or (XIV). Both of these



XIII



XIV

olefins were synthesized from 3,5-dimethoxybenzamide[10] by conversion first to the ketone with the appropriate Grignard reagent, followed by the action of methyl- or ethyl-magnesium halide to form the carbinol. These were dehydrated, reduced and demethylated to the resorcinols which were converted to the pyrones.

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(2) Adams, Loewe, Jelinek and Wolff, THIS JOURNAL, **63**, 1971 (1941).

(3) Adams, Pease, Cain and Clark, *ibid.*, **64**, 694 (1942).

(4) Adams, Chen and Loewe, *ibid.*, **67**, 1534 (1945).

(5) Mauthner, *J. prakt. Chem.*, **100**, 176 (1920).

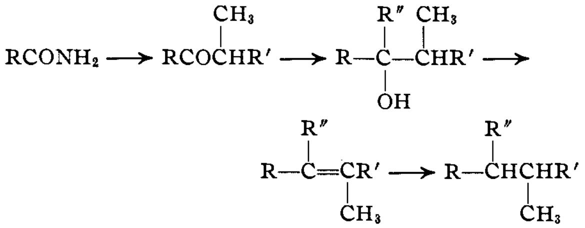
(6) McFadyen and Stevens, *J. Chem. Soc.*, 584 (1936).

(7) Tschugaeff, *Ber.*, **32**, 3332 (1889).

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

(9) Whitmore and Simpson, *ibid.*, **55**, 3809 (1933).

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



$$\mathrm{RCONH_2} \longrightarrow \mathrm{RCO\overset{\overset{CH_3}{|}}{C}HR'} \longrightarrow \mathrm{R{-}\underset{\underset{OH}{|}}{\overset{\overset{R''}{|}}{C}}{-}\overset{\overset{CH_3}{|}}{C}HR'} \longrightarrow$$

$$\mathrm{R{-}\underset{\underset{CH_3}{|}}{\overset{\overset{R''}{|}}{C}}{=}CR'} \longrightarrow \mathrm{R{-}\overset{\overset{R''}{|}}{C}H\underset{\underset{CH_3}{|}}{C}HR'}$$

R = 3,5-dimethoxyphenyl; R′ = C_2H_5, R″ = CH_3; R′ = CH_3, R″ = C_2H_5

Neither of the pyrones was identical with the pyrone (XII) prepared from the neopentyl type carbinol by the Tschugaeff method. The tertiary structure of the olefin (IX) obtained by the xanthate method is thus confirmed. The pyrones were converted to pyrans in the usual way.

Experimental

The procedures used for the conversion of a 5-alkylresorcinol dimethyl ether to the corresponding pyran have been described previously.[8]

Ethyl 3,5-Dimethoxybenzoate.—A mixture of 100 g. of 3,5-dimethoxybenzoic acid, 350 ml. of anhydrous benzene, 2 ml. of pyridine and 300 g. of purified thionyl chloride was refluxed for three hours. After removal of the solvent and excess thionyl chloride by distillation, 300 ml. of cold absolute ethanol was added to the cooled residue. The resulting solution was refluxed for four hours. The ethanol was removed by distillation and an ethereal solution of the residue was extracted with aqueous sodium bicarbonate. After removal of the ether the residue was distilled under reduced pressure. The product, collected at 120–125° (3 mm.), was a colorless liquid, n^{20}_D 1.5214. The yield was 100 g. (87%).

Anal. Calcd. for $C_{11}H_{14}O_4$: C, 62.86; H, 6.67. Found: C, 63.05; H, 6.79.

3,5-Dimethoxybenzhydrazide.—A mixture of 100 g. of ethyl 3,5-dimethoxybenzoate, 100 g. of 85% hydrazine hydrate and 110 ml. of absolute ethanol was refluxed for eight hours. The yield of brilliant white plates obtained by cooling the solution was 97 g. (83.5%). The product was purified from ethanol, m. p. 168–169° (cor.)

Anal. Calcd. for $C_9H_{12}N_2O_3$: C, 55.10; H, 6.12. Found: C, 55.17; H, 6.15.

3,5-Dimethoxybenzoyl-*p*-toluenesulfonylhydrazide.—A mixture of 100 g. of 3,5-dimethoxybenzhydrazide, 100 g. of *p*-toluenesulfonyl chloride and 100 ml. of pyridine was heated for one hour on a steam cone and then allowed to stand overnight. The solution was poured into 750 ml. of water and stirred until a granular, light brown solid was produced. The product was purified by recrystallization from aqueous ethanol. The total yield of large brilliant plates, m. p. 165–166°, was 117.5 g. (79%).

Anal. Calcd. for $C_{16}H_{18}N_2O_5S$: C, 54.86; H, 5.14. Found: C, 54.90; H, 5.34.

3,5-Dimethoxybenzaldehyde.—Into a one-liter Erlenmeyer flask heated by an oil-bath were placed 100 ml. of glycerol and 25 g. of 3,5-dimethoxybenzoyl-*p*-toluenesulfonylhydrazide. The mixture was stirred manually and heated to 125°. A hot (100°) solution of 20 g. of potassium carbonate in 100 ml. of glycerol was added all at once. The solution was heated rapidly to 135–140° and maintained at this temperature for about thirty seconds. After the evolution of gases partially subsided the solution was poured onto 300 g. of ice. The aqueous suspension was extracted three times with ether and the ether portions were combined and dried over anhydrous magnesium sulfate. After removal of the ether the liquid residue was distilled under reduced pressure. The fraction collected at 125–130° (1–2 mm.) was crude aldehyde and was purified by recrystallization from petroleum ether (b. p. 90–110°). The yield of fine lusterless needles, m. p. 45–46°, was 8 g. (68%). Mauthner[5] reported m.p. 45–46°.

3,5-Dimethoxybenzyl Alcohol.—The aldehyde was hydrogenated at room temperature and at 2–3 atm. pressure in the presence of platinum oxide catalyst. Ethanol was used as the solvent. The yield of fine white needles, m. p. 47–48°, from 16.6 g. of aldehyde was 16.0 g. (95%). The reported m. p. is 47–48°.[5]

3,5-Dimethoxybenzyl Chloride.—A solution of 22.5 g. of purified thionyl chloride in 100 ml. of anhydrous ether was added in 20-ml. portions with occasional shaking to a solution of 15 g. of 3,5-dimethoxybenzyl alcohol and 1 ml. of pyridine in 200 ml. of anhydrous ether. The mixture was allowed to stand for fifteen minutes and then was extracted twice with 100-ml. portions of cold water. The ether was allowed to evaporate *in vacuo* at low temperature. The crude chloride was purified by recrystallization from petroleum ether (b. p. 90–110°). The yield of fine needles, m. p. 46°, was 16.0 g. (96%).

Anal. Calcd. for $C_9H_{11}O_2Cl$: C, 57.91; H, 5.90. Found: C, 57.94; H, 6.09.

3,5-Dimethoxybenzyl Cyanide.—A mixture of 16 g. of 3,5-dimethoxybenzyl chloride, 300 ml. of ethanol, 30 g. of sodium cyanide and 75 ml. of water was refluxed for three hours. The solution was poured onto 400 g. of ice. The solid was collected on a filter and purified by recrystallization from petroleum ether (b. p. 90–110°). The yield of fine lusterless needles, m. p. 53°, was 14.5 g. (95%).

Anal. Calcd. for $C_{10}H_{11}NO_2$: C, 67.80; H, 6.21. Found: C, 67.81; H, 6.42.

2-(3,5-Dimethoxyphenyl)-2-methylpropionitrile.—3,5-Dimethoxybenzyl cyanide was methylated using a slight modification of the procedure described by Smith and Spillane[11] for the preparation of 2-(3,5-dimethylphenyl)-2-methylpropionitrile. The sodamide solution obtained from 3.5 g. of sodium, 200 ml. of liquid ammonia and a few crystals of ferric nitrate was allowed to evaporate to a volume of about 75 ml. The remaining ammonia was displaced by 200 ml. of anhydrous ether and a solution of 25 g. of 3,5-dimethoxybenzyl cyanide in 100 ml. of anhydrous ether was added all at once and the mixture refluxed for eighteen hours. Then 25 g. of methyl iodide was added to the cooled solution as rapidly as possible with stirring. The solution was refluxed for two hours, heating was discontinued and 50 ml. of ethanol was added with stirring. After washing and drying the reaction mixture was again subjected to methylation.

When reaction was complete the solvent was removed and the crude product obtained by distillation under reduced pressure was heated for one hour with 0.25 tablespoonful of Raney nickel and 200 ml. of absolute ethanol to remove any amide. Upon fractionation, a yield of 21.5 g. (72.5%) was obtained. The colorless product, b. p. 147–150°, n^{20}_D 1.5201, d^{20}_4 1.0813, became slightly yellow on standing.

Anal. Calcd. for $C_{12}H_{15}NO_2$: C, 70.24, H, 7.32. Found: C, 70.03; H, 7.53.

2-(3,5-Dimethoxyphenyl)-2-methylpropanoic Acid.—A mixture of 50 ml. of ethylene glycol, 1 g. of the propionitrile, 1 g. of potassium hydroxide and 1 ml. of water was refluxed for four hours. The solution was diluted with water, extracted with ether, acidified and extracted four times with ether. After removal of the solvent the crude acid was recrystallized from petroleum ether (b. p. 90–110°). The yield of colorless crystals, m. p. 99°, was 0.5 g. (46%).

Anal. Calcd. for $C_{12}H_{16}O_4$: C, 64.29; H, 7.14. Found: C, 64.45; H, 7.29.

2-Methyl-2-(3,5-dimethoxyphenyl)-3-pentanone.—A solution of 26 g. of 2-methyl-2-(3,5-dimethoxyphenyl)-propionitrile in 100 ml. of anhydrous ether was added to the Grignard reagent prepared from 41.2 g. of ethyl bromide, 5.9 g. of magnesium and 200 ml. of dry ether. The ether was replaced by 300 ml. of dry benzene and the solu-

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[11] Smith and Spillane, THIS JOURNAL, **65**, 202 (1943).

TABLE II

KETONES

R = 3,5-Dimethoxyphenyl	Yield, %	B. p., °C.	Mm.	n^{20}_D	d^{20}_4	Empirical formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
$RC(CH_3)_2COC_2H_5$	70	104	0.3	1.5165	1.0476	$C_{14}H_{20}O_3$	71.19	8.47	71.02	8.45
$RCOCH(CH_3)C_2H_5$[a]	76	124–128	0.5	1.5266	....	$C_{13}H_{18}O_3$	70.27	8.11	70.03	8.18
$RCOCH(CH_3)CH_3$[a]	71	117–119	1.0	1.5290	1.0928	$C_{12}H_{16}O_3$	69.23	7.69	69.28	7.82
$RC(CH_3)_2COC_5H_{11}$	78	140–145	0.5	1.5088	1.0131	$C_{17}H_{26}O_3$	73.38	9.35	73.33	9.51
$RCOCH(CH_3)C_5H_{11}$[a]	82	147	1.0	1.5136	....	$C_{16}H_{24}O_3$	72.72	10.00	72.58	9.31

[a] Ketones prepared from 3,5-dimethoxybenzamide contained traces of the amide which were not removed on redistillation. Refluxing an alcoholic solution with Raney nickel was helpful.

TABLE III

3,5-DIMETHOXYPHENYL OLEFINS

R = 3,5-Dimethoxyphenyl	Yield	B. p. °C.	Mm.	n^{20}_D	d^{20}_4	Empirical formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
$RC(CH_3)_2CH{=}CHCH_3$	75	103–106	0.5	1.5179	0.9858	$C_{14}H_{20}O_2$	76.32	9.15	76.43	9.34
$RC(CH_3){=}C(CH_3)C_2H_5$	91	110	1.0	1.5277	1.0126	$C_{14}H_{20}O_2$	76.32	9.15	76.46	9.27
$RC(C_2H_5){=}C(CH_3)CH_3$[b]	75	102–106	0.5	....	....	$C_{14}H_{20}O_2$	76.32	9.15	...	...
$RC(CH_3)_2CH{=}CHC_4H_9$	90	127–130	0.5	1.5080	0.9862	$C_{17}H_{26}O_2$	77.86	9.92	77.90	10.10
$RC(CH_3){=}C(CH_3)C_5H_{11}$	85	132–134	1.0	1.5131	0.9616	$C_{17}H_{26}O_2$	77.86	9.92	77.83	9.94

[b] The sample of this compound, made to check the identity of the corresponding pyrone, was too small for adequate purification.

TABLE IV

3,5-DIMETHOXYPHENYL ALKANES

R = 3,5-Dimethoxyphenyl	Yield, %	B. p. °C.	Mm.	n^{20}_D	d^{20}_4	Empirical formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
$R{-}C(CH_3)_2C_3H_7$[a]	92	115–117	1.5–2	1.5071	0.9834	$C_{14}H_{22}O_2$	75.68	9.91	75.69	10.08
$R{-}CH(CH_3)CH(CH_3)C_2H_5$[b]	91	98–100	0.5	1.5012	0.9787	$C_{14}H_{22}O_2$	75.68	9.91	75.85	10.01
$R{-}CH(C_2H_5)CH(CH_3)CH_3$[b,d]	73	104	.5	....	....	$C_{14}H_{22}O_2$	75.68	9.91	...	...
$R{-}C(CH_3)_2C_6H_{13}$[c]	93	122	.5	1.5006	0.9558	$C_{17}H_{26}O_2$	77.27	10.61	77.64	10.80
$R{-}CH(CH_3)CH(CH_3)C_5H_{11}$[a]	79	120	.5	1.5036	0.9523	$C_{17}H_{28}O_2$	77.27	10.61	77.51	10.73

[c] Olefin hydrogenated at roo re using Raney nickel. [d] Olefin subjected to two successive hydrogenations at 175° using copper chromite.

TABLE V

3,5-DIHYDROXYPHENYL ALKANES

R = 3,5-Dihydroxyphenyl	Yield, %	B. p. °C.	Mm.	Empirical formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
$R{-}C(CH_3)_2C_3H_7$	75	151–154	1.0	$C_{12}H_{18}O_2$	74.19	9.34	74.37	9.29
$R{-}CH(CH_3)CH(CH_3)C_2H_5$	84	145–146	1.0	$C_{12}H_{18}O_2$	74.19	9.34	74.03	9.34
$R{-}CH(C_2H_5)CH(CH_3)CH_3$[b]	50	145	0.5	$C_{12}H_{18}O_2$	74.19	9.34	...	...
$R{-}C(CH_3)_2C_6H_{13}$	80	161–163	0.5	$C_{15}H_{18}O_2$	76.27	10.17	76.42	10.12
$R{-}CH(CH_3)CH(CH_3)C_5H_{11}$	80	167–169	1.0	$C_{15}H_{18}O_2$	76.27	10.17	76.27	10.12

tion was refluxed for forty-eight hours. The reaction mixture was decomposed with dilute sulfuric acid and the benzene was removed by distillation. The resulting mixture of acid and crude ketone was heated for an additional two hours on the steam cone. After cooling the mixture was extracted with ether, and the ether was removed. The crude product was distilled twice under reduced pressure to give a yield of 21 g. (70%) of colorless liquid (Table II).

2-Methyl-2-(3,5-dimethoxyphenyl)-3-pentanol.—The ketone was hydrogenated at a temperature of 150–170° under a pressure of hydrogen of 3000 pounds in the presence of copper chromite. The product was fractionated under reduced pressure, those fractions having n^{20}_D 1.5249 ± 0.0001 being combined. The yield of colorless, viscous liquid, b. p. 129–130°(0.5 mm.), d^{20}_4 1.0980, was 15.2 g. (72.5%).

Anal. Calcd. for $C_{14}H_{22}O_3$: C, 70.59; H, 9.24. Found: C, 70.52; H, 9.44.

2-Methyl-2-(3,5-dimethoxyphenyl)-3-pentene.—A solution of 15.2 g. of the pentanol in 100 ml. of dry ether was allowed to react over a six-hour period with a suspension of 2.5 g. of metallic potassium (previously powdered in Stanolind) in 200 ml. of ether. An equimolar quantity of carbon disulfide was added and the mixture was stirred for one-half hour. To the thick white mass was added 9.0 g. of methyl iodide. The suspension was refluxed for six hours and allowed to stand overnight. The potassium iodide was removed by filtration. After removal of the ether the yellow residue was placed in a 50-ml. modified Claisen flask and distilled under reduced pressure. About one-half hour of careful heating was necessary before the actual distillation of light yellow product began. An alcoholic solution of the distillate was refluxed with Raney nickel and redistilled. The final product was a colorless liquid (Table III).

2-Methyl-2-(3,5-dimethoxyphenyl)-3-octanone.—A solution of 18.6 g. of 2-methyl-2-(3,5-dimethoxyphenyl)-propionitrile in 100 ml. of anhydrous ether was added to the Grignard reagent prepared from 42.1 g. of *n*-amyl bromide, 6.63 g. of magnesium and 150 ml. of anhydrous ether. After replacement of the ether with dry benzene the mixture was refluxed for forty-eight hours. The decomposition with dilute sulfuric acid and the purification of the product were carried out as described for the pentanone (Table II).

TABLE VI

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

3-Substituent	Yield,[e] %	M. p. (cor.) °C.	Solvent for recryst.	Empirical formula	Analyses, % Calcd. C	H	Found C	H
$—C(CH_3)_2C_3H_7$	73	218–220	Ethanol–water	$C_{20}H_{26}O_3$	76.50	8.28	76.33	8.31
$—CH(CH_3)CH(CH_3)C_2H_5$	30	177–178	Ethanol–water	$C_{20}H_{26}O_3$	76.50	8.28	76.63	8.30
$—CH(C_2H_5)CH(CH_3)CH_3$	28	181–182	Ethanol–water	$C_{20}H_{26}O_3$	76.50	8.28	76.47	8.45
$—C(CH_3)_2C_6H_{13}$	36.5	156–157	(1) Nitromethane (2) Ethanol–water	$C_{23}H_{32}O_3$	77.53	8.99	77.52	9.17
$—CH(CH_3)CH(CH_3)C_5H_{11}$	24	134–136	(1) Nitromethane (2) Ethanol–water	$C_{23}H_{32}O_3$	77.53	8.99	76.73	9.14

[e] The yield depended considerably on sample size.

TABLE VII

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	H	Found C	H
$—C(CH_3)_2C_3H_7$	65	158	0.02	$C_{22}H_{32}O_2$	80.43	9.82	80.18	9.75
$—CH(CH_3)CH(CH_3)C_2H_5$	72	160–162	.02	$C_{22}H_{32}O_2$	80.43	9.82	80.64	9.76
$—CH(C_2H_5)CH(CH_3)CH_3$[f]	40	176	.1	$C_{22}H_{32}O_2$	80.43	9.82	...	...
$—C(CH_3)_2C_6H_{13}$	65	176–176	.04	$C_{25}H_{38}O_2$	81.08	10.27	80.98	10.43
$—CH(CH_3)CH(CH_3)C_5H_{11}$	80	170–173	.04	$C_{25}H_{38}O_2$	81.08	10.27	80.81	10.48

[f] The sample of this compound, made primarily to check the identity of the corresponding pyrone, was too small for adequate purification. The pyrone, was purified to constant melting point.

2-Methyl-2-(3,5-dimethoxyphenyl)-3-octanol.—The ketone was hydrogenated in the presence of copper chromite under conditions identical with those described above. After fractionation under reduced pressure, the yield of colorless liquid, b. p. 162° (0.5 mm.), $n^{20}D$ 1.5138, $d^{20}{}_4$ 1.0262, was 15.5 g. (79%).

Anal. Calcd. for $C_{17}H_{28}O_3$: C, 72.86; H, 10.00. Found: C, 72.72; H, 10.19.

2-Methyl-2-(3,5-dimethoxyphenyl)-3-octene.—The preparation of the xanthate was carried out as described above. Gentle heating for three hours was necessary before the decomposition was complete (Table III).

Summary

1. Tetrahydrocannabinols have been prepared with the following alkyl groups in the 3-positions: $—C(CH_3)_2CH_2CH_2CH_3$, $—C(CH_3)_2CH_2(CH_2)_4CH_3$, $—CH(CH_3)CH(CH_3)CH_2CH_3$, $—CH(CH_3)CH(CH_3)CH_2(CH_2)_3CH_3$, $—CH(C_2H_5)CH(CH_3)_2$.

2. The resorcinols required for the first two were synthesized from 3,5-dimethoxybenzoic acid. This was converted to the resorcinol dimethyl ether derivatives by the following steps: $—COOH$, → $—CHO$ → $—CH_2OH$ → $—CH_2Cl$ → $—CH_2CN$ → $—C(CH_3)_2CN$ → $—C(CH_3)_2COCH_2R$ → $—C(CH_3)_2CHOHCH_2R$ → $—C(CH_3)_2CH{=}CHR$ → $—C(CH_3)_2CH_2CH_2R$. Finally, demethylation yielded the resorcinols which were converted by previously described methods to the corresponding pyrans.

3. The resorcinols for the last three substances mentioned in (1) were made from 3,5-dimethoxybenzamide. This was converted as follows to the resorcinol dimethyl ether derivatives: $—CONH_2$ → $—COCH(CH_3)R$ → $—C(R')(OH)CH(CH_3)R$ → $—C(R'){=}C(CH_3)R$ → $—CH(R')CH(CH_3)R$.

4. 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 one of four carbon atoms. Although the 1′,2′-dimethylalkyl derivative with a total of six carbon atoms present in the side-chain is about equal in potency to the 1′,1′-dimethylalkyl derivative, the isomeric 1′,2′-dimethylalkyl analog with seven carbon atoms in the straight chain exceeds in activity the corresponding 1′,1′-isomer and indeed has a value of 512. This is about sixteen times as potent as the most active homolog previously synthesized and seventy times the potency of natural tetrahydrocannabinol.

URBANA, ILLINOIS

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