

has been prepared and its properties studied. The name "triptycene" is proposed for this hydrocarbon. Being an analog of triphenylmethane whose symmetrical anion cannot assume the coplanar form demanded by the usual resonance

structures, triptycene is entirely lacking in the activity of its aliphatic hydrogen toward potassium exchange, chlorination, and oxidation which characterizes triphenylmethane.

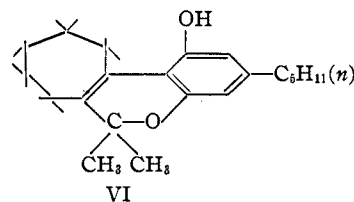
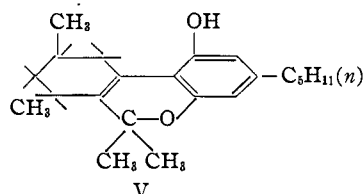
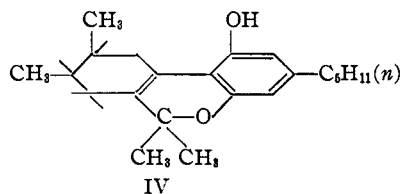
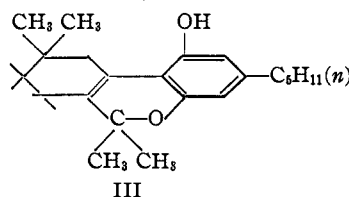
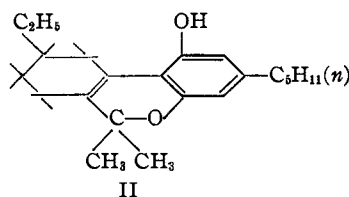
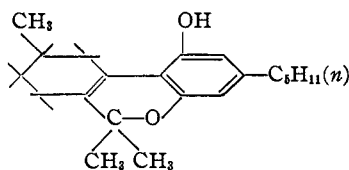
CAMBRIDGE, MASSACHUSETTS RECEIVED JULY 3, 1942

[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 Analogs with Marihuana Activity. XV<sup>1</sup>

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

The study of analogs of synthetic tetrahydrocannabinol (I) wherein the left-hand ring was modified has comprised those molecules in which the methyl group was eliminated and those in which the methyl group was shifted to the 8- and 10-positions.<sup>2</sup> This investigation has now been extended, and a variety of products have been synthesized as shown in formulas II-VI.



The pharmacological tests on these molecules by the dog-ataxia method as compared to tetrahydrocannabinol (I) as standard are given in Table I.

TABLE I  
PHARMACOLOGICAL ACTIVITY OF TETRAHYDROCANNABINOL ANALOGS

	Expts.	Potency	Mean dev.
1-Hydroxy-3- <i>n</i> -amylyl-6,6-dimethyl-9-ethyl-7,8,9,10-tetrahydro-6-dibenzopyran II	5	0.22	0.02
1-Hydroxy-3- <i>n</i> -amylyl-6,6,9,9-tetramethyl-7,8,9,10-tetrahydro-6-dibenzopyran III	7	.10	.02
1-Hydroxy-3- <i>n</i> -amylyl-6,6,8,9-tetramethyl-7,8,9,10-tetrahydro-6-dibenzopyran IV	10	.11	.03
1-Hydroxy-3- <i>n</i> -amylyl-6,6,7,9-tetramethyl-7,8,9,10-tetrahydro-6-dibenzopyran V	5	.75	.08
2,2-Dimethyl-3,4-pentamethylene-5-hydroxy-7- <i>n</i> -amylyl-1,2-benzopyran VI	4	.21	.02

These experiments confirm the results from the study of the previously described compounds that relatively minor changes in the left-hand ring structure reduce by 80 to 90% the activity of the

(1) For previous paper see Adams, Smith and Loewe, *This Journal*, **64**, 2087 (1942).

(2) Adams, Smith and Loewe, *ibid.*, **63**, 1973 (1941); see also Russell, Todd, Wilkinson, MacDonald and Woolfe, *J. Chem. Soc.*, 169, 826 (1941).

TABLE II  
 ETHYL  $\alpha$ -ALKYLCYCLOHEXANONE-2-CARBOXYLATES

Substituent	B. p.		Yield, %	$n_D^{20}$	$d_4^{20}$	Anal. Calcd. for		M. p. of 2,4-di- nitrophenylhy- drazones <sup>a</sup> (cor.), °C.	Anal. Calcd. for		
	°C.	mm.				C <sub>17</sub> H <sub>22</sub> O <sub>4</sub> N <sub>4</sub>	Found:		C	H	Found:
5-Ethyl	96-98	2	54	1.4720	1.043	66.84	9.13	122-122.5	54.10	6.02	15.00
5,5-Dimethyl	125-128	14	54	1.4716	1.020	66.85	9.11	89	54.31	6.06	14.82
4,5-Dimethyl	116	10	42	1.4771	1.038	66.68	8.94	146-147	54.16	5.80	15.00
3,5-Dimethyl	103	4	53	1.4560	1.021	66.47	9.16	175	54.09	5.91	14.98

<sup>a</sup> Prepared according to Shriner and Fuson, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1935 (1st ed.), p. 148, and recrystallized from petroleum ether (b. p. 60-110°).

molecules. Compound V, which has a potency not much below that of tetrahydrocannabinol (I), is the only exception; but the normal ataxia action is here accompanied by a convulsant action similar to that observed with tetrahydrocannabinol.

### Experimental

**3-Ethylcyclohexanol.**—Five hundred grams of *m*-ethylphenol (Eastman Kodak) was reduced with Raney nickel at 136 atm. and 200°. The product was rinsed from the bomb with ethanol, the catalyst removed by filtration, the ethanol removed on the steam-cone, and the residue distilled under reduced pressure. There was obtained 488 g. (89%) of a water-white liquid boiling at 96° (20 mm.) and 192.5-193° (748 mm.);  $n_D^{20}$  1.4619;  $d_4^{20}$  0.9164.

*Anal.* Calcd. for C<sub>8</sub>H<sub>16</sub>O: C, 74.94; H, 12.58. Found: C, 75.07; H, 12.67.

The 3,5-dinitrobenzoate of 3-ethylcyclohexanol after crystallization from aqueous ethanol melts at 133-134° (cor.).

*Anal.* Calcd. for C<sub>14</sub>H<sub>18</sub>O<sub>6</sub>N<sub>2</sub>: C, 55.89; H, 5.63; N, 8.69. Found: C, 56.26; H, 5.54; N, 8.67.

The 3,4-dimethylcyclohexanol<sup>3</sup> and the 3,5-dimethylcyclohexanol<sup>4</sup> were prepared in a similar manner. The constants were in agreement with those previously described.

**3-Ethylcyclohexanone.**—This was prepared by oxidation of 3-ethylcyclohexanol with sodium dichromate and sulfuric acid according to the "Organic Syntheses" procedure for the oxidation of menthol to menthone.<sup>5</sup> A yield of 72% of a liquid boiling at 81° (12 mm.) and at 99-100° (39 mm.) was obtained;  $n_D^{20}$  1.4499;  $d_4^{20}$  0.9145.

*Anal.* Calcd. for C<sub>8</sub>H<sub>14</sub>O: C, 76.21; H, 11.19. Found: C, 76.02; H, 11.27.

The semicarbazone of 3-ethylcyclohexanone melted at 166-167° after recrystallization from aqueous ethanol.

*Anal.* Calcd. for C<sub>8</sub>H<sub>17</sub>ON<sub>3</sub>: C, 58.99; H, 9.36; N, 22.93. Found: C, 59.23; H, 9.57; N, 23.07.

The *p*-nitrophenylhydrazone of 3-ethylcyclohexanone after recrystallization from petroleum ether (b. p. 60-110°) melted at 128-129° (cor.).

These data are not completely in accord with those given by Braun, Mannes and Reuter.<sup>6</sup> They obtained this

ketone by dry distillation of the calcium salt of  $\beta$ -ethylpimelic acid and report b. p. 192-194°,  $n_D^{20}$  1.4543; semicarbazone, m. p. 184°, *p*-nitrophenylhydrazone, m. p. 130°.

3,4-Dimethylcyclohexanone<sup>7</sup> and 3,5-dimethylcyclohexanone<sup>4</sup> were prepared in 70 and 73% yields, respectively, in the same manner as 3-ethylcyclohexanone.

3,3-Dimethylcyclohexanone was synthesized by the method of Crossley and Renouf<sup>8</sup> and cycloheptanone by ring expansion of cyclohexanone.<sup>9</sup>

All the ketones were readily converted to the keto esters by addition of a mixture of one mole of ketone and one mole of ethyl oxalate to one mole of sodium ethoxide in ethanol to form the glyoxylic esters. These were pyrolyzed, without purification, over powdered soft glass and a trace of iron powder.<sup>1,10</sup> These keto esters, with the exception of ethyl cycloheptanone-2-carboxylate, are new compounds and are listed in Table II.

**Ethyl Cycloheptanone-2-carboxylate.**—This ester was obtained by the above-mentioned procedure in 14% yield, b. p. 77-79° (0.04 mm.);  $n_D^{20}$  1.4700; copper salt, m. p. 193-194° (cor.); the 1-phenyl-3,4-pentamethylene-5-pyrazolone obtained by treatment of the ester with phenylhydrazine melted at 207-210° (cor.) with decomposition. Dieckmann<sup>11</sup> prepared this ester by the cyclization of diethylsuberate and reported b. p. 110-115° (12 mm.); copper salt, m. p. 195°; phenylpyrazolone, m. p. 210°.

**1-Hydroxy-3-*n*-amyl- $\alpha$ -alkyl-7,8,9,10-tetrahydro-6-dibenzopyrones.**—These were prepared from the keto esters

TABLE III

 1-HYDROXY-3-*n*-AMYL- $\alpha$ -7,8,9,10-TETRAHYDRO-6-DIBENZOPYRONE

Substituent	Crystallized from methanol, m. p. ° (cor.)	Yield, %	Anal. Calcd. for	
			C <sub>29</sub> H <sub>38</sub> O <sub>3</sub> : C, 8.34. Found: C	H
9-Ethyl	167-169	46	77.51	8.64
9,9-Dimethyl	190-190.5	33	76.70	8.75
8,9-Dimethyl	174.5-175.5	61	76.58	8.23
7,9-Dimethyl	151.5-152.5	63	76.55	8.20
3,4-Pentamethylene-5-hydroxy-7- <i>n</i> - amylcoumarin	178.5-179.0	45	75.81	8.00

(7) v. Auwers, Hinterseber and Treppmann, *Ann.*, **410**, 257 (1915).

(8) Crossley and Renouf, *J. Chem. Soc.*, **91**, 63 (1907); v. Auwers and Lange, *Ann.*, **401**, 325 (1913).

(9) Kohler, Tishler, Potter and Thompson, *This Journal*, **61**, 1059 (1939).

(10) Shapiro, Thesis, Master of Science, University of Illinois, 1940.

(11) Dieckmann, *Ber.*, **55B**, 2470 (1922).

(3) v. Auwers, *Ann.*, **420**, 84 (1920).

(4) v. Braun and Haensel, *Ber.*, **59B**, 1999 (1926).

(5) "Organic Syntheses," Coll. Vol. I (rev. ed.), p. 240.

(6) Braun, Mannes and Reuter, *Ber.*, **66B**, 1499 (1933).

TABLE IV  
1-HYDROXY-3-*n*-AMYL-7,6,6-DIMETHYL-7,8,9,10-TETRAHYDRO-6-DIBENZOPYRANS

Substituent	B. p. °/bath °/mm.		Mm.	Yield, %	$n_D^{20}$	Anal. Calcd. for $C_{21}H_{25}O_2$ : C.	
	°C.	Bath				80.44; H, 9.82.	Found:
9-Ethyl	172	187	0.1	83	1.5530	80.68	9.68
9,9-Dimethyl	M. p. 89-89.5			78			
8,9-Dimethyl	181-182	210-220	.05	97	1.5512	80.43	9.52
7,9-Dimethyl	186	190	.05	64	1.5473	80.13	9.61
						Anal. Calcd. for $C_{21}H_{25}O_2$ : C.	
						80.20; H, 9.62. Found:	
2,2-Dimethyl-3,4-pentamethylene-5-hydroxy-7- <i>n</i> -amyl-1,2-benzopyran	180-182	190	.05	71	1.5575	80.23	9.30

by the general procedure previously described.<sup>12</sup> The constants of these molecules are given in Table III.

**1-Hydroxy-3-*n*-amyl-7,6,6-dimethyl-7,8,9,10-tetrahydro-6-dibenzopyrans.**—The pyrans were formed in the usual way<sup>12</sup>; constants are given in Table IV.

### Summary

1. The following pyrans: (1) 1-hydroxy-3-*n*-amyl - 6,6 - dimethyl - 9 - ethyl - 7,8,9,10 - tetrahydro-6-dibenzopyran, (2) 1-hydroxy-3-*n*-amyl-6,6,9,9 - tetramethyl - 7,8,9,10 - tetrahydro - 6 - dibenzopyran, (3) 1-hydroxy-3-*n*-amyl-6,6,8,9-

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

tetramethyl - 7,8,9,10 - tetrahydro - 6 - dibenzopyran, (4) 1-hydroxy-3-*n*-amyl-6,6,7,9-tetramethyl-7,8,9,10-tetrahydro-6-dibenzopyran, and (5) 2,2-dimethyl-3,4-pentamethylene-5-hydroxy-7-*n*-amyl-1,2-benzopyran have been synthesized.

2. The pharmacological potencies of (1), (2), (3), and (5) are only about 10 to 20% that of the synthetic tetrahydrocannabinol standard; the potency of (4) is only slightly less than that of the standard, but the activity of this compound is accompanied by a convulsant action.

URBANA, ILLINOIS

RECEIVED AUGUST 5, 1942

[CONTRIBUTION FROM THE KEDZIE CHEMICAL LABORATORY, MICHIGAN STATE COLLEGE]

## The Condensation of Methyl Dipropyl Carbinols with Phenol in the Presence of Aluminum Chloride

BY RALPH C. HUSTON AND CARL R. MELOY<sup>1</sup>

Previous papers from this Laboratory<sup>2,3</sup> have described the condensations of *t*-butyl, *t*-amyl the *t*-hexyl and the *t*-heptyl alcohols with phenol in the presence of aluminum chloride. In a similar manner the dimethylamyl,<sup>4</sup> methylethylbutyl,<sup>5</sup> and diethylpropyl<sup>6</sup> carbinols have been condensed with phenol. In continuation of this investigation the methyldipropyl carbinols have now been prepared.

The 4-methylheptanol-4<sup>7</sup> was prepared by treating two moles of *n*-propylmagnesium bromide with one mole of ethyl acetate, while the 2,3-dimethylhexanol-3<sup>8</sup> resulted from the treat-

ment of one mole of the above Grignard reagent with one mole of 2-methylbutanone-3. Methyl Grignard was used with 2,4-dimethylpentanone-3 in preparing 2,3,4-trimethylpentanol-3.<sup>9</sup>

The alcohols were condensed with phenol in the presence of the anhydrous aluminum salt. Yields of from 47 to 65% of the *p-t*-alkylphenols were obtained with no isolation of other isomers or disubstituted products. The  $\alpha$ -naphthylurethans and 3,5-dinitrobenzoyl esters of the three *p-t*-alkylphenols were prepared.

Huston and Cline<sup>10</sup> isolated and identified from condensations between benzene and methyldipropyl carbinols, 4-methyl-4-phenylheptane, 2,3-dimethyl-3-phenylhexane, and 2,3,4-trimethyl-3-phenylpentane. These alkylbenzenes were nitrated, reduced, diazotized and hydrolyzed to the phenols.<sup>2,3,4</sup> The melting points and mixed melt-

(9) Whitmore and Laughlin, *ibid.*, **54**, 4392 (1932).

(10) Huston and Cline, Master's Thesis, Michigan State College, 1939.

(1) Taken from a thesis presented in partial fulfillment of requirements for the Ph.D. degree.

(2) Huston and Hsieh, *THIS JOURNAL*, **58**, 439 (1936).

(3) Huston and Hedrick, *ibid.*, **59**, 2001 (1937).

(4) Huston and Guile, *ibid.*, **61**, 69 (1939).

(5) Huston and Snyder, Master's Thesis, Michigan State College, 1938.

(6) Huston and Langdon, Master's Thesis, Michigan State College, 1938.

(7) Gortalow and Saytzeff, *J. prakt. Chem.*, **33**, 203 (1886).

(8) Clarke, *THIS JOURNAL*, **33**, 528 (1911).