TABLE IV

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

Substituent	B. p. °/bath °/mm. °C.	Bath	Mm.	Yield, %	$n^{20}D$	*Anal.* Calcd. for $C_{21}H_{32}O_2$: C, 80.44; H, 9.82. Found: C	H
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
2,2-Dimethyl-3,4-pentamethylene-5-hydroxy-7-*n*-amyl-1,2-benzopyran	180–182	190	.05	71	1.5575	*Anal.* Calcd. for $C_{21}H_{30}O_2$: C, 80.20; H, 9.62. Found: C 80.23	H 9.30

by the general procedure previously described.[12] The constants of these molecules are given in Table III.

1-Hydroxy-3-*n*-amyl-?-6,6-dimethyl-7,8,9,10-tetrahydro-6-dibenzopyrans.—The pyrans were formed in the usual way[12]; 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-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.

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

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[1]

Previous papers from this Laboratory[2,3] 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,[4] methylethylbutyl,[5] and diethylpropyl[6] carbinols have been condensed with phenol. In continuation of this investigation the methyldipropyl carbinols have now been prepared.

The 4-methylheptanol-4[7] was prepared by treating two moles of *n*-propylmagnesium bromide with one mole of ethyl acetate, while the 2,3-dimethylhexanol-3[8] resulted from the treatment 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.[9]

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 α-naphthylurethans and 3,5-dinitrobenzoyl esters of the three *p*-*t*-alkylphenols were prepared.

Huston and Cline[10] 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.[2,3,4] The melting points and mixed melt-

(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).

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

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

TABLE I

CONDENSATION OF METHYLDIPROPYLCARBINOL WITH PHENOL

Product	4-Methyl-4-*p*-hydroxyphenylheptane	2,3-Dimethyl-3-*p*-hydroxyphenylhexane	2,3,4-Trimethyl-3-*p*-hydroxyphenylpentane
Yield, %	65	47	60
M. p., °C.	63–63.5	72–73	57–58.5
B. p. °C.	282–284	151–152 279–281	122–124 275–277 116–117
B. p. Mm.	738	6 738	2 738 2
Carbon, % (calcd. 81.50)	81.17	80.91	80.96
Hydrogen, % (calcd. 10.75)	10.68	10.77	10.81
3,5-Dinitrobenzoyl esters M. p., °C.	124.5–126.0	97.0–98.0	103.0–103.5
3,5-Dinitrobenzoyl esters N, % (calcd. 7.00)	6.97	7.01	6.98
α-Naphthylurethans M. p., °C.	105.0–106.0	127.5–128.5	106.0–107.0
α-Naphthylurethans N, % (calcd. 3.73)	3.72	3.69	3.70

ing point determinations of the α-naphthylurethans of the phenols thus prepared indicated that they were the same as those prepared in the condensations. The position of the entering group was established through oxidation[11] of the *p*-nitro-*t*-alkylbenzene by heating a portion with 6 *N* nitric acid in a sealed Carius tube at 130°. In each case the product obtained was *p*-nitrobenzoic acid, which was identified by melting point and mixed melting point.

In answer to the suggestion that the alkyl groups might rearrange during condensation and to eliminate any doubt as to the correctness of the formulas assigned the tertiary-octylphenols, attention is called to the following:

(a) The alcohols were prepared by standard methods and checked as to properties with the literature.

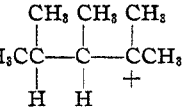
(b) In the rearrangement of alkyl groups during processes of condensation, primary groups may change to secondary or tertiary, and secondary groups may change to tertiary.[12]

We were unable to find instances of the reverse processes in which appreciable yields of primary or secondary groups were formed from groups of higher branching. These generalizations have been recently confirmd by a study of the condensation of secondary alcohols with benzene[13] and with phenol.[14]

(c) Two other possibilities of formation of tertiary octylphenols from 2,3,4-trimethylpentanol-2 might be proposed.

1. One of the tertiary hydrogens might shift to the number three carbon by the intermediate formation of 2,3,4-pentene-2 and the addition of hydrochloric acid. The product of condensation would then be 2,3,4-trimethyl-2-*p*-hydroxyphenylpentane[4] which melts at 74° and gives an α-naphthylurethan which melts at 115°.

2. The formation of the cation



might cause the migration of the methyl group on number three carbon to number two carbon which change might be followed by a migration of the tertiary hydrogen as outlined under (1). Condensation would then give 2,4,4-trimethyl-2-*p*-hydroxyphenylpentane.[4] This phenol melts at 83° and its α-naphthylurethan melts at 102°.

(d) There appears to be only one possibility of rearrangement in the case of 2,3-dimethylhexanol-3. Migration of the tertiary hydrogen would give 2,3-dimethyl-2-*p*-hydroxyphenylhexane[4] as the product of condensation. This compound is a liquid (b. p. 293°) which gives an α-naphthylurethan melting at 105°.

(e) Since 4-methylheptanol-4 contains no tertiary hydrogen, rearrangement without fragmentation does not appear to be possible.

(f) The *seventeen* possible tertiary octyl alcohols have been condensed with phenol yielding *seventeen* different *p*-*t*-octylphenols.[4,5,6]

Experimental

Condensations.—Since all of the condensations were carried out in a similar manner, a typical run is described. Thirty-five grams of phenol was dissolved in 32.5 g. of the octyl alcohol in a 500-ml., three-necked, round-bottomed flask equipped with a short reflux condenser, a

(11) Anschütz and Beckerhoff, *Ann.*, **327**, 219 (1903).

(12) Konowalow, *J. Russ. Phys.-Chem. Soc.*, **27**, 457 (1896); Estreicher, *Ber.*, **33**, 439 (1900); Schramm, *Monatsh.*, **9**, 613, 615 (1888); Grossin, *Bull. soc. chim.*, [2] **41**, 446 (1884); Verley, *ibid.*, [3] **19**, 72 (1898); Meyer and Bernhauer, *Monatsh.*, **53**, 721 (1929); Gilman and Calloway, THIS JOURNAL, **55**, 4197 (1933); Laughlin, Nash and Whitmore, *ibid.*, **56**, 1395 (1934); Ipatieff, Pines and Schmerling, *ibid.*, **60**, 353 (1938), etc.

(13) Huston and Kaye, THIS JOURNAL, **64**, 1576 (1942).

(14) Huston, Guile, Esterdahl and Curtis, "Condensation of Secondary Alcohols with Phenol in the Presence of Aluminum Chloride," in process of publication.

thermometer and a glycerol-sealed stirrer. Seventeen grams of anhydrous aluminum chloride was added in small portions by shaking from a small Erlenmeyer flask equipped with a long neck made of glass tubing. The reaction was carried out at 25–30° and the temperature kept constant by use of a water-bath, when necessary. After standing overnight the mixture was decomposed by pouring on ice and hydrochloric acid. The condensate was extracted from the water solution with ether and the phenols isolated from this ether extract by fractionation.

The 3,5-dinitrobenzoyl esters were prepared by the method of Shriner and Fuson.[15]

The use of pyridine as a catalyst resulted in high yields of the esters which were recrystallized from 60% alcohol.

The method of French and Wirtel[16] was employed in the preparation of α-naphthylurethans. Addition of a few drops of a solution of trimethylamine in ether caused an immediate reaction. Recrystallization was accomplished from warm petroleum ether.

(15) Shriner and Fuson, "Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1940, p. 138.

(16) French and Wirtel, THIS JOURNAL, **48**, 1736 (1926).

Summary

1. The methyldipropyl carbinols have been condensed with phenol in the presence of aluminum chloride to give good yields of the corresponding *p*-*t*-octylphenols.

2. The 3,5-dinitrobenzoyl esters and the α-naphthylurethans of these *p*-*t*-octylphenols have been prepared.

3. The structures have been established by synthesis.

EAST LANSING, MICHIGAN RECEIVED MAY 16, 1942

[CONTRIBUTION FROM THE LEDERLE LABORATORIES]

Water-soluble Compounds with Antihemorrhagic Activity

BY B. R. BAKER AND G. H. CARLSON

In a search for water-soluble compounds with antihemorrhagic activity, a number of derivatives of 2-methyl-1,4-naphthohydroquinone and of the quinone have been prepared and, to minimize duplication of efforts, the experience of this Laboratory is reported at this time.

The highly active sodium salts of 1-acetoxy-2-methyl-4-naphthyl hydrogen succinate[1] (a summary of bioassays is given in Table III) and of the corresponding hydrogen glutarate were sufficiently soluble for parenteral use but were rapidly decomposed in solution even at ordinary temperature.[2] Both the mono- and the disodium salts of the hydroquinone *bis*-hydrogen glutarate were readily hydrolyzed. Likewise the salt of the hydrogen succinate of 3-methyl-1-naphthol,[3] though somewhat more stable than that of 2-methyl-1,4-naphthohydroquinone, gradually decomposed in aqueous solution and further work with partially esterified polycarboxylic acids was discontinued.

Chloroacetyl chloride readily converted 1-acetoxy-2-methyl-4-naphthol to the acetoxymonochloroacetoxy derivative and the latter, with trimethylamine, yielded the readily soluble quaternary ammonium salt which, like the corresponding diammonium salt prepared from the 1,4-*bis*-chloroacetoxy-2-methylnaphthalene as well as the hydrochloride of 1-acetoxy-4-(β-aminopropionoxy)-2-methylnaphthalene, hydrolyzed in warm, aqueous solution. Accordingly, the purely organic esters proved impractical whether employed in alkaline or acidic media and were not further considered.

Partial esterification of phosphoric, thiophosphoric and sulfuric acids with 1-acetoxy-2-methyl-4-naphthol gave compounds which, as sodium salts, were stable in aqueous solution and could be sterilized by autoclaving. Whereas the phosphate and the sulfate showed antihemorrhagic activity equal to 50 and 35%, respectively, of that of an equimolecular amount of 2-methyl-1,4-naphthoquinone, the thiophosphate was less than

(1) Orientation of the substituents is established by the following reactions. Partial deacetylation of 1,4-diacetoxy-2-methylnaphthalene, prepared by reductive acetylation of 2-methyl-1,4-naphthoquinone [for the method see THIS JOURNAL, **64**, 1096 (1942)], gave an acetoxy-2-methylnaphthol, and its methyl ether, after deacetylation and treatment with ammonium sulfite at 180°, yielded an amine which, as the acetate, was identical with that prepared by reducing the coupling product of 3-methyl-1-naphthol and diazotized sulfanilic acid, acetylating the resulting 2-methyl-aminonaphthol (the hydrochloride of which was readily oxidized to 2-methyl-1,4-naphthoquinone) and converting the acetaminonaphthol to the corresponding methyl ether. By this series of reactions the methoxyl in the acetamino derivative and the acetoxyl group in the acetoxy-2-methylnaphthol are fixed in the 4- and 1-positions, respectively.

(2) The instability of apparently this same hydrogen succinate has been reported also by Buck and Ardis, THIS JOURNAL, **64**, 725 (1942).

(3) The naphthol and 3-methyl-1-tetralone [(a) Bachmann and Struve, THIS JOURNAL, **62**, 1618 (1940); (b) Tishler, Fieser and Wendler, *ibid.*, **62**, 2879 (1940)] were prepared by the improved methods given in the experimental section.