[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SHARP AND DOHME]

THE PREPARATION OF THE ACYL AND ALKYL DERIVATIVES OF RESORCINOL

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Since the announcement by Veader Leonard[1] about a year ago that *n*-hexylresorcinol possessed all of the qualifications enumerated by Davis, White and their co-workers[2] as essential to the ideal internal urinary antiseptic, great interest has been manifested by the medical profession in observing the clinical application of this substance in the treatment of infections of the urinary tract. Reports by a number of independent investigators[3] have already appeared in the medical journals corroborating Leonard's original clinical observations, while further clinical experience by Leonard and his associates[4] has confirmed their earlier findings as to the therapeutic efficiency of the drug.

Owing to the important place which hexylresorcinol has apparently assumed in medicine and for the reason that the writers originally undertook to synthesize the higher alkyl resorcinols in coöperation with Leonard's researches, it seems advisable to record the chemical aspects of this work together with a brief description of the new compounds produced.

In 1913 Johnson and Hodge[5] reported the synthesis of ethyl- and *n*-propylresorcinol by means of a condensation of the corresponding fatty acid with resorcinol in the presence of zinc chloride, according to the method of Nencki and Sieber[6] and Goldzweig and Kaiser,[7] and reduction of the ketone thus obtained with zinc amalgam and hydrochloric acid[8] while in 1921 Johnson and Lane[9] reported the synthesis of *n*-butylresorcinol by the same method.

In 1894 Komarowsky and Kostanecki[10] obtained benzoylresorcinol by condensing benzoic acid with resorcinol in the presence of zinc chloride. They also employed various substituted benzoic acids in this reaction but

[1] Leonard, *J. Am. Med. Assoc.*, **83**, 2005 (1924); *J. Urol.*, **12**, 6, 585 (1924).

[2] Davis, *J. Am. Med. Assoc.*, **70**, 581 (1918). Davis and White, *J. Urol.*, **2**, 107 (1918). Davis, White and Rosen, *ibid.*, **2**, 277 (1918). Davis, *ibid.*, **2**, 299 (1918); *Am. J. Med. Sci.*, **161**, 251 (1921); *J. Urol.*, **5**, 215 (1921).

[3] Henline, *J. Urol.*, **14**, 2 (1925). McCurry, *J. Am. Med. Assoc.*, **84**, 25, 1950 (1925). Elliott and Barbour, *Canadian Med. Assoc. J.*, **15**, 787 (1925).

[4] Leonard and Wood, *J. Am. Med. Assoc.*, **85**, 1855 (1925). Leonard and Frobisher, *J. Urol.*, **1**, 15, 1 (1926).

[5] Johnson and Hodge, THIS JOURNAL, **35**, 1014 (1913).

[6] Nencki and Sieber, *J. prakt. Chem.*, **23**, 150 (1881).

[7] Goldzweig and Kaiser, *ibid.*, **43**, 90 (1891).

[8] Clemmensen, *Ber.*, **46**, 1837 (1913).

[9] Johnson and Lane, THIS JOURNAL, **43**, 348 (1921).

[10] Komarowsky and Kostanecki, *Ber.*, **27**, 1997 (1894).

in no case did they reduce the resulting ketones. The chief interest in their work is their proof of the position of the benzoyl group as *ortho* to one hydroxyl group and *para* to the other.

In 1921, Karrer and Rosenfeld[11] prepared *n*-butyryl-, *iso*-hexylyl-, *n*-heptylyl- and *n*-octylylresorcinols by condensation of the acid nitriles with resorcinol in the presence of hydrogen chloride and subsequent hydrolysis of the resulting ketimide.

Among the most striking features of the investigations reported by Johnson and his associates were the reports by Rettger[12] of the pronounced rise in bactericidal power displayed by these compounds with each increase in the mass of the alkyl chain, while Leonard working later with our products found that, in spite of this rise, there was a coincident drop in their toxicity to laboratory animals.

During the past three years this interesting series of compounds has been under investigation in our Laboratories. We have prepared in pure crystalline form many of the normal alkyl resorcinols together with their corresponding ketones from the propyl to the octyl as well as the dodecyl derivatives. In addition, we have obtained in pure crystalline form the *iso*butyl, *iso*-amyl and *iso*-hexyl derivatives together with their intermediate ketones.

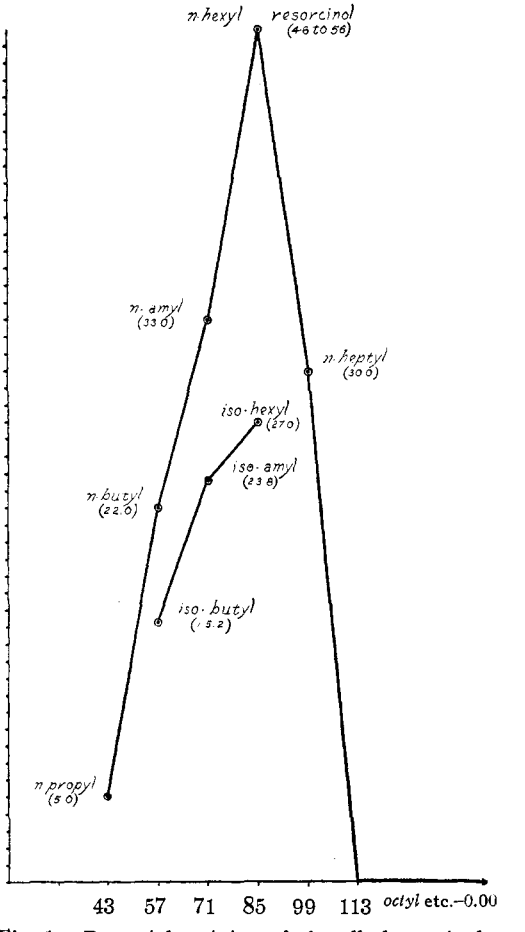

Fig. 1.—Bacterial activity of the alkylresorcinols. This curve is obtained by plotting the phenol coefficients (U. S. Hygienic Laboratory technic) as ordinates against the sum of the atomic weights of the atoms in the alkyl chain as abscissas.

These compounds were all examined by Leonard and his associates in

[11] Karrer and Rosenfeld, *Helvetica Chim. Acta*, **4**, 707 (1921).

[12] See papers by Johnson and Lane, Ref. 9.

the Department of Bacteriology of the Johns Hopkins School of Hygiene and Public Health and formed the basis of this report[13] before the symposium on "Chemistry in the Field of Micro-biology," at the last annual meeting of the American Chemical Society (Baltimore, 1925). The results reported at that time are shown in Fig. 1. It will be seen that there is a pronounced and steady rise in the phenol coefficient as the series is ascended, up to and including *n*-hexylresorcinol which occupies the peak of the curve, a sharp drop with *n*-heptylresorcinol and finally complete disappearance of bactericidal properties with octylresorcinol and the higher members of the series examined.

Experimental Part

The initial experiments were carried out in accordance with the procedure given by Johnson and Lane for the preparation of the acyl resorcinols. Their method was soon modified, however, since it was early observed that the higher temperatures materially increase the quantity of a tarry by-product which is not distillable, especially when large quantities are used, and also that the amounts of resorcinol and zinc chloride prescribed were partially responsible for this increase. If smaller quantities of these reagents are employed and the temperature is maintained at about 125–135° during the condensation, better yields and purer products are secured. In this connection it is well known that resorcinol acts upon itself when heated in the presence of zinc chloride with the formation of compounds closely resembling the fluoresceins.

During the reduction of the acyl resorcinols by the Clemmensen method, the reaction mixture is stirred vigorously. Reduction may be considered to be complete when a small portion of the reaction mixture in alcoholic solution shows no red color when treated with a few drops of ferric chloride. As there is no essential variation in the experimental procedure employed in the preparation of the different members of this series, but one example, that of the preparation of hexylylresorcinol and hexylresorcinol, will be given. The physical constants and combustion analyses relative to the remaining members of the series will be found in the table. All the ketones in alcoholic solution give a red coloration upon addition of ferric chloride solution, while the alkyl resorcinols give a greenish-yellow color with ferric chloride solution.

Hexylylresorcinol, $C_6H_3(COC_5H_{11}).(OH)_2(1,2,4)$.—To a solution of 125 g. of anhydrous zinc chloride in 300 g. of caproic acid (the process of solution being aided by vigorous stirring and heating) is slowly added 95 g. of resorcinol and the temperature is kept at about 125–135°. After the addition of the phenol the reaction mixture is stirred for about two hours while the above-mentioned temperature is maintained. At the end

[13] Leonard, *Science*, **62**, No. 1610, 408 (1925).

of this time cold water is added and the solution stirred. The oily layer which separates is washed three times with cold water. With some of the higher fatty acids there is a tendency to form the corresponding zinc salts, which should be filtered off, as their presence causes serious bumping during the distillation.

The washed oil is finally distilled in a vacuum (200–220° at 10 mm.) the water and excess acid distilling first and finally the ketone. On cooling, the distillate solidifies.

The yield of the distilled ketone is calculated on the basis of the amount of acid actually used up in the reaction. For example, in the experiment given above, the following amounts were recovered: hexylylresorcinol, 152 g.; caproic acid, 185 g. The amount of acid actually entering into the reaction was, therefore, 115 g. Theoretically, this amount of acid should yield 206 g. of ketone, so that the actual yield of ketone was about 75%.

This new ketone may be crystallized, in the form of white plates, from a mixture of petroleum ether and toluene and after recrystallization from the same mixed solvent it melts at 54.4° to 56°. The ketone distils without decomposition at 196–198° (6–7 mm.). It is soluble in alcohol, acetone, chloroform and ether, and is slightly soluble in petroleum ether. In alcoholic solution the ketone gives a deep red coloration with a drop of ferric chloride solution.

Anal. Subs., 0.1414: CO_2, 0.3602; H_2O, 0.0998. Calcd. for $C_{12}H_{16}O_3$: C, 69.18; H, 7.74. Found: C, 69.47; H, 7.89.

Hexylresorcinol, $C_6H_5(C_6H_{13}).(OH)_2(1,2,4)$.—The reduction of hexylylresorcinol by the Clemmensen method, namely, with zinc amalgam and dil. hydrochloric acid, was carried out as described by Johnson and Lane, except that the reduction mixture was stirred during the heating and the amount of zinc amalgam employed was only about half that prescribed by them.

One hundred and fifty-two g. of distilled ketone was reduced by 400 g. of zinc amalgam in 1200 cc. of 1:1 hydrochloric acid. If heated and stirred vigorously the reduction may be completed in from six to eight hours. Reduction may be considered to be complete when a few drops of the oily product dissolved in a few cubic centimeters of alcohol show no coloration upon the addition of a drop of ferric chloride solution. The reduced product is washed thrice with water and distilled in vacuum, 190–210° (9 mm.). On cooling, the distillate solidifies; 120 g. of the reduced product was recovered, a yield of about 85%.

This new product, hexylresorcinol, may be crystallized in the form of white needles from a mixture of petroleum ether and ligroin. When further crystallized from petroleum ether it melts at 67.5–69°. It distils without decomposition at 178–180° (6–7 mm.). With ferric chloride it gives a greenish-yellow coloration in alcoholic solution.

Solubility.—Hexylresorcinol is readily soluble in ether, chloroform, acetone, alcohol and vegetable oils, slightly soluble in petroleum ether, and very difficultly soluble in water.

Anal. Subs., 0.1584; CO_2, 0.4292; H_2O, 0.1302. Calcd. for $C_{12}H_{18}O_2$: C, 74.17; H, 9.34. Found: C, 73.90; H, 9.20.

TABLE I

BOILING POINTS, MELTING POINTS AND COMBUSTION ANALYSES OF SOME OF THE HIGHER ACYL AND ALKYL DERIVATIVES OF RESORCINOL[a,b]

	M. p., °C.	B. p., °C. (6–7 mm.)	Subs., g.	Analyses H_2O, g.	CO_2, g.	Calcd., % C	Calcd., % H	Found, % C	Found, % H
ACYL DERIVATIVES									
Amylyl	58.5–60	190–192	0.1432	0.0942	0.3551	68.00	7.27	67.62	7.34
Hexylyl	54.5–56	196–198	.1414	.0998	.3602	69.18	7.74	69.47	7.89
Heptylyl	48–50	204–206	.1631	.1216	.4181	70.22	8.17	69.90	8.32
Octylyl	62.5–64	214–216	.1163	.0854	.3016	71.14	8.53	70.72	8.20
Dodecylyl	84–85.5	237–239	.1401	.1164	.3812	73.92	9.65	74.19	9.27
*iso*Butyryl	67–68.5	173–175	.1562	.0949	.3816	66.64	6.72	66.62	6.78
iso-Amylyl	108–110	183–185	.1790	.1177	.4438	68.00	7.27	67.61	7.34
*iso*Hexylyl	76–77.5	192–194	.1658	.1164	.4202	69.14	7.74	69.11	7.84
ALKYL DERIVATIVES									
Amyl	71.5–73	168–170	0.1998	0.1626	0.5335	73.28	8.95	72.81	9.08
Hexyl	67.5–69	178–180	.1584	.1302	.4292	74.17	9.34	73.74	9.20
Heptyl	73–74.5	186–188	.2024	.1748	.5548	74.94	9.68	74.75	9.65
Octyl	74–75	199–201	.2694	.2411	.7410	75.61	9.98	75.00	9.99
Dodecyl	80–81.5	224–226	.1538	.1529	.4361	77.63	10.87	77.33	11.10
*iso*Butyl	62–63.5	166–168	.1393	.1089	.3676	72.24	8.50	71.96	8.73
iso-Amyl	61–62.5	177–178	.1799	.1464	.4802	73.28	8.95	72.79	9.08
*iso*Hexyl	70–71.5	182–183	.1512	.1217	.4123	74.17	9.34	74.36	8.98

[a] Johnson and Lane describe propylresorcinol as having a melting point of 82–83° and possessing a yellow color, and butylresorcinol as an oil. In repeating this work with certain modifications we find that both of these compounds are colorless crystalline solids, propylresorcinol melting at 81–82° and butylresorcinol at 47–48°.

[b] Nonylylresorcinol (pelargonic acid), b. p. 245–248° (12 mm.); decylylresorcinol (capric acid), b. p. 240–245° (10 mm.); undecylylresorcinol (undecylic acid), b. p. 255–260° (11 mm.); tridecylylresorcinol (tridecylic acid), b. p. 265–270° (11 mm.); α-phenyl-acetylresorcinol (phenylacetic acid), b. p., 220–225° (10 mm.); β-phenyl-propionylresorcinol (hydrocinnamic acid), b. p. 240–245° (12 mm.); nonylresorcinol, b. p. 220–225° (10 mm.); decylresorcinol, b. p. 235–240° (11 mm.); undecylresorcinol, b. p. 230–235° (10 mm.); tridecylresorcinol, b. p. 250–255° (12 mm.); α-phenyl-ethyl-resorcinol, b. p. 210–215° (11 mm.); α-phenyl-propylresorcinol, b. p. 240–45° (16 mm.).

Summary

All of the acyl and alkyl resorcinols thus far prepared may be obtained in crystalline form. The new compounds prepared are as follows:

Acyl Resorcinols.—*n*-Amylyl-, *n*-hexylyl-, *n*-heptylyl-, *n*-octylyl-, *n*-nonylyl-, *n*-decylyl-, *n*-undecylyl-, *n*-dodecylyl-, *n*-tridecylyl-, α-phenyl-acetyl-, β-phenylpropionyl-, *iso*butyryl-, *iso*-amylyl- and *iso*hexylyl resorcinols.

Alkyl Resorcinols.—Propyl-, *n*-butyl-, *n*-amyl-, *n*-hexyl-, *n*-heptyl-, *n*-octyl-, *n*-nonyl-, *n*-decyl-, *n*-undecyl-, *n*-dodecyl-, *n*-tridecyl-, β-phenyl-ethyl-, β-phenyl-propyl-, *iso*butyl-, *iso*-amyl-, *iso*hexylresorcinols.

The chief interest in this series of compounds lies in its biological rather than in its chemical importance. Of the groups hexylresorcinol stands out as the most interesting product because of its importance as a therapeutic agent.

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THE REACTION BETWEEN DUROQUINONE AND SODIUM MALONIC ESTERS[1]

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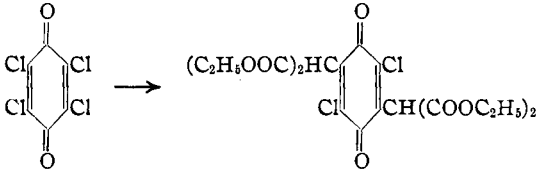
Malonic ester has been added to a great many α,β-unsaturated carbonyl systems, and the results of these reactions have been interpreted variously by Michael, Vorlander, Thiele and others. Perhaps the most complex α,β-carbonyl systems may be found in benzoquinone and its derivatives, for in such a substance there are two independent, and four dependent, conjugated systems, of four atoms each, two conjugated systems of six atoms each, besides the two carbonyl groups and the two double bonds, which might function independently of each other. Hence, the addition of such a reagent as malonic ester to a *p*-benzoquinone should lead to some very interesting results.

A review of the literature shows that very little work has been done on the reaction between malonic ester and benzoquinone derivatives. Practically all the work reported has been carried out with halogenated quinones such as bromanil, and the results can be explained in more than one way. Thus, Stieglitz,[2] in an attempt to prepare benzoquinone carboxylic acids, allowed sodium malonic ester to react with chloranil, obtaining a small yield of the *p*-dichlorodimalonic diethyl ester of benzoquinone. Later,



C. L. Jackson and his co-workers[3] replaced the halogen atoms in chloranil and bromanil with malonic ester and various alkoxyl groups, but only two of the halogen atoms could be so replaced. Liebermann and his

[1] Abstracted from a thesis by F. J. Dobrovolny, presented to the Graduate Faculty of the University of Minnesota, in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

[2] Stieglitz, *Am. Chem. J.*, **13**, 38 (1891).

[3] Jackson and co-workers, *Am. Chem. J.*, **17**, 597 (1895). *Proc. Am. Acad. Sci.*, **30**, 409 (1894).