

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ALBERTA]

## Some Alkylresorcinolcarboxylic Acids, their Germicidal Properties and Mercuration

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In this Laboratory ethyl and hexylresorcinol have been mercured to give mono and dimercuri derivatives.<sup>1</sup> These compounds were found to be only slightly soluble in dilute alkali solutions; moreover, the solutions thus produced soon gave deposits of metallic mercury. In view of these facts it was thought that the mercured alkylresorcinolcarboxylic acids would perhaps yield mercury compounds which would be more soluble and possibly more stable in alkali solutions. The present communication deals chiefly with the preparation and mercuration of ethyl, *n*-propyl, *n*-butyl and *n*-hexylresorcinolcarboxylic acids. Bleyer<sup>2</sup> has examined some physiological effects of alkylresorcinolcarboxylic acids (including 5-ethyl and 5-hexyl- $\beta$ -resorcylic acids<sup>3,4</sup>) and their dependence on the constitution of the alkyl side chains. He has found that only with the introduction of an amyl group do the cytolytic, homogenizing and toxin-destroying properties appear and attain great importance in the hexyl and heptyl compounds. Sabalitschka and Tietz<sup>5</sup> have studied the relation between chemical constitution and antimicrobial action. Their work includes various resorcylic acid derivatives such as 5-hexyl- $\beta$ -resorcylic acid. Hoffmann-La Roche and Company<sup>6</sup> have also worked on the 5-hexyl- $\beta$ -resorcylic and the 5-hexyl- $\gamma$ -resorcylic acids.

Because of the solubility of 4-ethyl and 4-*n*-propylresorcinol in water, the carboxylation of these two compounds was readily carried out with potassium bicarbonate in aqueous solution. This is similar to the preparation of  $\beta$ -resorcylic acid.<sup>7</sup> Although there is no direct proof for the structure of the two acids thus prepared, the authors believe that they are 5-ethyl- and 5-*n*-propyl- $\beta$ -resorcylic acids. By a similar procedure, Moore, Day and Suter<sup>8</sup> have recently prepared 5-*n*-butyl- $\beta$ -resorcylic acid from 4-*n*-butylresor-

cinol. Due to the limited solubility of *n*-butylresorcinol in water, the carboxylation of this compound was carried out by the method of Robertson and Robinson<sup>9</sup> in their preparation of *p*-orsellinic acid, using glycerol as the solvent. It is believed that by this procedure the carboxyl group enters the ortho position with respect to both hydroxyl groups. This belief seems to be substantiated by the fact that the 5-*n*-butyl- $\beta$ -resorcylic acid<sup>8</sup> prepared by carboxylation in aqueous solution melts at 172–173°, whereas the carboxylation of *n*-butylresorcinol in glycerol gives an acid melting at 115–116°.

Moore, Day and Suter<sup>8</sup> have shown that the introduction of the carboxyl group into *n*-butylresorcinol reduced the germicidal activity enough to prevent measuring the phenol coefficient of the acid when 20% alcohol was the solvent. The same effect has been found by the authors working with the sodium salts of the carboxylic acids and using *Bacillus typhosus* as the test organism. The phenol coefficients<sup>10</sup> were determined by the modified Rideal-Walker method.<sup>11</sup> The results are briefly summarized in Table I. For the sake of comparison the phenol coefficients of the uncarboxylated compounds as found by Dohme, Cox and Miller<sup>12</sup> are also shown.

TABLE I

Alkyl resorcinol	Phenol coeff- icients	Alkyl- resorcinol- carboxylic acid	Phenol coeff- icients
Ethyl	...	Ethyl	<0.7
Propyl	5	Propyl	< .7
Butyl	22	Butyl	.9
Hexyl	46–56	Hexyl	1.6

The acids were readily mercured in dilute alcoholic solution by the theoretical amount of mercuric acetate. The acetoxy group was immediately hydrolyzed to give hydroxymercuri and anhydromercuri compounds, the latter often being colored. The mercured compounds were soluble in dilute aqueous alkali but were disappointing in that they soon gave deposits of metal-

(1) Sandin, *THIS JOURNAL*, **51**, 479 (1929).(2) Bleyer, *Biochem. Z.*, **181**, 350 (1927).

(3) Made by F. Hoffmann-La Roche and Co., Basel.

(4) By  $\beta$ -resorcylic acid is meant, 2,4-dihydroxybenzoic acid. In the latter part of this paper,  $\gamma$ -resorcylic acid refers to 2,6-dihydroxybenzoic acid.(5) Sabalitschka and Tietz, *Arch. Pharm.*, **269**, 545 (1931).(6) Hoffmann-La Roche and Co., *Chem. Zentr.*, **99**, II, 1487 (1928).

(7) Nierenstein and Clibbens, "Organic Syntheses," John Wiley and Sons, New York, 1930, Vol. X, p. 94.

(8) Moore, Day and Suter, *THIS JOURNAL*, **56**, 2456 (1934).(9) Robertson and Robinson, *J. Chem. Soc.*, 2196 (1927).

(10) The authors express their thanks to Dr. R. M. Shaw of the Department of Bacteriology for valuable suggestions during this part of the work.

(11) Anderson and McClintic, *J. Infect. Dis.*, **8**, 1 (1911).(12) Dohme, Cox and Miller, *THIS JOURNAL*, **48**, 1688 (1926).

lic mercury. For that reason their germicidal powers were not determined.

### Experimental

**5-Ethyl- $\beta$ -resorcylic Acid (?)**.<sup>13</sup>—A solution of 10 g. of ethylresorcinol and 50 g. of potassium bicarbonate dissolved in 100 cc. of water was heated on a water-bath for four hours. It was then refluxed for one-half hour, during which time a rapid stream of carbon dioxide was passed through the solution. The dark red liquid was acidified while still hot with concentrated hydrochloric acid and on cooling a very bulky fibrous precipitate separated. The precipitate was collected on a filter, washed and crystallized from water. The yield was 4 g.

On repeating this experiment with longer heating (six hours) and with a longer passage of carbon dioxide (two hours) the yield was still 4 g. On working with larger quantities it was found possible after the removal of the first precipitate of carboxylic acid, to add more potassium bicarbonate, repeat the reaction and get a second crop of crystals. This was repeated until, in all, four crops of crystals had been removed from the same solution.

The acid was recrystallized from water three times using decolorizing carbon as required. The pure acid crystallized in white lustrous needles (m. p. 166–170° uncorr.) and was very soluble in hot water.

*Anal.* Calcd. for  $C_9H_{10}O_4$ : C, 59.30; H, 5.54. Found: C, 59.27; H, 5.43.

**5-Propyl- $\beta$ -resorcylic Acid (?)**.—The preparation of this compound was similar to the above. The acid crystallized in white lustrous needles (m. p. 177–182° uncorr.).

*Anal.* Calcd. for  $C_{10}H_{12}O_4$ : C, 61.20; H, 6.17. Found: C, 60.6; H, 6.02.

**5-Butyl- $\gamma$ -resorcylic Acid**.—Twenty grams of butylresorcinol in 40 g. of glycerol was heated at 130° with 40 g. of potassium bicarbonate in an atmosphere of carbon dioxide for three hours. The mixture was then poured into 1 liter of water and acidified. This caused the precipitation of a dark oil which later solidified. The yield of the crude acid was 16 g. It was crystallized from 5% alcohol. It formed white needles resembling the other acids of the series in appearance, m. p. 115–116° uncorr.

*Anal.* Calcd. for  $C_{11}H_{14}O_4$ : C, 62.80; H, 6.71. Found: C, 62.40; H, 6.72.

The mercuration of the alkylresorcinolcarboxylic acids was carried out by a standardized procedure and gave compounds with similar properties. For that reason only the method used for the mercuration of 5-ethyl- $\beta$ -resorcylic acid will be given.

**3-Hydroxymercuri-5-ethyl- $\beta$ -resorcylic Acid**.—A solution containing 7.096 g. (0.039 mole) of the carboxylic acid

in 400 cc. of water and 65 cc. of alcohol was heated on a water-bath. To this was added a hot solution containing 12.44 g. (0.039 mole) of mercuric acetate in 280 cc. of water and 20 cc. of acetic acid. A finely divided precipitate formed immediately. This precipitate, which was yellow for a few seconds, quickly turned white. The mixture was heated until the precipitate became flocculent. It was then filtered, washed with water and dried at 100°; yield, quantitative. The mercurated compound was a white amorphous solid, insoluble in water and in the ordinary organic solvents. It was slightly soluble in hot acetic acid, due probably to the formation of the acetoxymercuri compound. It dissolved in sodium hydroxide solution, but in a short time a deposit of metallic mercury began to form and the solution assumed a brown color. Strong acids readily removed mercury from the compound as the inorganic salt. The analysis indicated it to have the hydroxymercuri structure.

*Anal.* Calcd. for  $C_9H_{10}O_5Hg$ : Hg, 50.30. Found: Hg, 50.35.

**Anhydro-3-hydroxymercuri-5-propyl- $\beta$ -resorcylic Acid**.—The yellow color and the analysis of this compound indicated the anhydro structure.

*Anal.* Calcd. for  $C_{10}H_{10}O_4Hg$ : Hg, 50.81. Found: Hg, 50.65.

**Anhydro-3-hydroxymercuri-5-*n*-butyl- $\gamma$ -resorcylic Acid**.—The precipitate which formed was yellow at first, but on standing turned white.

*Anal.* Calcd. for  $C_{11}H_{12}O_4Hg$ : Hg, 49.04. Found: Hg, 48.46.

Hoffmann-La Roche and Company<sup>6</sup> have described both the 5-hexyl- $\beta$ -resorcylic and 5-hexyl- $\gamma$ -resorcylic acids. The authors have worked with the former compound only.

**Anhydro-3-hydroxymercuri-5-hexyl- $\beta$ -resorcylic Acid**.—This compound was light yellow in color which, with the analysis, indicated the anhydro structure.

*Anal.* Calcd. for  $C_{13}H_{16}O_4Hg$ : Hg, 45.93. Found: Hg, 45.71.

**Mercury Analyses**.—The mercury analyses were carried out by decomposing the compounds with hydrochloric acid and precipitating the mercury as the sulfide.<sup>14</sup>

### Summary

A number of alkylresorcinolcarboxylic acids have been prepared and mercurated. The germicidal properties of the unmercurated acids have been investigated.

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(13) Bleyer, *Biochem. Z.*, **181**, 350 (1927), does not report the preparation or properties of this compound.

(14) Whitmore, "Organic Compounds of Mercury," Chemical Catalog Co., New York, 1921, p. 362.