sicity, as manifested by solubility in dilute acid, and the reaction of both imino groups, together, with acetic anhydride.

The formation of acetyl derivatives from the condensation products of phenylacetaldehyde and acetophenone with urea furnished additional evidence in favor of the pyrimidine structures and the location of the cyclic double bond, previously assigned to these products.

NEW HAVEN, CONNECTICUT RECEIVED MARCH 5, 1934

[CONTRIBUTION FROM THE LAMBERT PHARMACAL COMPANY]

Alkylchlororesorcinols and Alkyl Ethers of Chlororesorcinol

BY R. R. READ, G. F. REDDISH AND E. M. BURLINGAME

Among the continually increasing number of phenolic substances interesting because of their germicidal properties are the chlorine substituted hydroxy alkylbenzenes. The relationship between germicidal activity, as measured in terms of phenol coefficient, and the nature of substituting groups has been reported upon frequently during the past decade. The work reported here deals with alkylchlororesorcinols and mono alkyl ethers of chlororesorcinol, the chlorine being attached to the nucleus in each case.

Experimental

The alkylchlororesorcinols were all prepared by the procedure shown schematically.

(1) Resorcinol ⟶ chlororesorcinol ⟶ chlororesorcinol ester ⟶ acylchlororesorcinol ⟶ alkylchlororesorcinol

and in a few cases by the procedure

(2) Acylresorcinol ⟶ acylchlororesorcinol ⟶ alkylchlororesorcinol

and in several other instances.

(3) Alkylresorcinol ⟶ alkylchlororesorcinol

The first method seems most satisfactory as not requiring any isolation of intermediates except the chlororesorcinol and in yielding few by-products.

A typical preparation follows: 27.0 g. of chlororesorcinol was melted in a three-necked flask equipped with stirrer, thermometer and reflux; 1.5 g. of anhydrous zinc chloride was added and while the melt was maintained just above the fusing point 32.4 g. of *n*-octanoyl chloride added over a period of twenty minutes. The melt was then maintained at steam-bath temperature one-half hour, after which the temperature was raised to 150° and there maintained one and one-half hours. Without isolating the ketone it was transferred to a larger flask, equipped with a heavy stirrer and reflux, which contained 100 g. of zinc, amalgamated with 2 g. of mercuric chloride, and 200 cc. of 17% hydrochloric acid. This mixture was heated to refluxing temperature while being violently stirred.

The vigor of the stirring and solubility of the ketone determined the reduction time. Alcohol in amounts up to 20% by volume was used when the reduction appeared to proceed too slowly.

After about eight hours the floating oil gave a negative test (olive-green) with alcoholic ferric chloride. The oil was taken up in two volumes of toluene, washed three times with hot water and dried by distilling off the toluene. The resultant oil distilled at 196–204° (6 mm.), the distillate being a white crystalline solid weighing 26 g. Redistillation gave 22 g. boiling at 195–197° (6 mm.). This was crystallized from ligroin and recrystallized from petroleum ether.

Since different bacteriologists vary considerably in their determination on identical products,[1] the phenol coefficient of a related substance is included in Table I for comparative purposes.

TABLE I

Chlororesorcinol derivative	Phenol coefficient[a]	B. p. °C.	B. p. Mm.	M. p., °C.	Chlorine, % Found	Chlorine, % Calcd.
Ethyl	6	140–142	8	solid	21.2	20.6
n-Butyl	45	153–158	5	70–72	17.7	17.7
n-Hexyl	240	172–175	6–7	43	15.4	15.5
n-Heptyl	625	185–187	7	48–49	14.3	14.6
n-Octyl	665	195–197	6	54–56	13.0	13.8
n-Hexyl resorcinol	60					

[a] Coefficients determined by the F. D. A. method using 0.5 cc. of *Staphylococcus aureus* at 20° with the following modification adopted due to low solubility of these substances. The chlorophenol was dissolved in 95% alcohol in such a concentration that the significant determinations were made in 5–8% alcohol solutions. Attempts to use only water as solvent can yield most variable results due to formation of emulsions instead of true solutions.

(1) Read and Miller, THIS JOURNAL, **54**, 1197 (1932), footnote 8; Blicke and Stockhaus, *J. A. Ph. A.*, **22**, 1092 (1933).

The mono alkyl ethers were prepared by the usual procedure, a typical example being: 5.7 g. of sodium was dissolved in 140 cc. of absolute alcohol contained in a flask equipped with stirrer and reflux and dropping funnel; 38.0 g. of chlororesorcinol was dissolved in the alcohol and 48.3 g. of *n*-octyl bromide was added during one hour while the contents of the flask was maintained at refluxing temperature. Refluxing was continued for one hour longer and after standing overnight the alcoholic solution was decanted from the sodium bromide and the alcohol distilled off. The residual oil was taken up in five volumes of toluene and the solution washed three times with hot water. The alkoxyphenol was extracted with a solution of 15 g. of sodium hydroxide in 250 cc. of water, the alkaline solution being used as three equal portions. This extract was acidified with hydrochloric acid, the oil taken up in 100 cc. of toluene and washed three times with hot water, small amounts of hydrochloric acid assisting in breaking the emulsion. A yellow oil was recovered from the toluene boiling at 145–165° (1 mm.) which on redistillation boiled at 184–187° (4–5 mm.); yield 23 g.

TABLE II

Chlororesorcinol mono ether	Phenol coefficient[a]	B. p., °C.	Mm.	Chlorine, % Found	Chlorine, % Calcd.
n-Butyl	50	128–134	1	18.7	17.7
n-Amyl	100	140–150	3	17.3	16.5
n-Hexyl	250	152–162	2	16.2	15.5
n-Heptyl	200	173–183	5	14.5	14.6
n-Octyl	65	184–187	4–5	14.2	13.8

The germicidal activity of the alkylchlororesorcinols is increased by somewhat less than 50% if tested at 37° against *Staphylococcus aureus* instead of at 20°. Since phenol increases in activity more rapidly, the phenol coefficient at 37° is less than at 20°.

As is not unusual with the higher alkylphenols the activity of both the alkylchlororesorcinols and the mono alkyl ethers of chlororesorcinols are much less as measured against *B. typhosus* than against *Staphylococcus aureus*, both at 20°. The values for the ethers are, the typhosus value in ( ) following the aureus value: butyl 50 (36), amyl 100 (50), hexyl 250 (50), heptyl 200 (62), octyl 65 (50). The values for nuclear alkyl substituted chlororesorcinols are, the typhosus value in ( ) following the aureus value: butyl 45 (45), hexyl 240 (70), heptyl 625 (45), octyl 665 (40).

Summary

As indicated by the effect on *Staphylococcus aureus* it appears that chlorine has much the same activating effect on alkylresorcinols as it has on alkylphenols, the effect being somewhat greater, possibly, if allowance is made for the fact that alkylresorcinols are usually much less active than the corresponding alkylphenols. However, as indicated by the effect on *B. typhosus*, chlorine does not have an activating effect. It is not apparent that a definite factor can be used to express the relation between alkylresorcinols and the corresponding alkylchlororesorcinols.

The mono alkyl ethers of chlororesorcinol are very much less active than the corresponding alkylchlororesorcinols against *Staphylococcus aureus*. Against *B. typhosus* they are of practically the same activity.

ST. LOUIS, MO. RECEIVED MARCH 5, 1934

[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA, NO. 126]

The 1,6-Reduction of Cyclic β-Bromobenzoylcrotonic Ester

BY ROBERT E. LUTZ

Cyclic β-bromobenzoylcrotonic methyl ester III, unlike the open chain isomer I, does not possess an unsaturated 1,4-dicarbonyl system, but it contains a somewhat analogous system in which the carbonyl group is conjugated through the double bond with the C—O groups in the γ-position.[1] This investigation was undertaken to test the hypothesis that these two types of conjugated systems may function in a similar sense, particularly with respect to reduction.

In the first paper dealing with the isomeric esters of β-bromobenzoylcrotonic acid[2] the evidence for the structures of the open chain and cyclic compounds I and III was outlined. The two types are reduced with comparable ease by means of zinc and glacial acetic acid but give different products. The *cis* and *trans* isomers I as

(1) In this paper the term conjugation is applied not only to systems of alternate multiple and single bonds, but to any analogous system in which one (or more) of the multiple unions is replaced by the single linkage of a reactive group such as the C—Cl, C—O, C—metal, O—metal, etc. (*cf.* Finkelstein, *Verhandlung d. Gesellschaft Deutscher Naturforscher u. Ärzte*, II, 176 (1911); see also Henrich, "Theories of Organic Chemistry," 1922, pp. 49–50. Such systems of conjugated reactive groups exist in allyl types (the halides, ethers, alcohols and magnesium halides), metal enolates, α-halogeno and hydroxycarbonyl compounds, ethylene dihalides, etc., and show in varying degree reactions which may be interpreted as taking place at the ends.

(2) Lutz and Winne, THIS JOURNAL, **56**, 445 (1934).