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.

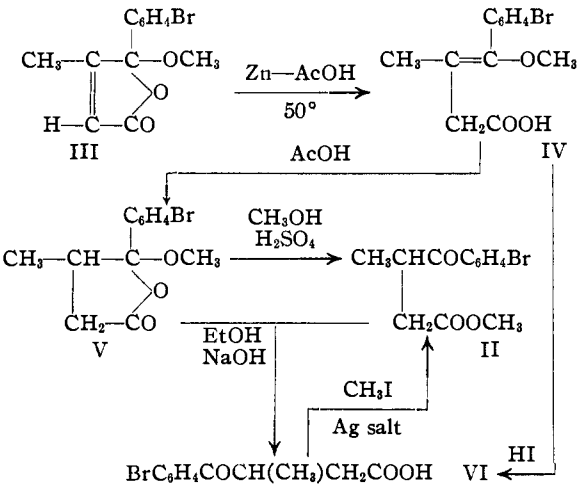
(2) Lutz and Winne, THIS JOURNAL, **56**, 445 (1934).

typical unsaturated 1,4-ketonic esters give β-bromobenzoylbutyric ester II as follows

$$BrC_6H_4COC(CH_3)=CHCOOCH_3 \xrightarrow[AcOH]{Zn} BrC_6H_4COCH(CH_3)CH_2COOCH_3$$

(*cis* and *trans*) I II

The cyclic methyl ester III, however, adds two hydrogen atoms and gives a product which is an *acid* but which is isomeric with β-bromobenzoylbutyric ester II and still contains the methoxyl group. When this acid is heated with glacial acetic acid, it undergoes rearrangement into a *second isomer* which is not an acid, and which is itself rearranged by the action of boiling methanol and sulfuric acid into β-bromobenzoylbutyric ester. The chain of reactions and the structures of the two isomers (IV, V) are represented as follows



The formulation of the acid IV as the methyl ether of the enol form of β-bromobenzoylbutyric acid is established by the following facts. It readily undergoes rearrangement into a γ-lactone V, a type of reaction which is characteristic of β, γ-unsaturated acids.[3] It is not hydrolyzed by short heating with alkali as are the cyclic and open chain β-bromobenzoylbutyric and crotonic esters, but it is quickly demethylated by means of hydriodic acid to give β-bromobenzoylbutyric acid VI. Ozonization gives methyl bromobenzoate and acetoacetic acid. Incidentally, the formulation III of the cyclic unsaturated ester is confirmed by these facts inasmuch as the position of the methoxyl group relative to the bromophenyl is shown. Rearrangements involving the location of the methoxyl group are very unlikely, since it has been shown that the various compounds of this series are stable under the conditions involved in the reduction.

The second isomer of β-bromobenzoylbutyric ester can hardly have any other than the cyclic structure V since the isomeric ester previously described must be of the open chain type II, it having been synthesized[2] from the *cis* and *trans* β-bromobenzoylcrotonic esters I by reduction, and from β-bromobenzoylbutyric acid VI by esterification through the silver salt. The mode of formation of the cyclic ester V through rearrangement of the β,γ-unsaturated acid IV lends support to this formulation.

The cyclic ester V is rearranged into the more stable open chain β-bromobenzoylbutyric ester II when heated with methanol and sulfuric acid. This reaction is in contrast with the rearrangement in the opposite direction of the open-chain unsaturated ester I into the more stable cyclic isomer, III.[2] This difference in stability relationships in the saturated and unsaturated tautomeric pairs (I, III and II, V) must be due to the enforced proximity of the carbonyl and carbomethoxyl groups in the *cis* unsaturated ester, and the lack of this effect in the corresponding saturated compound.

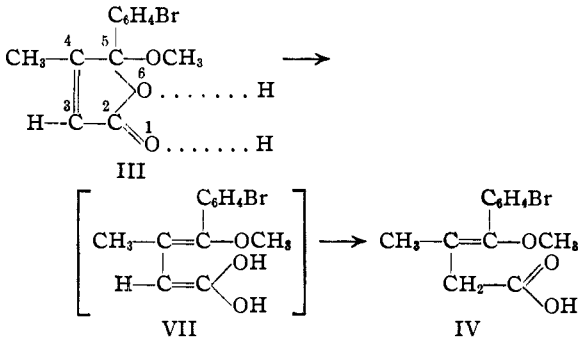
The reduction of the cyclic β-bromobenzoylcrotonic ester obviously does not involve a primary addition of hydrogen either 1,2 to the double bond or to the C—O linkage of the lactone bridge or 1,4 to the α,β-unsaturated carbonyl system, or rearrangement to and subsequent reduction of an unsaturated 1,4-dicarbonyl compound, because none of these mechanisms would account for the formation of IV as the primary reduction product. Two alternative hypotheses which would logically explain the results are 1,4-reduction of the allyl-oxy system C=C—C—O (numbered 3, 4, 5, 6 in formula III) and 1,6-reduction of the longer system[4] O=C—C=C—C—O (numbered 1–6). The 1,6-mechanism is very much the more plausible since it involves addition of hydrogen primarily to oxygen atoms, and since the ease of reduction is practically identical with that of the unsaturated 1,4-dicarbonyl system of the *cis* and *trans* esters.[5] This mech-

(3) Fittig, *Ann.*, **283**, 51 (1894); Fichter, Kiefer and Bernouilli, *Ber.*, **42**, 4710 (1909).

(4) This was misprinted in Ref. 2, p. 446.

(5) For evidence of 1,6-reductions of this class of compounds see (a) Conant and Lutz, THIS JOURNAL, **45**, 1048 (1923); (b) Lutz, *ibid.*, **51**, 3008 (1929); (c) Lutz and Taylor, *ibid.*, **55**, 1595 (1933). The allyl-oxy systems in such types as cinnamyl alcohols [(d) Klages, *Ber.*, **39**, 2587 (1906)] and pseudocodeine [(e) Lutz and Small, THIS JOURNAL, **54**, 4715 (1932); (f) two papers, *ibid.* (submitted for publication)] are much more difficult to reduce.

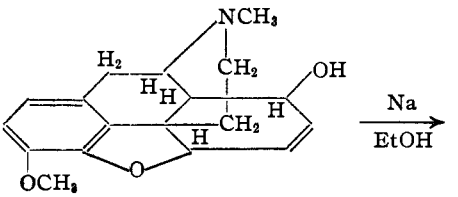
anism is illustrated below as addition of hydrogen at the ends of a typical conjugated system[1] (in which the C—O linkage of the lactone bridge takes the place of one of the C=O groups in the unsaturated 1,4-dicarbonyl system) followed by a shift of the double bonds and rupture of the 5,6-carbon–oxygen linkage, giving the intermediate VII which would promptly tautomerize into the acid IV.



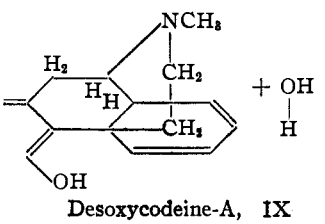
III

VII IV

The course of the reduction as interpreted above is analogous to that of the unsaturated 1,4-dicarbonyl compounds[5] and also to that phase of the reduction of the system O—C—C=C—C—O in pseudocodeine VIII which gives the dihydrodesoxycodeines, presumably through the primary formation of desoxycodeine-A IX.[5f]



Pseudocodeine, VIII



Desoxycodeine-A, IX

Each of these three types of reduction may be interpreted in terms of the addition of hydrogen to the oxygen atoms at the ends of comparable conjugated systems, fortuitous differences arising from the complete severance of oxygen from its point of attachment in the system in the case of the C—O linkages in contrast with the retention of the carbonyl oxygens in the case of conjugated systems of double bonds only. The lactone bridge oxygen (6) of cyclic β-bromobenzoylcrotonic ester III and the ether bridge oxygen of pseudocodeine VIII each remain in the respective molecules, however, through their second points of attachment, ring fission being involved, whereas the oxygen of the alcoholic hydroxyl of pseudocodeine is lost since it has no such second point of attachment.

Further studies in this field are in progress.

Experimental Part

The ease of reduction of cyclic β-bromobenzoylcrotonic methyl ester varies considerably according to the activity of the zinc dust used, some samples giving only partial reduction in glacial acetic acid at 50°. The presence of added zinc oxide was found to inhibit reduction almost completely, even at considerably higher temperatures than this. The most active zinc dust from freshly opened bottles, used in glacial acetic acid at 50°, gave almost complete reduction to the enol methyl ether in about an hour, with the formation of small amounts of the cyclic β-bromobenzoylcrotonic ester due to secondary rearrangement. The presence of added water has little effect on the reactions. Reduction at the boiling point of the solvent gives only the cyclic β-bromobenzoylbutyric ester, as expected, since the primary reduction product IV is unstable and is rearranged under these conditions.

3-(*p*-Bromophenyl)-3-methoxy-2-methyl-2-propene Carboxylic Acid (the Enol Methyl Ether of β-(Bromobenzoyl)-butyric Acid) IV.—A sample of cyclic β-bromobenzoylcrotonic methyl ester in an excess of glacial acetic acid, was treated with a large excess of a good grade of commercial zinc dust from a freshly opened bottle, and the mixture stirred mechanically, the temperature being maintained at 50–55° for three hours. At the beginning the temperature tends to rise and the mixture must be cooled, but toward the end the temperature must be maintained with a warm water-bath. The zinc dust was then filtered off and the solution diluted with water and allowed to stand until the oily product coagulated. It was then washed with water by decantation, and extracted with an excess of sodium bicarbonate solution, the small amount of insoluble material being extracted with ether and recovered. From this non-acidic fraction small amounts of cyclic β-bromobenzoylbutyric ester were isolated and identified. The sodium bicarbonate solution on acidification gave an oil which soon crystallized. The yields averaged 60–75%. It was purified by repeated crystallization from chloroform–ligroin mixtures and from chloroform alone. Care was necessary in working up the residues to avoid excessive heating, which causes considerable rearrangement. It crystallizes as rectangular scales of m. p. 122.5° (corr.). It is soluble directly in sodium bicarbonate solution.

Anal. Calcd. for $C_{12}H_{11}O_3Br$: C, 50.50; H, 4.60. Found: C, 50.36; H, 4.63.

The acid was unaffected by short refluxing with alcoholic sodium hydroxide. Heating for two minutes with hydriodic acid (sp. gr. 1.7) gave β-bromobenzoylbutyric acid in good yield (identified by mixed melting point).

Ozonization for one hour of 0.4 g. of the acid dissolved in a slight excess of aqueous sodium carbonate, gave a

precipitate of pure bromobenzoic methyl ester in 98% yield (identified by mixed melting point with an authentic sample). The filtrate on acidification gave the characteristic color reaction of acetoacetic acid with ferric chloride.

γ - Bromophenyl - γ - methoxy - β - methyl - γ - butyrolactone (Cyclic β-(Bromobenzoylbutyric) Methyl Ester), V.—Is prepared in good yield by the zinc and glacial acetic acid reduction of β-bromobenzoylcrotonic methyl ester at refluxing temperature, or by heating the above enol ether IV in glacial acetic acid for ten minutes at refluxing temperature; purified by repeated recrystallization from ethanol; rhombic truncated prisms of m. p. 98° (corr.).

Anal. Calcd. for $C_{12}H_{11}O_3Br$: C, 50.50; H, 4.60; Br, 28.04. Found: C, 50.49; H, 4.41; Br, 28.47, 28.24.

It was hydrolyzed on heating for one to two minutes with an excess of alcoholic sodium hydroxide in almost quantitative yield to β-bromobenzoylbutyric acid (identified by mixed melting points). A solution of 1.2 g. of the cyclic ester in 10 cc. of methanol with 0.4 cc. of concd. sulfuric acid was refluxed for two hours. Upon diluting with ice water and sodium carbonate solution and extraction with ether, 1.1 g. of the oily open chain β-bromobenzoylbutyric methyl ester was isolated and identified by boiling point (190–192° at 18 mm.), refractive index, n_D^{28} 1.547 (the analytical sample prepared previously[1] showed n_D^{28} 1.549), and by hydrolysis to β-bromobenzoylbutyric acid.

Summary

The zinc–acetic acid reduction of cyclic β-bromobenzoylcrotonic methyl ester gives as the primary reduction product the enol methyl ether of β-(bromobenzoyl)-butyric acid, which is rearranged under suitable conditions first into the cyclic, then into the open chain β-bromobenzoylbutyric methyl ester. The mechanism of the reduction is regarded as a 1,6-addition of hydrogen to a conjugated system of the type O=C—C-=C—C—O.

UNIVERSITY, VIRGINIA RECEIVED MARCH 7, 1934

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE STATE UNIVERSITY OF IOWA]

The Reaction of Chloroamines with Zinc Alkyls

BY GEORGE H. COLEMAN, H. P. ANDERSEN AND J. L. HERMANSON

Following the study of the reaction of monochloroamine[1] with Grignard reagents in which primary amines were formed, the work was extended to alkylchloroamines[2] with the thought of preparing secondary and tertiary amines. Both secondary and tertiary amines are formed by this reaction but the yields of secondary amines do not exceed 25% and the yields of tertiary amines are not above 10%. Tcherniak[3] reported the formation of triethylamine in the reaction of ethyldichloroamine with diethyl zinc.

The present work with zinc alkyls was undertaken for the purpose of comparing the yields of the various amines formed with those obtained with Grignard reagents as well as to determine the possibility of preparing tertiary amines in at least moderate yields.

When petroleum ether was used as a solvent in the reaction the yields of secondary amines were more than double those obtained with the corresponding Grignard reagents. In diethyl ether solution, however, the yields were of about the same order as those obtained with Grignard reagents.

For the preparation of tertiary amines the method has proven to be of no value. In none of the reactions with alkyldichloroamines was enough tertiary amine found to be identified. With dialkylchloroamines less than 2% of tertiary amine was formed.

Diethyl zinc was used in all but one reaction. The results with five chloroamines in diethyl ether

TABLE I

PERCENTAGE YIELDS OF AMINES FROM CHLOROAMINES AND ZINC ALKYLS IN DIETHYL ETHER SOLUTION

Chloroamines	Zinc alkyls	Yields, % Primary amines	Secondary amines	Tertiary amines
CH_3NCl_2	$Zn(C_2H_5)_2$	78	17	...
$C_2H_5NCl_2$	$Zn(C_2H_5)_2$	71	17	...
n-$C_4H_9NCl_2$	$Zn(C_2H_5)_2$	76	18	...
i-$C_5H_{11}NCl_2$	$Zn(C_2H_5)_2$	78	16	...
n-$C_4H_9NCl_2$	$Zn(n$-$C_3H_7)_2$	61	24	...
$(n$-$C_4H_9)_2NCl$	$Zn(C_2H_5)_2$	..	71	1.5

TABLE II

PERCENTAGE YIELDS OF AMINES FROM CHLOROAMINES AND ZINC ALKYLS IN PETROLEUM ETHER SOLUTION

Chloroamines	Zinc alkyls	Yields, % Primary amines	Secondary amines	Tertiary amines
CH_3NCl_2	$Zn(C_2H_5)_2$	44	46	...
$C_2H_5NCl_2$	$Zn(C_2H_5)_2$	49	42	...
n-$C_4H_9NCl_2$	$Zn(C_2H_5)_2$	57	43	...
i-$C_5H_{11}NCl_2$	$Zn(C_2H_5)_2$	52	42	...
$(C_2H_5)_2NCl$	$Zn(C_2H_5)_2$	..	70	1.8

(1) Coleman and Hauser, THIS JOURNAL, **50**, 1193 (1928); Coleman and Yager, *ibid.*, **51**, 567 (1929).
(2) Coleman, *ibid.*, **55**, 3001 (1933).
(3) Tcherniak, *Bull. soc. chim.*, [2] **25**, 166 (1876).