[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD COLLEGE.]

THE BROMINATION AND BROMINE DERIVATIVES OF CERTAIN δ-KETONIC ESTERS.

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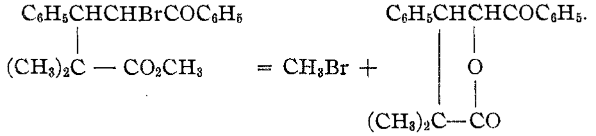
In connection with an investigation on the relative activity of various hydrogen atoms in substances that contain both ketonic and malonic ester groups it became necessary to study the action of bromine on ketonic esters which are so constituted that substitution can take place only in the α-position to the carbonyl group. It was desirable, also, that the resulting bromo-esters should be incapable of forming cyclopropane derivatives by loss of hydrogen bromide. The esters of α,α-dimethyl-β-phenyl-γ-benzoyl-butyric acid, $C_6H_5COCH_2CH(C_6H_5)$-$C(CH_3)_2CO_2H$, are the only known substances that meet both of these requirements. The methyl ester of this acid was, incidentally, treated with bromine by Kohler, Heritage, and Macleod;[1] but neither the resulting reactions nor its products were examined with any care.

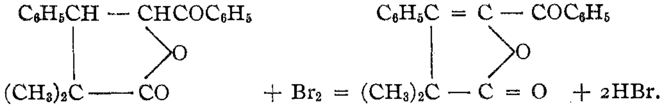
We have studied the bromination of the same ester under a variety of conditions and have found that the result depends upon the temperature, the solvent, and the rapidity with which the bromine is added. When bromine is added slowly to a cold solution of the ester in an indifferent solvent like chloroform the principal product is the bromo-ester already described. The maximum yield is about 75%, the rest of the product being composed, mainly, of two stereoisomeric γ-lactones. These are formed by loss of alkyl halide from the bromo-ester.



$$\begin{array}{l} C_6H_5CHCHBrCOC_6H_5 \\ \qquad | \\ (CH_3)_2C - CO_2CH_3 \end{array} = CH_3Br + \begin{array}{l} C_6H_5CHCHCOC_6H_5. \\ \qquad |\quad\ | \\ \qquad |\quad\ O \\ \qquad |\quad\ | \\ (CH_3)_2C{-}CO \end{array}$$

This process has been observed with simpler γ-bromo-esters;[2] but it takes place here with uncommon ease.

The amount of bromo-ester diminishes, while that of the lactones increases if the temperature is allowed to rise during the reaction, and particularly if the bromine is added too rapidly, a crotolactone may appear as a third by-product. This is due to the action of bromine on the saturated lactones.



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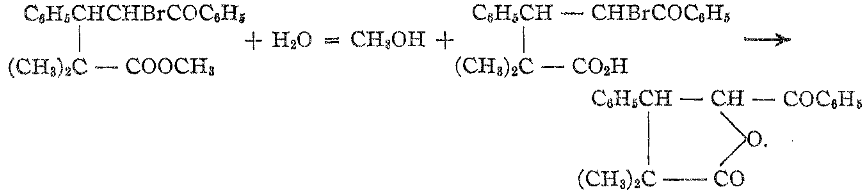
[1] *Am. Chem. J.*, **46**, 216 (1911).

[2] Marburg, *Ann.*, **294**, 104 (1896); Demarcay, *Ann. chim.*, [5] **20**, 433 (1880); Michael, *J. prakt. Chem.*, **37**, 503 (1888); Conrad, *Ber.*, **22**, 1005 (1889); Walden, *Ibid.*, **24**, 2025 (1891); Anschutz, *Ann.*, **353**, 148 (1907).

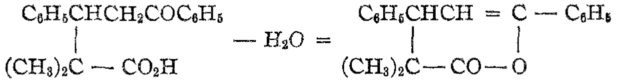
The crotolactone is the principal product when the bromination takes place in methyl alcohol. Under these conditions the bromination takes place slowly while lactone formation takes place rapidly owing to the ease with which the bromo-ester is hydrolyzed to the corresponding acid, which rapidly passes into lactones.



$$\begin{array}{l}C_6H_5CHCHBrCOC_6H_5\\ \quad |\\ (CH_3)_2C-COOCH_3\end{array} + H_2O = CH_3OH + \begin{array}{l}C_6H_5CH-CHBrCOC_6H_5\\ \quad |\\ (CH_3)_2C-CO_2H\end{array} \longrightarrow \begin{array}{l}C_6H_5CH-CH-COC_6H_5\\ \quad | \qquad\quad >O.\\ (CH_3)_2C-CO\end{array}$$

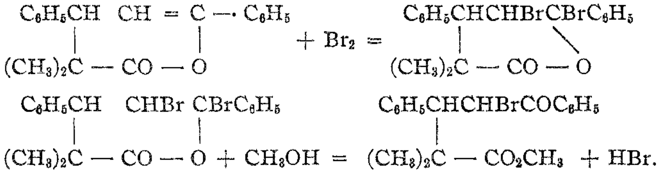
The saturated lactones are therefore constantly in contact with excess of bromine—the most favorable condition for the formation of the crotolactone.

While the two stereoisomeric lactones are usually formed together, we have never succeeded in getting more than one of the corresponding bromo-esters by direct bromination of the ester. The second isomer was, however, finally obtained in another way. When the δ-ketonic acid is digested with acetic anhydride it loses water and passes quantitatively into an unsaturated δ-lactone.



$$\begin{array}{l}C_6H_5CHCH_2COC_6H_5\\ \quad |\\ (CH_3)_2C-CO_2H\end{array} - H_2O = \begin{array}{l}C_6H_5CHCH=C-C_6H_5\\ \quad | \qquad\qquad |\\ (CH_3)_2C-CO-O\end{array}$$

In carbon tetrachloride this lactone readily combines with bromine to form an unstable dibromide which in contact with water rapidly loses hydrobromic acid and forms a mixture of the isomeric γ-lactones. The same addition of bromine takes place in methyl alcohol; but it is accompanied by ester formation. The result is therefore a mixture of bromo-esters and lactones, and the principal product is the stereoisomer of the bromo-ester obtained by direct bromination.

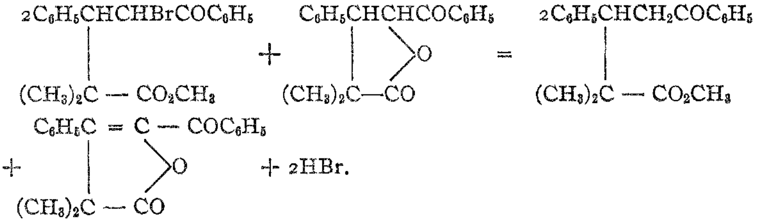


$$\begin{array}{l}C_6H_5CH\ \ CH=C-C_6H_5\\ \quad | \qquad\qquad |\\ (CH_3)_2C-CO-O\end{array} + Br_2 = \begin{array}{l}C_6H_5CHCHBrCBrC_6H_5\\ \quad | \qquad\qquad \diagdown\\ (CH_3)_2C-CO-O\end{array}$$

$$\begin{array}{l}C_6H_5CH\ \ CHBr\ CBrC_6H_5\\ \quad | \qquad\qquad |\\ (CH_3)_2C-CO-O\end{array} + CH_3OH = \begin{array}{l}C_6H_5CHCHBrCOC_6H_5\\ \quad |\\ (CH_3)_2C-CO_2CH_3\end{array} + HBr.$$

The two bromo-esters must be formed side by side in this reaction, because while the higher melting γ-lactone can be transformed into the lower melting isomer in a number of ways, it was not possible to change either of the bromo-esters into the other. The two substances gave the same products with all reagents tried. The only conspicuous difference in their chemical properties is their behavior when heated.

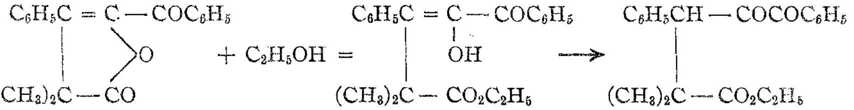
The lower melting ester begins to give off hydrogen bromide slowly below its melting point. The residue, after complete decomposition, is almost colorless and contains only products that are closely related to the original substance. We isolated the bromine-free δ-ketonic ester, the two isomeric γ-lactones and the crotolactone. These substances are formed as follows: A part of the bromo-ester slowly loses alkyl halide and gives γ-lactones. Meanwhile there is a small amount of decomposition into hydrogen bromide and oily products that could not be identified. The hydrogen bromide reduces a corresponding amount of bromo-ester to the bromine-free ketonic ester—a reaction that, as we have found, takes place fairly easily with α-bromo-ketones. The resulting bromine removes hydrogen from the γ-lactones and gives an equivalent quantity of crotolactone, regenerating hydrogen bromide in the process. It is possible also, but improbable, that some of the ketonic ester and crotolactone may be due to direct reaction between bromo-ester and lactone



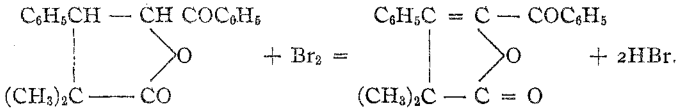
The relative amounts of the two products are not in accordance with this equation.

The higher melting bromo-ester does not change until it is heated above the melting point. It then undergoes deep seated decomposition into highly colored oils from which no pure substances could be isolated. That the difference in the behavior of the two substances is not due solely to the great difference in melting point is shown by the fact that the lower melting ester gives the same products at 200° which it gives at 125° and that even after prolonged heating of the higher melting ester at 200° some unchanged substance can be recovered. Many attempts were made to get an unsaturated δ-ketonic ester by eliminating hydrobromic acid from the bromo-ester, but all of them failed.

The structure of the crotolactone was established as follows: Analyses and molecular-weight determinations gave the empirical formula $C_{19}H_{16}O_3$. On reduction with zinc and acetic acid the substance gives α,α-dimethyl-β-phenyl-γ-benzoyl butyric acid—therefore it has the same carbon chain as this substance. It is insoluble in carbonate but dissolves in alkaline hydroxides, giving yellow solutions from which it is reprecipitated by acids—indicating that it is a γ-lactone. When its solutions in alcohols are saturated with hydrochloric acid, they slowly deposit esters that have the beautiful yellow color of aromatic α-diketones.



The substance is obtained almost quantitatively by the action of bromine on the γ-lactones



Experimental Part.

Preparation of Benzoylphenyldimethyl Butyrate.—The ester was made by essentially the same method that was used by Kohler, Heritage, and Macleod;[1] but although the zinc and a part of the bromo-ester were the same as those used in the earlier work and the benzene and benzalacetophenone were as pure as we could make them, the reaction started smoothly only once. In all other cases it had to be maintained and completed by protracted heating. As a consequence the intermediate addition product decomposed into unsaturated δ-lactone and basic zinc bromide almost as rapidly as it was formed, and the zinc soon became imbedded in a paste of the basic compound which prevented further contact with the reagents. This difficulty was obviated by placing the zinc in a perforated copper cup that was suspended from the cork holding the reflux condenser. As the cup was partially immersed in the benzene solution of the bromo-ester, the zinc compounds drained off as fast as formed and the zinc always presented a fresh surface.

Another consequence of the protracted heating necessary to complete the reaction was a difference in the character of the product. Except in the one case in which the reaction started promptly the product contained very little ester, being composed mainly of unsaturated δ-lactone and yellow oils. This made a different method of dealing with it advisable. The following proved satisfactory: After the reaction had been completed by heating it from 4 to 5 hours the benzene solution and as much of the paste as possible was poured into cracked ice and water. The material adhering to the flask and the copper cup was removed by washing with benzene and conc. hydrochloric acid, the washing added to the main portion and the whole acidified with excess of conc. hydrochloric acid. The liquid obtained in this way was filtered into a separatory funnel, and washed until free from hydrochloric acid. It was then distilled with steam to remove benzene and any volatile impurities and the residue dissolved in methyl alcohol—300 cc. for the product from 42 g. unsaturated ketone. In order to transform both ester and lactone into acid, the methyl alcohol solution was treated with 60 cc. of a 50% solution of sodium hy-

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[1] *Am. Chem. J.*, 36, 211 (1911).

droxide and the whole boiled for several hours. The solution was then cooled, filtered if necessary, and acidified. The resulting acid was thoroughly washed with water, dried at 120° and recrystallized from methyl alcohol. The yield was about 75% of pure acid melting at 159°.

Oxime of α,α-Dimethyl-β-phenyl-γ-benzoyl Butyric Acid, $C_6H_5C(NOH)CH_2CH(C_6H_5)C(CH_3)_2CO_2H$.—In order to make certain that the acid has the structure assigned to it, it was turned into the oxime. For this purpose one g. of the acid was added to a solution of 0.75 g. hydroxylamine hydrochloride and 1.8 g. potassium hydroxide dissolved in 25 cc. of water. The solution was heated on a steam bath for 5 hours, then diluted with water and cautiously acidified with dil. hydrochloric acid. This precipitated a solid which was purified by crystallization from methyl alcohol. It separated in small prisms that melted at 184.5° and decomposed slightly above the melting point.

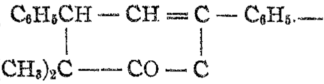
Calc. for $C_{19}H_{21}O_3N$: C, 73.3; H, 6.7. Found: C, 73.4; H, 6.7.

Bromination of Methyl-α,α-dimethyl-β-phenyl-γ-benzoyl Butyrate.—The methyl ester was obtained in calculated amount by esterifying the pure acid with methyl alcohol and hydrochloric acid. It melted at 92° and under 25 mm. pressure distilled without decomposition at 200°. It is readily brominated but the resulting bromo-ester is so easily hydrolyzed that it is necessary to handle it with great care. The most satisfactory results were obtained as follows: A concentrated solution of the ester in chloroform to which a few drops of bromine had been added was first warmed to start the reaction, then cooled with tap water, while more bromine was added drop by drop until a permanent color appeared in the solution. The chloroform was then evaporated in a current of dry air and the residue crystallized as rapidly as possible from ether or methyl alcohol. The yield was 70% of pure bromo-ester melting at 125°.

If the reaction is carried out in hot chloroform or the chloroform is removed by distillation, the yield is less because a part of the bromo-ester loses methyl bromide and forms γ-lactones. When the crude bromo-ester is allowed to remain in contact with methyl alcohol for any length of time the yield drops to 50% and the crystals that separate contain crotolactone as well as bromo-ester.

In the hope of getting an isomeric bromo-ester we also tried bromination in absolute methyl alcohol. For this purpose 3 g. of bromine was added to a cold solution of 5 g. of ester in methyl alcohol. No reaction was perceptible in the dark but in direct sunlight decolorization took place in a day. The methyl alcohol was evaporated in a current of air, the yellow oily residue dissolved in ether and this solution washed with sodium carbonate, sodium thiosulfate and water. The dried ethereal solution, on evaporation, deposited only the crotolactone melting at 117°.

Bromination of Unsaturated δ-Lactone,



—The lactone used in these experiments was separated from the crude product of the reaction between benzalacetophenone, bromoisobutyric ester and zinc. This separation is troublesome and we found, later, that it is much easier to prepare the lactone from dimethylphenylbenzoyl butyric acid. Thus when a solution of one g. of the acid in 10 cc. of acetic anhydride, to which a few drops of conc. sulfuric acid had been added, was allowed to stand at the ordinary temperature and then poured into water it deposited an oil that solidified immediately. A mixed melting point showed that the solid was pure lactone. The yield was quantitative.

The lactone combines with bromine very readily but all attempts to get the resulting dibromide sufficiently pure for analysis failed. Thus 5 g. of the lactone suspended in cold carbon tetrachloride decolorized 2.5 g. bromine without evolving more than a trace of hydrogen bromide. The carbon tetrachloride—on rapid evaporation in a current of dry air—deposited a white solid which when filtered, washed, and dried in a vacuum desiccator melted and decomposed at about 75°. This was undoubtedly a dibromide because it immediately liberated iodine from a solution of potassium iodide. When redissolved in carbon tetrachloride, however, it lost some hydrobromic acid and the solid that was precipitated from this solution by cautious addition of low-boiling ligroin, was less pure than the crude product.

Other preparations, obtained in the same way, were dissolved in methyl alcohol. The resulting solutions deposited either γ-lactone or bromo-ester, depending on the conditions, but the bromo-ester was always the same as the one obtained by direct bromination of the ester. The isomeric bromo-ester was however finally obtained by brominating the unsaturated δ-lactone in methyl alcohol. The bromine reacted at once but if the solution was evaporated immediately it left only a mixture of the isomeric γ-lactones which were evidently formed from the γ-bromo-acid. If on the other hand the solution in methyl alcohol was allowed to stand for some time it deposited a different substance which after recrystallization from methyl alcohol melted with decomposition at 172°.

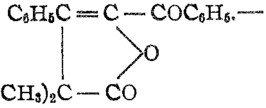
Calc. for $C_{20}H_{21}O_3Br$: Br, 20.6. Found: 20.7.

The composition and properties of this substance show that it is isomeric with the bromo-ester which had been obtained previously. When it is boiled with potassium acetate in alcoholic solution it gives, as does the isomeric ester melting at 125°—a mixture of the isomeric γ-lactones; and a mixture of the same substances is obtained when a solution of the salt that is formed by hydrolyzing either of the esters is acidified with excess of concentrated acid. Moreover when a methyl alcoholic solution of either the ester melting at 125° or that melting at 172° is saturated with hydrobromic acid and then allowed to stand for some time the final product in each case is the lactone that melts at 115°. There can therefore be no question that these substances are the two possible stereoisomeric γ-bromo-esters.

Behavior of the Lower Melting γ-Bromo-ester on Heating.—This bromo-ester begins to decompose freely a few degrees above the melting point, and once decomposition has commenced, it will continue even though the temperature be lowered 20–30 degrees. The behavior is the same under ordinary and diminished pressure although the relative amounts of the various products may be somewhat different. No gaseous product other than hydrogen bromide is formed. This was established by conducting the operation in an atmosphere of carbon dioxide which was subsequently absorbed in alkali. The pale yellow residue solidifies when rubbed with a little methyl alcohol. Careful recrystallization of this solid gave the bromine-free ester melting at 92°, a small quantity of the corresponding acid—which may have been formed by hydrolysis of the ester during crystallization—the γ-lactone melting at 115°, and dimethylphenylbenzoyl crotolactone. An experiment with the corresponding ethyl ester, in which the relative amounts of the various products were determined as accurately as possible, showed that of the material used 24% appeared as bromine free ester, 4% as the corresponding acid, 16% as γ-lactone, and 28% as crotolactone. No unsaturated ketonic ester was separated or detected.

Behavior of the Higher Melting γ-Bromo-ester on Heating.—The higher melting ester begins to decompose freely at about 180°. The gaseous products are hydrogen bromide and small quantities of free bromine. The dark brown residue fumes strongly in the air and gives methyl benzoate when dissolved in methyl alcohol—indicating the presence of benzoyl bromide. The product left after heating 10 g. at 170–180° for 3 hours still contained 1.6 g. of bromo-ester. The only other products isolated were 1.1 g. crotolactone and 0.6 g. benzoic acid. The balance consisted of uncrystallizable oils.

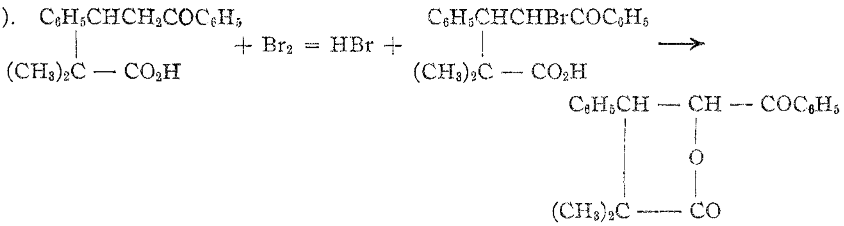
α,α-Dimethyl-β-phenyl-γ-benzoyl Crotolactone,



$$\begin{array}{l} C_6H_5C=C-COC_6H_5.— \\ \qquad\ \ | \qquad \ \ > O \\ (CH_3)_2C-CO \end{array}$$

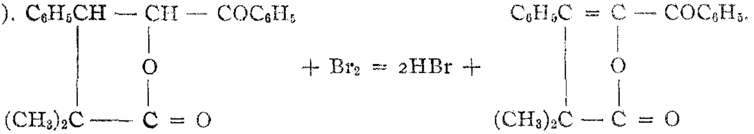
The crotolactone, as has been indicated in various parts of this paper, is formed in variable quantities whenever dimethylphenylbenzoyl butyric acid or its esters are treated with bromine, or the bromo-esters are heated. It is most readily obtained in quantity by digesting the acid with excess of bromine. The reaction takes place in two steps as shown by the equations

(I).



$$\begin{array}{l}C_6H_5CHCH_2COC_6H_5\\|\\(CH_3)_2C-CO_2H\end{array} + Br_2 = HBr + \begin{array}{l}C_6H_5CHCHBrCOC_6H_5\\|\\(CH_3)_2C-CO_2H\end{array} \longrightarrow \begin{array}{l}C_6H_5CH-CH-COC_6H_5\\|\qquad\quad|\\|\qquad\quad O\\|\qquad\quad|\\(CH_3)_2C-CO\end{array}$$

(II).



$$\begin{array}{l}C_6H_5CH-CH-COC_6H_5\\|\qquad\quad|\\|\qquad\quad O\\|\qquad\quad|\\(CH_3)_2C-C=O\end{array} + Br_2 = 2HBr + \begin{array}{l}C_6H_5C=C-COC_6H_5.\\|\qquad\quad|\\|\qquad\quad O\\|\qquad\quad|\\(CH_3)_2C-C=O\end{array}$$

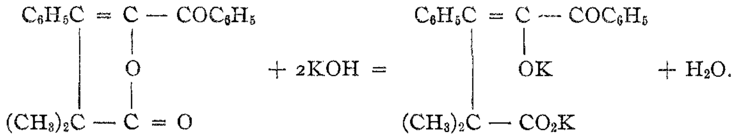
The first reaction takes place rapidly; the second requires prolonged heating. Our procedure was as follows: 15 g. of dry, powdered acid was suspended in 100 cc. carbon tetrachloride contained in a small flask sealed to the end of the inner tube of an inverted condenser. A small quantity of bromine was added and the whole warmed to start the reaction—sometimes it was necessary to add a crystal of iodine or a few drops of acetone as well. Bromine was then added, gradually, as long as it reacted briskly, and then, in one portion, enough more to bring the entire amount to 28 g. To complete the reaction the flask was heated in a steam bath until evolution of hydrogen bromide ceased—usually, 6–8 hours. The solvent was then distilled off, the oil dissolved in ether, and the solution washed with sodium carbonate, sodium thiosulfate and water. Some of the product usually crystallized from the ether during the process of washing; the balance was deposited on evaporation. It was purified by crystallization from methyl alcohol from which it separated in very pale yellow needles that melted at 117°.

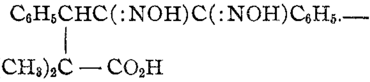
Calc. for $C_{19}H_{16}O_3$: C, 78.08; H, 5.47; mol. wt., 289. Found: C, 77.6, 77.7; H, 5.1, 5.4; mol. wt., 288, 308, 270.

The crotolactone is readily soluble in chloroform and carbon tetrachloride, moderately soluble in alcohol and ether. It neither combines with bromine nor reduces permanganate. It is insoluble both in sodium carbonate solution and in aqueous sodium hydroxide, but is readily attacked by alcoholic potassium hydroxide.

Reduction to α,α-Dimethyl-β-phenyl-γ-benzoyl Butyric Acid.—A solution of 0.5 g. of substance in acetic acid was boiled for 2 hours with a slight excess of zinc dust, then filtered while still hot and diluted with water. It deposited a solid which was recrystallized from methyl alcohol and was identified by a mixed melting point as the higher melting γ-lactone. Reduction in alcohol gave the same product but required prolonged heating. These results establish the carbon chain and afford good evidence for a cyclic structure.

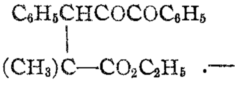
Reaction with Alkalies.—The lactone is readily soluble in strong alcoholic potassium hydroxide. The deep yellow solution remains clear on dilution with water, indicating the presence of a salt. From the dilute solutions acids precipitate a yellow solid that rapidly fades, and the product isolated is the unchanged lactone. The color and solubility changes indicate that the alkaline solution contains the di-potassium salt of an hydroxy acid, and that this acid readily passes back to the unsaturated lactone.



Reaction with Hydroxylamine,  $C_6H_5CHC(:NOH)C(:NOH)C_6H_5$, with $(CH_3)_2C - CO_2H$ below CH.—A solution of one g. of the crotolactone in 0.75 g. absolute alcohol was boiled for 5 hours with finely powdered hydroxylamine hydrochloride and one g. of barium carbonate. The mixture was then filtered into water and the solution allowed to stand. It deposited fine, white crystals which after recrystallization from methyl alcohol melted at 186°.

Calc. for $C_{19}H_{20}O_4N_2$: C, 67.05; H, 5.85. Found: C, 66.7; H, 55.

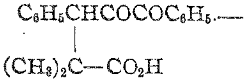
The substance, which is soluble both in alkalies and in concentrated acids, is evidently the dioxime of the acid that is formed when the lactone is dissolved in alkalies.

Ethyl α,α - Dimethyl - β - phenyl - γ - (phenylglyoxyl) Propionate,  $C_6H_5CHCOCOC_6H_5$, with $(CH_3)C—CO_2C_2H_5$ below CH.—A solution of 5 g. of the crotolactone in absolute alcohol was saturated with hydrogen chloride. A bright yellow color appeared almost immediately but nothing separated from the solution even after it had stood overnight. The alcohol was then evaporated in a current of dry air, the yellow residue dissolved in ether, the ethereal solution washed with sodium carbonate and water, and dried. On slow evaporation it deposited a crystalline mixture of yellow needles and very pale yellow plates. This was easily separated because the lightly colored substance was very sparingly soluble in ether. It was found to be unchanged lactone. The yellow needles after recrystallization melted at 93°.

Calc. for $C_{21}H_{22}O_4$: C, 74.56; H, 6.51; mol. wt., 338. Found: C, 74.1, 74.1; H, 6.4, 6.5; mol. wt., 336, 306, 311.

The diketonic ester is readily soluble in organic solvents. It does not react with bromine, gives no color reaction with ferric chloride, and is not oxidized by potassium permanganate in acetone. It is however very readily reduced. A solution of one g. of the substance in dil. acetic acid was completely decolorized by boiling for 5 minutes with a slight excess of zinc dust. The solution was filtered and poured into water. This precipitated a colorless solid which was recrystallized from methyl alcohol. It melted at 159° and was identified as α,α-dimethyl-β-phenyl-γ-benzoyl butyric acid.

β - Phenylglyoxyl - β - phenyl - α,α - dimethylpropionic Acid,



$C_6H_5CHCOCOC_6H_5$, $(CH_3)_2C{-}CO_2H$

.—The ester is decomposed by aqueous alkalies, but can be hydrolyzed by cautious treatment with sodium methylate. A saturated solution of sodium methylate (10 cc.) was added, drop by drop, to a solution of one g. of the ester in anhydrous ether. The solution first turned red, then deposited a crystalline yellow sodium salt. This was filtered, and washed with ether and anhydrous methyl alcohol. It was completely soluble in water. From the yellow solution hydrochloric acid precipitated a yellow solid which was recrystallized from methyl alcohol in which it is readily soluble.

Calc. for $C_{19}H_{18}O_4$: C, 73.54; H, 5.80. Found: C, 73.3; H, 5.8.

The acid melts at 145°. It is easily re-esterified with alcohol and hydrochloric acid.

Summary.

1. Bromination of δ-ketonic esters results in a mixture of bromo-ester, saturated γ-lactones, and an unsaturated γ-lactone. The mechanism of the reactions involved is given and the conditions most favorable for the formation of each class of substances are defined.

2. A method is given for preparing stereoisomeric bromo-derivatives of δ-ketonic esters in cases in which direct bromination gives only one of the possible forms.

3. A new type of crotolactones gives δ-diketones when the ring is opened.

CAMBRIDGE, MASS.