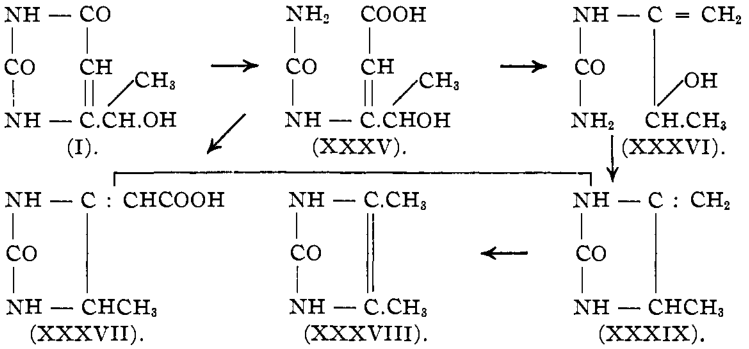
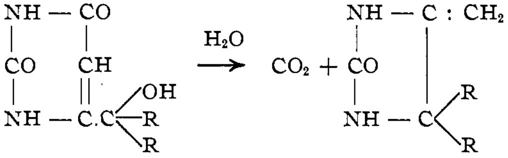
nucleoside (I) into dimethylglyoxalone (XXXVIII) therefore may be represented as follows:



(I). (XXXV). (XXXVI). (XXXVII). (XXXVIII). (XXXIX).

Our results show conclusively that a simple primary or secondary alcoholic grouping in position 4 of the uracil molecule cannot be removed from the pyrimidine by hydrolysis with acids with production of uracil. Whether a lengthening of the carbon chain and the introduction of other hydroxyl groups into such a grouping will weaken the attraction between the carbon atom 4 and the side chain remains to be established. An investigation planned to develop a method of synthesizing tertiary pyrimidine-nucleosides (XL) is now in progress. It will be of interest to determine whether such combinations will undergo rearrangements by hydrolysis giving combinations corresponding to Formula XLI.



(XL). (XLI).

New Haven, Conn.

[Contribution from the Chemical Laboratory of Harvard University.]

STUDIES IN THE CYCLOPROPANE SERIES.

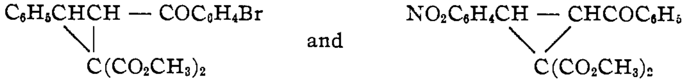
[THIRD PAPER.]

By E. P. Kohler, G. A. Hill, and L. A. Bigelow.

Received July 30, 1917.

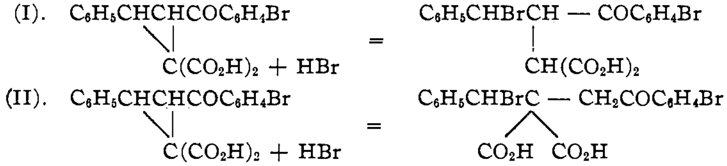
In the interpretation of two of the transformations of cyclopropane derivatives that were described in previous papers, we assumed the intermediate formation of substances for the existence of which we could secure no direct evidence. Thus, in order to account for the formation of ketolactones by the action of hydrobromic acid on the cyclopropane di-acids, we assumed the intermediate addition of hydrobromic acid, but failed to isolate any products containing bromine. A similar assumption was made in accounting for the products obtained by the interaction of alcoholates and cyclopropane esters. The experiments described in this paper were undertaken mainly with a view to filling these gaps.

The substances that we have used for the purpose are constituted exactly like those previously described, but they contain different substituents in the phenyl groups.

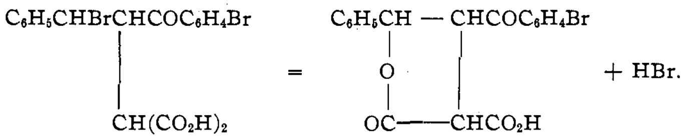


The nitro compound proved ill adapted for the work, because, while both it and its derivatives are as sparingly soluble as was expected, their tendency to crystallization is in many cases so low that separations are impossible. The products obtained from the bromine compound, on the other hand, crystallize exceedingly well, and with the help of these we have succeeded in following, step by step, the reaction between the cyclopropane di-acid and hydrobromic acid.

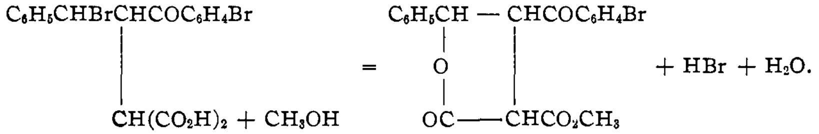
The first step in this reaction consists in addition of hydrobromic acid —the cyclopropane ring opening in two ways:



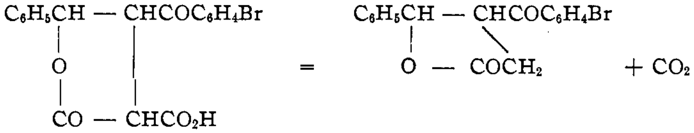
The two bromo acids formed in this way were isolated; they are both unstable. When the one that is formed in the first reaction—it constitutes more than 95% of the entire product—is dissolved in glacial acetic acid it immediately begins to lose hydrobromic acid and pass into a lactonic acid.



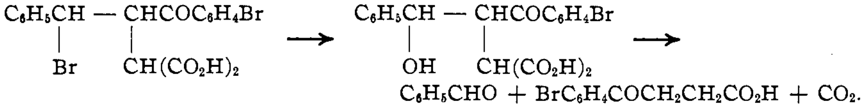
The same process takes place in methyl alcohol but is accompanied by esterification.



The methyl ester is stable but the lactonic acid very readily loses carbon dioxide. The product finally obtained when the bromo acid is allowed to remain in contact with glacial acetic, as well as when it is heated by itself, is a ketolactone.

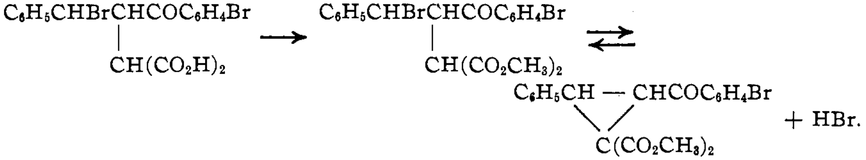


The lactone ring closes so easily that it is impossible to go back from the bromo acid to the cyclopropane derivative. When hydrobromic acid is eliminated with such gentle reagents as acetates, the sole product is a salt of the lactonic acid. Strong bases under the same condition form salts of a hydroxy dibasic acid and ultimately cleave this to benzaldehyde and *p*-bromobenzoylpropionic acid.



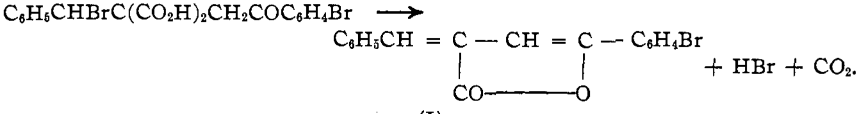
$$\underset{Br}{C_6H_5CH} - \underset{CH(CO_2H)_2}{CHCOC_6H_4Br} \longrightarrow \underset{OH}{C_6H_5CH} - \underset{CH(CO_2H)_2}{CHCOC_6H_4Br} \longrightarrow C_6H_5CHO + BrC_6H_4COCH_2CH_2CO_2H + CO_2.$$

While it is not possible, therefore, to start with the bromo acid and close a cyclopropane ring, it is possible to transform this acid, in part at least, into the corresponding cyclopropane ester. When the bromo acid is brought in contact with a cold, saturated solution of hydrobromic acid in methyl alcohol most of it as usual slowly goes into the ester of the lactonic acid; but the remainder—5 to 10%—goes into the dimethyl ester of the cyclopropane derivative. Apparently during the time required for closing the lactone ring under conditions unfavorable for lactone formation, a part of the bromo acid undergoes esterification and the resulting ester, owing to its active hydrogen in the γ-position, spontaneously passes into the cyclopropane.



These results supply a possible explanation for the conspicuous difference between the behavior of these cyclopropane acids and that of their esters towards hydrobromic acid. In methyl alcohol hydrobromic acid seems to have no effect whatsoever upon the esters. In glacial acetic acid a slow reaction can be detected even with the ester, but the process is accompanied by hydrolysis and the product is a lactonic ester. It seems probable, now, that hydrobromic acid attacks both acids and esters and that the reaction is reversible. The process, therefore, soon stops unless the effects are accumulated either by precipitation of the product in solid form or by its subsequent change into other substances.

The second bromo acid is even more unstable than the first. Its solutions in all solvents soon assume a yellow tint and even the dry solid gradually turns yellow. In both cases the acid loses both carbon dioxide and hydrobromic acid and passes into a yellow unsaturated lactone.



(I).

Experiments with Phenyl-(*p*-bromobenzoyl)-cyclopropane Di-acid.

Methyl β-Phenyl-γ-(4-bromobenzoyl)-ethylmalonate, $C_6H_5CH(CH_2COC_6H_4Br)CH(CO_2CH_3)_2$.—The addition of methyl malonate to benzal *p*-bromoacetophenone presented no difficulties. When carefully dried methyl alcohol was used as medium and a small quantity of sodium methylate as condensing agent, the yield of pure addition product averaged 92%. The substance crystallizes from methyl alcohol in colorless needles, is readily soluble in ether and boiling methyl alcohol, and melts at 96°.

Calc. for $C_{20}H_{19}O_5Br$: C, 57.3; H, 4.5. Found: C, 57.0; H, 4.4.

Ethyl β-Phenyl-γ-(4-bromobenzoyl)-ethylmalonate, $C_6H_5CH(CH_2COC_6H_4Br)CH(CO_2C_2H_5)_2$.—The ethyl ester closely resembles the methyl ester, but is more readily soluble and separates much more slowly from solutions. It melts at 75–76°.

Calc. for $C_{22}H_{23}O_5Br$: C, 59.1; H, 5.2. Found: C, 58.9; H, 5.2.

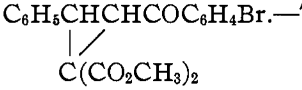
β-Phenyl-γ-(4-bromobenzoyl)-ethylmalonic Acid, $C_6H_5CH(CH_2COC_6H_4Br)CH(CO_2H)_2.H_2O$.—The concentrated filtrates from the esters were shaken with excess of cold, concentrated, alcoholic potassium hydroxide and allowed to stand for several hours. The resulting potassium salt was filtered off, washed with absolute alcohol, and dissolved in water. From the aqueous solution acids precipitated an oil that slowly solidified. The solid was recrystallized from boiling water in which it is very sparingly soluble and from which it crystallizes in transparent plates, containing water of crystallization. These lose water of crystallization in the air and become opaque. The specimen analyzed had been dried in a vacuum desiccator.

Calc. for $C_{18}H_{15}O_5Br$: C, 55.2; H, 3.8. Found: C, 55.0; H, 3.8.

Methyl β-Phenyl-γ-bromo-γ-(bromobenzoyl)-ethylmalonate, $C_6H_5CH(CHBrCOC_6H_4Br)CH(CO_2CH_3)_2$.—The methyl ester was brominated in chloroform, carbon tetrachloride, and carbon disulfide, under a great variety of conditions, but in all cases gave a mixture of monobrom substitution products that it was extremely difficult to separate. After many recrystallizations from methyl alcohol two products were obtained that melted sharply and gave other evidences of purity. One crystallizes in plates melting at 98°, the other in needles or prisms melting at 113°. Both are readily soluble in all common organic solvents except ligroin.

Calc. for $C_{20}H_{18}O_5Br_2$: C, 48.2; H, 3.6. Found: (98°) C, 48.3; H, 3.5; (113°) C, 48.5; H, 3.5.

Methyl 2-Phenyl-3-(4-bromobenzoyl)-cyclopropane Dicarbonate,



$$\begin{array}{l} C_6H_5CHCHCOC_6H_4Br \\ \quad |\diagup \\ \quad C(CO_2CH_3)_2 \end{array}$$

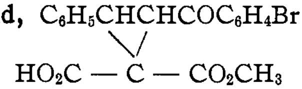
—The elimination of hydrobromic acid from the bromo esters was accomplished without difficulty, and the product contained only cyclopropane derivatives. With magnesium methylate each bromo ester gave only one cyclopropane ester, the higher melting bromine compound giving the lower melting cyclopropane derivative. Potassium acetate in the cold gave essentially the same result, but at the boiling point of methyl alcohol the principal product from both bromo esters was the higher melting cyclopropane. Both of the cyclopropane derivatives crystallize readily and a mixture of the two is easily separated by crystallization from methyl alcohol. One is deposited in thin plates melting at 104°, the other in compact tables that melt at 113°.

Calc. for $C_{20}H_{17}O_5Br$: C, 57.5; H, 4.1. Found: (104°) C, 57.3; H, 4.5; (113°) C, 57.2; H, 4.1.

Neither of these substances reduces permanganate, or combines with bromine. When the lower melting compound is boiled in methyl alcohol containing a small quantity of acid it is rapidly and completely transformed into the higher melting isomer. As this is most easily obtained in perfectly pure condition it was used in most of the following experiments.

Reduction.—The ester melting at 113°, like the corresponding compounds previously described, is rapidly reduced by zinc dust and acetic acid. One g. boiled for an hour with excess of zinc dust in 75% acetic acid, and then re-esterified with a 3% solution of hydrochloric acid in methyl alcohol gave 0.92 g. of the open-chained saturated compound melting at 96°. The ring is, therefore, opened exclusively between carbon atoms 1 and 3.

Hydrolysis to the Ester Acid,



$$\begin{array}{c} C_6H_5CHCHCOC_6H_4Br \\ \diagdown\diagup \\ HO_2C - C - CO_2CH_3 \end{array}$$

—Both of the cyclopropane esters show the same marked sensitiveness to alkaline reagents that was noted in earlier papers, undergoing both hydrolysis and ring cleavage with the greatest ease. For getting hydrolysis, without affecting the ring, a solution of the esters in moist ether was shaken with one equivalent of sodium dissolved in methyl alcohol. The hydrolysis was complete in less than 5 minutes. The sodium salt was then extracted with water, the acid precipitated by addition of hydrochloric acid and purified by recrystallization from methyl alcohol. It separated in fine plates melting at 175–176°.

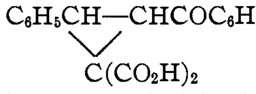
Calc. for $C_{19}H_{15}O_5Br$: C, 56,6; H, 3.7. Found: C, 56.7; H, 4.0.

Both esters give the same ester acid. When re-esterified either with methyl alcohol and hydrochloric acid or by digesting the silver salt with methyl iodide, this acid gives only the ester melting at 113°.

The corresponding ethyl compound crystallizes from ethyl alcohol in plates or small tablets that melt at 144°.

Calc. for $C_{20}H_{17}O_5Br$: C, 57.5; H, 4.1. Found: C, 57.6; H, 4.3.

As the ethyl ester acid is more easily purified than any of the preceding compounds and is easily converted into the dibasic acid, the best way to get the latter acid and its derivatives is to go directly to the ester acid without purifying any of the intermediate compounds. In a typical experiment the results were as follows: To a boiling solution of 144 g. of benzal-*p*-bromoacetophenone and 90 g. of ethyl malonate in 150 cc. of absolute alcohol sodium ethylate was added until the reaction to Congo paper was distinctly alkaline. The mixture was then allowed to stand for 24 hours without further heating. It was then cooled in a freezing mixture and centrifuged. The solid was washed with a small quantity of cooled alcohol, then thoroughly with water, and finally dried. Yield, 212 g. of colorless solid. The solid was dissolved in the minimum quantity of chloroform and treated with bromine until a permanent red color remained after warming on the water bath for 5 minutes (*ca* 77 g.). Most of the chloroform was removed by distillation under diminished pressure, the residue dissolved in ether, the ethereal solution washed with water, dried and freed from ether. This left a pale yellow oil. The oil was dissolved in methyl alcohol, the solution boiled for 2 hours with 55 g. of freshly fused potassium acetate, and then concentrated by distilling most of the alcohol. The residue was poured into 150 cc. of ether, the ethereal solution washed with water and sodium carbonate until free from acid, and then mixed with a solution of sodium ethylate containing 12 g. of sodium. After 10 minutes the orange-colored solution was extracted with water and the aqueous layer cautiously acidified until a small quantity of acid precipitated as an oil. This, when shaken in contact with the solution, extracted nearly all of the coloring matter, and addition of excess of acid then precipitated a solid acid that was almost colorless. One recrystallization from alcohol gave a colorless product melting at 143–144°. Yield, 154 g., about 75%.

2-Phenyl-3-(4-bromobenzoyl)-cyclopropane Di-acid,  $C_6H_5CH{-}CHCOC_6H_4Br$ with $C(CO_2H)_2$ bridging both CH groups.—Since the cyclopropane ring in the ester acid is not attacked by bases, further hydrolysis can be carried out by any of the commonly used methods. The dibasic acid crystallizes from boiling water, in which it is very sparingly soluble, in fine needles containing water of crystallization.

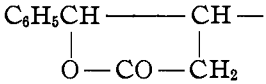
Calc. for $C_{18}H_{15}O_5Br.H_2O$: C, 52.8; H, 4.1. Found: C, 52.9; H, 4.4.

It is very readily soluble in common organic solvents, but larger quantities can be recrystallized from ether. From ordinary ether it crystallizes in needles containing one molecule of alcohol of crystallization.

Calc. for $C_{18}H_{15}O_5Br.C_2H_6O$: C, 55.2; H, 4.4. Found: C, 54.7; H, 4.4.

The acid readily decomposes on heating, but all efforts to confine the action to loss of carbon dioxide proved unsuccessful. Only substances due to ring cleavage could be isolated from the melt. More than 96% of the product consisted of a ketolactone and the corresponding unsaturated acid.

β-(4-Bromobenzoyl)-γ-phenyl-butyrolactone,



$$\begin{array}{lll} C_6H_5CH & \text{———} & CH — COC_6H_4Br \\ | & & | \\ O — & CO & — CH_2 \end{array}$$

.—The cyclopropane di-acid was heated at 160–180° until all evolution of carbon dioxide ceased. The yellow melt, while still hot, was poured into ether and the acid extracted from the solution with sodium carbonate. The ethereal solution on evaporation deposited a solid that crystallized from alcohol in colorless needles which melt at 116°.

Calc. for $C_{17}H_{13}O_3Br$: C, 59.1; H, 3.8. Found: C, 58.5; H, 4.0.

The reactions of this substance prove that it is a halogen substitution product of the lactone described in an earlier paper. In contact with alkalies it passes into a salt of an unsaturated acid that gives benzaldehyde both on oxidation with permanganate and on digestion with acids or bases.

$$\begin{array}{lll} C_6H_5CH \text{———} CH — COC_6H_4Br & & C_6H_5CH : C — COC_6H_4Br \\ | \qquad\qquad | & + KOH = & | \qquad\qquad + H_2O. \\ O — CO — CH_2 & & CH_2CO_2K \end{array}$$

When heated with hydrobromic acid in methyl alcohol it gives the hydrobromic acid addition product of the ester of the same acid.

Methyl β-(4-Bromobenzoyl)-γ-bromo-γ-phenyl Butyrate, C_6H_5CHBr-$CH(COC_6H_4Br)CH_2CO_2CH_3$.—This ester is formed when either the ketolactone melting at 113° or the unsaturated acid obtained from it is esterified with methyl alcohol and hydrobromic acid. It is readily soluble in ether, moderately in boiling methyl alcohol, from which it separates in colorless needles that melt, with decomposition, at about 140°.

Calc. for $C_{18}H_{16}O_3Br_2$: C, 49.1; H, 3.7. Found: C, 48.9; H, 3.7.

β-Bromobenzoyl-phenyl-isocrotonic Acid, $C_6H_5CH : C(COC_6H_4Br)$-CH_2CO_2H.—The lactone was suspended in ether and the suspension shaken with barely enough sodium methylate to open the lactone ring. The solid sodium salts formed in the process were extracted with water, and the ethereal layer dried and evaporated. The ether left only benzaldehyde. From the aqueous extract, hydrochloric acid precipitated an oil that soon solidified. The solid was dried and crystallized from a mixture of chloroform and ligroin. It gave a small quantity of granular crystals that, after recrystallization from ether, melted at 156°.

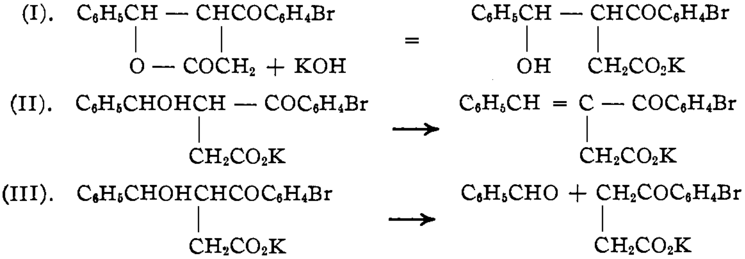
Calc. for $C_{17}H_{13}O_3Br$: C, 59.1; H, 3.8. Found: C, 58.8; H, 4.0.

The acid is readily soluble in alcohol and chloroform, moderately in ether and in carbon tetrachloride. Its solution in sodium carbonate immediately reduces permanganate.

β-(4-Bromobenzoyl)propionic Acid, $BrC_6H_4COCH_2CH_2CO_2H$.—The principal acid product of the action of alkalies on the lactone crystallized from chloroform and ligroin in thin plates that melted at 140°. In solubility and chemical properties it closely resembles benzoyl propionic acid.

Calc. for $C_{18}H_{16}O_3Br$: C, 49.1; H, 3.7. Found: C, 48.9; H, 3.8.

This acid is also formed when the unsaturated acid melting at 156° and the bromo ester melting at 140° are treated with bases, but in these cases much more vigorous action is required than with the lactone itself. These results indicate that the lactone is first opened to a hydroxy acid which then, in part, loses water and gives the unsaturated acid, but in the main undergoes cleavage to benzaldehyde and bromobenzoyl propionic acid.

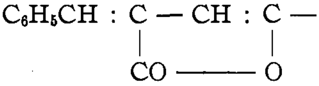


$$\text{(I).}\quad \begin{array}{ccc} C_6H_5CH & - & CHCOC_6H_4Br \\ | & & | \\ O & - & COCH_2 \end{array} + KOH \; = \; \begin{array}{ccc} C_6H_5CH & - & CHCOC_6H_4Br \\ | & & | \\ OH & & CH_2CO_2K \end{array}$$

$$\text{(II).}\quad \begin{array}{c} C_6H_5CHOHCH - COC_6H_4Br \\ | \\ CH_2CO_2K \end{array} \longrightarrow \begin{array}{c} C_6H_5CH = C - COC_6H_4Br \\ | \\ CH_2CO_2K \end{array}$$

$$\text{(III).}\quad \begin{array}{c} C_6H_5CHOHCHCOC_6H_4Br \\ | \\ CH_2CO_2K \end{array} \longrightarrow C_6H_5CHO + \begin{array}{c} CH_2COC_6H_4Br \\ | \\ CH_2CO_2K \end{array}$$

α-Benzal-γ-(4-bromophenyl)-crotolactone,



$$\begin{array}{ccccccc} C_6H_5CH & : & C & - & CH & : & C - C_6H_4Br \\ & & | & & & & | \\ & & CO & - & - & - & O \end{array}$$

.—In addition to the ketolactone that has just been described, the ethereal solution contained a very small quantity of another neutral substance that separated in minute lemon-yellow plates or flat needles. After many recrystallizations from alcohol this melted at 180–183°.

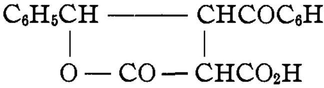
Calc. for $C_{16}H_{11}O_2Br$: C, 60.9; H, 3.5. Found: C, 61.4; H, 3.5.

The aqueous solution, obtained by extracting the product of heating the dibasic acid with sodium carbonate, on acidification precipitated an oil that solidified very slowly. About half of this solid consisted of the same unsaturated acid that was obtained by opening the lactone melting at 113° with alkalies. The rest failed to yield pure substances, but apparently was composed mainly of a stereoisomer of this acid, because when it was digested with potassium hydroxide, it gave benzaldehyde and about 80% of the possible amount of bromobenzoylpropionic acid.

β-(4-Bromobenzoyl)-γ-bromo-γ-phenyl-ethylmalonic Acid, C_6H_5CHBr-$CH(COC_6H_4Br)CH(CO_2H)_2$.—Dry hydrobromic acid was passed rapidly into a suspension of 20 g. of the cyclopropane di-acid in acetic acid. The acid dissolved as the temperature rose, and a new substance began to separate as the solution reached saturation. The current of hydrobromic acid was continued until the solution had returned to the ordinary temperature. It was then filled with a net-work of stout needles. These were filtered off, washed with a little cold glacial acetic acid, and then thoroughly with ice water. The pure white solid obtained in this way was dried over phosphorus pentoxide in a vacuum desiccator and recrystallized from absolute ether. It is readily soluble in ether, but separates at low temperatures in lustrous plates that contain ether of crystallization, which is given up at the ordinary temperature. The pure dry acid is stable at the ordinary temperature, but decomposes above 100°, giving hydrobromic acid and the same products that are obtained when the cyclopropane di-acid is heated. The yield of washed and dried product was 22 g., about 90% of the possible amount.

Calc. for $C_{18}H_{14}O_5Br_2$: C, 46.0; H, 3.0. Found: C, 45.9; H, 3.2.

2 - (4 - Bromobenzoyl) - 3 - phenyl - butyrolactone Carbonic Acid,



$$\begin{array}{l} C_6H_5CH \text{———} CHCOC_6H_4Br \\ \;\;| \qquad\qquad\quad | \\ O — CO — CHCO_2H \end{array}$$

—It is easy to eliminate hydrobromic acid from the bromo acid, but the resulting lactonic acid is so unstable that it is difficult to avoid loss of carbon dioxide. The following procedure gave a yield of about 80%: A solution of the acid in alcohol-free ether was shaken with a large excess of magnesium acetate that was suspended in a small quantity of water. A solid magnesium salt separated at once in long needles. These were filtered off along with unused magnesium acetate, washed with absolute alcohol and ether, suspended in ice water, and acidified with iced hydrochloric acid. This precipitated a crystalline solid which was dried and recrystallized from a mixture of absolute ether and ligroin. It crystallizes from this mixture only when it is allowed to evaporate slowly in contact with air. Under these conditions it separates in small flattened needles containing water of crystallization.

Calc. for $C_{18}H_{13}O_5Br.H_2O$: C, 53.1; H, 3.7. Found: C, 52.9; H, 4.1.

When the acid is heated it loses both water and carbon dioxide freely below 80°, and passes quantitatively into the phenyl-bromo-benzoylbutyrolactone already described.

The methyl ester of the acid is made far more easily than the acid itself, being formed whenever the bromo acid comes in contact with methyl alcohol, as well as when the lactonic acid is esterified in the usual way. It crystallizes from methyl alcohol in plates that melt at 104°.

Calc. for $C_{19}H_{15}O_5Br$: C, 56.1; H, 4.0. Found: C, 56.6; H, 3.8.

As the ester crystallizes well it can be made very easily without previously isolating the bromo acid. Thus, when a solution containing 4 g. of the cyclopropane di-acid in 6 g. of glacial acetic acid was saturated with hydrobromic acid in the course of 5 minutes and then poured into methyl alcohol and boiled for an hour, it gave a 93% yield of pure lactonic ester, the remainder of the product being largely the lactone melting at 113°. No cyclopropane ester could be detected in the product, showing that the dibasic acid combines very rapidly with hydrobromic acid. A different result was obtained when either the crude hydrobromic acid addition product or the carefully purified bromo acid was dissolved in cold methyl alcohol that had previously been completely saturated with hydrobromic acid. In this case, the principal product was also the lactonic ester, but mixed with it was the higher melting cyclopropane ester in amounts representing from 5 to 10% of the bromo acid used.

Bromo-phenyl-(4-bromobenzoyl)-dimethyl Malonic Acid, C_6H_5CHBr-$C(CO_2H)_2CH_2COC_6H_4Br$.—The acetic acid filtrates from the bromo acid just described, when cooled in a freezing mixture, slowly deposited a small quantity of a second product. This was likewise purified by crystallization from absolute ether, from which it separated in transparent plates.

Calc. for $C_{18}H_{14}O_5Br_2$: C, 46.0; H, 3.0. Found: C, 46.2; H, 3.3.

The composition shows that this acid is isomeric with the bromo acid previously described, and its structure is rendered probable by the fact that when heated it readily loses hydrobromic acid and carbon dioxide, and gives as one of the products the brilliant yellow crotolactone.

Methyl β-(4-Bromobenzoyl)-γ-phenylvinyl-malonate, C_6H_5CH :-$C(COC_6H_4Br)CH(CO_2CH_3)_2$.—The behavior of the cyclopropane ester towards alcoholates is exactly like that of the similar substances described in the earlier paper. The product obtained by brief treatment with magnesium methylate and subsequent acidification crystallizes in needles and melts at 104°. When this is allowed to remain in contact with a solution of hydrochloric acid in methyl alcohol it changes into a stereoisomer that crystallizes in hard, lustrous prisms that melt at 92–93°.

Calc. for $C_{20}H_{17}O_5Br$: C, 57.5; H, 4.1. Found: (104°) C, 57.3; H, 4.3; (93°) C, 57.6; H, 4.3.

These esters behave in every respect like the analogous substances described in earlier papers.

II. Experiments with Nitrophenyl-benzoyl-cyclopropane Di-acid.

Methyl β-(3-Nitrophenyl)-γ-benzoylethylmalonate, $NO_2C_6H_4CH(CH_2COC_6H_5)CH(CO_2CH_3)_2$.—Nitrobenzalacetophenone is sparingly soluble in alcohols. As a consequence the addition of malonic esters is not accomplished as easily as with other unsaturated ketones, and the yield of addition product is not so good. The procedure finally adopted is illustrated by the following experiment: A solution of sodium methylate was added to a boiling mixture containing 71 g. of unsaturated ketone, 44 g. methyl malonate, and 450 cc. of absolute methyl alcohol, until the reaction was distinctly alkaline. The mixture was boiled for several hours, during which the unsaturated ketone gradually dissolved, then allowed to stand for twenty-four hours. The product separated from the reddish liquid in rosets of fine needles. These, after crystallization from methyl alcohol, melted at 92°. Yield, 65.5 g., about 60%. This was the average yield, the maximum being 85.4%. The ester generally crystallizes from methyl alcohol in short needles melting at 92°, which contain methyl alcohol of crystallization, but occasionally it also separates in fine, silky needles that are free from alcohol and melt at 102°.

Calc. for $C_{20}H_{19}O_7N.0.5CH_3OH$: C, 61.4; H, 5.2. Found: (92°) C, 61.5; H, 5.5.
Calc. for $C_{20}H_{19}O_7N$: C, 62.3; H, 5.6. Found: (102°) C, 62.2; H, 4.9.

Ethyl β-(3-Nitrophenyl)-γ-benzoylethylmalonate, $NO_2C_6H_4CH(CH_2COC_6H_5)CH(CO_2C_2H_5)_2$.—The ethyl ester, made like the methyl ester, crystallizes in soft, white needles melting at 100–100.5°. It is moderately soluble in alcohol and ether. The average yield was about 70%, the maximum 94.4%.

Calc. for $C_{22}H_{23}O_7N$: C, 63.9; H, 5.6; N, 3.4. Found: C, 64.2; H, 5.6; N, 3.9.

Methyl β-(3-Nitrophenyl)-γ-bromo-γ-benzoyl-ethylmalonate, $NO_2C_6H_4CH(CHBrCOC_6H_5)CH(CO_2CH_3)_2$.—Bromination of the methyl ester in chloroform gave almost the calculated amount of crude, solid monobromo esters. The crude product, however, is a mixture of isomers. These were separated by systematic fractional crystallization from methyl alcohol. One melts at 149.5° and crystallizes in long, silky needles. The other in short, lustrous needles, and melts at 129.3°. Both are only moderately soluble in hot methyl alcohol.

Calc. for $C_{20}H_{18}O_7NBr$: Br, 17.22. Found: (149.5°) Br, 17.4; (129.3°) Br, 17.3.

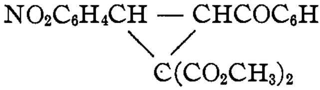
Ethyl β-(3-Nitrophenyl)-γ-bromo-γ-benzoyl-ethylmalonate, $NO_2C_6H_4CH(CHBrCOC_6H_5)CH(CO_2C_2H_5)_2$.—Bromination of the ethyl ester likewise gave an excellent yield of isomeric monobromo derivatives. These were separated by crystallization from ethyl alcohol. One of them was deposited in short, brittle needles that melted at 101°.

Calc. for $C_{22}H_{22}O_7NBr$: Br, 16.3. Found: Br, 16.4.

The second monobromo derivative separated either in soft, fine needles or in hard prisms. The melting point (98.5°) and composition of both forms was the same.

Calc. for $C_{22}H_{22}O_7NBr$: Br, 16.3. Found (needles): Br, 16.3; (prisms): Br, 16.5.

Methyl 2-(3-Nitrophenyl)-3-benzoyl-cyclopropane Dicarbonate,

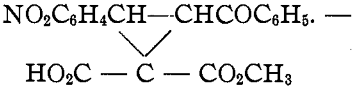


$$\begin{array}{c}NO_2C_6H_4CH - CHCOC_6H_5 \\ \diagdown\ \diagup \\ C(CO_2CH_3)_2\end{array}$$

—The cyclopropane esters were obtained from the bromo compounds in calculated quantities and the results were equally good whether magnesium methylate or potassium acetate were used for eliminating hydrobromic acid. The higher melting bromo compound gave a cyclopropane derivative that crystallized in large prismatic plates that melted at 109.3°. This is the stable form of the cyclopropane ester. The lower melting bromo compound gave a mixture of the ester melting at 109.3°, with an isomer that crystallized from methyl alcohol in fine, white needles and melted at 111.5°. Although higher melting, this is more soluble in methyl alcohol than its isomer, into which it passes when dissolved in methyl alcohol containing hydrochloric acid.

Calc. for $C_{20}H_{17}O_7N$: C, 62.65; H, 4.46. Found: (109.3°) C, 62.4; H, 4.6; (111.5°) C, 62.1; H, 4.5.

The Methyl Ester Acid,



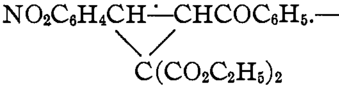
$$\begin{array}{c}NO_2C_6H_4CH - CHCOC_6H_5 \\ \diagdown\ \diagup \\ HO_2C - C - CO_2CH_3\end{array}$$

— Both cyclopropane derivatives gave the same ester acid when their solutions in moist ether were allowed to remain in contact for a short time with one equivalent of sodium methylate. This acid was also obtained as a by-product when sodium methylate was used for eliminating hydrobromic acid from the bromo ester. It crystallized from methyl alcohol in short, hard prisms and melted at 154.5°.

Calc. for $C_{19}H_{15}O_7N$: C, 61.76; H, 4.12. Found: C, 61.5; H, 4.4.

The ester acid corresponds to the stable cyclopropane ester melting at 109.3°, because this is formed when the acid is esterified either with methyl alcohol and hydrochloric acid, or by allowing the silver salt to react with methyl iodide.

Ethyl 2-(3-Nitrophenyl)-3-benzoyl-cyclopropane Dicarbonate,

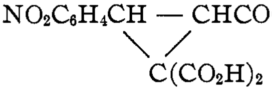


$$\begin{array}{c}NO_2C_6H_4CH - CHCOC_6H_5 \\ \diagdown\ \diagup \\ C(CO_2C_2H_5)_2\end{array}$$

—The ethyl ester was obtained by eliminating hydrobromic acid from the corresponding bromo compound. This reaction, as usual, gives a mixture of isomers. As this mixture is left as an oil that solidifies very slowly, it was found advantageous to hydrolyze to the ethyl ester-acid and re-esterify with alcohol and hydrochloric acid. By this procedure only the stable cyclopropane ester is formed. This crystallizes from alcohol in small plates and melts at 67°.

Calc. for $C_{22}H_{21}O_7N$: C, 64.24; H, 5.11. Found: C, 63.9; H, 5.2.

2 - (3 - Nitrophenyl) - 3 - benzoyl - cyclopropane Di - acid,

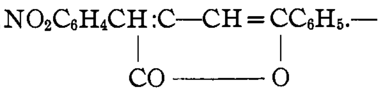


$$\begin{array}{l} NO_2C_6H_4CH - CHCOC_6H_5 \\ \qquad \diagdown \quad \diagup \\ \qquad C(CO_2H)_2 \end{array}$$

—Hydrolysis of the cyclopropane esters to the corresponding ester acid, was, as is usual with these substances, easy, but complete hydrolysis to the dibasic acid required prolonged action of alcoholic potassium hydroxide, and it was difficult to separate a pure dibasic acid from the highly colored product. By recrystallization from water, in which the substance is extremely sparingly soluble, a small quantity of colorless substance was isolated. This crystallized in small lustrous plates. A determination of water of crystallization, an analysis of the silver salt, and esterification with methyl alcohol and hydrochloric acid, which gave the stable dimethyl ester, showed that this was the dibasic acid crystallizing with 1 mol. of water.

Calc. for $C_{18}H_{13}O_7N.H_2O$: H_2O, 4.8. Found: H_2O lost at 45°, 4.8.
Calc. for $C_{18}H_{11}O_7NAg_2$: Ag, 37.96. Found: Ag, 37.5.

α-(3-Nitrobenz)-γ-phenylcrotolactone,

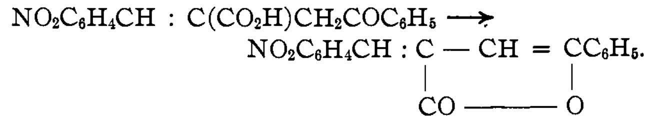


$$\begin{array}{l} NO_2C_6H_4CH:\overset{}{C} - CH = CC_6H_5 \\ \qquad\qquad\quad | \qquad\qquad\quad | \\ \qquad\qquad\ CO \text{———} O \end{array}$$

—The cyclopropane di-acid decomposes above 135°, and gives products analogous to those that have been obtained by heating similar acids. The only indifferent product that was isolated from the melt crystallized in small, yellow plates that were sparingly soluble in methyl alcohol, and melted at 208°.

Calc. for $C_{17}H_{11}O_4N$: C, 69.61; H, 3.75. Found: C, 69.4; H, 3.9.

This substance was synthesized by a method that proves its structure. A mixture of 8.75 g. sodium β-benzoyl-propionate, 9 g. meta-nitrobenzaldehyde, and 33 g. acetic anhydride were heated on a steam bath for a day, then poured into water. The putty-like mass that separated was washed with water by decantation, and then extracted with successive portions of boiling methyl alcohol until the residue was pure yellow in color. The melting point was 208,° and a mixed melting-point determination showed that this substance is the same as that obtained by heating the cyclopropane acid



$$\begin{array}{l} NO_2C_6H_4CHO + CH_2(CO_2Na)CH_2COC_6H_5 \longrightarrow \\ \qquad\qquad NO_2C_6H_4CH : C(CO_2H)CH_2COC_6H_5 \longrightarrow \\ \qquad\qquad\qquad\qquad NO_2C_6H_4CH : C - CH = CC_6H_5. \\ \qquad\qquad\qquad\qquad\qquad\qquad\quad | \qquad\qquad | \\ \qquad\qquad\qquad\qquad\qquad\qquad CO \text{———} O \end{array}$$

β-(3-Nitrobenzal)-β-benzoyl-propionic Acid, $NO_2C_6H_4CH : C(COC_6H_5)-CH_2CO_2H$.—The acid isolated from the product obtained by heating the dibasic acid crystallized from aqueous methyl alcohol in slender, white needles that melted at 172°.

Calc. for $C_{17}H_{13}O_5N$: C, 65.54; H, 4.53. Found: C, 65.3; H, 4.4.

A solution of the acid in sodium carbonate immediately reduces permanganate, and gives benzaldehyde as one of the products. The structure of the acid was definitely established by synthesis. For this purpose a mixture of 4.8 g. of meta-nitrobenzaldehyde and 6.1 g. of methyl β-benzoyl-propionate was added to a solution of 75 g. sodium in 15 cc. of absolute alcohol. After the solution had stood at the ordinary temperature for two days, the alcohol was removed by distillation, the syrupy residue dissolved in water, and acidified. The resulting oil treated with a little ether in part dissolved, and in part solidified. The solid after crystallization from aqueous methyl alcohol melted at 172°, and was found identical with the product obtained by heating the dibasic acid.

$$NO_2C_6H_4CHO + CH_2(COC_6H_5)CH_2CO_2CH_3 \longrightarrow NO_2C_6H_4CH : C(COC_6H_5)CH_2CO_2H.$$

Methyl β-(3-Nitrobenzal)-β-benzoyl-methylmalonate, $NO_2C_6H_4CH$:-$C(COC_6H_5)CH(CO_2CH_3)_2$.—A solution of the cyclopropane ester melting at 109.5° in absolute methyl alcohol was added to a similar solution of magnesium methylate, and the mixture boiled for nearly 8 hours. The resulting bright yellow magnesium derivative was poured into iced acid, and the colorless ester recrystallized from methyl alcohol. It separated in prismatic crystals that melted at 139.5°.

Calc. for $C_{20}H_{17}O_7N$: C, 62.54; H, 4.46. Found: C, 62.6; H, 4.8.

The substance behaves exactly like the corresponding esters obtained from other cyclopropane esters. When oxidized with permanganate in aqueous acetone, it gives meta-nitrobenzoic acid as one of the products. In anhydrous permanganate, on the other hand, it takes up only a small quantity of oxygen, and gives a sparingly soluble condensation product of unknown structure. This crystallized from glacial acetic acid in small white crystals that melted at 197°.

Analyses gave the following results:

I. 0.1300 g. substance gave 0.0527 g. H_2O and 0.3020 g. CO_2.

II. 0.1357 g. substance gave 0.0550 g. H_2O and 0.3133 g. CO_2.

Found: (I) 63.3% C and 4.5% H. (II) 63.0% C and 4.5% H.

CAMBRIDGE, MASS.

[CONTRIBUTION FROM THE LABORATORIES OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH.]

ON AMIDES, URAMINO COMPOUNDS, AND UREIDES CONTAINING AN AROMATIC NUCLEUS.

BY WALTER A. JACOBS AND MICHAEL HEIDELBERGER.

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The material for the present paper comprises a number of substances which figured as intermediates in an investigation, the results of which