contractions. These anomalies may also be related to differences in the relative positions of the valence electrons between the carbon atoms and the halogen atoms substituted in the α-, β-, γ- and δ-positions, thus causing varying differences in the degrees of contractions.

In conclusion, a quotation from Le Bas[1] should be noted:

"There is no doubt that in spite of the care taken, many parts of the present theory of molecular volumes may have to be altered later as data accumulate, and as our knowledge of the physical property increases. The identification and explanation of constitutive effects is not always easy. Some particular atomic values—generally those found in the homologous series R — X are taken as standard, and by the method of summation the value ΣnV_a is found. The difference, $V_m - \Sigma nV_a$, then measures the constitutive effect. Sometimes a mean atomic value is taken, and it then follows that no account is taken of variations. The great difficulty is to identify the effect with a particular atom or group. When this seems possible, it sometimes happens that other atoms or groups might equally well be identified with the effect in question. Only a careful examination of a large number of data can overcome these difficulties. It will generally be found that the constitutive effects are traceable to some modifications in particular atomic values, and a considerable advance is made when we are able to ascertain for certain which atoms are marked by the variation in question and by how much."

Apropos to the above quotation, and as a summary of the present paper, it has been shown that:

1. Halogen atoms which function positively appear to possess different atomic volumes from those which function negatively. Consequently, it is possible to correlate certain additive and constitutive effects apparent in the molecular volumes of certain compounds with their electronic formulas. These effects cannot be explained by means of the ordinarily employed structural formulas.

2. Definite relationships exist between the molecular volumes of six different chlorobenzenes and their respective electronic formulas. These relationships further confirm the electronic formula of benzene.

3. It is suggested that any variations in the relative positions of the valence electrons which determine the polarity of an atom may likewise cause variations in the atomic volume of the atom.

CINCINNATI, OHIO.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY.]

STUDIES IN THE CYCLOPROPANE SERIES.

[SECOND PAPER.]

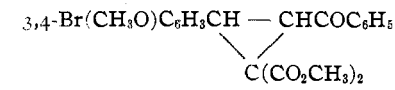
BY E. P. KOHLER AND J. B. CONANT.

Received May 15, 1917.

The cyclopropane derivatives described in our first paper had the great advantage of being so closely related to known substances that the structure of their transformation products could be determined with certainty.

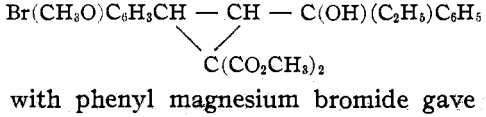
[1] *Loc. cit.*, p. 253.

They had the disadvantage that, being both low melting and readily soluble, they frequently gave oily products which could neither be crystallized nor distilled. We have continued the work with derivatives of the same type that are more sparingly soluble:



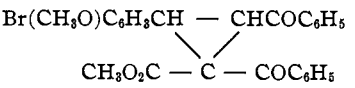
The methods of preparation, general plan, and character of the proof remain the same as in the earlier paper; but we have extended the work to include the behavior towards a number of reagents not previously used. The results obtained by treating these derivatives with oxidizing agents, reducing agents, hydrobromic acid, and basic reagents are essentially the same as those we described before; they are evidently characteristic of this type of cyclopropane derivatives and they are not greatly affected by substitution in the nucleus. The structure of all of the products formed in these reactions was established by synthesis. Of the reactions described here for the first time, those with Grignard reagents are the most important. It has been shown beyond question that the reaction between organic magnesium compounds and ethylenic compounds which contain a "conjugated system" frequently consists in 1,4 addition. A similar mode of addition might, therefore, be expected in the case of our cylcopropane derivatives if our previous conclusion, that a cylcopropane ring can conjugate with a carbonyl group is correct.

We have studied the behavior of the bromomethoxy compound towards both ethyl and phenyl magnesium bromides. As was to be expected in view of the number of active groups, the variety of products is great, their separation difficult, and the yield of definite solids comparatively small. From the products of the reaction with ethyl magnesium bromide, which was carried out under a great variety of conditions, we succeeded in isolating only one substance. The behavior of this substance leaves no doubt that it is a cyclopropane derivative formed by 1,2 addition to the carbonyl group

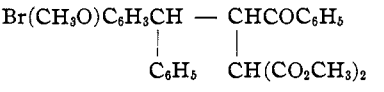


The reaction with phenyl magnesium bromide gave different results under different conditions. When the magnesium compound was slowly added to a benzene solution of the cyclic derivative the principal product was a substance melting at 184°. The analyses showed that this had been formed by replacing a methoxyl group with phenyl. The substance does not reduce permanganate, but is rapidly hydrolyzed by methylate in moist ether, and readily reduced by zinc in acetic acid, therefore probably contains a cyclopropane ring. Moreover, neither the original substance

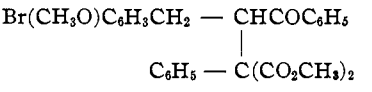
nor the reduction product can be hydrolyzed to a dibasic acid. This substance, therefore, is a cyclic diketonic ester:



A different product was obtained when the finely powdered solid ester was added to a cold solution containing a large excess of reagent. Analyses showed that this was formed by direct addition of the reagent, and a test with ethyl magnesium bromide indicated the absence of a hydroxyl group. The substance can be treated with sodium methylate in moist ether and recovered unchanged. It does not show the characteristic rapid hydrolysis that we have observed in the case of all of our cyclic derivatives. These facts are best represented by one of the following formulas:



(I).



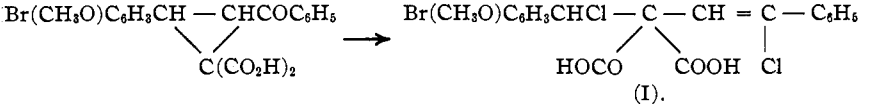
(II).

The second of these formulas is excluded by the fact that the substance while sparingly soluble in alcohol is readily soluble in sodium methylate and is reprecipitated upon addition of acid. We tried to get more conclusive evidence in favor of Formula I by oxidizing the substance with chromic acid, but failed. While we have little doubt as to its correctness, we prefer, for the present, to regard it as provisional.

Strauss, studying the action of phosphorus pentachloride on α,β-unsaturated ketones, discovered a peculiar relation between the resulting "ketochlorides" and the parent substances. In the case of benzalacetophenone, for example,

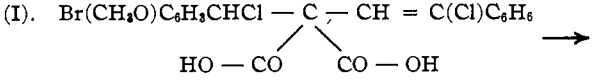
$$C_6H_5CH : CHCOC_6H_5 \longrightarrow C_6H_5CHClCH : CClC_6H_5.$$

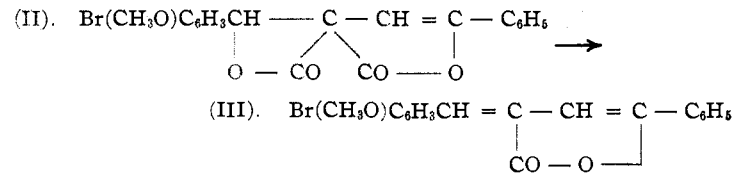
A similar reaction with our cyclic acids would be represented by the equation



(I).

We have found that the dibasic acid reacts very readily with phosphorus pentachloride and gives a product that is closely related to the dichloro acid represented by Formula I. An acid of this character would be expected to lose both hydrochloric acid and carbon dioxide very easily and give an unsaturated lactone:





Formula III represents the substance actually obtained. The structure was established by synthesis. The mechanism by which it is formed in the reaction with phosphorus pentachloride is still under investigation.

Experimental Part.

Anisalacetophenone, $CH_3OC_6H_4CH : CHCOC_6H_5$.—For preparing this on a large scale the following procedure was found most satisfactory: 110 g. of acetophenone, 130 g. of anisic aldehyde, 35 cc. of 10% sodium hydroxide and enough alcohol to make a clear solution were mixed in a securely closed fruit jar. The mixture was allowed to stand, with occasional shaking, at room temperature for 4 or 5 hours, during which it usually solidified to a hard cake. This was pressed into a porcelain funnel and sucked as dry as possible. The solid was then ground in a large mortar with a small quantity of water and alcohol and again filtered. After several such washings it was almost pure and one recrystallization from alcohol gave a pure product melting at 76°. The average yield of 4 such preparations was 85%.

Methyl β-(4-Methoxy-phenyl)-γ-benzoylethylmalonate, $CH_3OC_6H_4CH(CH_2COC_6H_5)CH(CO_2CH_3)_2$.—The addition of methylmalonate to the unsaturated ketone was most successful when strictly anhydrous substances were used, but a fairly good yield could be obtained even when 98% methyl alcohol was used as the solvent. A typical preparation was as follows: To a boiling solution of 200 g. of anisalacetophenone and 115 g. of methylmalonate in 200 cc. of absolute methyl alcohol, a solution of sodium methylate was added until the reaction was just alkaline, as indicated by turmeric paper, and the whole allowed to remain an hour without further heating. If the mixture had not solidified by this time, inoculation with a small quantity of solid product induced immediate crystallization. The solid, carefully washed with methyl alcohol and dried, was sufficiently pure for most reactions. Where absolutely pure substance was required it was recrystallized from methyl alcohol containing a small quantity of benzene. It separated in long, silky needles, very sparingly soluble in alcohol, moderately in cold benzene, readily in hot benzene. The crystals obtained from alcoholic solutions contain one molecule of alcohol of crystallization which they lose at 60°. The product from methyl alcohol melts at 58°, that from ethyl alcohol at 66°. A benzene solution deposits crystals (containing no solvent) that melt at 80°.

Calc. for $C_{21}H_{22}O_6 + C_2H_6O$: C, 66.4; H, 6.7. Found: C, 66.7; H, 6.4.
Calc. for $C_{21}H_{22}O_6$: C, 63.1; H, 6.0. Found: C, 63.2; H, 6.3.
Molecular weight calc. for $C_{21}H_{22}O_6$: 370. Found: 386, 383, 362.

Bromination of the Ester.—Bromine readily attacks the ester, but we found it impossible to confine the action to the aliphatic chain. Thus when we brominated in chloroform, using one molecule of bromine to one of the ester, in the manner described in our first paper, we obtained an oily product that could not be induced to crystallize. This lost hydrobromic acid when boiled with magnesium methylate, but the product also was an oil, and a qualitative test showed that it still contained halogen, proving that a part of the bromine had entered the nucleus.

We also tried bromination in carbon disulfide. This likewise gave an oily mixture of products, but on eliminating hydrobromic acid from this a solid bromine-free product was obtained. The amount of this indicated that only 10% of the original substance had escaped bromination in the nucleus.

When the ester is treated with excess of bromine in chloroform it reacts with approximately two molecules. The properties of this product showed that it is composed principally of methyl-β-(bromomethoxy-phenyl)-γ-bromo-γ-benzoylethylmalonate. As we could not get a solid product in this way we undertook the preparation of this substance by starting with bromoanisic aldehyde.

***m*-Bromoanisalacetophenone,** $Br(OCH_3)C_6H_3CH = CHCOC_6H_5$.—Cahours obtained bromoanisic aldehyde by treating anisic aldehyde directly with bromine. We found the yield by this method small, anisoyl bromide being formed as a by-product. A fairly good yield was obtained by using carbon tetrachloride as solvent and a small quantity of iodine as catalyst. The tetrachloride was removed under diminished pressure and the residue crystallized from ether. It separated in plates melting at 54°.

A few cc. of 10% sodium hydroxide were added to a solution of equivalent amounts of the aldehyde and acetophenone in the smallest possible quantity of alcohol. After standing overnight the solid condensation product had separated almost completely. This was washed with alcohol and water and recrystallized from alcohol. It separates in long yellow needles that melt at 107°.

Calc. for $C_{16}H_{13}O_2Br$: Br, 25.10. Found: Br, 25.06.

The ketone readily combines with one molecule of bromine and forms a dibromide melting at 179°.

Methyl β-(3,4-Bromomethoxy-phenyl)-γ-benzoylethylmalonate, $Br(CH_3O)C_6H_3CH(CH_2COC_6H_5)CH(CO_2CH_3)_2$.—The addition of methylmalonate to the unsaturated ketone was carried out like that with anisalacetophenone, but in order to get a sufficiently concentrated solution a small quantity of dry benzene was added to the anhydrous methyl alcohol

used as medium. The ester closely resembles the bromine-free analog, except that it is much less soluble. It was recrystallized from a mixture of acetone and alcohol, from which it separated in fine, white needles that melted at 125°.

Calc. for $C_{21}H_{21}O_6Br$: C, 56.2; H, 4.7; Br, 17.6. Found: C, 56.2; H, 4.7; Br, 17.8.

The ester is hydrolyzed with even greater difficulty than most esters of this kind, because it is so sparingly soluble that only dilute solutions can be obtained in boiling alcohol. When alcoholic potassium hydroxide was added to such solutions much of the ester was decomposed into the unsaturated ketone and potassium malonate. On allowing a saturated solution containing potassium hydroxide to stand in the cold, it slowly deposited a small quantity of ester salt, which was recrystallized from water.

Calc. for $C_{20}H_{18}O_6BrK$: K, 8.4. Found: (I) K, 8.1; (II) K, 9.2.

The salt decomposed with evolution of gas at 185°.

Bromination.—The ester was brominated in a warm chloroform solution; the bromine, added slowly, disappeared until one molecule had been added, when a permanent red color appeared. The solvent was evaporated under diminished pressure, the residue dissolved in ether and the solution washed with water until free from acid. The ethereal solution, dried and evaporated, left an oil which behaved exactly like that which had resulted from brominating the ester obtained from anisalacetophenone.

Dimethyl 2-(3,4-Bromomethoxy-phenyl)-3-benzoyl Cyclopropane, $Br(CH_3O)C_6H_3CH-CHCOC_6H_5$ / $C(CO_2CH_3)_2$ —Magnesium methylate was used at first for eliminating hydrobromic acid from the oily bromine compound. This gave a 71% yield of cyclopropane compound, showing that at least 75% of the oil was composed of γ-bromo derivatives. Later the more convenient potassium acetate was substituted for magnesium methylate because it was found to give almost the same yield of cyclopropane derivative. The procedure was as follows: About equal weights of bromine compound and potassium acetate were dissolved in wood alcohol and this solution boiled for several hours, during which the solution became slightly yellow and deposited a considerable quantity of crystalline solid. The mixture was allowed to stand overnight, the solid filtered off, washed with alcohol and water, and recrystallized to free it from a light yellow oil which was always formed by this method and clung tenaciously to the solid. The yields obtainable by this procedure are shown by the following typical results: 250 g. of anisic aldehyde and 210 g. acetophenone gave 390 g. of recrystallized unsaturated ketone—89% of the calculated amount. From 390 g. of unsaturated compound 485 g. of washed and dried bromine compound were obtained, an 83% yield. 793 g. of the

bromine compound gave 500 g. of pure recrystallized cyclopropane derivative—a yield of 53%.

The cyclopropane ester is very sparingly soluble in all common solvents except chloroform, slightly soluble in boiling alcohols and acetone, moderately in hot benzene and glacial acetic acid. It is best to recrystallize it from glacial acetic acid. It crystallizes in long needles melting at 153°.

Calc. for $C_{21}H_{19}O_6Br$: C, 56.4; H, 4.3. Found: C, 56.4; H, 4.4.

The ester does not reduce permanganate in acetone solution.

Reduction of the Cyclopropane Derivatives.

The cleanest method of opening the cyclopropane ring in these derivatives is by reduction with zinc and acetic acid. Excess of zinc dust was added to the ester suspended in glacial acetic acid, the mixture diluted with water until a slow evolution of hydrogen was perceptible, and then boiled for several hours, during which the ester dissolved. On cooling, the saturated ketonic ester from which the cyclopropane derivative had been made, crystallized from the solution

$$Br(CH_3O)C_6H_3CH - CHCOC_6H_5 \;\diagdown\diagup\; C(CO_2CH_3)_2 \;+ 2H = Br(CH_3O)C_6H_3CH - CH_2COC_6H_5 \;|\; CH(CO_2CH_3)_2$$

The ester acid and the dibasic acid were treated in the same way. The resulting acids, when esterified, gave the same saturated ester.

Action of Basic Reagents on the Cyclopropane Derivatives.

Hydrolysis to Ester Acid.—The ester showed the same sensitiveness to alkalies that was noted in the cyclopropane derivatives described in our first paper. If sodium methylate solution is added to a suspension of the ester in ether the rate of hydrolysis is dependent only upon the speed at which the ester dissolves in the ether. For getting the ester acid in quantity the following procedure was used: 100 g. of ester were dissolved in hot chloroform, the solution cooled to room temperature and treated with a solution of 6.8 g. of sodium in ordinary methyl alcohol. The mixture at once became hot and developed an orange color. After five minutes it was shaken with cold, dilute acid, separated, and the chloroform layer extracted with sodium carbonate. From the carbonate solution acids precipitated an oil which soon solidified. The solid, recrystallized from 75% methyl alcohol, gave 85 g. of pure ester acid.

Calc. for $C_{26}H_{17}O_6Br$: C, 55.6; H, 3.9. Found: C, 55.9; H, 4.4.

The acid is readily soluble in chloroform and benzene, moderately in cold alcohol, insoluble in water. When freshly precipitated as oil, it readily dissolves in ether, but the solid acid is practically insoluble even in boiling ether. It crystallizes in needles, and melts with decomposition at 178°. Its solution in sodium carbonate does not reduce permanganate or react with bromine. When its solution in methyl alcohol is saturated

with hydrochloric acid, it is re-esterified, the dimethyl ester crystallizing from the solution.

2-(3,4-Bromomethoxy-phenyl)-3-benzoyl-cyclopropane Di-acid.—For getting the dibasic acid it is best to hydrolyze first to the ester acid, in the manner described, and then to dissolve this in excess of strong potassium hydroxide. The hydrolysis is complete in 24 hours and if the concentration happens to be right a dipotassium salt separates. By acidifying and extracting with ether it is easy to get the acid, but it is difficult to purify it. The best results were obtained from a mixture of alcohol and water. It melts with decomposition between 210° and 220°. Its solution in sodium carbonate does not reduce permanganate or decolorize bromine.

Calc. for $C_{18}H_{15}O_6Br$: C, 54.4; H, 3.6. Found: C, 54.3; H, 3.6.

Isomeric Cyclopropane Ester.—When calcium or magnesium methylate was added to a solution of the ester melting at 153° in chloroform, or to its suspension in methyl alcohol and the mixture either boiled for a short while or allowed to stand for a few minutes, all of the ester disappeared. The product after acidification contained 3 isomeric substances which were separated by laborious fractional crystallization from methyl alcohol and acetone. One of these substances—obtained only in small quantities—crystallized in long needles melting at 129°. That this is a second cyclopropane ester is shown by the following facts: the substance does not react with bromine in chloroform and has only a very slight action on permanganate, which may be due to an impurity. When treated with sodium methylate it gives, along with other products, the same ester acid that is obtained from the ester melting at 153°, and when it is boiled with magnesium methylate or similar reagents it gives the same substances that are obtained from that ester.

Calc. for $C_{21}H_{22}O_6Br$: C, 56.4; H, 4.3. Found: C, 56.2; H, 4.6.

The two cyclopropane esters resemble the corresponding isomers described in our first paper in that one is transformed into the other by bases; they differ from that pair in that neither of them is affected by hydrochloric acid in methyl alcohol.

The two other products of this reaction were unsaturated esters melting at 129° and at 139°. These were more easily obtained by more vigorous treatment of the cyclopropane esters. The magnesium derivatives are always formed together, but the relative amounts depend upon the duration of heating. After boiling for 10 hours the principal product is the magnesium derivative of the higher melting ester. For preparing large quantities of these esters it was found best to use a large excess of methylate and a solution of the ester in a mixture of chloroform and methyl alcohol. After heating for several hours the solvents were evaporated, and the yellow magnesium derivatives decomposed with acids. The re-

sulting colorless solids were recrystallized from methyl alcohol or acetone.

Dimethyl β-Benzoyl-γ-(3,4-bromomethoxy-phenyl)-vinyl Malonate, $Br(CH_3O)C_6H_3 — CH = C(COC_6H_5)CH(CO_2CH_3)_2$ (129°), is readily soluble in hot methyl alcohol and acetone, sparingly soluble in the cold. It is easily distinguished from the cyclopropane ester which melts at the same temperature because it crystallizes in cubical crystals instead of needles.

Calc. for $C_{21}H_{22}O_6Br$: C, 56.4; H, 4.3. Found: C, 56.2; H, 4.2.

When treated with magnesium methylate, the ester gives a bright yellow magnesium derivative, from which acids regenerate it; but if the magnesium derivative is boiled with magnesium methylate for 2 or 3 hours and then acidified, the product is the isomeric ester melting at 139°. The ester does not react with bromine but rapidly reduces permanganate in acetone.

The higher melting isomer (139°) is slightly more soluble in acetone and alcohol, and crystallizes in needles. Like the lower melting ester it forms yellow sodium and magnesium derivatives, does not combine with bromine, and rapidly reduces permanganate in acetone.

Calc. for $C_{21}H_{22}O_6$ Br: C, 56.4; H, 4.3. Found: C, 56.2; H, 4.4.

β-Benzoyl - γ - hydroxy-γ-(3,4-bromomethoxy-phenyl)-ethylmalonic Acid, $Br(CH_3O)C_6H_3CH(OH)CH(COC_6H_5)CH(CO_2H)_2$.—The behavior of the two substances towards permanganate is like that of the simpler substances described in the preceding paper. In acetone that contains a small quantity of water or acetic acid they are rapidly oxidized to benzoic and bromoanisic acids. In the absence of water no acids are formed; the result is a sparingly soluble, crystalline product that melts with decomposition at 245°. As this is probably formed as a result of condensation as well as oxidation it was not further investigated. The analyses gave the following results:

I. C, 55.6; H, 3.8. II. C, 55.8; H, 3.9. II. Br, 18.0.

The hydrolysis of the esters is difficult. Concentrated alkalies give metallic derivatives that are almost insoluble. Alcoholic sodium methylate dissolves the esters; but acids reprecipitate them from the orange solutions. The color of the solutions fades when they are heated but only oily decomposition products are formed in the process. The color also fades slowly when the solutions are allowed to stand for several weeks and acids then precipitate a hydroxy dibasic acid. This was most easily obtained by suspending the lower melting compound in alcohol, adding an excess of base and allowing the solution to stand until both the solid and the color had disappeared. From the resulting solution acids precipitated an acid which after crystalization from ether and ligroin melted at 144°. Its solution in sodium carbonate does not reduce potassium permanganate

this is the principal reason for regarding the substance as a hydroxy acid rather than as an unsaturated acid with water of crystallization. The location of the hydroxyl group is unknown; the formula we give is consistent with the preparation and properties of the substance.

Calc. for $C_{19}H_{17}O_7$ Br: C, 52.2; H, 3.9. Found: C, 52.1; H, 3.8.

β-Benzoyl-γ-(3,4-bromomethoxy-phenyl)-vinylacetic Acid, $Br(CH_3O)C_6H_3CH = C(COC_6H_5)CH_2CO_2H$.—When the hydroxy dibasic acid is boiled with water it rapidly loses both water and carbon dioxide. The solution on cooling deposits an acid that melts at 178–180°, rapidly reduces permanganate but does not combine with bromine.

Calc. for $C_{18}H_{15}O_4$ Br: C, 57.7; H, 4.0. Found: C, 57.5; H, 3.9.

The structure of this acid was established by synthesis from methyl-β-benzoyl-propionate and bromoanisic aldehyde; a solution of 14 g. of the aldehyde in 13 g. of the ester was slowly dropped into a cold solution of 1.6 g. sodium in 30 cc. of methyl alcohol, and the mixture left overnight. The resulting viscous oil was acidified with cold dilute acid and the liquid extracted with ether. The ether, on evaporation, deposited an acid that was recrystallized from chloroform. It melted at 177° and a mixed melting point showed its identity with the product obtained from the hydroxy acid.

The high melting isomer (139) was hydrolyzed in exactly the same way as the lower melting (129°) compound, but the process was much slower because the yellow sodium derivative is very sparingly soluble both in concentrated and dilute alkalies. In contact with sodium methylate made from ordinary methyl alcohol, the solid sodium compound slowly disappears. The result is both hydrolysis and loss of carbon dioxide, the sole product being the same monobasic acid that is obtained by heating the hydroxybromic acid.

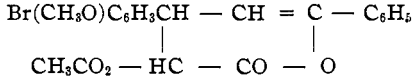
By first adding hydrobromic acid and then eliminating it again, it is easy to go back from the ethylenic esters to the cyclopropane derivatives. A solution of the ester (139°) in glacial acetic acid containing 5% of hydrobromic acid was heated at 80° for 2 hours, then poured into water. The product was separated into acid and indifferent products by shaking the ethereal extract with sodium carbonate, but neither the acid nor the indifferent ester could be obtained in pure condition. The ester was boiled with a methyl alcoholic solution of potassium acetate; this eliminated hydrobromic acid, and the cyclopropane derivative melting at 153° crystallized from the solution. The acid esterified in the usual manner gave an oily ester. This when likewise boiled with potassium acetate, gave the same cyclopropane derivative. Although the relations that we have described leave no room for doubt as to the structure of the unsaturated dibasic esters, we nevertheless attempted to synthesize them from sub-

stances of known structure. For this purpose we reduced anisalacetophenone, introduced bromine in the nucleus and in the α-position of the saturated ketone, and treated the resulting bromo ketone with sodium malonic ester.

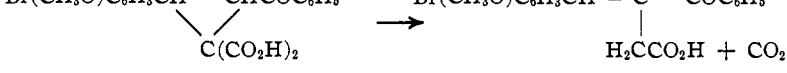
The reduction of the unsaturated ketone with zinc and acetic acid gave, principally, dimolecular products, but an excellent yield of saturated ketone was obtained by reducing with hydrogen in the presence of colloidal palladium. The saturated ketone in chloroform readily decolorized 2 mols. of bromine. The resulting oil—carefully washed until free from bromine, and dried—was dissolved in dry methyl alcohol and treated with the calculated quantity of sodium methyl malonate. The mixture was allowed to stand for 4 days, then acidified and extracted with ether. This gave a small quantity of ethanetetracarboxylic ester and an oil. The oil, shaken with sodium methylate and again acidified, gave a small quantity of a colorless solid melting at 116°.

Calc. for $C_{20}H_{17}O_5Br$; C, 57.5; H, 4,5. Found: C, 57.6; H, 4.0.

The analysis indicates a substance formed by loss of alcohol from the expected condensation product. The substance may be a lactone,



Action of Hydrobromic Acid on the Cyclopropane Derivatives.—Neither the cyclopropane esters nor the acids combine with halogen acids in methyl alcohol. Both are attacked by hydrobromic acid in glacial acetic acid; but while it was possible to prove that addition takes place no additive products could be isolated. In contact with the solution, or during the process of isolation these products undergo a series of changes which finally result in the same unsaturated monobasic acid that was obtained by treating the cyclic compounds with bases. This proves that the ring is opened between carbon atoms 1 and 2.



One series of intermediate steps in this process was established with considerable certainty: 10 g. of ester were added to 200 cc. of a 5% solution of hydrobromic acid in glacial acetic acid. The mixture was left at the ordinary temperature until all the suspended material had disappeared. The resulting dark red solution was diluted with water, extracted with ether, the ethereal solution washed thoroughly with water, and the ether evaporated. The oily residue was dissolved in dilute ammonia, the solution neutralized with acetic acid and treated with an aqueous solution of calcium nitrate. This precipitated a curdy calcium salt. The filtrate from the calcium salt contained soluble bromides, proving that the oil

contained a bromine compound in which the bromine was in the side chain.

(I). $Br(CH_3O)C_6H_3CH-CHCOC_6H_5$ (with $C(CO_2H)_2$ bridging) $+ HBr =$ $Br(CH_3O)C_6H_3CHBr-CHCOC_6H_5$ ($HC(CO_2H)_2$).

The calcium salt was washed, dried and analyzed; 3 different preparations gave the following results:

Calc. for $(C_{19}H_{16}O_6Br)_2Ca$: Ca, 4.6; Br, 18.2.
Found: (I) Ca, 4.0; (II) Ca, 5.2; (III) Ca, 3.6; (IV) Br, 19.4.

(II). $Br(CH_3O)C_6H_3CHBrCH-COC_6H_5$ (HO_2CCHCO_2H) $-HBr =$ $Br(CH_3O)C_6H_3CH=CHCOC_6H_5$ (O, $OC-CHCO_2H(Ca)$).

On heating with dilute acids, the calcium salt gave, along with some of the acid previously mentioned, an oil insoluble in sodium carbonate, evidently a lactone.

(III). $Br(CH_3O)C_6H_3CH-CHCOC_6H_5$ ($O-CO-CHCO_2H$) $=$ $Br(CH_3O)C_6H_3CH-CHCOC_6H_5$ ($O-CO-CH_2$) $+ CO_2$.

The lactone was dissolved in methyl alcoholic potassium hydroxide. This solution, on acidification, gave the monobasic unsaturated acid melting at 178° and a minute quantity of an acid melting at 155–156°.

(IV). $Br(CH_3O)C_6H_3CH-CHCOC_6H_5$ ($O-CO-CH$) $\longrightarrow$ $Br(CH_3O)C_6H_3CH=C-COC_6H_5$ (HO_2CCH_2).

Action of Phosphorus Pentachloride on the Cyclopropane Derivatives.

1-(3,4-Bromomethoxy-benzal)-3-phenyl-crotolactone, $Br(CH_3O)C_6H_3-CH=C-CH=C-C_6H_5$ (CO, O).—Phosphorus pentachloride has no action on the cyclopropane esters in boiling chloroform, but readily attacks both the ester acid and the dibasic acid. The ester acid is merely transformed into the acid chloride, from which the acid is regenerated by treatment with water. The dibasic acid undergoes more extensive change. Thus when a slight excess of the pentachloride was added to a chloroform solution of pure acid, hydrochloric acid was evolved at once and the solution assumed a pale yellow color. This deepened to red and more gas was evolved when the solution was warmed on a steam bath. The chloroform was evaporated, the residue poured into water and the mixture extracted with ether. The ethereal solution, on evaporation, deposited a canary-yellow solid, which crystallized from chloroform in long needles, and melted at 197°.

Calc. for $C_{18}H_{13}O_3Br$: C, 60.5; H, 3.5. Found: C, 60.3; H, 3.5.

The structure of this unsaturated lactone was established by the following synthesis: A mixture containing 10 g. of powdered sodium β-benzalpropionate, 10 g. of bromoanisic aldehyde, and 12 g. of acetic anhydride was heated at 100° for 6 hours, during which it changed into a solid, brownish yellow mass. This was disintegrated by boiling with a little alcohol, the insoluble part recrystallized from chloroform and acetone. This deposited long, canary-yellow needles that melted at 197°—identical with those obtained from the cyclopropane derivative.

α-(3,4-Bromomethoxy-benzal)-β-benzoyl-propionic Acid, $Br(CH_3O)C_6H_3CH = C(CH_2COC_6H_5)CO_2H$.—The lactone ring is easily opened by treating the substance with strong bases, but seems to close again, in part, when the resulting products are treated with acids. Thus from solutions of the lactone in sodium methylate, cold dilute acids precipitated a solid that was soluble in sodium carbonate, crystallized in pale, yellow silky needles, and melted at approximately 155°. Repeated crystallizations failed to give a substance with a sharp melting point, and free from yellow taint. The solutions of the substance in potassium hydroxide were colorless, those in alcohol pale yellow.

Calc. for $C_{18}H_{15}O_4Br$: C, 57.6; H, 4.0. Found: C, 57.3; H, 4.7.

When the alcoholic solution of the acid was saturated with hydrochloric acid, it passed completely into the yellow lactone.

Action of Organic Magnesium Compounds on the Cyclopropane Ester.

Methyl 2-(3,4-Bromomethoxy-phenyl) - 3 - (α,α-phenyl-hydroxylpropyl)-cyclopropane Dicarboxylate, $Br(CH_3O)C_6H_3CH\text{—}CHC(OH)(C_6H_5)C_2H_5$.—A flask containing a solution of ethyl magnesium bromide was connected through a narrow tube with a second flask containing a solution of the cyclic ester in benzene, kept at a temperature of 35°, and protected against excess of moisture. By means of dry compressed air the Grignard reagent was forced in small amounts into the solution of the ester, which was shaken vigorously. Each addition of the reagent caused a slight yellow precipitate which dissolved on shaking, until about one equivalent had been added, when a pale yellow solid began to separate. The mixture was then poured into iced acid, the organic material extracted with ether, the ethereal solution washed, dried and evaporated. From the oily residue a small quantity of solid was obtained by slow crystallization from methyl alcohol. The conditions were varied in a variety of ways, but the amount of solid product was always small. The solid was separated, by repeated crystallization from methyl alcohol, into two isomeric compounds that melted at 135° and 161.°

The lower melting substance crystallized from methyl alcohol in long needles.

Calc. for $C_{23}H_{25}O_6Br$: C, 58.0; H, 5.2. Found: C, 58.3; H, 4.9.

The substance rapidly liberates gas from ethyl magnesium bromide, showing the presence of a hydroxyl group. It is insoluble in ether, but dissolved immediately when sodium methylate is added to the suspension in ether. On adding acid to the resulting solution and then extracting with sodium carbonate, almost all of the material is found in the water solution. This rapid, complete hydrolysis under these conditions is characteristic of cyclopropane di-acids. Like the cyclopropane ester from which it was obtained, this substance is transformed into a yellow magnesium compound by digestion with magnesium methylate and the magnesium compound on acidification gives a different product—melting at 115–120° and which gives red solutions with sodium methylate. Like the original cyclopropane ester, also, the substance is easily reduced, giving a solid product melting at 128°. Our formula represents these facts.

The high melting ester was obtained in sufficient quantities only for analysis:

Calc. for $C_{23}H_{25}O_5Br$: C, 58.0; H, 5.2. Found: C, 58.2; H, 4.9.

Methyl 1-Benzoyl-2-(3,4-bromomethoxy-phenyl)-3-benzoyl-cyclopropane Carboxylate, $Br(CH_3O)C_6H_3CH-CHCOC_6H_5$ / $C_6H_5-CO-C-CO_2CH_3$.—Phenyl magnesium bromide, added in the same way as the ethyl compound, produced a sparingly soluble magnesium compound that separated as a yellowish, flocculent precipitate. After cooling the suspension in a freezing mixture, this was filtered off. When decomposed with iced acid it gave a solid that after one crystallization from alcohol melted sharply at 184°. It separated in long needles.

Calc. for $C_{26}H_{21}O_6Br$: C, 63.2; H, 4.4. Found: C, 62.8; H, 4.3.

The ester does not reduce permanganate in acetone and it is not affected by boiling with magnesium methylate.

1-Benzoyl-2(3,4-bromomethoxy-phenyl)-3-benzoyl-cyclopropane Acid, $Br(CH_3O)C_6H_3CH-CHCOC_6H_5$ / $C_6H_5CO-C-CO_2H$.—The ester is as readily hydrolyzed as the original cyclic ester. When sodium methylate was added to a suspension in moist ether, it dissolved in 5 minutes and the usual procedure showed almost complete hydrolysis. The acid was recrystallized from ether, in which it is sparingly soluble. It melts at 175° and shows no signs of decomposition at 220°—a peculiar stability that has been observed in the case of other β-ketonic acids that have a cyclic structure. A solution of the acid in sodium carbonate does not reduce permanganate.

Calc. for $C_{25}H_{19}O_6Br$: C, 62.5; H, 4.2. Found: C, 62.4; H, 4.2.

Methyl α-Benzoyl-β-(3,4-bromomethoxy-phenyl)-γ-benzoyl-propionate, $Br(CH_3O)C_6H_3-CHCH_2COC_6H_5$ (with $C_6H_5COCHCO_2CH_3$ below the CH).—The ester melting at 184° was dissolved in acetic acid and boiled with zinc dust for several hours. From the solution, after dilution with water, ether extracted a substance that crystallized in cubes and melted at 182°. A mixed melting point determination with the original substance gave 160°—showing that the two are different.

Calc. for $C_{20}H_{23}O_5Br$: C, 63.2; H, 4.80. Found: C, 63.1; H, 4.8.

The reduction product, suspended in moist ether, rapidly dissolved on addition of sodium methylate, and was reprecipitated, on subsequent treatment with acid. By suspending the ester in concentrated alcoholic potassium hydroxide it was possible to hydrolyze it to an acid that melted with decomposition at 135°. When heated in an open tube it effervesced at 120–140°. The residue, dissolved in ether, gave a small quantity of unchanged substance and a new compound that melted at 145°, and was insoluble in sodium carbonate, probably the corresponding diketone. These substances were not investigated further.

Methyl β-Benzoyl-γ-(3,4-bromomethoxy-phenyl)-γ-phenyl-ethyl-malonate, $Br(CH_3O)C_6H_3CH(C_6H_5)CH(COC_6H_5)CH(CO_2CH_3)_2$. — When the very finely powdered cyclic ester was dropped into an ice-cold solution containing a large excess of phenyl magnesium bromide it slowly disappeared on shaking. The solution changed color and finally deposited a greenish acid. The mixture was poured into iced hydrochloric acid, and the organic product extracted with ether. The dried ethereal solution on evaporation deposited a crystalline solid melting at 176°. The yield varied greatly; under the most favorable conditions a large excess (4 molecules) of very cold reagent, very finely divided ester added in very small quantities, the maximum yield was 30%.

Calc. for $C_{27}H_{25}O_6Br$: C, 61.7; H, 4.8. Found: C, 61.4; H, 5.3.

With ethyl magnesium bromide the substance gave only the very slow evolution of gas that is produced by substituted malonic esters. It, therefore, does not contain a hydroxyl group. The substance, while very sparingly soluble in methyl alcohol, dissolves rapidly in sodium methylate but the process does not result in the rapid hydrolysis to ester acid observed with all of our cyclopropane derivatives. When hydrolyzed with alcoholic potassium hydroxide it gives a dibasic acid.

β-Benzoyl-γ-(3,4-bromomethoxy-phenyl)-γ-phenyl-ethylmalonic Acid, $Br(CH_3O)C_6H_3CH(C_6H_5)CH(COC_6H_5)CH(CO_2H)_2$.—The ester was suspended in alcoholic potassium hydroxide and set aside. It slowly dissolved; in the course of 3 days a heavy deposit of potassium salt was formed. The

acid, obtained in excellent yield by acidifying both the solid salt and the solution, crystallized from ether with a molecule of water, which it lost at 80°.

Calc. for $C_{25}H_{21}O_6Br.H_2O$: C, 58.4; H, 4.5. Found: C, 58.3; H, 4.2.

Titration with standard base using phenolphthalein as indicator showed that the acid is dibasic. An acid having the structure that we assign to this substance would be expected to give benzoic acid and, probably, bromomethoxy-benzophenone when oxidized with chromic acid, while any other acid that could possibly be obtained in this manner, would be expected to give either anisic acid and benzophenone, or both anisic and benzoic acids. We oxidized the acid with excess of chromic acid in glacial acetic acid. In the cold we obtained only uncrystallizable products. When the oxidation was carried out at 100° a part of the product dissolved in sodium carbonate. No trace of the more sparingly soluble bromo-anisic acid could be detected. The part of the product that was insoluble in sodium carbonate could not be induced to crystallize. It failed to do so even when inoculated with bromomethoxy-benzophenone. The ketone used for this purpose was made as follows: One molecule of bromine was added to a solution of methoxy-benzophenone in chloroform; a vigorous reaction took place, the solution became deep red in color but no hydrobromic acid was evolved. On boiling this solution with a little iron wire, it gave off hydrobromic acid slowly and the color disappeared in several hours. The product recrystallized from alcohol, melted at 69°.

Calc. for $C_{14}H_{11}O_2Br$: Br, 27.4. Found: Br, 27.5.

Action of Nitric Acid on the Cyclopropane Esters.

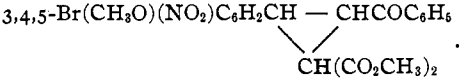
The ester melting at 153° was suspended in concentrated nitric acid. In the course of a few hours the solid began to liquefy and gas was slowly evolved. At the end of three or four days the original solid had completely disappeared and new crystals had taken its place. Both nitrous and nitric acids are necessary for this reaction; neither nitric acid that has been freed from oxides of nitrogen by the addition of a little urea, nor a solution of nitrous acid in glacial acetic acid has any effect on the cyclopropane derivative.

By recrystallization from methyl alcohol the product was separated into a colorless substance melting at 113°, and a very small quantity of a very sparingly soluble yellow compound that melted at 223°. The latter was not investigated further. The analyses of the former show that it is a nitro compound.

Calc. for $C_{21}H_{18}O_8N$: C, 51.2; H, 3.6; N, 2.8; Br, 16.4.
Found: C, 51.4; H, 3.5; N, 2.3; Br, 16.5.

As the substance does not reduce permanganate and it is easily hy-

drolyzed to an ester acid, it is, doubtless, a cyclopropane derivative with a nitro-group in the nucleus.



The corresponding ester acid was obtained by hydrolysis with sodium methylate:

Calc. for $C_{20}H_{16}O_8NBr$: C, 50.2; H, 3.3.
Found: C, 50.8; H, 3.8.

Summary.

1. The ring in (bromomethoxy-phenyl)-benzoyl-cyclopropane di-acid and its esters is more or less easily opened by reducing agents, halogen acids, bases, the Grignard reagent, and phosphorus pentachloride.

2. The various reagents open the ring in different positions; by using phosphorus pentachloride, bases, and reducing agents, it is possible to open the ring in three different ways.

3. The primary reaction between the cyclopropane derivative and a given reagent is similar to that between the corresponding ethylenic compound and the same reagent.

4. The cyclopropane derivative exhibits all the "peculiarities" of ethylenic compounds that contain conjugated systems; but it does not, like many ethylenic compounds, combine with the halogens or reduce permanganate.

CAMBRIDGE, MASS.

[CONTRIBUTIONS FROM THE SHEFFIELD CHEMICAL LABORATORY OF YALE UNIVERSITY.]

RESEARCHES ON PYRIMIDINES. LXXXIV.

THE TRANSFORMATION BY HYDROLYSIS OF SECONDARY PYRIMIDINE NUCLEOSIDES INTO IMIDAZOL COMBINATIONS.

BY TREAT B. JOHNSON AND SIDNEY E. HADLEY.

Received May 16, 1917.

In the fourth paper from the Sheffield Laboratory on pyrimidine nucleosides, Johnson and Hadley[1] described an unique transformation which the ethyl ether of the secondary alcohol derivative of uracil (I) undergoes when it is subjected to hydrolysis by heating with aqueous hydrobromic acid. They showed that this pyrimidine is broken down by such treatment with evolution of ethyl bromide and carbon dioxide, giving a characteristic, crystalline compound having the formula $C_5H_8ON_2$. In other words, the secondary nucleoside (II) is apparently an intermediate product of the reaction but, being unstable in the presence of acid at high temperatures, gradually loses carbon dioxide and is transformed into the com-

[1] THIS JOURNAL, 38, 1844 (1916).