papers by Hardy,[1] Langmuir,[2] Harkins, Brown and Davies,[3] Harkins, Davies and Clark,[4] and by Fraenkel.[5]

CHICAGO, ILL.

NOTE.

Acknowledgment.—In an article[6] entitled "A Study of Conditions Affecting the Precise Determination of Zinc as the Sulfide," by Harold A. Fales and Gertrude M. Ware, omission was made of an acknowledgment due to Prof. H. T. Beans, of Columbia University. The investigation described in this article was proposed by Dr. Beans and carried out under the direction of Dr. Fales during the absence of Dr. Beans in Government service. It is regretted that the omission of this acknowledgment occurred in the original publication.

HAROLD A. FALES.

NEW YORK, N. Y.

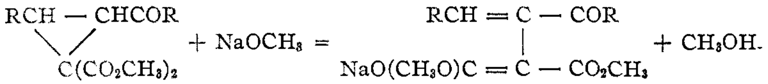
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY.]

STUDIES IN THE CYCLOPROPANE SERIES. IV.

BY E. P. KOHLER AND T. L. DAVIS.

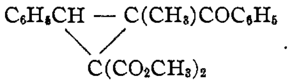
Received February 25, 1919.

One of the most characteristic properties of the cyclopropane derivatives under investigation in this laboratory is the ease with which the ring is opened by alcoholates. The product is a metallic derivative of an isomeric ethylenic ester.



The principal object of the present investigation was to secure additional information on this obscure process.

In earlier papers we assumed that the metallic derivative is formed as a result of two reactions—addition of alcoholate followed by loss of alcohol. We therefore selected for the present work dimethyl 2-phenyl-3,3-methylbenzoyl-cyclopropane dicarboxylate.



Owing to the presence of the methyl group in the 3 position in this sub-

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[1] Hardy, *Proc. Roy. Soc.*, 86B, 634 (1911–12).

[2] Langmuir, THIS JOURNAL, 39, 1848–1906 (1917); *Proc. Am. Acad.*, 3, 251–7 (1917); abstract in *Met. Chem. Eng.*, 15, 468 (1916).

[3] Harkins, Brown and Davies, THIS JOURNAL, 39, 354–64 (1917).

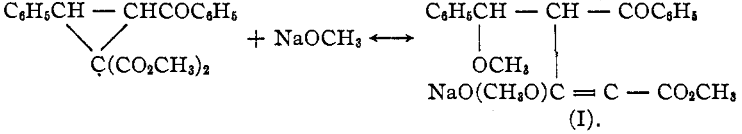
[4] Harkins, Davies and Clark, *Loc. cit.*, 1917, pp. 541–96.

[5] Fraenkel, *Phil. Mag.*, 33, 297–322 (1917).

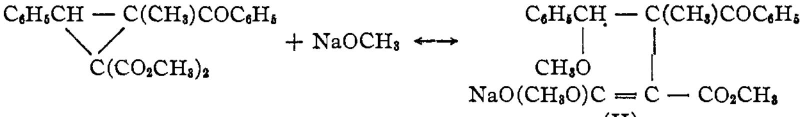
[6] THIS JOURNAL, 41, 487 (1919).

stance, any addition product with sodium alcoholate would be incapable of losing alcohol to form an ethylenic compound.

We have found that if the substance combines with sodium methylate at all, the amount of product is too small to be detected. As there seems to be no reason why this substance should not combine with alcoholates as readily as those described in earlier papers, we conclude that it is possible to have equilibria like the following:

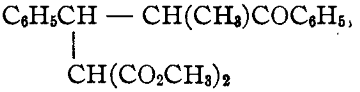


(I).

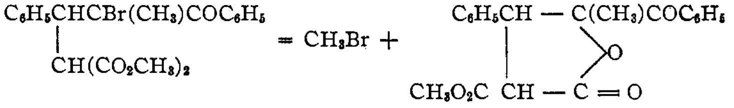


(II).

The substance I by losing methyl alcohol can pass into a stable, insoluble sodium derivative, hence the effect of alcoholate addition is cumulative. The substance II cannot lose alcohol in this way; the effect of a small amount of alcoholate addition is therefore negligible, the cyclopropane derivative being regenerated as the alcoholate is removed.

The influence of the methyl group was perceptible throughout the work. Thus sodium methyl malonate combines far more slowly with benzal-propiophenone than with benzal-acetophenone, and satisfactory results can be obtained only under carefully defined conditions. The product,  $C_6H_5CH(CH(CO_2CH_3)_2)-CH(CH_3)COC_6H_5$, has two dissimilar asymmetric carbon atoms. It therefore appears in two modifications, thereby increasing the difficulty of isolating pure substances.

Each of the isomeric addition products is readily brominated and both apparently give the same result—a mixture of monobromo derivatives of which only one could be obtained in solid form. This solid bromo compound evidently has bromine in the γ-position because it loses methyl bromide at comparatively low temperatures and forms a keto lactonic ester.



Like all similar γ-bromo esters it also readily loses hydrobromic acid when warmed with magnesium methylate or potassium acetate and forms a cyclopropane derivative.

The resinous oil that is left after removing the solid bromine compound constitutes more than 70% of the total product. It contains one or more monobromo compounds that cannot have bromine in the γ-position, for while they readily lose hydrobromic acid to potassium acetate, they do not yield cyclopropane derivatives.

The methyl group evidently has a pronounced effect upon the course of the bromination because the corresponding compound without this group gives more than 90% of γ-bromo derivatives. Inasmuch as these γ-bromo esters are also α-bromo ketones, this fact is of interest in connection with modern views on the bromination of ketones.

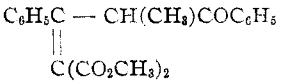
According to the best evidence available, α-bromination of ketones involves enolization, addition of bromine to the enol, and elimination of hydrobromic acid from the resulting bromohydrine.

$$>CHCOR \longrightarrow C:C(OH)R \longrightarrow >CBr.CBr(OH)R \longrightarrow >CBrCOR.$$

The speed of α-bromination therefore depends upon the amount of enolization and upon the rate of addition to the enol. As alkyl groups invariably depress enolization, α-bromination of the methyl compound is so much slower than that of the corresponding hydrogen compound, that most of the bromine goes elsewhere.

No way was found for locating the bromine in these oily bromine compounds. At first sight one would be inclined to assume bromination of the malonic ester residue; but the hydrogen in this group is so singularly inactive in the γ-ketonic esters that there are no facts to support such an assumption. When the oil is treated with a methyl alcoholic solution of potassium acetate it readily loses hydrobromic acid and forms an ester of a dibasic acid that is isomeric with the cyclopropane ester. That this is not a stereoisomeric cyclopropane derivative is shown by the fact that it is not attacked by zinc and acetic acid, a combination that reduces all cyclopropane derivatives which we have studied, including the ester obtained from the solid bromine compound. Under the influence of mineral acids or of traces of alcoholates this compound rapidly undergoes rearrangement to a new substance which is likewise an ester of a dibasic acid.

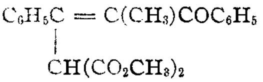
These two isomers of the cyclopropane derivatives are, doubtless, ethylenic compounds. The two possible formulas are



$$\begin{array}{l} C_6H_5C - CH(CH_3)COC_6H_5 \\ \quad \| \\ \quad C(CO_2CH_3)_2 \end{array}$$

(I).

and



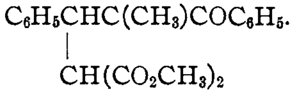
$$\begin{array}{l} C_6H_5C = C(CH_3)COC_6H_5 \\ \quad | \\ CH(CO_2CH_3)_2 \end{array}$$

(II).

We are unable to decide, as yet, whether the substances are structural isomers, or whether they are the two geometrical isomers represented by (II).

Experimental Part.

Dimethyl γ-Benzoyl-β-phenyl-propylmalonate,



$$C_6H_5\underset{\displaystyle CH(CO_2CH_3)_2}{\underset{|}{C}}HC(CH_3)COC_6H_5.$$

—Two stereomeric forms of this ester were obtained by condensing dimethyl malonate with benzal-propiophenone. It was exceedingly difficult to get satisfactory yields. The method which heretofore gave excellent results in similar condensations—using a small quantity of sodium methylate in boiling methyl alcohol—in this case almost completely failed. Attempts to condense with dry sodium methylate, and to add sodium methylmalonate to the ketone in absolute ether or benzene gave little better results. The best yield was obtained by condensing in a strong solution of sodium methylate in methyl alcohol. In order to avoid saponification of the malonic ester during the slow condensation, the methyl alcohol must be completely free from water. We used only alcohol that had been freshly distilled from metallic calcium or magnesium methylate. The following experiment illustrates the procedure:

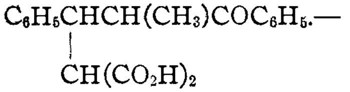
A hot solution of 4.6 g. sodium in 100 cc. of dry methyl alcohol was poured into a mixture of 88 g. of benzal-propiophenone and 60 g. of methyl malonate that had previously been brought to the temperature of a steam-bath. The orange-red mixture remained near the boiling point for half an hour without further external heating. When it began to cool it was protected from moisture with a calcium chloride tube, and set out-of-doors in winter or in an ice chest in summer. It usually began to deposit crystals in the course of 24 hours. The first crop consisted almost entirely of the ester melting at 91–93°. This was filtered off and a few days later a second crop was deposited, consisting of a mixture of the two isomers. After long standing a third crop separated, which consisted mainly of the ester melting at 88–90°. The total yield of pure product was 73.5 g.—52.4% of the calculated amount.

The oil, left after removing the solids, was dissolved in ether, the ethereal solution washed with water, dried, and distilled under diminished pressure. It gave 9.2 g. of pure benzal-propiophenone—10.5% of the amount used.

The principal product is always the higher melting ester. This crystallizes in bunches of slender, transparent needles. The lower melting isomer crystallizes in large rhomb-shaped plates. Both substances are readily soluble in hot methyl alcohol and crystallize slowly. It is comparatively easy to separate mixtures of the two. For this purpose the mixture is dissolved in methyl alcohol and the properly concentrated solution inoculated with the isomer that is present in larger quantity.

Calc. for $C_{21}H_{20}O_5$: C, 71.2; H, 6.2 Found: C, 71.3, 71.5; H, 6.5, 6.6.

γ-Benzoyl-β-phenyl-propylmalonic Acid,



$C_6H_5CHCH(CH_3)COC_6H_5$ with $CH(CO_2H)_2$ below.—The two esters can be hydrolyzed without isomerization. For this purpose 15 cc. of 2 : 3 aqueous potassium hydroxide solution was added to a warm solution of 20.5 g. of the lower melting ester in 80 cc. of methyl alcohol. A bright lemon-yellow color appeared at once and as quickly faded again. After standing for several days the solution deposited a potassium salt in pearly flakes. This was washed with a mixture of alcohol and ether, and dissolved in water. From the solution acids precipitated an oil that slowly solidified. The solid was recrystallized from moist ether. It separated in clusters of thick needles that contained water of crystallization and melted with decomposition at 67°.

Calc. for $C_{19}H_{18}O_5.H_2O$: C, 66.3; H, 5.8. Found: C, 66.5; H, 6.2.

The higher melting ester, on similar treatment, gave an acid that melted at approximately 160°. No solvent was found from which it could be recrystallized, hence it was not analyzed. Its behavior on heating showed however, that it is an isomeric dibasic acid.

γ-Benzoyl-β-phenylvaleric Acid, $C_6H_5COCH(CH_3)CH(C_6H_5)CH_2CO_2H$.—The dibasic acids were heated at 200° until carbon dioxide was no longer evolved, and the colorless melts poured into ether. The acid from the lower melting ester gave a monobasic acid that crystallized from ether in small, transparent needles which melted at 92–93°, while that from the higher melting ester crystallized in clusters of silky needles which melted at 115–117°. Both acids are readily soluble in ether and alcohol.

Calc. for $C_{18}H_{18}O_3$: C, 76; H, 6.4. Found: C, 76.0, 75.1; H, 6.4; 6.4.

Methyl γ-Benzoyl-β-phenylvalerate, $C_6H_5COCH(CH_3)CH(C_6H_5)CH_2CO_2CH_3$.—When the monobasic acids are esterified with methyl alcohol and hydrochloric acid in the usual way they give the same ester—a substance that crystallizes from methyl alcohol in large, rhomb-shaped prisms and melts at 92°.

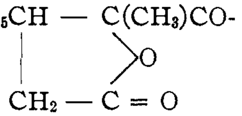
Calc. for $C_{19}H_{20}O_3$: C, 77.0; H, 6.8. Found, C, 77.0; H, 6.8.

This ester probably has the same configuration as the dibasic ester that melts at the same temperature, because it is the only product that is formed when the latter is hydrolyzed to the ester acid, and this decomposed by heating at 200°.

γ,γ-Bromo-benzoyl-β-phenylvaleric Acid, $C_6H_5COCBr(CH_3)CH(C_6H_5)CH_2CO_2H$.—The two isomeric monobasic acids, as would be expected from their behavior on esterification, give the same monobromo substitution product. The bromination was carried out in carbon tetrachloride. The solid product left after evaporating the solvent was purified by recrystallization from benzene. It separated in very fine needles that melted with decomposition at about 160°. The yield was quantitative.

Calc. for $C_{18}H_{17}O_3Br$: C, 60.8; H, 5.1. Found: C, 60.6; H, 5.3.

γ,γ-Methyl-benzoyl-β-phenyl-butyrolactone,



$$\begin{array}{l} C_6H_5CH - C(CH_3)CO\text{-} \\ \quad | \qquad\quad \rangle O \\ CH_2 - C = O \end{array}$$

C_6H_5.—The lactone was obtained by digesting the bromo acid with sodium carbonate and acidifying the resulting solution. It was recrystallized from ether from which it separated slowly in flat, six-sided plates that melted at 93°.

Calc. for $C_{18}H_{16}O_3$: C, 76.7; H, 5.3. Found: C, 76.4; H, 5.7.

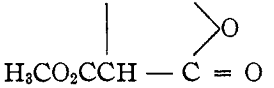
Dimethyl - γ,γ - bromo-benzoyl - β - phenyl-propylmalonate,

$$\begin{array}{l} C_6H_5\text{-}CHCBr(CH_3)COC_6H_5 \\ \;| \\ CH(CO_2CH_3)_2 \end{array}$$

—The two isomeric esters readily react with bromine and both give the same products. The bromination was carried out under a variety of different conditions, but the result was always the same—a relatively small amount of a solid monobromo derivative and an oil. The oil undoubtedly contained a mixture of stereo and structural isomers, but all our attempts at separation failed. Even the solid bromo ester was not easily obtained in a perfectly pure state. It crystallizes poorly from all solvents except methyl alcohol. Methyl alcoholic solutions become acid on boiling and the solid that separates becomes increasingly impure. The bromo compound crystallizes in short, coarse needles melting at 114–115°. The best yield was 16.6%.

Calc. for $C_{20}H_{23}O_6Br$: Br, 18.5. Found: Br, 17.8, 18.0.

Methyl - γ,γ - methyl-benzoyl - β - phenyl-butyrolactone Carboxylate,



$$\begin{array}{l} \quad C_6H_5CH - C(CH_3)COC_6H_5. \\ \qquad\; | \qquad\; \rangle O \\ H_3CO_2CCH - C = O \end{array}$$

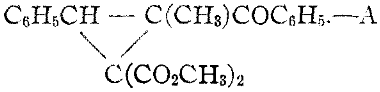
— For the purpose of locating the bromine atom the bromo compound was heated under diminished pressure. It effervesced freely at 130°. The pale yellow melt, left after effervescence had ceased, was dissolved in boiling methyl alcohol. This solution on cooling deposited the lactonic ester in colorless plates that melted at 85°.

Calc. for $C_{22}H_{11}O_5$: C, 71.0; H, 5.3. Found: C, 71.3; H, 5.7.

Since our structural formula for the solid bromine compound is based on that of the ketolactonic ester, we deemed it worth while to prepare this substance by a method that would leave no doubt as to its structure. We therefore dissolved the saturated ketonic ester in methyl alcohol and added the amount of potassium hydroxide calculated to hydrolyze only one of the ester groups. The solution became neutral in the course of a few hours. It was then treated with one equivalent of bromine and allowed to stand at the ordinary temperature until this had disappeared. The colorless solution, left after removing the precipitated potassium bromide, on slow evaporation deposited the same substance that had been obtained by heating the solid bromo ester. The latter is therefore a γ-bromo derivative.

The ease with which the solid bromo ester loses methyl bromide was shown in another experiment in which a methyl alcoholic solution of the substance was heated with precipitated calcium carbonate for half a day in a steam jacketed autoclave; all the bromine compound disappeared and the sole product was the ketolactonic ester.

Dimethyl 2-Phenyl-3,3-methyl-benzoyl-cyclopropane Dicarboxylate,



$$C_6H_5CH - C(CH_3)COC_6H_5 \text{ (ring closed through } C(CO_2CH_3)_2\text{)}$$

—A solution of 5 g. of the solid bromine compound and 2 g. of potassium acetate in methyl alcohol slowly deposited potassium bromide at the ordinary temperature. The solution was allowed to stand for several days, then partially evaporated and poured into water. This precipitated an oil which was extracted with ether. The ethereal solution was freed from acetic acid, dried, and allowed to evaporate slowly. It left a colorless oil which later solidified. One recrystallization from methyl alcohol gave a pure product, crystallizing in narrow prisms, and melting at 101°. The yield was 4.2 g. of pure product. The same substance was obtained when magnesium methylate or sodium methylate in dry methyl alcohol was used for eliminating hydrobromic acid.

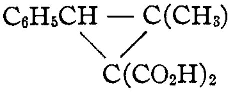
Calc. for $C_{21}H_{20}O_5$: C, 71.6; H, 5.7. Found: C, 71.9; H, 5.3.

Like all the cyclopropane derivatives that we have studied, this substance was not oxidized by permanganate but was readily reduced by zinc and acetic acid. Five g. of zinc dust was added to a solution of 3 g. of the substance in 50 cc. of glacial acetic acid and one cc. of water. The mixture was boiled for 2 hours, then cooled and diluted with water, and extracted with ether. The ethereal solution, on evaporation, gave the saturated ester melting at 91–93° as sole product of the reaction.

The Ester Acid.—Unlike all of the cyclopropane derivatives heretofore studied by us, this one is insensitive to alcoholates. It was recovered unchanged after protracted boiling with magnesium methylate and showed no evidence of addition when dissolved in cold conc. sodium methylate. In the presence of small quantities of water, however, it was rapidly hydrolyzed to the ester acid. This was purified by recrystallization from aqueous methyl alcohol. It separated in three-sided prisms which melted at 162° and began to decompose with evolution of gas at 185–190°. When re-esterified with methyl alcohol and hydrochloric acid it gave the same ester from which it had been obtained.

Calc. for $C_{20}H_{18}O_6$: C, 71.0; H, 5.3. Found: C, 70.2; H, 5.5.

2 - Phenyl - 3,3 - methyl-benzoyl-cyclopropane Dicarboxylic Acid



$$\begin{array}{l} C_6H_5CH - C(CH_3)COC_6H_5 \\ \quad\;\; \diagdown \; \diagup \\ \quad\;\; C(CO_2H)_2 \end{array}$$

.—The dibasic acid was made by hydrolyzing the ester in the cold with excess of alkali in methyl alcoholic solution. By recrystallization from moist benzene it was obtained in clusters of white needles that melted at 176–178° with decomposition.

Calc. for $C_{19}H_{16}O_5.2H_2O$: C, 63.3; H, 5.6. Found: C, 64.0; H, 5.6.

When the acid was re-esterified through the silver salt, it gave, as sole product, the ester from which it had been obtained; but with methyl alcohol and hydrochloric acid the result was different. A solution of 2 g. of the acid in methyl alcohol was cooled in a freezing mixture and saturated with hydrochloric acid. While standing overnight in a stoppered flask it deposited a crystalline solid that melted at 158.5–159.5°. The mother liquors, on evaporation, left more of the same substance and nothing else.

Calc. for $C_{22}H_{26}O_7$: C, 65.7; H, 6.5. Found: C, 65.6, 65.3; H, 6.3, 6.3.

The substance crystallizes in small pyramids. It is insoluble in sodium carbonate and gives no test for chlorine. It is exceedingly stable—showing no sign of decomposition when heated to 240°. Its structure has not been established.

The Oily Bromine Compounds.—A quantity of the oil left after removing the solid bromine compound as completely as possible was dissolved in methyl alcohol and boiled with half its weight of potassium acetate for several hours. Most of the alcohol was then distilled off and the residue poured into water. This precipitated an oil which was extracted with ether. The ethereal solution was washed with sodium carbonate, dried, and allowed to evaporate very slowly. It left a solid imbedded in a smaller quantity of oil. By systematic fractional crystallization from methyl alcohol, the solid gave a small quantity of the cyclopropane ester already described and an isomer that melted at 129–131°.

The cyclopropane ester was, doubtless, formed from some of the γ-bromo compound dissolved in the oil. As it is much easier to separate the isomers than to isolate the solid bromine compound it seemed probable that both the cyclopropane and its isomer could be obtained most easily by starting with the crude bromination product. This was confirmed by the following experiment: 154 g. of the addition product was dissolved in chloroform and brominated in the usual way. After removing the solvent as completely as possible under diminished pressure, the residue was dissolved in hot, dry methyl alcohol and boiled for half an hour with magnesium methylate containing 18 g. of magnesium. The mixture was poured into a suspension of ice in hydrochloric acid. The putty-like mass that was precipitated was thoroughly washed with water and dissolved in methyl alcohol. It gave, ultimately, 34 g. of the cyclopropane derivative and 63.3 g. of the isomer, a total of 97.3 g., corresponding to 63.6% of the addition product used. This is a much better result than was obtained by separating the bromine compounds.

The Ethylenic Isomer, $C_{21}H_{20}O_5$, m. p. 129–131°.—The substance obtained as described in the last experiment is sparingly soluble in ether and cold methyl alcohol, readily in boiling chloroform and boiling alcohol. It crystallizes in stout needles.

Calc. for $C_{21}H_{20}O_5$: C, 71.6; H, 5.7. Found: C, 72.1; H, 5.7.

The principal reason for regarding this substance as an ethylenic instead of a cyclopropane derivative is its behavior towards zinc and acetic acid. It was recovered unchanged after it had been boiled for 4 hours with the same combination that completely reduced the cyclopropane derivative in half the time. It neither combines with bromine nor reduces permanganate. This is not evidence against an ethylenic formula, because unsaturated compounds of this type would not be expected to give either of these reactions.

The Ethylenic Isomer, $C_{21}H_{20}O_5$, m. p. 145°.—The most characteristic property of the substance melting at 130° is the ease with which it undergoes isomerization when brought in contact with bases or mineral acids. The acids obtained by partially or completely hydrolyzing it either with bases or acids, therefore, correspond to an isomeric ester that melts at 145°. The easiest way to get this substance is to treat the lower melting ester with a small quantity of sodium methylate. Thus a trace of sodium methylate made in perfectly dry methyl alcohol was added to a solution of the lower melting ester in boiling absolute ether. After boiling the solution for half an hour most of the ether was distilled off and the remainder allowed to cool. It deposited the pure rearrangement product, melting at 145°.

Calc. for $C_{21}H_{20}O_5$: C, 71.6; H, 5.7. Found: C, 70.6; H, 5.8.

The substance is sparingly soluble in methyl alcohol and ether, and separates from both in large, transparent hexagons. It neither combines with bromine nor reduces permanganate. It was recovered unchanged when a solution of 5 g. in glacial acetic acid was boiled for 8 hours with zinc dust.

The Ester Acid.—A concentrated solution of sodium methylate in methyl alcohol was added little by little to a solution of the lower melting ester in ordinary ether. A white, crystalline sodium salt began to separate almost immediately. The mixture was kept at the ordinary temperature for half an hour, then poured into water. From the water solution acids precipitated an oil that eventually solidified. The solid was purified by recrystallization from aqueous methyl alcohol. It separated in needles melting with decomposition at about 189°.

Calc. for $C_{20}H_{18}O_6$: C, 71.0; H, 5.3. Found: C, 71.0; H, 5.4.

The Dibasic Acid.—The two isomeric esters and the ester acid all give the same dibasic acid on complete hydrolysis. This was isolated in the usual way and purified by crystallization from aqueous methyl alcohol. It crystallized in needles and melted with decomposition at about 180°.

Calc. for $C_{19}H_{16}O_6.0.5H_2O$: C, 68.5; H, 5.1. Found: C, 68.3; H, 5.2.

The acid was re-esterified both by treating its silver salt with methyl iodide and by saturating a methyl alcoholic solution with hydrochloric acid. In each case the sole product was the ester melting at 145°. In order to remove any doubt as to its basicity the acid was titrated against standard base and found to be dibasic. Both the ester acid and the dibasic acid lose carbon dioxide when heated, but they also lose benzaldehyde at the same time. Under diminished pressure the decomposition takes place slowly at 150°; benzaldehyde and carbon dioxide are given off and a pale yellow oil remains. This is soluble in alcohol but apparently rapidly polymerizes, because the alcohol deposits an impalpable, white powder that is insoluble in all common solvents and on heating gradually darkens before it finally melts with decomposition at about 250°.

Summary.

1. This paper describes the conditions under which it is possible to add methyl malonate to benzal-propiophenone and get a ketonic ester which has methyl in the α-position to the ketonic group.

2. It shows the influence of the methyl group upon the bromination of the ketonic ester.

3. It gives the properties of a cyclopropane derivative which has both methyl and benzoyl in combination with one of the carbon atoms of the ring, and shows to what extent these properties are determined by the presence of the methyl group.

CAMBRIDGE, MASS.