2. Acetylene silver arsenate was prepared according to the method used for acetylene silver phosphate. The analysis of the compound points to the following formula: $2(H_3AsO_4).Ag_3AsO_4.4C_2Ag_2$.

NOTRE DAME, INDIANA

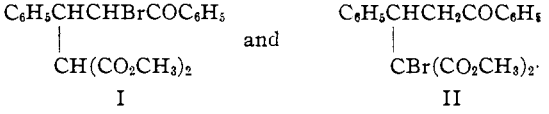
[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF HARVARD UNIVERSITY]

THE ACTION OF BROMINE ON CERTAIN DELTA KETONIC ESTERS

BY E. P. KOHLER

Received January 9, 1922

When bromine acts on δ-ketonic esters of the type obtained by adding malonic esters to α,β unsaturated ketones it replaces one hydrogen atom with the greatest ease.[1] In the cold the bromination stops sharply at this point. If the reaction is carried out in chloroform or carbon tetrachloride it invariably gives a mixture of 2 isomeric monobromo compounds in nearly equal amounts. As both of these readily lose hydrogen bromide and form a cyclopropane derivative[2] the bromine in each must be either in the α- or the γ-position. Thus the only possible formulas for the products obtained from dimethyl-benzoyl-phenyl-propylmalonate are,



I and II

Since the γ-bromo compound has 2 dissimilar asymmetric carbon atoms, the 2 bromo compounds may be stereo-isomeric forms represented by Formula I, or one may be a γ derivative and the other the α derivative represented by Formula II. When these substances were first encountered it was assumed that they were stereo-isomers because, on treatment with reagents that do not cause isomeric change, both gave the same unsaturated compound.[3] Later investigations[4] showed that this unsaturated compound in reality is a cyclopropane derivative which in nearly all respects behaves like an ethylenic compound. Although the cyclopropane derivative might be formed from an α- as well as from a γ-bromo compound, it nevertheless seemed most probable that the two substances were stereo-isomers. As the substances are formed in nearly equal amounts structural isomerism implied that the α- and γ-hydrogen atoms were replaceable with equal ease and if this were the case there seemed to be no adequate reason why the reaction should stop so sharply with the replacement of one hydrogen atom.

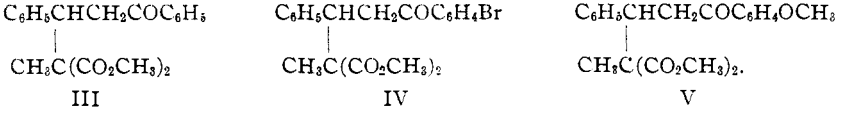
[1] *Am. Chem. J.*, **46**, 482 (1911).

[2] THIS JOURNAL, **39**, 1410 (1917).

[3] Ref. 1, p. 483.

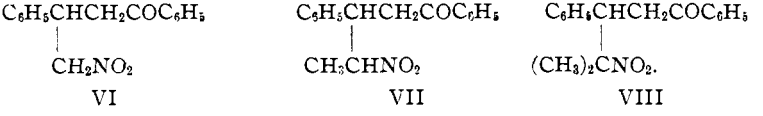
[4] Ref. 2, p. 1404.

Doubt as to the validity of this reasoning arose when it was discovered that while bromination in methyl alcohol that had been previously saturated with hydrogen bromide gave only the lower melting bromo derivative, it was not possible to transform the higher into the lower-melting compound by digestion with methyl alcoholic hydrobromic acid. It was found also, that when the α-position is blocked with a methyl group, bromination under all conditions gives only a single substance. Thus, no isomers could be obtained by brominating the substances represented by the formulas,



III IV V

Very closely related substances, on the other hand, on bromination under the same conditions, invariably give stereo-isomeric γ-bromo compounds. This is true, for example, of the series,[6]



VI VII VIII

In view of these conflicting analogies it became desirable to determine the structure of the bromine derivatives of the malonic esters beyond question. All attempts to accomplish this by replacing the halogen with other groups failed, owing to the ease with which the isomers lose hydrogen bromide. Of the many reagents tried, potassium thiocyanate alone in part replaces the bromine. Unfortunately the structure of the resulting thiocyanate is no easier to determine than that of the bromine compounds themselves.

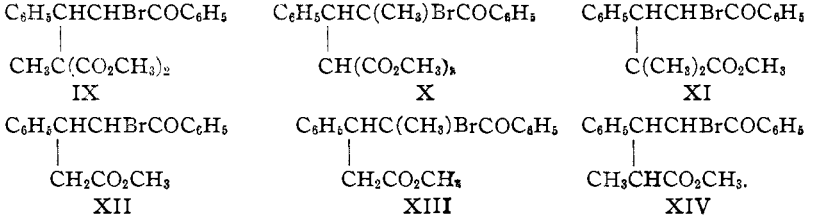
The principal difference between the 2 bromine compounds is in their behavior on heating. When the lower-melting isomer is heated under greatly reduced pressure it begins to evolve gas at about 125°, and above 150° it decomposes freely. The residue left, after the evolution of gas ceases, consists largely of a ketolactonic ester whose structure was established with certainty. The reaction by which this is formed is represented by the equation,

The low-melting bromine compound must, therefore, be a γ-bromo derivative.

[5] Ref. 2, p. 1411.

[6] THIS JOURNAL, **38,** 889 (1916).

The higher-melting bromine compound is much more stable. It does not decompose perceptibly below 200° and most of it can be recovered after it has been heated for hours at 225°. The products of decomposition at this high temperature indicate deep seated changes. The substance, therefore, is probably not a γ-bromo compound. The evidence, however, is not conclusive, for while the γ-bromo compounds represented by Formulas IX–XI lose methyl bromide on heating, those represented by XII–XIV do not.



IX X XI

XII XIII XIV

The process evidently depends upon the ease of ring formation and this, as is known, is affected by configuration as well as structure.

The matter was finally cleared up by the discovery of a third monobromo derivative. When the lower-melting isomer (102°)[7] is heated with bromine in chloroform it gives in addition to one of the dibromo compounds previously described (m. p. 132°) a small quantity of an isomeric compound melting at 120°. The structure of these two substances is, doubtless, different, for while the former gives nothing but the cyclopropane derivative when it is boiled with alcoholic potassium iodide,[8] the latter on similar treatment is reduced, first to a new monobromo derivative, and finally to the ketonic ester.

The monobromo compound (m. p. 77°) is different from either of those previously described. Like them it gives a mixture of isomeric cyclopropane derivatives when boiled with methyl alcoholic potassium acetate, and therefore is either an α- or a γ-bromo compound. When heated under diminished pressure it behaves exactly like the isomer that melts at 102°, losing methyl bromide rapidly at 150° and passing into the same keto-lactonic ester. These two substances are consequently the γ-bromo compounds represented by Formula I. and the isomer that melts at 113° must be an α-bromo derivative.

The behavior of these γ-ketonic esters towards bromine may therefore be summed up as follows. In methyl alcohol the sole product is one of the 2 possible stereo-isomeric γ-bromo compounds. In chloroform or carbon tetrachloride bromination gives a mixture of approximately equal amounts of α- and γ-bromo compounds. Since the reaction stops sharply with the replacement of one hydrogen atom it follows that a bromine

[7] The melting point previously given for this substance was 98°. Ref. 2, p. 1411.

[8] Ref. 2, p. 1413.

atom in either of these positions interferes with the introduction of bromine in the other one.

Experiments

1. Addition of Methyl Dimethylmalonate to Unsaturated Ketones.—Alkyl malonic esters do not combine nearly so readily as the unsubstituted esters with α,β unsaturated ketones. Inasmuch, however, as the addition products neither are capable of combining with a second molecule of unsaturated ketone to form dimolecular products nor are easily hydrolyzed to the corresponding acids it is possible to use larger amounts of condensing agent and still secure excellent yields. The procedure adopted in all cases was as follows. A solution of sodium methylate containing 1 g. of sodium in the minimal quantity of dry methyl alcohol was added to a hot conc. solution of equivalent quantities of the ester and ketone. The mixture was boiled for an hour and then allowed to cool very slowly. Most of the addition product separated in almost pure condition. The remainder, somewhat less pure, was obtained by acidifying and evaporating the filtrates. The products were purified by recrystallization from methyl alcohol. The yields were excellent, generally exceeding 95%.

Methyl β-phenyl-γ-benzoyl-ethylmethylmalonate, (Formula III).—The addition product obtained with benzal-acetophenone crystallizes in needles, is moderately soluble in all the common organic solvents except petroleum ether, and melts at 121–122°.

Analysis. Calc. for $C_{21}H_{22}O_5$: C, 71.2; H, 6.2. Found: C, 71.1; H, 6.4.

Methyl β-phenyl-γ-(4-bromobenzoyl)-ethylmethylmalonate, crystallizes in aggregates of fine needles less soluble in organic solvents than the corresponding bromine-free compound. It melts at 89°.

Analysis. Calc. for $C_{21}H_{21}O_5Br$: C, 58.2; H, 4.8. Found: C, 57.9; H, 5.0.

Methyl β-phenyl-γ-(4-methoxybenzoyl)-ethylmethylmalonate, (Formula V).—The product obtained by adding methyl dimethylmalonate to benzal-*p*-methoxyacetophenone crystallizes in fine needles and melts at 120–122°.

Analysis. Calc. for $C_{22}H_{24}O_6$: C, 68.7; H, 6.6. Found: C, 68.3; H, 6.6.

Bromination of the Methylmalonic Ester Addition Products

Two methods for introducing bromine into malonic ester addition products were described in an earlier paper.[9] The common method of brominating in a solvent in which hydrogen bromide is sparingly soluble goes rapidly and completely in the cold, stops sharply with the introduction of one bromine atom and gives a mixture of two isomeric substitution products. Bromination in methyl alcohol or better in methyl alcohol previously saturated with hydrogen bromide proceeds slowly in the sunlight, requires excess of bromine and even then is incomplete, but invariably gives only a single bromine compound. Both of these methods were tried with each of the foregoing compounds, the first at the temperature of a freezing mixture as well as at the boiling point of carbon tetra-

[9] Ref. 2, p. 1411.

chloride. Each substance under all conditions gave only a single monobromo derivative. The bromo compounds were purified by recrystallization from methyl alcohol.

Methyl β-phenyl-γ-bromo-γ-benzoyl-ethylmethylmalonate, (Formula IX).—The substance is sparingly soluble in ether, moderately in methyl alcohol and in carbon tetrachloride, and very readily soluble in chloroform. It crystallizes in stout needles or prisms, melts at 156–157°, and when the temperature is raised rapidly it begins to decompose at about 190°.

Analysis. Calc. for $C_{21}H_{21}O_6Br$: C, 58.2; H, 4.8. Found: C, 58.0; H, 4.9.

Methyl β-phenyl-γ-bromo-γ-(4-bromophenyl)-ethylmethylmalonate.—The single bromo compound obtained by brominating the corresponding ester, crystallizes in needles, melts at 140°, and when the temperature is raised rapidly, begins to decompose at about 90°.

Analysis. Calc. for $C_{21}H_{22}O_5Br_2$: C, 49.2; H, 3.9. Found: C, 49.2; H, 4.0.

Methyl β-phenyl-γ-bromo-γ-(4-methoxybenzoyl)-ethylmethylmalonate.—The ester melting at 122° gave under all conditions a single bromo compound which crystallized in needles, melted at 151° and when heated rapidly began to decompose at about 190°.

Analysis. Calc. for $C_{22}H_{23}O_6Br$: C, 57.0; H, 5.0. Found: C, 56.7; H, 5.3.

Replacement of Bromine in the Monobromo Compounds.—With a view to replacing the halogen with other groups and thus getting substances that could be manipulated without fear of obtaining cyclopropane compounds, the 2 isomeric monobromo derivatives of benzoyl-phenyl-ethylmalonate were treated with amines, cyanides, silver nitrite, silver acetate, alcoholates, and potassium thiocyanate. All of these, except the thiocyanate, gave under all conditions by which they could be induced to react either a cyclopropane derivative or secondary products formed from the cyclopropane derivative. When the lower-melting isomer (98°) was digested for several hours with potassium thiocyanate in dry methyl alcohol, it gave a mixture of the 2 isomeric cyclopropane derivatives (90%) and a thiocyanate (10%). The mixture was separated by fractional crystallization from a mixture of ether and methyl alcohol. The thiocyanate crystallizes in colorless needles, is moderately soluble in common organic solvents and melts at 133°.

Analysis. Calc. for $C_{21}H_{19}O_5SN$: C, 63.5; H, 5.0. Found: C, 63.8; H, 5.1.

The higher-melting isomer also gave a mixture of cyclopropane derivatives and a sulfur compound, but the yield of the latter was so small and its isolation so difficult that a complete separation of the mixture was not attempted.

Preparation of a Third Isomeric Bromo Compound

All methods of direct bromination gave only 2 of the 3 possible monobromo substitution products of methyl-phenyl-benzoyl-ethylmalonate; but there still remained the possibility that the third might result from reduction of a more highly brominated derivative. As was shown in an earlier paper[10] both of the monobromo compounds on further bromination give two solid α,γ-dibromo derivatives (112° and 94°) along with considerable quantities of oily products. These solid products were reduced with zinc and alcohol, zinc and acetic acid and also catalytically using

[10] Ref. 1, p. 484.

colloidal palladium; but it was found impossible to control the process. The result was always the cyclopropane, the bromine-free ketonic ester or, more frequently, a mixture of the two. This was doubtless due to the fact that the first step in each case was the removal of the 2 bromine atoms and the formation of the cyclopropane derivative. Attention was therefore directed to the oil obtained in brominating the lower-melting isomer (98°). By allowing a solution of this in a mixture of ether and petroleum ether to evaporate very slowly a third solid was obtained in small quantities. This proved to be a γ,γ-dibromo derivative.

Methyl β-phenyl-γ,γ-dibromo-γ-benzoyl-ethylmalonate, $C_6H_6CHCBr_2COC_6H_5$.—
$$\begin{array}{l} C_6H_6\underset{\displaystyle |}{C}HCBr_2COC_6H_5 \\ \quad CH(CO_2CH_3)_2 \end{array}$$
The third solid obtained by brominating the lower-melting monobromo compound, crystallized in plates and melted at 126°.

Analysis. Calc. for $C_{20}H_{18}O_5Br_2$: C, 48.2; H, 3.6. Found: C, 47.9; H, 3.8.

That this is neither an α,γ nor a β,γ derivative is shown by its behavior towards potassium iodide. When the α,γ-dibromo compounds are boiled with a methyl alcoholic solution of this reagent they lose bromine rapidly and pass into cyclopropane derivatives.[11] Dibromo compounds which have bromine in the α,β positions to carbonyl likewise lose bromine very rapidly when they are boiled with alcoholic solutions of potassium iodide, the product being an unsaturated ketone. The dibromo compound in question does not behave like either of these types. In the absence of free acid it is scarcely affected by potassium iodide. In the presence of acetic acid it is slowly reduced giving first a monobromo derivative and finally the saturated ketonic ester. It must, therefore, be the γ,γ-dibromo compound.

Methyl β-phenyl-γ-bromo-γ-benzoyl-ethylmalonate (Formula I).—A methyl alcoholic solution of 25 g. of the γ,γ-dibromo compound, 10 g. of potassium iodide and about 0.5 g. of acetic acid were boiled for 4 hours, then concentrated by distilling most of the methyl alcohol and poured into an aqueous solution of sodium hydrogen sulfite. From these organic compounds were extracted with ether. The ethereal solution was thoroughly washed with water and sodium carbonate, dried over calcium chloride, concentrated, and diluted with petroleum ether. That at once precipitated a small quantity of unchanged dibromo compound. The filtrate from the dibromo compound on slow evaporation deposited a mixture of needles and plates which was separated mechanically. The needles, after recrystallization from methyl alcohol, melted at 105° and were identified as phenyl-benzoyl-ethylmalonate. The plates after several recrystallizations from a mixture of ether and petroleum ether melted at 76–77°.

Analysis. Calc. for $C_{20}H_{19}O_5Br$: C, 57.3; H, 4.5. Found: C, 57.0; H, 4.6.

The new monobromo compound behaves toward reagents exactly like the two previously known. When heated with potassium acetate, it loses hydrogen bromide and gives mainly the cyclopropane derivative melting at 72°.

Behavior of the Three Isomeric Monobromo Compounds when Heated.—Twenty g. of the bromo compound melting at 102° was heated under atmospheric pressure in a distilling flask which was immersed in a metal bath. The volatile products were passed into a brine solution which was cooled in a freezing mixture. Decomposition commenced when the temperature of the bath reached about 190° and was complete after 2 hours' heating at 190–200°. The volatile products were hydrogen bromide, free

[11] Ref. 2, p. 1413.

bromine, and methyl bromide which collected as a liquid under the brine and was identified by the boiling point.

The pale yellow residue left in the flask partially solidified when rubbed with methyl alcohol. The solid after recrystallization melted at 106° and was identified as methyl phenyl-benzoyl-ethylmalonate. The filtrate from this contained a mixture of substances including about 8 g. of a new substance which melted at 93°. At this high temperature the decomposition evidently proceeds in two directions, one resulting in the loss of hydrogen bromide which reduces a part of the bromo compound to the ketonic ester, the other giving methyl bromide and the compound melting at 93°.

When the heating is conducted under greatly diminished pressure, the process is much cleaner. Heated under 8 mm. in contact with porous plate, the bromo compound begins to decompose at about 150° and the evolution of gas continues at a fair speed even when the temperature is subsequently lowered to 125°. Under these conditions the yield of the product melting at 93° exceeds 80%.

Methylphenyl-benzoyl-butyrolactone-carboxylate.—The substance which melts at 93° is readily soluble in the common organic solvents except petroleum ether. From methyl alcohol it separates in fine needles which slowly change to stout needles or prisms if allowed to remain in contact with the mother liquor.

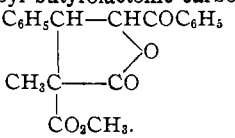
Analysis. Calc. for $C_{19}H_{16}O_5$: C, 70.4; H, 5.0. Found: C, 70.2; H, 5.1.

Although there could be little question as to the nature of this substance, it was deemed worth while to make it by a method that leaves no doubt as to its structure. For this purpose a methyl alcoholic solution of the ketonic ester was treated with the amount of potassium hydroxide calculated to hydrolyze only one of its ester groups. This solution became neutral in the course of several hours. An equivalent amount of bromine was then added. This disappeared slowly at the ordinary temperature and the resulting colorless solution, on evaporation, deposited almost the calculated quantity of the substance melting at 93°. It is therefore a γ-lactonic ester, and the bromine compound melting at 76° must be a γ-bromo derivative.

The Isomeric Bromine Compound melting at 77°, when heated under diminished pressure, began to decompose at about 150° and continued to effervesce freely when the temperature was lowered to 130°. The yellow melt left after heating for 2 hours gave mainly the ketolactonic ester which melts at 93°. This isomer is, therefore, likewise a γ-bromo compound.

The Isomer which Melts at 113° must be the α-bromo derivative. When it was heated under diminished pressure it began to decompose slowly at about 200°. From the dark melt left after 2 hours' heating at 200–225° more than half of the bromo compound was recovered. The only other substance isolated was the bromine-free ketonic ester. The volatile products were, in part, condensed in a receiver that was cooled in solid carbon dioxide and ether. They were composed mainly of hydrogen bromide, bromine, malonic ester, and a small quantity of benzal-acetophenone dibromide.

Methylmethyl-phenyl-benzoyl-butyrolactonic-carboxylate:



The γ-bromo compounds of the ketonic esters that are obtained by adding esters of methyl malonic acid to unsaturated ketones, lose methyl bromide rapidly at comparatively low temperatures. The yield of lactonic ester obtained by heating the bromo compound represented by the formula IX was nearly 90%. The substance crystallizes in needles and melts at 108°.

Analysis. Calc. for $C_{20}H_{18}O_5$: C, 71.0; H, 5.3. Found: C, 71.1; H, 5.5.

Summary

1. When ketonic esters, which have a malonic ester residue in the β-position to the carbonyl group, are brominated in methyl alcohol, the only product is a monobromo compound which has bromine α to carbonyl.

2. When the same esters are brominated in chloroform or carbon tetrachloride, the result is a mixture of monobromo derivatives. In one of these the bromine is α to carbonyl, in the other it is in the malonic ester residue.

3. A third monobromo derivative was obtained by first introducing two bromine atoms α to carbonyl and then replacing one of these with hydrogen.

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[CONTRIBUTION FROM THE DEPARTMENT OF PHARMACOLOGY, HARVARD MEDICAL SCHOOL]

THE SULFUR CONTENT OF ARSPHENAMINE AND ITS RELATION TO THE MODE OF SYNTHESIS AND THE TOXICITY. I[1]

BY WALTER G. CHRISTIANSEN

Received January 17, 1922

In the course of an investigation designed to bring out any existing relation between the sulfur content and the toxicity of arsphenamine, a large number of samples were prepared by hydrosulfite reduction of 3-nitro-4-hydroxyphenylarsonic acid using the same quantities of reagents, but reducing the nitro group under varying conditions.[2] Thus a series of specimens was obtained in which the toxicity, as determined by intravenous injection into white rats, varied from 50 to 150 mg./kg. The results are given in the accompanying graph (Fig. 1).

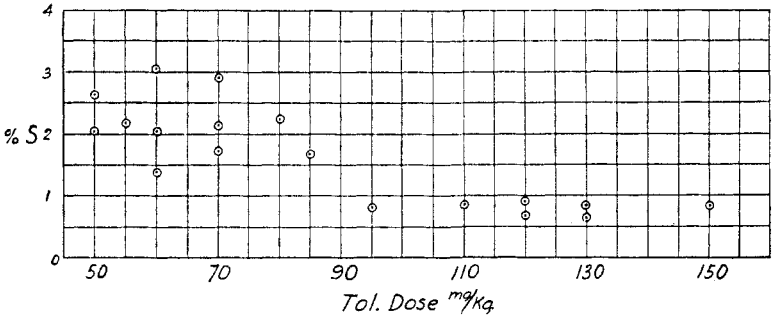

Fig. 1.—Sulfur content and tolerated dose of arsphenamine.

[1] This is the sixth of a series of studies on the properties contributing to the toxicity of arsphenamine being made under a grant from the United States Interdepartmental Social Hygiene Board to the Harvard Medical School; the work is under the general direction of Dr. Reid Hunt, who is also responsible for the biological tests reported in this paper.

[2] The conditions affecting the toxicity were discussed in THIS JOURNAL, **43**, 2202 (1921).