Decomposition of various fractions of the asymmetric lead compound resulted in the elimination of the active group, but yielded only inactive organo-lead products.

URBANA, ILLINOIS

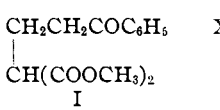
RECEIVED FEBRUARY 20, 1933
PUBLISHED JULY 6, 1933

[CONTRIBUTION FROM THE CHEMICAL LABORATORY, MCGILL UNIVERSITY]

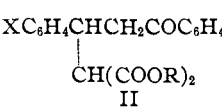
Addition Reactions of Vinyl Phenyl Ketone. III. Methyl Malonate

BY C. F. H. ALLEN AND H. W. J. CRESSMAN

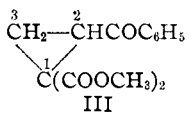
In continuation of the investigations described in the earlier papers in this series[1] methyl malonate has been added to vinyl phenyl ketone and the properties of the resulting ketonic ester (I) compared with certain closely related esters (II).[2]



I

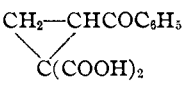


II

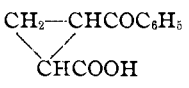


III

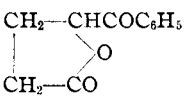
The addition product was transformed into the cyclopropane ester and acids (III, IV, V).



IV



V



VI

The cyclic ester (III) was readily hydrolyzed to the dibasic acid (IV). On being heated the latter lost carbon dioxide, giving a deeply colored oil from which three acidic substances were isolated—small amounts of the stereoisomeric monobasic acids (V) and the lactone (VI).

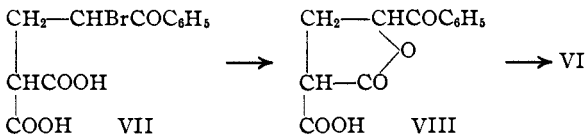
It was of major interest to see if these cyclic substances would react like the other cyclopropane derivatives having one unsubstituted carbon atom[1] when treated with reagents that attack the ring, and be opened only in the 1,2 position. Unfortunately the reactions were not clean-cut and the nature of all the oily by-products formed usually could not be determined, but in every case the greater part of the products were substances that could only have been formed by 1,2 ring opening.

Zinc dust and acetic acid reduced the ester (III) and acids (IV, V) to the open chain substances—*e. g.*, the keto ester (I), dibasic acid (XII) and γ-benzoylbutyric acid; thus the ring was opened in the 1,2 position. None were affected by concentrated sulfuric acid.

(1) (a) Allen and Bridgess, THIS JOURNAL, **51**, 2151 (1929); (b) Allen and Barker, *ibid.*, **54**, 736 (1932).

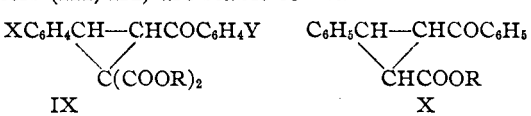
(2) (a) Kohler, *Am. Chem. J.*, **46**, 474 (1911); (b) Kohler and Conant, THIS JOURNAL, **39**, 1404, 1699 (1917); (c) Kohler, Hill and Bigelow, *ibid.*, **39**, 2405 (1917); (d) Kohler and Steele, *ibid.*, 41, 1093 (1919).

The dibasic acid was readily attacked by hydrogen bromide in acetic acid; the primary product was an oil containing bromine, that on long standing became crystalline; the solid was the lactone (VIII). It lost carbon dioxide on gentle heating and formed the lactone (VI). The only possible bromo acid that could give the lactone in this way is represented by formula (VII); again the ring must have opened in the 1,2 position.

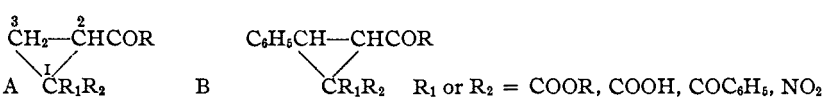


Under ordinary conditions hydrogen bromide in glacial acetic acid was without effect on the ester (III), but when heated in a sealed tube an oil containing bromine resulted. It was probably a mixture of open chain bromo esters formed by 1,2 opening of the ring, since on subsequent treatment with potassium acetate, the cyclopropane was re-formed. However, the oil contained some acidic substance that could be extracted by sodium carbonate solution; on acidification of the latter a black, intractable oil was produced; this oil rapidly reduced permanganate. Because of this, the possibility of ring opening in some other way was not excluded. However, there was no evidence of any lactones such as were found with the phenylated esters (IX, X).

The ester (III) was not attacked by dry bases, but when water was present it was hydrolyzed very rapidly to the dibasic acid (IV); the acid re-formed the ester with alcoholic sulfuric acid. This is in marked contrast to the ease with which the ring was opened by bases with substance (IX). Both esters (III, IX) are stable to heat.



There are now available for comparison all of the ketocyclopropane derivatives previously described except nitriles.[3] These comprise two series (A, B) that differ in structure only in the presence of a phenyl group on carbon atom 3.



The reactions that are used to open the ring act alike in series A; the resulting products always have a straight chain and are formed by a breaking of the bond in the 1,2 position, regardless of the nature of the reagent. The substances in series B are much more reactive with most reagents and the

(3) We have not yet been successful in adding benzyl cyanide to vinyl phenyl ketone, but have found that methyl cyanoacetate, malonitrile and cyanoacetamide give only trimolecular products.

ring has been opened in all three positions, the same reagent often giving two types of products.

Preparation and Proof of Structure of the Addition Product.—It was fairly easy to add methyl malonate to the solution of vinyl phenyl ketone, but in order to secure the best yield the ester had to be very pure and used in excess, otherwise a trimolecular product (XI) resulted.

$$(C_6H_5COCH_2CH_2)_2C(COOCH_3)_2 \quad XI$$

The structure of the addition product (I) was determined by hydrolysis and decarboxylation to the known γ-benzoylbutyric acid.

$$C_6H_5COCH_2CH_2CH(COOCH_3)_2 \longrightarrow C_6H_5COCH_2CH_2CH(COOH)_2 \longrightarrow C_6H_5COCH_2CH_2CH_2COOH$$

I XII

A. γ-Benzoylethylmalonate (I).—A mixture of 15 g. of β-chloropropiophenone, 12 g. of fused potassium acetate, 95 cc. of absolute methyl alcohol and 12 g. of methyl malonate was made faintly alkaline to moist litmus paper by adding a concentrated solution of sodium methylate, drop by drop, and refluxed for forty-five minutes. Most of the solvent was then distilled, the residue acidified with acetic acid and the unused ester removed by steam distillation. On inoculating with a little previously prepared solid, the oil crystallized—the average yield was 70%. After several recrystallizations from dilute methyl alcohol it formed needles, m. p. 42°; it is very soluble in the usual organic solvents except petroleum ether. It boils with some decomposition at 165–176°, at 5–6 mm. The ethyl ester was an oil.

Anal. Calcd. for $C_{14}H_{16}O_5$: C, 63.6; H, 6.1. Found: C, 63.3, 63.4; H, 6.1, 6.1.

The 2,4-dinitrophenylhydrazone of the keto ester formed at once on mixing a solution of 1 g. of 2,4-dinitrophenylhydrazine in 2 cc. of concentrated sulfuric acid and 15 cc. of methyl alcohol with 1.3 g. of the ester in 15 cc. of methyl alcohol. It was recrystallized from a mixture of chloroform and methyl alcohol, forming clusters of flat yellow plates, m. p. 139°; it is moderately soluble in alcohol but very soluble in ether and chloroform.

Anal. Calcd. for $C_{20}H_{20}O_8N_4$: N, 12.6. Found: N, 12.4.

B. Proof of Structure. (a) **Hydrolysis.**—A mixture of 4 g. of the ester in 50 cc. of 10% aqueous potassium hydroxide was refluxed for forty-five minutes and poured into a small amount of iced hydrochloric acid. A part of the dibasic acid separated and the rest was extracted by ether; it was purified by recrystallization from an ether–petroleum ether mixture, from which it separated in flaky rosets, melting with decomposition at 168–70°. The yield was 3.3 g. or 89%. It is moderately soluble in chloroform and very soluble in the other usual organic solvents except petroleum ether.

Anal. Calcd. for $C_{12}H_{12}O_5$: C, 61.0; H, 5.1. Found: C, 60.8; H, 5.2.

The dimethyl ester was regenerated by esterifying the acid in the usual way.

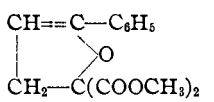
(b) **Decarboxylation.**—One gram of γ-benzoylethylmalonic acid was heated in an oil-bath at 175–80° as long as carbon dioxide was evolved; the residual oil was taken up in sodium carbonate solution and the monobasic acid precipitated by addition of hydrochloric acid. It was identified as γ-benzoylbutyric acid by mixed melting point with an authentic sample. The keto ester and acids neither reduced permanganate nor decolorized bromine.

C. The Trimolecular Product (XI).—This substance crystallized from methyl alcohol in hexagonal plates, m. p. 132°.

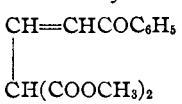
Anal. Calcd. for $C_{28}H_{22}O_6$: C, 69.4; H, 6.1; mol. wt., 396. Found: C, 69.5; H, 6.0; mol. wt., 364.

It did not form a pyrrylium salt, which excludes the possibility of its being an isomeric 1,5-diketone.

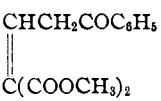
The Cyclopropane Derivatives.—The keto ester reacted readily with one or two moles of bromine, but the resulting bromo esters were oils, and it was not possible to establish their homogeneity. On treatment with potassium acetate in methyl alcohol, hydrogen bromide was eliminated and from the oily reaction product the cyclic ester (III) was separated. The other substances that might have been formed in this way are represented by formulas (XIII–XV). The dihydrofuran was excluded because the es-



XIII



XIV



XV

ter formed a 2,4-dinitrophenylhydrazone, showing the presence of a carbonyl group. Since it neither decolorized bromine nor reduced permanganate the ethylenic structures seem very improbable; the latter may have been present in the oily residues from the preparation as they rapidly reduced permanganate.

A mixture of 17 g. of the oil from bromination of 13.2 g. of the open chain keto ester, 17 g. of fused potassium acetate, and 35 cc. of absolute methyl alcohol was refluxed an hour and then poured into a large volume of water; the oil that first separated slowly crystallized. The crude material was dissolved in the minimum amount of dilute methyl alcohol, refluxed a few minutes with animal charcoal and filtered. On keeping for several hours in a freezing mixture the cyclopropane slowly crystallized. The yield was 5.7 g., which is 45% of the theoretical, calculated from the original keto ester. When a sufficient amount of residues from several preparations had accumulated they were combined and distilled *in vacuo;* in this way an additional amount of ester was produced, making the average total yield 78%. Methyl 2-benzoylcyclopropane-1,1-dicarboxylate (III) separates from 80% alcohol or 60% acetic acid in hexagonal plates, m. p. 74°; b. p. 185–90° at 4 mm. It is very soluble in the usual solvents except petroleum ether.

Anal. Calcd. for $C_{14}H_{14}O_5$: C, 64.1; H, 5.3. Found: C, 64.4, 64.0; H, 5.5, 5.8.

After the ester had crystallized, further concentration of the solutions yielded dark-colored oils that rapidly reduced permanganate; the amount of the oil was much greater if acetic acid was the solvent used in the preparation.

The 2,4-dinitrophenylhydrazone was prepared in the usual manner and crystallized in light yellow needles from a chloroform-alcohol mixture; m. p. 169°.

Anal. Calcd. for $C_{20}H_{18}O_8N_4$: N, 12.7. Found: N, 12.5.

The cyclic ester was not affected by sodium or magnesium methylates in absolutely dry alcohol, but in the presence of moisture it was hydrolyzed to the dibasic acid. If sodium methylate was added to the substance dissolved in moist ether, following the procedure of Kohler and Conant,[4] an oil resulted; this oil was doubtless the ester acid. On further treatment with alkali it gave the dibasic acid—the yield of the latter was much better when the hydrolysis was carried out in two steps as indicated, although it could be made directly.

The experimental details were so like those already published that they are omitted here. The oily "ester acid" was very soluble in all organic solvents except petroleum ether, but crystallized from none. The second step was modified as follows: the sodium salt that separated in the preparation of the "ester acid" was mixed with a 50% excess of 10% aqueous potassium hydroxide and the whole left at room temperature for a day. Upon acidification and evaporation of most of the solvent the acid crystallized—it is

(4) Ref. 2b, p. 1413.

quite soluble in water. It was recrystallized from an ether–petroleum ether mixture. From 4 g. of the di-ester, 3.5 g. of acid (97% yield) was obtained. It is readily soluble in all solvents except petroleum ether and water (moderately in this). It forms rods that melt at 170–172°.

Anal. Calcd. for $C_{12}H_{10}O_5$: C, 61.5; H, 4.3; mol. wt., 234. Found: C, 61.3; H, 4.3; mol. wt., 246.

When heated above the melting point it lost carbon dioxide very easily. The experimental details were essentially those described above under the open chain dibasic acid, except that it was necessary to treat the crude reaction product with decolorizing carbon. The oily product was taken up in ether, and extracted first with sodium carbonate and then with sodium hydroxide; on acidification of the former, a mixture of the two monobasic acids was obtained. The sodium hydroxide extracts, on acidifying, gave an oil which was extracted with ether; after the solvent had been allowed to evaporate the oily lactone was left and was treated as described below. The neutral product remaining in the ether after the above extractions was an oil, the nature of which was not determined, except to be sure it was not benzoylcyclopropane. A pyrolysis of 2 g. of the acid gave 0.8 g. of a mixture of the two acids and 0.4 g. of lactone.

The 2-benzoylcyclopropane-1-carboxylic acids (VI) were separated with some difficulty by dissolving in benzene; the higher melting form was the principal product, and being somewhat less soluble separated first; when pure it forms rosets of rods, m. p. 145°. The stereoisomer was very soluble in all solvents except petroleum ether, and was finally purified by recrystallizing from a benzene-petroleum ether mixture; it formed fine rods, m. p. 118–120°.

Anal. Calcd. for $C_{11}H_{10}O_3$: C, 69.5; H, 5.3; mol. wt., 190. Found: (145°) C, 69.4; H, 5.3; (118–120°) mol. wt. by titration, 193.

The *p*-bromophenacyl ester of the acid (145°) was prepared by refluxing for an hour a mixture of 15 cc. of methyl alcohol, 0.3 g. of the acid and an equal weight of *p*-bromophenacyl bromide. On adding a few drops of water to incipient cloudiness, and allowing to cool, the ester separated. It crystallized in leaflets, m. p. 122°.

Anal. Calcd. for $C_{19}H_{14}O_4Br$: Br, 20.7. Found: Br, 20.8.

The acid (118–120°) was not obtained in sufficient amount to convert into an ester.

The higher melting acid was recovered unchanged after being heated under the conditions of pyrolysis of the dibasic acid or by other methods for decarboxylation[5] but both the lower melting isomer and the lactone gave untractable oils;[6] thus it is not possible to say whether the lactone results from the dibasic acid directly or by way of the monobasic acid. None of the cyclopropane derivatives reduce permanganate nor decolorize bromine.

Reduction.—All the above cyclic compounds are easily reduced by zinc and acetic acid to open chain substances, the ring opening between carbon atoms 1 and 2 in each case. The di-ester (III) gave the γ-ketodi-ester (I), the di-acid gave the corresponding di-acid (XII), and the monobasic acid (V) gave γ-benzoylbutyric acid.

The experimental details were practically identical; *e. g.*, a mixture of 1 g. of the cyclic compound, 1 g. of zinc dust and 20 cc. of 80% acetic acid was refluxed for two hours and poured into water; the reduction product separated after several minutes, was carefully purified and identified by mixed melting point determinations with the respective open chain substances.

(5) Shepard, Winslow and Johnson, THIS JOURNAL, **52**, 2087 (1930); Koelsch, *ibid.*, **54**, 4748 (1932).

(6) A trace of a solid that was probably the lactone was found after one pyrolysis; the quantity was not sufficient for recrystallization but a mixed melting point with the lactone showed only a slight depression.

Action of Acids.—None of the cyclic compounds were attacked by concentrated sulfuric acid, being quantitatively recovered unchanged when a solution was poured upon ice.

As stated in the introduction, the dibasic acid gave an oily open chain monobromo acid with hydrogen bromide in acetic acid, which slowly became crystalline. The lactone acid (VIII) thus produced lost carbon dioxide on being heated alone or on boiling for several hours in alcoholic solution, resulting in the formation of γ-benzoylbutyrolactone (VI); the latter was synthesized by brominating γ-benzoylbutyric acid and treating the resulting oily bromo acid with cold aqueous sodium carbonate. Hydrogen bromide at room temperature did not appreciably attack the ester, either in alcohol or acetic acid. If a solution in the latter solvent was heated at 100° in a sealed tube for eight hours, an oil containing bromine resulted. The oil, on treatment with alcoholic potassium acetate, re-formed the cyclic ester in a 52% yield—thus the product must have contained some monobromo ester; the yield is somewhat lower than in the original preparation, but makes plausible the assumption that the ring again opened in the 1,2 position—if it opened in any other way the probability of forming a cyclopropane would be negligible; however, the point is not conclusively proved.

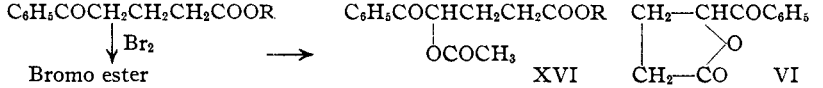
A cold solution of 1.5 g. of the dibasic acid in 15 cc. of glacial acetic acid was saturated with hydrogen bromide and after twelve hours poured into a little water and evaporated to small volume on the steam-bath. An oil containing halogen separated; after a week it became crystalline and no longer gave a test for halogen. It was recrystallized from benzene in which it is fairly soluble and from which it separated in fine rods, m. p. 122° with evolution of gas at 125–130°; yield, 60%.

Anal. Calcd. for $C_{12}H_{10}O_5$: C, 61.5; H, 4.3; mol. wt., 234. Found: C, 61.1, 61.6; H, 4.3, 4.3; mol. wt., 218.

It is moderately soluble in ether and methyl alcohol. This lactonic acid lost carbon dioxide when heated at 150–155° and formed the lactone quantitatively, or when a methyl alcoholic solution containing potassium acetate was refluxed for five hours.

A cold solution of 2 g. of the cyclic ester (III) in 15 cc. of glacial acetic acid was saturated with hydrogen bromide and heated in a sealed tube at 100° for eight hours. The contents of the tube were poured into water and the precipitated oil extracted with ether; the ethereal extract was shaken with sodium carbonate solution, washed, dried and the ether evaporated—it left 1.23 g. of a neutral oil containing bromine. Since it could not be made to solidify it was boiled with methyl alcoholic potassium acetate, as above; it yielded 0.49 g. (52%) of the cyclopropane di-ester (III), identified by mixed melting point. On acidification of the sodium carbonate extract, 0.53 g. of an untractable black oil, that reduced permanganate, was obtained.

γ-Benzoylbutyrolactone (VI).—Since it was not possible to secure the cyclopropane monobasic acids (V) in large enough quantities to make a study of the methyl esters, a synthesis of the latter was attempted starting with methyl γ-benzoylbutyrate. The latter was brominated, and the product treated with potassium acetate; this gave an open chain acetate ester (XVI). The use of other alkaline reagents and all methods of hydrolysis of the acetate ester gave the lactone (VI).



A new procedure for preparing γ-benzoylbutyric acid is described elsewhere.[7] The methyl ester was obtained in a yield of 80% by saturating a solution of 10 g. of the acid in 100 cc. of methyl alcohol with hydrogen chloride, distilling most of the solvent

(7) "Organic Syntheses," Vol. XIII.

after twelve hours, pouring the residue into water, and working up in the usual way; it was distilled *in vacuo*. b. p. 147–148° at 8 mm.; m. p. −2°; this ester is not described in the literature.

Anal. Calcd. for $C_{12}H_{14}O_3$: C, 70.0; H, 6.8. Found: C, 69.7; H, 6.8.

The 2,4-dinitrophenylhydrazone, prepared in the usual manner, crystallized from a 1:1 chloroform–methyl alcohol mixture in red leaflets, m. p. 149°.

Anal. Calcd. for $C_{18}H_{18}O_6N_4$: N, 14.5. Found: N, 14.9.

The ester was brominated in carbon tetrachloride solution by the customary procedure; the product was an oil that showed no tendency to solidify. A mixture of 14 g. of the oil, an equivalent equal weight of fused potassium acetate and 35 cc. of absolute methyl alcohol was refluxed for fifteen minutes, during which time a large amount of potassium bromide separated. The whole was poured into water and the precipitated oil allowed to stand for several hours, when it began to crystallize. It was recrystallized from methyl alcohol, forming needles, m. p. 60°. The yield was 8 g. or 70%. Methyl γ-acetoxy-γ-benzoylbutyrate (XVI) is moderately soluble in methyl alcohol and carbon tetrachloride, but very soluble in ether, chloroform and benzene.

Anal. Calcd. for $C_{14}H_{16}O_5$: C, 63.6; H, 6.1; CH_3COO, 22.4. Found: C, 63.1, 63.4; H, 5.5, 5.9; CH_3COO, 23.3.

The 2,4-dinitrophenylhydrazone, prepared in the usual manner, separated as pale yellow needles from methyl alcohol; m. p. 158°.

Anal. Calcd. for $C_{20}H_{20}O_8N_4$: N, 12.6. Found: N, 11.8.

When the oily bromo ester was treated with sodium methylate, a bromine-free oil was produced; this slowly solidified, and was found to be the lactone (XVI). The acetate ester (XXII), when hydrolyzed by acidic or basic reagents, also gave this lactone; as reagents were used dilute alcoholic and aqueous potassium or ammonium hydroxides, and dilute or concentrated sulfuric acid—a better product resulted from acid hydrolysis. In anhydrous alcohol sodium methylate gave a wine red solution from which only an intractable oil could be obtained.

Whether obtained from pyrolysis of the dibasic acid or by hydrolysis of the foregoing esters, the lactone was oily and was purified by shaking its ether solution successively with dilute sodium carbonate and potassium hydroxide; from the latter solution after acidification and extraction with ether, the lactone was deposited as an oil that usually crystallized on scratching. γ-Benzoylbutyrolactone is very soluble in chloroform, but moderately soluble in benzene, methyl alcohol, carbon tetrachloride, water and ether: it crystallizes from ether in plates and from water in prisms, m. p. 78°.

Anal. Calcd. for $C_{11}H_{10}O_3$: C, 69.5; H, 5.3. Found: C, 69.1, 69.4; H, 5.6, 5.5.

The 2,4-dinitrophenylhydrazone was secured by the general procedure, and separated from methyl alcohol in light yellow rosets, m. p. 174°.

Anal. Calcd. for $C_{17}H_{14}O_6N_4$: N, 15.1. Found: N, 14.7.

The lactone was also obtained by bromination of γ-benzoylbutyric acid, allowing the resulting oily bromo acid to stand in contact with aqueous sodium carbonate for several hours, and acidifying.

This work has been assisted by a generous grant from the Cyrus M. Warren Fund of the American Academy of Arts and Sciences.

Summary

1 Methyl malonate has been added to vinyl phenyl ketone to form a γ-ketonic ester.

2. This ester has been converted into several cyclopropane derivatives and their properties compared with certain closely related homologs.

3. In all reactions involving the ring, it was opened in the 1,2 position. This is in agreement with the results found with previous cyclopropanes of this type, but different from those having a phenyl group in the 2 position.

MONTREAL, CANADA RECEIVED FEBRUARY 23, 1933
PUBLISHED JULY 6, 1933

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

The Coupling Action of the Grignard Reagent. V. The Influence of the Halogen Atom of the Reagent

BY ELLSWORTH ELLINGBOE AND REYNOLD C. FUSON

The coupling action of the Grignard reagent on halogen compounds involves the linking of the radicals of the reagent as well as those of the compound upon which the reagent reacts. It has been observed in a large number of cases and is especially pronounced in connection with compounds containing the aryl halomethyl grouping, $\mathrm{Ar\overset{|}{C}X}$. The surprising fact that aryl polyhalomethyl derivatives such as benzal chloride and benzotrichloride also undergo coupling has recently been reported.[1] To these peculiarities of the reaction is to be added a much more puzzling observation—*that the course of the reaction depends on the nature of the halogen atom of the alkyl halide used in preparing the reagent.* This is demonstrated by the sharp contrast in the action of methylmagnesium *iodide* with that of methylmagnesium *chloride* on the benzal halides.[2]

The action of methylmagnesium iodide on benzal chloride has been found to give α-stilbene dichloride according to the equation

$$2C_6H_5CHCl_2 + 2CH_3MgI \longrightarrow C_6H_5CHClCHClC_6H_5 + CH_3CH_3 + MgI_2 + MgCl_2$$

but when benzal chloride was treated with methylmagnesium chloride *no α-stilbene dichloride was produced.* Instead there was obtained a mixture which has been shown to consist of four different compounds: namely, cumene, 1,2-diphenyl-1-chloropropane (I), and two forms of 2,4-diphenylbutane (II).

$C_6H_5CH(CH_3)CH(CH_3)C_6H_5$ (II) $\quad C_6H_5CH(CH_3)CHClC_6H_5$ (I) $\quad C_6H_5C(CH_3)=CHC_6H_5$ (III)

This difference in the action of the two methylmagnesium halides has been corroborated by numerous repetitions of the experiments in ques-

(1) Fuson and Ross, THIS JOURNAL, **55**, 720 (1933).

(2) That the halogen atom of a Grignard reagent has an influence on the course of the coupling reaction has been previously observed by Späth, *Monatsh.*, **34**, 1965 (1913).