The Reaction between Unsaturated Ketones and Organic Magnesium Compounds. The Secondary Products

BY E. P. KOHLER AND W. D. PETERSON

It is common knowledge that in the reaction between α,β-unsaturated ketones and Grignard reagents it is necessary to use a large excess of reagent in order to prevent the formation of secondary products, but of the nature of these products little is known. In the first paper of this series[1] one of these secondary products was isolated and analyzed, namely, the compound that is formed by adding phenylmagnesium bromide to benzal acetophenone. The composition and molecular weight of this compound were established correctly, but the formula that was proposed for it has long since been untenable because it was based on an erroneous interpretation of the primary reaction.

With the recent discovery that the primary products of this reaction behave like the enolates of β-ketonic esters and β-diketones,[2] the secondary products acquired a new interest. It seemed not unlikely that these products are formed in a second reaction which differs from the first only in the character of the magnesium derivative. In the case of benzal acetophenone and phenylmagnesium bromide the successive steps would be represented as follows

$$C_6H_5CH{=}CHCOC_6H_5 + C_6H_5MgBr \longrightarrow (C_6H_5)_2CHCH{=}C(C_6H_5)OMgBr$$
$$I$$

$$C_6H_5CH{=}CHCOC_6H_5 + (C_6H_5)_2CHCH{=}C(C_6H_5)OMgBr \longrightarrow$$

$$\begin{array}{cc} C_6H_5CHCH{=}C(C_6H_5)OMgBr & C_6H_5CHCH_2COC_6H_5 \\ | & \longrightarrow \quad | \\ (C_6H_5)_2CHCHCOC_6H_5 & (C_6H_5)_2CHCHCOC_6H_5 \\ II & III \end{array}$$

We have found that this surmise is correct. By taking advantage of the reaction between alpha bromo ketones and Grignard reagents[2] it is possible to secure a solution of the magnesium derivative represented by I that is free from the Grignard reagent. When an equivalent quantity of benzal acetophenone was added to such a solution it was converted, almost quantitatively, into the diketone represented by III. The proof of the structure of this diketone is as follows.

The substance reacts with two moles of methylmagnesium iodide without liberating gas; it therefore is a diketone. It readily forms a mono-oxime but, as would be expected in view of the number of substituents around the carbonyl groups, it cannot be converted into a di-oxime by the usual methods. By means of a Beckmann rearrangement, followed by hydrolysis of the product, the oxime was degraded to the corresponding acid and aniline.

(1) Kohler, *Am. Chem. J.*, **29**, 352 (1903).
(2) Kohler and Tishler, THIS JOURNAL, **54**, 1594 (1932).

$$C_6H_5CHCH_2COC_6H_5 \longrightarrow C_6H_5CHCH_2C{=}(NOH)C_6H_5 \longrightarrow$$
$$(C_6H_5)_2CHCHCOC_6H_5 \qquad (C_6H_5)_2CHCHCOC_6H_5$$
$$\qquad\qquad III \qquad\qquad\qquad IV$$

$$C_6H_5CHCH_2CONHC_6H_5 \longrightarrow C_6H_5CHCH_2COOH + C_6H_5NH_2$$
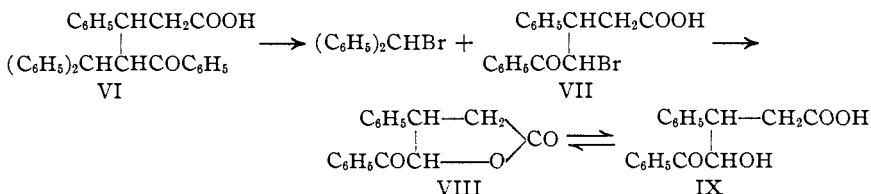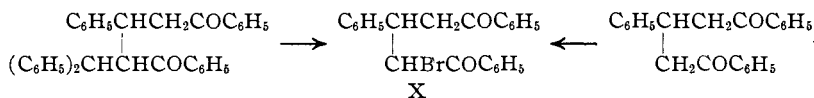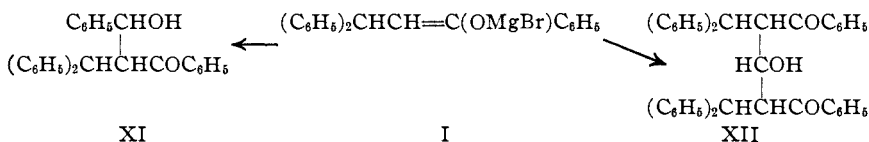$$(C_6H_5)_2CHCHCOC_6H_5 \qquad (C_6H_5)_2CHCHCOC_6H_5$$
$$\qquad\qquad V \qquad\qquad\qquad VI$$

The result is a δ-ketonic acid. Our plan was to brominate this acid and prove that the product was a γ-bromo acid by converting it into a lactone. The plan went awry because the bromination took an unexpected course. Fortunately, however, the result is equally conclusive.

$$C_6H_5CHCH_2COOH \longrightarrow (C_6H_5)_2CHBr + \begin{array}{c}C_6H_5CHCH_2COOH\\C_6H_5COCHBr\end{array} \longrightarrow$$
$$(C_6H_5)_2CHCHCOC_6H_5$$
$$\qquad VI \qquad\qquad\qquad\qquad\qquad\qquad VII$$

$$\begin{array}{c}C_6H_5CH{-}CH_2\\ \qquad\qquad\qquad \backslash CO \rightleftharpoons \begin{array}{c}C_6H_5CH{-}CH_2COOH\\C_6H_5COCHOH\end{array}\\C_6H_5COCH{-}{-}O\end{array}$$
$$\qquad\qquad VIII \qquad\qquad\qquad IX$$

This unexpected course of the bromination, of which another example had become known very much earlier,[3] enabled us to relate the diketone directly to a substance of known structure.

$$\begin{array}{ccc}C_6H_5CHCH_2COC_6H_5 & C_6H_5CHCH_2COC_6H_5 & C_6H_5CHCH_2COC_6H_5\\(C_6H_5)_2CHCHCOC_6H_5 \longrightarrow & CHBrCOC_6H_5 \longleftarrow & CH_2COC_6H_5\\ & X & \end{array}$$

In the light of these results it is evident that the primary addition products can combine with unsaturated ketones in the same manner as Grignard reagents and sodium enolates. They can also combine with substances which have active carbonyl groups. Thus when benzaldehyde was added to a solution containing the same primary addition product, it precipitated the magnesium derivative of the corresponding ketol, and a similar product was obtained from ethyl formate.

$$\begin{array}{ccc}C_6H_5CHOH & (C_6H_5)_2CHCH{=}C(OMgBr)C_6H_5 & (C_6H_5)_2CHCHCOC_6H_5\\(C_6H_5)_2CHCHCOC_6H_5 \longleftarrow & & HCOH\\ & & (C_6H_5)_2CHCHCOC_6H_5\\ XI & I & XII\end{array}$$

Since these primary products can combine both with alpha,beta-unsaturated ketones and with carbonyl compounds it is apparent that in the case of those unsaturated ketones and esters which form both 1,4 and 1,2 addition products, the secondary reactions may become very complicated. These complications, however, occur but seldom because the primary addition products are far less reactive than Grignard reagents. Thus the

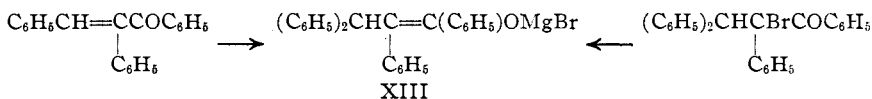(3) Kohler and Reimer, Am. Chem. J., 33, 333 (1905).

magnesium derivative which so readily combined with benzal acetophenone, showed little ability to react with methyl cinnamate and none at all to combine with acetone, cyclohexanone or methyl benzoate.

Complications of an entirely different kind, however, frequently arise when one equivalent of an unsaturated ketone is added to a Grignard reagent in the usual manner. Owing to the difference in the speeds of the primary and secondary reactions, the latter usually does not become significant until approximately half a mole of the ketone has been added. At that stage the solution contains three magnesium derivatives such as, for example

$$C_6H_5MgBr(C_6H_5)_2CHCH=CC_6H_5 \qquad\qquad C_6H_5CHCH=C(OMgBr)C_6H_5$$
$$\overset{|}{O}MgBr \qquad\qquad (C_6H_5)_2CH\overset{|}{C}HCOC_6H_5$$

The first two derivatives compete for any additional unsaturated ketone that is added but they are incapable of reacting with each other under any conditions. The third magnesium derivative, however, reacts with the Grignard reagent like any other saturated ketone. By the time all of the unsaturated ketone has been added, the solution contains primary, secondary and tertiary magnesium compounds that on hydrolysis yield a mixture which frequently cannot be separated and which at best gives a greatly diminished quantity of the primary product.

These complications can almost invariably be prevented by using a sufficient excess of Grignard reagent. Frequently they do not occur at all because the primary addition product is too sluggish to compete successfully with the Grignard reagent for the saturated ketone. The activity of these magnesium derivatives appears to depend largely on space relations, the addition products which are formed from ketones with a hydrocarbon residue in the alpha position being almost completely inert. Thus by allowing phenylmagnesium bromide to react either with benzal desoxybenzoin or with alpha bromo triphenylpropiophenone it is possible to make a magnesium derivative which differs from the one we have described only in that it has a phenyl group in the alpha position.

$$C_6H_5CH=CCOC_6H_5 \longrightarrow (C_6H_5)_2CHC=C(C_6H_5)OMgBr \longleftarrow (C_6H_5)_2CHCBrCOC_6H_5$$
$$\overset{|}{C}_6H_5 \qquad\qquad \overset{|}{C}_6H_5 \qquad\qquad\qquad \overset{|}{C}_6H_5$$
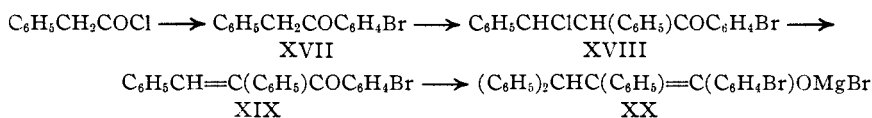$$XIII$$

This new magnesium derivative is almost completely inactive. It cannot be carbonated, will not combine either with benzaldehyde or benzal acetophenone, and does not react with ethyl formate; it reacts only with acids, bromine, oxygen and acid chlorides. And the mechanism of the reaction with acid chlorides may be different from that of the simpler magnesium derivatives. Grignard reagents, as is well known, convert acid chlorides first into ketones and finally into the magnesium derivatives of tertiary alcohols. The magnesium derivatives which are obtained by
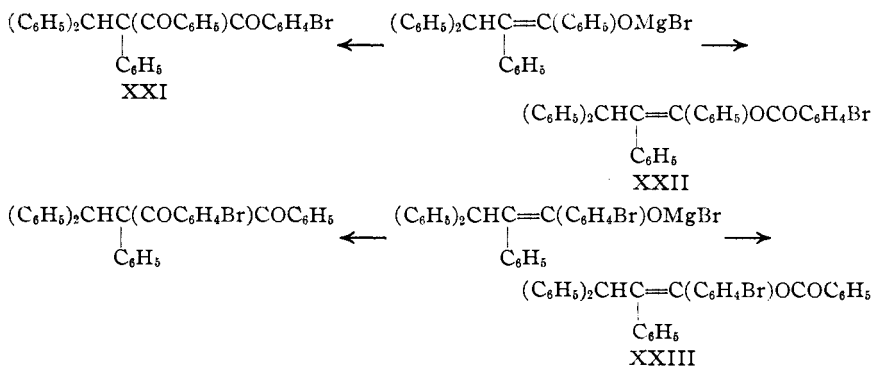
adding Grignard reagents to alpha, beta-unsaturated ketones which have no substituent in the alpha position convert the same acid chlorides into the magnesium derivatives of diketones. The magnesium derivative under consideration likewise reacts with these same acid chlorides, but the products are esters.

$$(C_6H_5)_2CHC(COC_6H_5)_2 \quad (C_6H_5)_2CHC=C(C_6H_5)OMgBr \quad (C_6H_5)_2CHC=CC_6H_5$$

$$\underset{XV}{|}{C_6H_5} \quad \overset{\longleftarrow}{} \quad \underset{XIV}{|}{C_6H_5} \quad \overset{\longrightarrow}{} \quad \underset{XVI}{|}{C_6H_5 \ OCOC_6H_5}$$
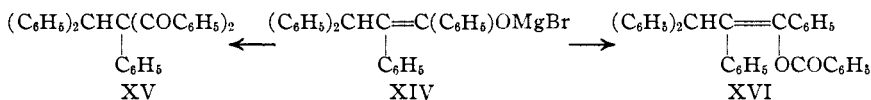
We suspected this difference in the direction of the reaction at the outset, because the melting points of the products obtained from acetyl and benzoyl chloride appeared to be too low for such a completely substituted diketone as is represented by XV. We were confirmed in this suspicion when we found that in the case of benzoyl chloride we obtained two isomeric products, both of which were rapidly hydrolyzed by methyl alcoholic solutions of potassium hydroxide too dilute to cleave beta diketones. But in order to prove the structure of these products conclusively it was necessary to compare products formed by introducing two different acyl groups in a different sequence. We therefore prepared the corresponding p-bromo compounds in a series of steps which is represented as follows

$$C_6H_5CH_2COCl \longrightarrow \underset{XVII}{C_6H_5CH_2COC_6H_4Br} \longrightarrow \underset{XVIII}{C_6H_5CHClCH(C_6H_5)COC_6H_4Br} \longrightarrow$$

$$\underset{XIX}{C_6H_5CH=C(C_6H_5)COC_6H_4Br} \longrightarrow \underset{XX}{(C_6H_5)_2CHC(C_6H_5)=C(C_6H_4Br)OMgBr}$$

With this material in hand it was possible to settle the matter conclusively by means of the reactions which are represented by the following equations

$$(C_6H_5)_2CHC(COC_6H_5)COC_6H_4Br \quad (C_6H_5)_2CHC=C(C_6H_5)OMgBr$$

$$\underset{XXI}{|}{C_6H_5} \quad \overset{\longleftarrow}{} \quad \underset{}{|}{C_6H_5} \quad \overset{\longrightarrow}{}$$

$$(C_6H_5)_2CHC=C(C_6H_5)OCOC_6H_4Br$$

$$\underset{XXII}{|}{C_6H_5}$$

$$(C_6H_5)_2CHC(COC_6H_4Br)COC_6H_5 \quad (C_6H_5)_2CHC=C(C_6H_4Br)OMgBr$$

$$\underset{}{|}{C_6H_5} \quad \overset{\longleftarrow}{} \quad \underset{}{|}{C_6H_5} \quad \overset{\longrightarrow}{}$$

$$(C_6H_5)_2CHC=C(C_6H_4Br)OCOC_6H_5$$

$$\underset{XXIII}{|}{C_6H_5}$$

We found that the products of these reactions are different, the one being hydrolyzed to bromobenzoic acid and the bromine-free ketone, and the other to benzoic acid and the bromo ketone. The substances are, therefore, esters.