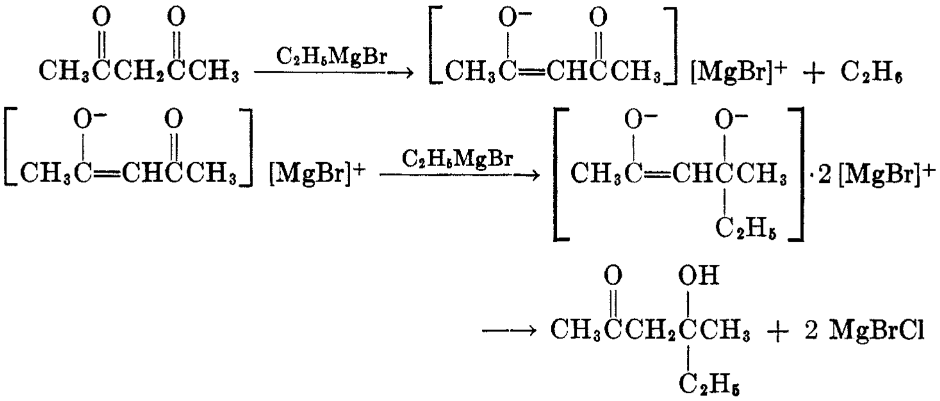
[Contribution from the Department of Chemistry and Chemical Engineering, Case Institute of Technology]

THE REACTION OF CERTAIN UNSYMMETRICAL β-DIKETONES WITH ETHYLMAGNESIUM BROMIDE

ALAN CHANEY[1] AND MELVIN J. ASTLE

Received July 3, 1950

It has been shown by Kohler and Erickson (4) that although two moles of Grignard reagent react with a β-diketone such as acetyl acetone, only one mole can be made to add to the diketone and the product isolated is a keto-alcohol. The first mole of the Grignard reagent reacts with the enol form of the diketone to give an enolate ion and a hydrocarbon. With acetyl acetone the reaction proceeds as follows:

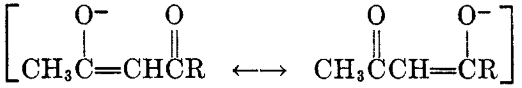


$$CH_3\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}CH_3 \xrightarrow{C_2H_5MgBr} \left[CH_3\overset{O^-}{\overset{|}{C}}=CH\overset{O}{\overset{\|}{C}}CH_3\right][MgBr]^+ + C_2H_6$$

$$\left[CH_3\overset{O^-}{\overset{|}{C}}=CH\overset{O}{\overset{\|}{C}}CH_3\right][MgBr]^+ \xrightarrow{C_2H_5MgBr} \left[CH_3\overset{O^-}{\overset{|}{C}}=CH\underset{\underset{C_2H_5}{|}}{\overset{O^-}{\overset{|}{C}}}CH_3\right]\cdot 2\,[MgBr]^+$$

$$\longrightarrow CH_3\overset{O}{\overset{\|}{C}}CH_2\underset{\underset{C_2H_5}{|}}{\overset{OH}{\overset{|}{C}}}CH_3 + 2\ MgBrCl$$

If an unsymmetrical diketone is used, two different enolate ions are possible and these ions are of such a nature that resonance will take place between them.



$$\left[CH_3\overset{O^-}{\overset{|}{C}}=CH\overset{O}{\overset{\|}{C}}R \longleftrightarrow CH_3\overset{O}{\overset{\|}{C}}CH=\overset{O^-}{\overset{|}{C}}R\right]$$

These two structures are not equivalent so that both will not contribute equally to the intermediate resonance state of the molecule.

The reaction of a Grignard reagent with unsymmetrical diketones should provide information concerning the directive influences of the R groups relative to methyl and should also provide some measure of the relative contributions of the two structures to the resonance state of the intermediate enolate ion.

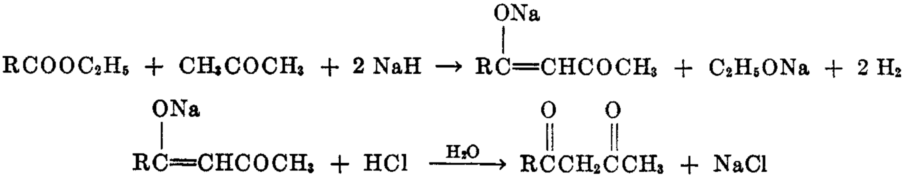
Four diketones of the type CH_3COCH_2COR were prepared in which R = ethyl, butyl, *tert*-butyl, and phenyl. These diketones were reacted with an excess of ethylmagnesium bromide. The ratio of the two possible keto alcohols produced from each diketone was determined so as to give some measure of the directive effects of the R group relative to methyl.

---

[1] From the M.S. thesis of Alan Chaney, June 1950.

EXPERIMENTAL PART

Preparation of the diketones. The four diketones used in this investigation were prepared through Claisen type condensations between an appropriate ester and a ketone using sodium hydride as a condensing agent. Since according to Adams and Hauser (1) better yields are obtained when simple ketones are condensed with more complex esters, the R group was incorporated in the ester which in each case was condensed with acetone according to the following equation.



$$RCOOC_2H_5 + CH_3COCH_3 + 2\,NaH \rightarrow R\overset{ONa}{\overset{|}{C}}{=}CHCOCH_3 + C_2H_5ONa + 2\,H_2$$

$$R\overset{ONa}{\overset{|}{C}}{=}CHCOCH_3 + HCl \xrightarrow{H_2O} R\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}CH_3 + NaCl$$

A mixture of 250 ml. of anhydrous benzene and 307 g. (3 moles) of ethyl propionate was placed in a three-necked flask provided with a mercury-sealed stirrer, a dropping-funnel, a condenser, and an inlet for dry nitrogen. After cooling to 0°, six moles (144 g.) of sodium hydride was added and all air was removed by sweeping with nitrogen. Dry acetone (175 g.) was then added slowly through the dropping-funnel at a maximum temperature of 5°. A nitrogen atmosphere was maintained in the flask at all times. During the addition of acetone a second portion (175 ml.) of dry benzene was added to keep the reaction mixture liquid. After stirring for two hours at 0–5°, the mixture was allowed to stand overnight without further cooling.

The next day after cooling to 0°, it was necessary to add a 100-ml. portion of benzene to liquefy the mixture and a 15% solution of hydrochloric acid was then added slowly at a maximum temperature of 10°, until the solution was acidic. Upon warming to room temperature the mixture separated into two layers. The aqueous layer was extracted with ether and this extract was combined with the organic layer and was washed with 1% hydrochloric acid. The solution was then extracted six times with 10% sodium hydroxide which removed the diketone as the sodium salt. The diketone was immediately regenerated by the slow addition of conc'd hydrochloric acid and extracted into ether.

The ether was distilled on a steam-bath and the residue containing the diketone was dissolved in twice its volume of hot methanol. This solution was treated with twice its volume of boiling water containing somewhat more than enough copper acetate to convert the diketone to the copper salt. The solution was filtered and cooled to room temperature; the copper salt of the diketone separated out on cooling. The copper salt was treated with 10% sulfuric acid to regenerate the diketone which was extracted into ether. After the removal of the ether on a steam-bath the diketone was recovered by distillation under diminished pressure.

Yield of 2,4-hexanedione, 256 grams (75%); b.p. 157°/740 mm.

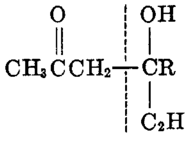
2,4-Octanedione was prepared similarly from ethyl valerate and acetone; yield 79%, b.p. 66.0–66.5°/5 mm.

2,2-Dimethyl-3,5-hexanedione was prepared from ethyl pivalate and acetone; yield, 51%, b.p. 70–71°/20 mm.

1-Phenyl-1,3-butanedione was prepared from ethyl benzoate and acetone; yield, 62%, m.p. 61.0–61.5°.

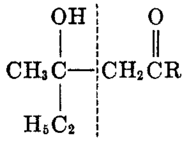
The Grignard reaction. The Grignard reaction was carried out in the usual way. Ethylmagnesium bromide was formed at about 10°, the diketone was added at 5°, and the mixture stirred for two hours. A 15% solution of hydrochloric acid was then added at a maximum of 10° and the mixture permitted to warm up to room temperature. The mixture was extracted with ether and washed with 5% hydrochloric acid. Ether and ethyl bromide were removed by distillation. The residue was used for the determination of keto-alcohols.

Analysis of the keto-alcohols. The two keto-alcohols produced from each Grignard reaction have the following type structures:



$$\mathrm{CH_3\overset{\overset{O}{\|}}{C}CH_2{-}\underset{\underset{C_2H_5}{|}}{\overset{\overset{OH}{|}}{C}}R}$$

I



$$\mathrm{CH_3\underset{\underset{H_5C_2}{|}}{\overset{\overset{OH}{|}}{C}}{-}CH_2\overset{\overset{O}{\|}}{C}R}$$

II

These compounds resemble diacetone alcohol in structure and like this compound will be hydrolyzed easily in alkaline solution to give a mixture of two ketones as indicated by the dotted lines. Compound II would give two methyl ketones on hydrolysis; compound I would give only one molecule of a methyl ketone. These methyl ketones can be determined by a modification of the iodoform reaction (6). The total moles of ketone can be determined by using a hydroxylamine method developed by Bryant (3) and Siggia (7).

The ketones obtained from the cleavage of the keto-alcohols in alkaline solution are: (a) $RCOC_2H_5$; (b) CH_3COCH_3; (c) $RCOCH_3$; and (d) $CH_3COC_2H_5$. It is evident that the hydroxylamine method will give the total moles of ketone present, *i.e.*, (a + b + c + d), while the iodoform reaction will give the moles of (b + c + d) present, since (a) will not react. Hence moles of (a) can be obtained by subtraction. Since ketones (a) and (b) were formed from the same keto-alcohol, then a = b, and (b) equals the moles of Ketoalcohol I present. Also, (a + b) subtracted from total ketone present gives (c + d). Since (c) and (d) are present in equal amounts, then one-half of (c + d) gives the amount of ketone (c) present; this is equal to the amount of keto-alcohol II originally present.

This analytical method was tested by weighing out samples of acetone, diethyl ketone, methyl butyl ketone, and acetophenone into an aqueous sodium hydroxide solution and carrying out the steps of the analysis in the same way as would be done with the unknown. Four mixtures containing three different ketones each were analyzed. The results were accurate to about 0.8% on the average. The largest error was 1.25%; therefore the method is accurate to within about 1%, which is sufficient for comparison with other work.

The *analysis* was carried out as follows: The keto-alcohols were hydrolyzed to a mixture of ketones by steam-distillation from an aqueous sodium hydroxide solution. The conversion of the keto-alcohols to ketones is very rapid and, although the reaction is only about 98% complete, it is completed by distillation of the low-boiling ketones. Any of the original diketone, which is present as an impurity, does not distill because it forms a salt, through the enol form, with sodium hydroxide. Traces of ether and ethyl bromide remaining in the residue will distill easily, but they do not interfere with the analysis.

Fifty ml. of 2.0 *N* sodium hydroxide solution is placed in a 250-ml. round-bottom flask equipped for steam-distillation. Ten ml. of the keto-alcohol is added and the flask allowed to stand for one hour before the distillation is started. The receiver is especially designed with a Dry Ice condenser, in addition to the water condenser, so that there is no possibility for the escape of any volatile material. The distillation is accomplished by maintaining the volume in the flask at the original volume until a total of 300 ml. of distillate is collected, or if necessary, until the distillate shows a negative test for ketones. The distillate is transferred to a 500-ml. volumetric flask and diluted to 500 ml. with pure methanol to ensure complete solubility.

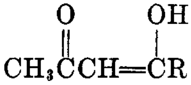
These solutions are then analyzed by means of the iodoform and the hydroxylamine methods as described previously.

The results in Table I are the average of two different determinations on two samples of each keto-alcohol residue. The average deviation between the two results was 0.23%. This fact combined with the errors in the method give results which are believed to be accurate to 1%.

DISCUSSION OF RESULTS

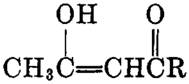
The results are summarized in Table I.

The hydrogen atoms on the central methylene carbon atom of the diketones are activated and two possible enol structures might be in equilibrium with the normal ketone. These structures would be III and IV.



$\mathrm{CH_3\overset{\overset{O}{\|}}{C}CH{=}\overset{\overset{OH}{|}}{C}R}$

III



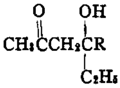
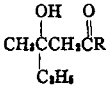
$\mathrm{CH_3\overset{\overset{OH}{|}}{C}{=}CH\overset{\overset{O}{\|}}{C}R}$

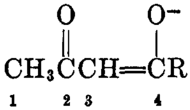
IV

Consequently, the initial reaction with a Grignard reagent is the reduction of the Grignard by these active hydrogens with the formation of a hydrocarbon. In this investigation, ethane was formed and escaped from the reaction media as a gas. The resulting solution might be considered to contain a mixture of two enolate ions V and VI.

TABLE I

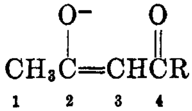
Products Obtained by the Reaction of Ethylmagnesium Bromide on β-Diketones

DIKETONE	PER CENT  $\mathrm{CH_3\overset{\overset{O}{\|}}{C}CH_2\underset{\underset{C_2H_5}{|}}{\overset{\overset{OH}{|}}{C}}R}$	PER CENT  $\mathrm{CH_3\underset{\underset{C_2H_5}{|}}{\overset{\overset{OH}{|}}{C}}CH_2\overset{\overset{O}{\|}}{C}R}$
2,4-Hexanedione $\mathrm{CH_3COCH_2COC_2H_5}$	48	52
2,4-Octanedione	41	59
2,2-Dimethyl-3,5-hexanedione $\mathrm{CH_3COCH_2COC(CH_3)_3}$	11	89
1-Phenyl-1,3-butanedione $\mathrm{CH_3COCH_2COC_6H_5}$	0	100



$\mathrm{\underset{1}{CH_3}\underset{2}{\overset{\overset{O}{\|}}{C}}\underset{3}{CH}{=}\underset{4}{\overset{\overset{O^-}{|}}{C}}R}$

V



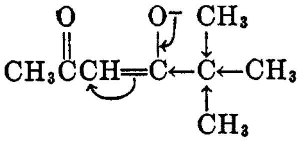
$\mathrm{\underset{1}{CH_3}\underset{2}{\overset{\overset{O^-}{|}}{C}}{=}\underset{3}{CH}\underset{4}{\overset{\overset{O}{\|}}{C}}R}$

VI

Since each ion can be converted into the other by a simple shift of electrons, these ions as such undoubtedly do not exist in the solution but they must exist as a resonance hybrid as previously indicated. This hybrid should give either ion V or VI upon the approach of the attacking reagent and the relative amounts of ions V and VI formed depends upon their relative stability, with the more stable ion having the higher probability of formation.

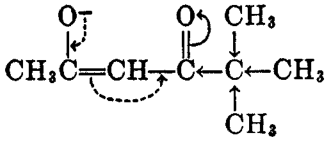
Grignard reagents are nucleophilic and require a center of low electron density before they can add to a molecule. Both ions V and VI can provide this center by means of an electromeric shift of electrons to the carbonyl oxygen leaving the carbon atom with only a sextet of electrons. If the Grignard reagent adds to ion V, it will add at carbon atom two because in this ion only this carbon atom can be involved in an electromeric shift of electrons as described above. Similarly addition of a Grignard reagent to ion VI would be at carbon atom four.

Consider the diketone in which the R group is a *tert*-butyl group. The three methyl groups are electropositive and cause an inductive effect to operate towards carbon atom 4. This inductive displacement will oppose any shift of electrons such as indicated below:



$$CH_3\overset{\overset{O}{\|}}{C}CH{=}\overset{\overset{O^-}{|}}{C}\leftarrow\underset{\underset{CH_3}{\uparrow}}{\overset{\overset{CH_3}{\downarrow}}{C}}\leftarrow CH_3$$

This inductive effect opposes the formation of a carbonyl group at carbon atom four. The opposition offered by the methyl group to formation of a carbonyl group at carbon atom two is much less and therefore ion V is more probable as an intermediate than ion VI. If we consider the second form of the enolate ion shown below:

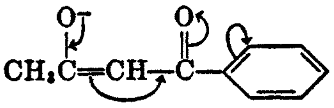


$$CH_3\overset{\overset{O^-}{|}}{C}{=}CH{-}\overset{\overset{O}{\|}}{C}\leftarrow\underset{\underset{CH_3}{\uparrow}}{\overset{\overset{CH_3}{\downarrow}}{C}}\leftarrow CH_3$$

the electron-releasing tendency of the *tert*-butyl group would help promote the electromeric displacement of the electrons to the oxygen at carbon atom four. This carbon atom being left with only a sextet of electrons could then cause a secondary electron displacement indicated by the dotted lines. The probability of finding a normal carbonyl group at carbon atom two would therefore be greater than at carbon atom four. In the cases in which the R group is *n*-butyl or ethyl, the opposition to the formation of the carbonyl group at carbon atom four is the same but the strength of the opposition is not as great and the amounts of each keto-alcohol produced are more nearly equal.

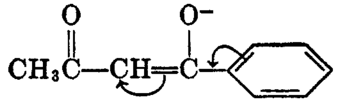
It is highly probable that the much greater effect of the *tert*-butyl as compared to the *n*-butyl group is a result of hyperconjugation in the case of the *tert*-butyl group.

The diketone in which the R group is phenyl presents a somewhat different problem. The phenyl group can act as either an electron sink or an electron well. If the phenyl group acts as an electron sink, the electrons may shift as indicated below:



This shift of electrons would be encouraged by the electronegative character of both the carbonyl group and the phenyl group at carbon atom four. The reverse shift of electrons would be discouraged by the electronegative character of the phenyl group. Thus the probability of finding a normal carbonyl group at carbon atom two is greater than at carbon atom four.

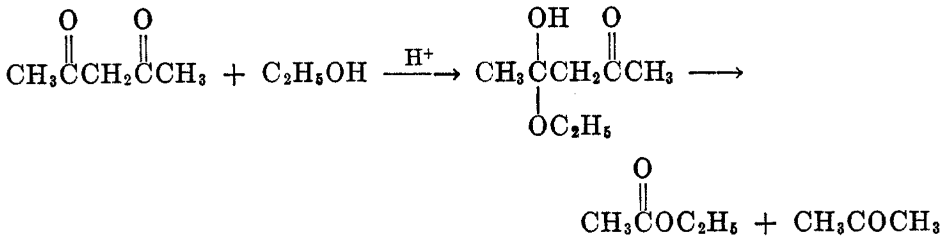
It is likely that the phenyl group would act as an electron well and if so electromeric shifts of the type shown below will occur at the approach of the nucleophilic Grignard reagent.



By such shifts a complete octet of electrons is maintained at all times around carbon atom four so that an electrophilic center can not be easily established at this position. Since electrons are much more mobile in the phenyl group than in the aliphatic groups, the magnitude of its effect should be greater as has been observed.

It should be emphasized that the discussion is limited to the nature of the products and does not consider the rate of reaction. There is evidence that the reaction rate is reduced by the phenyl group. It is probably that the difference in the amounts of the keto-alcohols formed by addition of the Grignard reagent is the result of deactivation of one positon preferentially over the other.

The results of this investigation may be compared with the results of Adkins and co-workers on the ethanolysis of β-diketones. Beckman and Adkins (2) studied the acidic ethanolysis of acetylaceton and proposed that the reaction proceed as indicated below:



$$CH_3\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}CH_3 + C_2H_5OH \xrightarrow{H^+} CH_3\underset{OC_2H_5}{\overset{OH}{C}}CH_2\overset{O}{\overset{\|}{C}}CH_3 \longrightarrow CH_3\overset{O}{\overset{\|}{C}}OC_2H_5 + CH_3COCH_3$$

Kutz and Adkins (5) treated three of the same diketones studied in the present investigation with hydrochloric acid in ethanol at 60°. Their work showed that ethanol added to 2,4-octanedione 61% next to the methyl group and 39% next to the butyl group; to 2,2-dimethyl-3,5-hexanedione, ethanol added 91% next to the methyl group and only 9% next to the *tert*-butyl group; to 1-phenyl-1,3-butanedione, ethanol added 100% next to the methyl group. These results agree very well with the results reported in this paper.

SUMMARY

Four unsymmetrical β-diketones were prepared and each was treated with an excess of ethylmagnesium bromide. The product of each of these reactions was

a mixture of two keto-alcohols. The relative amounts of the keto-alcohols in each reaction mixture was determined by analysis.

The Grignard reagent reacted predominantly at the carbonyl group next to the methyl group as follows: 2,4-hexanedione, 52%; 2,4-octanedione, 59%; 2,2-dimethyl-3,5-hexanedione, 89%; and 1-phenyl-1,3-butanedione, 100%.

The reactions are discussed in terms of the electronic theories.

CLEVELAND 6, OHIO

REFERENCES

(1) ADAMS AND HAUSER, *J. Am. Chem. Soc.*, **66**, 1220 (1944).
(2) BECKMAN AND ADKINS, *J. Am. Chem. Soc.*, **56**, 1119 (1934).
(3) BRYANT AND SMITH, *J. Am. Chem. Soc.*, **57**, 57 (1935).
(4) KOHLER AND ERICKSON, *J. Am. Chem. Soc.*, **53**, 2301 (1931).
(5) KUTZ AND ADKINS, *J. Am. Chem. Soc.*, **52**, 4036 (1930).
(6) SCOTTS' *Standard Methods of Analysis*, Volume II, Fifth Edition, D. van Nostrand Co., page 2136.
(7) SIGGIA, *Quantitative Organic Analysis via Functional Groups*, John Wiley and Sons, Inc., New York, 1949, page 16.