Reaction of Grignard reagents with β-dicarbonyl compounds. II. Synthesis of β-hydroxyketones from 2,4-pentanedione[1]

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Several new β-hydroxyketones having the formula $CH_3R'C(OH)CH_2COCH_3$ have been prepared by the action of Grignard reagents on 2,4-pentanedione. With benzyl-, *o*-xylyl-, *p*-xylyl-, 3,4-dimethylbenzyl-, 2,5-dimethylbenzyl-, 3,5-dimethylbenzyl-, and α-naphthylmethyl-magnesium chlorides, 60 to 75% yields of the β-hydroxyketones were obtained. Phenyl-, *p*-tolyl-, and *p*-trifluoromethylphenyl-magnesium bromide and 2,4-dimethylbenzylmagnesium chloride gave lower yields, whereas with α-naphthylmagnesium bromide no β-hydroxyketone was formed. The β-hydroxyketones were separated from non-ketonic by-products by means of Girard's reagent T or P. Solid derivatives of the β-hydroxyketones could not be prepared.

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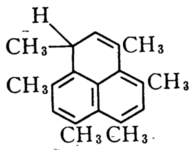
Our interest in synthesizing the β-hydroxyketones described in this paper arose out of the possibility of using one of them as starting material for the synthesis of the hexamethylphenalene I, which will be reported shortly (1).



I

Apart from diacetone alcohol, few tertiary β-hydroxyketones ($RR'C(OH)CH_2COR''$) have been synthesized and studied. In 1934, Colonge (2) reported the preparation of such compounds from aminomagnesium halides of the type RR′NMgX and a variety of ketones. Some 20 years later, Colonge and Grenet (3) observed that β-hydroxyketones could be prepared in 25 to 65% yields from α-bromoketones and magnesium in the presence of the parent or other ketones. In several experiments the unsaturated ketone was isolated instead of the hydroxyketone, a result which indicated the facile dehydration of the initial product. In the interval, Dubois (4) reported the formation of β-hydroxyketones in 30 to 70% yields from branched ketones and isopropylmagnesium chloride. It is pertinent to note that all three methods are essentially coupling reactions in which the yields are 50% or more only when highly branched ketones are employed. These syntheses, although interesting, are of no value for our purpose.

β-Hydroxyketones have also been prepared from Grignard reagents and β-diketones. In the first paper of this series (5), the literature relating to this reaction was reviewed and the preparation of a few β-hydroxyketones from methyl-, phenyl-, and benzyl-magnesium halides and dibenzoylmethane was reported. However, all attempts to isolate pure β-hydroxyketones formed in the corresponding reaction with 2,4-pentanedione were unsuccessful. Fractional distillation under very low (0.05 mm) pressure or vapor-phase chromatography resulted in dehydration and cleavage of the hydroxyketones, and chromatography over silica gel was tedious and gave inconclusive results. Thin-layer chromatography of a crude reaction mixture revealed the presence of several compounds.

It has now been found that by making use of Girard's reagent T (or P) several

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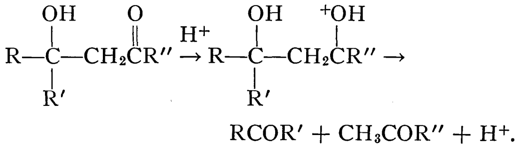
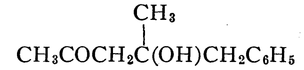
β-hydroxyketones not accessible by any other method can be prepared in moderately good yields. Whereas Girard and Sandulesco recovered the ketones from an aqueous solution by hydrolysis of their hydrazones, Teitelbaum (6) isolated them by displacement from their hydrazones by the addition of excess 37% formaldehyde. This variant proved to be ideally suited in the present instance, since in acidic media β-hydroxyketones are readily cleaved by a reversed acid-catalyzed aldol condensation:



$$\mathrm{R{-}\overset{OH}{\underset{R'}{C}}{-}CH_2\overset{O}{\overset{\|}{C}}R'' \xrightarrow{H^+} R{-}\overset{OH}{\underset{R'}{C}}{-}CH_2\overset{{}^+OH}{C}R'' \rightarrow RCOR' + CH_3COR'' + H^+}.$$

Nigam and Levi (7) have recently extended Teitelbaum's modification to the actual separation of certain unstable aldehydes and ketones present in essential oils by taking advantage of the different rates of regeneration of the aldehydes and ketones from their hydrazones by formaldehyde.

In the present work, the crude mixture obtained in the reaction of a Grignard reagent and 2,4-pentanedione was treated with Girard's reagent in methanol in the presence of an acidic exchange resin as catalyst. The hydroxyketones were regenerated from the aqueous solution of their hydrazones and recovered quantitatively by continuous extraction with a mixture of ether and petroleum ether. Fractionation of the ketones by adding formaldehyde solution in aliquots was not successful in this case as a means of removing the ketones formed by cleavage or dehydration, presumably because of the small difference in the rates of regeneration from the hydrazones. In any event, small amounts of by-products formed by cleavage or dehydration could be removed effectively by stirring the mixture at 45–50° under 0.01 mm for several hours. Bulb to bulb distillation of the residue under a high vacuum generally gave satisfactory yields of the β-hydroxyketones, which were shown to be pure by nuclear magnetic resonance and infrared spectra and elemental analysis.



$$\mathrm{CH_3COCH_2\overset{CH_3}{\overset{|}{C}}(OH)CH_2C_6H_5}$$

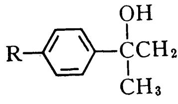
II

The reaction between benzylmagnesium chloride and 2,4-pentanedione was first examined and developed into a method of preparing 4-hydroxy-4-methyl-5-phenyl-2-pentanone (II) in 60–75% yields. All efforts to obtain solid derivatives of the β-hydroxyketone II were fruitless. Attempts to prepare the 2,4-dinitrophenylhydrazone by the modified procedure of Shine (8) gave only intractable oils, although the method did give a solid derivative with diacetone alcohol, as claimed. No reaction occurred when the hydroxyketone was heated in alcohol with 2,4-dinitrophenylhydrazine in the presence of the exchange resin used in the reaction with Girard's reagent. Derivatization of the hydroxyketone through the hydroxyl group with 2-bromoethyl isocyanate, as described by Johnson and Bublitz (9) for diacetone alcohol, likewise failed to give a solid derivative. Lastly, no derivative was obtained with 2,4-dinitrobenzenesulfenyl chloride as described by Kharasch *et al.* (10) or by Lefebvre *et al.* (11). However, although characterization of II by means of a derivative would have been desirable, it is felt that its structure was amply established by physical methods (see Experimental).

Encouraged by this initial success with benzyl chloride, the reaction was next carried out with a number of alkyl derivatives. Some of them were commercially available, but others had to be prepared. In the latter category were *o*- and *p*-xylyl chlorides and 3,5-dimethylbenzyl chloride. For reasons of simplicity, we attempted to prepare these compounds from the hydrocarbons and sulfuryl chloride in the presence of dibenzoyl peroxide instead of by chlorination in the vapor phase (12) or with *N*-chlorosuccinimide (13). It was found that with the usual amount of peroxide (0.001 mole) appreciable quantities (25–30%) of nuclear-chlorinated products were formed. These by-products do not cause complications because they do not form Grignard reagents; nevertheless, they markedly reduce the yield of the desired halide. However, if relatively large amounts of peroxide are added, say 10 times the usual amount, chlorination on the nucleus occurs to the extent of only 2 to 4% and α-chloro derivatives are isolated in 70% yields or more. In some cases, as in hemimellitene (1,2,3-trimethylbenzene), ring chlorination occurs almost exclusively, even in the presence of a large excess of peroxide.

The yields of β-hydroxyketones obtained with *o*-xylyl chloride, *p*-xylyl chloride, 3,5-dimethylbenzyl chloride, 3,4-dimethylbenzyl chloride, 2,5-dimethylbenzyl chloride, and α-chloromethylnaphthalene were of the same order as those obtained with benzyl chloride. However, 2,4-dimethylbenzyl chloride gave a lower yield, presumably because of extensive coupling during the preparation of the Grignard reagent. Apparently, the presence of methyl groups in the *o*- and *p*-positions favors coupling; for example, 2,4,6-trimethylbenzyl chloride gave an 87% yield of the substituted ethane (14).

Further experiments with phenylmagnesium bromide, *p*-tolylmagnesium bromide, and *p*-trifluoromethylphenylmagnesium bromide indicated a strong tendency of the resulting hydroxyketone to undergo dehydration. Elimination of water in hydroxyketone III (R = H or CH_3) presumably occurs easily, because it leads to a more highly conjugated system. If R = CF_3, this tendency should be reduced by the electron-withdrawing character of fluorine. This has, in fact, been observed; *p*-trifluoromethylmagnesium bromide gives a 30% yield of hydroxyketone contaminated with a little unsaturated ketone. With α-naphthylmagnesium bromide, no hydroxyketone was formed; a small amount of α-acetylnaphthalene (identified by its nuclear magnetic resonance spectrum) was isolated. A large amount of naphthalene was obtained from the non-ketonic fraction of the crude mixture that had been treated with Girard's reagent, an indication that Grignard reagent was utilized only in reaction with the enol form of 2,4-pentanedione. No definite explanation for this observation can be advanced at this time, but it could be due to steric hindrance.



$$R{-}C_6H_4{-}\overset{OH}{\underset{CH_3}{C}}CH_2COCH_3$$

III

EXPERIMENTAL

Benzyl chloride, 2,5-dimethylbenzyl chloride, 3,4-dimethylbenzyl chloride, and α-chloromethylnaphthalene were obtained from Aldrich Chemical Co., Inc.

o-Xylyl Chloride (ω-Chloro-o-xylene)

A solution of 235 ml (212 g, 2.0 moles) of *o*-xylene, 120 ml (202 g, 1.5 moles) of sulfuryl chloride, and 5.0 g (0.02 mole) of dibenzoyl peroxide was heated in a 2 l, round-bottomed flask on the steam bath under a reflux condenser connected to a gas absorption trap until evolution of gases ceased. The reaction mixture was fractionated in a short Vigreux column with a total condensation partial take-off stillhead. Unchanged *o*-xylene, recovered between 52 and 56° at 25 mm, amounted to 110–115 ml. *o*-Xylyl chloride was collected between 45 and 50° at 0.1 mm. The yield of product, which was nearly 96% α-chloro-*o*-xylene as determined by vapor-phase chromatography, was 110 g (90% based on the *o*-xylene consumed).

p-Xylyl Chloride (ω-Chloro-p-xylene)

This compound was obtained in a similar yield from *p*-xylene, sulfuryl chloride, and dibenzoyl peroxide.

2,4-Dimethylbenzyl Chloride

m-Xylene was chloromethylated as described by von Braun and Nelles (15); 200 g of *m*-xylene gave 130 g of 2,4-dimethylbenzyl chloride, b.p. 105–112° at 15 mm.

3,5-Dimethylbenzyl Chloride (α-Chloromesitylene)

A solution of 140 ml (120 g, 1.0 mole) of mesitylene, 80 ml (135 g, 1.0 mole) of sulfuryl chloride, and 3.0 g of dibenzoyl peroxide (0.0125 mole) was heated in a 1 l, round-bottomed flask on the steam bath under a reflux condenser connected to a gas absorption trap until evolution of gas ceased.

The crude products from two runs were combined and fractionated in a Vigreux-type column with a total condensation partial take-off stillhead. Unchanged mesitylene recovered between 55 and 60° at 9 mm amounted to 75–90 g. The 3,5-dimethylbenzyl chloride was collected between 52 and 55° at 0.1 mm. The yield of product, n_D^{20} 1.5305, which contained 96% α-chloro- and 4% 2-chloro-mesitylene as determined by vapor-phase chromatography, was 145–155 g (70–77% of the theoretical amount based on the mesitylene consumed).

TABLE I

β-Hydroxyketones

Compound prepared	Yield (%)	Formula	Calculated (%)		Found (%)	
			C	H	C	H
4-Hydroxy-4-methyl-5-(*o*-tolyl)-2-pentanone	60–75	$C_{13}H_{18}O_2$	75.72	8.74	75.55	8.51
4-Hydroxy-4-methyl-5-(*p*-tolyl)-2-pentanone	60–75	$C_{13}H_{18}O_2$	75.72	8.74	75.88	8.61
4-Hydroxy-4-methyl-5-(2,4-dimethylphenyl)-2-pentanone	50	$C_{14}H_{20}O_2$	76.36	9.00	76.51	8.97
4-Hydroxy-4-methyl-5-(2,5-dimethylphenyl)-2-pentanone	60–75	$C_{14}H_{20}O_2$	76.36	9.00	76.67	8.62
4-Hydroxy-4-methyl-5-(3,4-dimethylphenyl)-2-pentanone	60–75	$C_{14}H_{20}O_2$	76.36	9.00	76.13	8.89
4-Hydroxy-4-methyl-5-(3,5-dimethylphenyl)-2-pentanone	60–75	$C_{14}H_{20}O_2$	76.36	9.00	76.18	9.01
4-Hydroxy-4-methyl-5-(α-naphthyl)-2-pentanone	65–75	$C_{16}H_{18}O_2$	79.33	7.44	79.21	7.45
4-Hydroxy-4-phenyl-2-pentanone	60	$C_{11}H_{14}O_2$	74.13	7.83	77.01	7.12
4-Hydroxy-4-methyl-5-(*p*-trifluoromethylphenyl)-2-pentanone	30	$C_{12}H_{13}O_2F_3$	57.70	5.29	58.62	4.61
4-Hydroxy-4-(*p*-tolyl)-2-pentanone	15	$C_{12}H_{16}O_2$	75.00	8.33	80.45	7.32

4-Hydroxy-4-methyl-5-phenyl-2-pentanone (II)

Benzylmagnesium chloride was prepared from 36.0 g (1.5 moles) of magnesium turnings and 190 g (1.5 moles) of benzyl chloride dissolved in 1 l of absolute ether. A solution of 50.0 g (0.5 mole) of 2,4-pentanedione in 200 ml of absolute ether was added dropwise to the stirred solution of the Grignard reagent. After all the diketone solution was added, the reaction mixture was stirred for 6 h, or overnight if convenient, and then poured gradually into 2 l of a stirred, ice-cold, saturated solution of ammonium chloride in water. The ether layer was separated, dried carefully over anhydrous magnesium sulfate, filtered, and evaporated on the steam bath.

The residue was added to a solution of 100 g of Girard's reagent T in 200 ml of methyl alcohol, 2 g of Amberlite 50 resin was added as catalyst, and the solution was heated for 1 h under reflux on the steam bath. Most of the solvent was then removed under reduced pressure. The cold residue was treated with 500 ml of water, and the suspension was filtered on a Büchner funnel with the aid of Filter-Cel. The clear filtrate was extracted three times with 200 ml of pentane or petroleum ether, b.p. 30–60°, to remove the insoluble non-ketonic material. The aqueous layer was treated with 50 ml of 36% formalin solution and extracted in a continuous extractor for 24 h with petroleum ether, b.p. 30–60°. The ether extract was washed with 25 ml of water to remove formaldehyde and freed of solvent on the steam bath. Low-boiling ketones, such as phenylacetone (produced by slight cleavage), and unsaturated ketone (produced by dehydration during work-up) were removed from the crude hydroxyketone by stirring the mixture at 45° overnight under 0.01–0.02 mm. Under these conditions nearly all of the by-products passed over into a trap cooled in dry ice. The residue was then transferred to a Späth tube with two bulbs and distilled from an air bath at 65–70° under 0.02 mm. Only traces of distillate came over below 65°. The yield of colorless, highly refracting, viscous hydroxyketone, n_D^{20} 1.5163, was 57–72 g (60–75% yield).

Anal. Calcd. for $C_{12}H_{16}O_2$: C, 75.00; H, 8.33. Found: C, 75.22; H, 8.22.

The nuclear magnetic resonance spectrum of the product in deuteriochloroform revealed four singlets at τ 8.85, 8.00, 7.58, and 7.25, attributable to CH_3 in $CH_3C(OH)CH_2C_6H_5$, CH_3 in CH_3CO, CH_2 in $C_6H_5CH_2$, and CH_2 in CH_3COCH_2, respectively. The signal arising from OH appeared at τ 6.28, and aromatic protons showed up at τ 2.80. The infrared spectrum in chloroform gave a broad band with a peak at 3 500 cm^{-1} attributable to OH, and one at 1 695 cm^{-1} caused by C═O. Other bands characteristic of tertiary alcohols appeared at 1 365 and 925 cm^{-1}.

The compounds listed in Table I were all prepared by the same procedure from the appropriate Grignard reagent and 2,4-pentanedione. Their nuclear magnetic resonance spectra were similar to that of II, and revealed an additional signal arising from the ring methyl groups. However, the analytical figures for the last three compounds in the table are low in carbon and high in hydrogen. Furthermore, the nuclear magnetic resonance spectra of these compounds reveal extra bands not present in the spectra of the other β-hydroxyketones. For example, compound III (R = H) has extra bands at δ 6.43, 2.15, 2.82, and 2.95. These signals and the analytical figures are consistent with the presence of an unsaturated ketone and acetophenone. So far, these compounds have not been obtained completely free of these impurities, but they are nevertheless suitable for further syntheses.

Attempted Reaction between α-Naphthylmagnesium Bromide and 2,4-Pentanedione

α-Naphthylmagnesium bromide was prepared in the usual manner from α-bromonaphthalene (104.0 g, 0.5 mole), magnesium (15.0 g, 0.6 mole), and 400 ml of absolute ether. Towards the end of the reaction, 100 ml of benzene had to be added to keep the Grignard reagent in solution. A solution of 16.0 g (0.16 mole) of 2,4-pentanedione in ether was added. The reaction mixture was worked up in the usual way and treated with Grignard's reagent T (25.0 g dissolved in 125 ml of methanol) and 0.1 g of exchange resin. Only traces of ketonic products were extracted on work-up, and 36 g of naphthalene was recovered from the non-ketonic fraction.

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