Experimental

The procedures followed in the reduction of carboxylic acids were similar to those previously described[1] except that it was generally desirable to work with somewhat more dilute solutions because of the greater tendency of the reaction mixtures to thicken. In some cases decomposition of the reaction mixture by alkali is preferable to acidification; this variant of the procedure is illustrated in the description below of the preparation of *o*-aminobenzyl alcohol. The experimental results are summarized in Table I.

TABLE I

REDUCTION OF CARBOXYLIC ACIDS BY LITHIUM ALUMINUM HYDRIDE

Acid	Product	Yield, %
Trimethylacetic acid	Neopentyl alcohol	92
Stearic acid	Octadecanol-1	91
Sebacic acid	Decanediol-1,10	97
Ethyl hydrogen sebacate	Decanediol-1,10	91
Sorbic acid	Sorbyl alcohol	92
Furoic acid	Furfuryl alcohol	85
Phenylacetic acid	β-Phenylethanol	92
Cinnamic acid	Hydrocinnamyl alcohol	85
Triphenylacetic acid	No reduction at 25°	
Benzoic acid	Benzyl alcohol	81
Salicylic acid	*o*-Hydroxybenzyl alcohol	99
o-Chlorobenzoic acid	*o*-Chlorobenzyl alcohol	97
Anthranilic acid	*o*-Aminobenzyl alcohol	97
Phenylglyoxylic acid	Phenylethyleneglycol	80

Reduction of an Ether-soluble Acid. Phenylacetic Acid to β-Phenylethanol.—A solution of 4.75 g. (0.125 mole) of lithium aluminum hydride in 180 ml. of ether is placed in a one-liter three-necked flask equipped with reflux condenser, dropping funnel, and mechanical stirrer, and protected from moisture until completion of the reaction by calcium chloride tubes attached to the openings. Through the dropping funnel, a solution of 13.6 g. (0.1 mole) of phenylacetic acid in 150 ml. of ether is added at a rate such as to produce gentle reflux. Fifteen minutes after the addition has been completed and with continued stirring and cooling of the flask, water is added cautiously to decompose excess hydride. Then 150 ml. of 10% sulfuric acid is added (the flask may again have to be cooled in ice-water at this point) and a clear solution results. The contents of the flask are transferred to a separatory funnel and worked up in the usual way. The product is purified by fractional distillation through a 24-inch column under reduced pressure and there is obtained a 92% yield of β-phenylethanol, b. p. 112° (18 mm.), $n^{20}D$ 1.5318.

Reduction of a Compound Slightly Soluble in Ether. Anthranilic Acid to o-Aminobenzyl Alcohol.—The apparatus differs from that described above in that a continuous extractor is inserted between the flask and the reflux condenser. A solution containing 9.1 g. (0.24 mole) of lithium aluminum hydride in 600 ml. of ether is placed in the flask, and 13.7 g. (0.1 mole) of anthranilic acid is placed in the extractor thimble. The solution is warmed until all of the anthranilic acid has been transferred to the reaction flask. The flask is then cooled and the excess hydride is decomposed by the addition of water. To the mixture is then added 250 ml. of 10% sodium hydroxide solution. The ether layer is separated and the water layer extracted with two 200-ml. portions of ether. The residue from the combined ether extracts is dried *in vacuo* over calcium hydride for five hours. The product, *o*-aminobenzyl alcohol, m. p. 82°, is obtained in 97% yield.

Summary

Various types of carboxylic acids are smoothly converted to the corresponding primary alcohols by lithium aluminum hydride. Free hydroxyl and amino groups do not interfere. The double bonds in cinnamic acid, but not in sorbic acid or furoic acid, are simultaneously hydrogenated.

CHICAGO, ILLINOIS RECEIVED APRIL 25, 1947

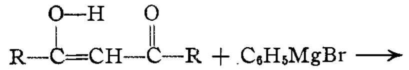
[CONTRIBUTION FROM THE LABORATORIES OF THE UNIVERSITY OF MARYLAND]

The Reaction of 5,5-Dimethylcyclohexanedione-1,3 (Dimedone) and its Ethyl Enol Ether with Phenylmagnesium Bromide

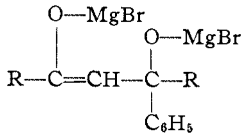
BY G. FORREST WOODS

The addition of ethyl cyanoacetate to 5,5-dimethyl-3-phenyl-Δ²-cyclohexenone in the Michael reaction would make available compounds rather closely related to morphine. The preparation of the above α,β-unsaturated ketone and the reaction of dimedone with phenylmagnesium bromide forms the subject of the present paper.

It was anticipated that the reaction of the strongly enolic dimedone[1] with phenylmagnesium bromide would proceed in accordance with the observations made by Kohler and Erickson[2] for the reaction of strongly enolic α,β-diketones with phenylmagnesium bromide. Kohler's representation of this reaction is as follows

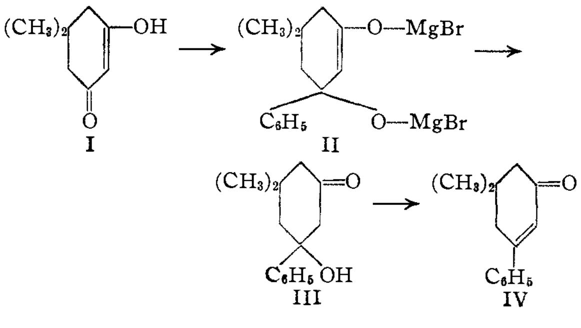


$$R-\overset{O-H}{\overset{|}{C}}=CH-\overset{O}{\overset{\|}{C}}-R + C_6H_5MgBr \longrightarrow$$



$$R-\overset{O-MgBr}{\overset{|}{C}}=CH-\underset{C_6H_5}{\underset{|}{\overset{O-MgBr}{\overset{|}{C}}}}-R$$

In the case of dimedone (1) the reaction was expected to proceed as shown below whereby product III would be obtained



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[1] Schwarzenbach and Felder, *Helv. Chim. Acta*, **27**, 1044 (1944).

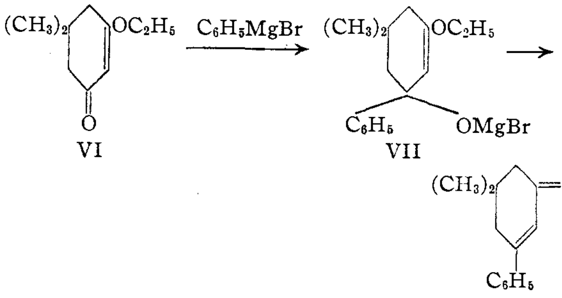
[2] Kohler and Erickson, THIS JOURNAL, **53**, 2301 (1931).

Further, it seemed reasonable to assume that compound (III) could be dehydrated readily to yield 5,5-dimethyl-3-phenyl-Δ^2-cyclohexenone (IV).

Kohler[2] observed that strongly enolic β-diketones gave no evidence of cleavage on reaction with phenylmagnesium bromide (the β-diketones he used were all alicyclic); and all the studies[3] thus far of reactions of cyclic β-diketones with Grignard reagents furnish no basis for prediction of cleavage of the type of cyclic β-diketone as represented by dimedone since all those studied were non-enolizable substances.

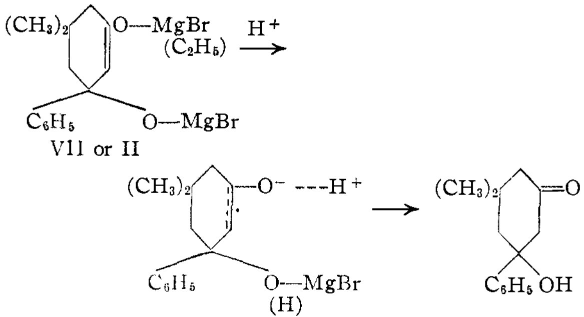
Dimedone is quite insoluble in ether and, therefore, the introduction of the diketone into the Grignard reagent solution presented a problem which was solved by using the Soxhlet extraction procedure—the first instance of such a procedure in a Grignard reaction which has been reported.[4] It has been known that certain products of such a Grignard reaction are altered by the procedure that is used for isolation. In this instance aqueous ammonium chloride was used for the decomposition of the Grignard complex which was kept cold during the addition. No solid could be isolated from the ethereal solution of the products or from the solution which was obtained by replacing ether with petroleum ether. Therefore removal of diphenyl and bromobenzene was accomplished by steam distillation and the following three products obtained by fractional distillation at low pressure. Three products were isolated: (1) the α,β-unsaturated ketone (IV), 16–30%; (2) a higher boiling hydrocarbon (V), 18–38% (whose structure is subsequently elucidated); and (3) a tar. The yield of 5,5-dimethyl-3-phenyl-Δ^2-cyclohexenone (IV) was too low and the procedure too complicated for this method to have any preparative value. However, the structure of the hydrocarbon (V) and the nature of the tar was of considerable interest. The identity of the hydrocarbon and the nature of the tar were elucidated by the study of the reaction of phenylmagnesium bromide with the ethyl enol ether of dimedone (VI) prepared by a modification of the procedure of Crossley and Renouf.[5]

Dimedone ethyl ether (VI), which is readily soluble in ether, reacts smoothly with phenylmagnesium bromide, and from this reaction, after mild treatment for decomposing the Grignard addition complex, no evidence of the alcohol (III) could be obtained—only the α,β-unsaturated ketone (IV) could be isolated, and this in good yield.



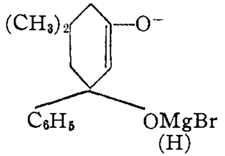
VI VII IV

The inability to isolate the alcohol (III) is not unusual if one examines the structures preceding its possible creation, the Grignard complex from either the enol ether (VII) or substance (II) from dimedone in the reaction with phenylmagnesium bromide



VII or II VIII III

It is proposed that substance (VIII), an intermediate of hydrolysis of the Grignard addition complex, will react further by either of two processes: (A) ketonization (whence H$^+$ migrates to the β-carbon of the ethylene link—or some equivalent proton donating–accepting process), or (B) ejection of the OMgBr$^-$ or OH$^-$ ion thus leading directly to the α,β-unsaturated ketone (IV). In other words we postulate that if the ion IX exists, it proceeds directly by mechanism (B) rather than (A) and thus the alcohol (III) never did exist.[6] The product of the reaction of the ethyl enol ether of dimedone is, of course, identical with compound (IV), 5,5-dimethyl-3-phenyl-Δ^2-cyclohexenone, obtained from the addition of dimedone to the solution of phenylmagnesium bromide.



IX

The reaction of 5,5-dimethyl-3-phenyl-Δ^2-cyclohexenone (IV) with phenylmagnesium bromide proceeded smoothly whereby a hydrocarbon was isolated in fair yield. This compound was identical with the hydrocarbon (V) encountered in 18–38% yield in the reaction of dimedone with phenyl-

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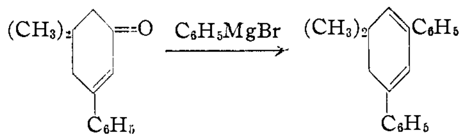
[3] Geissman and Tulagin, This Journal, **63**, 3352 (1941); Geissman and Morris, *ibid.*, **66**, 716 (1944); Geissman and Tulagin, *ibid.*, **66**, 719 (1944); Erickson and Kitchens, *ibid.*, **68**, 482 (1946).

[4] Indeed, since no instance of a reaction of dimedone, a most available diketone, with any Grignard reagent has been reported, it is presumed that this situation has occurred because of the high insolubility of dimedone in ether (as well as all relatively non-polar solvents).

[5] Crossley and Renouf, *J. Chem. Soc.*, **93**, 640 (1908).

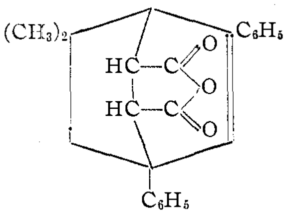
[6] A similar observation has been made by Kohler and Erickson, who reported that tetraphenylpropenone is the product isolated from the reaction of phenylmagnesium bromide on phenyldibenzoylmethane under conditions which did not cause cleavage. Unfortunately, the ethereal solution of the Grignard product was poured onto iced acid (This Journal, **53**, 2306 (1931)).

magnesium bromide. But here, too, a quantity of tar was obtained.



IV V

It was found that 5,5-dimethyl-1,3-diphenylcyclohexadiene-1,3 (V) progressively polymerizes yielding a tar which is believed to be the tar obtained as a residue in the reaction of dimedone with phenylmagnesium bromide. In spite of the tendency of this hydrocarbon to polymerize, this compound, which can be considered to be composed of two styrene-like and one butadiene structure, is capable of being recrystallized from alcohol and petroleum ether in which solvents the hydrocarbon has a surprising stability. The hydrocarbon (V) reacts readily with maleic anhydride to yield an addition product for which the structure (X) is written. The product isolated was the dibasic acid.



X

It then follows that although dimedone is strongly enolic under usual conditions, ether extracts of dimedone act toward phenylmagnesium bromide as if appreciable quantities of the β-diketone form are present. This would account for the formation of the hydrocarbon (V). Correspondingly, the amount of 5,5-dimethyl-3-phenyl-Δ^2-cyclohexenone formed in the same reaction comes from the smaller amount of enol form of dimedone in the ether extract in the reaction with phenylmagnesium bromide.

The addition of ethyl cyanoacetate to 5,5-dimethyl-3-phenyl-Δ^2-cyclohexenone (IV) in the Michael reaction would yield substances that would be precursors of morphine-like compounds. The similarity of compound (XII) to morphine is obvious. However, Koelsch[7] has correctly anticipated that this type of Michael reaction will not occur or, if it does, the equilibrium will not be very favorable. Such is the case, for it was impossible to obtain any evidence of an addition compound of 5,5-dimethyl-3-phenyl-Δ^2-cyclohexenone in the Michael reaction carried out under any of various procedures with ethyl cyanoacetate, diethyl malonate or nitromethane.

Experimental

Reaction of Dimedone with Phenylmagnesium Bromide.—An ethereal solution (1400 ml.) of phenylmagnesium bromide from 1.5 mole of bromobenzene and magnesium was prepared in the pot of a Soxhlet extractor. Dimedone (75 g.) was placed in the extraction thimble. Extraction of the dimedone into the Grignard reagent solution (stirring) was carried out for thirty-two hours. At the end of this time 50 g. (0.35 mole) of dimedone had been extracted. To the ethereal solution (cold, stirring) was added aqueous ammonium chloride. The ether layer was washed several times with water and dried over sodium sulfate. No crystals could be obtained from this solution at any time on concentrating by removing ether under reduced pressure. The ether was removed as completely as possible and the oil redissolved in petroleum ether (30–60°). This solution was then slowly reduced in volume as above and again no crystals were obtained.

The petroleum ether was removed and the oil subjected to steam distillation until most of the diphenyl had been removed. The undistilled oil was extracted with ether and the ethereal solution dried over sodium sulfate. After removal of the ether, the residue was distilled under reduced pressure to yield the following products:

(A) **5,5-Dimethyl-3-phenyl-Δ^2-cyclohexenone** (IV) gave a b. p. 110–135° (0.1 mm.) yield, 21.5 g. (31%). This product was contaminated with diphenyl. Several recrystallizations of this product from petroleum ether (30–60°) yielded white crystals, m. p. 54–54.5°.

Anal. Calcd. for $C_{14}H_{16}O$: C, 84.07; H, 8.00. Found: C, 84.22, 84.57; H, 7.70, 7.88.

The oxime of this substance prepared in the usual manner upon recrystallization from ethyl alcohol–water, yielded white needles, m. p. 156–157°.

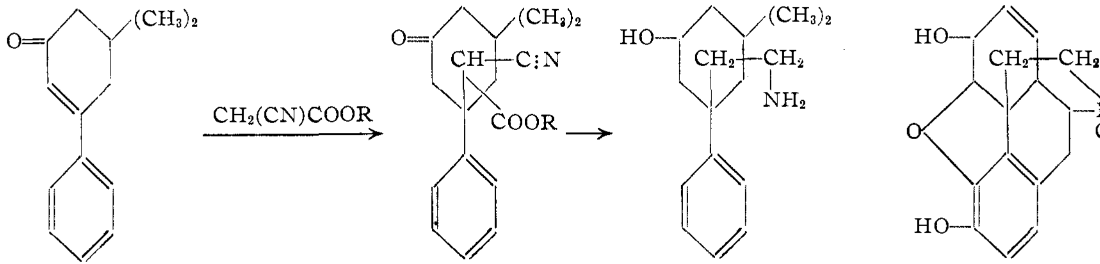
Anal. Calcd. for $C_{14}H_{17}ON$: C, 78.18; H, 7.91. Found: C, 77.97, 78.13; H, 7.64, 7.84.

The red 2,4-dinitrophenylhydrazone of 5,5-dimethyl-3-phenyl-Δ^2-cyclohexenone was prepared in the usual manner, m. p. 171–172°.

Anal. Calcd. for $C_{20}H_{20}O_4N_4$: C, 63.14; H, 5.30. Found: C, 63.28, 62.96; H, 5.43, 5.50.

(B) **5,5-Dimethyl-1,3-diphenylcyclohexadiene-1,3** (V) gave a b. p. 150–165° (0.1 mm.); yield 15.9 g. (18%). This product was recrystallized from ethyl alcohol and then from petroleum ether (30–60°) to yield coarse white crystals, m. p. 55–55.5°.

Anal. Calcd. for $C_{20}H_{20}$: C, 92.25; H, 7.73. Found: C, 92.17, 92.38; H, 7.68, 7.72.



IV XI XII Morphine

This substance was at first confused with the α,β-un-

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(7) Koelsch, This Journal, 67, 568 (1945).

saturated ketone above since they both have essentially the same melting point. But on mixing the two crystals at room temperature a liquid melt was obtained.

(C) A tar, the weight of which was 10–20 g., was always obtained.

5,5-Dimethyl-3-phenyl-Δ^2-cyclohexenone (IV).—To a solution (800 cc.) of phenylmagnesium bromide prepared from one mole of bromobenzene was added slowly ethyl enol ether of dimedone which was prepared according to the directions of Crossley and Renouf[6] (84 g., 0.5 mole) in 250 cc. of ether. The reaction was quite vigorous. After addition of dilute hydrochloric acid to the well-chilled Grignard reaction mixture, the ether layer was well washed with water and aqueous sodium bicarbonate. Evaporation of the ether yielded a brownish crystalline mass which, upon recrystallization from petroleum ether (30–60°), yielded coarse crystals of 5,5-dimethyl-3-phenyl-Δ^2-cyclohexenone; m. p. 54–54.5°; yield was 74 g., 74%. This product and its derivatives were identical with the α,β-unsaturated ketone obtained in (A) under the reaction of dimedone with phenylmagnesium bromide.

Reduction of 5,5-dimethyl-3-phenyl-Δ^2-cyclohexenone with Adams catalyst proceeded smoothly in alcohol. When one mole of hydrogen had been absorbed, the hydrogenation was arrested. Evaporation of this solution and recrystallization of the product in petroleum ether (30–60°) yielded white crystals, m. p. 46–47°, of 5,5-dimethyl-3-phenylcyclohexanone.

Anal. Calcd. for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 83.03, 83.11; H, 9.09, 9.12.

The oxime of this ketone prepared in the usual manner melted at 165° (mixed melting point with original α,β-unsaturated ketone oxime gave a 30° depression).

Anal. Calcd. for $C_{14}H_{19}ON$: C, 77.38; H, 8.81. Found: C, 77.53, 77.61; H, 8.93, 8.99.

The yellow 2,4-dinitrophenylhydrazone of 5,5-dimethyl-3-phenylcyclohexanone, m. p. 157–158°, gave a 12° depression with the red 2,4-dinitrophenylhydrazone of the α,β-unsaturated ketone.

Anal. Calcd. for $C_{20}H_{22}O_4N_4$: C, 62.81; H, 5.80. Found: C, 62.66, 62.53; H, 5.62, 5.63.

Preparation of 5,5-Dimethyl-1,3-diphenylcyclohexadiene-1,3 (V).—5,5-Dimethyl-3-phenyl-Δ^2-cyclohexenone (20 g., 0.1 mole) in 150 cc. of dry ether was added to an ethereal solution (600 cc.) of phenylmagnesium bromide prepared from 0.5 mole of bromobenzene. The Grignard reaction mixture was refluxed for one-half hour after addition of the ketone. After decomposing the Grignard addition complex with aqueous hydrochloric acid, the ether layer was washed several times with water and finally with sodium bicarbonate solution. After removal of the solvent, the residue was distilled to yield 14 g. (54%) of an oil, b. p. 144–150° (0.07 mm.), which solidified in the receiver. Recrystallization of this product from petroleum ether yielded white crystals, m. p. 55°, which were identical with the earlier obtained sample of 5,5-dimethyl-1,3-diphenyl-cyclohexadiene-1,3 from the reaction of dimedone with phenylmagnesium bromide.

Addition Product from Maleic Anhydride and 5,5-Dimethyl-1,3-diphenylcyclohexadiene-1,3 (X).—Maleic anhydride (1.96 g., 0.02 mole) and 5,5-dimethyl-1,3-diphenylcyclohexadiene-1,3 (5.2 g., 0.02 mole) were heated at 120° for one hour and cooled. The glass which formed on cooling was broken out from the flask and ground. The powder was warmed with 10% sodium hydroxide and the solution filtered. The filtrate was made acid with dilute hydrochloric acid, whereupon solid precipitated. The solid, upon recrystallization from acetone, yielded 4 g. of the dibasic acid of (X) as a white powder, m. p. 188°, (with evolution of water).

Anal. Calcd. for $C_{24}H_{24}O_4$: C, 76.57; H, 6.42. Found: C, 76.37, 76.64; H, 6.56, 6.57.

Attempted Michael Reaction with 5,5-Dimethyl-3-phenyl-Δ^2-cyclohexenone.—The procedures used were the same with all three active methylene compounds, ethyl cyanoacetate, nitromethane and diethyl malonate. Equal molar quantities (0.1 mole) of the α,β-unsaturated ketone and the methylene compound in 10 cc. of absolute alcohol were: (1) refluxed with 1 cc. of piperidine as catalyst, (2) refluxed with a trace of sodium ethylate, and (3) refluxed in the presence of an equal molar quantity of sodium ethylate. The 2,4-dinitrophenylhydrazones of each sample were precipitated and isolated in stepwise fashion in order to detect more easily any product obtained other than the starting α,β-unsaturated ketone. Each sample was tested as follows: a portion of the mixture was withdrawn and added to an acidic (hydrochloric acid) solution of 2,4-dinitrophenylhydrazine (one-fifth the calculated quantity for ketone in the sample). The precipitated 2,4-dinitrophenylhydrazone was removed by filtration, and to the filtrate another equal sample of 2,4-dinitrophenylhydrazine was added and a new precipitate isolated. This procedure was continued until no further 2,4-dinitrophenylhydrazone was obtained. In all instances the 2,4-dinitrophenylhydrazones were identical with the 2,4-dinitrophenylhydrazone of 5,5-dimethyl-3-phenyl-Δ^2-cyclohexenone.

Summary

1. The reaction of dimedone with phenylmagnesium bromide has been studied and the products, 5,5-dimethyl-3-phenyl-Δ^2-cyclohexenone and 5,5-dimethyl-1,3-diphenylcyclohexadiene-1,3, have been elucidated.

2. A method of preparation of 5,5-dimethyl-3-phenyl-Δ^2-cyclohexenone has been reported.

3. The failure of the Michael reaction with 5,5-dimethyl-3-phenyl-Δ^2-cyclohexenone was observed.

COLLEGE PARK, MARYLAND RECEIVED MARCH 19, 1947