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

CONJUGATE BIMOLECULAR REDUCTION OF MESITYL PHENYL KETONE

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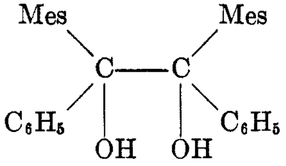
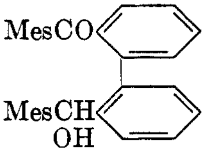
Mesityl phenyl ketone and other similarly hindered ketones, unable for the most part to undergo 1,2-addition with organometallic compounds, exhibit a remarkable capacity to condense with such reagents in the conjugate manner. Perhaps the outstanding example is the nuclear alkylation of duryl phenyl ketone by the action of *tert*-butyl, benzyl (1), and *sec*-butyl (2) Grignard reagents.

The object of the present work was to determine whether pinacol formation would likewise be inhibited and, if so, whether nuclear condensation might be realized. Previous work (3) had shown the mesityl α-mesitylvinyl ketone undergoes bimolecular reduction when treated with the binary mixture, $Mg + MgI_2$ (4). When mesityl phenyl ketone[1] was treated with this reagent, a product was obtained which is similar in composition and melting point to the pinacol (I) described by Kharasch, Morrison, and Urry (5). The product is not a pinacol, however, but a hydroxy ketone; the infrared spectrum indicates the presence of both a hydroxyl and a keto group.[2]



I

The presence of a hydroxyl group was confirmed by reactions of the compound. It reacts with acetic acid to yield a keto ester, readily forms ethers, and is converted to a monochloro derivative by the action of acetyl chloride. Further study has shown that the hydroxy ketone actually has structure II, being the product of a bimolecular reduction involving two *ortho* positions.[3]



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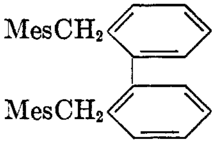

III

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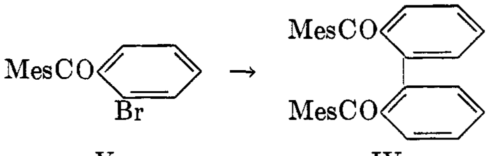
[1] In this paper Mes is used to represent mesityl.

[2] The authors are indebted to Miss Elizabeth Petersen for measuring and interpreting the infrared spectra mentioned in this paper.

[3] Although the hydroxy ketone has the same empirical formula as the original ketone, and therefore is not actually a reduction product, it is considered that its formation involves reduction followed by loss of two hydrogen atoms or the equivalent.

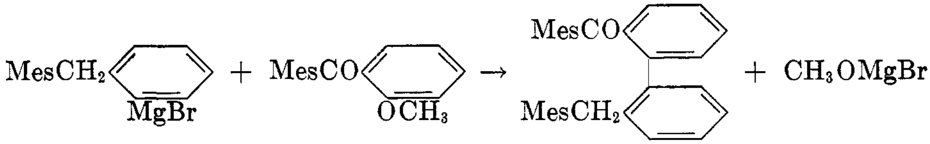
The skeletal structure of the hydroxy ketone (II) was established by reducing the compound to the corresponding hydrocarbon (III) with sodium and alcohol. This hydrocarbon, in turn, could be formed by reduction of the corresponding



V IV

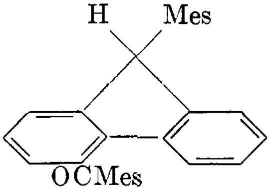
known diketone (IV) (6), which is readily made from *o*-bromophenyl mesityl ketone (V) by the Ullmann procedure.

The proof of structure of the keto alcohol (II) was completed by its conversion to two derivatives. Oxidation with chromic acid transforms it to the known diketone (IV). Reduction with hydriodic acid converts the carbinol group to a methylene group, producing the ketone, VI. This ketone was prepared also by condensation of the Grignard reagent (VII) from *o*-bromophenylmesitylmethane with mesityl *o*-methoxyphenyl ketone (VIII).



VII VIII VI

Dehydration of the keto alcohol (II) occurs when it is treated with certain acidic reagents. The product, believed to be 4-mesitoyl-9-mesitylfluorene (IX), was obtained in a similar way from the acetate and from the ethyl ether of the hydroxy ketone (II). Structure IX has been assigned on the basis of the analogy



IX

with the behavior of 2-phenylbenzohydrol, which yields 9-phenylfluorene under comparable conditions (7). In the synthesis of 4-hydroxy-1,9,9-trimethylfluorene (8) ring closure of this type occurs at a position *meta* to a hydroxyl group. Intramolecular alkylation at a position *meta* to a *meta*-directing group is also known to occur in the cyclization of diphenic acid, which, by treatment with acids, is converted to fluorenone-4-carboxylic acid (9).

It should be mentioned that the hydroxy ketone (II) is not the only product of the reduction of mesityl phenyl ketone. Under slightly different conditions of reaction two other compounds have been isolated, which are isomers having the empirical formula $C_{32}H_{32}O$. One, a yellow substance (m.p. 198°), was originally located by Speck (10). The other (m.p. 172°) is formed by thermal rearrangement of the yellow compound. The structures of these compounds will be the subject of a following paper.

EXPERIMENTAL

Bimolecular reduction of mesityl phenyl ketone. A 500-ml., three-necked flask was equipped with an air-tight stirrer, a dropping funnel, and a reflux condenser fitted with a rubber balloon to exclude the air. In this flask were placed 30 g. of powdered magnesium,[4] 22 g. of iodine, 180 ml. of dry toluene, and 60 ml. of dry butyl ether. To the refluxing, colorless mixture 60 g. of mesityl phenyl ketone, melted with 15 ml. of toluene, was added at a rapid rate. After a short time, the reaction mixture became deep red in color.

Two to three hours later, the balloon on the condenser was replaced by a stopper and the flask was cooled, first with cold water and then for one hour with an ice-bath. The reaction mixture was decanted from the unused magnesium and poured into a mixture of 60 ml. of concentrated hydrochloric acid, 2 l. of crushed ice, and 1 l. of ether. After being shaken for a short time, the mixture became bright red. The ether layer was washed in quick succession with 2 1-l. portions of water, and finally with 5% sodium bicarbonate solution. Evaporation of the solvent by use of a water aspirator and the heat of a steam cone was continued until the volume had been reduced to about 150 ml. at which time crystals began to form. After being allowed to stand at 0° overnight, the crude product was washed with two portions of acetone. The yield was 6.35 g. (10.5%) of crude product, m.p. 229–233°. Recrystallization from 500 ml. of ethyl acetate gave colorless, hexagonal plates, m.p. 239–240°.

Anal.[5] Calc'd for $C_{32}H_{32}O_2$: C, 85.68; H, 7.19.
Found: C, 85.88; 85.71; H, 7.24; 7.17.

Infrared analysis showed absorption bands at 1658, 1611, 1594, and 3439 cm.$^{-1}$, which are characteristic, respectively of the carbonyl, mesityl, phenyl, and hydroxyl groups.

Preparation of the chloride from the keto alcohol. A mixture of 3.74 g. of the keto alcohol and 50 ml. of acetyl chloride was heated under reflux for 4 hours. Removal of the excess acetyl chloride *in vacuo* left a residue, which was recrystallized from high-boiling petroleum ether to yield 3.00 g., or 77%, of the chloride. The prisms melted at 164–166° with decomposition.

Anal. Calc'd for $C_{32}H_{31}ClO$: C, 82.28; H, 6.69.
Found: C, 82.63; 82.62; H, 7.00; 6.66.

Infrared analysis showed bands at 1670, 1611, and 1596 cm.$^{-1}$, which are characteristic of the carbonyl, mesityl, and phenyl groups, respectively.

This chloride was hydrolyzed to the keto alcohol by the action of alcoholic potassium hydroxide.

Preparation of the ethyl ether of the keto alcohol. The keto alcohol (2 g.) was suspended in 250 ml. of absolute alcohol. A rapid stream of anhydrous hydrogen chloride was bubbled through the mixture for 10 minutes, and the solution was heated under reflux for one hour (11). At the end of this time, the volume of alcohol was reduced to 30 ml. by distillation. After the mixture had stood overnight 1.84 g. (87%) of needles were obtained. Recrystallization of the compound from alcohol gave m.p. 151–152°.

Anal. Calc'd for $C_{34}H_{36}O_2$: C, 85.67; H, 7.61.
Found: C, 85.80; 85.50; H, 7.60; 7.77.

Infrared analysis showed absorption bands at 1671, 1611, and 1596 cm.$^{-1}$, which are characteristic of the carbonyl, mesityl, and phenyl groups, respectively.

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[4] The magnesium used was that obtained from Baker and Adamson, Code 1900.

[5] The microanalyses were performed by Miss Emily Davis and Miss Rachel Kopel.

This ether was also obtained from the chloride by heating under reflux with absolute alcohol containing a few drops of pyridine (12). An attempted reduction of the keto alcohol by use of Adams' catalyst in alcohol at room temperature and a pressure of 50 p.s.i. gave the same ether.

Preparation of the acetate of the keto alcohol. A. *From the chloride.* The procedure of Gomberg and Davis (13) was modified so that 1 g. of the chloride in 50 ml. of dry benzene and 0.4 g. of silver acetate were heated under reflux, with the exclusion of moisture, for 3 hours. After removal of the precipitated silver chloride and evaporation of most of the benzene *in vacuo*, the addition of alcohol induced crystallization. The yield of pure product (m.p. 164–165°) was 0.88 g., or 84%.

B. *From the keto alcohol. By use of the pinacol-pinacolone rearrangement reagent of Gomberg and Bachmann* (4). A mixture of 0.5 g. of the keto alcohol, 3 ml. of acetic acid, and a trace of iodine was boiled for 3 minutes. Long prisms formed when the solution was cooled. Recrystallization from alcohol gave 0.30 g. (55%) of the same product, m.p. 164–165°.

Anal. Calc'd for $C_{34}H_{34}O_3$: C, 83.22; H, 6.99.

Found: C, 83.37; H, 7.26.

Infrared analysis showed bands at 1734, 1670, 1610, and 1596 cm.$^{-1}$, which are characteristic of the ester carbonyl, carbonyl, mesityl, and phenyl groups, respectively.

In an attempt to reduce the hydroxy ketone with zinc and acetic acid, the ester was formed in good yield. Heating a mixture of 1 g. of the keto alcohol in 15 ml. of glacial acetic acid with a trace of *p*-toluenesulfonic acid produced the ester in a yield of 0.79 g.

The keto alcohol was recovered quantitatively from the acetate by saponification with alcoholic potassium hydroxide.

Reduction of the keto alcohol. Treatment of 1.23 g. of keto alcohol (II) for one-half hour with a 60-ml. refluxing mixture of equal volumes of glacial acetic acid, acetic anhydride, and 48% hydriodic acid gave a solid, which was recrystallized from ethyl acetate; yield 0.87 g., or 73%. This product was shown to be identical with that (VI) prepared by the alternate synthesis which is described in the following section. The two products had identical infrared spectra, and a mixture melting point showed no depression.

Alternate synthesis of the reduction product (VI). *o*-Bromophenylmesitylmethane was prepared from *o*-bromobenzyl chloride and mesitylene by the Friedel-Crafts method. It crystallized from alcohol in colorless prisms, m.p. 61–62°.

Anal. Calc'd for $C_{16}H_{17}Br$: C, 66.44; H, 5.93.

Found: C, 68.63; H, 6.30.

A Grignard reagent was made by treating 14.5 g. of the bromo compound with 4.8 g. of magnesium in a mixture of 100 ml. of ethyl ether and 100 ml. of butyl ether to which 0.1 g. of methyl iodide had been added. The reaction mixture was stirred under reflux for 24 hours and filtered. A solution of 12.7 g. of mesityl *o*-methoxyphenyl ketone in 50 ml. of dry benzene was then added, and the solution stirred under reflux for 24 hours. The brown solution was decomposed with dilute hydrochloric acid, and the resulting mixture shaken with ether. After the ether solution had been washed with dilute acid, the solvents were removed by distillation *in vacuo*. The product (7.8 g., or 33%) crystallized in prisms from ethyl acetate; m.p. 220–221°.

Anal. Calc'd for $C_{32}H_{32}O$: C, 88.84; H, 7.46.

Found: C, 88.72; H, 7.44.

Oxidation of the keto alcohol. A solution of 4 g. of the keto alcohol, 100 ml. of benzene, and 50 ml. of acetic acid was added slowly, with stirring, to a mixture of 6.8 g. of sodium dichromate, 9 ml. of concentrated sulfuric acid, 5 ml. of acetic acid, and 30 ml. of water at room temperature. After the mixture had been stirred overnight, water was added, and the product extracted with benzene. The benzene solution was washed successively with water, 5% potassium hydroxide solution, and water. Evaporation of the solvent left 3.7 g. (92%) of crude product. It crystallized from toluene in needles, melting at 225–227°. A mixture melting point with 2,2'-dimesitoylbiphenyl showed no depression.

Preparation of 2,2'-dimesitoylbiphenyl. By use of the procedure of Fuson and Cleveland

(14), 25 g. of *o*-bromophenyl mesityl ketone was treated with 20 g. of copper bronze at 210° for 90 minutes. Extraction with hot toluene gave 14.5 g. (80%) of the coupled product, which after recrystallization from toluene gave needles, m.p. 226–227° (corr.) [Literature m.p. 219–220° (6)].

Anal. Calc'd for $C_{32}H_{30}O_2$: C, 86.06; H, 6.77.
Found: C, 86.29; H, 6.96.

Reduction of 2,2'-dimesitoylbiphenyl with sodium and alcohol.[6] The diketone (10 g.) was dissolved in a mixture of 300 ml. of absolute alcohol and 50 ml. of dry toluene. After the addition of 30 g. of sodium, the mixture was heated under reflux until the sodium had dissolved (about 2 hours). The mixture was decomposed by the addition of alcohol and then pouring on ice. Extraction with ether and evaporation of the solvent yielded a yellow oil which was induced to crystallize by the addition of acetone. The crude white crystals weighed 0.95 g. (10%); m.p. 205–208°. Repeated recrystallization of the hydrocarbon from an alcohol-benzene mixture and from acetone followed by vacuum sublimation gave m.p. 216–218° (corr.).

Anal. Calc'd for $C_{32}H_{34}$: C, 91.81; H, 8.19.
Found: C, 91.49; H, 7.78.

Infrared analysis showed the absence of both carbonyl and hydroxyl frequencies. This same hydrocarbon was obtained from the keto alcohol in about 30% yield.

Cyclization product (IX) *of the keto alcohol.* A. *From the keto alcohol*: A solution of 2 g. of the keto alcohol in 40 ml. of glacial acetic acid was heated with 0.04 g. of *p*-toluenesulfonic acid for 1 hour under reflux. When the solution was cooled, needles formed. The yield of the pure product after recrystallization from a benzene-alcohol mixture was 1.55 g., or 85%; m.p. 174–175°.

Anal. Calc'd for $C_{32}H_{30}O$: C, 89.26; H, 7.02.
Found: C, 89.06; H, 7.27.

This same product was obtained in a 50% yield by treatment of the keto alcohol with 85% phosphoric acid at reflux temperature for 14 hours.

B. *From the acetate.* A solution of 0.5 g. of the acetate of the keto alcohol in 10 ml. of toluene and 0.01 g. of *p*-toluenesulfonic acid was heated under reflux for 10 hours. After the removal of most of the solvent *in vacuo*, the addition of alcohol induced crystallization. The yield was 0.30 g., or 68%. The product was identified by the method of mixture melting points.

C. *From the ethyl ether.* By use of a procedure similar to that of Norris and Young (15) 0.7 g. of the ether dissolved in 100 ml. of absolute ethyl ether was treated for 6 hours with 2.0 g. of anhydrous aluminum chloride at room temperature. The dark solution was decomposed by the addition of water and hydrochloric acid. After being washed with water and dilute alkali, the ether layer was dried and evaporated. The crude product was recrystallized from alcohol; yield of cyclization product 0.42 g., or 65%. The compound was shown by the method of mixture melting points to be the same fluorene derivative (IX) as that obtained from the keto alcohol.

SUMMARY

Treatment of mesityl phenyl ketone with the binary mixture, Mg + MgI_2 produces the keto alcohol, II. Oxidation with chromic acid converts the keto alcohol to the corresponding diketone (IV), which is known. Reduction with hydriodic acid transforms the hydroxy ketone to the ketone, VI, which has been made by an independent synthesis.

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[6] The reductions with sodium and alcohol were performed in a manner similar to that employed by Fuson and McKusick (1).

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