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

Conjugate Addition of *t*-Butylmagnesium Chloride to *o*-Hydroxy Diaryl Ketones[1]

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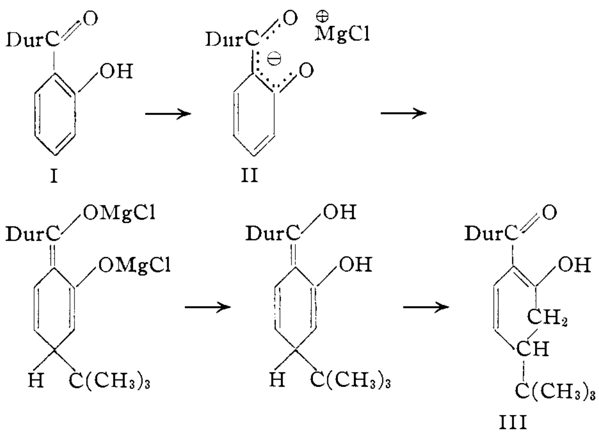
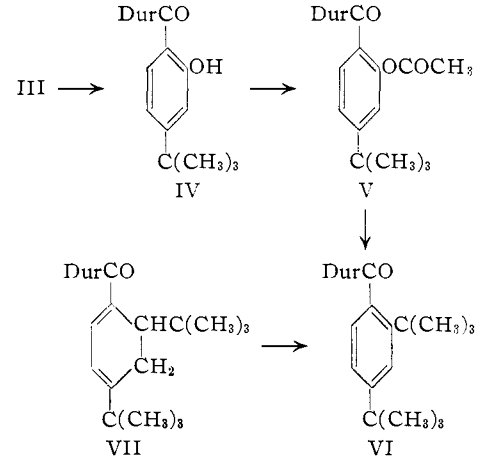
Four *o*-hydroxyl diaryl ketones have been found to condense with *t*-butylmagnesium chloride to give dihydro derivatives of the corresponding 2-hydroxy-4-*t*-butyl compounds. Duryl 2-hydroxyphenyl ketone (I, in text) gave a duryl 2-hydroxy-4-*t*-butyldihydrophenyl ketone, presumably the 3,5-dihydro derivative (III, in text), in a yield of 82%. The acetate of the dehydrogenation product was converted to 2,4-di-*t*-butylphenyl duryl ketone by treatment with the *t*-butyl reagent. The di-*t*-butyl ketone was identified by an independent synthesis. 2-Hydroxy-1-naphthyl mesityl ketone gave a similar product in 91% yield. The relatively unhindered ketones, 2-hydroxy-1-naphthyl phenyl ketone and 2-hydroxybenzophenone, behaved in a similar way, the products being obtained in yields of 17 and 28%, respectively.

The conjugate addition of Grignard reagents to phenolic ketones, realized earlier with duryl 4-hydroxyphenyl ketone,[2] now has been extended to a number of *o*-hydroxy diaryl ketones, the reagent in all cases being *t*-butylmagnesium chloride. Duryl 2-hydroxyphenyl ketone (I) has been found to give a duryl 2-hydroxy-4-*t*-butyldihydrophenyl ketone, which is presumably the 3,4-dihydro derivative III, in a yield of 82%. The transformation may be represented as follows, the critical step being the condensation of the Grignard reagent with the resonance-stabilized enolate II.



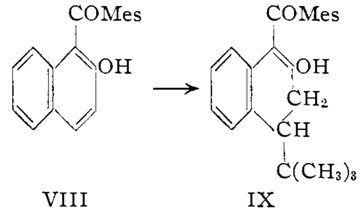
The dihydro compound III underwent dehydrogenation when heated with a palladium-on-carbon catalyst, and the resulting ketone IV yielded an acetate V when heated with acetic anhydride in the presence of pyridine. When the acetate was treated with the *t*-butyl Grignard reagent, the acetoxyl group was displaced by the *t*-butyl radical. The 2,4-di-*t*-butyl derivative VI was obtained in a yield of 66%. Acyloxyl groups in the *para* position had been displaced by the hydrocarbon radical of a Grignard reagent,[3] but this is the first example of such a displacement at an *ortho* position. Moreover, it marks the first time a *t*-butyl group has been introduced into an *ortho* position without destruction of the aromaticity of the ring.

The structure of the di-*t*-butylphenyl ketone VI was established by an independent synthesis, which



consisted in the dehydrogenation of 2,4-di-*t*-butyl-2,3-dihydrophenyl duryl ketone (VII).[4]

Similar results were obtained with 2-hydroxy-1-naphthyl mesityl ketone (VIII). This ketone was prepared by condensing 2-methoxynaphthalene with mesitoyl chloride by the Friedel–Crafts method, and demethylating the resulting methoxy ketone with aluminum chloride. The phenolic ketone reacted with the *t*-butyl Grignard reagent to give 2-hydroxy-4-*t*-butyl-3,4-dihydro-1-naphthyl mesityl ketone (IX) in a yield of 91%.



The new ketone IX gave a purplish-blue color with ferric chloride solution. It formed an acetate but not an oxime. Oxidation with permanganate converted it to mesitoic and phthalic acids. The presence of the enolic ketone system is supported by the infrared spectrum. The virtual disappearance of the hydroxyl band and the unusual shift of carbonyl absorption to 1585 and 1567 cm.$^{-1}$ are indicative of strong chelation between the two functions. On the other hand, the acetate exhibits absorption bands corresponding to a normal conjugated carbonyl group.

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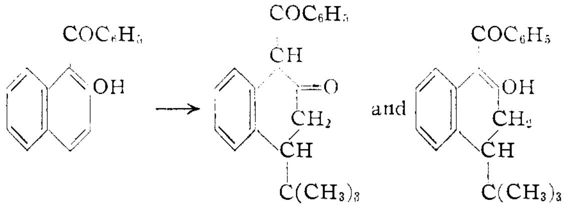
[1] This investigation was supported in part by a grant from the Office of Ordnance Research (Contract No. DA-11-022-ORD-874).

[2] R. C. Fuson, W. D. Emmons and G. W. Parshall, THIS JOURNAL, **76**, 5466 (1954).

[3] R. C. Fuson and W. D. Emmons, *ibid.*, **73**, 5175 (1951); R. C. Fuson and W. S. Friedlander, *ibid.*, **75**, 5410 (1953).

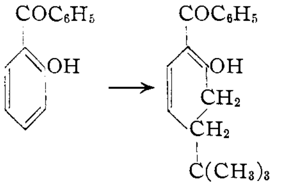
[4] R. C. Fuson, W. S. Friedlander and G. W. Parshall, *ibid.*, **76**, 5119 (1954).

In an effort to determine the role played by the hindering mesityl radical, the relatively unhindered analog, 2-hydroxy-1-naphthyl phenyl ketone (X), was studied. It reacted with the *t*-butyl Grignard reagent only under forcing conditions and yielded small amounts of two isomeric products. On the basis of elementary composition and infrared data, these were identified as 1-benzoyl-4-*t*-butyl-2-tetralone (XI) and its enol modification, 2-hydroxy-4-*t*-butyl-3,4-dihydro-1-naphthyl phenyl ketone (XII). Both formed pale yellow crystals, the enolic compound being the more soluble in ethanol.



X XI XII

2-Hydroxybenzophenone (XIII), in which steric hindrance must be slight, combined additively with the *t*-butyl reagent to give, in low yield, a product which, on the basis of elementary composition and infrared data, appears to be 2-hydroxy-4-*t*-butyl-3,4-dihydrophenyl phenyl ketone (XIV).



XIII XIV

Experimental[5]

Condensation of Duryl 2-Hydroxyphenyl Ketone with *t*-Butylmagnesium Chloride.—A solution of 12.8 g. of the ketone I[6] in 100 ml. of hot benzene was added rapidly to a Grignard reagent made from 6.08 g. of magnesium turnings, 28.0 g. of *t*-butyl chloride and 100 ml. of ether. The purple-red mixture was heated under reflux for one hour, with stirring, and decomposed with 600 ml. of a mixture of ice and water to which 60 ml. of hydrochloric acid had been added. The duryl 2-hydroxy-4-*t*-butyl-3,4-dihydrophenyl ketone (III), isolated in the usual way and recrystallized from ethanol. formed colorless crystals, m.p. 85.5–86.5°, yield 12.9 g. (82.1%).

Anal.[7] Calcd. for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.83; H, 9.27.

The compound gave a purple-blue coloration with ferric chloride solution. Its infrared spectrum[8] exhibits absorption bands assignable to a hindered, chelated carbonyl group (1641 cm.$^{-1}$), a conjugated ethylenic bond (1615 cm.$^{-1}$) and a chelated hydroxyl group (920 cm.$^{-1}$).

Duryl 2-Hydroxy-4-*t*-butylphenyl Ketone (IV).—A mixture of 1.00 g. of duryl 2-hydroxy-4-*t*-butyl-3,4-dihydrophenyl ketone and 0.10 g. of a palladium-on-carbon catalyst was heated at 250° for one hour. Some pale yellow impurities were removed by sublimation, and the black residue was extracted with boiling methanol. The crude product, recrystallized twice from methanol, formed colorless crystals, m.p. 183–184°, yield 0.55 g. (56%).

Anal. Calcd. for $C_{21}H_{26}O_2$: C, 81.25; H, 8.44. Found: C, 81.01; H, 8.54.

The compound gave a light pink coloration with ferric chloride solution. Its infrared absorption spectrum has bands assignable to a hindered, chelated carbonyl group (1635 cm.$^{-1}$) and a phenolic hydroxyl group (1343 cm.$^{-1}$).

The acetate V was made by heating a mixture of 0.42 g. of the hydroxy ketone, 2 ml. of acetic anhydride and 5 ml. of pyridine for 10 minutes. The product, recrystallized twice from methanol, formed colorless crystals, m.p. 172–173°, yield 0.39 g. (79%).

Anal. Calcd. for $C_{23}H_{28}O_3$: C, 78.37; H, 8.01. Found: C, 78.20; H, 7.92.

The infrared spectrum of the acetate has absorption bands assignable to a hindered, conjugated carbonyl group (1658 cm.$^{-1}$) and a vinyl ester carbonyl group (1765 cm.$^{-1}$).

2,4-Di-*t*-butylphenyl Duryl Ketone (VI).—A solution of 0.35 g. of 2-acetoxy-4-*t*-butylphenyl duryl ketone (V) in 15 ml. of hot benzene was added rapidly to a filtered Grignard reagent which had been prepared from 0.12 g. of magnesium turnings, 0.50 g. of *t*-butyl chloride and 15 ml. of ether. The deep red reaction mixture was heated under reflux for one hour, with stirring, and decomposed in the usual manner. The product was sublimed at 140° under a pressure of 0.1 mm. and then recrystallized from methanol. It formed colorless crystals, m.p. 155–156.5°, yield 0.23 g. (66%).

This compound was prepared also by dehydrogenation of 2,4-di-*t*-butyl-2,3-dihydrophenyl duryl ketone.[4] A mixture of the two samples melted at 155.5–157°. The infrared spectra of the two samples are identical.

Mesityl 4-Methoxy-1-naphthyl Ketone.[9]—A solution of 62.0 g. of mesitoyl chloride, 53.8 g. of 1-methoxynaphthalene and 100 ml. of carbon disulfide was added, dropwise and with vigorous stirring, to a cold mixture of 49.8 g. of aluminum chloride and 100 ml. of carbon disulfide. After completion of the addition, the brown mixture was stirred at room temperature for 12 hours. The mesityl 4-methoxy-1-naphthyl ketone, isolated by conventional procedures, crystallized from ethanol as yellow crystals, m.p. 120–121°, yield 77%.

Anal. Calcd. for $C_{21}H_{20}O_2$: C, 82.86; H, 6.62. Found: C, 82.87; H, 6.58.

The infrared spectrum of the compound has absorption bands at 1254 and 1659 cm.$^{-1}$, attributable, respectively, to an enol ether system and a hindered, conjugated carbonyl group.

4-Hydroxy-1-naphthyl Mesityl Ketone.—A solution of 15.0 g. of mesityl 4-methoxy-1-naphthyl ketone in 120 ml. of carbon disulfide was heated, under reflux, with 15.0 g. of anhydrous aluminum chloride for one hour and then stirred for 5 additional hours without heating. The very dark reaction mixture was poured into a mixture of 1 l. of ice-water and 100 ml. of hydrochloric acid. The dark red carbon disulfide layer was extracted with four 100-ml. portions of 5% sodium hydroxide solution. Acidification of the alkaline solution caused the product to separate. Three recrystallizations from benzene gave the pure, orange-yellow hydroxy ketone, m.p. 208–209°, yield 59%.

Anal. Calcd. for $C_{20}H_{18}O_2$: C, 82.73; H, 6.25. Found: C, 82.77; H, 6.40.

The infrared spectrum of this compound contains bands at 1638 and 3300 cm.$^{-1}$ attributable, respectively, to a hindered, conjugated carbonyl group and a hydroxyl group.

Mesityl 2-Methoxy-1-naphthyl. Ketone.—A mixture of 60.0 g. of anhydrous aluminum chloride and 180 ml. of carbon disulfide was cooled; and to it was added, dropwise with rapid stirring, a solution of 72.5 g. of mesitoyl chloride, 63.9 g. of 2-methoxynaphthalene and 160 ml. of carbon disulfide. After completion of the addition, which took 2 hours, the mixture was stirred at room temperature for 12 hours. The mesityl 2-methoxy-1-naphthyl ketone, after two recrystallizations from high-boiling petroleum ether, formed colorless crystals melting at 128–129.5°, yield 56.3%.

Anal. Calcd. for $C_{21}H_{20}O_2$: C, 82.86: H, 6.62. Found: C, 82.93; H, 6.72.

The infrared spectrum of this ketone exhibits bands assignable to a hindered, conjugated carbonyl group (1663 cm.$^{-1}$) and to an enol ether system (1237 cm.$^{-1}$).

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(5) All melting points are corrected.

(6) R. C. Fuson and W. C. Hammann, THIS JOURNAL, **73**, 1851 (1951).

(7) The microanalyses were carried out by Mrs. Katherine Pih, Mrs. Esther Fett, Mrs. Lucy Chang, Miss Emily Davis and Mr. Joseph Nemeth.

(8) The infrared spectra were determined and interpreted by Miss Helen Miklas and Mr. James Brader.

(9) This experiment was carried out by Dr. Victor Tullio.

2-Hydroxy-1-naphthyl Mesityl Ketone.—This compound was made by a procedure similar to that described for the demethylation of mesityl 4-methoxy-1-naphthyl ketone. From 15 g. of mesityl 2-methoxy-1-naphthyl ketone was obtained 10.8 g. (75.9%) of 2-hydroxy-1-naphthyl mesityl ketone. It crystallized from ethanol as light yellow needles, m.p. 110–110.5°.

Anal. Calcd. for $C_{20}H_{18}O_2$: C, 82.73; H, 6.25. Found: C, 82.55; H, 6.22.

This compound gave a dark red color with ferric chloride solution. Its infrared spectrum possesses a band assignable to a hindered, chelated carbonyl group (1623 cm.$^{-1}$) but none for a hydroxyl group.

Condensation of *t*-Butylmagnesium Chloride with 2-Hydroxy-1-naphthyl Mesityl Ketone.—A solution of 5.0 g. of the hydroxy ketone in 50 ml. of hot benzene was added rapidly to a Grignard reagent prepared from 2.07 g. of magnesium turnings, 9.3 g. of *t*-butyl chloride and 30 ml. of ether. The reaction mixture was heated under reflux, with stirring, for one hour and poured into a mixture of 500 g. of crushed ice and 50 ml. of hydrochloric acid. The light yellow organic layer was washed with two 200-ml. portions of water, dried over sodium sulfate and freed of solvents by distillation. Two recrystallizations of the residue from high-boiling petroleum ether produced 2-hydroxy-4-*t*-butyl-3,4-dihydro-1-naphthyl mesityl ketone as very slightly yellow crystals, m.p. 151–152.5°, yield 5.4 g. (91%).

Anal. Calcd. for $C_{24}H_{28}O_2$: C, 82.72; H, 8.10. Found: C, 82.74; H, 8.31.

This compound gave a purplish-blue color with ferric chloride solution. Its infrared spectrum has bands assignable to a hindered carbonyl group (1567 and 1585 cm.$^{-1}$) but none corresponding to a hydroxyl group.

The acetate was prepared by heating a mixture of 0.52 g. of the butylated ketone, 2 ml. of acetic anhydride and 5 ml. of pyridine for 10 minutes. The mixture was poured, with stirring, into 100 ml. of cold water, and the crude acetate was recrystallized twice from ethanol. It formed colorless needles melting at 173–174°, yield 0.48 g. (82%).

Anal. Calcd. for $C_{26}H_{30}O_3$: C, 79.96; H, 7.74. Found: C, 79.77; H, 7.68.

The infrared spectrum of this compound has absorption bands assignable to a conjugated ethylenic double bond (1642 cm.$^{-1}$), a hindered conjugated carbonyl group (1652 cm.$^{-1}$) and to a vinyl ester carbonyl group (1766 cm.$^{-1}$).

An attempt to prepare an **oxime** by treating 2-hydroxy-4-*t*-butyl-3,4-dihydro-1-naphthyl mesityl ketone with hydroxylamine hydrochloride in the presence of pyridine was unsuccessful, the ketone being recovered.

Oxidation of mesityl 2-hydroxy-4-*t*-butyl-3,4-dihydro-1-naphthyl ketone was accomplished by heating under reflux a mixture of 0.50 g. of the ketone, 2.00 g. of potassium permanganate, 1 ml. of 10% sodium hydroxide solution and 40 ml. of water for a period of 4.5 hours, at the end of which time the purple color had been discharged. The mixture was allowed to cool and then was acidified by careful addition of concentrated sulfuric acid. The acidic mixture was heated under reflux for 30 minutes and allowed to cool. The manganese dioxide was removed by the addition of 15 ml. of 5% sodium bisulfite solution. The mixture was extracted with 50 ml. of chloroform and then with two 50-ml. portions of ether.

The orange chloroform solution yielded mesitoic acid as slightly yellow crystals (from ethanol), m.p. 153°; a mixture with an authentic sample of the acid melted at 153–154°.

The colorless ether solution was found to contain phthalic acid, which, when recrystallized from water, melted at 192°, with decomposition; a mixture with an authentic sample of phthalic acid melted at 192° dec.

In attempts to effect etherification, 2-hydroxy-4-*t*-butyl-3,4-dihydro-1-naphthyl mesityl ketone was heated with methanol in the presence of hydrogen chloride and also was treated with methyl sulfate in the presence of sodium hydroxide. In each experiment the ketone was recovered unchanged.

In an effort to bring about dehydrogenation, mesityl 2-hydroxy-4-*t*-butyl-3,4-dihydro-1-naphthyl ketone was heated at 250° with a palladium-on-carbon catalyst for one hour in a nitrogen atmosphere. The ketone was recovered unchanged.

Condensation of 2-Hydroxy-1-naphthyl Phenyl Ketone.—This ketone, prepared by the method of Dischendorfer and Danziger,[10] failed to react with the *t*-butyl Grignard reagent under ordinary conditions. The following procedure then was employed. A solution of 5 g. of the ketone in hot benzene was added to a Grignard reagent prepared from 2.40 g. of magnesium turnings, 10.0 g. of *t*-butyl chloride and 80 ml. of ether. The mixture was heated under reflux, with vigorous stirring, for 48 hours and poured into 600 ml. of an ice–water mixture containing 40 ml. of hydrochloric acid.

The light yellow organic layer was washed with water and then with three 150-ml. portions of 5% sodium hydroxide solution. The organic layer, after being shaken with 5% sodium hydroxide solution, was dried over sodium sulfate and freed of solvents by evaporation. The light brown gummy residue was distilled *in vacuo*, the chief fraction being collected at 187° under a pressure of 0.06 mm. The orange-yellow glassy product so obtained, when recrystallized twice from ethanol, gave 1-benzoyl-4-*t*-butyl-2-tetralone (XI) as slightly yellow crystals, m.p. 157–158°, yield 0.92 g. (15%).

Anal. Calcd. for $C_{21}H_{22}O_2$: C, 82.32; H, 7.24. Found: C, 82.22; H, 7.44.

This compound gave no coloration with ferric chloride solution. Its infrared spectrum contains absorption bands at 1630 and 1682 cm.$^{-1}$ assignable to carbonyl group.

By concentration of the mother liquor a second product was isolated. Recrystallization from ethanol gave 2-hydroxy-4-*t*-butyl-3,4-dihydro-1-naphthyl phenyl ketone (XII) as pale yellow crystals, m.p. 118.5–119.5°, yield 1.04 g. (17%).

Anal. Calcd. for $C_{21}H_{22}O_2$: C, 82.32; H, 7.24. Found: C, 82.50; H, 6.98.

The compound gave a greenish-brown color with ferric chloride solution. Its infrared spectrum has bands assignable to a chelated carbonyl group (1630 cm.$^{-1}$), to a conjugated ethylenic bond (1611 cm.$^{-1}$) and weak hydroxyl absorption.

Condensation of 2-Hydroxybenzophenone with *t*-Butylmagnesium Chloride.—2-Hydroxybenzophenone (9.4 g.), prepared by the method of Ullmann and Goldberg,[11] was dissolved in 50 ml. of hot benzene, and the resulting solution was added rapidly to a Grignard reagent made from 6.0 g. of magnesium turnings, 28.0 g. of *t*-butyl chloride and 75 ml. of ether. The reaction mixture was heated under reflux, with stirring, for a period of 50 hours. The product, isolated in the usual way, was sublimed and then recrystallized from aqueous methanol. The 2-hydroxy-4-*t*-butyl-3,4-dihydrophenyl phenyl ketone separated in the form of pale yellow crystals, m.p. 74–75°, yield 3.5 g. (28%).

Anal. Calcd. for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86. Found: C, 79.53; H, 7.92.

The compound gave a purplish-blue coloration with ferric chloride solution. Its infrared spectrum has absorption bands assignable to a chelated carbonyl group (1635 cm.$^{-1}$) and conjugated ethylenic bond (1614 cm.$^{-1}$). There was also an indication of weak absorption in the hydroxyl region.

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[10] O. Dischendorfer and W. Danziger, *Monatsh.*, **48**, 335 (1927).

[11] F. Ullmann and I. Goldberg, *Ber.*, **35**, 2811 (1902).