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

Displacement of Methoxyl Groups in the β-Mesitoylnaphthalene Series with Grignard Reagents

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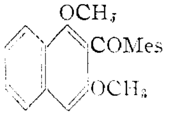
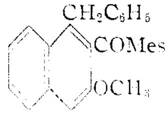
In 1,3-dimethoxy-2-naphthyl mesityl ketone the methoxyl group in the 1-position is replaced by the action of Grignard reagents whereas that in the 3-position is unattacked at ordinary temperatures. Similarly, Grignard reagents attack mesityl 3-methoxy-2-naphthyl ketone at the 1-position, the methoxyl group being unreactive.

Replacement of *o*-methoxyl groups by the hydrocarbon radical of a Grignard reagent has been realized with a number of substituted benzonitriles[2] and with hindered ketones of both the benzene and naphthalene[3] series.

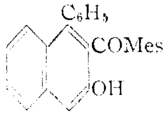
In 2,6-dimethoxyphenyl duryl ketone both methoxyl groups were replaced by methyl groups when the ketone was treated with the methyl Grignard reagent.[4] The present work was undertaken to determine whether both methoxyl groups in 1,3-dimethoxy-2-naphthyl mesityl ketone (I) could likewise be replaced. The possibility of displacement at the 3-position is of particular interest since that position is generally unreactive. It has been found that one of the methoxyl groups, assumed to be that in the 1-position, is readily replaced by a benzyl radical under the influence of the benzyl Grignard reagent, the methoxyl group in the 3-position being unaffected. Even at temperatures in the neighborhood of 75° the 1-benzyl-3-methoxy-2-naphthyl mesityl ketone (II) is not attacked by benzylmagnesium chloride. When "forcing" conditions were used with phenylmagnesium bromide, the 3-methoxyl group again resisted displacement. The only reaction observed at this position was cleavage of the ether to produce mesityl 1-phenyl-3-hydroxy-2-naphthyl ketone (III).



I

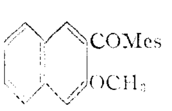


II

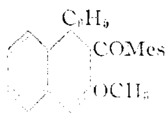


III

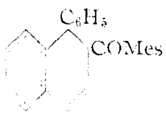
Similar results were obtained with mesityl 3-methoxy-2-naphthyl ketone (IV). Methylmagnesium iodide was without effect and phenylmagnesium bromide attacked the 1-position, giving the corresponding dihydro compound (V) in an 8% yield. It is a striking fact that the analogous reaction with mesityl 2-naphthyl ketone affords 1,2-dihydro-1-phenyl-2-naphthyl mesityl ketone (VI) in a yield of 84%.[5] Evidently the reaction is opposed by a methoxyl group in the 3-position.



IV



V



VI

Experimental

1,3-Dimethoxy-2-naphthyl Mesityl Ketone (I) (a) Ethyl 1,3-Dimethoxy-2-naphthoate.—Ethyl 1,3-dihydroxy-2-naphthoate[6] (15.2 g.) was dissolved in 41.2 g. of methyl sulfate at 80° in an atmosphere of nitrogen. After the source of heat had been removed, a solution of 13.8 g. of sodium hydroxide in 14 ml. of water was added to the dark brown solution. The reaction subsided after a few minutes and the temperature was maintained at 80° with occasional shaking for 4 hours. After being cooled, the contents of the flask were made alkaline by the addition of a large volume of dilute sodium hydroxide solution. The viscous, yellow-brown oil which separated was dissolved in ether and washed with water. After the solution had been dried over sodium sulfate, the ether was distilled. The yellow-brown gum which remained was dissolved in hot ethanol and the solution cooled; 10.2 g. (60%) of the pale yellow ethyl 1,3-dimethoxy-2-naphthoate was deposited; m.p. 92–92.5°.

Anal.[7] Calcd. for $C_{15}H_{16}O_4$: C, 69.21; H, 6.20. Found: C, 69.08; H, 6.19.

(b) **1,3-Dimethoxy-2-naphthoic Acid.**—The crude ethyl 1,3-dimethoxy-2-naphthoate in the form of a gum was saponified without further purification. The red-brown solution of the ester, 10.7 g. of potassium hydroxide and 95 ml. of absolute ethanol was boiled under reflux for 3 hours, at the end of which time, a tan-colored solid had separated. The crude potassium salt was collected on a filter and dissolved in water. Acidification of the aqueous solution with hydrochloric acid caused the separation of a tan-colored gum, which gradually solidified. The 1,3-dimethoxy-2-naphthoic acid (9.3 g., 68.5%) was dissolved in 10% potassium hydroxide solution. The potassium salt was recrystallized from dilute ethanol and an aqueous solution of the pure salt was acidified. The 1,3-dimethoxy-2-naphthoic acid melted at 121–122°.

(c) **Action of 1,3-Dimethoxy-2-naphthoyl Chloride on Mesitylene.**—A mixture of 7.9 g. of the crude 1,3-dimethoxy-2-naphthoic acid, 4.75 g. of thionyl chloride and 50 ml. of carbon tetrachloride was heated at 60° until all the acid had dissolved and the evolution of gas had ceased (about 4 hours). The excess thionyl chloride and carbon tetrachloride were distilled under reduced pressure. A solution of the residual 1,3-dimethoxy-2-naphthoyl chloride in 45 ml. of nitrobenzene was added slowly, with stirring, to a solution of 8.5 g. of mesitylene, 4.5 g. of aluminum chloride and 45 ml. of nitrobenzene, cooled in an ice-bath. After the addition was complete, the mixture was stirred for an additional 2 hours at 0° and the complex was decomposed with dilute hydrochloric acid.

The nitrobenzene layer was steam distilled to remove excess mesitylene and nitrobenzene, and the residue was dissolved in ether. The ether layer after being washed with a sodium hydroxide solution, yielded an orange-brown gum which solidified. Recrystallization of the solid from ethanol produced 5 g. (44%) of 1,3-dimethoxy-2-naphthyl mesityl ketone; m.p. 113–113.5°.

Anal. Calcd. for $C_{22}H_{22}O_3$: C, 79.01; H, 6.63. Found: C, 78.72; H, 6.84.

Action of Benzylmagnesium Chloride on 1,3-Dimethoxy-2-naphthyl Mesityl Ketone.—A solution of 0.44 g. of 1,3-dimethoxy-2-naphthyl mesityl ketone in 20 ml. of ether and 20 ml. of dry benzene was added, with stirring, to a benzylmagnesium chloride reagent prepared from 0.16 g. of magnesium, 0.83 g. of benzyl chloride and 60 ml. of anhydrous ether. The mixture was heated for 2 hours at the reflux

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(1) Allied Chemical and Dye Corporation Fellow, 1950–1951.

(2) H. Richtzenhain, *Ber.*, **77B**, 1 (1944); H. Richtzenhain and P. Nippus, *ibid.*, **77B**, 566 (1944); R. C. Fuson, R. Gaertner and D. H. Chadwick, *J. Org. Chem.*, **13**, 489 (1948).

(3) R. C. Fuson and S. B. Speck, THIS JOURNAL, **64**, 2446 (1942).

(4) R. C. Fuson and R. Tull, *ibid.*, **71**, 2543 (1949).

(5) R. C. Fuson and Y. F. Shealy, *J. Org. Chem.*, **16**, 643 (1951).

(6) K. Meyer and H. Bloch, *Org. Syntheses*, **25**, 73 (1946).

(7) The microanalyses were carried out by Miss Emily Davis, Miss Rachel Kopel and Mrs. Jean Fortney.

temperature, and the complex was decomposed with dilute hydrochloric acid while the container was immersed in an ice-bath.

The organic layer was washed with water and dried over sodium sulfate. Distillation of the ether and benzene left a light yellow solid. This residue was recrystallized from *n*-propyl alcohol to yield 0.45 g. (86%) of 1-benzyl-3-methoxy-2-naphthyl mesityl ketone; m.p. 166–167.5°.

Anal. Calcd. for $C_{28}H_{26}O_2$: C, 85.24; H, 6.64. Found: C, 84.76; H, 6.94.

The experiment was repeated in an ether–xylene solvent at the reflux temperature (*ca.* 75°) for 17 hours. The product was the same as that isolated as in the previous run at the lower temperature.

Action of Phenylmagnesium Bromide on 1,3-Dimethoxy-2-naphthyl Mesityl Ketone.—To a solution of a Grignard reagent prepared in ethyl ether from 7.8 g. of bromobenzene and 1.2 g. of magnesium was added 50 ml. of *n*-butyl ether. The ethyl ether was distilled through the reflux condenser while a stream of oxygen-free nitrogen was passed in. The 1,3-dimethoxy-2-naphthyl mesityl ketone in 50 ml. of *n*-butyl ether was slowly added to the Grignard reagent, and the reaction mixture was heated at 135°, with stirring, under nitrogen for 9 hours. At the end of this time, the complex was decomposed with dilute hydrochloric acid. The butyl ether layer was removed and the solvent was distilled under reduced pressure. The red-brown gum which remained slowly solidified. Recrystallization of the solid from high-boiling petroleum ether yielded 2 g. (55%) of orange-yellow needles of mesityl 1-phenyl-3-hydroxy-2-naphthyl ketone; m.p. 156–156.5°.

Anal. Calcd. for $C_{26}H_{22}O_2$: C, 85.22; H, 6.05. Found: C, 85.03; H, 6.24.

Mesityl 3-Methoxy-2-naphthyl Ketone (a) 3-Hydroxy-2-naphthyl Mesityl Ketone.—Thionyl chloride (32.7 g.) was introduced into a mixture of 40 g. of 3-hydroxy-2-naphthoic acid and 200 ml. of dry carbon tetrachloride, and the temperature was raised to the point of gentle reflux. The acid gradually disappeared; and, at the end of 7 hours, a clear solution had formed. The carbon tetrachloride and thionyl chloride were distilled under reduced pressure. The solid acid chloride was purified by dissolution in high-boiling petroleum ether, filtration of the hot solution and cooling of the filtrate. The yellow 3-hydroxy-2-naphthoyl chloride[8] was obtained in a yield of 43.5 g. (98%). It is stable if kept in a vacuum desiccator.

A solution of the 3-hydroxy-2-naphthoyl chloride (43.5 g.) in 200 ml. of nitrobenzene was added slowly, with stirring and cooling, to a solution of 58.8 g. of aluminum chloride, 200 ml. of dry nitrobenzene and 75.6 g. of mesitylene. The reaction was then carried out exactly as in the preparation of 1,3-dimethoxy-2-naphthyl mesityl ketone.

The ether layer, after a sodium hydroxide extraction, yielded a tarry residue. A mixture of an excess of high-boiling petroleum ether and the residue was heated and stirred, cooled to 35° and passed through a filter. After the solvent had been removed, a dark orange solid remained. After recrystallization from high-boiling petroleum ether, the yellow 3-hydroxy-2-naphthyl mesityl ketone melted at 140–140.5°; yield 40 g. (66%).

Anal. Calcd. for $C_{20}H_{18}O_2$: C, 82.73; H, 6.25. Found: C, 82.75; H, 6.35.

(b) Methylation of 3-Hydroxy-2-naphthyl Mesityl Ketone.—A solution of 32.7 g. of 3-hydroxy-2-naphthyl mesityl ketone in 121 g. of methyl sulfate was effected by heating the mixture to 120°. The source of heat was removed and the solution allowed to cool to 80°. A solution of 42.0 g. of sodium hydroxide in 42 ml. of water was added all at once, with shaking. The reaction was then carried out exactly as in the preparation of ethyl 1,3-dimethoxy-2-naphthoate.

The solvent was distilled from the ether layer and the residual gum was dissolved in hot, high-boiling petroleum ether. When the solution was cooled 30.3 g. (89%) of a tan-colored solid separated. The melting point of the needles of pure mesityl 3-methoxy-2-naphthyl ketone was 90–90.5°.

Anal. Calcd. for $C_{21}H_{20}O_2$: C, 82.86; H, 6.62. Found: C, 82.83; H, 6.72.

Treatment of Mesityl 3-Methoxy-2-naphthyl Ketone with Methylmagnesium Iodide.—The Grignard reagent was prepared from 0.96 g. of magnesium, 5.56 g. of methyl iodide, 20 ml. of anhydrous ether and 5 ml. of dry benzene. Under an oxygen-free nitrogen atmosphere, 4.0 g. of mesityl 3-methoxy-2-naphthyl ketone in 15 ml. of benzene was added dropwise with stirring. The mixture was boiled under reflux for 17 hours. Dilute hydrochloric acid was added slowly, with cooling, to the reaction mixture. A residual white solid slowly disappeared when the mixture was boiled under reflux and stirred for 24 hours under nitrogen. The organic layer was washed with water and dried over sodium sulfate. The yellow-orange gum left by evaporation of the ether was dissolved in high-boiling petroleum ether; cooling the solution caused the crystallization of 2.8 g. of a solid, which proved to be starting material.

Action of Phenylmagnesium Bromide on Mesityl 3-Methoxy-2-naphthyl Ketone.—The phenylmagnesium bromide reagent was prepared from 1.2 g. of magnesium and 7.72 g. of bromobenzene in 30 ml. of anhydrous ether. A solution of 5.0 g. of mesityl 3-methoxy-2-naphthyl ketone in 30 ml. of dry benzene was added dropwise, with stirring, under oxygen-free nitrogen. When the mixture was boiled under reflux for 6 hours, a white solid gradually separated. After being cooled in ice, the complex was decomposed with dilute hydrochloric acid. When the mixture was stirred and boiled under reflux under nitrogen for 15 hours, a white solid gradually disappeared, leaving a two-layer system. The organic portion was washed with water and dried over sodium sulfate. It yielded a yellow-brown gum which was dissolved in high-boiling petroleum ether. After several days, 0.5 g. (8%) of a white solid separated. The needles of dihydro-1-phenyl-3-methoxy-2-naphthyl mesityl ketone melted at 170.5–171° after several recrystallizations from high-boiling petroleum ether.

Anal. Calcd. for $C_{27}H_{26}O_2$: C, 84.78; H, 6.85. Found: C, 84.58; H, 6.65.

A very small amount of a second crop of crystals was harvested from the original high-boiling petroleum ether solution. This solid was difficultly soluble in the same solvent and decomposed on melting at 181–183°. It is probable that the white needles are the enol peroxide of the major crystalline product.

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[8] N. N. Vorozhtsov and N. D. Genkin, *J. Gen. Chem.* (*U. S. S. R.*), **8**, 357 (1938).