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

THE ACTION OF GRIGNARD REAGENTS ON 2-METHOXY-1-NAPHTHONITRILE

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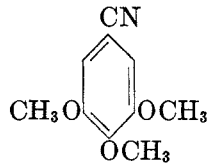
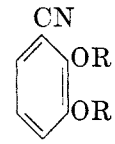
The replacement of a nuclear alkoxyl group by the action of a Grignard reagent appears to have been realized first by Haller and Schaffer (1), who prepared a compound believed to be 3,5-dimethoxy-4-butylphenyl isobutyl ketone by the interaction of isobutylmagnesium bromide and 3,4,5-trimethoxybenzonitrile (I). This result was confirmed later by Hurd and Winberg (2). Similar replacements were observed by Fuson and Speck, working with certain *o*-methoxyaryl mesityl ketones (3). Later Richtzenhain found that various Grignard reagents brought about replacement of 2-alkoxyl groups in 2,3-dialkoxybenzonitriles (II) (4, 5).



I



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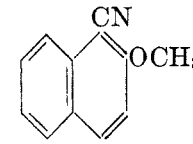

III

Since in the hindered ketones the replacement of methoxyl groups occurred more readily in the naphthalene than in the benzene series, it seemed probable that the methoxy nitriles of the naphthalene series might suffer replacement of the alkoxyl group more readily than those studied by Richtzenhain. With this idea in mind we prepared 2-methoxy-1-naphthonitrile (III) and treated it with ethylmagnesium bromide. A high yield was obtained of the product of 1,2 addition; there was no evidence that replacement of the methoxyl group had occurred. Benzylmagnesium chloride was found to react in a similar fashion.

The results obtained in an attempt to hydrolyze the imine resulting from addition of ethylmagnesium bromide to 2-methoxy-1-naphthonitrile are interesting. The product consisted of a small amount of the expected ketone, 1-propionyl-2-naphthol, accompanied by substantial amounts of β-naphthol and methyl β-naphthyl ether. The supposition that the latter products arise from hydrolytic cleavage of the ketone initially formed was substantiated by demonstrating that the ketone did, indeed, give rise to these products under the conditions of the original hydrolysis. A similar observation in regard to 10-methoxy-9-anthryl methyl ketimine was reported by Krollpfeiffer (6). 7-Methoxy-8-chloro-9-acetyltetrahydrophenanthrene was found by Kupchan and Elderfield (7) to behave in a similar way.

From a survey of the literature (8–15) it is evident that the ease of hydrolytic cleavage of alkyl aryl ketones in acidic media parallels the difference in electro-

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negativity of the alkyl and aryl groups. A similar parallel has been noted (16) with respect to the hydrolytic stability of carboxylic acids.

EXPERIMENTAL[2]

2-Methoxy-1-naphthonitrile. A. *From 1-bromo-2-methoxynaphthalene.* A solution of 40 g. of bromine in 100 ml. of glacial acetic acid was added, dropwise and with stirring, over a period of one hour to a solution of 39.5 g. of methyl β-naphthyl ether in 350 ml. of the same solvent. The product which separated was removed by filtration, and the remainder precipitated by pouring the filtrate into water. The crude 1-bromo-2-methoxynaphthalene weighed 53 g. (93% yield); m.p. 82–84°. This compound had been prepared previously by the action of phosphorus pentabromide on methyl β-naphthyl ether (17) and by the methylation of 1-bromo-2-naphthol (18). Its melting point was reported as 83–84° (17) and 85° (18).

The 1-bromo-2-methoxynaphthalene was converted to 2-methoxy-1-naphthonitrile by a procedure similar to that used by Newman (19) to prepare α-naphthonitrile from α-bromonaphthalene. The 2-methoxy-1-naphthonitrile separated from methanol in the form of white needles; m.p. 95–96°; yield 90%.

B. *From methyl β-naphthyl ether and cyanogen bromide.* The procedure was that employed by Karrer, Rebmann, and Zeller (20). From 20 g. of cyanogen bromide and 39.5 g. of methyl β-naphthyl ether was obtained 6 g. (13% yield) of 2-methoxy-1-naphthonitrile, m.p. 94–96°.

C. *From 2-methoxy-1-naphthaldehyde.* The aldehyde was made in 60% yields by a procedure similar to that employed by Wood and Bost (21) to prepare 2-ethoxy-1-naphthaldehyde. The product was purified by recrystallization from methanol; m.p. 81–84° (22). The aldehyde was converted to the corresponding oxime by the method of Brady and Goldstein (23). The yield of product twice recrystallized from benzene was 84%; m.p. 149–153°. A solution of 10 g. of the oxime in 40 ml. of acetic anhydride was heated under reflux for one hour and poured into water, with vigorous stirring. The crude product (99% yield) melted at 93–95°.

1-Bromo-2-ethylnaphthalene. 2-Ethylnaphthalene was prepared in 58% yield by reducing methyl β-naphthyl ketone according to Martin's modification (24) of the Clemmensen method. A solution of 80 g. of bromine in 75 ml. of carbon tetrachloride was added, dropwise with stirring, over a period of two hours to a mixture of 78 g. of 2-ethylnaphthalene, 250 ml. of carbon tetrachloride, a pinch of iron powder, and a crystal of iodine. During the addition and for two hours afterward the reaction mixture was cooled in an ice-bath and protected from light. The 1-bromo-2-ethylnaphthalene, isolated by conventional procedures, boiled at 125–126° (3 mm.); yield 75%. Analysis indicated that it was not quite pure: presumably, the contaminant was 2-ethylnaphthalene.

Anal. Calc'd for $C_{12}H_{11}Br$: C, 61.29; H, 4.72.
Found: C, 62.42; H, 4.91.

2-Ethyl-1-naphthonitrile. The procedure was similar to that employed by Newman (19) for the preparation of α-naphthonitrile. A yield of 15 g. (81%) of 2-ethyl-1-naphthonitrile (m.p. 63–67°) was obtained from 23.5 g. of the corresponding bromide. The nitrile was recrystallized from high-boiling petroleum ether; m.p. 66.5–67.5°.

Anal. Calc'd for $C_{13}H_{11}N$: C, 86.15; H, 6.12.
Found: C, 86.94; H, 6.42.

2-Ethyl-1-napthoic acid. A solution of a Grignard reagent, prepared from 23.5 g. of 1-bromo-2-ethylnaphthalene, 2.45 g. of magnesium, and 60 ml. of dry ether, was poured on a large excess of solid carbon dioxide. The acid was isolated in the usual way and purified by repeated recrystallization from benzene; m.p. 118–119°; the yield of crude product was 76%.

Anal. Calc'd for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04.
Found: C, 77.82, H, 6.23.

[2] Microanalyses were by Misses Theta Spoor, Betty Snyder, and Jane Wood.

2-Ethyl-1-propionaphthone. 2-Ethyl-1-naphthoyl chloride was prepared in 85% yield by treatment of the acid with thionyl chloride; b.p. 129–131° (2–3 mm.). A solution of 12 g. of the acid chloride in 50 ml. of dry ether was added slowly to a Grignard reagent prepared from 16.4 g. of ethyl bromide, 3.65 g. of magnesium, and 70 ml. of ether. The reaction mixture was allowed to reflux during the addition and for thirty minutes afterward and was poured into a chilled solution of aqueous ammonium chloride. The ketone, isolated in the usual way, crystallized from ethanol in diamond-shaped plates; m.p. 77–78°; yield 86%.

Anal. Calc'd for $C_{15}H_{16}O$: C, 84.81; H, 7.60.
Found: C 84.76; H, 7.88.

Treatment of the ketone with hydroxylamine failed to convert it to an oxime.

1-Propionyl-2-naphthol. This compound was made by rearrangement of β-naphthyl propionate, the procedure of Gulati, Seth, and Venkataraman (25). The product separated from dilute acetic acid in leaflets and from high-boiling petroleum ether in cubes. The pure 1-propionyl-2-naphthol had a light yellow color; m.p. 82–84°.

Anal. Calc'd for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04.
Found: C, 77.99; H, 6.13.

The melting point recorded by Gulati, Seth, and Venkataraman, however, was 70–71°. Because of the discrepancy in melting point values we converted our sample into 2-methyl-β-naphthoflavone according to the directions of Gulati, Seth, and Venkataraman. Our product melted at 109–109.5°, theirs at 110°.

Anal. Calc'd for $C_{20}H_{14}O_2$: C, 83.89; H, 4.92.
Found: C, 83.66; H, 5.06.

1-Propionyl-2-methoxynaphthalene. A mixture of 20 g. of 1-propionyl-2-naphthol, 100 ml. of 2 *N* sodium hydroxide solution, and 9.3 ml. of methyl sulfate was shaken mechanically for twenty hours at room temperature. An additional 15 ml. of sodium hydroxide solution (35%) was added, and the mixture heated under reflux for six hours. The ketone, isolated by usual methods, was a nearly colorless oil boiling at 141–143° at 2–3 mm.; $n^{20}D$ 1.6013.

Anal. Calc'd for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59.
Found: C, 78.01; H, 6.68.

The compound was also made by condensing 2-methoxy-1-naphthoyl chloride with ethylmagnesium bromide. The acid chloride (m.p. 67–71°) was prepared by way of the acid from 1-bromo-2-methoxynaphthalene by the method of Bretscher, Rule, and Spence (26).

A third method of preparation involved the condensation of propionic anhydride with methyl β-naphthyl ether in the presence of aluminum chloride. The anhydride (39 g.) was added over a period of thirty minutes to a mixture of 40 g. of the ether, 100 ml. of carbon disulfide, and 74 g. of aluminum chloride. The product weighed 34.7 g.; b.p. 144–147° (3 mm.). In a similar experiment in which propionyl chloride was the acylating agent, 8.5 g. of 1-propionyl-2-methoxynaphthalene was obtained from 15.8 g. of methyl β-naphthyl ether. In the condensation with propionyl chloride a solid by-product, presumably a position isomer, was isolated. It was recrystallized from methanol; m.p. 110–111°.

Anal. Calc'd for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59.
Found: C, 78.99; H, 6.66.

Reaction of ethylmagnesium bromide and 2-methoxy-1-naphthonitrile: Acid hydrolysis of 2-methoxy-1-propionaphthimine. A solution of 11 g. of 2-methoxy-1-naphthonitrile, 50 ml. of dry benzene, and 50 ml. of dry ether was added over a period of ninety minutes to a refluxing solution of a Grignard reagent prepared from 2.92 g. of magnesium, 14.0 g. of ethyl bromide, and 50 ml. of dry ether. The mixture was heated under reflux for an additional four hours and poured into a chilled ammonium chloride solution. The ether layer was washed three times with 10% sodium hydroxide solution, once with saturated sodium chloride solution, five times with 1/1 hydrochloric acid, and three times with saturated sodium chloride solution. In all cases the combined aqueous extracts were back-washed once with ether and the ether wash returned to the main ether layer.

The ether layer was evaporated, and the residual crystals purified by recrystallization from high-boiling petroleum ether; 1 g. of unchanged 2-methoxy-1-naphthonitrile was re-

covered. Evaporation of the petroleum ether filtrate left only a small amount of residue, indicating that very little, if any, 2-ethyl-1-naphthonitrile had been formed.

The hydrochloric acid extract was made alkaline with ammonia and extracted with ether. The ether extract was washed with aqueous sodium chloride solution and evaporated. The remaining oil was dissolved in 150 ml. of 1/1 hydrochloric acid and heated under reflux for three hours; an oil separated during this period, and was extracted with ether (A). Neutralization of the extracted acid solution precipitated an appreciable quantity of unhydrolyzed imine.

The ether solution (A) was extracted with dilute sodium hydroxide solution (B) and washed with aqueous sodium chloride solution. After the solvent had been removed by evaporation, the oily residue was dissolved in hot low-boiling petroleum ether. When the solution was cooled, 2 g. of solid separated which melted at 60–65°. Further recrystallization of the compound from high-boiling petroleum ether raised the melting point to 72–74°. The melting point was not depressed when the substance was mixed with methyl β-naphthyl ether.

Evaporation of the low-boiling petroleum ether filtrate left after removal of the methyl β-naphthyl ether, allowed the recovery of about 2 ml. of light-colored oil. This material was separated from remaining traces of methyl β-naphthyl ether by distillation under diminished pressure, and that portion of the distillate collected above 120° (3 mm.) was carefully redistilled from a very small modified Claisen flask. The main portion boiled at 152–154° (3–4 mm.); $n^{20}D$ 1.6010. The boiling point and refractive index identify this substance as 1-propionyl-2-methoxynaphthalene.

Acidification of the sodium hydroxide extract (B) precipitated a solid (1.7 g.) which melted at 116–120° without further purification and showed no depression of melting point when mixed with an authentic sample of β-naphthol. When treated with bromine in carbon tetrachloride this compound gave a derivative which was recrystallized twice from dilute ethanol. It formed long fine needles which melted at 81–83°. 1-Bromo-2-naphthol melts at 84° (27).

Hydrolysis of 1-propionyl-2-methoxynaphthalene. A suspension of 11 g. of the ketone in 150 ml. of 1/1 hydrochloric acid was heated under reflux for three hours, cooled, and extracted with ether. The ether extract, after being washed with dilute sodium hydroxide and saturated sodium chloride solution, was dried over calcium chloride and evaporated. The remaining oil, 9.3 g., was distilled under diminished pressure. Three fractions were collected. The lower-boiling fraction distilled at 95–100° (3–4 mm.) and amounted to 0.8 g. This material solidified in the receiver and melted at about 65° without further purification, and at 71–73° after recrystallization from high-boiling petroleum ether. The melting point was not depressed by mixing with an authentic sample of methyl β-naphthyl ether. About 0.2 g. was heated under reflux for fifteen minutes with 5 ml. of glacial acetic acid and 5 ml. of 48% hydrobromic acid and poured on ice. The precipitate was removed by filtration and dried. After recrystallization from high-boiling petroleum ether, the light orange colored plates melted at 119–122° and did not show a depression of melting point when mixed with an authentic sample of β-naphthol. The low-boiling fraction was therefore β-naphthyl methyl ether.

The second fraction (1.8 g.) distilled between 100° and 140° (3–4 mm.), the first few drops of distillate solidifying in the receiver. It was evidently a mixture and was not investigated further. The high-boiling fraction distilled at 152–154° (3–4 mm.) and weighed 6.0 g.; $n^{20}D$ 1.6041. On the basis of boiling point and refractive index it was assumed to be starting material.

The sodium hydroxide extract was washed once with ether and acidified with hydrochloric acid. The precipitate was dried (0.7 g.), and recrystallized from high-boiling petroleum ether; m.p. 116–119°. It did not depress the melting point of an authentic sample of β-naphthol. Its bromo derivative melted at 80–83°.

Reaction of benzylmagnesium chloride with 2-methoxy-1-naphthonitrile. A solution of the nitrile (11 g.) in 50 ml. of dry benzene and 50 ml. of dry ether was added over a period of

sixty minutes to a solution of benzylmagnesium chloride prepared from 2.92 g. of magnesium, 16 ml. of benzyl chloride, and 150 ml. of dry ether. An orange-red precipitate formed as the nitrile solution entered the Grignard solution; the color faded as mixing proceeded. After being stirred overnight at room temperature the reaction mixture was heated under reflux for four hours, cooled, and poured into cold dilute hydrochloric acid. Some of the imine hydrochloride separated as a white solid and remained with the aqueous layer when the ether layer was removed. From the ether layer by usual procedures were isolated 2.3 g. of unchanged 2-methoxy-1-naphthonitrile and about 1 g. of a solid (m.p. 52–54°) believed to be bibenzyl.

A portion of the crude imine hydrochloride was washed with ether, dried, and analyzed. The composition of the salt approximated that of the hydrochloride of the imine formed by 1,2 addition.

Anal. Calc'd for $C_{19}H_{18}ClNO$: C, 73.18; H, 5.82.
Found: C, 71.90; H, 6.19.

A second portion of the imine hydrochloride was dissolved in ammoniacal ether, reprecipitated with hydrogen chloride, triturated with concentrated hydrochloric acid, washed with ether, and dried. It melted at 192–193°.

SUMMARY

Ethylmagnesium bromide and benzylmagnesium chloride have been found to react normally with 2-methoxy-1-naphthonitrile; no replacement of the methoxyl group was observed.

1-Propionyl-2-methoxynaphthalene has been found to undergo hydrolytic cleavage with loss of the acyl group when heated with dilute hydrochloric acid.

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