[Contribution from the Department of Organic Chemistry, Radium Institute, University of Paris]

ORIENTING INFLUENCE OF THE METHYL GROUP IN *m*-METHYLACETANILIDE AND *m*-METHYLANISOLE

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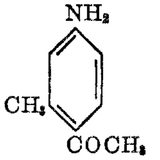
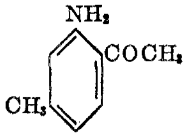
Received May 21, 1952

It has recently been found that the Friedel-Crafts acetylation of *m*-methylacetanilide followed by N-deacetylation results in the formation of 4-amino-2-methylacetophenone (I) as the main reaction-product, the reaction having thus affected the position *para* to the amino radical (1).

It is now found that in the acetylation of *m*-methylacetanilide in either carbon disulfide or nitrobenzene, very small amounts of a ketone isomeric with (I) are formed as a lower-boiling by-product. The constitution of this substance as 2-amino-4-methylacetophenone (II) was established by reduction of its diazo compound with hypophosphorous acid to 4-methylacetophenone, the constitution of the latter ketone being ascertained by hypobromite oxidation to *p*-toluic acid.



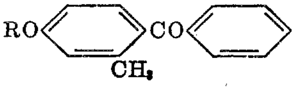
I



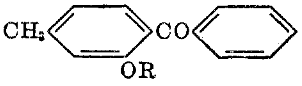
II

2-Amino-4-methylacetophenone had previously been obtained by Keneford, Morley, and Simpson (2), through a far more complicated method. Its formation in the course of the acetylation of *m*-methylacetanilide is reminiscent of the similar acetylation of *o*-methylacetanilide, which had been shown to result in 3-amino-4-methylacetophenone (1); this shows that the competitive influence of the methyl group is not to be underestimated in Friedel-Crafts reactions.

A parallel observation has now been made in the benzoylation of *m*-cresol methyl ether in the presence of aluminum chloride, under similar experimental conditions: the liquid reaction-product was a mixture of about two-thirds 4-methoxy-2-methylbenzophenone (III) and one-third 2-methoxy-4-methylbenzophenone (V). This was proved by demethylation of the mixture to the easily separable mixture of 4-hydroxy-2-methylbenzophenone (IV) and 2-hydroxy-4-methylbenzophenone (VI), whose constitutions had previously been determined (3). In this respect, the literature needs correction, Stadnikow and Baryschewa (4) having reported the Friedel-Crafts benzoylation of *m*-cresol methyl ether in



III; R = CH_3
IV; R = H



V; R = CH_3
VI; R = H

the presence of stannic chloride to give a solid 4-methoxy-2-methylbenzophenone melting at 172°, whereas it has now been found that methylation of 4-hydroxy-2-methylbenzophenone yields the pure methyl ether (III) in the form of a liquid. The constitituion of the product obtained by Stadnikow and Baryschewa will be dealt with in another paper.

EXPERIMENTAL

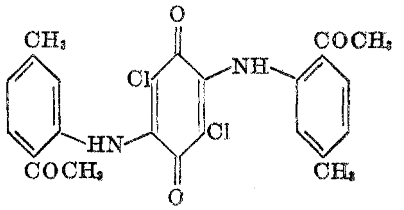
Acetylation of m-methylacetanilide. To 90 g. of freshly-redistilled *m*-methylacetanilide and 81 g. of acetyl chloride in 500 ml. of dry carbon disulfide, 250 g. of finely-powdered aluminum chloride was added in small portions. The mixture was refluxed on a water-bath for one hour, the carbon disulfide removed by distillation, and the viscous orange-brown residue poured onto ice. The crude solid N-acetylated amino ketone thus obtained was collected, and hydrolyzed by refluxing with 200 ml. of hydrochloric acid for an hour. After basification with sodium hydroxide, the amino ketones were taken up in ether, and were purified by vacuum-distillation.

1. A portion boiling at 150–170°/13 mm. was redistilled, giving 5 g. (5.5% yield) of a ketone, b.p. 165°/15 mm., which crystallized from aqueous methanol in pale yellow needles, m.p. 55°. The literature (2) gives m.p. 55.6° for 2-amino-4-methylacetophenone. Heating with acetyl chloride in benzene gave an N-acetylated derivative, crystallizing from methanol as colorless needles, m.p. 76° (lit. 75–76°).

Anal. Calc'd for $C_9H_{11}NO$: C, 72.5; H, 7.3.
Found: C, 72.4; H, 7.5.

The 2-amino-4-methylacetophenone was characterized as its condensation-product with chloranil (6) by heating for an hour a mixture of two moles of the amine with one mole of chloranil in ethanol. The precipitated *2,3-dichloro-3,5-bis(2-acetyl-5-methylanilino)-1,4-benzoquinone* (VII) crystallized from toluene as greenish-brown leaflets, m.p. 268°.

Anal. Calc'd for $C_{24}H_{20}Cl_2N_2O_4$: C, 61.1; H, 4.2.
Found: C, 60.8; H, 4.0.



VII

2. A portion boiling at 170–185°/13 mm. gave on redistillation a ketone, b.p. 178–179°/13 mm. (59 g.; yield: 65.5%), which formed from aqueous methanol colorless needles, m.p. 96°. This compound had already been identified as 4-amino-2-methylacetophenone (1).

Degradation of 2-amino-4-methylacetophenone to p-toluic acid. The amino ketone (4 g.), dissolved in 20 ml. of hydrochloric acid and 10 ml. of hot water, was diazotized with 2 g. of sodium nitrite. The diazo solution was treated with 35 ml. of hypophosphorous acid and kept at 0° for 36 hours. The pale yellow supernatant oil obtained was taken up in ether and the solution was washed with an aqueous solution of sodium hydroxide, then with water, dried over sodium sulfate, and the solvent removed. Yield, 3 g. of 4-methylacetophenone; this gave on oxidation with an aqueous solution of sodium hypobromite (made from 4 ml. of bromine and 8 g. of sodium hydroxide) an almost quantitative yield of *p*-toluic acid, m.p. 178–179°; the literature (5) gives m.p. 179–180°.

Benzoylation of m-cresol methyl ether. To a well-cooled solution of 150 g. of *m*-cresol methyl ether and 190 g. of benzoyl chloride in 500 ml. of carbon disulfide, 150 g. of aluminum chloride was added in small portions. The orange-colored mixture was kept at 5° for six hours and then decomposed with cold dilute hydrochloric acid; the organic layer was washed with an aqueous solution of sodium hydroxide, then with water, the solvent removed, and the residue vacuum-distilled. Yield, 242 g. of a liquid boiling at 214–215°/18 mm., n_D^{25} 1.5991.

A mixture of 23 g. of this product and 61 g. of redistilled pyridine hydrochloride was refluxed for one hour; the cooled mixture was poured into water, and the demethylation products were taken up in toluene. The toluene solution was washed with water and dried over sodium sulfate, the solvent removed, and the residue vacuum-distilled (about 230–240°/17 mm.). Yield, 16 g. of a product which was treated with petroleum ether to give 10 g. of a solid which crystallized from benzene as shiny colorless needles, m.p. 129°; the literature (7) gives m.p. 129° for *4-hydroxy-2-methylbenzophenone.* The mother liquors, freed from solvent and redistilled, yielded 5 g. of *2-hydroxy-4-methylbenzophenone*, crystallizing from petroleum ether as shiny colorless needles, m.p. 61–62° (lit. 63°).

Pure 4-methoxy-2-methylbenzophenone (III) was obtained in quantitative yield by treating the corresponding phenol (9.5 g.) with methyl sulfate (7 g.) in the presence of aqueous sodium hydroxide; it formed a pale yellow liquid, boiling at 219–220°/18 mm., $n_D^{21.5}$ 1.6005.

Anal. Calc'd for $C_{15}H_{14}O_2$: C, 79.6; H, 6.2.

Found: C, 79.5; H, 6.1.

SUMMARY

1. The Friedel-Crafts acetylation of *m*-methylacetanilide in the presence of aluminum chloride is shown to give 4-amino-2-methylacetophenone as the main product, and small amounts of the isomeric 2-amino-4-methylacetophenone.

2. Under similar conditions, the benzoylation of *m*-methylanisole is shown to yield a mixture of 4-methoxy-2-methyl- and 2-methoxy-4-methyl-benzophenone.

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