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On the Friedel-Crafts Acylation of *p*-Methylacetanilide

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For a polarographic investigation of *o*-aminoacetophenones [1] 2′-amino-5′-methylacetophenone (I) was needed; this compound has been prepared in yields varying from 0 to 10 % by Friedel-Crafts acetylation [2,3] of 4-methylacetanilide (II) with acetyl chloride; no other products have been reported isolated from this reaction. In the reinvestigation of the reaction described below the yield of characterised compounds reached nearly 90 %.

The acetylation of 4-methylacetanilide (II) was performed with excess of aluminium chloride and acetyl chloride in carbon disulphide; from the reaction mixture were isolated the following three compounds: 2′-amino-5′-methylacetophenone (I) 8 % yield, 5′-amino-2′-methylacetophenone (IV) 54 % yield, and 2,6-dimethyl-4(1H)-quinolone (III) 24 % yield. The presence of small amounts of 3—4 other compounds was indicated by thin-layer chromatography, but they were not characterised.

Variation of the experimental conditions influenced the yield somewhat, but not significantly.

The major product (IV) was proved to be the hitherto unknown 5′-amino-2′ methylacetophenone from the analysis, IR (non-hydrogenbonded carbonyl absorption 1675 cm^{-1}), and the NMR-spectrum; the aromatic proton at highest field (H4, neighbour to the amino group and not influenced appreciably by the carbonyl group) shows a *meta* and an *ortho* coupling. IV was reduced electrolytically to the hitherto unknown 1-(5′-amino-2′-methylphenyl)ethanol.

The structure of III was established from the analysis, the NMR-spectrum, and the identity with the product obtained by condensation of *p*-toluidine with ethylacetate.[4]

The quinolone III seems not to be formed by further reaction of 2′-acetamino-5′-methylacetophenone (I) as I on treatment with acetyl chloride and aluminium chloride under a variety of conditions failed to produce III; neither did *N,N*-diacetylated *p*-toluidine under similar conditions produce III.

Ethyl-3-(4′-toluidino) crotonate (V) yields on heating to 160° III; V reacted with carbon disulphide in the presence of aluminium chloride, but treatment of V with acetyl chloride and aluminium chloride only yielded acetylated products and no III. The reaction mechanism for the formation of III is thus not clear, although it seems probable that a derivative of 3-(4′-toluidino)crotonic acid is an intermediate.

Chlorination in acetic acid of II yields 3-chloro-4-acetaminotoluene, and nitration of II in a 3:1 mixture of nitric and sulphuric acid yields 3-nitro-4-acetaminotoluene, whereas nitration with a mixture containing a high concentration of sulphuric acid produces a mixture of 2- and 3-nitro-4-acetaminotoluene. Under acidic conditions protonation of the amino group induces a higher proportion of the 2-isomer.

The Friedel-Crafts acetylation of II using aluminium chloride as Lewis acid produces the 2- and 3-isomers in a ratio of 7:1 which indicates a high degree of

coordination of the nitrogen atom with the Lewis acid. Similar results have been obtained on acetylation of *o*- and *m*-methylacetanilide.[5,6]

Experimental. Friedel-Crafts acylation of p-methylacetanilide. To a well stirred mixture of *p*-methylacetanilide (II) (30 g) and anhydrous aluminium chloride (160 g) in carbon disulphide (160 ml) was added acetyl chloride (30 g) from a dropping funnel during 1 h with gentle refluxing. The refluxing was continued for 14 h. The supernatant carbon disulphide was decanted, and the precipitated adduct decomposed with 600 ml N hydrochloric acid with stirring. The mixture was extracted five times with 50 ml chloroform and after removal of the solvent by distillation the residue was hydrolysed by refluxing with a mixture of 50 ml conc. hydrochloric acid, 50 ml water, and 50 ml ethanol for 2 h.

After cooling, the aqueous-alcoholic solution was washed three times with 30 ml chloroform, which was washed with water. The combined aqueous layers were made alkaline with sodium hydroxide and extracted five times with 50 ml chloroform which was then dried (potassium carbonate) and removed *in vacuo* leaving residue A (23 g). The alkaline aqueous solution slowly deposited crystals of III and after 8 days the crystals (4.3 g) were filtered.

The residue A was dissolved in ether (120 ml); from this solution further 4.1 g of III precipitated. The ether was removed and the residue dissolved in 15–20 ml hot benzene; upon cooling, yellow crystals of IV (14.2 g) precipitated. After filtering, the benzene was evaporated and the residue dissolved in benzene containing 10 % acetic acid. The solution was chromatographed on a column of silica gel using benzene–10 % acetic acid as eluent. The first eluted compound was I (2.3 g), then *p*-toluidine (0.4 g), followed by (IV (2.0 g), bringing the total yield of I, IV, and III to 2.3, 16.2, and 8.4 g, respectively.

2'-Amino-5'-methylacetophenone (I), m.p. 42° (41–42°).[7] IR (neat, cm^{-1}): >CO=1640 (s).

2,6-Dimethyl-4(1H)quinolone (III), m.p. 286° (280°).[8] (Found: C 76.77; H 6.49; N 8.04. Calc. for $C_{11}H_{11}NO$: C 76.28; H 6.40; N 8.09). NMR (CF_3COOH): δ=2.65 (singlet), $\sum$H=3; [illegible] $\sum$H=3; δ=7.15 (singlet), [illegible]nglet), $\sum$H=2; δ=8.3 (singlet), $\sum$H=1.

5'-Amino-2'-methylacetophenone (IV), m.p. 96–97° (ethanol). (Found: C 72.5; H 7.6; N 9.3. Calc. for $C_9H_{11}NO$: C 72.46; H 7.43; N 9.39). IR (KBr, cm^{-1}): 3470 (m), 3380 (m), 2920 (m), 1675 (s), 1625 (s), 1495 (m), 1310 (m), 1220 (s), 960 (m), 860 (m), 835 (m). NMR ($CDCl_3$): δ=2.38 (singlet), $\sum$H=3; δ=2.48 (singlet), $\sum$H=3; δ=3.75 (broad singlet), $\sum$H=2; δ=6.67 (quartet J_o=8 Hz, J_m=3 Hz), $\sum$H=1; δ=6.93 (doublet J_m=3 Hz), $\sum$H=1; δ=7.0 (doublet J_o=8 Hz), $\sum$H=1.

Acetate, m.p. 94–95° (ethanol). (Found: C 68.6; H 6.9; N 7.3. Calc. for $C_{11}H_{13}NO_2$: C 69.09; H 6.85; N 7.32).

Benzoate, m.p. 137–138° (ethanol). (Found: C 76.0; H 5.9; N 5.3. Calc. for $C_{16}H_{15}NO_2$: C 75.87; H 5.97; N 5.53).

1-(5'-Amino-2'-methylphenyl)ethanol (VI). 2.2 g of IV was reduced electrolytically at − 1.76 V (SCE) in 150 ml of a prereduced borate buffer (pH=9.1) containing 30 % of ethanol with a consumption of 2.0 *F*/mole. The reduction completed, the mixture was extracted three times with 50 ml chloroform which was dried over potassium carbonate. Removal of the solvent *in vacuo* gave 2.0 g of a compound, m.p. 105–106°. After crystallisation (ethanol) m.p. 108–109°. (Found: C 71.4; H 8.6; N 9.3. Calc. for $C_9H_{13}NO$: C 71.49; H 8.67; N 9.26). NMR ($CDCl_3$): δ=1.40 (doublet J=7 Hz), $\sum$H=3; δ=2.19 (singlet), $\sum$H=3; δ=3.19 (singlet), $\sum$H=3; δ=4.99 (quartet J=7 Hz), $\sum$H=1; δ=6.45 (quartet J_o=8 Hz, J_m=3), $\sum$H=1; δ=6.82 (doublet), $\sum$H=1; δ=6.90 (doublet J_o=8 Hz), $\sum$H=1.

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