421. *The Preparation of Some* m- *and* p-*Alkylanilines.*

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m- and *p*-Alkylanilines have been prepared in high yields by catalytic reduction of *m*- and *p*-acetamidophenyl alkyl ketones in acetic acid, with palladium–barium sulphate as catalyst and perchloric acid as activator.

We required a number of *m*- and *p*-alkylanilines for synthetical work. Recorded preparations of the *p*-compounds from alkylbenzenes, from aniline, or *N*-alkylarylamines, or of *m*-alkylanilines from their *p*-analogues, are tedious. Alkyl *m*- and *p*-aminophenyl ketones would be convenient starting materials. Reduction of such compounds has been effected by the Huang-Minlon modification of the Wolff–Kishner reduction (Buu-Hoï, Eckert, and Royer, *Compt. rend.*, 1951, **232**, 1356; 1951, **233**, 1461; Linnell and Vora, *J. Pharm. Pharmacol.*, 1951, **3**, 670; Nineham, *J.*, 1952, 635) though yields were not reported. The Clemmensen reduction is unsatisfactory (von Braun and Weissbach, *Ber.*, 1929, **62**, 2416; Day, *J.*, 1930, 252; Brady and Day, *J.*, 1934, 114; Taylor and Watts, *J.*, 1952, 1123).

We achieved a practicable synthesis of the desired compounds by hydrogenating the acetamidophenyl ketones at 95° in presence of palladium–barium sulphate in acetic acid containing perchloric acid (Rosenmund and Karg, *Ber.*, 1942, **75**, 1850). The *p*-acetamidoketones are readily available from Friedel–Crafts reactions, and we obtained the *m*-compounds by catalytic reduction of the nitro-ketones (Leonard and Boyd, *J. Org. Chem.*, 1946, **11**, 405; Marvel and Overberger, *J. Amer. Chem. Soc.*, 1946, **68**, 185; Marvel, Allen, and Overberger, *ibid.*, p. 1089).

Direct hydrogenation of the nitro- or amino-ketones under the conditions used with the acetamido-compounds gave small amounts of alkylanilines and large quantities of high-boiling oils. The latter, apparently secondary amines, were formed exclusively in the absence of perchloric acid, and probably arose from the initially formed primary amine by condensation with unreduced ketone and further reduction. Such processes are hindered by protonisation by perchloric acid, and of course prevented by acetylation.

Papa, Schwenk, and Whitman (*J. Org. Chem.*, 1942, **7**, 587) reduced *m*-nitroacetophenone to *m*-ethylaniline with Raney alloy and sodium hydroxide. We found it better to use amino-ketones and obtained moderate yields of *p*-alkylanilines by this method, which was, however, less satisfactory in the *m*-series. The reaction is very inconvenient except on the small scale. Clemmensen reduction of *m*-nitroacetophenone gave only a poor yield (9·5%) of *m*-ethylaniline.

Experimental

Ethereal extracts were dried with anhydrous Na_2SO_4. 72% Perchloric acid was used.

Reductions of m-*Nitroacetophenone.*—(i) *With Raney alloy.* The most successful of a number of experiments was carried out as follows. The ketone (50 g.) in ethanol (125 c.c.) and aqueous sodium hydroxide solution (1750 c.c.; 10%) was heated and stirred under reflux at 90—100° during the addition of Raney alloy (150 g.) as quickly as gas evolution permitted (various surface active agents were examined, but failed to mitigate frothing). After the addition the mixture was heated and stirred for several hours and then steam-distilled. The distillate was saturated with salt, and the product was isolated by ether and distilled, giving 39% of *m*-ethylaniline, b. p. 93—95°/6 mm. The *picrate* formed yellow needles, m. p. 170—171° (Found: C, 48·6; H, 4·3. $C_8H_{11}N,C_6H_3O_7N_3$ requires C, 48·0; H, 4·0%), from aqueous methanol. The *toluene*-p-*sulphonyl* derivative crystallised from the same solvent, as colourless needles, m. p. 80° (Found: C, 65·7; H, 6·3. $C_{15}H_{17}O_2NS$ requires C, 65·4; H, 6·2%). The yield of *m*-ethylaniline decreased in larger-scale experiments, 11·4% being obtained from 150 g. of the ketone. Reduction with Raney alloy in acid solution gave mainly *m*-aminoacetophenone, with a little of the alkyl compound.

(ii) *With palladium–charcoal.* When the nitro-ketone (2 g.), methanol (40 c.c.), and the catalyst (0·3 g.) were shaken with hydrogen, 3 mols. were rapidly absorbed, and uptake then ceased. Filtration and concentration of the solution gave *m*-aminoacetophenone (1·5 g.).

(iii) *With palladium–barium sulphate.* (*a*) The ketone (20 g.), methanol (300 c.c.), and catalyst (2 g.), treated as in (ii), gave 96% of *m*-aminoacetophenone.

(*b*) The ketone (5 g.), acetic acid (50 c.c.), perchloric acid (2·5 c.c.), and catalyst (5 g.) were shaken with hydrogen at 95°. 5 Mols. of hydrogen were absorbed in 1·5 hr., and after that a very slow continuous uptake was observed. Filtration, basification, and ether-extraction provided a dark oil (2·5 g.) which gave red oily drops with nitrous acid, but remained immiscible when refluxed with concentrated hydrochloric acid. From the latter treatment, by basification and ether-extraction, an oil resulted which on distillation yielded *m*-ethylaniline (0·2 g.), b. p. 97—98°/8 mm., and then a viscous liquid, b. p. *ca.* 190°/8 mm. In a similar experiment on 2 g. of the ketone at room temperature, in which reduction was interrupted when 5 mols. of hydrogen had been absorbed, 0·5 g. of the primary amine was obtained. When the perchloric acid was omitted the high-boiling oil was the sole product. Similar results attended hydrogenation in acetic acid under pressure. The ketone (5 g.), acetic acid (100 c.c.), and catalyst (5 g.) were treated with hydrogen at 130 atm. Reduction to *m*-aminoacetophenone occurred in 20 min. The temperature was then raised to 200°, and kept there until absorption ceased (4 hr.). Worked up as before the product gave a small primary amine fraction, and a large amount of viscous oil, b. p. 192—198°/10 mm., soluble in hydrochloric acid and giving the nitrosamine test.

m-Nitropropiophenone similarly gave small amounts of *m*-propylaniline, b. p. 118—119°/12—13 mm. (Found: C, 80·5; H, 10·1. Calc. for $C_9H_{13}N$: C, 80·0; H, 9·7%) [the *picrate* formed glistening yellow flakes, m. p. 155° (Found: C, 48·95; H, 4·5. $C_9H_{13}N,C_6H_3O_7N_3$ requires C, 49·45; H, 4·4%), from aqueous methanol], and variable amounts of a secondary amine, b. p. *ca.* 200°/9—10 mm. *m*-Nitrobutyrophenone in the absence of perchloric acid gave a viscous oil, b. p. 216—218°/11 mm. (Found: C, 75·9; H, 9·95; N, 6·8%), and only traces of a primary amine.

Reduction of m-*Acetamidoacetophenone.*—The amide (3 g.), palladium–barium sulphate (3 g.) (further experiments showed it satisfactory to use 1 g. of catalyst to 5 g. of the amide), acetic acid (30 c.c.), and perchloric acid (3 c.c.) were shaken at 95° with hydrogen. After 1 hr. uptake ceased. The material isolated by basification and ether-extraction was refluxed with hydrochloric acid (80 c.c.; 8N) for ½ hr., and a light brown oil (2·2 g.) was recovered by basification and ether-extraction. Distillation gave *m*-ethylaniline (1·6 g., 78%), b. p. 100—102°/9—10 mm., as the sole product.

m-*Acetamidopropiophenone.*—*m*-Nitropropiophenone (20 g.), methanol (400 c.c.), and palladium–charcoal (1·5 g.) were shaken with hydrogen, uptake (3 mols.) of which ceased after 4 hr. Filtration, evaporation, and distillation gave *m*-aminopropiophenone (13·3 g.) as a pale yellow oil, b. p. 167—169°/9—10 mm. (Elson, Gibson, and Johnson, *J.*, 1930, 1128, gave b. p. 168—169°/15 mm.), which slowly crystallised. A boiling solution of the amine (10 g.) in benzene (35 c.c.) was treated slowly with acetic anhydride (10 c.c.). *m*-Acetamidopropiophenone (10·7 g., 84%), m. p. 92° (Keneford and Simpson, *J.*, 1948, 354, give m. p. 92—93°), crystallised from the filtered solution.

Reduction of m-*Acetamidopropiophenone.*—The acetyl derivative (5 g.), acetic acid (50 c.c.), palladium–barium sulphate (1 g.), and perchloric acid (5 c.c.) were treated with hydrogen at 95°. Uptake (1250 c.c.) of the latter was complete in 90 min., and the product was worked up as described for *m*-acetamidoacetophenone, giving *m*-aminopropylbenzene (3·1 g., 87%) as an oil, b. p. 107—110°/8 mm. It was identified as its picrate.

Reduction of m-*Amino-* and m-*Nitro-butyrophenone.*—(i) The nitro-compound (40 g.) in methanol (400 c.c.), with palladium–charcoal (3 g.), was rapidly reduced with evolution of heat to *m*-aminobutyrophenone (29·2 g., 86%), b. p. 178°/9—10 mm. (Elson *et al.* give b. p. 179—180°/16 mm.).

(ii) *With Raney alloy.* *m*-Aminobutyrophenone (10·3 g.), methanol (400 c.c.), and aqueous sodium hydroxide solution (900 c.c.; 10%), at 95°, were stirred and treated with Raney alloy (90 g.; added as pellets to enable reaction to proceed in the bulk of the liquid), giving in the usual way *m*-butylaniline (4·55 g.), b. p. 125—128°/9—10 mm., and some unchanged starting material. The benzoyl derivative formed plates, m. p. 68—70° (Reilly and Hickinbottom, *J.*, 1920, **117**, 107, give m. p. 68°). On the large scale the yield became insignificant, *m*-aminobutyrophenone being the chief product, as it was when *m*-nitrobutyrophenone was similarly reduced.

Reduction of m-*Acetamidobutyrophenone.*—The amide was prepared by using acetic anhydride in boiling benzene, as for *m*-acetamidopropiophenone, or with acetic anhydride alone at 95°. Initially obtained as a yellow oil (95% by the first method), b. p. 244—246°/9 mm., m-*acetamido-*

butyrophenone slowly crystallised, and formed needles, m. p. 82—83° (Found: C, 69·9; H, 7·3. $C_{12}H_{15}O_2N$ requires C, 70·2; H, 7·4%), from ether–light petroleum. By the second method, with seeding, the compound was obtained in 69% yield after removal of excess of acetic anhydride.

The amide (3 g.), palladium–barium sulphate (1 g.), acetic acid (30 c.c.), and perchloric acid (3 c.c.) were shaken with hydrogen at 95°, and the product was worked up as usual. *m*-Butylaniline (1·8 g., 72%), b. p. 124—125°/9 mm., was identified as its benzoyl derivative.

Reductions of p-*Aminoacetophenone.*—(i) *With Raney alloy.* The ketone (10 g.), ethanol (500 c.c.), and aqueous sodium hydroxide (500 c.c.; 10%), treated with Raney alloy (50 g.) and processed in the usual way, gave *p*-ethylaniline (4·6 g., 51%), b. p. 100—103°/11 mm.

(ii) *Catalytic.* The ketone (5 g.), acetic acid (50 c.c.), and palladium–barium sulphate (2 g.) were treated as usual at 95°. The rate of uptake of hydrogen gradually decreased, but on addition of more catalyst (2 g.) and perchloric acid (2 c.c.) absorption was resumed and continued until approx. 5 mols. had been taken up. Basification and ether-extraction afforded a brown oil (4·5 g.). Attempted distillation suggested the presence of an acetyl derivative, so the oil (4·1 g.) was boiled with concentrated hydrochloric acid (10 c.c.), and the product was isolated by basification and ether-extraction. Distillation gave *p*-ethylaniline (1·35 g.), b. p. 100°/10—11 mm. (reduction of *p*-nitroethylbenzene gave material b. p. 100—102°/10 mm.), and a viscous oil, b. p. *ca.* 200°/10—11 mm.

Reductions of p-*Aminopropiophenone.*—(i) *With Raney alloy.* The amine (55 g.), ethanol (950 c.c.), and aqueous sodium hydroxide (1650 c.c.; 10%) when reduced in the usual way with Raney alloy (165 g.) gave *p*-propylaniline (31 g., 62%), b. p. 108—110°/9—10 mm.

(ii) *Catalytic.* When the ketone (5 g.), palladium–barium sulphate (2 g.), acetic acid (50 c.c.), and perchloric acid (2 c.c.) were hydrogenated at 95° as usual, reaction ceased when 1250 c.c. of hydrogen had been consumed, but on addition of more catalyst (2 g.) reduction continued, a total of 1570 c.c. of hydrogen being absorbed. Filtration, basification, and ether-extraction gave an oil (4·0 g.) which when crystallised from benzene–ligroin (b. p. 60—80°) gave plates of *p*-acetamidopropylbenzene, m. p. 93—94° (Found: C, 74·9; H, 8·7. Calc. for $C_{11}H_{15}ON$: C, 74·5; H, 8·5%) (Willgerodt and Sckerl, *loc. cit.*, give m. p. 87°). In a second identical experiment the crude product (4·0 g.) was boiled with concentrated hydrochloric acid (20 c.c.). The product, isolated by basification and ether-extraction, gave *p*-propylaniline (2·3 g., 50%), b. p. 111—113°/10—11 mm., and a viscous oil, b. p. 220—230°/10—11 mm.

Reduction of p-*Acetamidopropiophenone.*—*p*-Aminopropiophenone (12 g.) in boiling benzene (200 c.c.) was treated gradually with acetic anhydride (12 c.c.). Crystals were deposited immediately, and after being kept overnight *p*-acetamidopropiophenone (15·7 g., 96%), m. p. 168°, was collected. When this (5 g.), acetic acid (50 c.c.), palladium–barium sulphate (1 g.), and perchloric acid (5 c.c.) were hydrogenated at 95°, 1225 c.c. of hydrogen were absorbed in 1 hr., and reduction then ceased. In the usual way *p*-propylaniline (3·05 g., 78%), b. p. 107—108°/8 mm., was isolated, and identified as its acetyl derivative, m. p. 93—95°, alone and mixed with that described above.

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