

115. *The Preparation of p*-Dimethylaminoacetophenone and its Homologues.

By A. W. NINEHAM.

The preparation is described of *p*-dimethylaminoacetophenone and its homologues in acceptable yields from readily available starting materials. The orientation of some new homologues is established, and a previous description of *p*-dimethylaminopropiophenone is shown to be erroneous.

METHODS for the preparation of *p*-dimethylaminoacetophenone have been reported by Weil (*Monatsh.*, 1908, **29**, 906), Staudinger and Kon (*Annalen*, 1911, **384**, 111), Hurd and Webb (*J. Amer. Chem. Soc.*, 1927, **49**, 551), von Braun and Weissbach (*Ber.*, 1930, **63**, 493), Kumler (*J. Amer. Chem. Soc.*, 1946, **68**, 1184), and Haddow *et al.* (*Phil. Trans.*, 1948, *A*, **241**, 147). In the first three cases yields were poor; in the last two no details or yields were given. Since the present work was carried out, a preparation in 70% yield from *p*-nitroacetophenone by reductive methylation has been described (Pearson and Bruson, *J. Amer. Chem. Soc.*, 1951, **73**, 864) but the unavailability of starting materials prevents its general application to homologues. There is one report (Skraup and Nieten, *Ber.*, 1924, **57**, 1294) which claims *p*-dimethylaminopropiophenone, but the present work seems to show this claim to have been erroneous and that small yields of mixed *ortho*- and *para*-isomers appear to have been produced by the two methods described. No other homologues have been reported. The general procedure for the preparation of aromatic ketones described by Kosolapoff (*J. Amer. Chem. Soc.*, 1947, **69**, 1651) has now been successfully applied to dimethylaniline and diethylaniline. Workable yields have been obtained in the former case by using acetic, propionic, *n*-butyric, and *n*-valeric acids, to give *p*-dimethylaminoacetophenone, -propicphenone, -butyrophenone, and -valerophenone, and in the latter case by using acetic acid to give *p*-diethylaminoacetophenone. The temperature of refluxing dimethylaniline appeared to be optimum and the use of light petroleum (b. p. 60–80°) was unsatisfactory.

The product described by Skraup and Nieten (*loc. cit.*) as *p*-dimethylaminopropiophenone was a yellow oil, boiling at 270–272°, forming a phenylhydrazone, m. p. 58°. No analysis of either product was recorded. *p*-Dimethylaminopropiophenone prepared as described above was closely similar to *p*-dimethylaminoacetophenone in properties. The evidence of the present work seems clearly to confirm that the compound derived from dimethylaniline and propionic acid has the structure claimed: its behaviour is similar to that of the known acetophenone homologue, and it yields a phenylhydrazone, hydrazone, and azine, and a quaternary salt with methyl iodide. The orientation of the compound was established in two ways. First, reduction with hydrazine and ethylene glycol gave *p*-*n*-propyldimethylaniline, which was quaternised with methyl iodide, the product not depressing the melting point of authentic trimethyl-*p*-*n*-propylphenylammonium iodide (Cull, Davies, and Hulbert, *J. Soc. Chem. Ind.*, 1938, 349). Secondly, the ketone was reduced by lithium aluminium hydride to the secondary carbinol which did not depress the melting point of authentic 1-*p*-dimethylaminophenylpropanol (Sachs and Sachs, *Ber.*, 1905, **38**, 514). Attempts to orientate the compound by oxidation were unsuccessful. Clemmensen reduction led to what appeared to be a mixture of *p*-*n*-propylaniline and 3 : 4-bis-*p*-dimethylaminophenylhexane-3 : 4-diol. Skraup and Nieten's compound was found to give a phenyl-

hydrazone, m. p. 60—60.5° (lit., m. p. 58°), which gave analyses satisfactory for that of dimethylaminopropiophenone and may be the *ortho*-isomer. Small amounts of this material, yielding the same phenylhydrazone, were isolated from our phosphoric oxide condensations.

p-Dimethylaminopropiophenone was also obtained in 12% yield by condensation of propionic anhydride with dimethylaniline and anhydrous aluminium chloride in carbon disulphide. The orientation of *p*-dimethylaminobutyrophenone was also established by reduction with lithium aluminium hydride to 1-*p*-dimethylaminophenylbutanol which did not depress the melting point of a sample obtained by treating *p*-dimethylaminobenzaldehyde with *n*-propylmagnesium bromide.

EXPERIMENTAL

p-Dimethylaminoacetophenone.—Redistilled dimethylaniline (300 g.) was stirred in a 1-l. 3-necked flask, and glacial acetic acid (60 g., 1 mol.) run in. "Hyflo Supercel" (4 g.) was added, followed by phosphoric oxide (75 g.) which caused the mixture to become hot. It was refluxed (at about 170—200°) for 45 minutes, with stirring, poured on ice, and rendered alkaline to litmus. After filtration, the solution was extracted with benzene, washed with water, and dried, and the solvent removed. The residue was distilled, giving unchanged dimethylaniline, b. p. <100°/15 mm., a mixture of the product with a little dimethylaniline, b. p. 110—150°/15 mm., and the desired product, b. p. 155—165°/12 mm., which solidified in the receiver. Distillation was stopped, and the residue in the flask crystallised. The collected solids were crystallised from light petroleum (b. p. 60—80°), then having m. p. 102° (40 g., 25% based on the acetic acid used). Recrystallisation from light petroleum (b. p. 60—80°) gave *p*-dimethylaminoacetophenone, m. p. 103—103.5° (corr.) (Found: N, 8.7. Calc. for C₁₀H₁₃ON: N, 8.7%). An alternative method of working up, in which the dimethylaniline was removed by steam-distillation, gave somewhat lower yields, probably because the product is somewhat steam-volatile. In this procedure, the residue was crystallised from light petroleum and the mother-liquors were found to contain considerable quantities (nearly equal in weight to that of the product) of by-products, which were not fully examined, but did contain a small amount of, probably, *o*-dimethylaminoacetophenone.

p-Dimethylaminoacetophenoneazine, prepared from the ketone and 50% hydrazine hydrate, formed flat orange leaflets, m. p. 259—260°, from 2-ethoxyethanol or nitrobenzene (Found: N, 17.5. C₂₀H₂₆N₄ requires N, 17.4%). By using half the amount of ketone in the same preparation, the unstable *hydrazone*, sintering at 95° (decomp.), was obtained in 84% yield as a colourless crystalline mass (Found: N, 22.6. C₁₁H₁₈N₃ requires N, 23.7%).

p-Dimethylaminopropiophenone.—(a) The two procedures of Skraup and Nieten (*loc. cit.*) were followed; that involving the use of *p*-dimethylaminophenylmercuric chloride gave the result reported in their work.

In the alternative, propionyl chloride (117 g.) was refluxed overnight with redistilled dimethylaniline (339 g.) and powdered anhydrous zinc chloride (60 g.). The decanted liquors were distilled, giving a small fore-run, b. p. <120°. The residue was treated with aqueous sodium hydroxide, dimethylaniline removed by steam-distillation, and the residue, after ether-extraction and drying, was distilled giving a light yellow oil, b. p. 175—180/32 mm., a deeper yellow oil, b. p. up to 135°/1.5 mm., and a viscous orange oil, b. p. 140—145°/0.1 mm., which solidified in the receiver. A large residue (150 c.c.) remained undistilled. The first fraction, with phenylhydrazine, gave a solid, crystallising slowly from dilute acetic acid, or methanol, forming highly refractive colourless rectangular plates, m. p. 60—65°, which gave analyses for the *phenylhydrazone* of a dimethylaminopropiophenone, possibly the *ortho*-isomer (Found: N, 15.7. C₁₇H₂₁N₃ requires N, 15.7%). The second fraction partly solidified when kept and was filtered; the solid, crystallised from methanol and then from light petroleum (b. p. 40—60°), had m. p. 58—58.5° and was *N*-methylpropionanilide (lit., m. p. 58.5°) (Found: C, 73.3; H, 8.0; N, 9.1. Calc. for C₁₀H₁₃ON: C, 73.6; H, 8.0; N, 8.6%). The third fraction, crystallised from methanol, had m. p. 101° and was *p*-dimethylaminopropiophenone (5 g.) (see below).

(b) Redistilled dimethylaniline (600 g., 5 moles), propionic acid (148 g., 2 moles), and "Hyflo Supercel" (8 g.) were stirred and treated with phosphoric oxide (156 g., 1.1 moles), giving, by the procedure described for *p*-dimethylaminoacetophenone, *p*-dimethylaminopropiophenone (98 g., 55% based on the propionic acid used), which crystallised in shining plates, m. p. 103°, from light petroleum (b. p. 60—80°) (Found: C, 74.8; H, 8.6; N, 8.1. C₁₁H₁₅ON requires C, 74.6; H, 8.4; N, 7.9%). The product did not depress the m. p. of the product, m. p. 101°, recorded under (a).

The ketone was converted into *trimethyl-p-propionylphenylammonium iodide*, colourless prisms (from ethanol), m. p. 145° (Found : I, 39.4. $C_{12}H_{18}ONI$ requires I, 39.8%).

The *phenylhydrazone*, prepared in warm 50% acetic acid, crystallised from methanol in red prisms, m. p. 137—138°, which decomposed when kept for 3 weeks (Found : N, 15.7. $C_{17}H_{21}N_3$ requires N, 15.7%).

p-Dimethylaminopropiophenone hydrazone was obtained when the ketone was refluxed with a large excess of 50% hydrazone hydrate in methanol, forming a light yellow crystalline mass which slowly decomposed with deepening of colour. A small amount of the *azine* was also obtained as deep yellow prisms (from toluene), m. p. 214—215° (Found : N, 15.9. $C_{22}H_{30}N_4$ requires N, 16.0%).

The yellow oil left on evaporation of the collected mother-liquors from crystallisation of the ketone distilled at *ca.* 140°/20 mm. Its phenylhydrazone slowly crystallised and recrystallised from methanol in colourless prisms, m. p. 60.5°, not depressed in admixture with the phenylhydrazone of m. p. 60—65° recorded under (a). The oil was possibly *o*-dimethylaminopropiophenone and was redistilled (b. p. 245—250°/766 mm.; a pale green oil), but was still not pure (Found : C, 76.4; H, 8.4; N, 8.7%).

Orientation of p-Dimethylaminopropiophenone.—(i) *By a modified Wolff-Kishner reduction.* The ketone (4.78 g., 0.027 mole) was mixed with 96% hydrazine hydrate (7.5 c.c.) in redistilled ethylene glycol (100 c.c.) containing dissolved sodium (25 g.) and refluxed for 66 hours at 205—210° (metal-bath). The whole was poured into water, filtered, and extracted with ether. The extract was dried and evaporated, and the residual oil (2 g.) was distilled (b. p. 110—115°/13 mm.). Admixture with methyl iodide and storage at room temperature gave trimethyl-*p*-propylphenylammonium iodide, m. p. 185—187° (from ethanol). An authentic specimen, prepared from *N*-*n*-propylaniline (Hickinbottom, *J.*, 1930, 992), was rearranged to *p*-*n*-propylaniline, b. p. 220—222°, by anhydrous cobalt chloride (Cull, Davies, and Hulbert, *J. Soc. Chem. Ind.*, 1938, 349), and methylated with methyl sulphate and aqueous sodium hydroxide, to give trimethyl-*p*-propylphenylammonium iodide, m. p. 191—192° (from ethanol).

(ii) *By lithium aluminium hydride reduction.* *p*-Dimethylaminopropiophenone (0.05 mole) in ether (500 c.c.) was added to a suspension of lithium aluminium hydride (0.03 mole) in ether (100 c.c.), and the whole stirred at 30° for 1 hour. Water and ammonium chloride solution were then added successively, and the separated ethereal solution was dried ($MgSO_4$). Removal of ether *in vacuo* at room temperature left a residual solid which was crystallised from light petroleum (b. p. 40—60°). A 55% yield of 1-*p*-dimethylaminophenylpropanol was obtained, of m. p. 46—47°, which was unaltered in admixture with a sample prepared according to Sachs and Sachs (*Ber.*, 1905, 38, 514).

p-Dimethylaminobutyrophenone.—This ketone was obtained (37%) analogously from dimethylaniline and *n*-butyric acid, as colourless glistening platelets, m. p. 73—74°, not raised by further crystallisation from light petroleum (b. p. 60—80°) (Found : C, 75.5; H, 8.8; N, 7.3. $C_{12}H_{17}ON$ requires C, 75.4; H, 8.9; N, 7.3%).

The structure was established as above, by reduction with lithium aluminium hydride in ether to 1-*p*-dimethylaminophenylbutanol (61%), m. p. 38—40° not depressed on admixture with a sample (m. p. 37—39°) prepared from *n*-propylmagnesium bromide and *p*-dimethylaminobenzaldehyde (17% yield). The latter preparation was essentially that described by Sachs and Weigert (*Ber.*, 1907, 40, 4362) but they did not obtain a pure product; theirs melted at 35°. Purification was achieved by keeping a light petroleum (b. p. 40—60°) solution at 5° for some hours (Found : C, 74.6; H, 10.1; N, 7.1. Calc. for $C_{12}H_{19}ON$: C, 74.6; H, 9.9; N, 7.3%).

p-Dimethylaminovalerophenone.—This ketone was obtained (28%) from dimethylaniline and *n*-valeric acid (Adams and Marvel, *J. Amer. Chem. Soc.*, 1920, 42, 312). It consists of small glistening colourless crystals, m. p. 45—46° [from light petroleum (b. p. 40—60°)] (Found : C, 76.1; H, 9.5; N, 7.1. Calc. for $C_{13}H_{19}ON$: C, 76.1; H, 9.3; N, 6.8%).

p-Diethylaminoacetophenone.—This ketone was obtained (13—14%) from *p*-diethylaniline, acetic acid, and phosphoric oxide as colourless flat glistening needles, m. p. 47—48° (softening at 40°) (Found : C, 75.6; H, 9.0; N, 7.1. $C_{12}H_{17}ON$ requires C, 75.4; H, 8.9; N, 7.3%).

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