248. p-*Aminodimethylaniline. Part VI.** *Some Cationoid Halogenations* meta *to a Dimethylamino-group.*

By John H. Gorvin.

Halogenation of dimethylaniline derivatives in concentrated sulphuric acid in presence of silver sulphate has given products in which the chlorine or bromine atom lies *meta* to the basic group. The applicability of the reaction depends on the nature of the other substituents present. The process has been applied in particular to the preparation of 4-amino-3-bromodimethylaniline.

The method of cationoid halogenation of aromatic compounds in sulphuric acid in presence of silver sulphate (Derbyshire and Waters, *J.*, 1950, 573, 3694; Barker and Waters, *J.*, 1952, 150; Gorvin, *Chem. and Ind.*, 1951, 910; cf. Birckenbach and Goubeau, *Ber.*, 1933, **66**, 1283) has now been utilised for the direct introduction of a halogen atom *meta* to a dialkylamino-group. Thus bis-*p*-dimethylaminophenylmethane, which gives the 2 : 2'-dinitro-compound when nitrated in concentrated sulphuric acid, correspondingly gave the 2 : 2'-dibromo-compound in 80—85% yield when shaken in concentrated sulphuric acid with bromine and silver sulphate. The analogous chlorination gave the 2 : 2'-dichloro-derivative in 77% yield. The compounds were identified by comparison with authentic specimens (cf. Jones and Mason, *J.*, 1934, 1190).

---

* Part V, *J.*, 1951, 1697.

In the preparation of 4-amino-3-bromodimethylaniline this procedure could be either applied directly to a *p*-acylaminodimethylaniline or used to obtain the intermediate *m*-bromodimethylaniline from dimethylaniline. Bromination of both *p*-acetamido- and *p*-formamido-dimethylaniline proceeded very slowly in sulphuric acid, so that the theoretical yield of silver bromide was not obtained after 48 hours; the only products isolated were 4-acetamido-3-bromo- (70%) and 3-bromo-4-formamido-dimethylaniline (54%) respectively. The position of entry of the Br^+ cation therefore corresponds to that of the NO_2^+ cation (Hodgson and Crook, *J.*, 1932, 2976). The sluggishness of the reaction is consistent with partial inhibition of nuclear substitution *ortho* to an acylamino-group owing to steric hindrance (cf. Ungnade and Hansbury, *J. Org. Chem.*, 1952, **17**, 742), but the effect is possibly complicated by salt formation (MacMillan, *J.*, 1952, 4020). The introduction of a deactivating group into *p*-acetamidodimethylaniline inhibited the reaction completely; 4-acetamido-*NN*-dimethyl-2-nitroaniline (Part II, *J.*, 1942, 755) was recovered unchanged in 78% yield after 6 days' exposure to the brominating medium.

Cationoid bromination of dimethylaniline resembled the corresponding nitration (Groll, *Ber.*, 1886, **19**, 198; cf. Fitch, *Org. Synth.*, 1947, **27**, 62) in that a quantity (*ca.* 20%) of the *p*-isomer was formed, but in this case there was isolated in addition some 3 : 4-dibromodimethylaniline (*ca.* 7%). The main product, *m*-bromodimethylaniline (*ca.* 64%), was difficult to obtain free from the *p*-isomer and unchanged dimethylaniline, but for the immediate purpose this step was unnecessary; when the mixed bases were nitrosated in dilute hydrochloric acid 3-bromo-*NN*-dimethyl-4-nitrosoaniline hydrochloride separated together with a little *NN*-dimethyl-*p*-nitroaniline. The nitroso-compound (*ca.* 33% based on dimethylaniline) could be satisfactorily reduced to 4-amino-3-bromodimethylaniline (Kharasch and Piccard, *J. Amer. Chem. Soc.*, 1920, **42**, 1855). The 3 : 4-dibromodimethylaniline formed in the reaction may have been derived from either or both of the isomers (cf. Vorländer, *Ber.*, 1919, **52**, 282); *p*-bromodimethylaniline is slowly brominated in concentrated sulphuric acid, to yield the 3 : 4-dibromo-compound as sole product.

Cationoid chlorination of dimethylaniline was essentially analogous to the bromination. From the resulting mixture of bases was obtained 3-chloro-*NN*-dimethyl-4-nitrosoaniline hydrochloride (*ca.* 28% based on dimethylaniline), readily reduced to 4-amino-3-chlorodimethylaniline (cf. Part III, *J.*, 1946, 532). From a specimen of the mixed bases, freed from *m*-chlorodimethylaniline and unchanged dimethylaniline by diazotised sulphanilic acid, was obtained *p*-chlorodimethylaniline (*ca.* 20%). No 3 : 4-dichloro-compound could be isolated in this reaction, but it was subsequently established that *p*-chlorodimethylaniline is chlorinated normally, but very slowly, in concentrated sulphuric acid to give the previously unknown 3 : 4-dichlorodimethylaniline, identical with the product obtained from diazotised 4-amino-3-chlorodimethylaniline by the Sandmeyer procedure. The impression that chlorine reacts less readily than bromine under the conditions used is supported by the failure to achieve the cationoid chlorination of *p*-acetamidodimethylaniline; after 48 hours only unchanged material (65%) could be isolated.

The use of carbon tetrachloride as a solvent for chlorine in this type of chlorination (Gorvin, *loc. cit.*) is satisfactory only with substances which react rapidly under the conditions employed. In presence of silver sulphate the independent reaction between carbon tetrachloride and sulphuric acid (cf. Grignard and Urbain, *Compt. rend.*, 1919, **169**, 17; Mauguin and Simon, *ibid.*, p. 34) proceeds slowly at room temperature with withdrawal of Ag^+ cations from the system as silver chloride; consequently the yield of chlorination product is reduced. The amount of silver chloride produced when carbon tetrachloride reacts with an excess of sulphuric acid is in agreement with the essentially hydrolytic scheme :

$$CCl_4 + HO{\cdot}SO_3H = COCl_2 + 2HCl + SO_3$$

since the chlorosulphonic acid usually written in the equation is unstable under these conditions (Williams, *J.*, 1869, **22**, 306). Although *p*-nitrotoluene is chlorinated so rapidly that there is little interference from the competing reaction, bis-*p*-dimethylaminophenylmethane reacted more slowly and the presence of carbon tetrachloride reduced the yield of 2 : 2′-dichloro-derivative from 77% to 39%. The fairly rapid chlorination of benzoic acid gave products of a nature substantially unaffected by the presence of the solvent, but with dimethylaniline the final yield of 4-amino-3-chlorodimethylaniline, isolated as the acetyl derivative, was reduced to half. An attempt to chlorinate *p*-chlorodimethylaniline under similar conditions resulted only in the recovery of unchanged material. The use of a solvent for chlorine is not however really necessary, since large amounts of material can be chlorinated in a reasonably sized flask by shaking in an atmosphere of chlorine; the progress of the reaction may be followed by the fall in pressure and further amounts of chlorine introduced as required.

From a theoretical standpoint these halogenation results provide further evidence for the concept, based mainly on nitration studies, of the substantial inhibition of the *ortho-para*-directing power of the dialkylamino-group by salt formation in concentrated sulphuric acid and its replacement by the *meta*-directing influence of the $-NHR_2^+$ group. The procedure, which is likely to find application chiefly among dialkylanilines already containing an *ortho-para*-directing group in the *para*-position, is distinguished by the exceptional ease of recovery of silver halide, and of subsequent isolation of the product; losses due to concurrent sulphonation or other side reactions were not considerable in the examples studied.

EXPERIMENTAL

Di-(2-bromo-4-dimethylaminophenyl)methane.—A solution of bis-*p*-dimethylaminophenylmethane (2·54 g., 0·01 mol.) and silver sulphate (3·12 g., 0·01 mol.) in concentrated sulphuric acid (30 c.c.) was shaken with bromine (3·2 g., 0·02 mol.). Heat was evolved and after 2 hours the theoretical amount of silver bromide was obtained on filtration. The filtrate was poured into ice-water containing sodium sulphite and neutralised with ammonia. The crude product (3·98 g., 97%; m. p. 95—97°) formed needles (80—85%) (from ethanol), m. p. 103—104°, not depressed by di-(2-bromo-4-dimethylaminophenyl)methane prepared by the Sandmeyer procedure from di-(2-amino-4-dimethylaminophenyl)methane. The pure product had m. p. 104—105° (Found: C, 49·5; H, 4·9; Br, 38·2. Calc. for $C_{17}H_{20}N_2Br_2$: C, 49·5; H, 4·9; Br, 38·8%) (Jones and Mason, *loc. cit.*, reported m. p. 103°).

Di-(2-chloro-4-dimethylaminophenyl)methane.—A solution of bis-*p*-dimethylaminophenylmethane (1·27 g., 0·005 mol.) and silver sulphate (1·56 g., 0·005 mol.) in concentrated sulphuric acid (20 c.c.) was shaken with excess of dry chlorine in a stoppered 500-c.c. flask fitted with a tap. After 4 hours pressure ceased to fall. The excess of chlorine was removed in a current of air and the acid solution poured into ice-water containing sodium sulphite. After removal of silver chloride (quantitative) the filtrate was neutralised and extracted with ether, to give crude di-(2-chloro-4-dimethylaminophenyl)methane (1·6 g.) as an oil which rapidly solidified (m. p. 89—92°). One crystallisation from ethanol gave 1·25 g. (77%), m. p. 97°, and further crystallisation gave needles, m. p. 99—100°, unchanged by authentic material, m. p. 99—100°, prepared from di-(2-amino-4-dimethylaminophenyl)methane (Jones and Mason, *loc. cit.*, gave m. p. 96°; von Braun and Kruber, *Ber.*, 1913, **46**, 3463, reported m. p. 96—97°) (Found: C, 63·3; H, 6·2; Cl, 21·65. Calc. for $C_{17}H_{20}N_2Cl_2$: C, 63·2; H, 6·2; Cl, 21·9%).

Passage of a slow stream of dry chlorine for 6½ hours through a sulphuric acid solution of the reactants gave only an 85% recovery of silver chloride and a 48% yield of 2 : 2′-dichloro-derivative purified to m. p. 95—96°.

4-Acetamido-3-bromodimethylaniline.—A solution of *p*-acetamidodimethylaniline (1·78 g., 0·01 mol.) and silver sulphate (1·56 g., 0·005 mol.) in concentrated sulphuric acid (25 c.c.) was shaken with bromine (1·6 g., 0·01 mol.) for 48 hours and then poured into ice-water containing sodium sulphite. The silver bromide (1·5 g., 80%) was removed and the filtrate neutralised with ammonia, whereupon *4-acetamido-3-bromodimethylaniline* (1·66 g., 65%; m. p. 121—123°) separated. A further 5% was obtained by ether-extraction of the filtrate. The acetyl derivative formed square platelets (from aqueous ethanol), m. p. 123·5—124·5°, unchanged by admixture with the acetylation product of 4-amino-3-bromodimethylaniline prepared from *m*-bromodimethylaniline (Kharasch and Piccard, *loc. cit.*) (Found: C, 47·1; H, 5·2; Br, 31·4. $C_{10}H_{13}ON_2Br$ requires C, 46·7; H, 5·1; Br, 31·1%).

Shaking for 24 hours only gave a 70% recovery of silver bromide and a 55% total yield of acetyl derivative, m. p. 121—123°.

3-Bromo-4-formamidodimethylaniline.—*p*-Formamidodimethylaniline (1·64 g., 0·01 mol.) was brominated in a similar manner; again the reaction was sluggish and after 48 hours the yield of silver bromide was 1·6 g. (85%). Neutralisation gave a precipitate of 3-*bromo*-4-*formamidodimethylaniline* (1·3 g., 54%; m. p. 116—118°), which separated from aqueous ethanol in felted needles, m. p. 118·5—119·5° (Found : C, 44·6; H, 4·6. $C_9H_{11}ON_2Br$ requires C, 44·5; H, 4·6%). Its structure was verified by hydrolysis (50% sulphuric acid) and acetylation of the resulting base to 4-acetamido-3-bromodimethylaniline.

Bromination of Dimethylaniline in Sulphuric Acid.—(a) *General procedure.* A solution of dimethylaniline (4·84 g.) and silver sulphate (6·42 g.) in concentrated sulphuric acid (50 c.c.) was shaken overnight with bromine (6·4 g.); heat of reaction was apparent after 5 minutes. Silver bromide was precipitated quantitatively. The acid solution, adjusted to pH 2—3, gave 3 : 4-dibromodimethylaniline (*ca.* 0·76 g., 7%) on being kept at 0°; this crystallised from dilute hydrochloric acid and from light petroleum (b. p. 40—60°) in needles or hexagonal plates, m. p. 66·5—67°, not depressed by 3 : 4-dibromodimethylaniline prepared by the bromination of *m*-bromodimethylaniline (Found : Br, 57·4. Calc. for $C_8H_9NBr_2$: Br, 57·3%). The picrate (yellow leaflets) had m. p. 150—151° (Found : Br, 31·3. Calc. for $C_{14}H_{12}O_7N_4Br_2$: Br, 31·5%). Vorländer and Siebert (*Ber.*, 1919, **52**, 290) record m. p. 69—70° for the base and m. p. 142—146° for the picrate.

The filtrate from 3 : 4-dibromodimethylaniline was brought to a standard volume : 30% of the solution was shaken for 2 hours at pH 3—4 with a diazo-solution prepared from sulphanilic acid (2·5 g.). The resulting mixture was made alkaline and extracted with ether to give an oil (0·5 g.) which solidified. This, when freed from traces of 3 : 4-dibromodimethylaniline by adjustment of the pH of an acidic solution, gave *p*-bromodimethylaniline (*ca.* 20%), characterised by its mixed m. p. with authentic material and through the picrate, m. p. 136—138° (Fahim and Galaby, *J.*, 1950, 3531, record m. p. 136—137°).

A further volume (5%) of the standard solution was coupled with a diazo-solution prepared from *p*-nitroaniline. The yield of crude azo-compound was *ca.* 71%. After allowance for the presence of 7% of unchanged dimethylaniline (corresponding to the amount of 3 : 4-dibromo-compound), the maximum amount of *m*-bromodimethylaniline in the mixture was *ca.* 64%. Attempts to obtain *m*-bromodimethylaniline free from the *p*-isomer and dimethylaniline were only partly successful.

(b) *Nitrosation of bromination product.* In a bromination of the type described above there were obtained on neutralisation of the sulphuric acid solution and extraction with ether 7·2 g. (90%) of an oil. This was dissolved in a mixture of hydrochloric acid (20 c.c.; *d* 1·2) and water (65 c.c.), and sodium nitrite (5·1 g.) in water (24 c.c.) was run in at 0°, followed by 10% hydrochloric acid (13 c.c.). After 3 hours the precipitate was collected, washed with 3% hydrochloric acid (25 c.c.), and dried. The powdered material was washed with dry ether, and the suspension filtered, to give 3-bromo-*NN*-dimethyl-4-nitrosoaniline hydrochloride in *ca.* 33% yield (based on dimethylaniline) : the ethereal filtrate on slow evaporation gave crystals of *NN*-dimethyl-*p*-nitroaniline (*ca.* 2%) derived from unchanged dimethylaniline present in the oil.

(c) *Reduction of the nitroso-compound.* The method of Kharasch and Piccard (*loc. cit.*) gave the base which was acetylated and reprecipitated from acetic acid with ammonia to give 4-acetamido-3-bromodimethylaniline, m. p. 122—123°, in *ca.* 22% yield (based on dimethylaniline).

A comparable bromination of dimethylaniline in 100% sulphuric acid gave results essentially similar to those obtained in the ordinary concentrated acid.

Bromination of p-*Bromodimethylaniline in Sulphuric Acid.*—A solution of the base (2·0 g.) and silver sulphate (1·56 g.) in concentrated sulphuric acid (20 c.c.) was shaken with bromine (1·6 g.). Reaction was sluggish, and the recovery of silver bromide after 24 hours was 74%. At pH 2—3 there was precipitated 3 : 4-dibromodimethylaniline (0·9 g., 46%), m. p. 67°, unchanged by previously obtained samples. The filtrate on adjustment of pH afforded a further amount of product in addition to unchanged *p*-bromodimethylaniline.

Chlorination of Dimethylaniline in Sulphuric Acid.—A solution of dimethylaniline (2·42 g.) and silver sulphate (3·12 g.) in concentrated sulphuric acid (25 c.c.) was shaken with excess of dry chlorine in a 1-l. flask fitted with a tap; the reaction appeared to be complete in *ca.* 2½ hours. It was left overnight and worked up in the usual way. The recovery of silver chloride was quantitative. On neutralisation and extraction with ether, *ca.* 95% of mixed bases was obtained. The oil, dissolved in a mixture of hydrochloric acid (10 c.c.; *d* 1·2) and water (35 c.c.), was treated at 0° with sodium nitrite (2·2 g.) in water (20 c.c.); subsequently 10% hydrochloric acid (20 c.c.) was added. After 5 hours at 0° the precipitated 3-chloro-*NN*-dimethyl-4-nitrosoaniline hydrochloride was filtered off, washed with 3% hydrochloric acid (15 c.c.), and dried. The powdered material after being washed with dry ether weighed 1·23 g.

(28% based on dimethylaniline). Stannous chloride reduction and subsequent acetylation converted it into 4-acetamido-3-chlorodimethylaniline (19%), m. p. 116—117°. Recrystallisation from aqueous alcohol gave needles, m. p. 117—118°, unchanged by authentic material (Part III).

The mixed bases obtained in a similar experiment (in which 100% sulphuric acid was used) were treated with diazotised sulphanilic acid as described for the corresponding bromination. The uncoupled base gave no precipitate at pH 2. It was purified through its picrate (crude yield, *ca.* 20%) and had m. p. 35°, unchanged by *p*-chlorodimethylaniline (Part I). p-*Chlorodimethylaniline picrate* crystallised from ethanol in needles, m. p. 126—128° (Found: C, 43·8; H, 3·5; Cl, 9·3. $C_{14}H_{13}O_7N_4Cl$ requires C, 43·7; H, 3·4; Cl, 9·2%).

3 : 4-*Dichlorodimethylaniline*.—(*a*) A solution of *p*-chlorodimethylaniline (1·07 g.) and silver sulphate (1·07 g.) in concentrated sulphuric acid (15 c.c.) in a 250-c.c. flask fitted with a tap, was shaken with excess of chlorine for 60 hours, then left for 120 hours. The solution was worked up in the usual way and 3 : 4-*dichlorodimethylaniline* (0·79 g., 61%; m. p. 37—39°) was precipitated at pH 2—3. It was very soluble in light petroleum (b. p. 40—60°), but crystallised from dilute hydrochloric acid in needles, m. p. 38—39° (Found: C, 50·4; H, 5·1; Cl, 37·3. $C_8H_9NCl_2$ requires C, 50·55; H, 4·8; Cl, 37·3%). Its *picrate* crystallised from ethanol in flakes, m. p. 138—139° (Found: Cl, 17·1. $C_{14}H_{12}O_7N_4Cl_2$ requires Cl, 16·9%). The aqueous filtrate from the dichloro-compound was brought to pH 10; unchanged *p*-chlorodimethylaniline (0·1 g., 9%, m. p. 35°) slowly crystallised.

(*b*) 4-Acetamido-3-chlorodimethylaniline (0·74 g.) was hydrolysed with hydrochloric acid, and the solution diazotised and added to excess of cuprous chloride in hydrochloric acid at 80°. After neutralisation with ammonia the mixture was steam-distilled. Ether-extraction of the distillate gave an oil (0·37 g.) which afforded a picrate (0·59 g.), m. p. 135—136°, not depressed by 3 : 4-dichlorodimethylaniline picrate described above. The base, regenerated from the picrate and crystallised from dilute hydrochloric acid, had m. p. 38—39°, unchanged by 3 : 4-dichlorodimethylaniline.

Reaction of Carbon Tetrachloride with Sulphuric Acid.—Carbon tetrachloride (1·54 g., 0·01 mol.) was shaken with a solution of silver sulphate (6·24 g., 0·02 mol.) in concentrated sulphuric acid (15 c.c.). Carbonyl chloride was evolved. The silver chloride was filtered off after 4 hours, washed with water and alcohol, and dried: its weight (2·86 g.) was equivalent to the formation of 2HCl from each molecule of CCl_4. No further precipitation of silver chloride occurred in the filtrate on storage; after passage of a current of dry air for an hour and subsequent dilution only a slight precipitate was formed as a result of the hydrolysis of residual carbonyl chloride.

The author thanks Mr. P. W. Legg for experimental assistance and Mr. P. R. W. Baker for the microanalyses.

THE WELLCOME LABORATORIES OF TROPICAL MEDICINE,
LONDON, N.W.1.

[*Received, January 22nd,* 1953.]