[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

The Activation of Aromatic Halogen by Ortho Ammonium Salt Groups

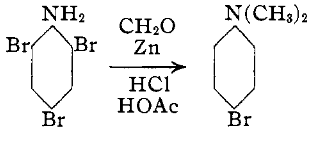
BY WILLIAM S. EMERSON, F. B. DORF AND A. J. DEUTSCHMAN, JR.

In order to complete a study of the reductive alkylation of aromatic primary amines[1] by extending the reaction to include acid reducing agents, an examination was made of compounds where the active 2,4,6-positions were blocked. This blocking was necessary because aniline and aldehydes react to form polymers in the presence of acid, whereas Clark, Gillespie and Weisshaus[2] had already shown that 2,4,6-tribromoaniline could be methylated in 77% yield with formaldehyde and formic acid. When, in the present work, zinc and hydrochloric acid was substituted for formic acid as the reducing agent, a new difficulty arose. Bromine was removed from the benzene ring.

The removal of aromatic bromine with hydrogen and a catalyst[3] or alkaline reagents such as sodium amalgam or sodium and alcohol[4] is well known. However, few cases of such reduction using a metal and acid have been reported, and in nearly all of these instances the halogen was activated by the strongly positive nitro group in the *ortho* or *para* position.[5]

The same activation can be produced by an ammonium salt group. Jackson and Calvert[6] obtained 2,4-dibromoaniline from 2,4,6-tribromoaniline and *m*-phenylenediamine from 1,3-diamino-2,4,6-tribromobenzene by reduction with tin and hydrochloric acid. Under the same conditions 1,3,5-tribromobenzene remained unchanged. Using this same reagent Blanksma[5a] obtained *m*-toluidine from 2,4,6-tribromo-3-aminotoluene. In view of these three reactions the removal of bromine in the case of the nitrobromobenzenes[5] may have occurred after the reduction of the nitro group, the activation then being due in all cases to the ammonium salt.

We have found that in the reductive alkylation of brominated aromatic primary amines with formaldehyde using amalgamated zinc and hydrochloric acid as the reducing agent, one or both ortho bromine atoms were removed during the formation of the tertiary amine. Under these same conditions 2,4,6-trichloroaniline was methylated without halogen removal.



Positive (meta directing) groups are known to activate halogens in the ortho and para positions. It is now clear that ammonium salts not only direct an entering group to the meta position[7] but also activate halogens in the ortho and para positions in exactly the same way as other groups with a positively charged atom attached to the ring.

Experimental

N,N-Dimethyl-*p*-bromoaniline.—To a solution of 15 g. of 2,4,6-tribromoaniline in 200 cc. of glacial acetic acid was added 25 cc. of 40% aqueous formaldehyde and 100 g. of amalgamated zinc.[8] This mixture was refluxed twenty-four hours, 200 cc. of concentrated hydrochloric acid being added during the first five hours. After the excess hydrochloric acid had been neutralized with sodium hydroxide, the mixture was cooled and extracted with four 100-cc. portions of benzene. The benzene was distilled from the combined extracts and then the product was distilled at 140–145° (22 mm.). It solidified in the receiver. After one crystallization from aqueous alcohol it melted at 52.5–53.0° (56°)[9]; yield 8 g. (88%).

Anal. Calcd. for $C_8H_{10}NBr$: Br, 40.0. Found: Br, 39.7.

The hydroiodide crystallized from methyl alcohol in needles melting at 143–144° (145°).[9]

Other Dimethylanilines.—Following the same general procedure described above for the preparation of N,N-dimethyl-*p*-bromoaniline, five other substituted dimethylanilines have been prepared.

N,N-Dimethyl-2-bromo-4-methylaniline was obtained in 75% yield from 2,6-dibromo-4-methylaniline and was identified as the picrate, m. p. 112.0–113.5° (115°).[10]

N,N-Dimethyl-4-bromo-3-methylaniline was prepared in 63% yield from 2,4,6-tribromo-3-methylaniline. It melted at 54° (55°)[11] and was further characterized by means of its hydrochloride, m. p. 149–150°.

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(1) Emerson and Walters, THIS JOURNAL, **60**, 2023 (1938); Emerson and Robb, *ibid.*, **61**, 3145 (1939).

(2) Clark, Gillespie and Weisshaus, *ibid.*, **55**, 4571 (1933).

(3) Busch and Stöve, *Ber.*, **49**, 1063 (1916); Kelber, *ibid.*, **50**, 305 (1917); *ibid.*, **54**, 2255 (1921); Rosenmund and Zetzsche, *ibid.*, **51**, 578 (1918); Brown, Durand and Marvel, THIS JOURNAL, **58**, 1594 (1936).

(4) For several references see Houben and Weyl, "Die Methoden der organischen Chemie," Vol. II, p. 359.

(5) (a) Blanksma, *Rec. trav. chim.*, **24**, 320 (1905); (b) Willstätter and Kubli, *Ber.*, **42**, 4151 (1909).

(6) Jackson and Calvert, *Am. Chem. J.*, **18**, 465 (1896).

(7) Noelting and Collin, *Ber.*, **17**, 261 (1884); Pinnow, *ibid.*, **27**, 3161 (1894); Clemo and Smith, *J. Chem. Soc.*, 2414 (1928).

(8) Prepared by the method of Martin, THIS JOURNAL, **58**, 1440 (1936).

(9) Fries, *Ann.*, **346**, 128 (1906).

(10) Von Braun, *Ber.*, **41**, 2100 (1908).

(11) Von Braun and Kruber, *ibid.*, **46**, 3460 (1913).

Anal. Calcd. for $C_9H_{13}NBrCl$: Cl, 14.2. Found: Cl, 14.2.

N,N-Dimethyl-4-bromo-2-methylaniline was obtained in 68% yield from 4,6-dibromo-2-methylaniline and in 54% yield from 4-bromo-2-methylaniline. In the latter reaction 3 g. of tar also was obtained. The product distilled at 120–130° (20 mm.); d^{20}_{20} 1.3300; $n^{20}\text{D}$ 1.5660; $M^{20}\text{D}$ calcd. 53.4; found 52.4. It was characterized as the hydrochloride, which proved to be too hygroscopic for a melting point determination and was therefore analyzed directly.

Anal. Calcd. for $C_9H_{13}NBrCl$: Cl, 14.2. Found: Cl, 13.9.

N,N-Dimethyl-2,4-dimethylaniline was prepared in 90% yield from 6-bromo-2,4-dimethylaniline. Its picrate melted at 122.0–122.5° (121–123°).[12]

N,N-Dimethyl-2,4,6-trichloroaniline.—Under these same conditions 2,4,6-trichloroaniline was methylated without loss of chlorine. The N,N-dimethyl-2,4,6-trichloroaniline was identified by its physical properties: b. p. by Siwoloboff method 246° (247°);[10] d^{20}_{20} 1.3140; $n^{20}\text{D}$ 1.5660; $M^{20}\text{D}$ calcd. 55.6, found 55.7.

Summary

In the reductive alkylation of aromatic primary amines containing bromine in the ortho positions, one or both bromine atoms are removed when amalgamated zinc and hydrochloric acid is used as the reducing agent. With formaldehyde as the alkylating agent, substituted dimethylanilines are produced. This bromine removal is due to the activation of the bromine by the strongly positive ammonium salt ortho to it.

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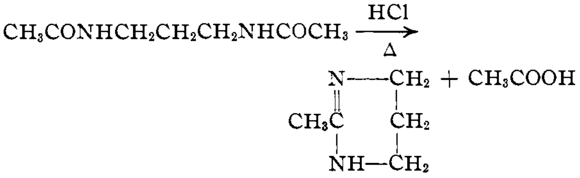
[12] Fichter and Müller, *Helv. Chim. Acta*, **8**, 290 (1925).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF SWARTHMORE COLLEGE]

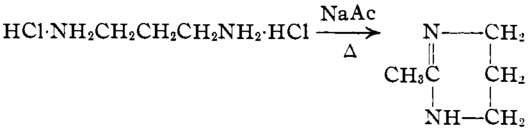
A Synthesis of Tetrahydropyrimidines

BY SAMUEL R. ASPINALL

Very little is known about the chemistry of reduced pyrimidines. An examination of the literature shows that only three derivatives of tetrahydropyrimidine have been reported and these were prepared in small yields and impure condition. Almost nothing is stated about their reactions. Hofmann,[1] in reporting the preparation of 2-methyl-3,4,5,6-tetrahydropyrimidine[2] by heating diacetyltrimethylenediamine in a stream of dry hydrogen chloride, described the compound as a dark brown oil, but recorded no yields nor physical constants of the base nor of any of its derivatives.

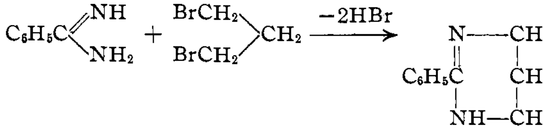


Hofmann also reported the 2-phenyl derivative but the description of the procedure and the compound was vague. Haga and Majima[3] obtained the 2-methylpyrimidine in a state of reasonable purity by fusing the hydrochloride of trimethylenediamine with sodium acetate.



Harries and Haga[4] had used the same method to prepare 2,4,6-trimethyl-3,4,5,6-tetrahydropyrimidine from 2,4-diaminopentane. This type of reaction, analogous to the preparation of 2-methyl-4,5-dihydroimidazole by fusing ethylenediamine hydrochloride with sodium acetate, is known to give very poor results.[5]

Pinner[6] reported 2-phenyl-3,4,5,6-tetrahydropyrimidine to be a minor, oily by-product when benzamidine and trimethylene dibromide were allowed to react for several weeks.



Its analysis, by means of the chloroplatinic acid salt, was very poor.

Later, Branch and Titherley[7] reported that they were unable to obtain any 2-phenyl-3,4,5,6-tetrahydropyrimidine using Hofmann's method, but a modification of Pinner's technique yielded,

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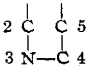
[1] Hofmann, *Ber.*, **21**, 2336 (1888).

[2] The pyrimidine nucleus is numbered as follows:



[3] Haga and Majima, *Ber.*, **36**, 333 (1903).

[4] Harries and Haga, *ibid.*, **32**, 1191 (1899).

[5] Chitwood and Reid, THIS JOURNAL, **57**, 2424 (1935).

[6] Pinner, *Ber.*, **26**, 2122 (1893).

[7] Branch and Titherley, *J. Chem. Soc.*, **101**, 2342 (1912).