6. *The Nuclear Alkylation of Aromatic Bases. Part V. The Action of Methyl Alcohol on* m-*Toluidine Hydrochloride.*

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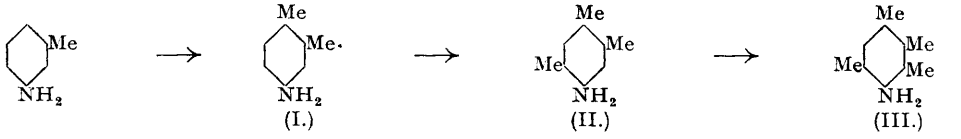
The action of methyl alcohol on *m*-toluidine hydrochloride in equimolecular proportion at 210—235° gives *o*-4-xylidine in 30% yield. With 3 mols. of methyl alcohol, *ψ*-cumidine is obtained in about 50% yield, whereas with 4 mols. at higher temperatures the products are *iso*duridine, *iso*durenol, and pentamethylphenol.

In an earlier communication on the Hofmann–Martius reaction (Hey, J., 1931, 1581) a study was made of the action of methyl alcohol on the hydrochlorides of *o*- and *p*-toluidine at 250—300°. In view of the importance of *o*-4-xylidine as an intermediate in the preparation of riboflavin (vitamin B_2) attention has now been directed to the application of this reaction to *m*-toluidine hydrochloride, which when heated in an autoclave with methyl alcohol should give rise successively to *o*-4-xylidine (I), *ψ*-cumidine (II), and *iso*duridine (III).



(I.) (II.) (III.)

Limpach (*Ber.*, 1888, **21**, 643) states briefly that the action of methyl alcohol on *m*-toluidine hydrochloride at 250° gives a primary base identical with *o*-4-xylidine, and a casual mention of the formation of *o*-4-xylidine from *m*-toluidine was also made by Liebermann and Kardos (*Ber.*, 1914, **47**, 1563). Noelting and Forel (*Ber.*, 1885, **18**, 2680) reported the formation of *ψ*-cumidine from *o*-4-xylidine hydrochloride and methyl alcohol at 300—320°. Noelting and Baumann (*ibid.*, p. 1145) reported the formation of *iso*duridine from the action of methyl alcohol on *ψ*-cumidine hydrochloride at 200° and finally at 300°, and stated that the same base was formed in similar manner from mesidine hydrochloride, a claim which was contested by Limpach (*loc. cit.*). These reactions called for further investigation, especially that which leads to the formation of *o*-4-xylidine from *m*-toluidine, in order that the yields obtainable by this and alternative methods might be compared.

Reactions have now been carried out at 210° to 280° between *m*-toluidine hydrochloride and various proportions of methyl alcohol. When the two reactants were used in equimolecular proportion at 210—235°, the main basic product was *o*-4-xylidine (I); there were no phenolic by-products, but a considerable quantity of methylated acridines was formed. With 2 mols. of methyl alcohol at 200—235° the main basic product was *ψ*-cumidine (II): again no phenolic by-products were encountered, but methylated acridines were formed. The best yield of *ψ*-cumidine, however, was obtained when 3 mols. of methyl alcohol were used at 210—220°. With 4 mols. of methyl alcohol at 260—280° the products were *iso*duridine (III), *iso*durenol, pentamethylphenol, and methylated acridines.

The aromatic bases formed in these reactions were purified by distillation with a Dufton column and identified by means of the melting point of the acetyl derivatives, together with a mixed melting point with an authentic specimen (aceto-*o*-xylidide has m. p. 99°, aceto-*ψ*-cumidide 165°, and aceto*iso*duridide 217°). Earlier work (Hey, *loc. cit.*) has shown that both phenols and acridine derivatives are formed as by-products during the Hofmann–Martius reaction. The tendency to phenol formation was shown to increase with the progressive introduction of methyl groups into the nucleus. This observation is supported in the present work, which also clearly demonstrates that the reactivity of the nuclear positions in these reactions is in the order $p > o > m$. It is also clear, in agreement with Liebermann and Kardos (*loc. cit.*), that the tendency for the formation of acridine derivatives is appreciably greater with *m*-toluidine than with *o*- and *p*-toluidine. In view of the earlier work by Liebermann and Kardos the acridine by-products were not examined in the present investigation.

The maximum yield of *o*-4-xylidine so far obtained by this method was of the order of 30%, calculated on *m*-toluidine hydrochloride in the one-stage process. The method used by Karrer, Becker, Benz, Frei, Salomon, and Schöpp (*Helv. Chim. Acta*, 1935, **18**, 1435) in the synthesis of riboflavin involves the nitration of pure *o*-xylene, the separation of 4- and 5-nitro-*o*-xylene, and the subsequent reduction of 4-nitro-*o*-xylene, the overall yield of *o*-4-xylidine being approximately 15%, calculated on *o*-xylene. The unsatisfactory character of Karrer's method has also been the subject of comment by Wisansky and Ansbacher (*J. Amer. Chem. Soc.*, 1941, **63**, 2532).

In earlier work on the Hofmann–Martius reaction (Hey, *loc. cit.*; see also Hey and Jackson, J., 1934, 645) it was conclusively proved that after methylation had been effected at the *p*- and *o*-positions with reference to the amino-group further methylation could take place at the *m*-positions, resulting finally in a fully methylated aromatic nucleus. Up to that time the possibility of *m*-alkylation was frequently denied and the persistence of this view may be traced back to the erroneous statements of Limpach (*loc. cit.*). It is unfortunate that in recent publications the same incorrect statements continue to be made. For example, in a reference to the Hofmann–Martius reaction in "The Organic Chemistry of Nitrogen" by N. V. Sidgwick (Ed. by T. W. J. Taylor and W. Baker, Oxford, 1937, p. 77), one finds "the *p*-alkyl-aniline is formed if the *p*-position is free and, if not, an *o*-alkyl-aniline can be formed, but the *m*-position is never occupied." The same misunderstanding is implicit in a statement due to Drumm, O'Connor, and Reilly (*J. Amer. Chem. Soc.*, 1940, **62**, 1241; see also

Watson, *Ann. Reports*, 1941, 123), who, in an examination of the products formed in the rearrangement of dibenzylaniline hydrochloride, reported the formation of *p*-aminodiphenylmethane, 1-amino-2 : 4-dibenzylbenzene, and a compound regarded as 1-amino-2 : 4 : 6-tribenzylbenzene and referred to the last as the first example of the introduction of more than two groups in this reaction. The present authors emphasise once again the fact that *m*-methylation in the Hofmann–Martius reaction has been established beyond question.

Experimental.

General Method.—The dry methyl alcohol and dry *m*-toluidine hydrochloride were heated in an iron autoclave of approximately 300 c.c. capacity immersed in an oil-bath. The autoclave was fitted with a pressure gauge and thermometer pocket but was without a stirrer. The product was distilled with steam, first from acid solution in order to remove phenols, and then from alkaline solution to remove volatile aromatic bases. The non-volatile residue, contaminated with some ferric hydroxide from the walls of the autoclave, was extracted repeatedly with hot benzene, which removed the acridine derivatives. The volatile aromatic bases were redistilled through a Dufton column. The following results were obtained :

(a) *With* 1 *mol. of methyl alcohol.* (i) A mixture of *m*-toluidine hydrochloride (48 g.) and methyl alcohol (11 g.) was heated at 215—220° for 6 hours. Steam-distillation from acid solution gave no phenols, but after basification volatile aromatic bases (10·5 g.; yield, 26%, calculated as xylidine on *m*-toluidine) were collected, which distilled at 210—230°. Redistillation gave mainly *o*-4-xylidine, b. p. 222—228°, m. p. 47—48° (acetyl derivative, m. p. and mixed m. p. 96—98°). The authentic specimen of aceto-*o*-4-xylidide was prepared by reduction of 4-nitro-*o*-xylene and subsequent acetylation. Evaporation of the benzene extract gave a mixture of methylated acridines (8·1 g.).

(ii) Repetition of this experiment at 210—235° for 8 hours gave no phenolic products, but volatile aromatic bases (14 g.; yield, 35%), b. p. 210—230°, which consisted mainly of *o*-4-xylidine, and methylated acridines (7 g.).

(b) *With* 2 *mols. of methyl alcohol.* *m*-Toluidine hydrochloride (48 g.) and methyl alcohol (22 g.) were heated together for 9 hours at 200—235°. No phenols were obtained, but steam-distillation from alkaline solution gave aromatic bases (17 g.), b. p. 225—240°. Redistillation gave mainly ψ-cumidine, b. p. 230—236°, m. p. 64° (acetyl derivative, m. p. and mixed m. p. 162—164°). The methylated acridines were not isolated.

(c) *With* 3 *mols. of methyl alcohol.* *m*-Toluidine hydrochloride (48 g.) and methyl alcohol (33 g.) were heated at 210—220° for 5½ hours. No phenolic products were obtained, but the volatile aromatic bases (24·5 g.; yield, 54%, calculated as ψ-cumidine on *m*-toluidine), b. p. 220—240°, consisted almost exclusively of ψ-cumidine, b. p. 232—236°, m. p. 64° (acetyl derivative, m. p. 163—164°). The benzene extract yielded a residue of methylated acridines (6·3 g.).

(d) *With* 4 *mols. of methyl alcohol.* (i) *m*-Toluidine hydrochloride (48 g.) and methyl alcohol (44 g.) were heated at 260—280° for 10 hours. Steam-distillation from acid solution gave a phenolic product (10·5 g.), which after repeated crystallisation from light petroleum yielded pentamethylphenol, m. p. and mixed m. p. 124—125°. Concentration of the mother-liquors deposited crude *iso*durenol, which after several crystallisations melted at 79—81°, both alone and on admixture with an authentic specimen. After basification volatile aromatic bases (16 g.) were collected which distilled at 255—260°. The bases solidified on cooling. Redistillation gave pure *iso*duridine, b. p. 258—259°, which on acetylation gave aceto*iso*duridide (white needles from alcohol), m. p. and mixed m. p. 217·5° (Found : C, 75·2; H, 8·8; N, 7·5. Calc. for $C_{12}H_{17}ON$: C, 75·4; H, 8·9; N, 7·3%). Evaporation of the benzene gave a residue of methylated acridines.

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