PREPARATION OF 3:4-DICHLORO- AND 3:4:5-TRICHLORO-ANILINES

BY N. S. JOHARY, S. S. GUHA AND P. C. GUHA

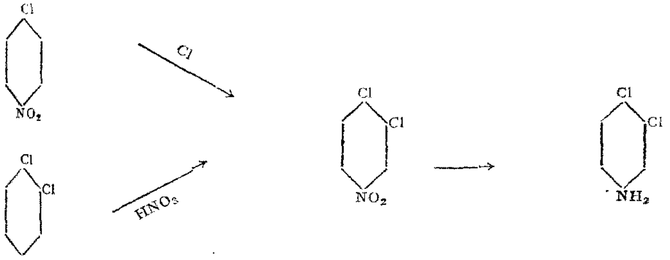
(Department of Organic Chemistry, Indian Institute of Science, Bangalore-3)

During a course of research on synthetic antimalarials, it was required to prepare large quantities of 3 : 4-dichloro- and 3 : 4 : 5-trichloro-anilines. A survey of the literature showed that the syntheses of 3 : 4-dichloro- and 3:4: 5-trichloro-anilines have been accomplished by many chemists, but nowhere any details were recorded. It was, therefore, thought desirable to investigate into their methods of preparation with a view to finding out the best one and ascertaining necessary details for the successful laboratory and semi-large-scale preparation of these valuable amines.

3 : 4-DICHLORO-ANILINE

3:4-Dichloro-aniline was prepared by Beilstein and Kurbatow[1] by the chlorination of *m*-chloro-aniline or reduction of 1 : 2-dichloro-4-nitrobenzene, and by Chattaway, *et al.*,[2] by the molecular transformation of *m*-chloro-phenyl-acetyl-nitrogen chloride. 1 : 2-Dichloro-4-nitrobenzene has been prepared by the nitration of *o*-dichlorobenzene[3, 4, 5] and by the chlorination of *p*-chloro-nitrobenzene.[6, 7, 8]

Of the various methods for the preparation of 3 : 4-dichloro-aniline mentioned above, only that using 1 : 2-dichloro-4-nitrobenzene is of any practical importance, as the other methods give the desired amine either as a side product or in a very imperfect yield.



The nitration of commercial *o*-dichlorobenzene, which is usually associated with its *p*-isomer and difficult to purify, gave a mixture of the nitrated products, which was found difficult to separate. The preparation of 1:2-dichloro-4-nitrobenzene from commercial *o*-dichlorobenzene, therefore, had to be abstained.

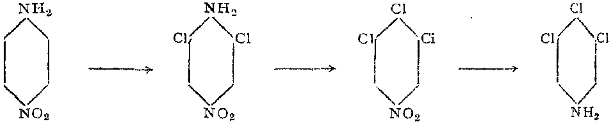
It was found that pure 1:2-dichloro-4-nitrobenzene could easily be prepared by the chlorination of *p*-chloro-nitrobenzene in a fused state with the use of a catalyst. Iron powder, ferric chloride and iodine were tried but proved to be inefficient catalysts. A mixture of iron and iodine, however, was found to be an excellent catalyser for this purpose, the chlorination being completed within a few hours at 100–105°, giving 1:2-dichloro-4-nitrobenzene as the exclusive product in a very good yield.

1:2-Dichloro-4-nitrobenzene so obtained was readily reduced to 3:4-dichloro-aniline with iron and acetic acid; the use of iron and hydrochloric acid giving a much less pure product.

3:4:5-TRICHLORO-ANILINE

3:4:5-Trichloro-aniline was first prepared by Zincke and Schaum.[9] Soon after, Cohen, Bennett and Crosland[10] reported its synthesis from *p*-nitro-aniline, but did not give any details. Subsequently Holleman[11] gave a detailed account of its preparation from the same compound which was shortly repeated by Dyson, George and Hunter.[12]

The following are the various steps of the synthesis:—



(I) (II) (III) (IV)

Holleman[11] prepared 2:6-dichloro-*p*-nitro-aniline (II) by the action of potassium chlorate on a hydrochloric acid solution of *p*-nitroaniline, a method first discovered by Witt[13]; while Flurscheim[14] prepared it by the direct chlorination of *p*-nitroaniline. It was noticed that the method of Flurscheim, though taking a longer time, was more satisfactory in the sense that it gave a better yield of a purer product.

Considerable difficulty was incurred during the diazotisation of 2:6-dichloro-*p*-nitroaniline. Holleman[11] used sodium nitrite and hydrochloric acid, but we completely failed to repeat their experiment, every time a dark brown resinous product being formed which never entered into solution. The failure of this very general method of diazotisation can be attributed to the complete insolubility of the nitro-amine in strong or dilute hydrochloric acid and its extremely feebly basic character.

2 : 6-Dichloro-*p*-nitroaniline was found to diazotise successfully with nitrosyl-sulphuric acid by a modification of the method described by Hodgson and Walker.[15] The diazotised solution of 2 : 6-dichloro-*p*-nitroaniline underwent Sandmeyer's reaction in the usual way giving 3 : 4 : 5-trichloro-nitrobenzene, from which 3 : 4 : 5-trichloro-aniline was obtained by reduction with iron and acetic acid.

EXPERIMENTAL

p-*Chloro-nitrobenzene* was prepared by the nitration of chloro-benzene by the method of Bashioum and Powers.[16]

Chlorination of p-*chloro-nitrobenzene.*—1 : 2-*Dichloro-4-nitro-benzene.*—*p*-Chloro-nitrobenzene (200 g.) was heated in an oil-bath maintained at 100–105°, and iron powder (6 g.) and iodine (1 g.) were added to the molten mass. A rapid stream of dry chlorine was introduced till the increase in weight registered 45 g. (12 hours). The molten mass was cooled to 40°, washed first with warm dilute solution of caustic soda, and then with warm water, dried and distilled, the fraction distilling between 246–56°/685 mm., mainly between 248–52°/685 mm., being collected; yield 220 g. (93%). After one crystallisation from alcohol, m.p. 42–43°.

3 : 4-*Dichloro-aniline.*—1 : 2-Dichloro-4-nitrobenzene (210 g.) was dis-dissolved in hot 50% acetic acid (850 c.c.). The solution was heated on water-bath and iron filings (140 g.) were gradually added to the vigorously stirred solution. Stirring and heating were continued for 3–4 hours by which time the reduction of the nitro-compound was complete. The mixture was made alkaline with caustic soda (295 g.) and steam distilled, when a considerable amount of oil collected with the distillate and solidified on cooling. Yield 145 g.

Very pure 3 : 4-*Dichloro aniline* could be obtained by any one of the following methods:—

(1) The oil was dissolved in minimum quantity of boiling hydrochloric acid (15%), filtered and cooled when the *hydrochloride* of the amine crystallised out in the form of long shiny needles or pearly leaflets, depending on the concentration and the acidity of the solution and the rate of cooling. Recrystallised from water containing a few drops of hydrochloric acid, it was obtained as long, glistening needles, m.p. 245° (d). [Found: N, 7·2; $C_6H_5N_2Cl_2 \cdot HCl$ requires N, 7·07 per cent.]

3: 4-Dichloroaniline regenerated from the recrystallised hydrochloride by caustic soda was obtained in the form of shiny white leaflets from dilute ethanol, m.p. 72·5–73° C. Beilstein and Kurbatow give m.p. 71·5° C.

(2) The oil collected in the steam distillate was subjected to a second steam distillation in presence of theoretical amount of sulphuric acid. All the impurities passed with the steam distillate and were rejected. On cooling the contents of the distilling flask the very sparingly soluble sulphate of the base crystallised out in the form of pearly leaflets. These were collected by filtration, taken into hot dilute caustic soda solution and subjected to a third steam distillation, when pure 3: 4-dichloro aniline passed over. Further purification could be done by recrystallisation from dilute alcohol as before.

2: 6-*Dichloro*-p-*nitroaniline* was prepared by the chlorination of *p*-nitroaniline by the method of Flurscheim (*loc. cit.*). Yellow needles from glacial acetic acid, m.p. 190° C.

Diazotisation of 2: 6-*Dichloro*-p-*nitroaniline*; 3: 4: 5-*Trichloro-nitro benzene*.—Recrystallised 2: 6-Dichloro-*p*-nitro aniline (100 g.) was dissolved in 100 c.c. of cold concentrated sulphuric acid and the solution was diluted with 1 litre of glacial acetic acid.

The resulting suspension was added to the cold nitrosyl-sulphuric acid, keeping the temperature at 5–10° during the addition. Nitrosyl sulphuric acid was prepared by carefully dissolving 37 gm. of sodium nitrite in 260 c.c. of concentrated sulphuric acid at 0°, heating to 70° on a water-bath and again cooling to 0°. After the addition was complete, the mixture was left for one hour at the same temperature, at the end of which the diazotisation was complete as proved by diluting a small portion of the reaction mixture with three to four times its volume of water when a clear solution resulted.

The diazotised solution was slowly stirred into 65 gm. of cuprous chloride in 350 c.c. of hydrochloric acid, maintaining the temperature between 15–20°. A considerable quantity of nitrogen evolved after which the mixture was heated on a water-bath at 60–70° for one hour and 3: 4: 5-trichloronitrobenzene isolated by steam distillation as a light yellow oil which solidified on cooling. Yield 75–80 gm. Crystallised from 80% alcohol it was obtained in the form of cream coloured large prisms, m.p. 72–73°.

3: 4: 5-*Trichloro-aniline*.—3: 4: 5-Trichloro-nitrobenzene (80 gm. was reduced with hot 50% acetic acid (300 c.c.) and iron filings (60 gm.) as in the case of 3: 4-dichloro-aniline. After the reduction was complete (5 hours), the reaction mixture was made alkaline with caustic soda (110 gm.) and 3: 4: 5-trichloro-aniline isolated by steam distillation. Yield 61 gm.

The amine was purified, as in the case of 3 : 4-compound, by converting it into its *hydrochloride* and crystallising the salt from acidulated water. Long, shiny, colourless needles, m.p. 220–21° (d). [Found: N, 6·07%; $C_6H_4NCl_3HCl$ requires N, 6·01%.]

The free base was regenerated from the hydrochloride by means of caustic soda and recrystallised from dilute alcohol. Long, lustrous, colourless needles, m.p. 101°. Dyson, George, and Hunter[12] give m.p. 89°; Cohen, Bennett, and Crosland[10] give m.p. 94–95°; and Zincke and Schaum[9] give m.p. 100°.

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