The Chemistry of Aryltetraamines. II. The Synthesis of 2,3,5,6-Tetraaminopyridine.

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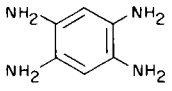
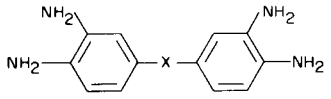
Various aromatic tetraamines have been prepared in recent years including tetraaminobenzene (**1**) (1), tetraaminobiphenyl (**2**) (1) and a variety of substituted biphenyl species such as **3** (2,3), **4** (4), **5** (5,6) and **6** (7). The development of most of these compounds can be related to current research in the field of thermally stable polymers (8).



2, X = nil
3, X = CO



4, X = O
5, X = SO_2
6, X = S

We now wish to report the recent synthesis of a new heterocyclic tetraamine, 2,3,5,6-tetraaminopyridine. Two altogether different synthetic approaches have been developed for the preparation of this new aromatic tetraamine.

Nitration of 2-aminopyridine (**7**) has been shown to give rise to a mixture of 3-nitro-2-aminopyridine (**8**) and 5-nitro-2-aminopyridine (**9**) (9-12). Under similar conditions we have found that 2,6-diaminopyridine (**10**) or its diacetamido derivative **11** undergo nitration to give a new dinitro species, 2,5-dinitro-2,6-diaminopyridine (**12**).

The direct reduction of this dinitro compound was acheived only after numerous unsuccessful attempts using various chemical and catalytic methods. Following a procedure described by Tomasik and co-workers (13) for the reduction of 3,5-dinitro-2-aminopyridine to the corresponding 2,3,5-triaminopyridine trihydrochloride, we were able to successfully reduce **12** catalytically to the corresponding 2,3,5,6-tetraaminopyridine trihydrochloride monohydrate (**13**) using palladium on carbon in ten percent hydrochloric acid.

A second synthetic approach to the tetraamine system was based on the azo coupling property of various substituted pyridines (14). Ostromeslensky (15) has reported that 2,6-diaminopyridine (**10**) undergoes azo coupling with diazotized aniline primarily at the 3-position to give the 3-phenylazo-2,6-diaminopyridine (**14**) together with small amounts of the corresponding 3,5-bisphenylazo-2,6-diaminopyridine (**15**). Reduction of **14** with Raney nickel in acetic anhydride was reported by Chichibabin and co-workers (16) to give rise to the 2,3,6-triacetamido derivative **16** while reduction of the same 3-phenylazo compound in this laboratory with Raney nickel in dimethylformamide has given the corresponding 2,3,6-triaminopyridine dihydrochloride (**17**).

Using an excess of diazotized aniline and tetrahydrofuran as a co-solvent we have been able to effectively direct the course of the azo-coupling reaction to give exclusively the bisarylazo species **15**. Subsequent catalytic reduction of **15** with either Raney nickel in dimethylformamide or palladium on carbon in tetrahydrofuran followed by acidification with anhydrous hydrochloric acid gives the same tetraaminopyridine trihydrochloride (**13**) as was obtained from the stepwise nitration and reduction of 2,6-diaminopyridine (**10**).

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover or Mel- apparatus. The infrared absorption spectra were recorded on either a Perkin-Elmer Model 137 or a Model 521 spectrophotometer. The pmr spectra were determined with a Varian T-60 spectrometer using tetramethylsilane as an internal reference.

Interpretation of pmr data: δ chemical shift p.p.m. (multiplicity, number of protons). s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet. Analyses were performed by M-H-W Laboratories, Garden City, Michigan.

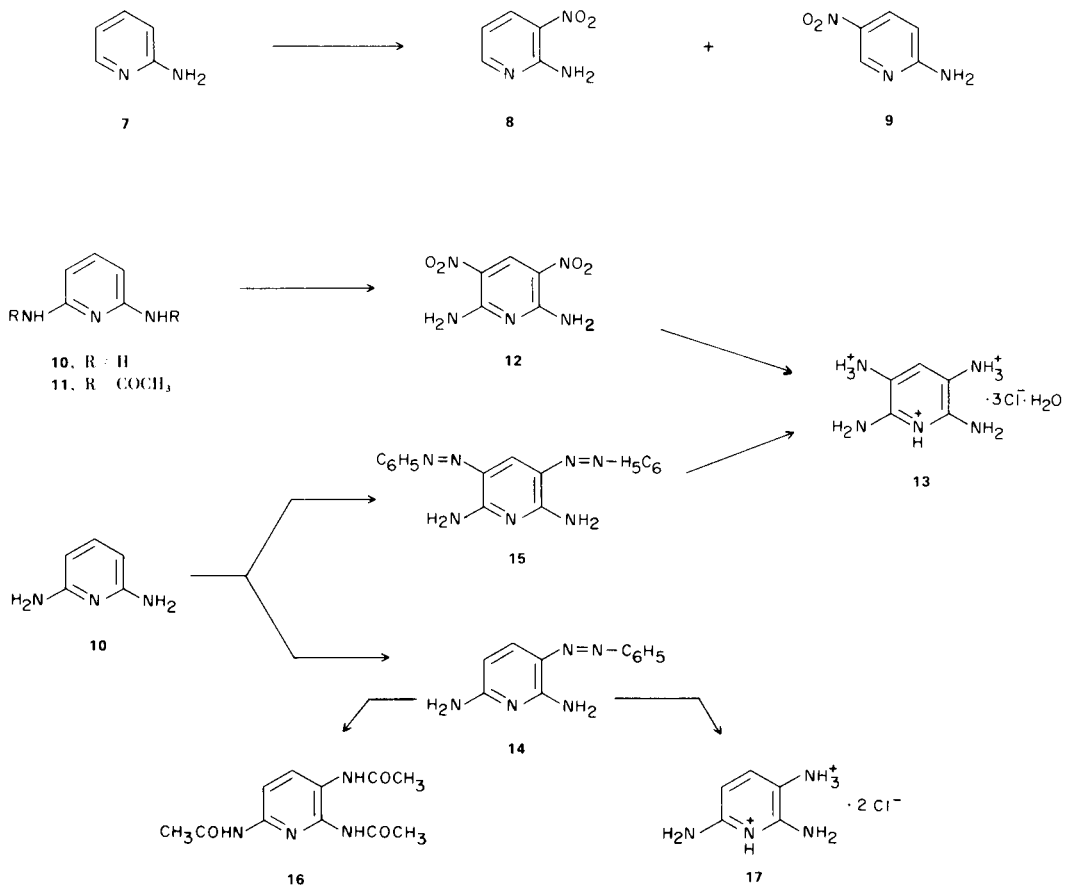
3,5-Dinitro-2,6-diaminopyridine (12).

A Solution of 20 g. (0.183 mole) of 2,6-diaminopyridine (**10**) in 200 ml. of concentrated sulfuric acid was cooled to 10° and then treated dropwise with 30 ml. of fuming (90%) nitric acid. The solution was allowed to come to room temperature slowly and subsequently heated 60-70° for one hour. The resulting yellow solution was then poured onto ice and stirred for fifteen minutes to give a crude orange-brown solid in nearly quantitative yield. Recrystallization from dioxane gave yellow plates, m.p. 348-350° dec.; ν max (potassium bromide) 3470, 3440, 3360 and 1625 cm^{-1}; pmr δ (DMSO) 8.3 (broad s, 4), 9.18 (s, 1).

Anal. Calcd. for $C_5H_5N_5O_4$: C, 30.43; H, 2.52; N, 35.49. Found: C, 30.15; H, 2.52; N, 35.17.

2,3,5,6-Tetraaminopyridine Trihydrochloride Monohydrate (13) from Compound 12.

A suspension of 1.5 g. (0.002 mole) of **12** in 75 ml. of 10% hydrochloric acid was hydrogenated with 5% palladium-on-char-



coal catalyst (0.5 g.) at 50 p.s.i. The resulting yellow solution was filtered to remove the catalyst and then treated with excess tetrahydrofuran to precipitate the tetraamine salt **13**. Slow crystallization from dilute, aqueous acid gives colorless plates of **13**. m.p. $>360°$; ν max (potassium bromide 3500, 3400, 3300, 3000-2550 (broad) and 1655 cm^{-1}; pmr δ (DMSO), 7.75 (broad s); δ (D_2O), 8.05 (s, 1H).

Anal. Calcd. for $C_5H_{14}N_5OCl_3$: C, 22.52; H, 5.25; N, 26.28. Found: C, 23.01; H, 5.52; N, 26.33.

3,5-Bisphenylazo-2,6-diaminopyridine (**15**).

A solution of 93 g. (1 mole) of aniline in 5 liters of 2% hydrochloric acid was diazotized at 6-10° with a solution of 69 g. (1 mole) of sodium nitrite in 500 ml. of water. The above solution was then treated with 29 g. (0.26 mole) of 2,6-diaminopyridine (**10**) in 1 liter of 6-*N* hydrochloric acid; stirred for one-half hour and allowed to slowly come to room temperature. The dihydrochloride of **15** began to precipitate and the entire mixture was neutralized with excess sodium acetate. Excess tetrahydrofuran was added to solublize the monoarylazo system and the solution was stirred for an additional hour to allow for further azo-coupling at the C-5 position. After one hour a heavy orange-brown precipitate had formed which was filtered and slurred in hot methanol to give 62.3 g. (76%) of **15**. Recrystallization from chloroform/methanol followed by sublimation to remove any residual 3-arylazo impurity gave red needles, m.p. 213° (Lit. 212°) (15); ν max (potassium bromide) 3400, 3300, 1650 and 1510 cm^{-1}; pmr δ (DMSO) 8.4 (s, 1), 8.0 (m, 5), 7.63 (m, 5), 8.22 broad s, 4).

Anal. Calcd. for $C_{17}H_{15}N_7$: C, 64.35; H, 4.73; N, 30.91. Found: C, 64.32; H, 4.87; N, 31.08.

2,3,5,6-Tetraaminopyridine Trihydrochloride (**13**) from Compound **15**.

A solution of 1 g. (0.003 mole) of **15** in 40 ml. of dimethylformamide was hydrogenated at 32 p.s.i. with approximately 1 g. of Raney nickel catalyst. The reduction was terminated after six hours whereupon the solution was filtered to remove the catalyst and then acidified with hydrogen chloride gas. Addition of ether produced a heavy, red oil which was separated, washed repeatedly with ether and then dissolved in methanol. Trituration with ether gave 0.45 g. (56.5%) of colorless crystals, m.p. $>360°$.

The infra-red spectrum of this product was identical with the reduction product arising from 3,5-dinitro-2,5-diaminopyridine (**12**).

Acknowledgement.

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