# Heterocyclic Studies: Aryltetraamines III. The Chemistry of 2,3,5,6-Tetraaminopyridine

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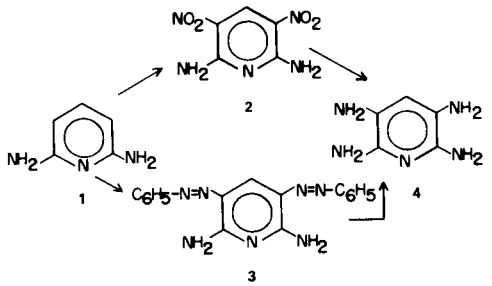
Various aromatic tetraamines have been prepared and used as monomers to synthesize heat resistant polymers such as polybenzimidazoles and polyimidazopyrrolones. 2,3,5,6-Tetraaminopyridine **4** is a very unique aromatic tetraamine since it has two very reactive amino groups at the 3 and 5 positions and two less reactive ones at the 2 and 6 positions. We have recently reported (1) the synthesis of 2,3,5,6-tetraaminopyridine trihydrochloride by catalytic reduction of either 3,5-dinitro-2,6-diaminopyridine **2** or 3,5-bisphenylazo-2,6-diaminopyridine **3** followed by acidification with hydrochloric acid. Recently, polymerization of tetraaminopyridine trihydrochloride with tetracarboxylic acid dianhydrides or a diacid chloride was reported (2).

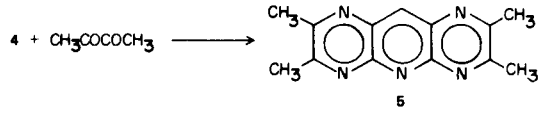
We now wish to describe the synthesis of the free tetraaminopyridine **4** and its reactions with 2,3-butanedione and acetic anhydride in order to more fully characterize this new heteroaromatic tetraamine.

Catalytic reduction of either **2** or **3** was carried out with palladium on carbon in dimethylformamide (DMF) and the free base was isolated by adding ether or tetrahydrofuran (THF) to the filtrate of the reduction mixture. The free base **4** could be obtained in a quantitative yield from the reduction of **3**. Although the tetraaminopyridine trihydrochloride we reported earlier is stable and can be stored



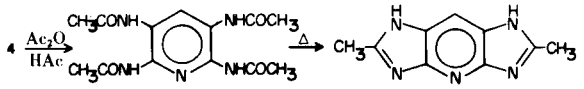
at room temperature without decomposition, the free base is not stable at room temperature and decomposes slowly, liberating ammonia.

The condensation reaction of **4** with two equivalents of 2,3-butanedione was carried out in ethanol or acetic acid under a nitrogen atmosphere to give the thermally stable



fused ring product **5**.

The acetylation reaction of **4** in excess acetic anydride was complex and two kinds of tetraacetamides were formed depending on the reaction condition. When **4** was treated with a mixture of acetic anhydride and acetic acid, 2,3,5,6-tetraacetamidopyridine **6** was obtained. Compound **6** was isolated as white needles which gave the pyrolysis product **7** when heated above its melting point.

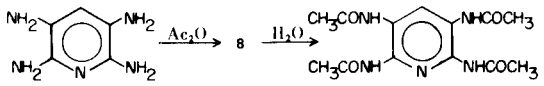


However, a somewhat different acetylation reaction took place when **4** was treated with freshly distilled acetic anhydride. The product **8** in this case was a yellow crystalline material and gave the correct elemental analysis for $C_{13}H_{17}N_5O_4$, which is the same as the formula of **6**. Compound **8** was found to be much more soluble in organic solvents than **6**. It was also soluble in water to some extent while **6** was not, however, **8** was not stable in water and could be converted to **6** by the action of water or aqueous sodium carbonate. The nmr spectrum of **8** taken in deuterated chloroform with a small amount of absolute ethanol did not show the formation of ethyl acetate, unlike the reaction between *N*-acetyl-2-pyridone with ethanol to give ethyl acetate (3). Instead, **6** was isolated unchanged after one week at room temperature.

At room temperature, the spectrum of **8** in deuterated DMF shows four non-equivalent peaks in the methyl proton region; $\delta$ 1.96, 2.27, 2.33, and 2.51, respectively. When the probe was heated to 60°, the four peaks began to collapse and at 120°, two new peaks were observed at $\delta$ 2.18 and 2.35, which were integrated equally for six protons each. On cooling to room temperature, however, the splitting pattern reverted to the original one and the change was found to be reversible below 120°.

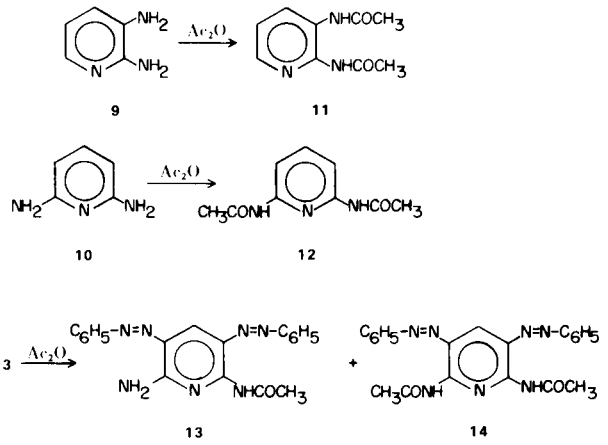
When the probe temperature was raised to 145°, an

irreversible change was observed. The peak heights at δ 2.18 and 2.35 began to decrease and a pair of new peaks gradually appeared at δ 2.08 and 2.17. After 90 minutes at 145°, the peaks at δ 2.18 and 2.35 disappeared completely and only the two new peaks at δ 2.08 and 2.17 remained. This final spectrum was identical with that of **6** taken in deuterated DMF at 145° and in fact, thermally converted **6** was isolated in a 64% yield by pouring this nmr solution into water.



**4** **6**

In order to confirm that this unusual acetylation giving rise to **8** is peculiar to **6**, three diaminopyridine derivatives were subjected to acetylation reaction under similar conditions. 2,3-Diaminopyridine **9** and 2,6-diaminopyridine **10** gave the normal diacetyl derivatives, *i.e.*, 2,3-diacetamidopyridine **11**, and 2,6-diacetamidopyridine **12**. The amino groups of **3** were less reactive and a mixture of mono- and diacetylated compounds **13** and **14** was obtained by treating **3** with acetic anhydride at 85° for 2.5 hours. However, if the reaction was carried out at 100° for 2 hours, only **14** was obtained in a good yield.

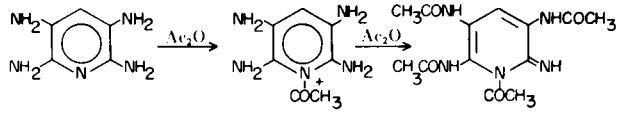


**9** **11**

**10** **12**

**13** **14**

Based on these results it appears that the tetraamine **4** reacts in a truly unique manner under acetylation conditions. Presumably, the initial attack occurs at the ring nitrogen during acetylation in freshly distilled acetic anhydride. The resulting acetylated species must then undergo subsequent acetylation at the 3,5 and 6 position to give rise to the rather unstable pyridonimine species **8**.



**4** **8**

This unique species is then apparently converted to the symmetrical tetraacetamido structure **6** either by heat or treatment with water or aqueous base. This reaction appears to be irreversible once the more stable symmetrical isomer has been formed. The direct synthesis of **6** from the tetraamine **4** with acetic anhydride/acetic acid presumably proceeds *via* the initial protonation of the central ring nitrogen and subsequent acetylation.

## EXPERIMENTAL

2,3,5,6-Tetraaminopyridine (**4**).

A solution of 5.0 g. (0.016) mole of **3** (4) in 60 ml. of freshly distilled dimethylformamide was purged with nitrogen and then reduced in a hydrogen atmosphere (31 psi) with 0.8 g. of 10% palladium on carbon. The reduction was complete after 2.5 hours. The solution was filtered and quickly purged with nitrogen.

After standing two days at 0° in the refrigerator, a heavy, light green-yellow solid had precipitated which was washed with methanol and finally with anhydrous ether. The crude product was dried under vacuum for 2 hours at 50° to give 1.86 g. (98%) of **4**, m.p. > 360° dec.; ν (potassium bromide): 3500, 3350 (-$NH_2$), 1675 and 1650 $cm^{-1}$; δ ($d_6$-DMSO): 5.58 (s, 1, Ar), 7.5 (broad s, $NH_2$).

*Anal.* Calcd. for $C_5HgN_5$: C, 43.16; H, 6.47; N, 50.35. Found: C, 43.43; H, 5.96; N, 51.0.

2,3,7,8-Tetramethylpyrido[2,3-*b*:6,5-*b*']dipyrazine (**5**).

To a dispersion of 139 mg. (1 mmole) of **4** in 10 ml. of absolute ethanol was added 0.18 ml. (176 mg, 2 mmoles) of 2,3-butanedione. The mixture gave a brown solution after stirring at room temperature for 5 hours under a nitrogen stream. It was then stirred at room temperature overnight and heated at reflux for 4 hours. The resulting dark solution was concentrated under reduced pressure to give a dark solid, which was recrystallized from chloroform to give 80 mg. of off-white needles. The mother liquor was concentrated and chromatographed on a silica gel plate (25 g. of silica gel on a 8″ x 8″ glass plate) to give an additional 30 mg. of the product. The total yield was 110 mg. (48%). A part of the sample was recrystallized from chloroform to give white needles and then sublimed at 200° at 1 mm Hg, m.p. 340° (decolor); ν (potassium bromide): 1640, 1580 $cm^{-1}$; δ ($d_6$-DMSO): 2.62 (s, 6, $CH_3$), 2.7 (s, 6, $CH_3$), 8.3 (s, 1, Ar).

*Anal.* Calcd. for $C_{13}H_{13}O_5$: C, 65.25; H, 5.48; N, 29.27. Found: C, 65.01; H, 5.75; N, 29.19.

2,3,5,6-Tetraacetamidopyridine (**6**).

A mixture of 139 mg. (1 mmole) of **4** in 1.5 ml. of acetic anhydride and 1 ml. of acetic acid was stirred at room temperature. The initial red slurry became brown solution after 2 hours. It was stirred at room temperature overnight. White needles precipitated out of the solution. The mixture was heated at 60° for 3 hours and then concentrated under reduced pressure to give a tan solid. The ir and tlc showed this contained **6** as a major product and **8** as a minor one.

Recrystallization from methanol gave 70 mg. of off-white needles. The mother liquor gave an additional 30 mg. of the product. The total yield of **6** was 100 mg. (33%). It was recrystallized from methanol again to give white needles, m.p. 282-284°; ν (potassium bromide): 3500, 3230, 1670 $cm^{-1}$; δ ($d_6$-DMSO): 2.12 (s, 6, $COCH_3$-3,5), 2.15 (s, 6, $COCH_3$-2,6), 8.54 (s, 1, H-4), 9.30 [s

(broad), 2, NH-3,5], 10.07 [s (broad), 2, NH-2,6].

*Anal.* Calcd. for $C_{13}H_{17}N_5O_4$: C, 50.81; H, 5.58; N, 22.79. Found: C, 50.47; H, 5.24; N, 22.47.

2,6-Dimethyldiimidazolo[4,5-*b*:5′,4′-*e*]pyridine (**7**).

Compound **6**, 145 mg. was heated at 290° under a nitrogen stream. The compound melted immediately and gas was evolved vigorously and the nitrogen gas from the outlet had a strong acetic acid odor. The gas evolution subsided after 1 minute and the melt solidified. The solid was heated for an additional 1 minute and cooled to room temperature. The yield of the tan solid was 90 mg. (102%). The sample was sublimed at 250-270° at 1 mm Hg to give 50 mg. of pale tan solid. It was sublimed again for analysis, m.p. > 360°; $\nu$ (potassium bromide): 3400-2500, 1420, 1370, 1340 $cm^{-1}$.

*Anal.* Calcd. for $C_9H_5N_5$: C, 57.74; H, 4.85; N, 37.41. Found: C, 57.82; H, 4.71; N, 37.14.

1-Acetyl-3,5,6-triacetamido-2-pyridonimine (**8**).

A mixture of 300 mg. of **4** and 6 ml. of distilled acetic anhydride was heated at 60° for 5 minutes and then cooled to room temperature with stirring. After 10 minutes the mixture became a brown clear solution. It was stirred overnight and the resulting precipitate was collected by filtration and washed with a mixture of benzene and petroleum ether to remove acetic anhydride and acetic acid. The light yellow-green solid **8′** weighed 560 mg. (85%); $\nu$ (potassium bromide): 3500, 3300, 1710 $cm^{-1}$.

Recrystallization from benzene/petroleum ether gave 500 mg. of yellow crystals **8**, m.p. 180° (decolor); $\nu$ (potassium bromide): 3270, 1740, 1690 $cm^{-1}$.

*Anal.* Calcd. for $C_{13}H_{17}N_5O_4$: C, 50.81; H, 5.58; N, 22.79. Found: C, 50.82; H, 5.34; N, 22.79.

Compounds **8** and **8′** were considered to be the same compound with different crystalline forms since **8** (yellow crystals) was converted to **8′** (yellow small crystals) by crystallizing quickly from benzene/petroleum ether or by evaporating the benzene solution and **8′** was changed to **8** easily by slow crystallization.

Conversion of **8** to **6** by Water.

A dispersion of 50 mg. of **8** in 2 ml. of water was stirred at room temperature. After 3 days small white needles began to precipitate, although **8** did not go into solution completely. Yellow crystals of **8** disappeared after stirring 7 days and the precipitated white needles **6** were collected on a filter. The yield was 20 mg. (40%).

In another run, 100 mg. of **8** was dissolved in 4 ml. of water by heating and the solution was refluxed gently for 5 minutes. On cooling, small white needles of **6** appeared. The yield was 40 mg. (40%). Prolonged heating did not improve the yield.

2,3-Diacetamidopyridine (**11**).

A mixture of 150 mg. of 2,3-diaminopyridine, which was very dark, and 2 ml. of acetic anhydride was heated at 60° for 1 minute and the insoluble material was filtered off. The dark brown filtrate was left standing at room temperature for 2 hours and then kept in a refrigerator for 1 day. The precipitate was filtered by suction and washed with a mixture of benzene and petroleum ether. The product thus obtained was light tan in color and weighed 230 mg. (87%). Recrystallization from benzene gave colorless small needles, m.p. 172-173° (lit. (5) 169-171°); $\nu$ (potassium bromide): 1660 $cm^{-1}$; $\delta$ (deuteriochloroform): 2.15 (s, 3, $COCH_3$-3), 2.24 (s, 3, $COCH_3$-2), 7.22 [dd (J = 8.5, 5 Hz), 1, H-5], 8.13 [dd (J = 5, 1.8 Hz), 1, H-6], 8.36 [dd (J = 8.5, 1.8 Hz), 1, H-4], 9.41 [s (broad), 1, NH-3], 10.06 [s (broad), 1, NH-2].

2,6-Diacetamidopyridine (**12**).

Acetic anhydride, 6 ml. was added to 500 mg. of 2,6-diaminopyridine and the mixture was heated at 60° for 1 minute to dissolve the diamine. The solution was stirred at room temperature and a white crystalline solid began to precipitate in a minute. After 30 minutes the solid was collected by filtration and washed with a mixture of benzene and petroleum ether. The yield was 730 mg. (83%). It was recrystallized from benzene to give colorless needles, m.p. 207-209° (lit. (6) 203°); $\nu$ (potassium bromide): 1670 $cm^{-1}$; $\delta$ ($d_6$DMSO): 2.12 (s, 6, $COCH_3$-2,6), 7.72 (s, 3, H-3,4,5), 10.05 [s (broad), 2, NH-2,6].

3,5-Bisphenylazo-2-acetamido-6-aminopyridine **13** and 3,5-Bisphenylazo-2,6-diacetamidopyridine (**14**).

A mixture of 100 mg. of 3,5-bisphenylazo-2,6-diaminopyridine **3** and 2 ml. of acetic anhydride was heated at 85° for 2.5 hours with stirring; however, the solid did not go into the solution completely. The mixture was chilled in a refrigerator and the solid was filtered and washed with benzene/petroleum ether. It weighed 120 mg. Recrystallization from acetone gave 45 mg. (36%) of **13** as light orange needles, m.p. 248-251° (with dec.). A further recrystallization failed to raise the melting point; $\nu$ (potassium bromide): 3300, 1690 (shoulder), 1680 $cm^{-1}$; $\delta$ (deuteriochloroform): 2.66 (s, 6, $COCH_3$-2,6), 7.4-8.0 (m, 10, $N_2C_6H_5$-3,5), 8.61 (s, 1, H-4), 10.45 [s (broad), 2, NH-2,6].

*Anal.* Calcd. for $C_{21}H_{19}N_7O_2$: C, 62.83; H, 4.77; N, 24.42. Found: C, 63.00; H, 4.86; N, 24.26.

The mother liquor was concentrated and the residual solid was recrystallized from benzene to give 50 mg. (44%) of **14** as small light orange needles, m.p. 225-227°. Recrystallization from benzene raised the melting point to 227-229°; $\nu$ (potassium bromide): 3330, 3150, 1680 $cm^{-1}$; $\delta$ (deuteriochloroform): 2.60 (s, 3, $COCH_3$-2), 7.4-8.0 (m, 12, $N_2C_6H_5$-3,5 and $NH_2$-6), 8.65 (s, 1, H-4), 10.68 [s (broad), 1, NH-2].

*Anal.* Calcd. for $C_{19}H_{17}N_7O$: C, 63.50; H, 4.77; N, 27.28. Found: C, 63.44; H, 4.77; N, 27.43.

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