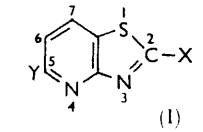
680. *The Synthesis of Thiazolopyridines and Bisthiazolopyridines.*

By J. A. Baker and S. A. Hill.

Treatment of 2,6-diaminopyridine with bromine and ammonium thiocyanate in acetic acid leads to the 3-thiocyanato- and 3,5-dithiocyanato-derivatives and not to thiazolopyridines as previously reported. The thiocyanato-compounds are isomerised to the corresponding thiazolo- and bisthiazolo-pyridines in boiling water and pentyl alcohol, respectively. A study of infrared spectra supports these conclusions. 2-Amino- and 2-amino-5-methyl-pyridine with thiocyanogen chloride in acetic acid, containing acetic anhydride, give unidentified substances which are not nuclear thiocyanato-derivatives.

The literature gives little information, and some contradiction, on derivatives of thiazolo[4,5-*b*]pyridine (I; X = Y = H) and bisthiazolo[4,5-*b*:5′,4′-*e*]pyridine (II; X = Y = H). The thiocyanation of 2,6-diaminopyridine to give the diamino-derivatives (I and II; X = Y = NH_2) has been reported by several workers. Berstein and his co-workers,[1] using bromine and potassium thiocyanate in acetic acid, obtained two products claimed to be these amino-compounds, melting at 138—139° and >300°, respectively, but no evidence of structure or analysis was offered. Maggiolo [2] used a similar method and reported the preparation of the diaminobisthiazolopyridine (II; X = Y = NH_2), giving its m. p. as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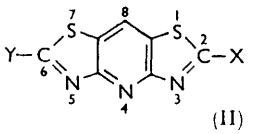
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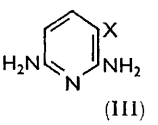
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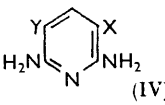
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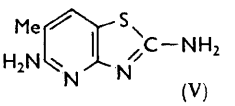
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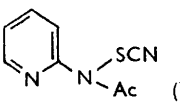
(VI)

152—153°. He analysed his substance but, unfortunately, his theoretical figure for carbon was shown as 26·9% whereas it is 37·7%. Yamamoto and Takahashi,[3] using thiocyanogen from cupric thiocyanate, obtained the diaminothiazolopyridine (I; X = Y = NH_2) with m. p. 137°.

[1] Berstein, Stearns, Shaw, and Lott, *J. Amer. Chem. Soc.*, 1947, **69**, 1151.
[2] Maggiolo, *J. Amer. Chem. Soc.*, 1951, **73**, 5815.
[3] Yamamoto and Takahashi, *J. Pharm. Soc. Japan*, 1951, **71**, 169.

Takahashi and Euda [4] reported that the diaminothiazolopyridine (I; X = Y = NH_2) was readily hydrolysed by hot 10% sodium hydroxide solution to 2,6-diamino-3-mercaptopyridine (III; X = SH), which is surprising in view of the stability of the thiazole and benzothiazole ring systems. The formation of 2,6-diamino-3-mercaptopyridine is, however, readily explained if the substance assumed to be the thiazolopyridine derivative is, in fact, 2,6-diamino-3-thiocyanatopyridine (III; X = SCN).

Work in these laboratories has shown that this is indeed the case. Treatment of 2,6-diaminopyridine with bromine and ammonium thiocyanate in 50% acetic acid gave two products, which were readily separated, since one was very soluble, and the other nearly insoluble, in cold methanol. The former (m. p. 141—141·5°) gave ammonia readily in boiling 10% sodium hydroxide solution and its analysis agreed with the formula, $C_6H_6N_4S$. On being boiled in aqueous solution for several hours, it afforded an isomer (m. p. 227—228°), which did not readily give ammonia with hot aqueous sodium hydroxide. Infrared spectra, determined in potassium chloride discs, included a sharp peak at 2160 $cm.^{-1}$, characteristic of the thiocyanato-group,[5] for the former but not the latter substance. It is concluded that the initial product is the thiocyanato-compound (III; X = SCN), which isomerises to the thiazolopyridine derivative (I; X = Y = NH_2).

Acetylation of 2,6-diamino-3-thiocyanatopryridine was accompanied by cyclisation to 2,5-diacetamidothiazolo[4,5-*b*]pyridine (I; X = Y = NHAc). Proof of this rests on the following evidence. The acetylated product gave ammonia only very slowly in 10% aqueous sodium hydroxide at 100°; hydrolysis with concentrated hydrochloric acid for one hour at 95° gave a hydrochloride having the melting point of 2,5-diaminothiazolo[4,5-*b*]pyridine hydrochloride; 2,6-diamino-3-thiocyanatopyridine did not cyclise in concentrated hydrochloric acid at 95° (1 hr.); the infrared spectrum of the acetyl derivative did not show a band at ~2160 $cm.^{-1}$.

The less soluble fraction, 2,6-diamino-3,5-dithiocyanatopyridine, (IV; X = Y = SCN), from the thiocyanation of 2,6-diaminopyridine behaved similarly, giving ammonia readily with hot, aqueous sodium hydroxide, and being cyclised in boiling pentyl alcohol, in which it was not very soluble. The product of cyclisation, (II; X = Y = NH_2), was poorly soluble in organic solvents and dilute acids, but was more soluble in hot, concentrated mineral acids, from which salts crystallised on cooling. The salts were almost insoluble in cold water, and very dilute solutions exhibited a marked blue fluorescence. Acetylation of 2,6-diamino-3,5-dithiocyanatopyridine was accompanied by cyclisation to the 2,6-diacetamido-derivative (II; X = Y = NHAc), proof of this following the same lines as for the monothiocyanato-compound.

With zinc and hydrochloric acid 2,6-diamino-3,5-dithiocyanatopyridine gave the zinc salt of 2,6-diamino-3,5-dimercaptopyridine (IV; X = Y = SH), which by reaction with benzoyl chloride afforded 2,6-diphenylbisthiazolo[4,5-*b*:5′,4′-*e*]pyridine (II; X = Y = Ph).

Thiocyanation of 2,6-diamino-3-methylpyridine gave 2,6-diamino-3-methyl-5-thiocyanatopyridine (IV; X = Me, Y = SCN). This gave 2,5-diamino-6-methylthiazolo-[4,5-*b*]pyridine (V) on being cyclised in boiling pentyl alcohol.

All the diaminothiazolo- and diaminobisthiazolo-pyridines described gave dark, uncrystallisable solids of undetermined structure when treated with nitrous acid.

Maggiolo [2] reported that the presence of two activating substituents is necessary for thiocyanation of the pyridine ring by " nascent " thiocyanogen. This statement has been confirmed in these laboratories. Chlorothiocyanogen has recently been reported [6] to be a more energetic reagent for thiocyanation than thiocyanogen, and, therefore, thiocyanation of 2-aminopyridine and of 2-amino-5-methylpyridine was attempted with this reagent in glacial acetic acid, freed from water by the addition of acetic anhydride. The

[4] Takahashi and Ueda, *J. Pharm. Soc. Japan*, 1953, **73**, 442; *Chem. Abs.*, 1954, **48**, 5187.
[5] Lieber, Rao, and Ramachandran, *Spectrochim. Acta*, 1959, **13**, 296; Smith and Emerson, *J. Amer. Chem. Soc.*, 1960, **82**, 3076.
[6] Bacon and Guy, *J.*, 1960, 318.

products were shown by analysis to be acetylated thiocyanato-compounds, but this substituent was shown not to be in a ring, by the following evidence: their ultraviolet absorption spectra were very different from that for 2,6-diamino-3-thiocyanatopyridine; the infrared spectrum of the product from 2-amino-5-methylpyridine had no band in the region of 2160 cm.$^{-1}$; on being refluxed with 10% aqueous sodium hydroxide, the products freely gave ammonia, and the solutions, after neutralisation, afforded picrates of the original bases. The presence of an acetyl group was proved by distillation of the substances with dilute sulphuric acid, followed by detection of acetic acid in the distillates. From these observations the products are tentatively assigned the structures of *N*-thiocyanato-compounds as, for example, (VI).

Experimental

Thiocyanation of 2,6-*Diaminopyridine*.—A stirred solution of 2,6-diaminopyridine (4·36 g.) and ammonium thiocyanate (12 g.) in 50% v/v acetic acid (40 ml.) was treated with bromine (4 ml.) in glacial acetic acid (8 ml.), the temperature being held at 20—25°. The mixture was then made alkaline with concentrated aqueous ammonia, at <35°, then cooled, and the precipitate was collected, washed with water, and dried at 50°, giving an orange solid (7·7 g.). This was extracted with cold methanol, leaving an insoluble residue (A). Treatment of the solution with charcoal, followed by removal of the solvent *in vacuo* at room temperature, afforded a pale yellow solid (B) (5·1 g.), m. p. 134—136°.

Residue A was dissolved at 40° in 10% hydrochloric acid (315 ml.), and the solution was treated with charcoal and filtered. The material was reprecipitated with concentrated aqueous ammonia, collected, washed, and dried, to give pale yellow 2,6-*diamino*-3,5-*dithiocyanatopyridine* (2·45 g.), decomp. ~200° (placed in apparatus a few degrees below this temperature). Crystallisation from 70% dioxan (charcoal) or nitromethane afforded almost colourless needles (Found: C, 37·9; H, 2·5; S, 28·4. $C_7H_5N_5S_2$ requires C, 37·7; H, 2·3; S, 28·7%), $\lambda_{max.}$ (in 50% EtOH) 265, 323 mμ (log ε 3·94 and 4·01). This compound readily gave ammonia on being heated at 100° with 10% aqueous sodium hydroxide.

Solid B, when crystallised rapidly from water (charcoal), afforded 2,6-*diamino*-3-*thiocyanatopyridine* as white, sternutatory needles, m. p. 141—141·5° (Found: C, 42·8; H, 3·6; S, 19·3. $C_6H_6N_4S$ requires C, 43·4; H, 3·6; S, 19·3%), $\lambda_{max.}$ (in 50% EtOH) 256, 315 mμ (log ε 3·93 and 4·01). This compound readily gave ammonia with 10% aqueous sodium hydroxide at 100°.

2,6-*Diaminobisthiazolo*[4,5-b:5′,4′-e]*pyridine*.—A solution of 2,6-diamino-3,5-dithiocyanatopyridine (1 g.) in pentyl alcohol (150 ml.) was refluxed for 6 hr., then cooled, and the powder (0·9 g.) collected. It had m. p. >300°. Since it was highly insoluble in a variety of organic solvents, the material was recrystallised, as its *sulphate*, from 50% sulphuric acid (Found: C, 26·6; H, 2·2; S, 30·3. $C_7H_5N_5S_2,H_2SO_4$ requires C, 26·2; H, 2·2; S, 29·9%). The sulphate was hygroscopic. A hydrochloride was also obtained by crystallisation of the base from concentrated hydrochloric acid and water (1 : 1). These salts had m. p.s >300° and were only very slightly water-soluble. The base did not give ammonia with 10% aqueous sodium hydroxide at 100°. The base in 50% EtOH had $\lambda_{max.}$ 239, 339, and inflexions 255, 280 mμ.

2,6-*Diacetamidobisthiazolo*[4,5-b:5′,4′-e]*pyridine*.—2,6-Diamino-3,5-dithiocyanatopyridine was refluxed with acetic anhydride for 1 hr. and the solution then diluted with water; this gave a 98% yield of the *diacetamido-compound*, m. p. >300° (Found: C, 41·9; H, 3·0; S, 21·3. $C_{11}H_9N_5O_2S_2$ requires C, 43·0; H, 3·0; S, 20·9%). This compound, after hydrolysis with concentrated hydrochloric acid at 95° for 2 hr., gave a solution with a marked blue fluorescence.

Cyclisation of the dithiocyanato-compound was not effected by concentrated hydrochloric acid at 95° in 2 hr.

2,5-*Diaminothiazolo*[4,5-b]*pyridine*.—A solution of 2,6-diamino-3-thiocyanatopyridine (1·2 g.) in water (20 ml.) was refluxed for 4 hr. After treatment with charcoal, the hot solution was set aside overnight, and the crystals were then collected and recrystallised from butan-1-ol (charcoal), giving 0·4 g. of the pale yellow *base*, m. p. 227—228° (Found: C, 43·4; H, 3·7; N, 33·2; S, 19·3. $C_6H_6N_4S$ requires C, 43·4; H, 3·6; N, 33·7; S, 19·3%), $\lambda_{max.}$ (in 50% EtOH) 263, 327 mμ (log ε 3·50, 4·06). This compound did not readily give ammonia in 10% aqueous sodium hydroxide at 100°. A hydrochloride, m. p. 247—248°, and a sulphate, m. p. 250°

(decomp.), were obtained by crystallisation of the base from 10% hydrochloric and sulphuric acid, respectively.

2,5-*Diacetamidothiazolo*[4,5-b]*pyridine*.—2,6-Diamino-3-thiocyanatopyridine was refluxed in acetic anhydride for 1 hr., and the solution then diluted with water, giving the *diacetamido-compound* (92%), m. p. >300° (Found: C, 47·7; H, 4·0; S, 12·9. $C_{10}H_{10}N_4O_2S$ requires C, 48·0; H, 4·0; S, 12·8%).

2,6-*Diamino-3-methyl-5-thiocyanatopyridine*. A solution of 2,6-diamino-3-methylpyridine (4·1 g.), ammonium thiocyanate (5·6 g.), and ammonium acetate (3·5 g.) in acetic acid (40 ml.) and water (5 ml.) was treated with bromine (1·9 ml.) in acetic acid (3·8 ml.) with stirring at 25°. The mixture was then made alkaline with concentrated aqueous ammonia at <40°, then cooled, and the yellow solid (4·8 g.) was collected, washed, and dried. This solid was boiled with 50% alcohol (100 ml.; charcoal), and the hot solution was filtered, diluted with water (150 ml.), and set aside; this gave the thiocyanato-compound (3·7 g.), m. p. 156—158°. Recrystallisation raised the m. p. to 162—163° (Found: C, 46·7; H, 4·6; S, 18·0. $C_7H_8N_4S$ requires C, 46·65; H, 4·5; S, 17·8%); $\lambda_{max.}$ (in 50% EtOH) were at 256, 321 mμ (log ε 3·92, 4·03). This compound readily evolved ammonia at 100° in aqueous sodium hydroxide solution.

2,5-*Diamino-6-methylthiazolo*[4,5-b]*pyridine*.—A mixture of 2,6-diamino-3-methyl-5-thiocyanatopyridine (2·7 g.) and pentyl alcohol (15 ml.) was refluxed for 3 hr. After cooling, the solid was collected and recrystallised from water (100 ml.; charcoal), giving buff crystals of the *thiazolopyridine* (1·2 g.), m. p. 239—240·5°. Recrystallisation raised the m. p. to 244—244·5° (Found: C, 46·8; H, 4·4; S, 18·1. $C_7H_8N_4S$ requires C, 46·65; H, 4·5; S, 17·8%); $\lambda_{max.}$ (in 50% EtOH) were at 267, 328 mμ (log ε 3·59, 4·17). This compound did not readily evolve ammonia at 100° in 10% aqueous sodium hydroxide.

Reduction of 2,6-*Diamino-3,5-dithiocyanatopyridine with Zinc and Hydrochloric Acid*.—A solution of the dithiocyanato-compound (2·2 g.) in dilute hydrochloric acid (150 ml.) was stirred and zinc powder (5 g.) added in portions. Stirring was then continued for a further hour. The mixture was made alkaline with concentrated aqueous ammonia and cooled, and the precipitate was collected, washed with dilute ammonia solution, and dried, affording 2·4 g. of yellow solid, which resisted purification, and the crude material was used for subsequent reactions. It was assumed to be the zinc salt of 2,6-diamino-3,5-dimercaptopyridine from its behaviour during the subsequent reaction.

2,6-*Diphenylbisthiazolo*[4,5-b:5′,4′-e]*pyridine*.—The crude zinc salt described above (1 g.) was refluxed with benzoyl chloride (4 ml.) for 15 min., then cooled, treated with 10% aqueous sodium hydroxide (15 ml.), and cooled, and the precipitate was collected, washed, and dried. After being mixed with charcoal, the solid was extracted with hot nitrobenzene. The cooled extract afforded yellow plates (0·4 g.), m. p. >300°. The sample for analysis was recrystallised from isophorone (Found: C, 66·1; H, 3·4; N, 12·8; S, 18·9. $C_{19}H_{11}N_3S_2$ requires C, 66·1; H, 3·25; N, 12·5; S, 18·6%), $\lambda_{max.}$ (in 50% EtOH) 274, 358, 372, inflexion 295 mμ (log ε 4·52, 4·62, 4·57, and 4·09).

The same compound was obtained on refluxing the crude zinc salt with benzaldehyde in acetic acid. The sample for analysis was crystallised from isophorone (Found: C, 66·1; H, 3·3; S, 18·5%).

Reaction of Chlorothiocyanogen with 2-*Aminopyridine and* 2-*Amino-5-methylpyridine*.—A solution of chlorothiocyanogen was prepared in the following way. Dry chlorine was passed into glacial acetic acid, previously treated overnight with 5% of its volume of acetic anhydride, and the concentration was determined iodometrically. Potassium thiocyanate, dried at 100° for 4 hr., was then added in equimolar amount, and the mixture was shaken for 20 min. The potassium chloride produced was not removed before use of the reagent, the strength of which was about 0·7M.

A solution of 2-aminopyridine (1·88 g.) in 5 ml. of the acetic acid–acetic anhydride mixture was added to the equivalent of chlorothiocyanogen solution, and the mixture set aside for 28 hr. The mixture was then filtered, made alkaline with concentrated aqueous ammonia, and cooled, and the precipitate was collected, washed, and dried. Crystallisation from alcohol afforded white needles of a *substance*, m. p. 198—199° (Found: C, 49·8; H, 3·7; S, 16·5. $C_8H_7N_3OS$ requires C, 49·7; H, 3·7; S, 16·6%). This gave ammonia readily at 100° in 10% aqueous sodium hydroxide (1·5 hr.) and the solution, after being neutralised, gave a picrate which, crystallised from ethanol–ethyl acetate (1 : 2 by vol.), had m. p., and mixed m. p. with 2-aminopyridine picrate, 222—223° (decomp.).

The substance, m. p. 198—199°, when distilled with diluted sulphuric acid, gave a distillate, which was neutralised with excess of lime and then evaporated to dryness. On being heated, the residue gave acetone, detected by the formation of indigo-blue with *o*-nitrobenzaldehyde paper, indicating the presence of acetic acid in the distillate.

The reaction of chlorothiocyanogen with 2-amino-5-methylpyridine was carried out in a similar manner. The product formed very pale yellow needles, m. p. 186—187° (Found: C, 51·7; H, 4·2; N, 20·3; S, 15·6. $C_9H_9N_3OS$ requires C, 52·15; H, 4·4; N, 20·2; S, 15·5%). This *substance* readily gave ammonia in 10% aqueous sodium hydroxide at 100°, and the solution after neutralisation gave 2-amino-5-methylpyridine picrate (from ethanol–ethyl acetate 1 : 2 by vol.), m. p. and mixed m. p. 247—248·5°. On distillation with diluted sulphuric acid, the substance gave an acid distillate, which, after neutralisation to litmus with aqueous ammonia, gave a red colour with neutral ferric chloride solution, indicating the presence of acetic acid in the distillate.

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