Isothiazolopyridines. I. Synthesis and Spectra of Isothiazolo[3,4-*b*]-, 3-Aminoisothiazolo[4,3-*b*]-, Isothiazolo[5,4-*b*]-, and 3-Methylisothiazolo[5,4-*c*]pyridines. Preparation and Spectra of Some 2,3- and 3,4-Disubstituted Pyridines[1]

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Isothiazolo[3,4-*b*]pyridine was synthesized from 2-aminonicotinonitrile in three steps: by the reaction with ammonia and hydrogen sulfide to produce 2-aminothionicotinamide; oxidative cyclization with hydrogen peroxide to give 3-aminoisothiazolo[3,4-*b*]pyridine, followed by diazotization and reduction with hypophosphorous acid. 3-Aminoisothiazolo[4,3-*b*]pyridine was prepared in a similar way from 3-aminopicolinonitrile via 3-aminothiopicolinamide. Isothiazolo[5,4-*b*]pyridine was synthesized from 2-chloronicotinonitrile in three steps: by the reduction with formic acid in the presence of Raney nickel to obtain 2-chloronicotinaldehyde; transformation of the latter into 2-thiocyanonicotinaldehyde; and finally cyclization with ammonia to obtain isothiazolo[5,4-*b*]pyridine. 3-Methylisothiazolo[5,4-*c*]pyridine was prepared by cyclization of 4-acetyl-3-thiocyanopyridine with ammonia. N.m.r. and u.v. spectra of the isothiazolopyridines, their derivatives, and the pyridine intermediates were recorded and interpreted.

L'isothiazolo pyridine-[3,4-*b*] a été synthétisée à partir de l'amino-2 nicotinonitrile en trois étapes: par la réaction avec de l'ammoniac et de l'hydrogène sulfuré pour donner l'amino-2 thionicotinamide: par la cyclisation par voie oxydante avec de l'eau oxygénée pour donner l'amino-3 isothiazolo pyridine-[3,4-*b*] suivie par une diazotisation et par une réduction avec de l'acide hypophosphoreux. L'amino-3 isothiazolo pyridine-[4,3-*b*] a été préparée en suivant un procédé similaire à partir de l'amino-3 picolinonitrile en passant par l'amino-3 thiopicolinamide. L'isothiazolo pyridine-[5,4-*b*] a été synthétisée à partir du chloro-2 nicotinonitrile en trois étapes: par réduction avec l'acide formique en présence de nickel de Raney pour obtenir la chloro-2 nicotinaldehyde; par la transformation de ce dernier produit en thiocyano-2 nicotinaldehyde; et finalement par la cyclisation en présence d'ammoniac pour obtenir l'isothiazolo pyridine-[5,4-*b*]. La méthyl-3 isothiazolo pyridine-[5,4-*c*] a été préparée par cyclisation de l'acétyl-4 thiocyano-3 pyridine avec de l'ammoniac. Les spectres r.m.n. et u.v. des isothiazolo pyridines, de leurs dérivés ainsi que des intermédiaires des pyridines ont été enregistrés et interprétés.

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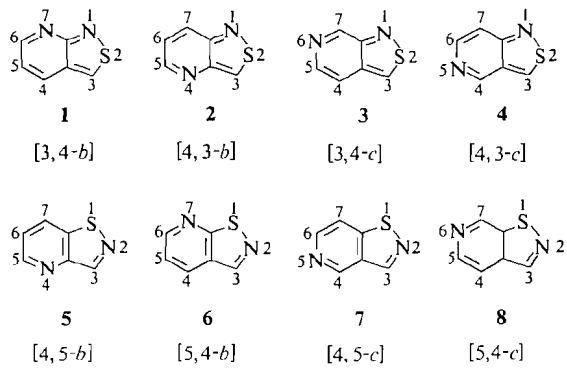
Introduction

Isothiazolopyridines (**1**–**8**) form a new class of heteroaromatic compounds, four of which possess ortho-quinoid structures (**1**–**4**) while the other four, benzenoid (**5**–**8**). Since isothiazolopyridines have remained hitherto an unknown class of compounds, it seemed to be of significance to synthesize and study them and their derivatives. In this work the preparation and spectra of isothiazolo[3,4-*b*]-, -[4,3-*b*]-, -[5,4-*b*]-, and -[5,4-*c*]pyridines were investigated.

Discussion

The first derivatives of isothiazolo[3,4-*b*]- (**1**) and -[4,3-*b*]pyridine (**2**) prepared were the 3-amino compounds **11** and **18**, respectively

Isothiazolopyridines



(Schemes 1 and 2). They were obtained by a general method involving the oxidative cyclization of the appropriate pyridine *o*-aminothiocarboxamides. The precursor of 3-aminoisothiazolo[3,4-*b*]pyridine (**11**) was 2-aminonicotinonitrile (**9**) (1) which was transformed into 2-aminothionicotinamide (**10**) by the addition of

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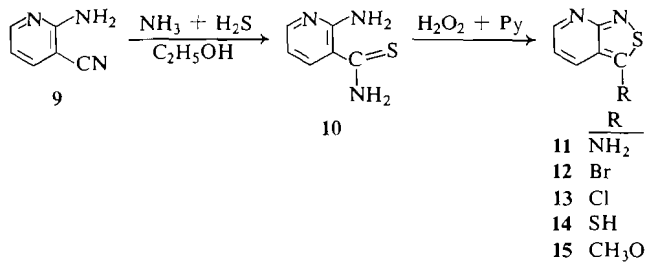
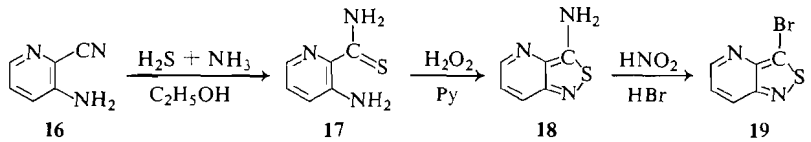
[2]Holder of an NRCC Studentship, 1967–1971.



SCHEME 1



SCHEME 2

hydrogen sulfide to the cyano group. Oxidation of 2-aminothionicotinamide (**10**) with 30% hydrogen peroxide in pyridine produced 3-aminoisothiazolo[3,4-*b*]pyridine (**11**) (Scheme 1).

The mechanism of the oxidative cyclization of the aromatic and heterocyclic thioamides with hydrogen peroxide in pyridine is not known. However, it has been suggested by Davis (2) that the intermediates in such reactions could be *S*-oxides, in analogy to the *S*-oxides formed from aliphatic thioamides and hydrogen peroxide (3).

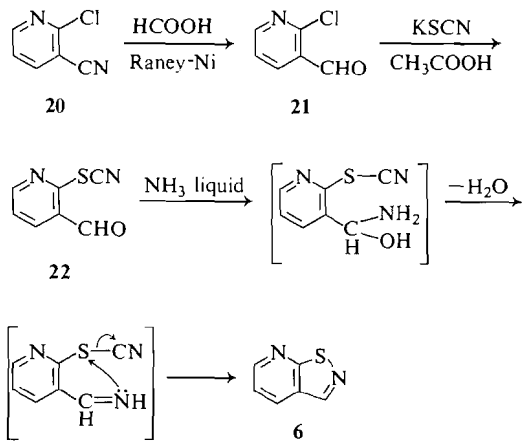
3-Aminoisothiazolo[3,4-*b*]pyridine (**11**) was diazotized in a mixture of 70% nitric and 85% orthophosphoric acid (1:4) and the diazonium salt reduced with 30% hypophosphorous acid to obtain the new parent compound, isothiazolo-[3,4-*b*]pyridine (**1**).

3-Bromiosothiazolo[3,4-*b*]pyridine (**12**) was prepared by the diazotization of **11** in 48% fuming hydrobromic acid.

3-Chloroisothiazolo[3,4-*b*]pyridine (**13**) was obtained by the Gattermann reaction of **11**. 3-Mercapto- (**14**) and 3-methoxyisothiazolo-[3,4-*b*]pyridine (**15**) were prepared by a nucleophilic substitution of the chlorine atom in **13** (Scheme 1). The red color of the compound **14** indicates that its dominating tautomeric form may be a thione.

In the isothiazolo[4,3-*b*]pyridine series, the starting material was 3-aminopicolinonitrile (**16**) which was transformed into 3-aminopicolinonitrile (**17**) with hydrogen sulfide. 3-Aminoisothiazolo[4,3-*b*]pyridine (**18**) was obtained by the oxidative cyclization of **17** with 30% hydrogen peroxide in pyridine solution (Scheme 2). The presence of the amino group in the 3-position in **18** was proved by the i.r. spectrum and replacement of the amino group by a bromo atom when **18** was diazotized in 48% hydrobromic acid. The efforts to deaminate **18** in order to obtain unsubstituted isothiazolo[4,3-*b*]pyridine (**2**) were unsuccessful.

The general method for the synthesis of isothiazolo[5,4-*b*]pyridine (**6**) (Scheme 3) and 3-



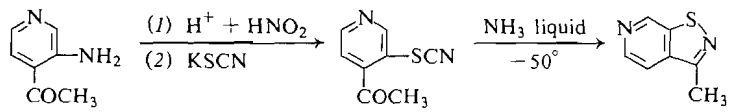
SCHEME 3

methylisothiazolo[5,4-*c*]pyridine (**25**), a derivative of **8**, (Scheme 4) was based on the reaction of *o*-thiocyano-formyl- or *o*-thiocyano-acetyl-pyridine with ammonia. The starting material for the preparation of **6** was 2-chloronicotinonitrile (**20**) (1) which was reduced with formic acid – Raney nickel to obtain 2-chloronicotinaldehyde (**21**). 2-Thiocyanonicotinaldehyde (**22**) was prepared by the treatment of **21** with potassium thio-

TABLE 1. N.m.r. spectra of 2,3- and 3,4-disubstituted pyridines

No.	Compound	Chemical shifts, δ (p.p.m.) H-2	H-4	H-5	H-6	Other	Coupling constants (Hz) $J_{4,5}$	$J_{4,6}$	$J_{5,6}$
10	2-Aminothionicotinamide*	—	7.57	6.59	8.03	$CSNH_2$ 9.73, 9.43; NH_2 6.82	7.5	2	5
17	3-Aminothiopicolinamide†	—			7.94	$CSNH_2$ 9.5, 9.22		2	4
21	2-Chloronicotinaldehyde‡	—	8.25	7.43	8.62	*CHO* 10.45	8.5	2	4
22	2-Thiocyanonicotinaldehyde*	—	8.52	7.65	8.63	*CHO* 10.15	8	2	5
23	4-Acetyl-3-aminopyridine‡	8.22	—	7.41	7.91	NH_2 6.34; CH_3 2.29	—	—	5
24	4-Acetyl-3-thiocyanopyridine‡	9.13	—	7.87	8.81	CH_3 2.36	—	—	5

*Solvent: DMSO-d_6 + $CDCl_3$ (3:1).
†Solvent: DMSO-d_6.
‡Solvent: $CDCl_3$.



23 **24** **25**

SCHEME 4

cyanate in glacial acetic acid in nitrogen atmosphere. Cyclization of 2-thiocyanonicotinaldehyde (**22**) with a large excess of liquid ammonia at −50° for 4 h produced isothiazolo[5,4-*b*]pyridine (**6**).

The synthesis of 3-methylisothiazolo[5,4-*c*]-pyridine (**25**) was based on a principle similar to one applied in the case of **6** (Scheme 4). 4-Acetyl-3-aminopyridine (**23**) was diazotized and the diazonium salt was treated with potassium thiocyanate to obtain 4-acetyl-3-thiocyanopyridine (**24**) which was cyclized into **25** either with liquid ammonia at −50° for 5 h, or with ammonia in a pressure bomb at about 130° for 15 h.

Spectra

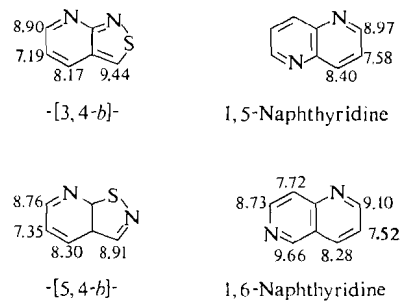
Nuclear Magnetic Resonance Spectra

The n.m.r. spectra of the 2,3-disubstituted pyridines (Table 1) **10**, **17**, **21**, and **22** display three sets of well resolved quartets of the AMX type (protons 3, 4, and 6). The three coupling constants $J_{4,5}$, $J_{4,6}$, and $J_{5,6}$ can be measured directly from the spectra. The spectra of the 3,4-disubstituted pyridines **23** and **24** exhibit a singlet for H-2 and a pair of doublets for H-5 and -6, consequently, there is no observable coupling between H-2 and other ring protons.

The three pyridine ring protons of isothiazolo-[3,4-*b*]pyridine (**1**) and its derivatives **11**–**15**, isothiazolo[5,4-*b*]pyridine (**6**), and 3-aminoisothiazolo[4,3-*b*]pyridine (**18**) also show three sets of quartets of the AMX type (Table 2). If we compare the chemical shifts of protons 2, 3, and 4 in 1,5- and 1,6-naphthyridine (4) (Scheme 5), we notice a similarity between **1** and **6** on one hand, and the two naphthyridines on the other hand.

Ultraviolet Spectra

The u.v. absorption data of 2,3- (**10**, **17**, **21**, **22**, and **26**) and 3,4-disubstituted pyridines (**23** and **24**) are given in Table 3. All of these compounds show three main bands designated as the α-, p- and β-bands (5). In the 2,3-substituted amino-



SCHEME 5. Chemical shifts (δ) of isothiazolo[3,4-*b*]-, -[5,4-*b*]pyridine, 1,5- and 1,6-naphthyridine.

TABLE 2. N.m.r. spectra of isothiazolopyridines

No.	Compound	Chemical shifts, δ (p.p.m.) H-3	H-4	H-5	H-6	H-7	Other	Coupling constants (Hz) $J_{4,6}$	$J_{5,6}$	$J_{4,5}$	$J_{5,7}$
1	Isothiazolo[3,4-*b*]pyridine*	9.44	8.17	7.19	8.90	—	—	2	4	8.8	—
11	3-Amino-†	—	8.27	6.77	8.55	—	NH_2 8.05	1.8	4	8.5	—
12	3-Bromo-†	—	8.17	7.44	8.96	—	—	1.8	4	8.5	—
13	3-Chloro-*	—	8.04	7.23	8.91	—	—	1.8	4	8.5	—
14	3-Mercapto-‡	—	8.49	7.07	8.64	—	—	1.8	5.5	7.5	—
15	3-Methoxy-†	—	8.10	7.09	8.77	—	OCH_3 4.30	2	4	8.5	—
6	Isothiazolo[5,4-*b*]pyridine*	8.91	8.30	7.35	8.76	—	—	1.5	4.8	8	—
18	3-Aminoisothiazolo[4,3-*b*]pyridine*	—	7.72	7.25	8.30	—	NH_2 7.81	1.8	3.8	8.9	—
25	3-Methylisothiazolo[5,4-*c*]pyridine*	—	7.76	8.60	—	9.31	CH_3 2.75			5.5	1.0

*Solvent: $CDCl_3$.
†Solvent: DMSO-d_6 + $CDCl_3$ (3:1).
‡Solvent: DMSO-d_6.

TABLE 3. The u.v. absorption maxima and log ε values of some disubstituted pyridines

No.	Compound	α-Band λ_{max} (nm)	α-Band log ε	p-Band λ_{max} (nm)	p-Band log ε	β-Band λ_{max} (nm)	β-Band log ε
10	2-Aminothionicotinamide*	345	3.65	268	3.83	217	4.25
		299	3.72				
17	3-Aminothiopicolinamide*	372	3.87	311	3.75	223	4.30
				264	3.89		
26	4-Aminothionicotinamide*	335sh		257	3.87	228	4.19
		294	3.67				
21	2-Chloronicotinaldehyde*	290sh	2.44	272	3.01	238	2.97
				265	3.09	210	3.52
22	2-Thiocyanonicotinaldehyde†	302sh	3.07	266	3.61	226	4.01
23	4-Acetyl-3-aminopyridine*	373	3.69	252	3.68	223	4.20
24	4-Acetyl-3-thiocyanopyridine*	320	3.66	247	3.74	224	4.20

*Solvent: 95% ethanol.
†Solvent: absolute methanol.

pyridinethioamides **10** and **17**, the bathochromic shift of the α-band is considerably larger than in the 3,4-substituted isomer, 4-aminothionicotinamide (**26**). This is in conformity with the u.v. absorption of the three isomeric aminopyridines: 2- and 3-aminopyridines absorb at 287 and 288 nm, respectively, as compared with the absorption by 4-aminopyridine at 268(sh) nm (6). In the u.v. spectrum of 4-acetyl-3-thiocyanopyridine (**23**) the α-band is displaced more toward the longer wavelength than in the spectrum of 4-acetyl-3-thiocyanopyridine (**24**) due to the conjugation of acetyl and amino groups.

The u.v. spectra of isothiazolo[3,4-*b*]- (**1**) (Table 4) and -[5,4-*b*]pyridine (**6**) (Table 5) consist of only two absorption bands each. The long wavelength bands at 296 and 298 nm, respectively, actually are not pure α-bands, but are overlapping with the p-bands due to the large bathochromic shift of the latter. The u.v. bands of **1** and **6** at 213 and 228 nm, respectively, are the β-bands, comparable to those present in the spectra of thiazolo[4,4-*c*]pyridine (7) and benzo[*b*]thiophene (8) at 216 and 227 nm, respectively. The u.v. spectra of **1** and **6** are also similar to those of 1,6- and 1,7-naphthyridine (9), but not to any other naphthyridines. The spectra of the halogen derivatives **12**, **13**, and **19**, and of 3-methylisothiazolo[5,4-*c*]pyridine (**25**) display only two bands.

Experimental

The melting points were determined on a Gallenkamp melting point apparatus and are corrected. N.m.r. spectra were obtained on a Varian high resolution n.m.r. model HA-100 spectrometer. Solvents used were deuterio-

TABLE 4. The u.v. absorption maxima and log ε values of isothiazolo[3,4-*b*]pyridine and its derivatives

No.	Compound*	α-Band		p-Band		β-Band	
		λ_{max} (nm)	log ε	λ_{max} (nm)	log ε	λ_{max} (nm)	log ε
1	Isothiazolo(3,4-*b*)pyridine	296	3.86			213	4.03
11	3-Amino-	400	3.98	302	3.89	245	4.45
				293	3.93	228	4.52
12	3-Bromo-	330	3.86			213	4.29
		303	4.00				
13	3-Chloro-	328sh	3.67			216	4.06
		303	3.83				
14	3-Mercapto-	314	3.56	248sh	3.38	211	3.79
		306	3.59				
15	3-Methoxy-	352	3.58	297sh	3.62	219	4.18
				289	3.66		

*Solvent: 95% ethanol.

TABLE 5. The u.v. absorption maxima and their log ε values of some isothiazolopyridine derivatives

No.	Compound*	α-Band		p-Band		β-Band	
		λ_{max} (nm)	log ε	λ_{max} (nm)	log ε	λ_{max} (nm)	log ε
18	3-Aminoisothiazolo[4,3-*b*]pyridine	390	3.54	307	3.38	245	4.09
				297	3.47	226	4.08
19	3-Bromoisothiazolo[4,3-*b*]pyridine	324	4.00			213	4.29
		306	4.14				
6	Isothiazolo[5,4-*b*]pyridine	307sh	3.40			228	4.19
		298	3.46				
25	3-Methylisothiazolo[5,4-*c*]pyridine	326sh	3.69			224sh	4.01
		313	3.74			209	4.15

*Solvent: 95% ethanol.

chloroform and dimethyl sulfoxide-d_6 and concentrations of solutions were 10–40 mg of solute per 0.5 ml of solvent. Tetramethylsilane was used as an internal reference. The u.v. spectra were recorded on a Unicam model SP-800 spectrophotometer and absolute ethanol and methanol were used as solvents. The i.r. spectra were taken in potassium bromide pellets on a Perkin–Elmer model 521 grating spectrometer. The mass spectra were obtained on an AEI-MS-902 double focusing mass spectrometer. The low resolution mass spectra were used to check the purity of compounds. The high resolution mass spectra served the purpose to prove the empirical formulas of unstable compounds, or when a small amount of material was available.

The elemental analyses were carried out by Dr. C. Daesslé, Montreal, and by A. Bernhardt, Germany.

*2-Aminothionicotinamide (**10**)*

Alcoholic ammonia (65 ml) containing 5 g of NH_3 (five-fold excess) was added to 2-aminonicotinonitrile (**9**) (7.0 g, 58.8 mmol) dissolved in absolute ethanol (16 ml) and triethylamine (5.9 g, 58.8 mmol). The reaction mixture was stirred magnetically and saturated with hydrogen sulfide for 1½–2 h. A yellow crystalline compound precipitated in less than an hour. The flask was loosely stoppered and allowed to stand at room temperature for 2 days to complete the reaction. Then the solution was poured onto crushed ice and the yellow substance was collected by suction filtration and dried at 60–70°. By this procedure 6.9 g of 2-aminothionicotinamide (**10**) was obtained. A further 0.6 g of the product was recovered by concentrating the filtrate under reduced pressure, pouring the solution on crushed ice, and filtering. 2-Aminothionicotinamide (**10**) was obtained in a nearly pure form (yield 7.5 g, 83%). Recrystallization from benzene gave yellow prisms, m.p. 132–133°. I.r. (KBr): 3420, 3310, 3180 cm^{-1} (NH_2).

Anal. Calcd. for $C_6H_7N_3S$ (mol. wt. 153.15): C, 47.0; H, 4.6; N, 27.4; S, 20.9. Found: C, 47.1; H, 4.7; N, 27.5; S, 20.8. *M/e*: 153 (P); 155 (P + 2).

*3-Aminoisothiazolo(3,4-b)pyridine (**11**)*

2-Aminothionicotinamide (**10**) (4.6 g, 0.03 mol) was dissolved in pyridine (10 ml) and warmed at 35° with stirring. Hydrogen peroxide (30%) (3.6 ml) was added very slowly to the reaction mixture. After the addition was completed, a yellow solid precipitated. The solution was further stirred at 35° for 10 min and let stand at room temperature for 16 h. The resulting precipitate was filtered off, washed with water, and dried. Crystallization

from ethanol gave 3.67 g (80% yield) of fine needles of 3-aminoisothiazolo(3,4-*b*)pyridine, m.p. 203.5–204.5°. I.r. (KBr): 1620, 3297–3258 (broad), 3100 cm^{-1} (NH_2).

Anal. Calcd. for $C_6H_5N_3S$ (mol. wt. 151.13): C, 47.7; H, 3.3; N, 27.8; S, 21.2. Found: C, 47.8; H, 3.2; N, 27.8; S, 21.3. *M/e*: 151 (P); 153 (P + 2).

*Isothiazolo[3,4-b]pyridine (**1**)*

3-Aminoisothiazolo[3,4-*b*]pyridine (**11**) (2.7 g, 17.9 mmol) was dissolved in 85% phosphoric acid (120 ml) and 70% nitric acid (30 ml) was added. The resulting solution was cooled to −5 to −2° and sodium nitrite (1.32 g, 19.1 mmol) in water (12 ml) was added with stirring over a period of 30 min. The reaction mixture was stirred for another 10 min at this temperature and then was added in portions to a stirred 30% hypophosphorous acid (50 ml) at 25–35°, to which a small amount of cuprous oxide has been added. The reaction mixture was stirred for 1 h at room temperature. It was then made alkaline with 20% sodium hydroxide solution with cooling. The mixture was extracted thrice with 400 ml portions of ether. The ethereal extract was washed with water, dried over sodium sulfate, and evaporated to dryness under reduced pressure. Crystallization from *n*-hexane produced 0.59 g (24% yield) of pure isothiazolo[3,4-*b*]pyridine (**1**) as short colorless needles, m.p. 58.5°.

M/e: 136 (P); 138 (P + 2). Calcd. mass from the exact mass measurement: 136.008933. Calcd. mass for $C_6H_4N_2S$: 136.009519. Delta mass: 0.000585.

*3-Bromoisothiazolo[3,4-b]pyridine (**12**)*

3-Aminoisothiazolo[3,4-*b*]pyridine (**11**) (0.97 g, 6.4 mmol) was suspended in 48% fuming hydrobromic acid (25 ml). Sodium nitrite (0.7 g, 10 mmol) was added in small portions over a period of 20 min with stirring. The temperature of the mixture was kept at −4° to −20°. When the addition was completed, the mixture was stirred at 0° for a further 30 min and let stand overnight at room temperature. It was poured slowly onto 200 g of crushed ice and made strongly alkaline with 20% sodium hydroxide. The solution was extracted thrice with 150 ml portions of ether and the combined ethereal extract was dried over sodium sulfate. The solvent was evaporated under reduced pressure leaving 0.84 g of a crude yellow substance. Chromatography followed by crystallization from ethyl acetate gave 0.52 g (38% yield) of pure 3-bromoisothiazolo[3,4-*b*]pyridine (**12**) as yellow prisms m.p. 158–159°.

Anal. Calcd. for $C_6H_3N_2SBr$ (mol. wt. 215.12): C, 33.5; H, 1.4; N, 13.0; S, 14.9; Br, 37.2. Found: C, 33.4; H, 1.6; N, 13.3; S, 14.8; Br, 37.5. *M/e*: 214 (P); 216 (P + 2).

*3-Chloroisothiazolo[3,4-b]pyridine (**13**)*

Cuprous chloride was prepared from 3.0 g of cupric sulfate, 0.66 g of sodium chloride, 0.5 g of sodium hydrogen sulfite, and 0.36 g of sodium hydroxide and was dissolved in 10 ml of concentrated hydrochloric acid.

3-Aminoisothiazolo[3,4-*b*]pyridine (**11**) (0.9 g, 6 mmol) was dissolved in a mixture of 40 ml of 80% phosphoric acid and 10 ml of 70% nitric acid. The acid mixture was cooled to −5 to −2° (acetone – Dry Ice bath) and stirred magnetically. Sodium nitrite (0.44 g, 6.5 mmol) in water (4.0 ml) was added dropwise to the cooled stirred solution. The resulting diazonium solution was stirred for another 20 min at −5° and subsequently added slowly with stirring to the pre-cooled cuprous chloride solution at −5 to −2°. The reaction mixture was stirred at this temperature for 20 min and at room temperature for another hour. It was then made alkaline with 20% sodium hydroxide solution. The mixture was extracted with three 150 ml portions of ether. The combined ethereal extract was washed with water, dried over sodium sulfate, and evaporated to dryness under reduced pressure leaving 0.71 g of a crude yellow solid. Crystallization from *n*-hexane gave 0.46 g (45% yield) of pure 3-chloroisothiazolo[3,4-*b*]pyridine (**13**) as pale yellow needles, m.p. 96–97°. I.r. (KBr): 1003 cm^{-1} (strong) (Cl).

Anal. Calcd. for $C_6H_3N_2SCl$ (mol. wt. 170.56): C, 42.4; H, 1.8; N, 16.4; S, 18.8; Cl, 20.8. Found: C, 42.3; H, 1.6; S, 18.9; Cl, 20.7. *M/e*: 170 (P); 172 (P + 2).

*3-Mercaptoisothiazolo[3,4-b]pyridine (**14**)*

A solution of 3-chloroisothiazolo[3,4-*b*]pyridine (0.3 g, 1.8 mmol) and thiourea (0.2 g, 2.6 mmol) in 20 ml of absolute ethanol was refluxed for 3 h. The crystalline precipitate was dissolved in 40 ml of 1 *N* sodium hydroxide solution and filtered. Acidification of the filtrate with acetic acid produced a flocculent precipitate which was filtered off, washed with water, and dried to obtain 0.16 g (56% yield) of 3-mercaptoisothiazolo[3,4-*b*]pyridine (**14**). Crystallization from ethanol produced **14** in the form of fine dark purple needles, m.p. 188–189°.

M/e: 168 (P); 170 (P + 2). Calcd. mass from the exact mass measurement: 167.981477. Calcd. mass for $C_6H_4N_2S_2$: 167.981592. Delta mass: 0.000114.

*3-Methoxyisothiazolo[3,4-b]pyridine (**15**)*

3-Chloroisothiazolo[3,4-*b*]pyridine (0.3 g, 1.8 mmol) was dissolved in 30 ml of absolute methanol and a solution of sodium methoxide, prepared from 0.1 g of sodium and 5 ml of methanol, was added. The yellow solution was neutralized with dilute acetic acid and diluted with 50 ml of water. The precipite was filtered off, washed with water and dried. Chromatography and crystallization from methanol gave 0.12 g (41% yield) of **15**, m.p. 104–105°.

M/e: 166 (P); 168 (P + 2). Calcd. mass from the exact mass measurement: 166.027814. Calcd. mass for $C_7H_6N_2SO$: 166.021082. Delta mass: 0.006732.

*3-Aminothiopicolinamide (**17**)*

Alcoholic ammonia (58 ml) was added to 3-aminopicolinonitrile (**16**) (6.3 g, 0.54 mol) dissolved in a mixture of 14.5 ml of absolute ethanol and 53.1 g (0.054 mol) of triethylamine. The solution was stirred and saturated with hydrogen sulfide for 90 min; a yellow substance precipitated. The flask was loosely stoppered and let stand at room temperature for 2 days. The solution was poured onto crushed ice and the yellow product filtered off. Crystallization from benzene gave 2.95 g (36% yield) of 3-aminothiopicolinamide (**17**), m.p. 161–162°.

Anal. Calcd. for $C_6H_7N_3S$ (mol. wt. 153.15): C, 47.0; H, 4.6; N, 27.4; S, 20.93. Found: C, 47.0; H, 4.8; N, 27.6; S, 20.8. *M/e*: 153 (P); 155 (P + 2).

*3-Aminoisothiazolo[4,3-b]pyridine (**18**)*

3-Aminothiopicolinamide (**17**) (0.42 g, 2.7 mmol) was dissolved in 1.7 ml of pyridine by heating at 35° with stirring. Hydrogen peroxide (30%, 1.0 ml) was added dropwise to the reaction mixture to maintain the temperature below 35°. The flask was stoppered and let stand at room temperature for 16 h. It was then poured onto a

small amount of crushed ice and the yellow product filtered off. Crystallization from benzene produced 0.124 g (30% yield) of 3-aminoisothiazolo[4,3-*b*]pyridine (**18**) as fine yellow needles, m.p. 195–196°. I.r. (KBr): 1652, 3310, 3250, 3080 cm^{-1} (NH_2).

Anal. Calcd. for $C_6H_5N_3S$ (mol. wt. 151.13): C, 47.7; H, 3.3; N, 27.8; S, 21.2. Found: C, 47.4; H, 3.4; N, 28.0; S, 21.0. *M/e*: 151 (P); 153 (P + 2).

*3-Bromoisothiazolo[4,3-b]pyridine (**19**)*

3-Aminoisothiazolo[4,3-*b*]pyridine (**18**) (90 mg, 0.59 mmol) was suspended in 5 ml of 48% hydrobromic acid. Sodium nitrite (70 mg, 1.0 mmol) was added in small portions over a period of 3 min with constant stirring at −4 to 0°. The mixture was stirred for 30 min at 0° and let stand at room temperature overnight. Crushed ice was added and the solution was made strongly alkaline with 20% sodium hydroxide solution. The mixture was extracted continuously with ether in liquid–liquid extractor. The ethereal extract was dried over sodium sulfate and the solvent evaporated to dryness leaving 53 mg of a brown substance. Chromatography and crystallization from benzene gave 28 mg (21% yield) of 3-bromoisothiazolo[4,3-*b*]pyridine (**19**) as yellow needles, m.p. 145–156°.

M/e: 214 (P); 216 (P + 2). Calcd. mass from the exact mass measurement: 215.916945. Calcd. mass for $C_6H_3z_2SBr$: 215.916411. Delta mass: 0.000543.

*2-Chloronicotinaldehyde (**21**)*

Raney nickel alloy (50–50; 30 g) was stirred with 3 l of 2 *N* sodium hydroxide solution for 30–40 min, the temperature being allowed to rise. The alkaline solution was decanted and the Raney nickel was washed twice with distilled water. A solution of 2-chloronicotinonitrile (**20**) (20.0 g, 0.141 mol) in 300 ml of 98% formic acid was added to the moist Raney nickel catalyst and the mixture was stirred for 30 min at 45–80°. The mixture was diluted with 280 ml of ethanol–water (2:1, v/v), filtered, and the catalyst washed twice with 50 ml of warm ethanol. The filtrate together with the ethanol washings was diluted with water and extracted several times with ether. The ethereal extract was washed with dilute sodium bicarbonate solution and water, and dried over sodium sulfate. The solvent was evaporated leaving 14.5 g of an oily brown substance which on distillation at 66–70°/5 mm Hg produced 11.8 g (58% yield) of a colorless oil which solidified immediately on cooling. Crystallization from ether–chloroform gave a pure 2-chloronicotinaldehyde (**21**) as colorless needles, m.p. 42–43°. I.r. (KBr): 2280 (—C*H*O) and 1688 cm^{-1} (—CH*O*).

M/e: 141 (P); 143 (P + 2). Calcd. mass from the exact mass measurement: 140.998452. Calcd. mass for C_6H_4NOCl: 140.998139. Delta mass: 0.000313.

*2-Thiocyanonicotinaldehyde (**22**)*

Potassium thiocyanate (7.4 g, 0.0754 mol) was added to 2-chloronicotinaldehyde (**21**) (6.0 g, 0.0427 mol) in glacial acetic acid (60 ml). The reaction mixture was stirred at room temperature and was kept under nitrogen atmosphere overnight. The solution was poured onto crushed ice and the yellow precipitate was collected by suction after a few hours. Crystallization from ethyl acetate yielded 4.6 g (65%) of 2-thiocyanonicotinaldehyde (**22**) as long yellow needles m.p. 143–144°. I.r. (KBr): 2163 cm^{-1} (SCN).

M/e: 164 (P); 166 (P + 2). Calcd. mass from the exact mass measurement: 164.004568. Calcd. mass for $C_7H_4N_2OS$: 164.004433. Delta mass: −0.000135.

*Isothiazolo[5,4-b]pyridine (**6**)*

Liquid ammonia in a large excess was added over a 3 h period to 2-thiocyanonicotinaldehyde (**22**) (4.1 g, 0.025 mol) placed in a 300 ml two-necked flask equipped with a magnetic stirrer and immersed in an ethanol – Dry Ice bath kept below 50°. The mixture was kept at this temperature with constant stirring for 5 h. Ammonia was allowed to evaporate slowly at room temperature leaving 3.06 g of a tan solid. Crystallization from *n*-hexane gave 1.3 g (38% yield) of isothiazolo[5,4-*b*]pyridine (**6**) in the form of fine colorless needles, m.p. 54.5–55.5°.

M/e: 136 (P); 138 (P + 2). Calcd. mass from the exact mass measurement: 136.009204. Calcd. mass for $C_6H_4N_2S$: 136.009519. Delta mass: 0.000315.

*4-Acetyl-3-thiocyanopyridine (**24**)*

4-Acetyl-3-aminopyridine (**23**) (1.08 g, 7.2 mmol) was dissolved in concentrated sulfuric acid (2.5 g) and water (5 ml), cooled to −4 to −2°, and diazotized with a solution of 0.58 g (8.2 mmol) of sodium nitrite in 2.5 ml of water. The resulting diazonium salt solution was stirred at this temperature for 10 min and then added dropwise with stirring to a solution of 0.88 g of potassium thiocyanate (9.0 mmol) in 2.5 ml of aqueous cuprous thiocyanate (prepared from 0.2 g of cupric sulfate, 0.88 g of potassium thiocyanate and 0.35 g of ferrous sulfate) was added to the mixture which was further stirred at room temperature for another hour. The reaction mixture was poured onto a small amount of crushed ice and neutralized with solid sodium bicarbonate. The brown precipitate was filtered off, dried, and crystallized from *n*-hexane to obtain 0.86 g (45% yield) of a pure 4-acetyl-3-thiocyanopyridine (**24**) as long colorless needles, m.p. 83–84°. I.r. (KBr): 2158 cm^{-1} (SCN).

M/e: 178 (P); 180 (P + 2).

Anal. Calcd. for $C_8H_6N_2SO$: C, 53.9; H, 3.4; N, 15.7; S, 17.99. Found: C, 53.2; H, 3.6; N, 15.6; S, 18.1.

*(a) Cyclization of 4-Acetyl-3-thiocyanopyridine (**24**) with Ammonium Hydroxide Under High Pressure*

A mixture of 1.78 g (0.01 mol) of 4-acetyl-3-thiocyanopyridine (**24**) and 100 ml of concentrated ammonium hydroxide was placed in a glass-liner within a stainless steel pressure bomb equipped with a magnetic stirrer and heated in a silicon oil bath at 130° for 5 h. The reaction mixture was evaporated to dryness leaving a brown solid substance. Chromatography and crystallization of the product from *n*-hexane gave 0.31 g (20% yield) of 3-methylisothiozolo[5,4-*c*]pyridine (**25**) as pale orange prisms, m.p. 57–58°.

M/e: 150 (P); 152 (P + 2); mol. wt. 150.13. Calcd. mass from the exact mass measurement M: 150.02448. Delta mass: 0.00042. Calcd. mass for $C_7H_6N_2S$: M 150.0249. Delta mass: 0.00042.

*(b) Cyclization of 4-Acetyl-3-thiocyanopyridine (**24**) with Liquid Ammonia*

Liquid ammonia was added in a large excess over a 3 h period to 1.0 g (6.7 mmol) of 4-acetyl-3-thiocyanopyridine (**24**) placed in a 200 ml two-neck flask equipped with a magnetic stirrer and immersed in an ethanol – Dry Ice bath kept below −50°. The reaction mixture was further stirred for another 5 h and then ammonia was allowed to

evaporate slowly at room temperature leaving a brown solid substance. Crystallization of the product from *n*-hexane gave 0.185 g (22% yield) of 3-methylisothiozolo-[5,4-*c*]pyridine (**25**), m.p. 57–58°.

The n.m.r. and mass spectra of this compound were exactly the same as for **25** prepared by the procedure *a*.

*4-Aminothionicotinamide (**26**)*

This compound was prepared from 4-aminonicotinonitrile (**27**) by the procedure used in preparing 2-aminothionicotinamide (**10**). From 0.7 g (5.9 mmol) of **27**, 0.56 g (62% yield) of **26** was obtained as fine pale yellow needles, m.p. 157–158°.

Anal. Calcd. for $C_6H_7N_3S$ (mol. wt. 153.15): C, 47.0; H, 4.6; N, 27.4; S, 20.9. Found: C, 47.4; H, 4.5; N, 27.7; S, 20.6. *M/e*: 153 (P); 155 (P + 2).

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