Isomeric Phenylthioimidazo[1,2-*a*]pyridines as Anthelmintics

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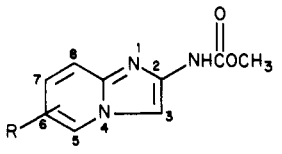
A series of isomeric imidazo[1,2-*a*]pyridine-2-carbamates was prepared for testing as anthelmintics. The analogues were synthesized by reacting the appropriate 2-aminopyridine and methyl chloroacetylcarbamate. Steric hindrance in the 2,6-disubstituted derivative resulted in the formation of the isomeric 3-substituted analogue as the major product. Carbon-13 NMR proved useful in the structural assignments in this series. None of the analogues exhibited the potency of methyl 6-(phenylsulfinyl)imidazo[1,2-*a*]pyridine-2-carbamate when tested against *Nematospiroides dubius* in mice.

The introduction of a phenylthio group at the 6 position of imidazo[1,2-*a*]pyridine-2-carbamates effected a dramatic improvement in the anthelmintic potency of these compounds.[1] As a result, methyl 6-(phenylsulfinyl)imidazo-[1,2-*a*]pyridine-2-carbamate (**1a**) was found to be a potent, broad-spectrum anthelmintic.[1] In an attempt to gain some insight into the nature of this activity enhancement, the synthesis and biological study of the 3-, 5-, 7- and 8-(phenylthio)imidazo[1,2-*a*]pyridine-2-carbamates, **1c–f**, were undertaken.

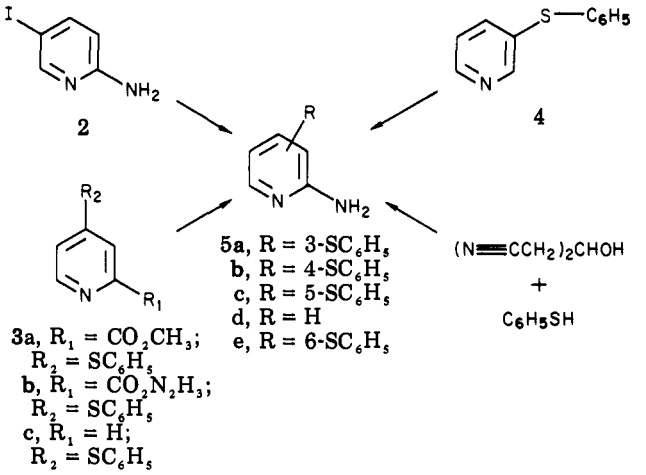


1a, R = 6-$C_6H_5S(\rightarrow O)$
b, R = 6-C_6H_5S
c, R = 3-C_6H_5S
d, R = 7-C_6H_5S
e, R = 8-C_6H_5S
f, R = 5-C_6H_5S
g, R = H

Chemistry. Preparation of Aminopyridines. The prerequisite phenylthio-2-aminopyridines **5a–d** were obtained by various synthetic pathways (Scheme I). Application of the Chichibabin reaction on **4** yielded a mixture of aminated pyridines, consisting of 52% **5c** and 48% **5a**. **5c** was also obtained by displacement of iodine from **2** with sodium thiophenolate. The same aminating conditions when applied to **3c** produced **5b** in such low yields as to offer no synthetic utility. Therefore, an alternate route from the chloropicolinic ester **3a** was utilized proceeding via a Curtius reaction on **3b**. **5e** was prepared in 47% yield from 3-hydroxyglutaronitrile[2] and thiophenol.[3]

Preparation of Carbamates. The conversion of **1g** into **1c** or **6** was accomplished by taking advantage of the electrophilic nature of the 3 position of the imidazo[1,2-*a*]pyridine ring system[4] (Scheme III). Reaction of phenylsulfenyl chloride with **1g** yielded **1c**. The position of the phenylthio group was indicated by the absence of the 3-proton in the ^1H NMR spectrum of **1c**. *p*-Chlorophenylsulfenyl chloride was reacted in a similar manner to yield **6**.

Scheme I. Syntheses of Substituted 2-Aminopyridines

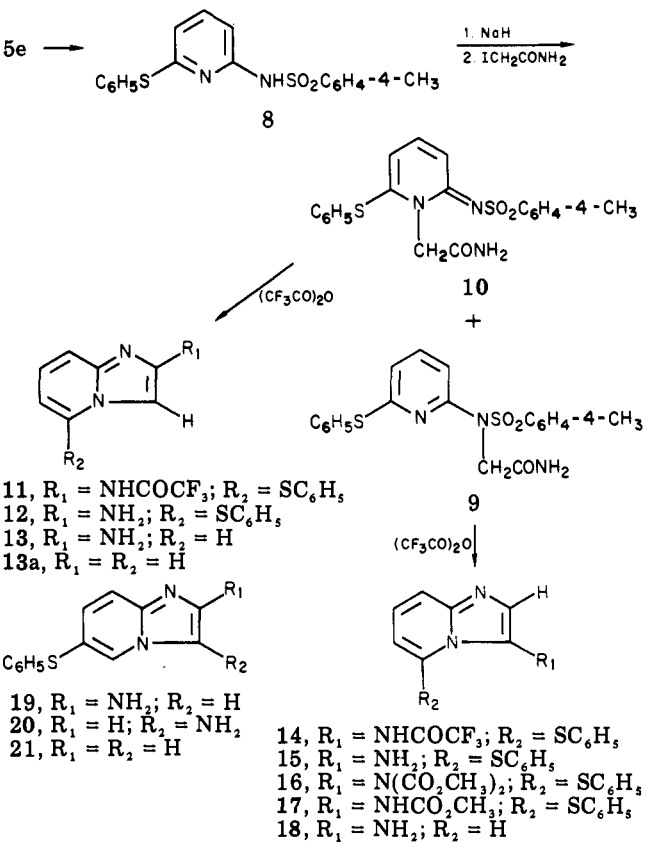


3a, $R_1 = CO_2CH_3$; $R_2 = SC_6H_5$
b, $R_1 = CO_2N_2H_3$; $R_2 = SC_6H_5$
c, $R_1 = H$; $R_2 = SC_6H_5$

5a, R = 3-SC_6H_5
b, R = 4-SC_6H_5
c, R = 5-SC_6H_5
d, R = H
e, R = 6-SC_6H_5

$(N{\equiv}CCH_2)_2CHOH$ + C_6H_5SH

Scheme II



11, $R_1 = NHCOCF_3$; $R_2 = SC_6H_5$
12, $R_1 = NH_2$; $R_2 = SC_6H_5$
13, $R_1 = NH_2$; $R_2 = H$
13a, $R_1 = R_2 = H$

19, $R_1 = NH_2$; $R_2 = H$
20, $R_1 = H$; $R_2 = NH_2$
21, $R_1 = R_2 = H$

14, $R_1 = NHCOCF_3$; $R_2 = SC_6H_5$
15, $R_1 = NH_2$; $R_2 = SC_6H_5$
16, $R_1 = N(CO_2CH_3)_2$; $R_2 = SC_6H_5$
17, $R_1 = NHCO_2CH_3$; $R_2 = SC_6H_5$
18, $R_1 = NH_2$; $R_2 = H$

(1) R. J. Bochis, R. A. Dybas, P. Eskola, P. Kulsa, B. O. Linn, A. Lusi, E. P. Meitzner, J. Milkowski, H. Mrozik, L. E. Olen, L. H. Peterson, R. L. Tolman, A. F. Wagner, F. S. Waksmunski, J. R. Egerton, and D. A. Ostlind, *J. Med. Chem.*, 21, 235 (1978).
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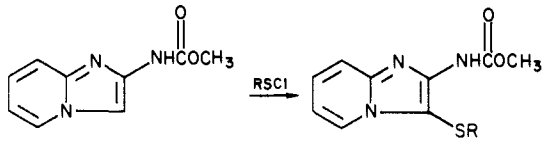
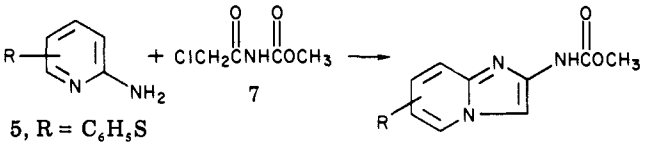
Scheme III. Synthesis of 3 3-(Arylthio)imidazo[1,2-a]pyridines



1g

1c, R = C_6H_5
6, R = C_6H_4Cl-p

Table I. Preparation of Imidazo[1,2-a]pyridine-2-carbamates



5, R = C_6H_5S

1, R = C_6H_5S

no.	no.	% yield	mp (recrystn solvent), °C	anal.
5a	1e	51	169-171 (EtOH)	C, H, N, S
5b	1d	53	223-224 dec (EtOH)	C, H, N, S
5c	1b	60	244-246 dec (EtOH/DMF)	C, H, N, S
5d	1g	30		

The reaction of aminopyridines **5a–d** with methyl *N*-(chloroacetyl)carbamate (**7**) in hexamethyl phosphoramide (HMPT) proceeded smoothly, yielding the desired carbamates **1b**, **1d**, **1e**, and **1g** (Table I). However, presumably due to steric hindrance at the ring nitrogen, **5e** yielded a gross mixture of products. TLC examination of the mixture did not indicate the presence of **1f**. The method of Bristow et al.[5] also offered synthetic difficulties (Scheme II). **5e** was reacted with *p*-toluenesulfonyl chloride to yield **8**. Alkylation of **8** yielded two carbamylmethyl derivatives in a 15:1 ratio. Since steric factors have been reported to be an influence on the site of alkylation of 2-aminopyridines,[6] the structure of the major component was tentatively assigned as the exo-alkylated isomer **9** and the minor component as the ring-substituted **10**. This is in marked contrast to the 5-phenylthio derivative of **8**, where the same alkylating conditions yielded only ring alkylation.[1] The assignments were firmly established by comparison of the ^{13}C NMR spectra of the respective cyclized derivatives **12** and **15** with related structures **18–21** (Table II).

The isomeric amino derivatives **12** and **15** were obtained by the hydrolysis the trifluoroacetamides **11** and **14**. These amides were derived from **9** and **10** by reaction with trifluoroacetic anhydride, respectively.

Structure Assignments of Aminated Analogues. Carbon-13 NMR provided a method, employing both ^{13}C chemical shifts and ^{1}H–^{13}C coupling constants, to determine 2- vs. 3-substitution in imidazo[1,2-a]pyridines. The chemical-shift data reported in Table II was useful in light of the large chemical shifts for C-2 and C-3 in the unsubstituted **13a**. Also, the electron-donating property of the amino group results in a shielding of the β carbon with a simultaneous deshielding at the α carbon.

Fully coupled ^{13}C spectra were recorded in order to measure ^{1}H–^{13}C coupling constants. In **12** and **15**, the hydrogen-bearing carbon in the imidazole ring is readily identified as having a one-bond coupling greater than 180 Hz, since it is adjacent to nitrogen. Indeed, in **12**, the imidazole protic carbon appears at 92.8 ppm with ^{1}J = 194.0 Hz and at 119.4 ppm with ^{1}J = 187.2 Hz in **15**. A large two-bond coupling (14.3 Hz) in **15** indicated that the amino-bearing carbon comes at 133.6 ppm. However, assignment of the amino-bearing carbon in **12** was not as apparent. By examination of the fully coupled and off-resonance decoupled spectra of **21**, one was able to assign lines for C-2 and C-3. Carbon-2 exhibited a ^{1}J = 188.4 and a $^{2}J_{C2\text{-}H3}$ = 10.2, while carbon-3 displayed a ^{1}J = 195.1 and a $^{2}J_{C2\text{-}H3}$ = 16.2. These data now fix the amino-bearing carbon in **12** at 152.4 ppm with a ^{2}J = 8.2 Hz.

The assignments are consistent with the spectra obtained for the previously reported amines, **19**[1] and **20**.[7] Comparison of the shift data in Table II demonstrates that **12** and **19** are 2-amino analogues, while **15** and **20** are 3-amino derivatives; therefore, the sites of the open carbamylmethyl precursors must be as suggested. Interestingly, **18** must be assigned as the cyclized 3-aminoimidazopyridine as a result of the effects on the chemical shifts when compared with the chemical shifts in **13a**. This is contrary to the reported pyridylacetonitrile structure for **18**.[5]

Biology. The carbamates **1a–g** were administered in the diet to mice infected with *Nematospiroides dubius* for a period of 5 days in our regular screening assay.[1] At necropsy, the worm burdens of the treated mice were compared to those of the untreated infected controls. These data are recorded in Table III.

Results and Conclusions

The data in Table III indicate a dramatic isomeric specificity for potent anthelmintic activity within phenylthioimidazo[1,2-a]pyridines. None of the isomeric derivatives approached the potency of **1a** or **1b**.

Inactivation by metabolic hydroxylation is undoubtedly a contributing factor to loss of activity in some cases, and potency improvement has been achieved by retarding metabolism in both the benzimidazole **8a,b** and imidazo[1,2-a]pyridine[4] series. However, it is unlikely that this phenomenon can explain the variation in activity among the compounds described in this article.

Studies on the metabolism of imidazo[1,2-a]pyridines are limited and offer little insight into the fate of these compounds in animals.[10] However, in view of the electrophilic nature of enzymatic hydroxylation, one might expect preference at sites of high electron density. The charge densities of this ring system have been calculated.[11] Clearly, substitution at the more electrophilic centers did not improve biological activity, except in the cases of **1a** and **1b**, and does not alone account for the activity variations encountered.

The evidence is now convincing that the mode of action of benzimidazoles and, by extrapolation, imidazo[1,2-a]-

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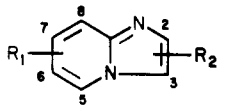
Table II. Carbon-13 NMR Assignments for Imidazo[1,2-*a*]pyridines



chemical shift (J, Hz),[a] δ

no.	C-2	C-3	C-5	C-6	C-7	C-8	C-8a
12	152.4 ($^2J_{H_3C_2}$ = 8.4)	92.8 (^1J = 194.0)	124.7	113.8	121.6	118.5	142.6
15	119.4 (^1J = 187.2)	133.6 ($^2J_{H_2C_3}$ = 14.3)	128.1	118.1	120.3	121.0	140.9
19[b]	152.8 (^2J = 8.4)	93.4 (^1J = 193.2)	129.4 (^1J = 186.5)	113.3	127.4	113.8	130.0
20[c]	116.8 (^1J = 187.3)	131 (^2J = 14.2)	126.7 (^1J = 187.6)	114.6	125.1	117.7	137.9
18[d]	116.8 (^1J = 186.0)	130.5 (^2J = 14.4)	122.1 (^1J = 183.8)	110.5	120.5	116.8	139.3
13a[e]	134.1	113.3	127.0	112.2	124.6	117.6	145.6
21[f]	133.9 (^1J = 188.4, ^2J = 10.2)	113.7 (^1J = 195.1, ^2J = 16.2)	130.9 (^1J = 189.1, ^3J = 5.7)	116.6	129.1	117.7	143.6

[a] All shifts are measured in Me_2SO-d_6 and are reported in δ (parts per million) downfield from Me_4Si. [b] See ref 1. [c] See ref 7. [d] Prepared by the method in ref 5. [e] R. Pugmire, M. J. Robins, D. M. Grant, and R. K. Robins, *J. Am. Soc.*, 93(8), 1887 (1971). [f] Supplied by L. Peterson.

Table III. Percent Reduction[a] of *N. dubius* in Mice at Necropsy[b]

compd	ppm in diet:	% reduction 1000	500	250	125	62.5
1a[c]				100	100	90
1b[c]			100	98	75	20
1d		0				
1e		0				
1f		0				
1g		54				
thiabendazole[d]		87	47	0	0	0
cambendazole[e]		100	80	20	0	0
fenbendazole[f]			100	97	74	0

[a] <20% recorded as 0, compared with untreated, infected controls. [b] These results were obtained by a modification of the method of Baker.[15] There were three mice per treated group. The results are an average of the number of worms per mouse. [c] See ref 1. [d] 2-(4-Thiazolyl)benzimidazole (Merck & Co.). [e] Isopropyl 2-(4-thiazolyl)-5-benzimidazolecarbamate (Merck & Co.). [f] Methyl phenylthio-2-benzimidazolecarbamate (Hoechst).

pyridines, on both helminths and fungi,[12,13] is specific binding to the B subunit of the tubulin dimer with resulting inhibition of the microtubule assembly. Shier-Neiss, Lai, and Morris[14] have shown that benzimidazole substitution can have a profound effect on binding and, hence, on activity. For example, while some altered tubulins from *Aspergillus nidulans*, resistant to benomyl, did not bind benomyl, they were still able to bind thiabendazole and vice versa. It is possible that the structural requirements of the helminth B-tubulin binding site are such that some bulky substituents impede binding of the imidazo[1,2-*a*]pyridines with resulting loss of activity, thus explaining the variations seen. Unfortunately, helminth tubulins have not yet been isolated; therefore, definitive studies cannot be undertaken at this time.

Experimental Section

Melting points were determined in a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were obtained in a Nujol mull with a Perkin-Elmer spectrophotometer 137. ^1H NMR spectra were determined with a Varian HA-100 NMR spectrometer. Some of these data are recorded in Tables IV and V. ^{13}C NMR were determined on Varian XL-100 and CFT-20 spectrometers. These data are recorded in Table II. Where indicated, preparative HPLC separations were carried out on a Prep LC system 500 over Prep-Pak (silica gel). Column volumes necessary for elution of the components are recorded as cv's and solvent system. Elemental analyses were performed by the Analytical Department of Merck Sharp & Dohme Research Laboratories and are within ±0.4% of the calculated values. Magnesium sulfate was used to dry all organic extracts.

4-(Phenylthio)-2-picolinoylhydrazide (3b). A solution of ethyl 4-chloropicolinate[16] (6.84 g, 40 mmol), thiophenol (4.4 g, 40 mmol), and $NaOCH_3$ (2.16 g, 40 mmol) in MeOH (65 mL) was heated at reflux for 2 h under a N_2 atmosphere. The cooled reaction mixture was treated with 95% N_2H_4 (1.5 g, 46.8 mmol), heated at reflux for 90 min, cooled, filtered, and concentrated to dryness in vacuo. The residue was taken up in CH_2Cl_2 and washed with 2.5 N NaOH. The organic layer was separated, dried, and concentrated in vacuo to yield 7.3 g of a yellow oil. Crystallization from EtOH yielded 3.7 g (32%) of **3b**, mp 111–112.5 °C. Anal. ($C_{12}H_{11}N_3SO$) C, H, N, S. The residue from the crystallized mother liquors was passed over 140 g of silica gel and eluted with EtOAc to yield an additional 1.5 g (15%) of **3b**: NMR ($CDCl_3$) δ 8.20 (d, J = 7 Hz, H-6), 7.83 (d, J = 2 Hz, H-3), 7.48 (s, Ar H), 6.89 (dd, J = 7 and 2 Hz, H-5).

2-Amino-4-(phenylthio)pyridine (5b). From 3b. A solution of **3b** (29.88 g, 122 mmol) in H_2O (70 mL) containing concentrated HCl (10.5 mL) at 0 °C was treated dropwise with a solution of $NaNO_2$ (9.05 g, 131 mmol) in H_2O (15 mL). During the addition, the azide deposited as a thick viscous gum. After 20 min at 0 °C, the mixture was extracted twice with CH_2Cl_2. The organic layer was separated, washed with cold H_2O, and dried over $MgSO_4$. The solvent was removed in vacuo (bath temperature <30 °C). The residue was taken up in 150 mL of 50% aqueous HOAc and heated on the steam bath until N_2 evolution had ceased (~20 min). The cooled reaction mixture was filtered, basified with 50% NaOH,

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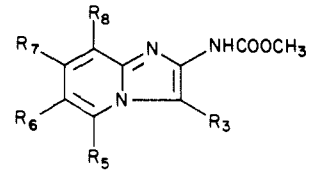
Table IV. Chemical-Shift Data[a] of Imidazo[1,2-a]pyridine-2-carbamates



	chemical shift (multiplicity; J, Hz),[a] δ						
no.	R_3	R_5	R_6	R_7	R_8	NH	OCH_3
1g	H, 7.84 (s)	H, 8.49 (dd; 7, 2)	H, 6.8 (dd; 7, 2)	H, 7.14 (dd; 9, 2)	H, 7.36 (dd; 9, 2)	10.3 (s)	3.69 (s)
1b	H, 8.94 (s)	H, 7.97 (d; 2)	C_6H_5S	H, 7.20 (dd; 9, 2)	H, 7.49 (d; 9)	10.42 (s)	3.7 (s)
1c	C_6H_5S	H, 8.19 (dd; 7, 2)	H, 7.14 (dd; 9, 8)	H, 7.44 (td; 9, 8, 2)	H, 7.63 (dd; 9, 2)	9.72 (s)	3.56 (s)
1d	H, 7.84 (s)	H, 8.5 (dd; 7, 2)	H, 6.78 (dd; 7, 2)	C_6H_5S	H, 7.18 (d; 2)	10.32 (s)	3.64 (s)
1e	H, 7.93 (s)	H, 8.45 (d; 7)	H, 6.8 (t; 9, 7, and 2)	H, 6.7 (dd; 9, 2)	C_6H_5S	10.5 (s)	3.64 (s)
1f	H, 7.70 (s)	C_6H_5S	H, 7.18 (dd; 7, 2)	H, 7.38 (dd; 9, 7)	H, 7.74 (dd; 9, 2)	10.42 (s)	3.60 (s)

[a] All shifts measured in Me_2SO-d_6 and are reported in δ (parts per million) downfield from Me_4Si, followed by multiplicity (s, singlet; d, doublet; dd, doublet of doublets; m, complex multiplet) and coupling constants (J, Hz) in parentheses.

Table V. Chemical-Shift Data[a] of Phenylthio-2-aminopyridines

	chemical shift (multiplicity; J, Hz), δ					
no.	H_3	H_4	H_5	H_6	NH_2	ArH
5a		7.64 (dd; 7, 2)	6.64 (dd; 7, 5)	8.04 (dd; 5, 2)	5.28 (br s)	7.11 (s)
5b	6.13 (d; 2)		6.4 (dd; 6, 2)	7.86 (d; 6)	4.33 (br s)	7.46 (m)
5c	6.48 (d; 9)	7.55 (dd; 9, 2)		8.25 (d; 2)	4.76 (br s)	7.16 (m)m

[a] All shifts measured in $CDCl_3$ and are reported in δ (parts per million) downfield from Me_4Si, followed by multiplicity (s, singlet; d, doublet; dd, doublet of doublets; m, complex multiplet, br s, broad singlet) and coupling constants (J, Hz) in parentheses.

and extracted with CH_2Cl_2. After the mixture was washed with H_2O and dried, the organic layer was evaporated to yield 11.9 g of a solid. Recrystallization from PhH yielded 4.3 g (17.3%) of **5b**, mp 106–108 °C. Anal. ($C_{11}H_{10}N_2OS$) C, H, N, S. Chromatography of the residues from evaporation of the mother liquors over silica gel and elution with EtOAc yielded an additional 3.4 g (13.7%) of **5b**. ^1H NMR assignments are recorded in Table V.

From 3c. Commercial $NaNH_2$ (1.3 g, 33.5 mmol) and **3c**[17] (5.25 g, 28 mmol) in dimethylaniline (8 mL) were heated at 160 °C for 6 h. The cooled reaction mixture was diluted with H_2O (25 mL) and extracted with CH_2Cl_2. The combined extracts were washed with brine, dried, and evaporated to dryness in vacuo. The residue was chromatographed over 300 g of silica gel. Elution with CH_2Cl_2 yielded dimethylaniline, followed by 1.65 g (31%) of starting **3c**. Elution with MeOH–CH_2Cl_2 (2:98) yielded 0.213 g (3.7%), which was identical by NMR, IR, TLC with that obtained from **3b**.

3-(Phenylthio)pyridine (4). 3-Aminopyridine (67.6 g, 0.718 mol) was added to concentrated HCl (160 mL) with cooling. The suspension was cooled to 0 °C and $NaNO_2$ (57.6 g, 0.834 mol) in 400 mL of H_2O was added dropwise while keeping the reaction temperature below 5 °C. After 10 min, urea was added portionwise until a negative test for nitrous acid (starch–iodide) was obtained. The cold diazonium solution was slowly poured into a preheated solution of C_6H_5SH (80 mL) in 800 mL of H_2O containing 160 g of NaOH. The reaction mixture was heated on the steam bath until N_2 evolution had ceased. After cooling, the mixture was extracted with ether. The organic layer extracts were washed, dried, and evaporated in vacuo to yield 74.2 g of a red oil. The oil was fractionally distilled in vacuo. After a small forerun, 56.3 g of **4**, bp 128–129 °C (0.6 mm), as a light yellow oil was obtained. Anal. ($C_{11}H_9NS$) C, H, N, S.

2-Amino-3-(phenylthio)pyridine (5a). Following the procedure described for the preparation of **5b**, $NaNH_2$ (1.3 g, 33.5 mmol), **4** (5.25 g, 28 mmol), and dimethylaniline yielded a crude product, which was chromatographed over 300 g of silica gel. Elution of CH_2Cl_2 yielded 0.887 g (17%) of starting **4**, followed by 0.943 g (16.6%) of **5a**, mp 108–109 °C. Anal. ($C_{11}H_{10}N_2S$) C, H, N. Further elution with CH_2Cl_2 yielded 1.01 g (17.7%) of **5c**.

2-Amino-5-(phenylthio)pyridine (5c). The copper-catalyzed displacement with sodium thiophenylate of **2** yielded **5c**, mp 123–125 °C.[1]

2-Amino-6-(phenylthio)pyridine (5e). From thiophenol and 3-hydroxyglutaronitrile, **5e** was obtained in 47% yield.[2,3] The yield was maximized by passing the crude amine through the Prep HPLC (2.2–4 cv; EtOAc–CH_2Cl_2, 1:2).

2-[(Methoxycarbonyl)amino]-3-(phenylthio)imidazo[1,2-a]pyridine (1c). A suspension of **1g** (1.9 g, 10 mmol) in DMF (50 mL) containing $(C_2H_5)_3N$ (1.01 g, 10 mmol) was treated dropwise with benzenesulfenyl chloride (1.44 g, 10 mmol). After 2 h at room temperature, the mixture was filtered, diluted with H_2O, and extracted with $(C_2H_5)_2O$. The combined extracts were washed with H_2O, dried, and evaporated in vacuo. Recrystallization of the residue from EtOH yielded 0.665 g (22%) of 1c: mp 171–173 °C; NMR (Me_2SO-d_6) δ 3.6 (s, OCH_3), 7.75–6.8 (m, 8 protons), 8.23 (dt, J = 7, 2, and 2 Hz), 9.68 (s, NH). Anal. ($C_{15}H_{13}N_3O_2S$) C, H, N, S.

Under the same conditions, *p*-chlorophenylsulfenyl chloride, $(C_2H_5)_3N$, and **1g** yielded 2-[(methoxycarbonyl)amino]-3-[(*p*-chlorophenyl)thio]imidazo[1,2-a]pyridine (**6**), mp 204–207 °C (EtOH), in 35% yield. Anal. ($C_{15}H_{12}ClN_3O_2S$) C, H, N.

Imidazo[1,2-a]pyridine-2-carbamates 1b–e,g. The reaction of the appropriate 2-aminopyridine and methyl (chloroacetyl)-carbamate (**7**) was accomplished by the previously reported method.[1] The results are summarized in Table I. The ^1H NMR assignments are reported in Table IV.

2-(4-Methylbenzenesulfonamido)-6-(phenylthio)pyridine (8). A cooled solution of **5e** (15.15 g, 75 mmol) in C_5H_5N (75 mL) was treated portionwise with TsCl (15.75 g, 82 mmol). The mixture was warmed on the steam bath for 90 min and poured onto 600 mL of ice–H_2O. After 3 h, the solids were collected by filtration, washed with H_2O, and dried to yield 29.1 g of crude **8**. Recrystallization from ether–hexane yielded 22.7 g (94%) of **8**, mp 104–105 °C. Anal. ($C_{18}H_{16}N_2O_2S$) C, H, N, S.

2-[*N*-(Carbamoylmethyl)-4-methylbenzenesulfonimido]-6-(phenylthio)pyridine (9) and 1-(Carbamoylmethyl)-1,2-dihydro-2-(4-methylbenzenesulfonimido)-6-(phenylthio)pyridine (10). A solution of **8** (83.5 g, 0.235 mol)

(17) R. H. Sprague and L. G. S. Brooker, *J. Am. Chem. Soc.*, 59, 2698 (1937).

in DMF (450 mL) at 10 °C was treated portionwise with a 57% NaH oil dispersion (10.9 g, 0.258 mol). After the solution was stirred at room temperature for 4 h, 2-iodoacetamide (47.5 g, 0.257 mol) was added in one portion. The mixture was stirred, with occasional cooling at 20 ± 2 °C, for 4 h and then poured into 4000 mL of H_2O. The solids were collected by filtration, washed with H_2O, and dried: yield 94 g. The cake was suspended in 740 mL of EtOAc, heated to reflux, and filtered. Upon cooling, the filtrate yielded 62.6 g (64.4%) of **9**: mp 148–149 °C; NMR (Me_2SO-d_6) δ 2.4 (s, Ar CH_3), 4.38 (s, CH_2), 6.72 (dd, J = 8.2 Hz), 7.10 (s, NH), 7.19 (dd, J = 8.2 Hz, H-4), 7.39 (d, J = 8 Hz), 7.65 (d, J = 8 Hz, Ar H), 7.46 (s, Ar H), 7.63 (d, J = 8 Hz, H-5). Anal. ($C_{20}H_{19}N_3O_3S$) C, H, N.

The EtOAc-insoluble portion was nearly pure **10** and weighed 5.08 g (5.2%), mp 223–226 °C dec. Recrystallization from DMF-EtOH yielded analytically pure **10**, mp 225–226 °C dec. NMR (Me_2SO-d_6) 2.33 (s, Ar CH_3), 5.16 (s, CH_2), 6.23 (dd, J = 8 and 2 Hz, H-3), 7.27 and 7.67 (d, J = 8 Hz, tolyl H), 7.17 (dd, J = 8 and 2 Hz, H-5), 7.4–7.6 (m). Anal. ($C_{20}H_{19}N_3O_3S$) C, H, N, S.

The EtOAc filtrates were evaporated to dryness, and the residue was passed through the Prep HPLC to yield an additional 12.9 g (13.2%) of **9** (1.1–1.9 cv; EtOAc–CH_2Cl_2, 7:3). Further elution yielded 0.52 g (0.52%) of **10**.

5-(Phenylthio)-2-(trifluoroacetamido)imidazo[1,2-*a*]pyridine (11). A suspension of **10** (2.6 g, 6.28 mmol) in TFAA (40 mL) was heated at reflux for 90 min. The solvent was removed in vacuo, and the residue was taken up in CH_2Cl_2, washed with saturated aqueous $NaHCO_3$, and H_2O. The organic layer was dried and evaporated in vacuo to yield 2.02 g of an amorphous residue. Chromatography over 200 g of silica gel and elution with EtOAc–CH_2Cl_2 (1:4) yielded 0.924 g (43.8%) of **11**: mp 115–117 °C (*n*-hexane); NMR ($CDCl_3$) δ 7.03 (dd, J = 7 and 2 Hz), 7.26 (dd, J = 9 and 6 Hz), 7.38 (br s, Ar H), 7.5 (dd, J = 8 and 2 Hz, H-8), 8.25 (H-3), 11.4 (s, NH). Anal. ($C_{15}H_{10}F_3N_3OS$) C, H, N, S.

2-Amino-2-(phenylthio)imidazo[1,2-*a*]pyridine (12). The amide **11** (3.5 g, 10.3 mmol) was stirred in 2.5 N NaOH (40 mL) at room temperature for 24 h. The precipitate was collected by filtration, washed with H_2O, and dried to yield 2.47 g (91%) of **12**, mp 175–179 °C. After recrystallization from EtOH, the melting point was 177–178 °C. Anal. ($C_{13}H_{11}N_3S$) C, H, N.

Methyl 5-(Phenylthio)imidazo[1,2-*a*]pyridine-2-carbamate (1f). The amine **12** (75 mg, 3.1 mmol) and $(C_2H_5)_3N$ (314 mg, 3.1 mmol) in CH_2Cl_2 (40 mL) was treated dropwise with methyl chloroformate (293 mg, 3.1 mmol) at 0 °C. The mixture was stirred at room temperature for 1 h and diluted with ice–H_2O. The organic layer was separated, dried over $MgSO_4$, and evaporated in vacuo. The residue was chromatographed over silica gel and eluted with EtOAc/$MeCl_2$ (1:1) to yield 300 mg of **1f**, mp 228–230 °C. Anal. ($C_{15}H_{13}N_2O_2S$) C, H, N, S.

3-(Trifluoroacetamido)-5-(phenylthio)imidazo[1,2-*a*]pyridine (14). A suspension of **9** (40 g, 96.7 mmol) in TFAA (400 mL) was heated at reflux for 18 h. The cooled mixture was diluted with 400 mL of ether, and the solids were collected by filtration. The cake was vigorously stirred with 500 mL of saturated aqueous $NaHCO_3$. The crude trifluoroacetamide, **14**, was collected by filtration, washed with H_2O, and dried to yield 25 g (76.7%), mp 195–197 °C. After recrystallization from EtOH, the melting point was 202–203 °C. Anal. ($C_{15}H_{10}F_3NOS$) C, H, N.

3-Amino-5-(phenylthio)imidazo[1,2-*a*]pyridine (15). A suspension of **14** (25 g, 0.0741 mmol) was heated in 2.5 N NaOH (190 mL) on the steam bath for 20 min. After cooling, the mixture was extracted with CH_2Cl_2–ether (1:5). The combined extracts were washed with H_2O, dried, and evaporated to dryness in vacuo. The residue, 16.4 g (91.2%), was recrystallized from CH_3CN to yield **15**, mp 102–104 °C. Anal. ($C_{13}H_{11}N_3S$) C, H, N.

Methyl *N*-(Methoxycarbonyl)-*N*-[5-(phenylthio)imidazo[1,2-*a*]pyridin-3-yl]carbamate (16) and Methyl 5-(Phenylthio)imidazo[1,2-*a*]pyridine-3-carbamate (17). A solution of **15** (26.6 g, 0.11 mmol) in C_5H_5N (500 mL) at 0 °C was treated dropwise with methyl chloroformate (28 mL). After allowing the mixture to warm to room temperature, it was heated at 80 °C for 3 h. The cooled reaction mixture was diluted with H_2O (4000 mL) and extracted with ether. The extracts were washed with H_2O, dried, and evaporated in vacuo to a red gum. TLC (EtOAc–CH_2Cl_2, 1:1, on SiO_2) indicated a gross mixture of components. Chromatography on silica gel and elution with EtOAc–CH_2Cl_2 (1:1) yielded 1.7 g (4.3%) of **16**, mp 152–154 °C (EtOH). Anal. ($C_{17}H_{15}N_3O_4S$) C, H, N, S.

Further elution with EtOAc–CH_2Cl_2 (3:1) yielded 1.8 g (5.4%) of **17**, mp 139–140 °C (EtOH). Anal. ($C_{15}H_{13}N_3O_2S$) C, H, N, S.

Preparation of 17 by Partial Hydrolysis of 16. A solution of **16** (120 mg, 0.33 mmol) in MeOH (5 mL) was stirred with $NaOCH_3$ (10 mg, 18 mmol) for 5 h at room temperature. After the solvent was evaporated in vacuo, the residue was partitioned between CH_2Cl_2 and H_2O. The organic layer was separated, dried, and evaporated in vacuo to yield 97 mg (96%) of **17**: mp, NMR, IR, and TLC were identical with that obtained above.

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Chemical Modification of Aminoglycosides. 3. Synthesis of 2″-Deoxykanamycins from Neamine[1]

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The preparation of 2″-deoxykanamycin B (**12**) and 2″,3′,4′-trideoxykanamycin B (**14**) from neamine (**1**) is described. Key intermediates in the synthesis of these 2″-deoxyaminoglycoside antibiotics are 3′,4′-bis-*O*-(*p*-nitrobenzoyl)-1,2′,3,6′-tetrakis-*N*-(trifluoroacetyl)neamine (**6**) and 3′,4′-dideoxy-1,2′,3,6′-tetrakis-*N*-(trifluoroacetyl)neamine (**9**). The amino groups of these intermediates are blocked by the trifluoroacetyl group, a blocking group not widely used in aminoglycoside chemistry.

The value of aminoglycoside antibiotics for the treatment of infections caused by Gram-negative bacteria is widely recognized. The quest for novel aminoglycosides which possess good potency to pseudomonads and are not readily inactivated by R-factor-carrying bacteria, but which still possess a favorable toxicity profile, has attracted many investigators. Both chemical and biochemical synthesis of useful aminoglycosides have been rewarding.[2-5]

(1) Presented in part at the 176th National Meeting of the American Chemical Society, Miami Beach, FL, Sept 11–14, 1978. For the previous paper in this series, see Magerlein, B. J. In "Aminocyclitol Antibiotics"; Rinehart, K. L., Jr.; Suami, T., Ed.; American Chemical Society: Washington, DC, 1980; pp 169–182.

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