Methyl 6-(Phenylsulfinyl)imidazo[1,2-*a*]pyridine-2-carbamate, a Potent, New Anthelmintic

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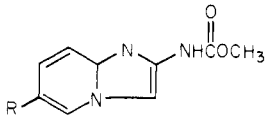
A series of methyl imidazo[1,2-*a*]pyridine-2-carbamates was synthesized for anthelmintic testing. The preparation of this class of compounds was simplified by utilization of a novel one-step condensation of the appropriately substituted 2-aminopyridine with methyl chloroacetylcarbamate. The most potent compound, methyl 6-(phenylsulfinyl)-imidazo[1,2-*a*]pyridine-2-carbamate, was orally effective against a broad range of helminths in sheep and cattle, at a dosage of 2.5 mg/kg. Limited trials in swine and dogs demonstrated anthelmintic activity at higher dosages. Limited observations in sheep and cattle indicated that, in both species, a single oral dose of 200 mg/kg was well tolerated.

The anthelmintic activity of imidazo[1,2-*a*]pyridines has previously been reported from these laboratories.[1] A correlation of their structure–activity relationships with benzimidazole anthelmintic agents was also demonstrated. However, these compounds, presumably because of metabolic inactivation, did not achieve the in vivo efficacy indicated by their potency in vitro. We now wish to report an extension of this research to imidazo[1,2-*a*]pyridines having highly potent, broad-spectrum anthelmintic activity.

A number of 5-thioether derivatives of methyl benzimidazole-2-carbamate have recently been reported to have potent, broad-spectrum anthelmintic activity.[2,3] We have similarly found that introduction of the phenylthio group at the 6 position of methyl imidazo[1,2-*a*]pyridine-2-carbamate confers a marked enhancement of in vivo activity. This activity is further improved by oxidation to the sulfoxide. Thus methyl 6-(phenylsulfinyl)imidazo-[1,2-*a*]pyridine-2-carbamate (**1b**) was shown to be a highly



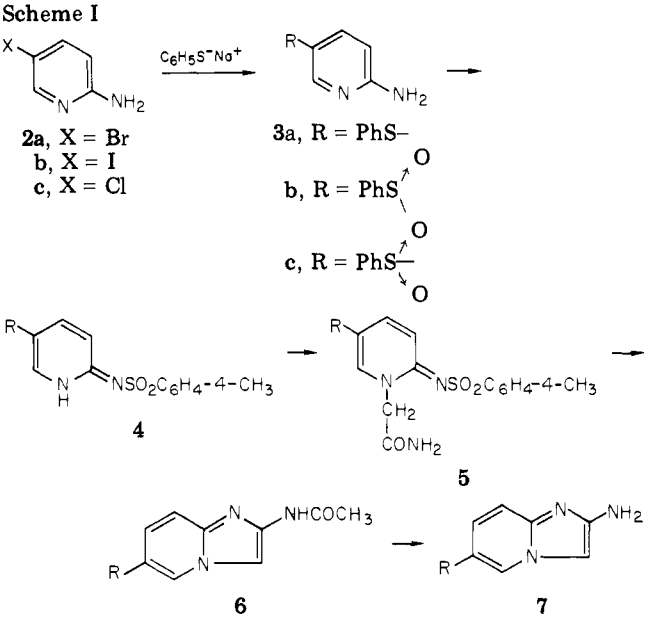
1a, R = C_6H_5S–
b, R = $C_6H_5S(\rightarrow O)$–
c, R = C_6H_5-$S(\rightarrow O)_2$–
d, R = H

effective, broad-spectrum anthelmintic agent in several animal species.

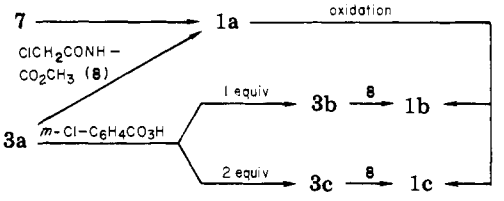
Chemistry. The reported method (Scheme I) for the synthesis of imidazo[1,2-*a*]pyridine-2-carbamates[1,4] requires a five-step sequence from an appropriately substituted 2-aminopyridine (**3**). We have found that **1** can be prepared in a single step, in good yield, by reaction of **3** with methyl (chloroacetyl)carbamate (**8**) (Scheme II). Oxidation of **1a** to **1b** or **1c** was accomplished with an excess of peracetic acid or with 1 or 2 equiv of *m*-chloroperbenzoic acid, respectively. Aminopyridines (**3**) were obtained by reaction of **2a** or **2b** with sodium thiophenate.[5] Improved yields were obtained by heating in methanol at 150 °C in the presence of a copper catalyst. In all cases, the chloro analogue, **2c**, failed to react. Compounds **3b** and **3c**, prepared by oxidation of **3a** with 1 or 2 equiv of *m*-chloroperbenzoic acid, respectively, were also cyclized to **1b** and **1c**.

Biological Data. In preliminary screening tests (Table I) with mice, **1b**, administered in the diet as low as 62.5

Scheme I



Scheme II



ppm for a period of 5 days, showed significant removal of *Nematospiroides dubius*. Table I lists these results with data on a number of commercial anthelmintic agents for comparison. Testing in mice also indicated that a single oral dose of 100 mg/kg of **1b** was partially effective against *Syphacia obvelata*. However, when administered at 0.1% in the diet over a 6-day period, 100% efficacy was achieved with **1a–c**.

The more potent analogue, **1b**, was administered to sheep harboring patent experimental infections of six species of gastrointestinal nematodes as a single oral dose of from 2.5 to 7.5 mg/kg. At 2.5 mg/kg, the compound was more than 98% effective against *Haemonchus contortus*, *Ostertagia circumcincta*, *Trichostrongylus axei*, *Cooperia oncophora*, and *Oseophagostomum columbianum* in controlled critical trials. At dosages of 2.5, 5.0, or

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

Compd	ppm in diet			
	500	250	125	62.5
1a	100	98	75	20
1b		100	100	90
1c		98	87	62
1d	0[c]			
Thiabendazole[d]	47	0	0	
Cambendazole[e]	80	20		
Fenbendazole[f]		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.[10] There were three mice per treated group. The results are an average of the number of worms per mouse. [c] At 1000 ppm, a reduction of 54% was observed. [d] 2-(4-Thiazolyl)benzimidazole (Merck & Co.). [e] 2-(4-Thiazolyl)-5-benzimidazolecarbamate isopropyl ester (Merck & Co.). [f] Methyl 5-(phenylthio)-2-benzimidazolecarbamate (Hoechst).

7.5 mg/kg, the efficacy against *Trichostrongylus colubriformis* was similar and ≃95%.

When tested against a benzimidazole tolerant strain of *H. contortus* (Ogdensburg isolate),[6] it was determined that a somewhat higher dosage level of compound **1b** was required for comparable efficacy: 7.5–15.0 mg/kg.

Compound **1b** was administered to experimentally infected cattle harboring six species of gastrointestinal nematodes and lungworm at dosages ranging from 2.5 to 7.5 mg/kg. Anthelmintic efficacy was greater than 95% for *Haemonchus placei*, *Ostertagia ostertagi*, *T. axei*, *T. colubriformis*, *C. oncophora*, *Oesophagostomum radiatum*, and *Dictyocaulus viviparus* in controlled critical trials. Additional trials demonstrated that compound **1b** had significant (90–95%) anthelmintic activity against hypobiotic (retarded, inhibited) L_4 *O. ostertagi* at dosage levels of 7.5–15.0 mg/kg.

Limited critical trials in experimentally infected swine have demonstrated 100% removal of *Oesophagostomum spp* by compound **1b** administered at 10 mg/kg po.

In dogs with natural infections of *Ancylostoma caninum*, *A. brazilienses*, and *Trichuris vulpis*, a single oral dose of 10 mg/kg of compound **1b** was ineffective against both genera. A dose of 15 mg/kg was 100% effective against hookworms but only partially effective in removing the whipworms.

Limited observations in sheep and cattle to date indicate that in both species, a single oral dose as high as 200 mg/kg of compound **1b** was well tolerated with no grossly discernible toxic reactions.

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. NMR spectra were determined with a Varian HA100 NMR spectrometer. These data are recorded in Table II. Elemental analyses were performed by the Analytical Department of Merck Sharp & Dohme Research Laboratories and are within ±0.4% of calculated values.

2-Amino-5-iodopyridine (2b). Iodination of 2-aminopyridine was accomplished in 60% yield according to the method of Magidson and Menschikoff:[7] mp 126–128 °C after recrystallization from PhH.

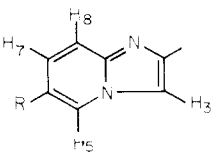
2-Amino-5-(phenylthio)pyridine (3a). A suspension of Cu powder (9.0 g), NaOMe (34.5 g, 0.638 mol), thiophenol (70.8 g, 0.642 mol), and 2-amino-5-iodopyridine (**2b**, 100 g, 0.455 mol) in 800 mL of MeOH was heated at 150 °C for 12 h. After cooling, the reaction mixture was combined with three similar experiments and filtered, and the filtrates were evaporated in vacuo. The residue was partitioned between EtOAc and H_2O. The organic layer was separated, washed with H_2O, dried, and evaporated in vacuo. Recrystallization from MeOH yielded 325 g (80.9%) of **3a**, mp 123–125 °C. Anal. ($C_{11}H_{10}N_2S$) C, H, N, S. Alternatively, a suspension of potassium phenyl thiolate (12.0 g, 81 mmol) and 2-amino-5-bromopyridine (**2a**) in 50 mL of 1-methyl-2-pyrrolidinone was heated at reflux under N_2 for 4.5 h. The reaction was diluted with H_2O and the product was collected by filtration. Recrystallization from $CHCl_3$–hexane yielded 5.8 g (49%) of purified **3a**.

2-Amino-5-(phenylsulfinyl)pyridine (3b). A solution of 2-amino-5-(phenylthio)pyridine (**3a**) (10.1 g, 50 mmol) and 200 mL of CH_2Cl_2 was treated dropwise with 200 mL of CH_2Cl_2 containing 85% *m*-chloroperbenzoic acid (10.15 g, 50 mmol) at 20 °C. After the addition was complete, the reaction mixture was stirred an additional 15 min and washed with 500 mL of saturated H_2O–$NaHCO_3$ solution. The organic layer was separated, washed with H_2O, and dried. Evaporation of the solvent in vacuo yielded 9.2 g (85.2%) of **3b**, mp 164–171.5 °C. Recrystallization from EtOH yielded 2-amino-6-(phenylsulfinyl)pyridine (**3b**), mp 173–175 °C. Anal. ($C_{11}H_{10}N_2OS$) C, H, N, S.

2-Amino-5-(phenylsulfonyl)pyridine (3c). The reaction of 15.1 g (74.6 mmol) of **3a** with 31.8 g (156 mmol) of *m*-chloroperbenzoic acid as above yielded 11.4 g (64%) of **3c**: mp 201–203 °C after recrystallization from EtOH. Anal. ($C_{11}H_{10}N_2O_2S$) C, H, N.

Methyl 6-(Phenylthio)imidazo[1,2-*a*]pyridine-2-carbamate (1a). Scheme I. A. 1,2-Dihydro-2-(4-methylbenzenesulfonimido)-5-phenylthiopyridine (4). 2-Amino-5-(phenylthio)pyridine (92.4 g, 0.457 mol) and TsCl (79.3 g, 0.416 mol) in 600 mL of pyridine were heated for 1 h on the steam bath. After dilution with 3000 mL of H_2O, the product was collected by

Table II. Chemical Shift Data[a] of Imidazo[1,2-*a*]pyridine-2-carbamate



Compd	H_3	H_5	H_7	H_8
1a	7.90 (s)	8.84 (d, J = 2 Hz)	7.14 (dd, J = 9, 2 Hz)	7.43 (d, J = 9 Hz)
1b	7.98 (s)	9.12 (s)	7.12 (dd, J = 9, 2 Hz)	7.55 (d, J = 9 Hz)
1c	8.07 (s)	9.39 (d, J = 2 Hz)	7.68 (dd, J = 9, 2 Hz)	7.62 (d, J = 9 Hz)
1d[b]	7.81 (s)	8.45 (dt, J = 7, 2, 2 Hz)	7.15 (qd, J = 9, 7 Hz)	7.40 (d, J = 9 Hz)

[a] All shifts are measured in Me_2SO-d_6 and are reported in δ ppm downfield from Me_4Si followed by multiplicity and coupling constants J; s, singlet, d, doublet, dd, doublet of doublets; dt, doublet of triplets; qd, quartet of doublets. [b] When R = H, H_6 = δ 6.84 (td, J = 7, 7, 2 Hz).

filtration, washed with H_2O, and dried: 142.2 g (96%). Recrystallization from EtOH gave 4, mp 124–126 °C. Anal. ($C_{18}H_{16}N_2O_2S_2$) C, H, N, S.

B. 1-Carbamoylmethyl-1,2-dihydro-2-(4-methylbenzenesulfonimido)-5-phenylthiopyridine (5). The Na salt of 4 was prepared by treating *N*-(5-phenylthio-2-pyridinyl)-4-methylbenzenesulfonamide (4) (142.2 g, 0.399 mol) with 57% NaH oil dispersion (18.56 g, 0.441 mol) in 600 mL of DMF. The reaction mixture was heated on a steam bath until evolution of H_2 was complete (~15 min). 2-Chloroacetamide (41.2 g, 0.441 mol) was added in one portion to the cooled reaction mixture. After heating on a steam bath for 2 h, the reaction mixture was diluted with H_2O. The crude product was taken up in $CHCl_3$. After washing and drying, the solvent was evaporated in vacuo. Recrystallization of the residue from EtOH yielded 95.2 g (58%) of **5**, mp 164–165 °C. Anal. ($C_{20}H_{19}N_3O_3S_2$) C, H, N.

C. 2-Acetamido-6-(phenylthio)imidazo[1,2-*a*]pyridine (6). A suspension of **5** (5.4 g, 0.013 mol) in 18 mL of Ac_2O was heated at reflux for 1 h. The solvent was removed in vacuo and the residue dissolved in 30 mL of EtOH. After treatment with 2.5 N NaOH, the precipitate was collected by filtration, washed with H_2O, and dried: yield 0.80 g (21%) of **6**. Recrystallization from DMF–EtOH yielded **6**, mp 259–261 °C dec. Anal. ($C_{15}H_{13}N_3OS$) C, H, N, S.

D. 2-Amino-6-(phenylthio)imidazo[1,2-*a*]pyridine (7). A suspension of 2-acetamido-6-phenylthioimidazo[1,2-*a*]pyridine (**6**) (0.800 g, 2.8 mmol) in 40 mL of 30% aqueous NaOH was heated at 130 °C for 2 h. The cooled reaction mixture was extracted with CH_2Cl_2. The extracts were washed with saturated aqueous NaOH, dried, and evaporated in vacuo to yield 0.600 g (88.8%) of an oil which slowly crystallized. Recrystallization from hexane yielded **7**, mp 109–111 °C. Anal. ($C_{13}H_{11}N_3S$) C, H, N.

E. Methyl 6-(Phenylthio)imidazo[1,2-*a*]pyridine-2-carbamate (1a). A suspension of 2-amino-6-(phenylthio)imidazo[1,2-*a*]pyridine (**7**) (18.0 g, 75 mmol) in 200 mL of H_2O was treated dropwise with $ClCO_2Me$ (12.6 g, 133 mmol). The reaction mixture was vigorously stirred for 30 min and then treated with 100 mL of saturated aqueous $NaHCO_3$. The product was collected by filtration, washed, and dried. Recrystallization from DMF–EtOH (50:50) yielded **1a**: mp 245–247 °C dec; yield 8.3 g (37.2%). Anal. ($C_{15}H_{13}N_3O_2S$) C, H, N, S.

Scheme II. A. Methyl (Chloroacetyl)carbamate (8). A suspension of 2-chloroacetamide (122.6 g, 1.31 mol) in 300 mL of 1,2-dichloroethane was cooled to 0 °C and treated with oxalyl chloride (200 g, 1.57 mol). The reaction mixture was heated at reflux for 4 h. After cooling to 5 °C, 68 mL of MeOH was added dropwise while keeping the internal temperature below 15 °C with external cooling. After addition was complete, the product was separated by filtration and washed with CH_2Cl_2 and Et_2O: mp 132–134 °C; yield 129.2 g (65%). Recrystallization from CH_2Cl_2 yielded methyl (chloroacetyl)carbamate (**8**), mp 142–144 °C (lit.[8] 143–145 °C).

B. A suspension of 2-amino-6-(phenylthio)pyridine (**3a**) (135 g, 0.667 mol) and methyl (chloroacetyl)carbamate (**8**) (100.9 g, 0.667 mol) in 325 mL of HMPT was heated at 100 °C for 5 h. After dilution with 2000 mL of H_2O, the product was collected by filtration, successively washed with H_2O, MeOH, and CH_2Cl_2, and dried. The yield was 132 g (66.1%) of methyl 6-(phenylthio)imidazo[1,2-*a*]pyridine-2-carbamate (**1a**), mp 244–246 °C. Recrystallization from DMF yielded **1a**, identical (MS, NMR, IR, and TLC) with the product derived by Scheme I.

Methyl 6-(Phenylsulfinyl)imidazo[1,2-*a*]pyridine-2-carbamate (1b). A suspension of methyl 6-(phenylthio)-imidazo[1,2-*a*]pyridine-2-carbamate (**1a**) (134 g, 0.447 mol) in 2700 mL of HOAc was treated dropwise with 535 mL of 30% H_2O_2. The suspension was stirred until a solution was obtained (~5 h) and then poured into 8 L of ice water. The product was collected by filtration and dried to yield 125 g (88.5%) of crude **1b**, mp 240 °C dec. The product was purified via the hydrochloride salt as follows. Crude **1b** (240 g) was heated in 3 L of MeOH and treated with 260 mL of MeOH containing 38 g of HCl. The precipitate from the cooled mixture was collected by filtration and washed with cold MeOH. Trituration with H_2O liberated the purified free base. After recrystallization from DMF–EtOH (50:50), **1b** was obtained: 143 g (59.5% recovery); mp 247–249 °C dec. Anal. ($C_{13}H_{15}N_3O_3S$) C, H, N.

Alternatively, a suspension of **1a** (4.26 g, 0.014 mol) in 1000 mL of CH_2Cl_2 was treated with 85% *m*-chloroperbenzoic acid (2.88 g, 0.014 mol) at room temperature. After 3 h, the solution was washed with saturated aqueous $NaHCO_3$ and dried, and the solvent was removed in vacuo. The residue was chromatographed over silica gel and eluted with 50% EtOAc–CH_2Cl_2 to yield 1.5 g (34%) of **1b**, mp 247–249 °C dec.

From 3b. A suspension of 2-amino-5-(phenylsulfinyl)pyridine (**3b**) (1.74 g, 7.9 mmol) and methyl (chloroacetyl)carbamate (**8**) (1.77 g, 11.6 mmol) in 12 mL of HMPT was treated as in Scheme II for **1a** to yield 600 mg (35%) of **1b**, mp 247–249 °C.

Methyl 6-(Phenylsulfonyl)imidazo[1,2-*a*]pyridine-2-carbamate (1c). From 1a. **1a** (0.5 g, 0.00159 mol) was added to a solution of trifluoroperacetic acid prepared from 415 μL of trifluoroacetic anhydride with 65 μL of 90% H_2O_2 in 5 mL of CH_2Cl_2. The solution was refluxed for 90 min. After washing the solution with saturated aqueous $NaHCO_3$, the solvent was removed in vacuo. The residue was chromatographed over 50 g of silica gel and eluted with 50% EtOAc–CH_2Cl_2 to yield 150 g (40%) of methyl 6-(phenylsulfonyl)imidazo[1,2-*a*]pyridine-2-carbamate (**1c**), mp >300 °C.[9] Recrystallization from CH_2Cl_2 gave mp >320 °C. Anal. ($C_{15}H_{13}N_3O_4S$) C, H, N, S.

From 3c. The reaction of 2-amino-5-phenylsulfonylpyridine (**3c**) (13.75 g, 58.7 mmol) and methyl (chloroacetyl)carbamate (**8**) (0.67 g, 70 mmol) in 88 mL of HMPT as in Scheme II for **1a** yielded 12.0 g (61%) of **1c**, mp 320 °C.

Methyl Imidazo[1,2-*a*]pyridine-2-carbamate (1d). 2-Aminopyridine (3.76 g, 40 mmol) and methyl (chloroacetyl)-carbamate (**8**) (7.52 g, 49 mmol) in 50 mL of HMPT were allowed to react as in Scheme II for **1a**. However, the reaction time was reduced to 30 min. After workup and recrystallization from DMF–EtOH (50:50), 2.3 g (30.2%) of **1d** was obtained: mp 233–234 °C dec (lit.[1a] 240–241 °C dec). Anal. ($C_9H_9N_3O_2$) C, H, N.

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