Acknowledgment. This study was supported in part by research grants (CA-08793, CA-13038, and CA-16056) from the National Institutes of Health. We are indebted to Dr. M. T. Hakala and Miss A. I. Mulhern for the cell-culture data and to Mrs. S. C. Chang and Mr. Norman Angelino for the pyridoxal phosphokinase and pyridoxine-P oxidase determinations. Dr. B. Lachmann synthesized analogue 7. Pyridoxol hydrochloride was a gift of Pfizer and Co.

References and Notes

(1) W. Korytnyk and M. Ikawa, *Methods Enzymol.*, **18A**, 524 (1970).
(2) W. Korytnyk and B. Paul, *J. Med. Chem.*, **13**, 184 (1970).
(3) W. Korytnyk, G. Grindey, and B. Lachmann, *J. Med. Chem.*, **16**, 865 (1973).
(4) W. Korytnyk, A. C. Ghosh, P. G. G. Potti, aad S. C. Srivastava, *J. Med. Chem.*, **19**, 999 (1976).
(5) D. E. Metzler and E. E. Snell, *J. Am. Chem. Soc.*, **77**, 2431 (1955).
(6) W. Korytnyk and H. Ahrens, *Methods Enzymol.*, **18A**, 475 (1970).
(7) M. Ya. Karpeisky, N. Sh. Padukova, and V. L. Florentiev, *Tetrahedron Lett.*, 4489 (1970).
(8) W. Korytnyk, N. Angelino, B. Lachmann, and P. G. G. Potti, *J. Med. Chem.*, **15**, 1262 (1972).
(9) L. J. Morris, *Chem. Ind. (London)*, 1238 (1962); P. L. Nichols, Jr., *J. Am. Chem. Soc.*, **74**, 1091 (1952).
(10) I.-Y. Yang, C. M. Harris, D. E. Metzler, W. Korytnyk, B. Lachmann, and P. G. G. Potti, *J. Biol. Chem.*, **250**, 2947 (1975).
(11) R. N. Renand and L. C. Leitch, *Can. J. Chem.*, **42**, 2089 (1964).
(12) H. J. Dauben, Jr., L. R. Honnen, and K. M. Marmon, *J. Org. Chem.*, **25**, 1442 (1960).
(13) C. R. Norayanan and K. N. Iyer, *J. Org. Chem.*, **30**, 1734 (1965).
(14) V. Prey and H. Berbalk, *Monatsh. Chem.*, **82**, 990 (1951).
(15) W. Korytnyk and P. G. G. Potti, *J. Med. Chem.*, **20**, 1 (1976).
(16) W. Korytnyk, S. C. Srivastava, N. Angelino, P. G. G. Potti, and B. Paul, *J. Med. Chem.*, **16**, 1096 (1973).
(17) W. Korytnyk, M. T. Hakala, P. G. G. Potti, N. Angelino, and S. C. Chang, *Biochemistry*, **15**, 5458 (1976).
(18) H. Ahrens and W. Korytnyk, *Methods Enzymol.*, **18A**, 475 (1970).
(19) W. Korytnyk and H. Ahrens, *Methods Enzymol.*, **18A**, 475 (1970).
(20) T. H. Vaughn, R. R. Vogt, and J. A. Nieuwland, *J. Am. Chem. Soc.*, **56**, 2120 (1934).

Mercapto Heterocyclic Carboxylic Acids, Analogues of 3-Mercaptopicolinic Acid[1]

Benjamin Blank,* Nicholas W. DiTullio, Franklin F. Owings, Linda Deviney, Clara K. Miao, and Harry L. Saunders

Division of Research and Development, Smith Kline & French Laboratories, SmithKline Corporation, Philadelphia, Pennsylvania 19101. *Received July 8, 1976*

3-Mercaptopicolinic acid (3-MPA), a potent hypoglycemic agent in fasted rats, provided the impetus for substituting this compound with a 5-mercapto group (**1**), a 6-carboxyl group (**2**), and a 5-mercapto and 6-carboxyl group (**3**) and for replacing the pyridine ring with other heterocycles: quinoline (**4**), thiazole (**5**), pyrazine (**6**), isoquinoline (**7**), and indole (**8**). The methyl sulfoxide (**9**) and sulfone (**10**) of 3-MPA were also prepared. The new compounds 1–10, with the exception of 8, did not lower blood glucose levels in 48-h fasted rats. 8 was toxic at doses which were hypoglycemic.

3-Mercaptopicolinic acid (3-MPA), by inhibiting gluconeogenesis, produces hypoglycemia in a number of animal models.[2] 3,5-Dimercaptopicolinic acid (**1**), 3-mercapto-2,6-pyridinedicarboxylic acid (**2**), and 3,5-dimercapto-2,6-pyridinedicarboxylic acid (**3**) were prepared and evaluated biologically to determine how the hypoglycemic activity of 3-MPA would be affected by additional mercapto or carboxyl groups. The importance of the pyridine ring of 3-MPA was determined by replacing it with other heterocyclic rings: quinoline (**4**), thiazole (**5**), pyrazine (**6**), isoquinoline (**7**), and indole (**8**).

3-Methylsulfinylpicolinic acid (**9**) and 3-methylsulfonylpicolinic acid (**10**) were prepared to determine what effect altering the oxidation state of sulfur would have on hypoglycemic activity.

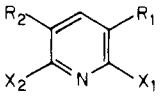
1, **2**, and **4** were prepared from bromo heterocyclic *N*-oxides (**11**) (Scheme I). Subjecting the intermediates **11** to the conditions of the Reissert–Kaufmann reaction[3] produced reasonable yields of products **12**. Treatment of **12** with the mercaptide ion generated from *p*-methoxybenzyl mercaptan (MBM)[4] gave the intermediates **13**. Subsequent alkaline hydrolysis and removal of the methoxybenzyl (MB) protecting group[2a] yielded respectively **14** and the desired mercapto acids **1**, **2**, and **4**. However, **3** could not be prepared by this route since neither 3,5-dibromo-2-cyanopyridine *N*-oxide (**11d**) nor methyl 3,5-dibromo-2-pyridinecarboxylate *N*-oxide (**11e**) (Table III) gave the Reissert–Kaufmann intermediate. The intermediate 1-methoxy compounds prepared by treatment of **11d** and **11e** with dimethyl sulfate reverted to **11d** and **11e** when allowed to react with aqueous cyanide.

Compound **3** was prepared from 3,5-dibromo-2,6-lutidine[5] which was oxidized to the diacid **15**. The diacid, in turn, was esterified to the diester **12d** and used as shown in Scheme I (**12d** → **13d** → **14d** → **3**).

An alternative synthesis involving attempted tetrazotization and sulfuration of 3,5-diamino-2,6-pyridinedicarboxylic acid (**17b**) or the corresponding diamino diester **17c** gave chiefly unchanged starting materials. These results were attributed to the poor solubilities of **17b** and **17c** in aqueous acid. Compounds **17b** and **17c** were prepared from diethyl 2,6-dimethyl-3,5-pyridinedicarboxylate. This ester was converted in turn to the 3,5-diamide **16a**,[6] to 3,5-diamino-2,6-lutidine (**16b**), and to 3,5-diacetamido-2,6-lutidine (**16c**). Oxidation of **16c** to 3,5-diacetamido-2,6-pyridinedicarboxylic acid **17a** and hydrolysis gave **17b** which was esterified to give **17c**. These intermediates are listed in Table I.

The thiazole analogue of the ethyl ester of 3-MPA was derived from ethyl 2-amino-4-thiazolecarboxylate (**18**).[7] This was brominated according to the method of Garreau[8] to give ethyl 2-amino-5-bromo-4-thiazolecarboxylate (**19a**). Deamination to give ethyl 5-bromo-4-thiazolecarboxylate (**19c**), reaction with MBM to give ethyl 5-*p*-methoxybenzylthio-4-thiazolecarboxylate (**19d**), and removal of the MB group were carried out as described in the Experi-

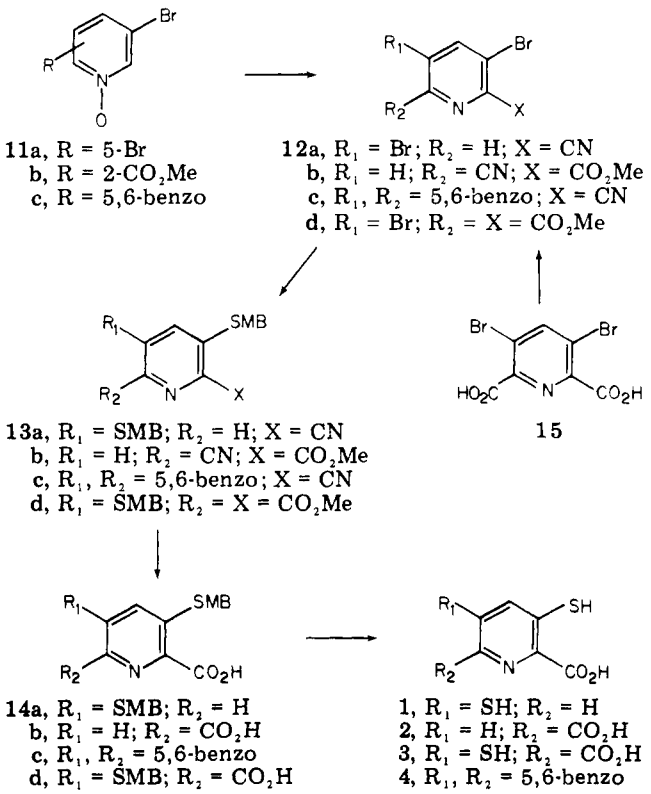
Table I. Pyridines



No.	R_1	R_2	X_1	X_2	Mp, °C	Recrystn solvent	% yield	Formula[a]
1	SH	SH	CO_2H	H	163-164	MeCN	30	$C_6H_5NO_2S_2$
2	SH	H	CO_2H	CO_2H	199-200[b]	H_2O	54	$C_7H_5NO_4S$[c]
3	SH	SH	CO_2H	CO_2H	210-212[b]	MeCN	20	$C_7H_5NO_4S_2$
9	SOMe	H	CO_2H	H	157-158[b]	MeCN	30	$C_7H_7NO_3S$
10	SO_2Me	H	CO_2H	H	147-148[b]	MeOH	50	$C_7H_7NO_4S$
12a	Br	Br	CN	H	113-115[d]	MeOH-H_2O	61	$C_6H_2Br_2N_2$
12b	Br	H	CO_2Me	CN	141-143	MeOH	60	$C_8H_5BrN_2O_2$
12d	Br	Br	CO_2Me	CO_2Me	69-71	MeOH	64	$C_9H_7Br_2NO_4$
13a	SMB[e]	SMB[e]	CN	H	76-78	MeOH	75	$C_{22}H_{20}N_2O_2S_2$
13b	SMB[e]	H	CO_2Me	CN	142-144	MeOH	60	$C_{16}H_{14}N_2O_3S$
13d	SMB[e]	SMB[e]	CO_2Me	CO_2Me	136-138	EtOAc-petr ether	55	$C_{25}H_{25}NO_6S_2$
14a	SMB[e]	SMB[e]	CO_2H	H	95	$CHCl_3$-hexane	75	$C_{22}H_{21}NO_4S_2$
14b	SMB[e]	H	CO_2H	CO_2H	190-192	MeOH	75	$C_{15}H_{13}NO_5S$
14d	SMB[e]	SMB[e]	CO_2H	CO_2H	196-198[b]	MeOH	85	$C_{23}H_{21}NO_6S_2$
15	Br	Br	CO_2H	CO_2H	>300	H_2O	48	$C_7H_3Br_2NO_4$[f]
16a	$CONH_2$	$CONH_2$	Me	Me	340-342[b]	*g*	69	$C_9H_{11}N_3O_2$
16b	NH_2	NH_2	Me	Me	169-171	EtOAc-petr ether	40	$C_7H_{11}N_3$
16c	NHAc	NHAc	Me	Me	255-257	MeCN	87	$C_{11}H_{15}N_3O_2$
17a	NHAc	NHAc	CO_2H	CO_2H	262	*h*	56	$C_{11}H_{11}N_3O_6$[i]
17b	NH_2	NH_2	CO_2H	CO_2H	278[b]		78	$C_7H_7N_3O_4$[j]
17c	NH_2	NH_2	CO_2Me	CO_2Me	191-193	C_6H_5Me	45	$C_9H_{11}N_3O_4$
21a	SMe	H	CO_2Me	H	58-60	C_6H_6-petr ether	54	$C_8H_9NO_2S$
21b	SOMe	H	CO_2Me	H	124-126	CCl_4	80	$C_8H_9NO_3S$
21c	SO_2Me	H	CO_2Me	H	88-90	C_6H_6-hexane	75	$C_8H_9NO_4S$

[a] Compounds for which formulas are given were analyzed for C, H, and N and often also for either Br or S; analytical values were within ±0.4% of the calculated values unless otherwise noted. [b] With decomposition. [c] Contains 0.75 mol of H_2O. [d] Lit. mp 117-117.5 °C: H. Tani, *Yakugaku Zasshi*, 81, 141 (1961); *Chem. Abstr.*, 55, 14 450*b* (1961). [e] SMB = *p*-$CH_3OC_6H_4CH_2S$-. [f] C: calcd, 25.18; found, 24.21 for the hemihydrate. [g] Reference 6. [h] See Experimental Section. [i] Hydrate. [j] Contains 0.25 mol of H_2O.

Scheme I



11a, R = 5-Br
b, R = 2-CO_2Me
c, R = 5,6-benzo

12a, R_1 = Br; R_2 = H; X = CN
b, R_1 = H; R_2 = CN; X = CO_2Me
c, R_1, R_2 = 5,6-benzo; X = CN
d, R_1 = Br; R_2 = X = CO_2Me

13a, R_1 = SMB; R_2 = H; X = CN
b, R_1 = H; R_2 = CN; X = CO_2Me
c, R_1, R_2 = 5,6-benzo; X = CN
d, R_1 = SMB; R_2 = X = CO_2Me

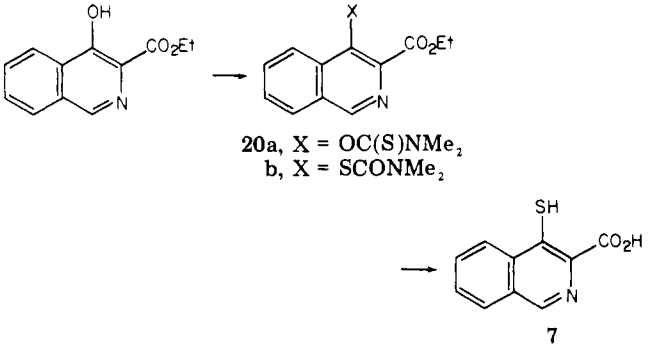
15

14a, R_1 = SMB; R_2 = H
b, R_1 = H; R_2 = CO_2H
c, R_1, R_2 = 5,6-benzo
d, R_1 = SMB; R_2 = CO_2H

1, R_1 = SH; R_2 = H
2, R_1 = H; R_2 = CO_2H
3, R_1 = SH; R_2 = CO_2H
4, R_1, R_2 = 5,6-benzo

mental Section. Hydrolysis of **19d** gave 5-*p*-methoxybenzylthio-4-thiazolecarboxylic acid (**19f**). Attempts to convert ethyl 5-mercapto-4-thiazolecarboxylate (**5**) or **19f** to the mercapto acid gave product contaminated with disulfides and decarboxylated materials.

Scheme II



20a, X = $OC(S)NMe_2$
b, X = $SCONMe_2$

7

Treatment of **18** with thiocyanogen yielded ethyl 2-amino-5-isothiocyanato-4-thiazolecarboxylate (**19b**). Several attempts to convert **19b** to **5** or to another intermediate capable of being converted subsequently to **5** or its derived acid gave results comparable to those described above. These compounds are listed in Table II.

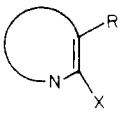
6 was prepared by alkaline hydrolysis of methyl 3-mercaptopyrazine-2-carboxylate.[9]

4-Mercapto-3-isoquinolinecarboxylic acid (**7**) was obtained from a reaction pathway that started with ethyl 4-hydroxyisoquinoline-3-carboxylate[10] and made use of the Newman–Kwart method of preparing thiophenolic compounds (Scheme II).[2a,11,12]

The indole analogue (**8**) of 3-MPA was readily accessible by basic hydrolysis of 3-isothiocyanato-2-indolecarboxylic acid.[13] The crude product was washed with chloroform to give analytically pure **8**. More vigorous purification conditions (e.g., recrystallization) gave less pure product.

3-Methylthiopicolinic acid[2a] was esterified to give **21a** which was oxidized to the corresponding sulfoxide **21b** and sulfone **21c**. Hydrolysis of these esters gave the sulfoxide

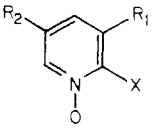
Table II. Heterocycles



No.	Heterocycles	R	X	Mp, °C	Recrystn solvent	% yield	Formula[a]
4	Quinoline	SH	CO_2H	164-166[b]	DMF-H_2O	35	$C_{10}H_7NO_2S$
5	Thiazole	SH	CO_2Et	60	EtOH-H_2O	28	$C_6H_7NO_2S_2$
6	Pyrazine	SH	CO_2H	203-204	H_2O	61	$C_5H_4N_2O_2S$
7	Isoquinoline	SH	CO_2H	245-246	DMF	55	$C_{10}H_7NO_2S$
8	Indole	SH	CO_2H	155		46	$C_9H_7NO_2S$
	Indole	SAc	CO_2H	210-212	EtOH-H_2O	40	$C_{11}H_9NO_3S$
12c	Quinoline	Br	CN	128-130	EtOAc-cyclohexane	80	$C_{10}H_5BrN_2$
13c	Quinoline	SMB[c]	CN	131-133	MeOH	74	$C_{18}H_{14}N_2OS$
14c	Quinoline	SMB[c]	CO_2H	158-160[b]	$CHCl_3$	65	$C_{18}H_{15}NO_3S$
19a	2-Aminothiazole	Br	CO_2Et	115-117	Sublimed	75	$C_6H_7BrN_2O_2S$
19b	2-Aminothiazole	SCN	CO_2Et	178	MeOH-H_2O	98	$C_7H_7N_3O_2S_2$
19c	Thiazole	Br	CO_2Et	75-79	MeOH-H_2O	43	$C_6H_6BrNO_2S$
19d	Thiazole	SMB[c]	CO_2Et	87	EtOH-H_2O	20	$C_{14}H_{15}NO_3S_2$
19e	Thiazole	SMB[c]	CO_2Me	100	EtOH	61	$C_{13}H_{13}NO_3S_2$
19f	Thiazole	SMB[c]	CO_2H	182	EtOH	31	$C_{12}H_{11}NO_3S_2$
20a	Isoquinoline	$OC(S)NMe_2$	CO_2Et	118-119	C_6H_6-petr ether	85	$C_{15}H_{16}N_2O_3S$[d]
20b	Isoquinoline	$SCONMe_2$	CO_2Et	79-81	C_6H_6-petr ether	80	$C_{15}H_{16}N_2O_3S$

[a] See footnote *a*, Table I. [b] With decomposition. [c] SMB = *p*-$CH_3OC_6H_4CH_2S$-. [d] C: calcd, 59.19; found, 60.42.

Table III. *N*-Oxides



No.	R_1	R_2	X	Mp, °C	Recrystn solvent	% yield	Formula[a]
11a	Br	Br	H	139-141[b]	C_6H_5Me-petr ether	77	$C_5H_3Br_2NO$
11b	Br	H	CO_2Me	124-126[c]	C_6H_5Me	70	$C_7H_6BrNO_3$
11c	Br	5,6-Benzo	H	95-97[d]	C_6H_5Me	75	C_9H_6BrNO
11d	Br	Br	CN	185-187	MeOH	65	$C_6H_2Br_2N_2O$
11e	Br	Br	CO_2Me	136-138	Heptane	52	$C_7H_5Br_2NO_3$

[a] See footnote *a*, Table I. [b] Lit. mp 143.5-144.5 °C: H. J. den Hertog, C. H. Henkens, and K. Kilz, *Recl. Trav. Chim. Pays-Bas*, 72, 296 (1953). [c] Reference 2a. [d] Lit. mp 96-101 °C: J. G. Murray and C. R. Hauser, *J. Org. Chem.*, 19, 2008 (1954).

and sulfone acids **9** and **10** (Table I).

Discussion

The changes to 3-MPA represented by structures **1–10** led to compounds devoid of hypoglycemic activity at a dose of 300 mg/kg po or ip. The single exception was **8**. At a dose of 200 mg/kg ip, **8** lowered blood glucose levels in the 48-h fasted rat at the 1- (45%) and 2-h (51%) sampling times. However, by the last time interval (4 h after drug treatment) most of the animals were dead. Hyperglycemia was seen with some of the agents (**1**, **2**, and **3**). This has not been an uncommon observation and may be a simple stress phenomenon.[14,15]

The lack of hypoglycemic activity noted with **1–4** and **7** might be explained on the basis of steric factors since 3-MPA analogues with additional substituents have little or none of the hypoglycemic activity of 3-MPA.[2a] In addition, **1**, **2**, and **3** would be expected to have pK_a values which differ considerably from those of 3-MPA [pK_a (3-MPA) 4.51 and 7.23; pK_a (**2**) 3.27, 4.60, 7.57].

Isomers of 3-MPA, in which the mercapto group is capable of existing as a thione tautomer, likewise were not hypoglycemic.[2a] Hence, the inactivity of **6** might be explained on this basis.

The inactivity of the thiazole analogue **5**, which contains the additional hetero sulfur atom, cannot be explained readily, since the isosteric properties of sulfur and –CH=CH– are well established in medicinal chemistry.[16] That **5** is the ester rather than the acid does not provide an explanation since the methyl ester of 3-MPA produced significant hypoglycemia at a comparable dose.[2a]

Experimental Section

All melting points were obtained in a Thomas-Hoover capillary melting point apparatus and are uncorrected. Microanalyses were determined by the Analytical and Physical Chemistry Section of Smith Kline & French Laboratories. Where analyses are reported by the symbols of the elements, results were within ±0.4% of the calculated value.

General Procedures. A. *N*-Oxides 11a–e. N-Oxidation was carried out in $CHCl_3$ with *m*-chloroperoxybenzoic acid (MCPBA) as described earlier[2a] except for the preparations of **11d** and **11e**, where peroxytrifluoroacetic acid was used as the oxidant[17] (see Table III).

B. Cyano Derivatives 12a–c. The Reissert–Kaufmann reaction was carried out as described by Matsumara et al.[3b]

C. *p*-Methoxybenzylthio Esters 13a–d. Displacement of bromine with *p*-methoxybenzyl mercaptan (MBM)[4] was carried out by stirring in dry THF in the presence of NaH at room temperature for 30 min and refluxing for 2–3 h.[2a] In the preparation of **13d**, the reaction mixture was poured into aqueous HOAc rather than H_2O and a small amount of acidic products was isolated in addition to **13d**.

D. *p*-Methoxybenzylthio Acids 14a–d. Hydrolysis was carried out overnight with KOH in refluxing aqueous EtOH to give **14a** and **14b**. The quinoline **13c** (1 g), 1 g of KOH, and 50 mL of ethylene glycol were heated under reflux in an N_2 atmosphere for 3–5 h to effect hydrolysis. Hydrolysis of **13d** was accomplished by refluxing the diester for 90 min in 10%

NaOH–THF (1:10 by volume; 3 mL of solution per gram of diester) and stirring overnight at room temperature. The mixture was warmed to redissolve the product and was filtered. The filtrate was acidified to give the acid **14d**.

E. Heterocyclic Mercapto Acids 1–4. The methoxybenzyl group was removed as described previously[2a] with $Hg(OAc)_2$ in trifluoroacetic acid (TFA).

Ethyl 5-Bromo-4-thiazolecarboxylate (19c). A flask containing 0.27 mol of **19a** and 2100 mL of 50% H_2SO_4 was cooled to −5 °C and a solution of 22.5 g of $NaNO_2$ in 135 mL of H_2O, cooled to −5 °C, was added over about 5 min. The resulting cold diazonium solution was added dropwise to 680 mL of 30% H_3PO_2, cooled to −5 °C, at such a rate that the temperature of the solution was kept below 5 °C. The solution was stirred 1 h below 5 °C. It was diluted with 3000 mL of H_2O, cooled, and adjusted to pH 6 with 10 N NaOH and then to pH 7–8 with solid Na_2CO_3. The mixture was filtered, the filtrate was extracted with EtOAc, and the EtOAc was dried and evaporated to give 31 g of solid.

The aqueous solution was acidified with HCl and extracted with EtOAc. The EtOAc extract was dried and evaporated to give 20 g of the bromo acid, mp 167 °C.

Ethyl 5-*p*-Methoxybenzylthio-4-thiazolecarboxylate (19d). A slurry of 1.3 g (0.025 mol) of a mineral oil dispersion of NaH (57%) in 38 mL of dry Me_2SO was stirred under N_2 while 4.9 g (0.025 mol) of MBM[4] in 38 mL of dry Me_2SO was added dropwise at room temperature. The suspension was stirred 1 h at room temperature. A solution of 6.5 g (0.025 mol) of **19c** in 61 mL of dry Me_2SO was added dropwise. The mixture was stirred under N_2 at room temperature overnight and then poured into an ice–$CHCl_3$ mixture. The $CHCl_3$ layer was separated and washed with H_2O. Reextraction of the aqueous phases with C_6H_6 yielded 4.5 g of product, mp 70–75 °C. The analytical sample was purified by chromatography on Florisil (Fisher Scientific Co., Fair Lawn, N.J.) (EtOAc–cyclohexane, 1:4 by volume) and recrystallized from EtOH–H_2O.

5-*p*-Methoxybenzylthio-4-thiazolecarboxylic Acid (19f). A mixture of 1 g (3 mmol) of **19d** and 10 mL of 2.5 N NaOH was refluxed for 3 h. The solution was cooled, stirred with C_6H_6, and filtered, and the layers were separated. The aqueous phase was acidified with dilute HCl and the solid formed was filtered.

Ethyl 5-Mercapto-4-thiazolecarboxylate (5). To a stirred solution of 4.6 g (0.015 mol) of **19d** in 45 mL of TFA was added a solution of 15 g of $Hg(OAc)_2$ in 60 mL of TFA. The cherry red solution was stirred overnight at room temperature under N_2. After the TFA was removed at reduced pressure the residue was azeotroped twice with C_6H_5Me. The residue was triturated well three times with fresh portions of C_6H_6 and filtered. The solid was redissolved in TFA and the solution was saturated with H_2S. The black sulfide was filtered and washed with TFA. The filtrates were evaporated and the residue was azeotroped twice with C_6H_5Me. The crude product was dissolved in hot *n*-BuOH; the solution was cooled and filtered. The filtrate was evaporated, the residue was dissolved in MeOH, and the solution was diluted with small portions of H_2O. The initially formed gums were removed by decantation of the solution, the solution was concentrated and cooled, and the resulting precipitate was recrystallized from EtOH–H_2O and hexane.

3,5-Diamino-2,6-lutidine (16b). Powdered 2,6-dimethyl-3,5-pyridinedicarboxamide (**16a**) (36.7 g, 0.19 mol)[6] was added in one portion to a rapidly stirred solution of 11 mL of Br_2 in 330 mL of 2.5 N NaOH at 0 °C. Most of the diamide dissolved after stirring for 15–25 min. The mixture was rapidly brought to 90 °C with a steam bath and kept at that temperature for 90 min. The mixture was cooled and filtered to give 6 g of recovered **16a**. The filtrate was extracted continuously for 18 h with $CHCl_3$ to give 9.4 g of **16b** (43% based on the amount of **16a** actually used).

3,5-Diacetamido-2,6-lutidine (16c). A mixture of 9.4 g of **16b** and 100 mL of Ac_2O was stirred for 90 min at room temperature (exothermic) whereupon the solid dissolved and the product reprecipitated. The reaction mixture was diluted with Et_2O, cooled, and filtered. The solid was triturated twice with Et_2O and dried in a vacuum desiccator over NaOH.

3,5-Diacetamido-2,6-pyridinedicarboxylic Acid (17a). To a solution of 12.5 g of **16c** in 400 mL of H_2O was added 48 g of $KMnO_4$. The mixture was heated and stirred on a steam bath for 4 h. The hot mixture was filtered through a mat of Supercel and the filter cake was washed three times with hot H_2O. The filtrates were cooled and adjusted to pH 3 with dilute HCl. The gelatinous precipitate was cooled, filtered, washed with H_2O, and dried.

A sample was dissolved in 14% aqueous NH_3 with warming. On cooling the ammonium salt precipitated. It was collected and suspended in 35 mL of hot EtOH. The hot suspension was diluted with H_2O until solution was effected. After cooling the solid was collected and washed with EtOH and Et_2O. The solid was redissolved in H_2O, filtered, and acidified. The mixture was filtered and washed with H_2O, EtOH, Me_2CO, and Et_2O prior to drying.

3,5-Diamino-2,6-pyridinedicarboxylic Acid (17b). A mixture of 6.5 g (0.023 mol) of **17a** and 65 mL of 1.5 N HCl was stirred and heated 2 h on a steam bath and then refluxed 1 h. The mixture was left at room temperature overnight and filtered. The filter cake was washed with H_2O, EtOH, and Et_2O to give a pale yellow solid.

The solid was dissolved in a small volume of aqueous NH_3, the solution was filtered and acidified with HOAc, and the resulting yellow solid was collected and washed with EtOH and Et_2O. The solid was the monoammonium salt of **17b**, mp 285 °C dec. Anal. ($C_7H_{10}N_4O_4$) C, H, N.

Dimethyl 3,5-Diamino-2,6-pyridinedicarboxylate (17c). This ester was prepared using a procedure suggested by Brenner and Huber for preparing the esters of amino acids.[18]

A suspension of 2.5 g of **17b** in 185 mL of MeOH was cooled to −10 °C; $SOCl_2$ (47 mL) was added at such a rate that the temperature remained below 5 °C. The cooling bath was removed and after the reaction mixture reached room temperature it was refluxed for 16 h (almost complete solution was effected). Solvents were removed and the residue was dissolved in H_2O. The aqueous solution was neutralized with solid $NaHCO_3$ and extracted with $CHCl_3$. The extracts were dried and evaporated to give crude **17c**.

3,5-Dibromo-2,6-pyridinedicarboxylic Acid (15). A mixture of 42.7 g (0.16 mol) of 3,5-dibromo-2,6-lutidine[5] and 130 g of $KMnO_4$ in 1000 mL of H_2O was stirred and warmed on a steam bath. Since the lutidine began to steam distill into the condenser, about 15 mL of dioxane was used to wash the crystals back into the reaction vessel whereupon a vigorous reaction ensued, and the mixture refluxed up into the condenser. When the reaction had subsided, heating was resumed for 4 h on the steam bath using a little additional dioxane to wash the condenser. The reaction mixture was filtered hot through Supercel and the filter cake was washed several times with hot H_2O. The filtrates were concentrated, cooled, and acidified. The resulting solid was filtered, washed with cold H_2O, and dried. The yield in two crops was 15 g, mp >300 °C.

The MnO_2 filter cake was extracted once with $CHCl_3$ and once with Me_2CO. Evaporation of the combined extracts gave 17.4 g of recovered starting material, mp 58–62 °C. The yield of **15** based on lutidine used was 48%.

3-Mercapto-2-pyrazinecarboxylic Acid (6). A mixture of 1.6 g (9 mmol) of methyl 3-mercapto-2-pyrazinecarboxylate[9] in 30 mL of MeOH and 10 mL of 2.5 N NaOH was stirred at room temperature for 4 h under N_2. The MeOH was removed and the aqueous residue was adjusted to pH 3. The orange solid was removed and recrystallized.

4-Mercapto-3-isoquinolinecarboxylic Acid (7). The carbamates **20a** and **20b** were prepared using the method described previously.[2a]

A solution of **20b** (1 g) in 40 mL of 50% H_2SO_4 was heated overnight on a steam bath. The cooled, yellow solution was adjusted to pH 8 with solid Na_2CO_3; the alkaline solution was extracted with C_6H_6 and readjusted to pH 4 with dilute H_2SO_4. The resulting precipitate was filtered, washed with H_2O, dried, and recrystallized.

3-Mercapto-2-indolecarboxylic Acid (8). A mixture of 9.7 g (0.05 mol) of 3-isothiocyanato-2-indolecarboxylic acid[13] in 200 mL of 2.5 N NaOH was stirred under reflux overnight under N_2. The cooled filtrate was acidified in an N_2 atmosphere to pH 2 with dilute HCl. The solids were collected and triturated with 5% Na_2CO_3. The mixture was filtered; the filtrate was acidified again under N_2. The solid was collected, dried, and triturated three times with $CHCl_3$. The solid was redissolved in 5% Na_2CO_3, the solution was filtered, and the filtrate was again acidified. All

operations again were performed in an N_2 atmosphere. After drying, the solid was again triturated with $CHCl_3$; yield 5 g (50%); mp 155 °C.

The material insoluble in Na_2CO_3 was the disulfide of 3-mercaptoindole, mp 219–220 °C. Anal. ($C_{16}H_{12}N_2S_2$) C, H, N.

3-Acetylthio-2-indolecarboxylic Acid. Treating **8** with Ac_2O in aqueous $NaHCO_3$ as described for 3-MPA[2a] gave this derivative which helped confirm the structure of **8**.

Methyl 3-Methylsulfinylpicolinate (21b). A solution of 1.83 g (0.01 mol) of **21a**, 2.2 g of 85% MCPBA, and 50 mL of $CHCl_3$ was stirred at room temperature for 22 h. The solution was extracted with 5% Na_2CO_3 and H_2O, dried, and evaporated.

Methyl 3-Methylsulfonylpicolinate (21c). A solution of 1.83 g (0.01 mol) of **21a** and 5 g of MCPBA in 100 mL of $CHCl_3$ was stirred 20 h at room temperature and refluxed for 30 min. The product was isolated as described for **21b**. The crude product contained **21b**. The mixture was placed on a silica column (70–230 mesh, E. Merck, distributed by Brinkmann Instruments, Inc., Westbury, N.Y.) and the column was developed with EtOAc. Pure sulfone was obtained readily from the first fractions off the column.

3-Methylsulfinylpicolinic Acid (9). A mixture of 2.2 g (0.01 mol) of **21b**, 15 mL of 2.5 N NaOH, and 40 mL of MeOH was stirred under reflux for 90 min. The solvent was removed and the residue was diluted with water and acidified with IRA-120 ion-exchange resin (Rohm and Haas Co., Philadelphia, Pa.). The mixture was filtered and the filtrate was evaporated. The residue was dried by being azeotroped several times with dry EtOH before being recrystallized.

3-Methylsulfonylpicolinic Acid (10). A mixture of 1.4 g (6.5 mmol) of **21c**, 25 mL of MeOH, and 10 mL of 2.5 N NaOH was refluxed 90 min. The MeOH was removed and the residue was made strongly acidic with cooling. The solid was removed, washed with H_2O, and recrystallized.

Evaporation of the recrystallization filtrates gave a small amount of the decarboxylated material, methyl 3-pyridylsulfone, mp 47–49 °C (C_6H_6–petroleum ether). Anal. ($C_6H_7NO_2S$) C, H, N, S.

Ethyl 2-Amino-5-isothiocyanato-4-thiazolecarboxylate (19b). All equipment was dried carefully under N_2 before use and covered with Al foil to protect the reaction mixture from light.[19] Dry, commercial MeOH was dried further over molecular sieves prior to use.

In the equipment, treated as described and cooled to −5 °C, was placed 17.3 g (0.01 mol) of **18** and 39 g of KSCN in 100 mL of MeOH. To this stirred solution cooled to −5 °C was added dropwise a solution of 44 g of Br_2 in 30 mL of MeOH saturated with NaBr. The addition was carried out below 5 °C. The solution was stirred 30 min at −5 to 0 °C and left overnight at 6–10 °C. The solution was poured into 600 mL of H_2O and stirred 1 h. The solid was collected and dried.

3,5-Dibromopicolinic Acid. A solution of 2.6 g (0.01 mol) of **12a** and 70 mL of 50% H_2SO_4 was stirred 18 h under reflux. The solution was cooled and poured over several volumes of ice. The precipitate was filtered, washed with H_2O, dried, and recrystallized from C_6H_5Me to give 82% of product, mp 169–170 °C. Anal. ($C_6H_3Br_2NO_2$) C, H, Br, N.

Methyl Esters (12d, 19e, 21a, and Methyl 3,5-Dibromopicolinate). Refluxing 1 g of the appropriate acid 16 h with 10 mL of 14% BF_3 in MeOH under N_2 gave the desired methyl esters.[2a]

Methyl 3,5-dibromopicolinate: yield 68%; mp 102–104 °C (MeOH). Anal. ($C_7H_5Br_2NO_2$) C, H, Br, N.

Biochemistry. Hypoglycemic activity was measured in 48-h fasted male rats weighing ca. 200 g. On the morning of the test day, a zero time tail-vein sample was obtained, followed by the intraperitoneal or oral administration of the test compound. For intraperitoneal administration the compound was suspended in 0.9% saline and for oral administration the compound was suspended in 0.5% tragacanth. A similar group of animals receiving only the vehicle served as controls. Tail-vein samples were obtained at 1, 2, and 4 h after drug administration. Glucose determinations have been described previously.[2] Tolbutamide, after an oral dose of 200 mg/kg, lowered blood glucose levels in this test system 28% at 1 h, 47% at 2 h, and 48% at 4 h after treatment. These values were significant at the $p \leq 0.001$ level.

Acknowledgment. We are indebted to Dr. Stephen T. Ross and Mr. David L. Ladd for the details of the preparation of **19a** and **19c**. We are obliged to members of the Analytical and Physical Chemistry Section staff for thiol determinations. We also thank Dr. B. M. Sutton for his helpful comments and suggestions in the preparation of this manuscript.

References and Notes

(1) Presented in part at the 172nd National Meeting of the American Chemical Society, San Francisco, Calif., August 30–Sept 3, 1976.
(2) (a) B. Blank, N. W. DiTullio, C. K. Miao, F. F. Owings, J. G. Gleason, S. T. Ross, C. E. Berkoff, H. L. Saunders, J. Delarge, and C. L. Lapière, *J. Med. Chem.*, **17**, 1065 (1974); (b) N. W. DiTullio, C. E. Berkoff, B. Blank, V. Kostos, E. J. Stack, and H. L. Saunders, *Biochem. J.*, **138**, 387 (1974).
(3) (a) P. J. L. Daniels, U.S. Patent 3 585 206 (June 15, 1971); *Chem. Abstr.*, **75**, 63 629f (1971); (b) E. Matsumara, M. Ariga, and T. Ohfuji, *Bull. Chem. Soc. Jpn.*, **43**, 3210 (1970); (c) A. R. Katritsky and E. Lunt, *Tetrahedron*, **25**, 4291 (1969).
(4) H. Tanaka and A. Yokoyama, *Chem. Pharm. Bull.*, **8**, 280 (1960).
(5) L. van der Does and H. J. den Hertog, *Recl. Trav. Chim. Pays-Bas*, **84**, 951 (1965); W. Drzeniek and P. Tomasik, *Rocz. Chem.*, **43**, 1865 (1969); *Chem. Abstr.*, **72**, 66 755t (1970).
(6) H. H. Fox, *J. Org. Chem.*, **17**, 542 (1952).
(7) H. Erlenmayer and Ch. J. Morel, *Helv. Chim. Acta*, **25**, 1073 (1942).
(8) Y. Garreau, *C. R. Hebd. Seances Acad. Sci.*, **222**, 963 (1946); *Chem. Abstr.*, **40**, 4374[4] (1946).
(9) J. H. Jones, W. J. Holtz, and E. J. Cragoe, Jr., *J. Med. Chem.*, **12**, 285 (1969).
(10) A. M. Kim and V. P. Mamaev, *Izv. Sib. Otd. Akad. Nauk SSSR, Ser. Khim. Nauk*, 79 (5) (1968); *Chem. Abstr.*, **70**, 87 532s (1969).
(11) M. B. Newman and H. A. Karnes, *J. Org. Chem.*, **31**, 3980 (1966).
(12) H. Kwart and E. R. Evans, *J. Org. Chem.*, **31**, 410 (1966).
(13) M. S. Grant and H. R. Snyder, *J. Am. Chem. Soc.*, **82**, 2742 (1960).
(14) R. B. Sanders and N. B. Parekh, *Pharmacology*, **3**, 305 (1970).
(15) R. M. Walters, R. J. Dudl, J. P. Palmer, and J. W. Ensinck, *J. Clin. Invest.*, **54**, 1214 (1974).
(16) A. Burger in "Medicinal Chemistry", Part 1, 3rd ed, A. Burger, Ed., Wiley-Interscience, New York-London-Sydney-Toronto, 1970, p 73.
(17) V. Tortella, F. Macioci, and G. Roma, *Farmaco, Ed. Sci.*, **23**, 236 (1968).
(18) M. Brenner and W. Huber, *Helv. Chim. Acta*, **36**, 1109 (1953).
(19) J. L. Wood, *Org. React.*, **3**, 240 (1946).