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Mercaptopyridinecarboxylic Acids, Synthesis and Hypoglycemic Activity†

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3-Mercaptopicolinic acid (1), its isomers, analogs, and derivatives were prepared and tested for hypoglycemic activity in 48-hr fasted rats. Several compounds [1, 5-mercaptopicolinic acid (3), 4-methyl-3-mercaptopicolinic acid (11), 3-phenylthiopicolinic acid (17), 3-benzylthiopicolinic acid (18), the *S*-acetyl (20) and *S*-benzoyl (21) derivatives of 1, the disulfide of 1 (22), and the methyl ester of 1 (24)] were active with 1 being the most potent. *p*-Methoxybenzyl mercaptan (MBM) was used as a novel sulfurating agent to introduce sulfur in a protected form and was used to prepare 1, 6-mercaptopicolinic acid (4), 5-mercaptonicotinic acid (7), methyl 6-chloro-3-mercaptopicolinate (15), (3-mercapto-2-pyridyl)methanol (25), 3-mercaptopicolinamide (30), 2-acetyl-3-mercaptopyridine (35), 3-acetylthiopyridine (54), and 3-mercaptopyridine *N*-oxide (59). The protecting group was usually removed in the final step by mercuric acetate in trifluoroacetic acid. The Newman-Kwart route to thiols was also utilized. The hypoglycemic activity of 1 seems highly specific, with relatively minor chemical changes causing marked changes in the ability of closely related compounds to lower glycemic levels in fasted rats.

Diabetes is a condition characterized by an insufficiency of insulin which results in a number of metabolic derangements. Among these is an enhanced rate of gluconeogenesis and an elevated blood glucose level. Current therapy focuses on trying to normalize the observed, elevated blood glucose levels.

Using drug therapy one can try to modulate glycemic levels in one of several ways: stimulate insulin secretion, potentiate insulin activity, increase the peripheral uptake and oxidation of glucose, and inhibit gluconeogenosis. Of these possible approaches we chose to see what effects inhibition of gluconeogenesis had on glycemic levels.

Our search for inhibitors of gluconeogenesis centered around the structure of quinolinic acid, a compound reported to have this property.[1] This search led to 3-mercaptopicolinic acid (1), a good hypoglycemic agent in fasted rats and an inhibitor of glucose synthesis from three-carbon precursors *in vitro*.[2] To further develop this finding, positional isomers, derivatives, and analogs of 1 were prepared and tested in 48-hr fasted rats.

All of the isomeric mercaptopyridinecarboxylic acids have been described in the literature[3-10] and, with the exceptions of 3 and 7, were prepared using these procedures. In general, these acids were prepared by treating the corresponding halo acid with hydrosulfide (2, 4–6, 8, and 9). In those instances where the isomers have the mercapto group in the 3 or 5 position of the pyridine (1, 3, and 10) sulfuration was accomplished by treating the diazonium salt of the corresponding amino acid with polysulfide.

5-Aminopicolinic acid still served as the immediate precursor of 3 but it was derived from commercially available 2-chloro-5-nitropyridine. Treatment of this reagent with the anion of diethyl malonate in DMSO gave the nitropyridyl malonate[11] which was oxidized with potassium permanganate to 5-nitropicolinic acid.[12] This acid was reduced catalytically to the desired amino acid.[12] 7 was prepared from methyl 5-bromonicotinate[13] and *p*-methoxybenzyl mercaptan, of which more will be said later.

The 4-, 5-, and 6-methyl and 5-chloro analogs of 1 (11–14) were prepared from the corresponding quinolinic acids. These preparations were patterned after the synthesis of 1.[3] The required quinolinic acids were obtained by oxidation of suitably substituted quinolines.

S-Alkyl, aralkyl, and acyl derivatives of 1 (16, 18–21) were obtained from 1 using Schotten–Baumann conditions. Esterification of 1 proved unexpectedly difficult. Most of the usual methods yielded the disulfide diester. However, the methyl ester 24 could be prepared by treating 1 with boron trifluoride–methanol. The anilide of 1 (33) was prepared by allowing 20 to react with aniline in the presence of dicyclohexylcarbodiimide to produce 34. Subsequent acid hydrolysis yielded 33. The known *S*-phenyl derivative of 1 (17) was made by treating the diazonium salt of 3-aminopicolinic acid with thiophenol.[14]

Although 1 was most conveniently prepared by the

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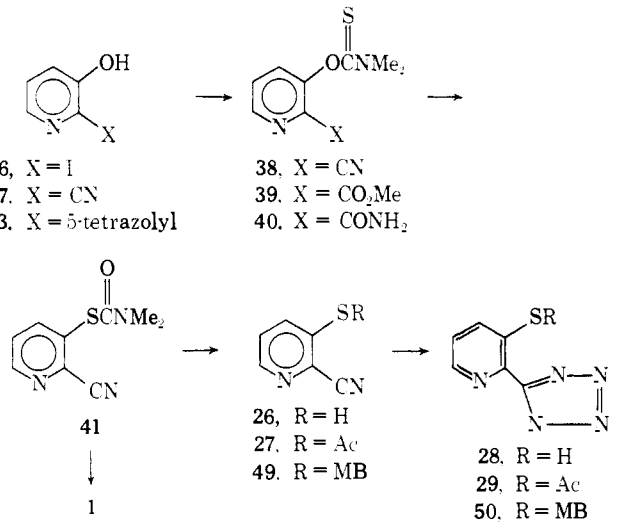
method of Sucharda and Troszkiewiczowna,[3] an alternative synthesis was devised (Scheme I). This route, based on the work of Newman and Karnes[15] and Kwart and Evans,[16] also provided useful intermediates for the syntheses of the nitrile 26 and tetrazole 28 (26 → 49 → 50 → 28).

Scheme I



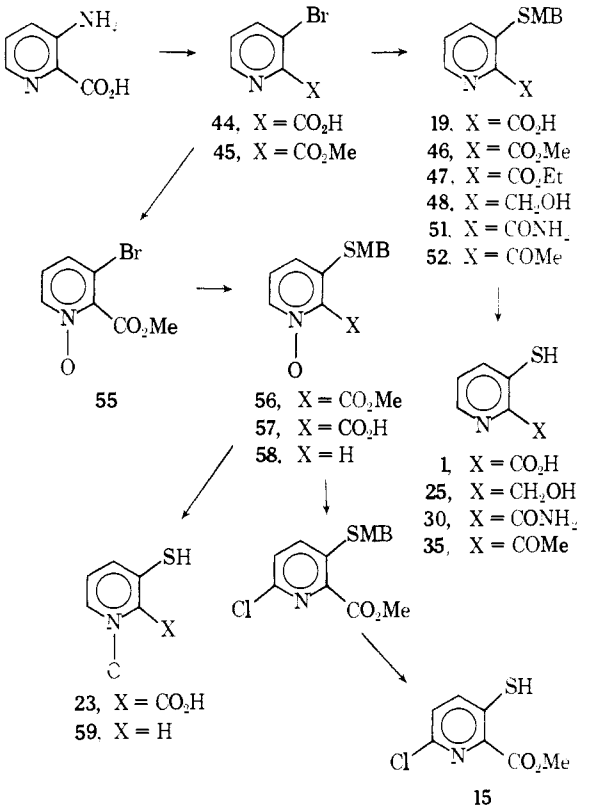
The synthesis of the tetrazole analog of 1 stemmed from the observations of others who noted that the pK_a's of carboxylic acids and tetrazoles were comparable. For example, the tetrazole analogs of nicotinic acid and flufenamic acid have biological activity comparable to the carboxylic acids.[17,18]

Attempts to prepare 28 by alternative routes using the intermediates 38, 41, or 43 failed. Treatment of 38 or 41 with sodium azide in dimethylformamide led to complex mixtures which did not warrant further investigation, while attempted acylation of 43 with dimethylthiocarbamoyl chloride resulted in the isolation of a rearrangement product, the *O*-[2-(2-dimethylamino-1,3,4-thiadiazol-5-yl)-3-pyridyl] ester of dimethylthiocarbamic acid.[19]

Although the described routes to 1 and the other mercaptopyridine acids were satisfactory, there were instances where appreciable amounts of the disulfides were formed. Consequently, a search was made for an alternative sulfuration procedure which would allow more exclusive formation of the mercaptans. A route which provided this exclusivity as well as other benefits made use of the reaction of halopyridines with *p*-methoxybenzyl mercaptan (MBM). The methoxybenzyl group (MB) has been used sparingly as a protective group in peptide syntheses to protect the sulfur of cysteine[20] and in one instance MBM was added to an unsaturated system.[21] However, in this latter case the workers were unable to remove the protecting group.

In our hands MBM was used to displace the halogen in a variety of halopyridines. The protecting group was readily removed subsequently at room temperature with mercuric acetate in either formic or trifluoracetic acid. This procedure permitted sulfur to be introduced as a relatively unreactive thioether, stable to most reaction conditions other then oxidation. Thus metalations, hydride reductions, and hydrolyses were carried out without affecting the oxidation state of the sulfur. The mild treatment required to remove the MB group as a final or penultimate step allowed the preparation of mercapto compounds containing groups which were sensitive to hydrolytic or reductive conditions. The utility of MBM as a reagent and of the MB group as a protecting group is exemplified by reactions shown in Scheme II.

Scheme II



5-Mercaptonicotinic acid (7) was derived from methyl 5-bromonicotinate[13] and MBM in the same way 1 was derived from 45 (Scheme II). The *N*-oxide of 1 (23) was prepared similarly.

The methyl ester of 6-chloro-3-mercaptopicolinic acid (15) was synthesized uniquely. Treatment of methyl 3-*p*-methoxybenzylthiopicolinate *N*-oxide (56) with phosphorus oxychloride effected deoxygenation as well as chlorination at C_4 and C_6 of the pyridine, with the latter isomer predominating. Chromatographic separation of the isomers and subsequent treatment with mercuric acetate in trifluoroacetic acid yielded 15.

Borohydride reduction of 46 led to the alcohol 48. Basic hydrolysis of 46 gave the acid 19 which, on treatment with methyllithium, yielded the methyl ketone 52. Treatment of 19 with thionyl chloride followed by reaction with ammonia led to the amide 51. Allowing 19, 48, 51, and 52 to react with mercuric acetate in trifluoroacetic acid gave respectively 1, (3-mercapto-2-pyridyl)methanol (25), 3-mercaptopicolinamide (30), and 2-acetyl-3-mercaptopyridine (35).

3-Acetylthiopyridine (54) and 3-mercaptopyridine *N*-oxide (59) were prepared from the corresponding MB derivatives and were also tested for hypoglycemic activity.

Discussion

Significant hypoglycemia was produced by 1, 11, 18, 20, 21, and 22 when they were administered intraperitoneally to fasted rats at a dose of 300 mg/kg. 3 and 17 produced a hypoglycemic response after oral treatment while 24 significantly lowered glucose levels at a dose of 150 mg/kg both parenterally and orally. However, only 1, and its de-

Table I. Mercaptopyridinecarboxylic Acids

No.	Position of SH	Position of CO_2H	R	Mp, °C	Recrystn solvent[a]	% yield	Formula	Hypoglycemic act. in the 48-hr fasted rat[b] 1 hr	2 hr	4 hr
1	3	2	H	181–182[c]	A	30	$C_6H_5NO_2S$	−9[d]	−13[d]	−33[d]
								−13[e,f]	−22[d,e]	−29[e,g]
2	4	2	H	196–200[h]	A	16	$C_6H_5NO_2S$	−4	0	2
3	5	2	H	218–220[i]	B–A	33	$C_6H_5NO_2S$[i]	2	3	5
								−6[e,f]	−11[d,e]	−12[e]
4	6	2	H	196–198[j]	C	15	$C_6H_5NO_2S$	−6[f]	−7[f]	−13[d]
5	2	3	H	270[k]	A	80	$C_6H_5NO_2S$	−1	−2	−3
6	4	3	H	243–245[l]	A	10	$C_6H_5NO_2S$	−5	−4	0
7	5	3	H	204–206[m]	A	48	$C_6H_5NO_2S$	8[f]	8[d]	5
8	6	3	H	185–187[n]	A	25	$C_6H_5NO_2S$	8[g]	9[d]	10[d]
9	2	4	H	304–306[o]	D	60	$C_6H_5NO_2S$	−5[f]	−5[f]	2
10	3	4	H	223–225[p]	A	35	$C_6H_5NO_2S$	−3	−4	3
11	3	2	4-CH_3	194–196	A	38	$C_7H_7NO_2S$	−14[g]	−28[g]	−17[f]
								−13[d,q]	−11	−8
12	3	2	5-CH_3	177–178	B	51	$C_7H_7NO_2S$[r]	19[d]	21[d]	14[f]
13	3	2	6-CH_3	177–178	A	31	$C_7H_7NO_2S$	10[s]	−1[s]	3[s]
14	3	2	5-Cl	146–149	A	17	$C_6H_4ClNO_2S$[t]	5[u]	0[u]	−1[u]
15	3	2	6-Cl	106–107	E–F	71	$C_7H_6ClNO_2S$[v]	6	3	2

[a]The abbreviations have the following meanings: A, H_2O; B, EtOH; C, MeOH; D, base–acid; E, Et_2O; F, ligroine (bp 40–60°). [b]Results are expressed as the per cent difference in milligram per cent between the mean change in control and treated groups after a drug dose of 300 mg/kg ip, unless specified otherwise. [c]Lit.[3] mp 183.5°. [d]$p < 0.01$. [e]Dose 150 mg/kg po. [f]$p < 0.05$. [g]$p < 0.001$. [h]Lit.[4] mp 188–190°. [i]Hemihydrate. [j]Lit.[6] mp 196–197°. [k]Lit.[3] mp 270°. [l]Lit.[9] mp 236–238°. [m]Lit.[7] mp 162–165°. [n]Lit.[8] mp 273–275°. [o]Lit.[6] mp 304–306°. [p]Lit.[5] mp 225°. [q]Dose 300 mg/kg po. [r]Sample contained *ca.* 0.2 mol of EtOH (nmr). C: calcd, 49.69; found, 50.40. [s]Dose 300 mg/kg iv. [t]C: calcd, 38.00; found, 38.48. N: calcd, 7.39; found, 8.07. [u]Dose 240 mg/kg ip. [v]Methyl ester.

rivatives **20** and **24**, consistently produced significant hypoglycemic effects when the dosage was reduced or when the drug was administered orally.

Modifications, with the exceptions of those cited above, to either sulfur (**16, 44, 46**), the carboxyl group (**25, 27, 30, 32, 33, 35**), or the pyridine nitrogen (**23**) of **1** drastically reduced or abolished hypoglycemic activity. Similar effects were noted when the juxtaposition of mercaptan, carboxylic acid, and pyridine nitrogen was altered (**2–10**). Methyl or chloro substituents in the pyridine ring were deleterious, particularly in the 5 and 6 positions (**1** *vs.* **11** *vs.* **12–15**).

Interestingly, with the exception of the ester **24** and the hydrazide **32**, replacement of the carboxyl group of **1** with some other carbonyl moiety caused a reversal of biological action, resulting in a hypoglycemic response being converted to a hyperglycemic response (**1** *vs.* **30, 33, 34, 35**). **41**, in which both the mercapto and carboxyl groups of **1** were modified, was a very potent hyperglycemic agent as was 3-aminopicolinic acid.

The ability of **1** to produce hypoglycemia was confirmed in fasted mice and guinea pigs and in alloxan-diabetic rats. That the hypoglycemia resulted from an effect on gluconeogensis was confirmed *in vitro* using rat kidney cortex slices and liver perfusion studies.

Moreover, the inability of **1** to lower glucose levels in fed animals lends support to the supposition that **1** acts by inhibiting gluconeogenesis while its effectiveness in alloxanized animals indicates that it does not act by stimulating insulin release.[2]

In summary, it appears that the hypoglycemic activity of **1** is highly specific, with relatively minor chemical changes causing marked changes in the ability of closely related compounds to lower glycemic levels in fasted rats.

Experimental Section

Melting points were determined in a Thomas-Hoover apparatus and are uncorrected. Elemental analyses were preformed by the Analytical and Physical Chemistry Department of Smith Kline & French Laboratories. The identification of compounds listed in Tables I–IV is supported by spectral and analytical data. Analyses (C, H, and N) for compounds reported in this paper were within ±0.4% of the theoretical values except where specifically noted.

Quinolines. 3-Methyl- and 4-methyl-8-hydroxyquinoline were prepared by Skraup reactions.[22,23] We were able to improve the yields in each case by carefully controlling the initial exotherm and by modifying the subsequent isolation procedures. The 3-methyl isomer was purified conveniently by absorbing the basified reaction mixture on Celite, placing the Celite atop a large Florisil column, and washing the column with $CHCl_3$. The solvent was evaporated to give the product. This technique was not useful with the 4-isomer, but prolonged steam distillation of the basified reaction mixture improved markedly the reported yield of this isomer. Both isomers were prepared on a 2 *M* scale.

3-Chloroquinoline was prepared by chlorination of quinoline with SCl_2.[24] The crude product was subjected to careful fractionation to give 31% of product that was 98% pure by glpc.

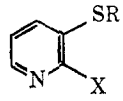
Quinolinic Acids. 4-, 5-, and 6-methylquinolinic acids resulted when the appropriate 8-hydroxyquinoline was oxidized with fuming nitric acid (*d* 1.48).[25] The oxidation of the 4-isomer was particularly vigorous and required an especially slow and careful addition of the solid quinoline to the stirred acid at *ca.* 10–20°.

5-Chloroquinolinic Acid. A solution of 800 g of $KMnO_4$ in 8 l. of H_2O was added slowly over 3 hr to 100 g (0.61 mol) of 3-chloroquinoline in 1 l. of H_2O at 80–100°. The addition was accompanied by the constant passage of a stream of CO_2 through the mixture. Heating was continued until the $KMnO_4$ color disappeared. The mixture was filtered through a mat of Celite and the pH of the filtrate was adjusted to 4 with concentrated HCl (much foaming). The Cu salt of the diacid was precipitated slowly by the addition of 75 g of $Cu(OAc)_2$ in 75 ml of HOAc and 2.5 l. of H_2O. The salt weighed 60 g after filtering, washing with H_2O, and vacuum drying. It was suspended in 2 l. of H_2O and saturated with H_2S with stirring and heating on a steam bath. The mixture was filtered hot through Celite and the filtrate was evaporated. The residue was recrystallized from a minimal volume of H_2O to give 31% of product.

Imides and Aminopicolinic Acids. These conversions were carried out as described by Suchard[a][25] for quinolinimide and 3-aminopicolinic acid. The isomeric amino acids obtained from the Hofmann rearrangement could be identified readily by the ir absorption of the respective carboxylic acid groups. The picolinic acids had a strong absorption at *ca.* 6.1 μ while the nicotinic acids absorbed at *ca.* 5.95 μ.

Displacements with *p*-Methoxybenzyl Mercaptan (46, 53, 56, 57, and 58). A solution of 0.175 mol of MBM[21] in a small volume

Table II. Derivatives of 1



No.	R	X	Mp, °C	Recrystn solvent[a]	% yield	Formula	Hypoglycemic act. in the 48-hr fasted rat[b] 1 hr	2 hr	4 hr
16	CH_3	CO_2H	158–160	A	79	$C_7H_7NO_2S$	0	8[e]	15[d]
17	C_6H_5	CO_2H	166–168[c]	B	25	$C_{12}H_9NO_2S$	7	−9	−7
							−26[c,f]	−27[d,f]	−20[f,g]
18	$C_6H_5CH_2$	CO_2H	154–156	C	60	$C_{13}H_{11}NO_2S$	−5	−25[c]	6
19	MB	CO_2H	170–172	A	75	$C_{14}H_{13}NO_3S$			
20	Ac	CO_2H	114–116	D–E	60	$C_8H_7NO_3S$	−5[g]	−24[d]	−31[d]
							−17[d,h]	−25[d,h]	−16
21	C_6H_5CO	CO_2H	151–152	F	72	$C_{13}H_9NO_3S$	−27[d]	−49[d]	−51[d]
							−2[h]	7[h]	7[h]
22	Disulfide of 1		202[i]	G–H	*j*	$C_{12}H_8N_2O_4S_2$	−14	−27[d]	−40[d]
							−14[d,h]	−5[h]	−5[h]
23	*N*-Oxide of 1		137–138	I	35	$C_6H_5NO_3S$	−5[d]	−4	10[g]
24	H	CO_2Me	64–66	J–K	58	$C_7H_7NO_2S$	−17[d,k]	−28[d,k]	−21[d,k]
							−17[d,h]	−20[d,h]	−4[h]
25	H	CH_2OH	153–155	C	66	$C_6H_7NOS \cdot HCl$	10	10	3
26	H	CN	95–97	F	60	$C_6H_4N_2S$			
27	Ac	CN	63–65	L	50	$C_8H_6N_2OS$[l]	5	0	−9
28	H	5-Tetrazolyl	183–185	H	40	$C_6H_5N_5S$	Death		
29	Ac	5-Tetrazolyl	165–166	D–E	30	$C_8H_7N_5OS$	Death		
30	H	$CONH_2$	172–174	H	50	$C_6H_6N_2OS$[m]	−12[g]	10[c]	8[c]
31	Ac	$CONH_2$	146–149	F–D–E	25	$C_8H_8N_2O_2S$[n]			
32	H	$CONHNH_2$	305[o]	A	50	$C_6H_7N_3OS \cdot HCl$	−2	−7	−4
33	H	$CONHC_6H_5$	127–129	C	50	$C_{12}H_{10}N_2OS$	40[g]	100[d]	76[d]
34	Ac	$CONHC_6H_5$	116–118	D–K	64	$C_{14}H_{12}N_2O_2S$	53[d]	58[c]	29
35	H	$COCH_3$	180	L	30	$C_7H_7NOS \cdot HCl$	24[d,k]	12[c,k]	8[g,k]

[a]The abbreviations have the following meanings: A, MeOH; B, aqueous HOAc; C, EtOH; D, $CHCl_3$; E, ligroine (bp 40–60°); F, CCl_4; G, DMF; H, H_2O; I, MeCN; J, C_6H_6; K, hexane; L, purified by chromatography. [b]Results are expressed as the per cent difference in milligram per cent between the mean change in control and treated groups after a drug dose of 300 mg/kg ip unless specified otherwise. [c]$p < 0.01$. [d]$p < 0.001$. [e]Lit.[27] mp 162°. [f]Dose 300 mg/kg po. [g]$p < 0.05$. [h]Dose 150 mg/kg po. [i]Lit.[3] mp 206°. [j]Obtained as a by-product in the synthesis of 1. [k]Dose 150 mg/kg ip. [l]C: calcd, 53.92; found, 54.41. [m]N: calcd, 18.17; found, 17.49. Contains <5% of 1. [n]N: calcd, 14.27; found, 13.73. Contains <5% of **20**. [o]Lit.[9] mp 310°.

of dry DMSO or THF was added slowly below 20° to a stirred suspension of 0.16 mol of NaH in 100 ml of the same solvent under N_2. The mixture was stirred 1 hr at room temperature and then 0.16 mol of the appropriate halide was added (usually slightly exothermic). The mixture was kept at 70–90° for 2–3 hr under N_2, cooled, and diluted with ice H_2O. If the product precipitated, it was filtered, washed, dried, and recrystallized. If dilution produced a gum, it was extracted into $CHCl_3$ and the $CHCl_3$ was washed with H_2O, dried, and evaporated. The residue solidified when triturated with Et_2O or Et_2O-petroleum ether. If the starting halide was also an ester, acidification of the aqueous phases often yielded a crop of the corresponding sulfurated acid. The recent revelation that most commercial samples of NaH contain appreciable amounts of NaOH[26] may account for the varying amounts of acid found in these reactions.

Displacement of the bromine in the *N*-oxide **55** with MBM to give **56** was complicated by concomitant hydrolysis to the corresponding acid **57**. This acid, depending upon the solvent, decarboxylated to some degree during the displacement reaction to yield substantial amounts of 3-*p*-methoxybenzylthiopyridine *N*-oxide (**58**). This material was identical with samples prepared from 3-bromopyridine *N*-oxide[27] and MBM.

57 was prepared in DMSO and the reaction mixture was warmed 2 hr on a steam bath. Longer heating caused extensive decarboxylation. The mixture was cooled, diluted with H_2O and a little acid, and extracted with $CHCl_3$. The $CHCl_3$ was removed and the residue was triturated with Et_2O-petroleum ether to give crude **57**.

Methyl 6-*p*-methoxybenzylthiopicolinate: yield 42%; mp 68–70° (MeOH). *Anal.* ($C_{15}H_{15}NO_3S$) C, H, N, S.

5-*p*-Methoxybenzylthionicotinic acid: yield 52%; mp 202–203° (EtOH). *Anal.* ($C_{14}H_{13}NO_3S$) C, H, N, S.

Methyl 6-Chloro-3-*p*-methoxybenzylthiopicolinate. A mixture of 2 g (6.4 mmol) of **56**, 9 g of $POCl_3$, and 150 ml of $CHCl_3$ was refluxed for 1 hr. At this time **56** was completely consumed. The solution was poured into ice H_2O and a saturated solution of Na_2CO_3 was added slowly to pH 7–8. Solid was filtered and the filtrate was extracted with $CHCl_3$. The $CHCl_3$ was dried and evaporated and the residue crystallized on standing. The crystals were washed with cold MeOH and recrystallized from hot MeOH to give product, mp 105°. The MeOH filtrates were concentrated and the residue was chromatographed on silica gel using mixtures of CCl_4–$CHCl_3$–CH_2Cl_2. The total yield of the 6-isomer was 50% while the yield of the oily 4-isomer was 15%. *Anal.* ($C_{15}H_{14}ClNO_3S$) C, H, N.

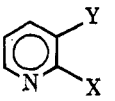
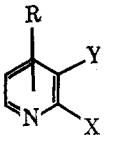
Cleavage of the *p*-Methoxybenzyl Group. A. HCO_2H (4 and 7). A solution of the SMB compound (0.012 mol) in 60 ml of 90% HCO_2H under N_2 was diluted with a solution of 10.8 g of $Hg(OAc)_2$ in 50 ml of H_2O. The mixture was stirred 30 min at room temperature. The resulting precipitate was filtered, washed with H_2O, and resuspended in H_2O. The suspension was saturated with H_2S and the precipitated sulfide was filtered. The filtrate was evaporated and the residue was purified.

B. TFA (1, 15, 23, 25, 28, 30, 35, 54, and 59). A solution of the SMB compound (4 mmol) in 15 ml of TFA under N_2 was diluted with a solution of 4 g of $Hg(OAc)_2$ in 30 ml of TFA. The cherry-colored solution was stirred at room temperature for 3–24 hr (60 hr for **15**). If a Hg^{2+} salt precipitated (**15** and **23**), it was filtered and washed with a little TFA and C_6H_6. The solid was suspended in H_2O or MeOH and the suspension was saturated with H_2S. The precipitate was filtered and washed, the filtrate was evaporated, and the residue was purified.

If the Hg^{2+} salt was soluble, the Hg^{2+} was precipitated by saturating the reaction solution with H_2S. The solid was removed and the filtrate was taken to dryness. The residue was dissolved in a mixture of dilute HCl and C_6H_6. The aqueous phase was washed with C_6H_6 and evaporated. The residual HCl salt can be isolated as such (**25** and **35**), or decomposed readily to the zwitterionic picolinic acid, often by recrystallization, or converted directly to an *S*-acetyl derivative with Ac_2O in dilute base.

Esterification with BF_3–MeOH (24, 45, 46, and 55). The acid was stirred and refluxed for 20 hr under N_2 with 10 ml of 14%

Table III. Intermediates

No.	X	Y	Mp, °C	Recrystn solvent	% yield	Formula	Hypoglycemic act. in the 48-hr fasted rat[a] 1 hr	2 hr	4 hr
									
36	I	OH	198–201[b]		94	C_5H_4INO			
37	CN	OH	210–213[c]		60	$C_6H_4N_2O$			
38	CN	OC(=S)NMe$_2$	115–117	C_6H_6–pet. ether	80	$C_6H_9N_3OS$	36[d]	−13	Death
39	CO_2Me	OC(=S)NMe$_2$	76–77	C_6H_6–Pet. ether	20	$C_{10}H_{12}N_2O_3S$	8	5	19
40	$CONH_2$	OC(=S)NMe$_2$	125–126	CCl_4–$CHCl_3$	45	$C_9H_{11}N_3O_2S$			
41	CN	SC(=O)ONMe$_2$	96–97	C_6H_6–pet. ether	70	$C_9H^cN_3OS$	91[e]	107[d]	131[f]
42	5-Tetrazolyl	H	209–210[g]	H_2O	90	$C_6H_5N_5$	4[d]	7[d]	10[d]
43	5-Tetrazolyl	OH	248–250	H_2O	70	$C_6H_5N_5O$	14[d]	19	14
44	CO_2H	Br	141–144[h]	$CHCl_3$	50	$C_6H_4BrNO_2$	3	9[f]	12[f]
45	CO_2Me	Br	34–36	Cyclohexane	93	$C_7H_6BrNO_2$			
46	CO_2Me	SMB	98–100	CCl_4	60	$C_{15}H_{15}NO_3S$	−8	−9	−14
47	CO_2Et	SMB	110–112	CCl_4	16	$C_{16}H_{17}NO_3S$			
48	CH_2OH	SMB	105–107	MeOH	50	$C_{14}H_{15}NO_2S$			
49	CN	SMB	97–99	MeOH	50	$C_{14}H_{14}N_2OS$			
50	5-Tetrazolyl	SMB	158–160	MeOH	70	$C_{14}H_{13}N_5OS$			
51	$CONH_2$	SMB	252	DMF–H_2O	95	$C_{14}H_{14}N_2O_2S$			
52	$COCH_3$	SMB	110–112	Chromatogr	75	$C_{15}H_{15}NO_2S$			
53	H	SMB	44–45	Et_2O–pet. ether	48	$C_{13}H_{13}NOS$			
54	H	SAc	123–125	Me_2CO	35	$C_7H_7NOS \cdot HCl$	−12	−6	−6
									
R									
4-CH_3	CO_2H	CO_2H	191[i]	EtOH–H_2O	65	$C_8H_7NO_4$	1	9[f]	8[d]
5-CH_3	CO_2H	CO_2H	185–187[j]	H_2O	50	$C_8H_7NO_4$	−1	6	5
6-CH_3	CO_2H	CO_2H	164–166[k]	EtOH–EtOAc	57	$C_8H_7NO_4$	13[e]	15[e]	17[f]
5-Cl	CO_2H	CO_2H	144–145[l]	H_2O	31	$C_7H_4ClNO_4$	17[e]	−2	−2
4-CH_3	Imide		238–239	HOAc	45	$C_8H_6N_2O_2$			
5-CH_3	Imide		145	HOAc	70	$C_8H_6N_2O_2$			
6-CH_3	Imide		242–244[m]		43	$C_8H_6N_2O_2$			
5-Cl	Imide		230	HOAc	53	$C_7H_3ClN_2O_2$			
4-CH_3	CO_2H	NH_2	224–226	MeOH	35	$C_7H_8N_2O_2$			
5-CH_3	CO_2H	NH_2	202–204	ErOH–H_2O	14	$C_7H_8N_2O_2$			
6-CH_3	CO_2H	NH_2	204–207[n]	EtOH–Me_2CO	22	$C_7H_8N_2O_2$			
5-Cl	CO_2H	NH_2	194–195	H_2O	38	$C_6H_5ClN_2O_2$			
H	CO_2H	NH_2					42[e]	62	Death
H	CO_2H	OH					−2	−1	4
H	CO_2H	CO_2H					−5[o]	−9[o]	−2[o]
H	CO_2H	H					−1[p]	−4[p]	4[p]

[a]Results are expressed as the per cent difference in milligram per cent between the mean change in control and treated groups after a drug dose of 300 mg/kg ip. [b]Lit. mp 192°: O. V. Schickh, A. Binz, and A. Schulz, *Chem. Ber.*, **69**, 2593 (1936). [c]Lit. mp 211–213°: F. W. Broekman, A. van Veldhuizen, and H. Jannsen, *Recl. Trav. Chim. Pays-Bas*, **81**, 792 (1962). DMSO used as a solvent and reaction heated on a steam bath for 2.5 hr. [d]$p < 0.05$. [e]$p < 0.001$. [f]$p < 0.01$. [g]Lit. mp 211–211.5°: J. M. McManus and R. M. Herbst, *J. Org. Chem.*, **24**, 1464 (1959). [h]Preparation was described by J. S. Paul and J. T. Sheehan, U. S. Patent 3,553,203 (Jan 5, 1971), but no melting point given. [i]Lit. mp 190°: M. P. Oparina, *Chem. Ber.*, **64**, 569 (1931). [j]Lit.[22] mp 181°. [k]Lit.[22] mp 164°. [l]Lit. mp 129–130°: J. C. Cochran and W. F. Little, *J. Org. Chem.*, **26**, 808 (1961). [m]Lit.[22] mp 244°. [n]Lit.[22] mp 205°. [o]Dose 668 mg/kg po. [p]Dose 150 mg/kg po.

BF_3 in MeOH/g of acid. The solution was cooled, the MeOH was evaporated, and the residue was dissolved in $CHCl_3$. The $CHCl_3$ was washed with 5% $NaHCO_3$ and H_2O, dried, and evaporated. This residue was recrystallized.

Methyl 5-bromonicotinate: yield 67%; mp 95–97° (MeOH–H_2O) (lit.[13] mp 98–99°).

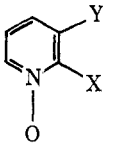
Methyl 6-chloropicolinate: yield 60%; mp 92–94° (H_2O). *Anal.* ($C_7H_6ClNO_2$) C, H, Cl, N.

Attempts to esterify 1 with alcohols and acid catalysis (HCl, H_2SO_4) or using the acid chloride of 1 led solely to the disulfide diesters. This contrasted with the findings of Portnyagina and Karp.[10]

Thioethers 16, 18, and 19. To 100 ml of 5% Na_2CO_3 and a cosolvent, if the Na salt of the thiol was insoluble, was added 5 g (0.04 mol) of Na_2CO_3 and 0.02 mol of mercaptan. The alkylating agent (0.022 mol) was added and the mixture was stirred 2 hr at room temperature under N_2. The cosolvent, if any, was evaporated and the aqueous residue was layered with $CHCl_3$. If the starting mercaptan was also an acid the aqueous phase was adjusted to pH 2–3 with dilute HCl. The layers were separated and the aqueous phase was extracted several times with $CHCl_3$. The organic phases were washed with H_2O, dried, and evaporated. The residue was collected and purified.

Acylation of Mercaptans 20 and 21. To a stirred solution of 0.015 mol of mercaptan and 2.3 g of $NaHCO_3$ in 25 ml of 5% $NaHCO_3$ (with a cosolvent if needed) was added a slight molar

Table IV. Pyridine *N*-Oxides



No.	X	Y	Mp, °C	Recrystn solvent	% yield	Formula	Hypoglycemic act. in the 48-hr fasted rat[a] 1 hr	2 hr	4 hr
55	CO_2Me	Br	124–126	C_6H_5Me	70	$C_7H_6BrNO_3$			
56	CO_2Me	SMB	141–143	CCl_4	33	$C_{15}H_{15}NO_4S$			
57	CO_2H	SMB	145	DMF–Et_2O	20	$C_{14}H_{13}NO_4S$			
58	H	SMB	144–146	MeCN	33	$C_{13}H_{13}NO_2S$			
59	H	SH	147–150	EtOH–Et_2O	40	$C_5H_5NOS \cdot HCl$	11[b]	−1	−1

[a]Results are expressed as the per cent difference in milligram per cent between the mean change in control and treated groups after a drug dose of 300 mg/kg ip. [b]$p < 0.05$.

excess of acylating agent. Stirring was continued under N_2 for 2–3 hr at room temperature. The product was isolated as described for the thioethers.

3-Acetylthiopicolinanilide (34). To a vigorously stirred, cooled solution of 1 g of **20** in 15 ml of CH_2Cl_2 was added 1 g of dicyclohexylcarbodiimide in 2 ml of CH_2Cl_2. The color of the solution turned from orange to yellow in *ca.* 15 sec whereupon 0.5 g of $C_6H_5NH_2$ in 1 ml of CH_2Cl_2 was added immediately. There was an immediate precipitate. Stirring was continued for 30 min and the dicyclohexylurea was filtered. The filtrate was diluted with EtOAc and washed with 5% HCl and H_2O. The organic phase was dried and distilled. The residue was recrystallized once from Et_2O and then from $CHCl_3$–hexane.

3-Mercaptopicolinanilide (33). A solution of 1.5 g (5.5 mmol) of **34** in 25 ml of 1:1 dioxane–concentrated HCl was stirred 2 days at room temperature. The solution was taken to dryness *in vacuo*. The residue was triturated with EtOH, filtered, washed with EtOH, and recrystallized.

(3-*p*-Methoxybenzylthio-2-pyridyl)methanol (48). To a stirred suspension of 22.4 g (0.077 mol) of **46** in 400 ml of MeOH was added 14 g (0.37 mol) of $NaBH_4$. The mixture was stirred under reflux for 1 hr (tlc showed unreacted **46**). An additional 7 g of $NaBH_4$ was added and then a further 7 g was added after a second hour of refluxing. The MeOH was removed and the residue was diluted with H_2O. The solids were filtered and contained a mixture of product and **46**. The mixture was stirred and heated on a steam bath for 1 hr with 200 ml of 10% NaOH. The solids were filtered and dissolved in $CHCl_3$. The $CHCl_3$ was washed with H_2O until neutral and the aqueous washes and filtrate were combined and acidified to give **19**. The $CHCl_3$ was dried and evaporated and the residue was recrystallized to give **48**.

Carbamic Acid Dimethylthio-*O*-3-pyridyl Esters 38–40. A solution of 3-hydroxypicolinic acid methyl ester[28] or amide[29] or **37**[29] (0.25 mol), 31 g of dimethylthiocarbamoyl chloride, 95 g of DABCO (triethylenediamine), and 300 ml of dry DMF was stirred at 25° for 4 hr. The solution was poured into H_2O and cooled. The solid was filtered, dried, and recrystallized.

The amide **40** was extracted into Et_2O and the Et_2O was washed with dilute HCl. Neutralization of the HCl extracts with solid Na_2CO_3 gave solid amide.

Carbamic Acid Dimethylthio-*S*-(2-cyano-3-pyridyl) Ester (41). **38** was added to a bath at 200–210°. After 15–30 min the melt was removed from the bath, cooled, and dissolved in hot C_6H_6 (Darco). The filtered solution was diluted with petroleum ether and cooled.

3-Mercaptopicolinonitrile (26). A solution of 3.4 g (0.017 mol) of **41** and 5 g of Na_2CO_3 in 20 ml of H_2O and 125 ml of MeOH was stirred and refluxed under N_2 for 20 hr. The MeOH was removed and the aqueous residue was acidified to pH 2. The easily oxidized solid was rapidly filtered, washed, and dried.

On standing the aqueous filtrate deposited the disulfide of **26**, mp 210–212° dec (DMF–H_2O). *Anal.* ($C_{12}H_6N_4S_2$) C, H, N, S.

Tetrazoles 42, 43, and 50. A mixture of 0.01 mol of picolinonitrile, 0.013 mol of NaN_3, 0.013 mol of NH_4Cl, and 14 mg of LiCl in 10 ml of dry DMF was stirred 20 hr under N_2 at 125°. The mixture was cooled and the DMF was removed *in vacuo*. The residue was triturated with H_2O at pH 2–3. The resulting solid was filtered, washed with H_2O, and dried.

Carbamic Acid Dimethylthio-*O*-[2-dimethylamino-1,3,4-thiadiazol-5-yl)-3-pyridyl] Ester. To a stirred, cooled solution of 1.7 g of **43** in 15 ml of dry DMF was added 3.7 g (0.05 mol) of DABCO and 3.1 g of dimethylthiocarbamoyl chloride. The solution was stirred 3 hr at room temperature and diluted with H_2O whose pH was adjusted to 2 with dilute HCl. The resulting gum was dissolved in $CHCl_3$ and the $CHCl_3$ was washed with H_2O, dried, and evaporated. The residual oil was triturated with Et_2O to produce a solid. The solid weighed 500 mg, mp 172–173° (MeOH). *Anal.* ($C_{12}H_{15}N_5OS_2$) C, H, N.

3-*p*-Methoxybenzylthiopicolinamide (51). A solution of 5.5 g (0.02 mol) of **19** in 200 ml of $CHCl_3$ (dried over $CaCl_2$) was stirred under reflux. $SOCl_2$ (20 ml) was added dropwise whereupon a precipitate formed. Continued heating caused the precipitate to dissolve. After 4.5 hr the solvents were removed. The residue was evaporated once with C_6H_5Me and dissolved in Me_2CO. The Me_2CO solution was added to cold aqueous NH_3. The precipitated amide was filtered, washed with H_2O, EtOH, and Et_2O, and recrystallized.

2-Acetyl-3-*p*-methoxybenzylthiopyridine (52). A suspension of 5.2 g (0.018 mol) of **19** in 100 ml of dry THF was warmed to effect solution. Then 45 ml of a 1.6 *M* solution of MeLi in Et_2O was added slowly with cooling. When the solution's color became deep brown the addition was halted. When the solution's color lightened the addition was started again. This operation was repeated until all of the MeLi was added. The mixture was left standing 1 hr at room temperature. Excess MeLi was decomposed with a saturated solution of NH_4Cl. The pH of the mixture was adjusted to *ca.* 8, the layers were separated, and the aqueous phase was extracted with Et_2O. The Et_2O was dried and evaporated to give 4.8 g of crude **52**. A portion of the product (2.8 g) was placed on a Florisil column. The column was washed with petroleum ether and petroleum ether–Et_2O (5:1 and 4:1). The product was eluted with the petroleum ether–Et_2O mixtures. Pure product (1.8 g) was recovered.

Methyl 3-Bromopicolinate *N*-Oxide (55). A solution of 0.05 mol of **45**, 0.075 mol of 85% *m*-chloroperbenzoic acid, and $CHCl_3$ was stirred under reflux for 20 hr. The solution was cooled, extracted well with 5% Na_2CO_3 and H_2O, dried, and taken to dryness. The residue was recrystallized.

Biochemistry. Hypoglycemic activity was measured in 48-hr fasted male rats weighting *ca.* 200 g. Glycogen reserves are depleted in these animals and they have elevated rates of gluconeogenesis. 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. The initial dose was usually 300 mg/kg ip. Subsequent testing, as indicated, was usually performed at a dose of 150 mg/kg po. Tail-vein blood samples were obtained at 1, 2, and 4 hr after drug administration and were analyzed for glucose by the potassium ferricyanide–potassium ferrocyanide oxidation–reduction reaction with a Technicon autoanalyzer. The results are expressed as the per cent difference in milligram per cent of blood glucose between the mean change in control and treated groups at 1, 2, and 4 hr after drug treatment.

These values are calculated by determining the mean differ-

ences in milligram per cent between zero-time samples and samples taken at 1, 2, and 4 hr in the control groups (ΔC) and in the treated groups (ΔT). $\Delta T - \Delta C$/control blood glucose value at that hour equals per cent changes (Tables I-IV). Normally the zero-time values are in the 55-65 mg per cent range.

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Adrenergic Agents. 2. Synthesis and Potential β-Adrenergic Agonist Activity of Some Ring-Chlorinated Relatives of Isoproterenol

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A series of 2-, 5-, and 6-chloro-substituted analogs of isoproterenol was prepared in an attempt to find potent and tissue selective bronchodilators with a prolonged duration of action. Compounds were examined for potential bronchodilator activity in an *in vitro* test for relaxation of the spontaneous tone of a guinea pig tracheal chain preparation. Potential cardiac stimulant activity was evaluated in a similar *in vitro* test which monitors changes in the rate of spontaneously beating guinea pig right atria. Substitution of the 2 position of isoproterenol and several derivatives bearing different N substituents generally resulted in compounds with greater tracheal muscle relaxant potency than their nonchlorinated counterparts; however, a high degree of tracheobronchial *vs.* cardiac tissue specificity was not observed. None of the 2-chloro derivatives demonstrated the *in vitro* specificity of clorprenaline, although all were more potent. Chlorination of the 2 position of isoproterenol did not alter the duration of bronchodilator activity. Thus, both this compound and the prototype had the same duration of effectiveness after subcutaneous administration of equiactive doses in a test for inhibition of acetylcholine-induced bronchospasm in guinea pigs. In all instances chlorination of position 5 or 6 of isoproterenol and several derivatives decreased β-adrenergic agonist potency as determined in the *in vitro* tests. A marked decrease in potency was also observed for some 5-chlorocatecholamines in which the meta OH was methylated and for similar para-methoxylated 6-chloro-substituted analogs.

The influence of additional aromatic substitution upon the biological activity of adrenergic catecholamines has been the subject of only limited study. A 6-OH analog **1a** of epinephrine induces release of norepinephrine in isolated mouse heart.[1] Sympathomimetic activity is claimed[2,3] for 5-hydroxynorepinephrine (**1b**) and several 5-acyloxy derivatives. Various 2-alkyl-, cycloalkyl-, and alkoxy-substituted catecholamines, *e.g.*, **1c** and **1d**, have been patented for their sympathomimetic and broncholytic actions.[4-6] The 2-, 5-, and 6-methyl and methoxyl derivatives of isoproterenol were only weakly active in a test for norepinephrine-releasing ability in mouse heart.[7]