in anhydrous THF (50 mL) was added dropwise to a stirred suspension of NaH (57% oil suspension, 5.13 g, 127 mmol) in THF (25 mL), and the mixture was heated under N_2 at 60 °C for 1 h, the reaction mixture was maintained at 60 °C overnight, and then evaporated under reduced pressure. The residue was dissolved in H_2O, and this solution was warmed to 40 °C, kept at ambient temperature for several hours, and washed with Et_2O. The aqueous phase was layered over hot $CHCl_3$, acidified with concentrated HCl, and stirred vigorously for 1 h. The $CHCl_3$ phase was separated and stripped on a rotavapor to give a 6:4 mixture (10 g) of **4f** (R_5 = H) and **5f** (R_6 = H), respectively: NMR (Me_2SO-d_6) δ 7.01 (s, 0.4 H, =CH).

This mixture was dissolved in MeOH (750 mL), saturated with dry HCl, refluxed overnight, and evaporated in vacuo. The residue was chromatographed on a column of silica gel packed in $CHCl_3$ to afford 7.5 g (56%) of **5f**: mp 133–134 °C ($CHCl_3$–Et_2O).

4-Oxo-4*H*,5*H*-[1]benzothiopyrano[4,3-*b*]pyran-2-carboxylic Acid Methyl Ester 6,6-Dioxide (5i). A solution of *m*-chloroperbenzoic acid (2.07 g, 12 mmol) in $CHCl_3$ (50 mL) was added dropwise to a stirred solution of **5b** (R_6 = Me; 1.37 g, 5 mmol) in $CHCl_3$ (50 mL) at 5 °C. The stirring was continued at room temperature for 4 h, and the reaction mixture was washed with aqueous $NaHCO_3$ and H_2O, dried, and evaporated to dryness. The residue was crystallized from $CHCl_3$–Et_2O: mp 212–214 °C; yield 1.03 g (67%).

General Synthesis of Carboxylic Acids 5b–i. The aforementioned procedure for the hydrolysis of **5a** (R_6 = Me) to the corresponding carboxylic acid **5a** (R_6 = H) was adopted for the preparation of **5b–i** from their methyl esters.

2-Hydroxyethylammonium salts of **5b–h** were obtained by adding methanolic 2-aminoethanol to a solution (or suspension) of the corresponding acid in MeOH.

General Synthesis of Carboxylic Acids 6b–g. 1,4-Dihydro-4-oxo-5*H*-[1]benzothiopyrano[4,3-*b*]pyridine-2-carboxylic Acid (6b). A solution of **5b** (R_6 = H; 3 g, 11.5 mmol) in concentrated ammonium hydroxide (50 mL) was heated on a steam bath for 2 h and evaporated in vacuo. The residue was dissolved in H_2O (75 mL) and added to a mixture of concentrated HCl (5 mL) and ice. The precipitate was collected by filtration and washed successively with 0.07 N HCl, acetone, and Et_2O to give 2.52 g (84%) of the title acid, mp 256–257 °C (Me_2SO–H_2O).

This acid was dissolved in a methanolic solution of 2-aminoethanol (0.6 g), the resulting solution was treated with charcoal and filtered, and the filtrate was evaporated. Crystallization of the residue from MeOH–Et_2O afforded the hydroxyethylammonium salt of **6b**, mp 158–161 °C.

1,4-Dihydro-9-(1-methylpropyl)-4-oxo-5*H*-[1]benzothiopyrano[4,3-*b*]pyridine-2-carboxylic Acid 6,6-Dioxide (6j). To a suspension of **6g** (1.33 g, 4.2 mmol) in 98% HCOOH (20 mL) was added 30% H_2O_2 (3.5 mL). The resulting solution (obtained within 10 min) was stirred at room temperature for 22 h and diluted with H_2O, and the precipitate was collected by filtration. Recrystallization from aqueous acetone afforded 0.98 g (67%) of **6j**, mp 263–264 °C.

3-Methyl-4-oxo-2-(1*H*-tetrazol-5-yl)-4*H*,5*H*-[1]benzothiopyrano[4,3-*b*]pyran (11). A solution of the nitrile **10**[22] (3.14 g, 12.3 mmol), NaN_3 (0.88 g, 12.3 mmol), and NH_4Cl (0.13 g, 2.4 mmol) in DMF (18 mL) was heated at 110 °C for 18 h and evaporated in vacuo. The residue was dissolved in H_2O (50 mL), washed with ethyl acetate, and acidified with 10% HCl. The precipitate was collected by filtration and recrystallized from aqueous acetone to give 2.5 g (62%) of **11**: mp 247–248 °C; NMR (Me_2SO-d_6) δ 2.31 (s, 3 H, CH_6), 3.88 (s, 2 H, CH_2), 7.25 (m, 3 H, H-7, H-8, H-9), 7.95 (m, 1 H, H-10), 11.1 (br, 1 H, NH). Anal. ($C_{14}H_{10}N_4O_2S$) C, H, N.

3-Methyl-4-oxo-2-(1*H*-tetrazol-5-yl)-4*H*,5*H*-[1]benzothiopyrano[4,3-*b*]pyran 6,6-Dioxide (12). Compound **11** (1.75 g, 5.9 mmol) was suspended in a solution of *m*-chloroperbenzoic acid (4 g, 23 mmol) in $CHCl_3$ (200 mL) and the mixture was stirred at ambient temperature for 22 h. The solids were collected by filtration and recrystallized from MeOH to give 1.54 g (80%) of **12**: mp 268–270 °C; NMR (Me_2SO-d_6) δ 2.40 (s, 3 H, CH_3), 4.72 (s, 2 H, CH_2), 8.03 (m, 3 H, H-7, H-8, H-9), 8.46 (m, 1 H, H-10), 10.96 (br, 1 H, NH). Anal. ($C_{14}H_{10}H_4O_4S$) C, H, N.

Passive Cutaneous Anaphylaxis (PCA) Test. Adult male Charles River rats (140–160 g, six rats per group) were sensitized at two sites with an intradermal injection (0.1 mL) of rat serum containing reaginic antibodies to chicken ovalbumin. After a 48-h latent period, the animals were challenged iv with 10 mg/kg of chicken ovalbumin dissolved in a 1% solution of Evans blue. Thirty minutes later, the rats were sacrificed and skinned. The area of the dermal bluing which occurred at the sites of sensitization was measured (ca 20-mm diameter spot in the control rats) and the results were used for calculation of the drug-induced percent inhibition of this effect. For iv administration, the test compounds (30, 10, and 3 mg/kg) were injected at the same time as the antigen challenge. When given ip and po, the compounds were administered 15 min prior to the challenge. The dose that inhibited the PCA by 50% (ID_{50}) was determined graphically from a dose–response curve for each compound. Disodium cromoglycate was tested at 9, 3, 1, and 0.3 mg/kg iv and at 60, 30, 15, 8, and 4 mg/kg ip.

Studies on Anticoccidial Agents. 13. Synthesis and Anticoccidial Activity of Nitropyridine-2- and -3-sulfonamides and Derivatives

Yasuhiro Morisawa,* Mitsuru Kataoka, Hitoshi Nagahori, Toshiaki Sakamoto, Noritoshi Kitano, Kenichi Kusano, and Kiyoshi Sato

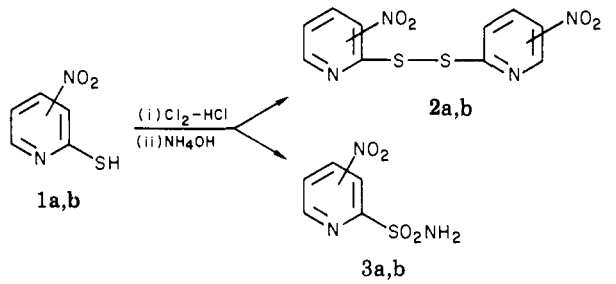
Central Research Laboratories, Sankyo Company, Ltd., Shinagawa-ku, Tokyo, Japan. *Received June 17, 1980*

Eight nitropyridinesulfonamides and pyridinesulfonamide *N*-oxides as their bioisosteres were prepared and evaluated for anticoccidial activity. Of these compounds, 2-, 4- and 5-nitropyridine-3-sulfonamides and pyridine-2- and -3-sulfonamide *N*-oxides were found to be active against *Eimeria tenella*. Thus, the relative positions, ortho or meta, of the substituents in nitropyridine-3-sulfonamides and pyridinesulfonamide *N*-oxides are important for anticoccidial activity. N-Substituted analogues of 5-nitropyridine-3-sulfonamide were also prepared and optimal anticoccidial activity was attained with the sulfonamide and its lower *N*-alkyl derivatives. The mode of action of 5-nitropyridine-3-sulfonamide was examined and found to be active in the sporozoite and the first schizogony stages.

In previous papers[1] we reported that some nitropyridinecarboxamides showed anticoccidial activity against *Eimeria tenella*. As a continuation of the study to evaluate various nitropyridine analogues, we have now synthesized

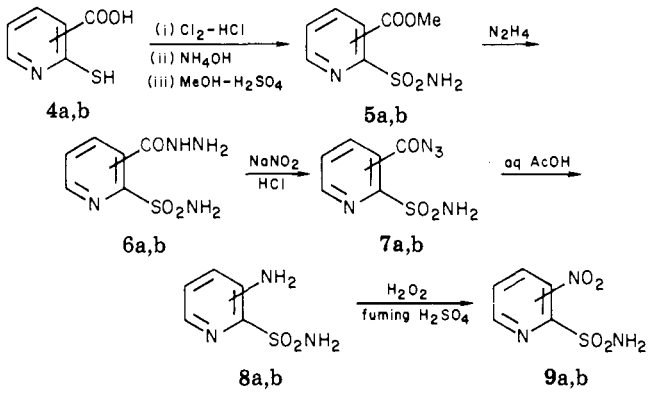
0022-2623/80/1823-1376$01.00/0

Scheme I



a, 5-NO_2; b, 3-NO_2

Scheme II

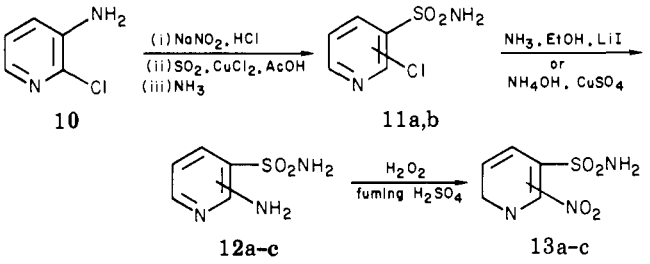


a, substituted at C_4; b, substituted at C_6

and evaluated some isomeric nitropyridine-2- and -3-sulfonamides, their derivatives, and pyridinesulfonamide *N*-oxides.

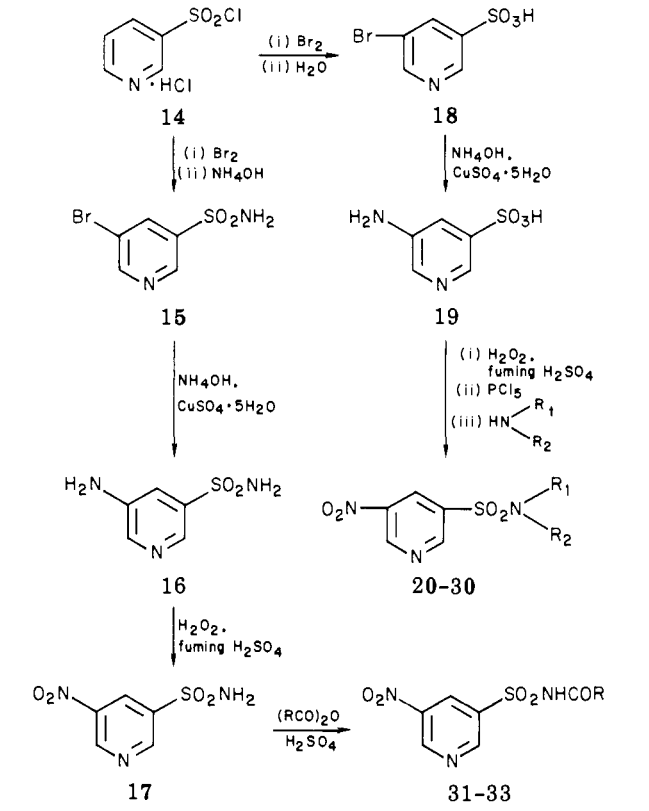
Chemistry. (A) Nitropyridine-2-sulfonamides. Caldwell et al.[2] reported that oxidation of 2-mercapto-5-nitropyridine (**1a**) with chlorine resulted in formation of 2-chloro-5-nitropyridine. However, if one applies the modified oxidation of Comrie et al.[3] and amidation, the 2-mercapto derivative **1a** could be converted to 5-nitropyridine-2-sulfonamide (**3a**), together with the disulfide **2a** (Scheme I). A similar transformation has been effected in the synthesis of 3-nitropyridine-2-sulfonamide (**3b**), along with disulfide **2b**, starting from 2-mercapto-3-nitropyridine (**1b**). For the synthesis of 4-nitropyridine-2-sulfonamide (**9a**), several attempts to prepare 2-mercapto-4-nitropyridine from 2-chloro-4-nitropyridine were unsuccessful, because of the labile NO_2 group: Treatment of 2-chloro-4-nitropyridine with thiourea in the presence of base or with $NaSH{\cdot}3H_2O$ in EtOH gave 2-chloro-4-ethoxypyridine.[4] Therefore, the unstable NO_2 function was introduced in the last step as shown in Scheme II. 2-Mercaptoisonicotinic acid (**4a**) was oxidized with Cl_2 to the corresponding sulfonyl chloride, which was then amidated and esterified to give 2-sulfamoylisonicotinate (**5a**). Curtius reaction of the methyl ester **5a** through its hydrazide (**6a**) and azide (**7a**) gave 4-aminopyridine-2-sulfonamide (**8a**), which was oxidized with H_2O_2 and fuming H_2SO_4 to 4-nitropyridine-2-sulfonamide (**9a**). A similar synthetic approach was conducted for the preparation of 6-nitropyridine-2-sulfonamide (**9b**).

Scheme III



a, substituted at C_2; b, substituted at C_4; c, substituted at C_6

Scheme IV



(B) Nitropyridine-3-sulfonamides. 2-Nitropyridine-3-sulfonamide (**13a**) was prepared from 3-amino-2-chloropyridine (**10**) as shown in Scheme III. Diazotization of **10**, followed by sulfonation[5] with SO_2 in AcOH in the presence of $CuCl_2$ and amidation, produced 2-chloropyridine-3-sulfonamide (**11a**), which had already been synthesized by Thunus[6] using a different route. Heating **11a** in a sealed tube with alcoholic ammonia in the presence of LiI gave **12a**, which was converted to **13a** by oxidation. In a similar manner, 4-nitropyridine-3-sulfonamide (**13b**) was prepared from 4-chloropyridine-3-sulfonamide (**11b**),[7] and 6-nitropyridine-3-sulfonamide (**13c**) was prepared from 6-aminopyridine-3-sulfonamide (**12c**).[8] The synthesis of 5-nitropyridine-3-sulfonamide (**17**) is outlined in Scheme IV. By an adaptation of the procedure previously described by Bachman[9] for the preparation of

(1) (a) Y. Morisawa, M. Kataoka, N. Kitano, and T. Matsuzawa, *J. Med. Chem.*, **20**, 129 (1977); (b) Y. Morisawa, M. Kataoka and N. Kitano, *ibid.*, **20**, 483 (1977); (c) Y. Morisawa, M. Kataoka, T. Sakamoto, H. Nagahori, N. Kitano, and K. Kusano, *ibid.*, **21**, 194 (1978).
(2) W. T. Caldwell and E. C. Kornfeld, *J. Am. Chem. Soc.*, **64**, 1695 (1942).
(3) A. M. Comrie and J. B. Stenlake, *J. Chem. Soc.*, 3514 (1958).
(4) Z. Talik, *Rocz. Chem.*, **36**, 1313 (1962).
(5) H. Meerwein, G. Dittmar, R. Göllner, K. Hafner, F. Mensch, and O. Steinfort, *Chem. Ber.*, **90**, 841 (1957).
(6) L. Thunus, *Ann. Pharm. Fr.*, **32**, 377 (1974); *Chem. Abstr.*, **82**, 72937*b* (1975).
(7) J. Delarge, *Ann. Pharm. Fr.*, **31**, 467 (1973); *Chem. Abstr.*, **80**, 59828*f* (1974).
(8) C. Naegeli, W. Kündig, and H. Brandenburger, *Helv. Chim. Acta*, **21**, 1746 (1938).

Table I. Anticoccidial Activity of Nitropyridinesulfonamides

compd	position of SO_2NH_2	position of NO_2	concn of drug in feed, %	ACI[a]
3a	2	5	0.015	32
3b	2	3	0.015	55
9a	2	4	0.015	107
9b	2	6	0.015	120
13a	3	2	0.015	144
13b	3	4	0.015	144
13c	3	6	0.015	120
17	3	5	0.015	194
17	3	5	0.007	195
17	3	5	0.0035	194
17	3	5	0.00175	158
5-nitronicotinamide			0.015	198
			0.007	186
			0.0035	158
1-[(4-amino-2-*n*-propyl-5-*pyrimidinyl*)*methyl*]-2-picolinium chloride hydrochloride			0.015	95

[a] ACI = percent survival + percent relative weight gain − lesion score − oocyst score.

Table II. Anticoccidial Activity of Pyridinesulfonamide *N*-Oxides

no.	position of SO_2NH_2	concn of drug in feed, %	ACI[a]
34	2	0.015	183
35	3	0.015	160
36	4	0.015	120

[a] See Table I, footnote *a*.

5-bromonicotinic acid from nicotinoyl chloride, pyridine-3-sulfonyl chloride (**14**) was brominated and then amidated to produce 5-bromopyridine-3-sulfonamide (**15**). Treatment of **15** with NH_4OH at 170 °C in the presence of $CuSO_4$ gave the 5-amino derivative **16**. Usual oxidation of **16** with H_2O_2 and fuming H_2SO_4 produced **17**.

(C) **5-Nitropyridine-3-sulfonamide Derivatives and Pyridinesulfonamide *N*-Oxides.** In order to examine the effect of changes in the sulfonamide side chain on the anticoccidial activity, some N-substituted derivatives of **17** were prepared as shown in Scheme IV. *N*-Alkyl, *N*-(alkoxyalkyl), *N*-benzyl, and *N*-phenyl derivatives were obtained from the corresponding aminosulfonic acid **19** by oxidation, chlorination, and treatment with the appropriate amines. *N*-Alkanoyl groups were introduced into the sulfonamide function of **17** with acid anhydride containing a trace of H_2SO_4. As the bioisosteres of nitropyridinesulfonamides, three isomeric pyridinesulfonamide *N*-oxides, **34–36**, were prepared from the corresponding sulfonamides by the usual method.[10]

Biological Results. The compounds listed in Tables I–III were tested for *E. tenella* using the 1-[(4-amino-2-*n*-propyl-5-pyrimidinyl)methyl]-2-picolinium chloride hydrochloride (Amprolium) resistant strain by the procedure described in a preceding paper,[11] and the results were compared with that of the parent 5-nitronicotinamide. For an ACI above 180, the anticoccidial activity was determined as excellent, 180–160 as marked, 160–140 as moderate, 140–120 as slight, and below 120 as inactive.

Among eight isomeric nitropyridinesulfonamides, 2-, 4- and 5-nitropyridine-3-sulfonamides were active, especially the last compound which exhibited very high activity even at a relatively low screening dose (35 ppm) and showed greater potency than the parent compound, 5-nitronicotinamide (Table I). Three isomeric pyridinesulfonamide *N*-oxides as the bioisostere were also evaluated, and the 2- and 3-sulfonamides **34** and **35** showed excellent and moderate activity, respectively. Thus, the relative positions of the substituents, ortho or meta, in nitropyridine-3-sulfonamides and pyridinesulfonamide *N*-oxides are important for activity.

N-Monosubstitution of **17** with lower alkyl or alkoxyalkyl groups (**20**, **21**, **24**, and **25**) was found to retain the same level of activity as the unsubstituted parent compound **17**; N-acylation of **17** (**31** and **32**) also essentially maintained significant activity, but with higher alkyl (**22**), hydroxyethyl (**23**), and benzyl (**27**) groups activity was considerably decreased. *N,N*-Disubstitution (**28–30**) diminshed the activity, while substitution by a phenyl group (**26**) almost canceled the activity. Thus, among the compounds herein, optimal anticoccidial activity was attained in 5-nitropyridine-3-sulfonamide (**17**) and its lower *N*-alkyl derivatives.

In order to investigate the mode of action of the compound, the activity of **17** in several development stages of *E. tenella* was examined. Ten-day-old chicks were inoculated with 50 000 sporulated oocysts of *E. tenella*. Infected groups were medicated through feed with 5-nitropyridine-3-sulfonamide (70 ppm) for various periods as shown in Table IV. No incidence of oocysts appeared in group 1 and 2, and lesion score was reduced in groups 1–3. These results indicate that 5-nitropyridine-3-sulfonamide is active in the sporozoite and the first schizogony stages.

Experimental Section

Melting points are uncorrected. IR and NMR were determined on a Perkin-Elmer 221 and a Varian A-60. Spectral data were consistent with the assigned structures. Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within 0.3% of the theoretical values.

5-Nitropyridine-2-sulfonamide (**3a**). 2-Mercapto-5-nitropyridine[12] (**1a**; 2.0 g, 12 mmol) in concentrated HCl (10 mL) and H_2O (2.5 mL), cooled to −20 °C, was chlorinated at such a rate as to keep the temperature at −15 to −25 °C. After 15 min, the mixture was added to concentrated NH_4OH at −20 °C, kept at room temperature for 3 h, and extracted with EtOAc. The extract was dried and the solvent was removed to give a syrupy residue (1.24 g), which was chromatographed over silica gel, eluting with *n*-hexane–EtOAc (3:2). The first eluate yielded **2a** (0.65 g, 16.4%), mp 158–160 °C, on recrystallization from *n*-hexane–EtOAc. Anal. ($C_{10}H_6N_4O_4S_2$) C, H, N, S. The second eluate gave **3a** (0.12 g, 4.6%), mp 188–189 °C from *n*-hexane–EtOAc. Anal. ($C_5H_5N_3O_4S$) C, H, N, S.

3-Nitropyridine-2-sulfonamide (**3b**). By a similar method described above, **1b**[13] (1.56 g, 10 mmol) was converted to the disulfide **2b** (0.06 g, 1.9%) and the sulfonamide **3b** (0.30 g, 15.0%). **2b**: mp 238–240 °C dec from *n*-hexane–EtOAc. Anal. ($C_{10}H_6N_4O_4S_2$) C, H, N, S. **3b**: mp 153–154 °C from *n*-hexane–EtOAc. Anal. ($C_5H_5N_3O_4S$) C, H, N, S.

Methyl 2-Sulfamoylisonicotinate (**5a**). 2-Mercaptoisonicotinic acid[14] (**4a**; 15.5 g, 0.1 mol) in concentrated HCl (126 mL) and H_2O (28 mL) was chlorinated for 2 h, keeping the temperature below 5 °C. The mixture was poured onto ice (300 g), and the crystalline sulfonyl chloride which separated was filtered, added to cooled concentrated NH_4OH (300 mL), and stirred for 1 h. The

(9) G. B. Bachman and D. D. Micucci, *J. Am. Chem. Soc.*, **70**, 2381 (1948).
(10) T. Naito and R. Dohmori, *Chem. Pharm. Bull.*, **3**, 38 (1955).
(11) Y. Morisawa, M. Kataoka, J. Watanabe, N. Kitano, and T. Matsuzawa, *J. Med. Chem.*, **17**, 1083 (1974).
(12) A. R. Surrey and H. G. Lindwall, *J. Am. Chem. Soc.*, **62**, 1697 (1940).
(13) H. Saikachi, *Yakugaku Zasshi*, **64**, 201 (1944); *Chem. Abstr.*, **45**, 4717*b* (1951).

Table III. Physical Properties and Anticoccidial Activity of N-Substituted 5-Nitropyridine-3-sulfonamide

no.	R_1	R_2	method	mp, °C	recrystn solvent	yield, %	formula	ACI[a]
20	H	Me	C	136-137	EtOAc-hexane	10.3	$C_6H_7N_3O_4S$	195
21	H	Et	C	117-118	EtOAc-hexane	10.2	$C_7H_9N_3O_4S$	190
22	H	*n*-C_8H_{17}	C	194-196	EtOAc-hexane	14.1	$C_{13}H_{21}N_3O_4S$	126
23	H	CH_2CH_2OH	C	105-107	EtOAc-hexane	8.1	$C_7H_9N_3O_5S$	120
24	H	CH_2CH_2OEt	C	72-73	EtOAc-hexane	7.9	$C_9H_{13}N_3O_5S$	192
25	H	$(CH_2)_3OC_3H_7$-*i*	C	71-73	EtOAc-hexane	24.5	$C_{11}H_{17}N_3O_5S$	193
26	H	Ph	C	140-142	EtOAc-hexane	26.3	$C_{11}H_9N_3O_4S$	86
27	H	CH_2Ph	C	130-132	EtOAc-hexane	27.8	$C_{12}H_{11}N_3O_4S$	168
28	Me	Me	C	159-160	EtOAc-hexane	10.4	$C_7H_9N_3O_4S$	175
29	Et	CH_2CH_2OEt	C	69-70	EtOAc-hexane	8.3	$C_{11}H_{17}N_3O_5S$	178
30	Et	*n*-C_4H_9	C	67-69	EtOAc-hexane	23.1	$C_{11}H_{17}N_3O_4S$	175
31	H	COMe	D	176-178	EtOH	43.3	$C_7H_7N_3O_5S$	186
32	H	COC_7H_{15}	D	103-105	EtOH	67.3	$C_{13}H_{19}N_3O_5S$	187
33	H	$COCMe_3$	D	145-147	EtOH	49.4	$C_{10}H_{13}N_3O_5S$	122

[a] See Table I, footnote *a*. The concentration of the drugs in feed was 0.015%.

Table IV. Mode of Action of 5-Nitropyridine-3-sulfonamides on *E. tenella* Infection in Chicks (30 ppm)[a]

group no.	unmedicated period after inoculation, days	medicated period, days	rel wt gain	mortality	rel oocyst prodn	mean lesion score of cecum
1	0	7	86.4	0	0	0.4
2	1	6	80.1	0	0	0.4
3	2	5	63.7	0	1.9	3.0
4	3	4	45.2	0	17.1	3.2
5	4	3	38.8	20	12.4	3.6
6	5	2	35.2	20	17.1	3.4
infected unmedicated control			36.1	20	100	3.8
uninfected unmedicated control			100	0	0	0

[a] Five birds per group.

reaction mixture was acidified to pH 3.0 with 6 N HCl, and the solvent was removed in vacuo to dryness. The residue was extracted with hot EtOH, and the crude 2-sulfamoylisonicotinic acid obtained was esterified with H_2SO_4 (20 mL) and MeOH (300 mL) under reflux for 5 h. After MeOH was removed, the residue was diluted with cold H_2O, neutralized with $NaHCO_3$, and extracted with EtOAc. The solid residue, after evaporation of the solvent, was recrystallized from petroleum ether and EtOAc to give **5a** (12.3 g, 56.9%), mp 140–142 °C. Anal. ($C_7H_8N_2O_4S$) C, H, N, S.

Methyl 2-Sulfamoylpyridine-6-carboxylate (5b). By a similar method to that described above, **5b** was prepared from **4b**[14] in 23.0% yield: mp 177–179 °C (EtOAc–petroleum ether). Anal. ($C_7H_8N_2O_4S$) C, H, N, S.

2-Sulfamoylisonicotinohydrazide (6a). A mixture of the ester (**5a**; 12.3 g, 0.057 mol) and 80% $N_2H_4 \cdot H_2O$ (123 mL) in MeOH (195 mL) was refluxed for 1 h and concentrated into a small volume. Addition of EtOAc yielded **6a** (8.9 g, 72.4%), mp 196–198 °C. Anal. ($C_6H_8N_4O_3S$) C, H, N, S.

2-Sulfamoylpyridine-6-carbohydrazide (6b). This compound was similarly prepared from **5b** in 65.9% yield: mp 214–216 °C (EtOH–EtOAc). Anal. ($C_6H_8N_4O_3S$) C, H, N, S.

2-Sulfamoylisonicotinoyl Azide (7a). A solution of $NaNO_2$ (0.22 g, 3.2 mmol) in H_2O (1.1 mL) was added dropwise below 5 °C to a solution of **6a** (0.44 g, 2.1 mmol) in 1 N HCl (4.4 mL) and stirred for 1 h to give **7a** (0.346 g, 74.0%), mp 126–127 °C. Anal. ($C_6H_5N_5O_3S$) C, H, N, S.

2-Sulfamoylpyridine-6-carboxyazide (7b). This compound was prepared from **6b** in 73.3% yield by a similar method: mp 132–134 °C. Anal. ($C_6H_5N_5O_3S$) C, H, N, S.

4-Aminopyridine-2-sulfonamide (8a). A solution of **7a** (0.313 g, 1.4 mmol) in 50% aqueous AcOH (5.5 mL) was heated at 95 °C for 1 h. After cooling, the solution was given a pH 7–8 with aqueous NaOH and extracted with EtOAc. The extract was dried and the solvent removed to leave a crystalline residue, which was recrystallized from petroleum ether–EtOAc to give a pure product **8a** (0.11 g, 46.1%), mp 235–237 °C. Anal. ($C_5H_7N_3O_2S$) C, H, N, S.

6-Aminopyridine-2-sulfonamide (8b). By a similar method described above, **8b** was prepared from **7b** in 77.7% yield, mp 166–168 °C (EtOAc–hexane). Anal. ($C_5H_7N_3O_2S$) C, H, N, S.

4-Nitropyridine-2-sulfonamide (9a). Method A. A solution of **8a** (0.5 g, 2.9 mmol) in concentrated H_2SO_4 (1.3 mL) was added dropwise at 0 °C to a mixture of fuming H_2SO_4 (6 mL) and 35% H_2O_2 (3 mL). The mixture was stirred at 15–18 °C for 30 h, poured into ice–water, neutralized with NH_4OH, and extracted with EtOAc. The extract was washed with H_2O and dried, and the solvent was removed to give a crystalline residue, which was recrystallized from petroleum ether and EtOAc to give **9a** (0.308 g, 52.3%), mp 121–122 °C. Anal. ($C_5H_5N_3O_4S$) C, H, N, S.

6-Nitropyridine-2-sulfonamide (9b). This material was similarly prepared from **8b** in 34.1% yield: mp 206–208 °C (EtOAc–petroleum ether). Anal. ($C_5H_5N_3O_4S$) C, H, N, S.

2-Chloropyridine-3-sulfonamide (11a). A diazonium salt solution of 3-amino-2-chloropyridine (**10**; 19.25 g, 0.15 mol) in concentrated HCl (50 mL) and an aqueous solution (18 mL) of $NaNO_2$ (11.4 g, 0.165 mol) was added at 15–30 °C to a solution of 30% SO_2 containing $CuCl_2 \cdot 2H_2O$ (6 g) in AcOH (120 mL). After 10 min, the mixture was poured into ice–water and extracted with $CHCl_3$. The extract was washed with water, dried, and then, under cooling, saturated with NH_3. After 16 h, the crystalline product deposited was separated and recrystallized from EtOAc to give **11a** (9.25 g, 32.1%), mp 189–190 °C (lit. mp 187–188 °C). Anal. ($C_5H_5ClN_2O_2S$) C, H, N, Cl, S.

2-Aminopyridine-3-sulfonamide (12a). Method B. A mixture of **11a** (6.6 g, 34.3 mmol) and LiI (2.64 g, 19.7 mmol) in EtOH (100 mL) containing 10% NH_3 was heated at 115 °C for 40 h. The residue after removal of the solvent was dissolved in EtOAc and chromatographed over silica gel, eluting with benzene–EtOAc–EtOH (8:8:1), to give the starting material recovered (12.0 g, 18.2%) and **11a** (3.5 g, 72%), mp 176–177 °C on recrystallization from EtOAc. Anal. ($C_5H_7N_3O_2S$) C, H, N, S.

2-Nitropyridine-3-sulfonamide (13a). This material was prepared from **12a** in 31.0% yield by method A, mp 152–153 °C (benzene–EtOAc). Anal. ($C_5H_5N_3O_4S$) C, H, N, S.

4-Aminopyridine-3-sulfonamide (12b) was prepared from **11b**[7] in 50% yield by method B, mp 213–215 °C (H_2O). Anal. ($C_5H_7N_3O_2S$) C, H, N, S.

(14) J. Delarge, *Farmaco, Ed. Sci.*, **22**, 1069 (1967); *Chem. Abstr.*, **69**, 2830*u* (1968).
(15) F. E. Reinhart, *J. Franklin Inst.*, **236**, 316 (1943); *Chem. Abstr.*, **37**, 6652*g* (1943).

4-Nitropyridine-3-sulfonamide (13b) was prepared from 12b by method A in 7% yield, mp 150 °C dec. Anal. ($C_5H_5N_3O_4S$) C, H, N.

6-Nitropyridine-3-sulfonamide (13c) was prepared from 12c[8] by method A in 6% yield, mp 172–173 °C. Anal. ($C_5H_5N_3O_4S$) C, H, N.

5-Bromopyridine-3-sulfonamide (15). A mixture of 14[15] (2.14 g, 10 mmol) and Br_2 (1.92 g, 12 mmol) was heated at 130 °C for 8 h, cooled, and added portionwise to 20% NH_4OH (30 mL) under stirring. After 1 h, the solution was saturated with NaCl and extracted with EtOAc. The extract was washed with NaCl-saturated aqueous solution, dried, and evaporated to give 15 (1.54 g, 65.0%), mp 178–179 °C on recrystallization from petroleum ether and EtOH. Anal. ($C_5H_5BrN_2O_2S$) C, H, Br, N.

5-Aminopyridine-3-sulfonamide (16). A mixture of 15 (2.4 g, 10.1 mmol) and $CuSO_4 \cdot 5H_2O$ (0.005 g) in concentrated NH_4OH (4.8 mL) was heated at 170 °C for 5 h, cooled, treated with Na_2S, and extracted with EtOAc. The extract was dried and evaporated, and the residue was recrystallized from *n*-hexane and EtOH to give 16 (1.07 g, 61.5%), mp 177–179 °C. Anal. ($C_5H_7N_3O_2S$) C, H, N, S.

5-Nitropyridine-3-sulfonamide (17). This compound was prepared from 16 in 76.5% yield by method A, mp 182–183 °C. Anal. ($C_5H_5N_3O_4S$) C, H, N, S.

5-Bromopyridine-3-sulfonic Acid (18). A mixture of 14 (12.0 g, 56.1 mmol) and Br_2 (10.8 g, 67.5 mmol) was heated at 130 °C for 8 h, cooled, diluted with H_2O (150 mL), and heated again at 80–90 °C for 1.5 h. The reaction mixture was concentrated into a small volume and diluted with acetone to give 18 (13 g, 97.4%). Recrystallization from H_2O gave analytically pure product: mp >300 °C; NMR (DMF-d_7) δ 9.0 (1 H, d, J = 1.5 Hz), 8.90 (1 H, d, J = 2.0 Hz), 8.42 (1 H, dd, J = 1.5 and 2.0 Hz). Anal. ($C_5H_4BrNO_3S$) C, H, N, Br.

5-Aminopyridine-3-sulfonic Acid (19). A suspension of 18 (75.4 g, 0.32 mol) in concentrated NH_4OH (170 mL) containing $CuSO_4 \cdot 5H_2O$ (8 g, 0.032 mol) was heated at 170 °C in a sealed tube for 20 h, cooled, and treated with Na_2S. After the CuS was separated, the filtrate was concentrated and acidified with HCl (pH 2) to give the product (47.0 g, 85.3%). Recrystallization from aqueous EtOH gave an analytically pure sample, mp >300 °C. Anal. ($C_5H_6N_2O_3S$) C, H, N, S.

***N*-Ethyl-5-nitropyridine-3-sulfonamide** (21). **Method C.** A solution of 19 (20 g, 0.115 mol) in concentrated H_2SO_4 (50 mL) was added dropwise below 10 °C to a mixed solution of 30% fuming H_2SO_4 (200 mL) and 30% H_2O_2 (100 mL), and stirring was continued at room temperature for 40 h. The mixture was poured into ice–water, neutralized with Na_2CO_3, and again acidified with HCl (pH 1.5). The solution was concentrated to leave a syrupy residue, which gave a powdered product by addition of acetone. The crystalline compound that separated was extracted with MeOH. The extract was concentrated to a small volume, and addition of acetone produced crude 5-nitropyridine-3-sulfonic acid (18 g, 76.9%), which was used in the next step without purification.

A mixture of the acid (2.0 g, 9.8 mmol), PCl_5 (2 g), and $POCl_3$ (60 mL) was stirred under reflux for 6 h and concentrated to dryness. The residual oil was crystallized by stirring in $CHCl_3$. The precipitate formed was filtered and added under cooling to 20% aqueous ethylamine (4.4 g, 19.6 mmol). The mixture was stirred at room temperature for 1 h, diluted with H_2O, and extracted with EtOAc. The extract was washed with H_2O, dried, and evaporated to afford an oil, which was purified by silica gel chromatography, eluting with EtOAc, and recrystallized from *n*-hexane and EtOAc to give 21 (0.23 g, 10.2%), mp 117–118 °C. Anal. ($C_7H_9N_3O_4S$) C, H, N, S.

***N*-Octanoyl-5-nitropyridine-3-sulfonamide** (32). **Method D.** *A mixture of 17 (1 g, 4.9 mmol), octanoic anhydride (3.5 mL),* and 3 drops of concentrated H_2SO_4 was stirred at 90 °C for 1 h to separate a crystalline product. After *n*-hexane was added, the precipitate that deposited was collected by filtration and recrystallized from *n*-hexane and EtOAc to give 32 (1.09 g, 67.3%), mp 103–105 °C. Anal. ($C_{13}H_{19}N_3O_5S$) C, H, N, S.

Pyridine-3-sulfonamide *N*-Oxide (35). A solution of pyridine-3-sulfonamide (0.5 g, 3.2 mmol) in 40% peracetic acid (4 mL) was stirred at 80 °C for 1.5 h. The solution was concentrated to dryness in vacuo to leave an oil, which was crystallized from EtOH to give 35 (0.37 g, 67.3%), mp 167–170 °C. Anal. ($C_5H_6N_2O_3S$) C, H, N, S.

Pyridine-4-sulfonamide *N*-Oxide (36). This compound was similarly prepared from pyridine-4-sulfonamide in 57.6% yield, mp 233 °C. Anal. ($C_5H_6N_2O_3S$) C, H, N, S.

Acknowledgment. We express our gratitude to Dr. K. Murayama, Director of these Laboratories, to Dr. N. Soma and Dr. A. Ogiso, Assistant Directors, and to Dr. I. Kawamoto for the encouragement and discussions.

7-(Aminoacyl) and 7-(Aminoalkyl) Derivatives of 1,2,6,7-Tetrahydroindolo[1,7-*ab*][1,5]benzodiazepines as Potential Antidepressant Agents[1]

Edward J. Glamkowski,* James M. Fortunato,

Chemical Research Department

and Harry M. Geyer III

Department of Biological Sciences, Hoechst-Roussel Pharmaceuticals Inc., Somerville, New Jersey 08876.
Received June 2, 1980

The synthesis of 7-(aminoacyl) and 7-(aminoalkyl) derivatives of 1,2,6,7-tetrahydroindolo[1,7-*ab*][1,5]benzodiazepines is described. These compounds were evaluated for antidepressant activity by their ability to inhibit tetrabenazine-induced ptosis in mice. Many compounds were found to be active in this animal model, and structure-activity relationships are discussed. Two analogues in particular, one from the 7-(aminoacyl) series (13) and one from the 7-(aminoalkyl) series (26), were of comparable potency to the antidepressant drugs desipramine and amitriptyline.

The benzodiazepines as a class have provided many useful psychotherapeutic agents, particularly for the treatment of anxiety and sleep disorders. Yet little has been reported on benzo- and dibenzodiazepines with antidepressant properties.[2] We recently described the

(1) Presented in part at the American Chemical Society/Chemical Society of Japan Chemical Congress. See "Abstracts of Papers", ACS/CSJ Chemical Congress, Honolulu, HI, Apr 2–6, 1979; American Chemical Society: Washington, D.C., 1979; Abstr MEDI 9.

(2) (a) Hunziker, F.; Künzle F.; Schmutz, J. *Helv. Chim. Acta* **1966**, *49*, 244, and references therein. (b) Monro, A. M.; Quinton, R. M.; Wrigley, T. I. *J. Med. Chem.* **1963**, *6*, 255. (c) Nose, T.; Kowa, Y. *Jpn. J. Pharmacol.* **1970**, *21*, 47.

0022-2623/80/1823-1380$01.00/0