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Registry No. 2, 85803-58-3; 2 maleate, 85803-59-4; 3, 85803-57-2; 4, 85803-52-7; 4 maleate, 85803-53-8; 5, 85803-49-2; 6, 85803-50-5; 6 maleate, 85803-51-6; 7, 57598-33-1; 8, 85803-54-9; 9a, 85803-62-9; 9b, 85803-63-0; 10, 85803-55-0; 10 maleate, 85803-56-1; 12, 85803-60-7; 12 fumarate, 85803-61-8; 13, 85803-66-3; 14, 58255-18-8; 15, 85803-64-1; 16, 85803-65-2; 17, 85803-67-4; 2-thienylglyoxal, 51445-63-7; ethylenediamine, 107-15-3; *N*-methylpiperazine, 109-01-3; 2-fluorobenzaldehyde, 446-52-6; 2-fluorobenzonitrile, 394-47-8.

Synthesis and Antibacterial Activity of Some 3-[(Alkylthio)methyl]quinoxaline 1-Oxide Derivatives

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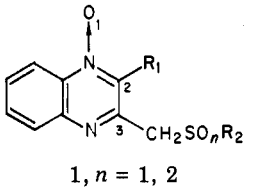
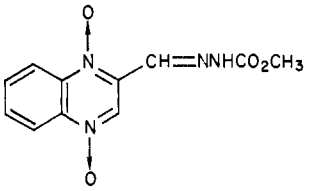
Some 3-[(alkylthio)methyl]quinoxaline 1-oxide derivatives (1) have been synthesized and screened for antibacterial activity. 2-Acetyl-3-[(methylsulfonyl)methyl]quinoxaline 1-oxide (**7a**) was found to possess good in vitro activity against some pathogens important to veterinary medicine including *Treponema hyodysenteriae*, a causative agent in swine dysentery. In an in vivo experiment, this compound (**7a**) completely protected pigs against a swine dysentery challenge over a 21-day period.

A wide variety of quinoxaline 1,4-dioxides have been described of value as antibacterial agents, animal growth promotants, and as agents for improving feed efficiency of animals.[1-3] Although a number of reports deal with the chemistry of quinoxaline 1-oxides,[4] only a few describe useful in vitro antibacterial activity.[5] Furthermore, to our knowledge, no quinoxaline 1-oxides have been reported with in vivo antibacterial activity. This paper describes the synthesis of certain 3-[(alkylthio)methyl]quinoxaline 1-oxide derivatives (1) having in vitro antibacterial activity against some pathogens important to veterinary medicine, i.e., *Escherichia coli*, *Pasteurella multocida*, *Salmonella choleraesuis*, and *Treponema hyodysenteriae*, as well as in vivo activity against swine dysentery.



1, n = 1, 2



2 (carbadox)

Synthesis. Until recently there were few methods available for the selective synthesis of suitable 2,3-disubstituted quinoxaline 1-oxide precursors required for this study, but it has been demonstrated in these laboratories that certain quinoxaline 1,4-dioxides bearing an electron-withdrawing group in the 2-position can be selectively monodeoxygenated to afford good yields of the desired starting materials.[6] In particular, the 3-[(alkylthio)-methyl]quinoxaline 1-oxide compounds (1) were prepared in the manner shown in Scheme I. Several 2-substituted 3-methylquinoxaline 1-oxides (**3a–c**)[6] were converted to the corresponding 3-bromomethyl derivatives (**4a–c**) via bromination with bromine–methanol. Alternatively, the chloromethyl intermediate **4d** was obtained from a 3-methylquinoxaline 1,4-dioxide by selective deoxygenation and simultaneous chlorination of the methyl group with *p*-toluenesulfonyl chloride.[7] Various alkylthio side chains were added to intermediate **4** to afford **5** by procedures developed previously for the synthesis of 2(3)-[(alkylthio)methyl]quinoxaline 1,4-dioxides (method A).[8] Oxidation of the sulfur with 1 or 2 equiv of *m*-chloroperbenzoic acid (MCPBA), method B or C, gave rise to the corresponding sulfoxides **6** or sulfones **7**, respectively. Alternatively, **7** could be synthesized from **4** in a one-step process by a displacement reaction[9] with sodium alkylsulfinates (method D). The aminolysis[8] of **6** or **7**, where $R_1 = CO_2CH_3$, allowed the synthesis of some carboxamides ($R_1 = CONH_2$, $CONHCH_3$; method E). The deacylation of **6** or **7**, where $R_1 = COCH_3$, afforded analogues unsubstituted in the 2-position (R_1 = H; method F).

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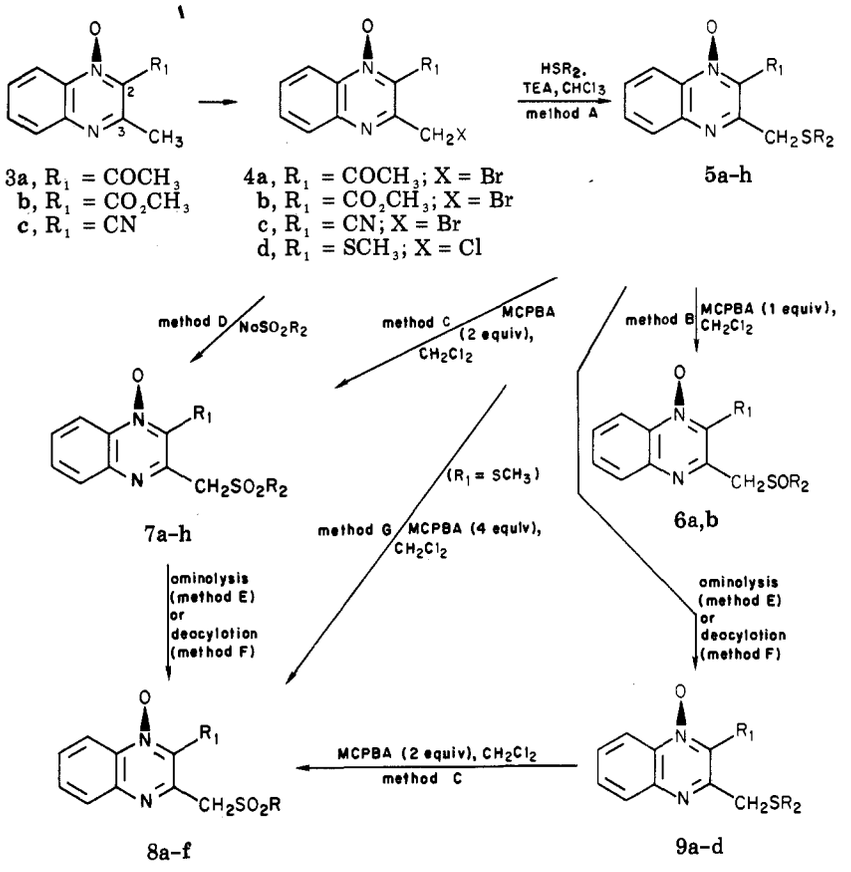
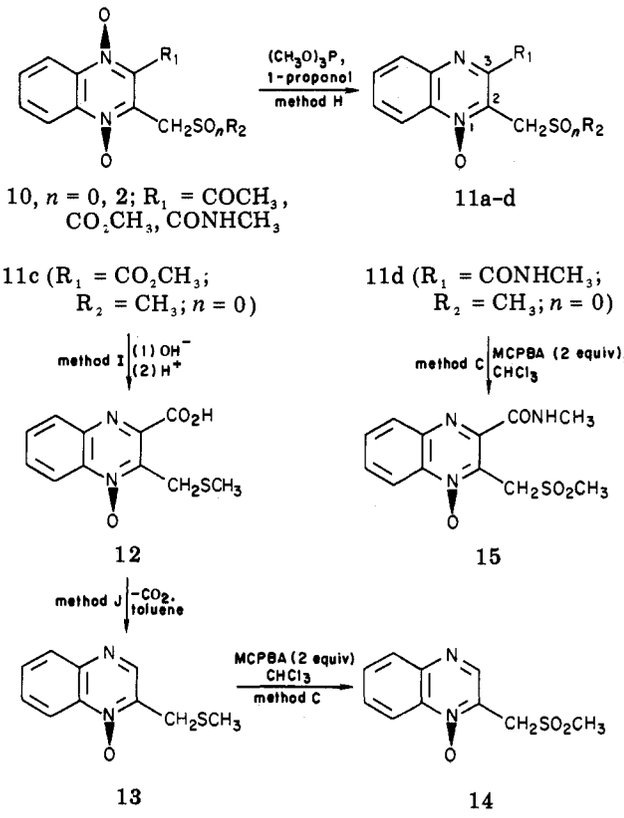
Scheme I

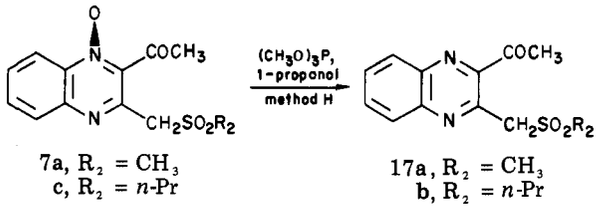


Scheme II



Some 2-[(alkylthio)methyl]quinoxaline 1-oxides (**11**), i.e., isomers of 1, were obtained as summarized in Scheme II. The key reaction for the synthesis of these compounds was the selective monodeoxygenation of appropriately substituted quinoxaline 1,4-dioxides (**10**) with trimethyl phosphite in refluxing 1-propanol.[6] Finally, the quinoxalines **17a** and **17b**, i.e., deoxides, were prepared as illustrated in Scheme III starting from the corresponding quinoxaline 1-oxides **7a** and **7c**, respectively.

Scheme III

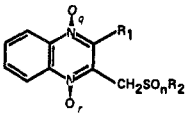


Biological Results and Discussion

The prepared compounds (Table I) were evaluated in vitro and in vivo for antibacterial activity against Gram-negative and Gram-positive bacteria. Carbadox (**2**), a quinoxaline 1,4-dioxide of commercial importance, was used as a reference antibacterial agent.[10] The in vitro data for the most potent analogues, i.e., the 3-[(alkylthio)-methyl]quinoxaline 1-oxides, are summarized in Table II. The MIC's obtained were unexpectedly low in view of the fact that quinoxaline 1-oxides are generally assumed to be inactive or at best possess weak activity relative to quinoxaline 1,4-dioxides.[5] In contrast, the isomeric 2-[(alkylthio)methyl]quinoxaline 1-oxides and the deoxides **17a** and **17b** were devoid of in vitro antibacterial activity. Upon in vivo screening against *E. coli* and *S. choleraesuis*, either by the oral or subcutaneous route of treatment at a dose of 50 mg/kg in mice, the compounds listed in Table II were inactive. The positive control, carbadox, gave 100% protection.

(10) Carbadox (Mecadox, Pfizer Inc., New York) is highly effective as a growth promotant for swine: see ref 1c.

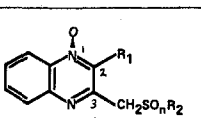
Table I. Physical Properties of [(Alkylthio)methyl]quinoxalines



compd	R_1	R_2	n	q	r	method[a]	mp, °C	formula[b]
5a	$COCH_3$	CH_3	0	1	0	A	139-141.5	$C_{12}H_{12}N_2O_2S$
6a	$COCH_3$	CH_3	1	1	0	B	173-175	$C_{12}H_{12}N_2O_3S$
17a	$COCH_3$	CH_3	2	0	0	H	191-194	$C_{12}H_{12}N_2O_3S$
7a	$COCH_3$	CH_3	2	1	0	C, D	200-201	$C_{12}H_{12}N_2O_4S$
11a	$COCH_3$	CH_3	2	0	1	H	177-180	$C_{12}H_{12}N_2O_4S$
5b	$COCH_3$	Et	0	1	0	A	77-79.5	$C_{13}H_{14}N_2O_2S$
7b	$COCH_3$	Et	2	1	0	C	153.5-155	$C_{13}H_{14}N_2O_4S$
5c	$COCH_3$	*n*-Pr	0	1	0	A	62-64	$C_{14}H_{16}N_2O_2S$
17b	$COCH_3$	*n*-Pr	2	0	0	H	93.5-95	$C_{14}H_{16}N_2O_3S$
7c	$COCH_3$	*n*-Pr	2	1	0	C	140-142	$C_{14}H_{16}N_2O_4S$[c]
11b	$COCH_3$	*n*-Pr	2	0	1	H	108-110	$C_{14}H_{16}N_2O_4S$
5d	$COCH_3$	CH_2CH_2OH	0	1	0	A	113-116	$C_{13}H_{14}N_2O_3S$[d]
6b	$COCH_3$	CH_2CH_2OH	1	1	0	B	165-167	$C_{13}H_{14}N_2O_4S$
7d	$COCH_3$	CH_2CH_2OH	2	1	0	C	173-175	$C_{13}H_{14}N_2O_5S$
5e	CO_2CH_3	CH_3	0	1	0	A	96-98	$C_{12}H_{12}N_2O_3S$
11c	CO_2CH_3	CH_3	0	0	1	H	86-89	$C_{12}H_{12}N_2O_3S$
7e	CO_2CH_3	CH_3	2	1	0	D	140-141	$C_{12}H_{12}N_2O_5S$
5f	CO_2CH_3	CH_2CH_2OH	0	1	0	A	131-135	$C_{43}H_{14}N_2O_4S$[e]
7f	CO_2CH_3	CH_2CH_2OH	2	1	0	C	123-128	$C_{13}H_{14}N_2O_6S$
8a	$CONH_2$	CH_3	2	1	0	E	264-265	$C_{11}H_{11}N_3O_4S$
9a	$CONHCH_3$	CH_3	0	1	0	E	144-146	$C_{12}H_{13}N_3O_2S$
11d	$CONHCH_3$	CH_3	0	0	1	H	152-154	$C_{12}H_{13}N_3O_2S$
8b	$CONHCH_3$	CH_3	2	1	0	C	205-207	$C_{12}H_{13}N_3O_4S$
15	$CONHCH_3$	CH_3	2	0	1	C	223-226	$C_{12}H_{13}N_3O_4S$
9b	$CONHCH_3$	Et	0	1	0	E	134-137	$C_{13}H_{15}N_3O_2S$
8c	$CONHCH_3$	Et	2	1	0	C	164-170	$C_{13}H_{15}N_3O_4S$
9c	$CONHCH_3$	CH_2CH_2OH	0	1	0	E	141-143	$C_{13}H_{15}N_3O_3S$
8d	$CONHCH_3$	CH_2CH_2OH	2	1	0	C	130-135	$C_{13}H_{15}N_3O_5S$[f]
12	CO_2H	CH_3	0	0	1	I	144-145	$C_{11}H_{10}N_2O_3S$
9d	H	CH_3	0	1	0	F	98-99	$C_{10}H_{10}N_2OS$
13	H	CH_3	0	0	1	J	74-75	$C_{10}H_{10}N_2OS$
8e	H	CH_3	2	1	0	F	196-197	$C_{10}H_{10}N_2O_3S$
14	H	CH_3	2	0	1	C	190-191	$C_{10}H_{10}N_2O_3S$
5g	SCH_3	CH_3	0	1	0	A	75-80	$C_{11}H_{12}N_2OS_2$
7g	SCH_3	CH_3	2	1	0	D	194-197	$C_{11}H_{12}N_2O_3S_2$
8f	SO_2CH_3	CH_3	2	1	0	G	197-200	$C_{11}H_{12}N_2O_5S_2$
5h	CN	CH_3	0	1	0	A	126-127	$C_{11}H_9N_3OS$
7h	CN	CH_3	2	1	0	C	224-225	$C_{11}H_9N_3O_3S$

[a] The letters relate to the general procedures given under Experimental Section. [b] Analyses for C, H, and N were within ±0.4% of the theoretical values except where indicated. [c] C: calcd, 54.60; found, 53.93. [d] C: calcd, 56.17; found, 55.53. [e] C: calcd, 53.11; found, 52.47. [f] C: calcd, 48.04; found, 48.99.

Table II. In Vitro Antibacterial Activity of 3-[(Alkylthio)methyl]quinoxaline 1-Oxides



				MIC,[a] μg/mL				
compd	R_1	R_2	n	*P.m.*[b]	*S.p.*[c]	*E.c.*[d]	*S.c.*[e]	*T.h.*[f]
6a	$COCH_3$	CH_3	1	3.12	6.25	25	25	6.25
6b	$COCH_3$	CH_2CH_2OH	1	3.12	25	25	6.25	
7a	$COCH_3$	CH_3	2	0.78	1.56	12.5	12.5	0.19
7b	$COCH_3$	Et	2	6.25	1.56	25	50	0.78
7c	$COCH_3$	*n*-Pr	2	3.12	6.25	100	200	
7d	$COCH_3$	CH_2CH_2OH	2	1.56	6.25	25	50	3.12
7e	CO_2CH_3	CH_3	2	0.78	3.12	3.12	6.25	1.56
7f	CO_2CH_3	CH_2CH_2OH	2	1.56	0.78	6.25	25	1.56
7h	CN	CH_3	2	200	25	>200	>200	
8a	$CONH_2$	CH_3	2	1.56	0.78	1.56	3.12	6.25
8b	$CONHCH_3$	CH_3	2	0.78	6.25	3.12	6.25	3.12
8c	$CONHCH_3$	Et	2	6.25	12.5	12.5	25	6.25
8d	$CONHCH_3$	CH_2CH_2OH	2	3.12	6.25	6.25	25	12.5
8f	SO_2CH_3	CH_3	2	3.12	6.25	25	25	>25
carbadox (2)[g]				0.78	0.19	0.39	0.19	0.19

[a] Minimum inhibitory concentration; determined under anaerobic conditions as previously described in ref 2 and 3. [b] *Pasteurella multocida*, strain 59A004. [c] *Streptomyces pyogenes*, strain 2C203. [d] *Escherichia coli*, strain 51A266. [e] *Salmonella choleraesuis*, strain 58B242. [f] *Treponema hyodysenteriae*, strain 94A002. [g] Reference 1c.

Most notably, identical MIC's were determined for compound **7a** and carbadox (i.e., 0.19 μg/mL) when evaluated in vitro against *T. hyodysenteriae*, a causative agent in swine dysentery[11] (Table II). Compound **7a** was ad libitum fed (50 g of **4**/ton of feed) to growing pigs exposed to swine dysentery (*T. hyodysenteriae*) inoculum.[15] Both **7a** and carbadox (25 g/ton), a positive control in this experiment, completely protected the pigs against the swine dysentery challenge over a 21-day period. All of the nonmedicated exposed control pigs developed swine dysentery, and 33% mortality was observed.

Experimental Section

Biology. Experimental Infections in Mice. Male and female mice weighing 11–13 g obtained from Blue Spruce Farms, Alamont, NY, were used in all experiments. Acute systemic infections were produced by intraperitoneal inoculation of 1 to 10 times the number of organisms necessary to kill 100% of the nonmedicated mice in 4 days. Standardized bacterial cultures of *Escherichia coli* (51A266) and *Salmonella choleraesuis* (58B242) were suspended in 5% hog gastric mucin. Treatment was initiated 0.5 h after infection. A second treatment was administered at 4.0 h and a third at 24 h.

Experimental Infections in Swine. Growing healthy pigs averaging approximately 12 kg in body weight were equivalently allotted into pens of six pigs each (three male and three female per pen). Pigs were fed a medicated grower ration, fasted for 24 h, and then challenged orally via gavage with 100 mL each of intestinal scrapings obtained from previously infected pigs diluted with an equal volume of buffered saline (*T. hyodysenteriae*, TH141TP).[15] Approximately 2 h later, pigs were ad libitum fed (a) basal ration with no medication, (b) basal ration with 25 g/ton of carbadox, or (c) basal ration with 50 g/ton of compound **7a**. Experimental groups were ad libitum fed appropriately medicated and nonmedicated rations for 21 days and observed daily for signs of swine dysentery and/or mortality. The results of this experiment indicate that 50 g of **7a** in a ton of feed ad libitum fed to growing pigs completely protected them against artificially induced swine dysentery. Carbadox at 25 g/ton also protected like pigs against the swine dysentery challenge. All of the challenged nonmedicated control pigs developed swine dysentery, and 33% mortality was observed.

Antimicrobial Susceptibility Tests. Minimum inhibitory concentrations were determined under anaerobic conditions as previously described.[2,3]

Chemistry. General. Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. NMR spectra were recorded on Varian A-60 and T-60 spectrometers with Me_4Si as internal standard. IR spectra were determined with a Perkin-Elmer Model 21 spectrophotometer. UV spectra were recorded on a Cary Model 14 spectrophotometer, and mass spectra were obtained with a Perkin-Elmer RMU-6E mass spectrometer. All compounds gave spectral data consistent with the proposed structure. Microanalyses were performed by the Pfizer Analytical Department.

2-Acetyl-3-(bromomethyl)quinoxaline 1-Oxide (4a). To a stirred suspension of 2-acetyl-3-methylquinoxaline 1-oxide[6] (43.2 g, 0.21 mol) in methanol (750 mL) was added bromine (50 g, 0.31 mol) over a period of 1 h. The reaction mixture was then stirred for 2 days at room temperature, and the resulting white solid was collected by suction filtration, washed with methanol, and dried to give 34.5 g (57% yield) of **4a**, mp 163–165 °C dec.

A similar procedure was used to prepare **4b** (mp 134–136 °C dec), starting with methyl 3-methyl-2-quinoxalinecarboxylate 1-oxide,[6] and **4c** (mp 146–147 °C dec), starting with 2-cyano-3-methylquinoxaline 1-oxide[12] (in yields of 51 and 79%, respectively).

3-(Chloromethyl)-2-(methylthio)quinoxaline 1-Oxide (4d). To a solution of 3-methyl-2-(methylthio)quinoxaline 1,4-dioxide[13] (10.0 g, 0.045 mol) in methylene chloride (100 mL) was slowly added *p*-toluenesulfonyl chloride (9.5 g, 0.049 mol).[7] The reaction mixture was allowed to stir at room temperature for 4 days and was then washed with 5% sodium bicarbonate solution, dried, and evaporated to affford crude **4d**. Recrystallization of the crude product from methanol afforded 2.80 g (26%) of **4d**, mp 131–133 °C dec.

2-Acetyl-3-[(methylthio)methyl]quinoxaline 1-Oxide (5a). Method A. A solution of 2-acetyl-3-(bromomethyl)quinoxaline 1-oxide (2.0 g, 7.1 mmol) and triethylamine (0.78 g, 7.8 mmol) was stirred at room temperature, and methyl mercaptan gas was bubbled in for 1.5 h. The reaction was allowed to stir overnight, and the resulting yellow solid was collected by suction filtration to afford 1.0 g (58% yield) of **5a**, mp 139–141.5 °C.

Methyl 3-[[(2-Hydroxyethyl)thio]methyl]-2-quinoxalinecarboxylate 1-Oxide (5f). Method A. To a solution of methyl 3-(bromomethyl)quinoxalinecarboxylate 1-oxide (2.0 g, 6.73 mmol) in chloroform (30 mL) was added triethylamine (1.29 mL, 10.1 mmol) and 2-mercaptoethanol (0.72 mL, 10.1 mmol), and the resulting mixture was stirred at room temperature for 2 days. The reaction mixture was washed with 1 N HCl, and water and was then concentrated under reduced pressure. The resulting white solid was triturated with ether and filtered, and the filtrate was dried to give 1.25 g of **5f** (63% yield), mp 131–135 °C.

A similar procedure was used to prepare compounds **5b–e, g,h.**

2-Acetyl-3-[(methylsulfinyl)methyl]quinoxaline 1-Oxide (6a). Method B. To a solution of 2-acetyl-3-[(methylthio)-methyl]quinoxaline 1-oxide (1.0 g, 4.0 mmol) in methylene chloride (20 mL) cooled to 0 °C was added dropwise a solution of 85% *m*-chloroperbenzoic acid (0.82 g, 4.0 mmol) in methylene chloride (5 mL). The reaction mixture was stirred for 4 h at 0 °C, washed with a saturated solution of sodium bicarbonate, dried, and evaporated. The resulting solid was chromatographed with silica gel (ethyl acetate/methanol as solvent) to afford 0.65 g (62% yield) of **6a**, mp 173–175 °C.

This procedure was also used to prepare **6b.**

2-Acetyl-3-[(methylsulfonyl)methyl]quinoxaline 1-Oxide (7a). Method C. To a solution of 2-acetyl-3-[(methylthio)-methyl]quinoxaline 1-oxide (1.0 g, 4.0 mmol) in chloroform (30 mL) was added 85% *m*-chloroperbenzoic acid (1.76 g, 8.9 mmol). The reaction mixture was stirred at room temperature for 4 h and then washed with saturated sodium bicarbonate solution and water. The chloroform layer was dried and concentrated to afford a solid. Trituration of the solid gave a light yellow solid, which was collected by filtration and dried to give 0.97 g (85% yield) of **7a**, mp 200–201 °C.

Compounds **7b–d,f,h, 8b–d, 14,** and **15** were prepared by method C.

Method D. A mixture of 2-acetyl-3-(bromomethyl)quinoxaline 1-oxide (12.0 g, 43 mmol), sodium methylsulfinate[14] (55 mL, 1 M, 55 mmol), and ethanol (180 mL) was heated to reflux for 1.5 h. The mixture was concentrated in vacuo and partitioned between chloroform (700 mL) and water (200 mL). The chloroform layer was separated, washed with water, dried, and evaporated to give a solid. The solid was triturated with absolute ethanol to afford 9.2 g (76% yield) of **7a**, mp 201–202 °C.

This method was also used to prepare compounds **7e** and **7g.**

***N*-Methyl-3-[[(2-hydroxyethyl)thio]methyl]-2-quinoxalinecarboxamide 1-Oxide (9c). Method E.** To a slurry of methyl 3-[[(2-hydroxyethyl)thio]methyl]-2-quinoxalinecarboxylate (1.14 g, 3.87 mmol) in water (10 mL) was added a 40% solution of methylamine in water (7 mL), and the resulting mixture was heated on a steam bath for 1 h. The reaction mixture was cooled in a freezer overnight, and the resulting solid was collected by suction filtration, washed with cold water, and dried to afford

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(14) Sodium methylsulfinate was prepared according to L. Field and R. D. Clark, in "Organic Syntheses", Collect. Vol. IV, N. Rabjohn, Ed., Wiley, New York, 1963, p 674. The resulting solution (i.e., CH_3SO_2Na in water, salt, and sodium sulfate) was used directly in the reaction.

(15) R. H. Rainier, R. R. Chalquest, W. E. Babcock, and G. W. Thrasher, *J. Am. Vet. Med. Assoc.*, **163**, 457 (1973).

0.38 g (34% yield) of product **9c**, mp 141–143 °C.

Compounds **9a,b** were prepared by method **E**. Compound **8a** was synthesized with a concentrated ammonium hydroxide solution instead of methylamine in the above procedure.

3-[(Methylsulfonyl)methyl]quinoxaline 1-Oxide (8e). Method F. 2-Acetyl-3-[(methylsulfonyl)methyl]quinoxaline 1-oxide (0.50 g, 18 mmol) was added to methylamine–water (40%, 20 mL). The reaction mixture was heated under reflux for 5 min, and the mixture turned purple. While the mixture was cooled to room temperature, a solid formed, which was collected by suction filtration. The solid was washed with water and dried to afford 0.34 g (80%) of **8e**, mp 196–197 °C.[16]

This method was used to prepare **9d**.

2-(Methylsulfonyl)-3-[(methylsulfonyl)methyl]quinoxaline 1-Oxide (8f). Method G. 2-(Methylthio)-3-[(methylthio)methyl]quinoxaline 1-oxide (0.46 g, 1.8 mmol) was dissolved in methylene chloride (30 mL) and 85% *m*-chloroperbenzoic acid (1.57 g, 7.8 mmol) was added. The reaction mixture was allowed to stir at room temperature overnight. The reaction was worked up in the same manner as described above for **7a**, which gave 0.51 g (89%) of **8f**, mp 197–200 °C.

2-Acetyl-3-[(methylsulfonyl)methyl]quinoxaline (17a). Method H. 2-Acetyl-3-[(methylsulfonyl)methyl]quinoxaline 1-oxide (0.61 g, 2.2 mmol) was suspended in 1-propanol (10 mL) containing trimethyl phosphate (0.56 g, 4.8 mmol).[6] The reaction mixture was heated under reflux for 4 h. While the solution was cooled to room temperature, crystals formed. The solid was collected by suction filtration and washed with ether to afford 0.39 g (69%) of **17a**, mp 191–194 °C.

Compounds **11a–d** and **17b** were prepared by method **H**. Quinoxaline 1,4-dioxide precursors were synthesized by procedures similar to those described previously.[3,8]

2-[(Methylthio)methyl]quinoxaline-3-carboxylic Acid 1-Oxide (12). Method I. Methyl 2-[(methylthio)methyl]-quinoxaline-3-carboxylate 1-oxide (2.00 g, 7.6 mmol) was treated with 1 N sodium hydroxide solution (30 mL) for 2 h at room temperature. The reaction mixture was neutralized with 1 N hydrochloric acid solution, and the resulting solid was collected by suction filtration, washed with water, and dried to afford 1.22 g (77%) of **12**, mp 144–145 °C.

2-[(Methylthio)methyl]quinoxaline 1-Oxide (13). Method J. A solution of 2-[(methylthio)methyl]quinoxaline-3-carboxylic acid 1-oxide (1.00 g, 4.0 mmol) in toluene (20 mL) was heated under reflux for 1 h. The reaction mixture was cooled to room temperature and evaporated, leaving an amber oil. The oil was crystallized from benzene–hexane to yield 0.67 g (81%) of **13**, mp 74–75 °C.

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Registry No. **3a**, 61522-57-4; **3b**, 61528-76-5; **3c**, 85976-66-5; **4a**, 85957-66-0; **4b**, 85957-67-1; **4c**, 85957-68-2; **4d**, 85957-69-3; **5a**, 85957-70-6; **5b**, 85976-67-6; **5c**, 85957-71-7; **5d**, 85957-72-8; **5e**, 85957-73-9; **5f**, 85957-74-0; **5g**, 85957-75-1; **5h**, 85957-76-2; **6a**, 85957-77-3; **6b**, 85957-78-4; **7a**, 85957-79-5; **7b**, 85957-80-8; **7c**, 85957-81-9; **7d**, 85957-82-0; **7e**, 85957-83-1; **7f**, 85957-84-2; **7g**, 85957-85-3; **7h**, 85957-86-4; **8a**, 85957-87-5; **8b**, 85957-88-6; **8c**, 85957-89-7; **8d**, 85957-90-0; **8e**, 85957-91-1; **8f**, 85957-92-2; **9a**, 85957-93-3; **9b**, 85957-94-4; **9c**, 85957-95-5; **9d**, 85957-96-6; **10a**, 85957-97-7; **10b**, 85957-98-8; **10c**, 56944-42-4; **10d**, 34930-76-2; **11a**, 85957-99-9; **11b**, 85958-00-5; **11c**, 85958-01-6; **11d**, 85958-02-7; **12**, 85958-03-8; **13**, 85958-04-9; **14**, 85958-05-0; **15**, 85958-06-1; **17a**, 85958-07-2; **17b**, 85958-08-3; 3-methyl-2-(methylthio)quinoxaline 1,4-dioxide, 39576-50-6; methyl mercaptan, 74-93-1; 2-mercaptoethanol, 60-24-2; sodium methylsulfinate, 20277-69-4.

(16) This deacylation procedure described herein was an outgrowth of a serendipitous result obtained with some substituted 2-acetylquinoxaline 1,4-dioxides and methylamine–water. It is assumed that deacylation is facilitated by the electron-withdrawing *N*-oxide functionality on the quinoxaline ring.

Nitrogen Bridgehead Compounds. 33.[1] New Antiallergic 4*H*-Pyrido[1,2-*a*]pyrimidin-4-ones. 2.

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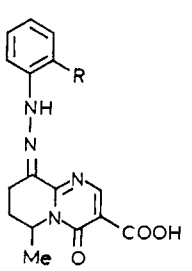
A series of 9-hydrazono-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones was prepared. The compounds were evaluated in the rat passive cutaneous anaphylaxis test for antiallergic activity. Structure–activity relationship studies revealed that the presence of a monosubstituted hydrazone moiety in position 9 and an unsubstituted 2-position are necessary for the intravenous activity.

We recently reported[2] the synthesis and pharmacological investigation of antiallergic 9-(phenylhydrazono)-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones of type **1** on rat reaginic passive cutaneous anaphylaxis (PCA). Structure–activity relationship studies revealed that the presence of a carboxy group in the 3-position was necessary for activity, the most potent derivatives bore a methyl group in the 6-position, and the biological effect was due to the 6-*S* enantiomers. The substituents on the phenyl group caused subtle differences in the potency: meta



1 R = H

2 R = COOH

substituents and a hydroxy or carboxy group in the ortho position (compound **2**) slightly enhanced the activity observed following intravenous injection. The orally active 6-*S* enantiomer of **1** was selected for further development.[3]

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