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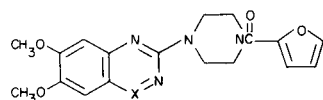
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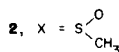
A series of 3-amino-1,2,4-benzothiadiazine 1-oxides were obtained from the corresponding 3-thiomethyl ethers by displacement with a series of amines; examples of the last included variously substituted piperazines and piperidines.

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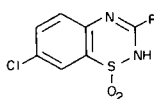
The finding that postsynaptic α -receptor blocking agents such as prazosin (**1**) lower blood pressure in hypertension without the side effects classically associated with α blockers (**1**) has spurred considerable work on the preparation of related compounds. It has, for example, been noted that the quinazoline ring carbon at 4 can be replaced by a methylsulfonyl group (**2**). The observation that **4** lowers blood pressure in experimental animals (**3,4**) is particularly intriguing since this molecule incorporates features of both postsynaptic α -blockers and the direct vasodilator diazoxide **3**. We thus considered it of interest to investigate the corresponding sulfoxides.



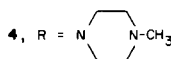
1, X = C-NH₂



2, X = S(=O)₂CH₃

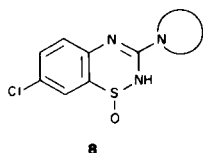
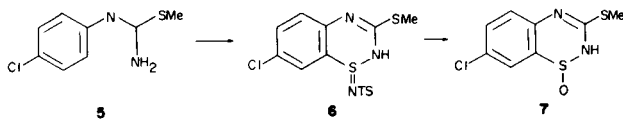


3, R = CH₃



4, R = N-CH₃

Access to the requisite starting material was provided by a sequence which depends on cycloaddition of *N*-sulfinylsulfonamides to arylamidines (**5,6**) followed by hydrolysis of the exocyclic tosylhydrazone moiety. This intermediate was then condensed with a series of amines which have been associated with adrenergic blocking activity.



Replacement of the thiomethyl group at **3** was accomplished in a straightforward manner by heating **7** with the appropriate amines at reflux in isoamyl alcohol. (Preliminary

experiments using DMF or acetonitrile as the reaction medium led to complex mixtures.)

Compounds were evaluated for antihypertensive activity by oral administration to SH rats. None of the agents gave any lowering of blood pressure up to the maximum screening dose (100 mg/kg).

EXPERIMENTAL

Melting points were determined using a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer 399 infrared spectrophotometer. The CHN analysis were obtained from Galbraith Laboratories, Inc., Knoxville, Tennessee. Mass spectral data for compound **8a** was procured from the School of Pharmacy, Ohio State University.

7-Chloro-3-(4-benzyl-1-piperazinyl)-2*H*-1,2,4-benzothiadiazine 1-Oxide (**8a**).

A mixture of 2.50 g (0.01 mole) of 7-chloro-3-methylthio-2*H*-1,2,4-benzothiadiazine 1-oxide (**6**) and 5.2 ml (0.03 mole) of 1-benzylpiperazine in 12.0 ml of isoamyl alcohol was heated at reflux for 18 hours. The solid which separated was collected on a filter and thoroughly washed with cold ethyl acetate. This material was recrystallized from chloroform/hexane, and the product collected on a filter and dried 12 hours *in vacuo* at 80° to yield 2.15 g (57.5%) of **8a** as a white crystalline solid, mp 247-250° dec; ir (potassium bromide): 3250 (w), 3180 (w), 3020 (w), 2940 (w), 2820 (w,b), 1620 (s) [C-N], 1565 (s) [C=N], 1495 (s), 1440 (s,b), 1380, 1355, 1340 (w), 1320, 1270 [S=O], 1245, 1210 (w), 1150, 1115, 1070, 1020 (s,b), 955 (w), 905 (s), 880, 825 (s), 740 (s), 700 (s) cm⁻¹; ms: m/e 375; CHN analysis (see table); single lc peak (RT 3.4, FR 1.5 ml/minute, 254 uv detection); microbondapak C-18 10μ particle size column, 1:1:1 acetonitrile: distilled water:methanol as eluent.

General Method for Compounds **8a-8p**.

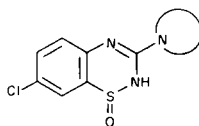
To a well stirred suspension of 2.50 g (0.01 mole) of 7-chloro-3-methylthio-2*H*-1,2,4-benzothiadiazine 1-oxide (**7**) in 15 ml of 3-methyl-1-butanol, there was added 0.03 mole of the amine. The mixture was brought to a reflux and heated for 18 hours. The reaction mixture was then allowed to cool to room temperature. The precipitate was collected on a filter, thoroughly washed with cold ethyl acetate, dried, and recrystallized from chloroform:hexane.

Acknowledgement.

The authors wish to express their appreciation to Dr. Ernest Belair and Mr. Robert Buyan for performing the biological assays.

Table I

7-Chloro-3-substituted-(2H)-1,2,4-benzothiadiazine 1-Oxides (8)



Compound No.	N	Mp (°C)	Yield (%)	Molecular Formula (Analysis Formula)	Analysis Calcd./Found		
					C	H	N
8a	4-Benzylpiperazino-	247-250 dec	57.5	C ₁₈ H ₁₉ ClN ₄ OS	57.66	5.12	14.95
8b	4-Formylpiperazino-	232-235 dec	41.6	C ₁₂ H ₁₃ ClN ₄ OS	57.39	5.38	14.56
8c	4(4-Chlorophenyl)piperazino-	255-257 dec	68.4	(C ₁₂ H ₁₃ ClN ₄ OS·H ₂ O)	43.56	4.58	16.74
8d	4(Piperidino)-1-piperidyl-	257-258 dec	15.3	C ₁₇ H ₁₆ Cl ₂ N ₄ OS	43.56	4.21	16.94
8e	4(3-Hydroxypropyl)piperazino-	249-250 dec	20.5	C ₁₇ H ₁₆ Cl ₂ N ₄ OS	51.64	4.09	14.18
8f	3-Hydroxymethylpiperidino-	251-253 dec	49.4	C ₁₇ H ₂₃ ClN ₄ OS	51.58	4.13	13.91
8g	4-Methylpiperazino-	240-242 dec	58.4	C ₁₃ H ₁₆ ClN ₃ O ₂ S	55.64	6.33	15.27
8h	4(4-Methoxyphenyl)piperazino-	252-255 dec	65.2	C ₁₈ H ₁₉ ClN ₄ O ₂ S	55.26	6.53	14.88
8i	4(2-Methoxyphenyl)piperazino-	260-263 dec	58.7	C ₁₈ H ₁₉ ClN ₄ O ₂ S	49.04	5.60	16.34
8j	4-Phenylpiperazino-	252-253 dec	52.8	C ₁₇ H ₁₆ ClN ₃ O ₂ S	49.07	5.76	16.00
8k	4-Benzoylpiperazino-	> 285 dec	82.5 (a)	C ₁₂ H ₁₅ ClN ₄ OS	49.74	5.15	13.39
8l	4-Hydroxypiperazino-	247-248 dec	21.2	(C ₁₂ H ₁₅ ClN ₄ OS·2H ₂ O)	49.57	5.25	13.29
8m	4-Phenylpiperidino-	244-245 dec	34.3	C ₁₂ H ₁₃ ClN ₃ OS	43.04	5.73	16.74
8n	Morpholino-	255-257 dec	71.9	(C ₁₂ H ₁₄ ClN ₃ OS·3/2H ₂ O)	43.44	5.73	16.95
8o	Piperidino-	247-249 dec	51.2	C ₁₈ H ₁₉ ClN ₄ O ₂ S·1/4H ₂ O	54.67	4.98	14.17
8p	4(2-Furancarboxyl)piperazino-	221-224 dec	61.4	C ₁₈ H ₁₉ ClN ₄ O ₂ S	54.77	4.99	13.94
				C ₁₆ H ₁₅ ClN ₄ O ₃ S	55.30	4.91	14.33
					54.98	5.06	14.25
					56.52	4.76	15.53
					56.15	4.92	15.52
					56.01	4.84	13.55
					56.38	5.06	13.18
					46.37	5.19	13.52
					46.53	5.20	13.21
					59.32	5.13	11.53
					59.31	5.11	11.54
					46.23	4.24	14.71
					46.09	4.21	14.89
					49.99	5.08	14.60
					49.82	5.16	14.92
					(Spectral, lc evidence)		

(a) Recrystallized from methanol.

REFERENCES AND NOTES

- (1a) A. Scriabine, J. W. Constantine, H.-J. Hess and W. K. McShane, *Experientia*, **24**, 1150 (1968); (b) M. E. Kosman, *J. Am. Med. Assoc.*, **238**, 15 (1977).
 (2) R. D. Dillard, T. T. Yen, P. Stark and D. E. Parey, *J. Med. Chem.*, **23**, 717 (1980).

- (3) M. Shimizu, K. Yoshida, T. Kadokawa, N. Hatano, J. Kuwashima, K. Makatsuju, I. Nose and M. Kobayashi, *Experientia*, **33**, 55 (1977).
 (4) H. Wollweber, H. Horstmann, K. Stoepel, B. Garthoft, W. Puls, H. P. Kraus and G. Thomas, *Arzneim.-Forsch.*, **31**, 279 (1981).
 (5) G. Kuesze, C. Seyfied and A. Trede, *Ann. Chem.*, **715**, 223 (1968).
 (6) N. Finch, S. Ricca, Jr. and L. H. Werner, *J. Org. Chem.*, **45**, 3416 (1980).