# Preparation of 3-Amino-1,2,4-benzothiadiazine 1-Oxides



Donn D. Ross and Daniel Lednicer*

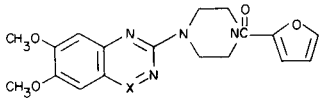
Adria Laboratories, PO Box 16529,
Columbus, Ohio 43216

Received January 6, 1982

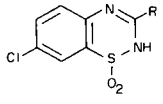
A series of 3-amino-1,2,4-benzothiadiazine 1-oxides were obtained from the corresponding 3-thiomethyl ethers by displacement with a series of amines; examples of the last included variously substituted piperazines and piperidines.

*J. Heterocyclic Chem.*, **19**, 975 (1982).

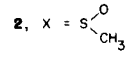
The finding that postsynaptic α-receptor blocking agents such as prazocin (**1**) lower blood pressure in hypertension without the side effects classically associated with α blockers (1) has spurred considerable work on the preparation of related compounds. It has, for example, been noted that the quinazoline 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-bockers and the direct vasodilator diazoxide **3**. We thus considered it of interest to investigate the corresponding sulfoxides.



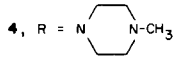
**1**, X = C-NH$_2$



**3**, R = CH$_3$

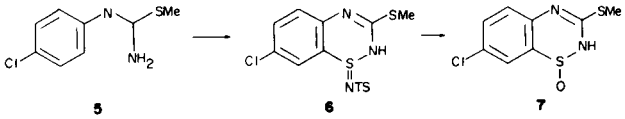


**2**, X = S(=O)CH$_3$

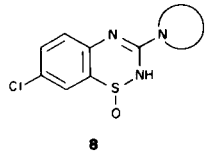


**4**, R = N(CH$_2$CH$_2$)$_2$N-CH$_3$

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.



**5** **6** **7**



**8**

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 adminstration 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**.

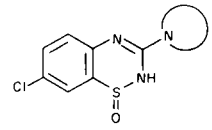
To a well stirred suspension of 2.50 g (0.01 mole) of 7-chloro-3-methylthio-(2*H*)-1,2,4-benzothiadiazine 1-oxide (**7**) in 15 ml of 3-methyl-1-butanol, there was added 0.03 mole of the amine. The mixture was brought to a reflux and heated for 18 hours. The reaction mixture was then allowed to cool 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-(2*H*)-1,2,4-benzothiadiazine 1-Oxides (**8**)



| Compound No. |  | Mp (°C) | Yield (%) | Molecular Formula (Analysis Formula) | Analysis Calcd./Found C | H | N |
|---|---|---|---|---|---|---|---|
| **8a** | 4-Benzylpiperazino- | 247-250 dec | 57.5 | $C_{18}H_{19}ClN_4OS$ | 57.66 | 5.12 | 14.95 |
| | | | | | 57.39 | 5.38 | 14.56 |
| **8b** | 4-Formylpiperazino- | 232-235 dec | 41.6 | $C_{12}H_{13}ClN_4OS$ | 43.56 | 4.58 | 16.74 |
| | | | | ($C_{12}H_{13}ClN_4OS\cdot H_2O$) | 43.56 | 4.21 | 16.94 |
| **8c** | 4-(4-Chlorophenyl)piperazino- | 255-257 dec | 68.4 | $C_{17}H_{16}Cl_2N_4OS$ | 51.64 | 4.09 | 14.18 |
| | | | | | 51.58 | 4.13 | 13.91 |
| **8d** | 4-(Piperidino)-1-piperidyl- | 257-258 dec | 15.3 | $C_{17}H_{23}ClN_4OS$ | 55.64 | 6.33 | 15.27 |
| | | | | | 55.26 | 6.53 | 14.88 |
| **8e** | 4-(3-Hydroxypropyl)piperazino- | 249-250 dec | 20.5 | $C_{14}H_{19}ClN_4O_2S$ | 49.04 | 5.60 | 16.34 |
| | | | | | 49.07 | 5.76 | 16.00 |
| **8f** | 3-Hydroxymethylpiperidino- | 251-253 dec | 49.4 | $C_{13}H_{16}ClN_3O_2S$ | 49.74 | 5.15 | 13.39 |
| | | | | | 49.57 | 5.25 | 13.29 |
| **8b** | 4-Methylpiperazino- | 240-242 dec | 58.4 | $C_{12}H_{15}ClN_4OS$ | 43.04 | 5.73 | 16.74 |
| | | | | ($C_{12}H_{15}ClN_4OS\cdot 2H_2O$) | 43.44 | 5.73 | 16.95 |
| **8h** | 4-(4-Methoxyphenyl)piperazino- | 252-255 dec | 65.2 | $C_{18}H_{19}ClN_4O_2S$ | 54.67 | 4.98 | 14.17 |
| | | | | ($C_{18}H_{19}ClN_4O_2S\cdot \frac{1}{4}H_2O$) | 54.77 | 4.99 | 13.94 |
| **8i** | 4-(2-Methoxyphenyl)piperazino- | 260-263 dec | 58.7 | $C_{18}H_{19}ClN_4O_2S$ | 55.30 | 4.91 | 14.33 |
| | | | | | 54.98 | 5.06 | 14.25 |
| **8j** | 4-Phenylpiperazino- | 252-253 dec | 52.8 | $C_{17}H_{17}ClN_4OS$ | 56.52 | 4.76 | 15.53 |
| | | | | | 56.15 | 4.92 | 15.52 |
| **8k** | 4-Benzoylpiperazino- | >285 dec | 82.5 (a) | $C_{18}H_{17}ClN_4O_2S$ | 56.01 | 4.84 | 13.55 |
| | | | | ($C_{18}H_{17}ClN_4O_2S\cdot \frac{1}{4}C_4H_{10}O$) | 56.38 | 5.06 | 13.18 |
| **8ℓ** | 4-Hydroxypiperazino- | 247-248 dec | 21.2 | $C_{12}H_{14}ClN_3OS$ | 46.37 | 5.19 | 13.52 |
| | | | | ($C_{12}H_{14}ClN_3O_5\cdot 3/2H_2O$) | 46.53 | 5.20 | 13.21 |
| **8m** | 4-Phenylpiperidino- | 244-245 dec | 34.3 | $C_{18}H_{18}ClN_3OS$ | 59.32 | 5.13 | 11.53 |
| | | | | ($C_{18}H_{18}ClN_3OS\cdot \frac{1}{4}H_2O$) | 59.31 | 5.11 | 11.54 |
| **8n** | Morpholino- | 255-257 dec | 71.9 | $C_{11}H_{12}ClN_3O_2S$ | 46.23 | 4.24 | 14.71 |
| | | | | | 46.09 | 4.21 | 14.89 |
| **8o** | Piperidino- | 247-249 dec | 51.2 | $C_{12}H_{14}ClN_3OS$ | 49.99 | 5.08 | 14.60 |
| | | | | ($C_{12}H_{14}ClN_3OS\cdot \frac{1}{4}H_2O$) | 49.82 | 5.16 | 14.92 |
| **8p** | 4-(2-Furancarboxoyl)piperazino- | 221-224 dec | 61.4 | $C_{16}H_{15}ClN_4O_3S$ | (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. Yoshuda, 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).