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SELECTIVE REACTION OF AMINO ACID SULFOXIMINES WITH NITROUS ACID; FACILE STEREOSPECIFIC CONVERSION TO AMINO ACID SULFOXIDES

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Abstract: N-Unsubstituted sulfoximines of amino acids can be readily converted to the corresponding amino acid sulfoxides in high yields by treatment with stoichiometric quantities of nitrous acid. Under the conditions employed, reaction with L-methionine-S (or R)-sulfoximine is specific for the sulfoximine nitrogen atom, and no reaction occurs at the α-amino group. Conversion to the sulfoxide proceeds with complete retention of configuration at the sulfur atom.

Our continuing interest in the chemistry and biochemistry of sulfoximines (1-7) led us to study their reactions with reagents such as nitrous acid and hydrogen peroxide. A recent review (8) of sulfoximine chemistry indicates no previous report of the action of nitrous acid on sulfoximines. However, Williams et al (9) have reported that methyl-p-tolyl sulfoximine is stereospecifically converted by nitrous acid to the sulfoxide. On the other hand, Whitehead and Bentley (10) reported that treatment of dimethyl sulfoximine with nitrous acid gave dimethyl sulfone. In the present work we have explored the scope and selectivity of this reaction, which appears to be of interest and of potential usefulness in amino acid chemistry.

Early studies showed that L-methionine sulfoximine produces convulsions in animals (11). Previous work in this laboratory showed that only one of the 4 stereoisomers of this sulfoximine induces convulsions, namely L-methionine-S-sulfoximine (5). Furthermore, it was found that only this isomer specifically inhibits the enzyme glutamine synthetase irreversibly, and is phosphorylated by this enzyme in the presence of ATP and Mg^{++} (or Mn^{++}) to form methionine sulfoximine phosphate (4). Subsequently, it was observed that L-methionine-S-sulfoximine (but not the other 3 stereoisomers) inhibits γ-glutamyl cysteine synthetase by an

analogous mechanism (7). However, it is not certain that such enzymatic inhibition is responsible for all of the observed toxicity. In pursuing this problem we have studied the action of various biological and chemical agents on methionine sulfoximine. We found, in confirmation of Reiner et al (12), that L-methionine-SR-sulfoximine is converted to the corresponding sulfone by treatment with hydrogen peroxide at 22-28° C for one week or more (about 30% in 1 week and about 70% in 1 month).

Reaction of methionine sulfoximine with one equivalent of nitrous acid (via $NaNO_2$ + HCl) gave the corresponding sulfoxide in high yields (Table I). Furthermore, the reaction proceeded with stereospecificity. Under these conditions the reaction was selective for the sulfoximine nitrogen and did not involve the α-amino group. Indeed, a twenty-fold excess of nitrous acid over amino acid was required to completely convert the α-amino group to an α-hydroxy group; this finding is similar to those reported earlier with simple amino acids (13).

When 100 nmoles of L-methionine-R-sulfoximine in 0.5 ml of 0.8 M HCl was treated with 0.5 ml of 2.2 mM $NaNO_2$ at 0° for 30 minutes, quantitative conversion to L-methionine-R-sulfoxide was observed, as shown by automated amino acid analysis (Table I). When an analogous reaction was performed on L-methionine-S-sulfoximine, the corresponding S-sulfoxide was obtained.

Reaction of S-methyl-L-cysteine-SR-sulfoximine (14) with one equivalent of nitrous acid gave the corresponding SR-sulfoxide. We also found that dimethyl sulfoximine reacts with nitrous acid to give dimethyl sulfoxide rather than the sulfone as reported by Whitehead and Bentley (10); our result is in accord with that of Williams et al (9) on the reaction of methyl-p-tolyl sulfoximine. Methylphenyl-SR-sulfoximine (16) and methylphenyl-S-sulfoximine (17) gave the corresponding sulfoxides, with complete retention of configuration in the latter case. L-Methionine-SR-sulfoximine phosphate (2,3) did not react with one equivalent of nitrous acid; this is in accord with the proposed structure (2,3,6) of methionine sulfoximine phosphate, in which the phosphorus is attached to the sulfoximine nitrogen. Similarly, N,S-dimethylphenyl-SR-sulfoximine failed to react under these conditions.

Conversion of sulfoximines to sulfoxides via the (N,N-dialkylamino)oxosulfonium salts of sulfoximines has been reported using aluminum amalgam (8); such conversion of sulfoximine to sulfoxide requires alkylation and salt formation and entails some reduction to the sulfide. Another method of stereospecific conversion of sulfoximines to sulfoxides has been achieved by Cram et al (18) utilizing nitrosyl hexafluorophosphate. The

latter compound and nitrous acid are both nitrosating reagents; it would appear that the conversion of sulfoximine to sulfoxide observed here proceeds through the N-nitroso derivative, which decomposes to the sulfoxide and N_2O as suggested for the reaction with nitrosyl hexafluorophosphate (18).

The reaction described here appears to be a general one and represents a facile and economical method of preparing optically pure amino acid sulfoxides from the corresponding amino acid sulfoximines. It may also be useful in modifying peptides containing a sulfoximine moiety (19,20); the toxic properties of such peptides (21) might be altered by selective treatment with nitrous acid.

Table I

Compound	(μmoles)	$NaNO_2$ (μmoles)[e]	Product	Yield (%)
L-methionine-SR-sulfoximine	(0.10)	0.11	L-methionine-SR-sulfoxide	95[a]
L-methionine-SR-sulfoximine	(0.10)	200		b
L-methionine-R-sulfoximine (4)	(0.10)	0.11	L-methionine-R-sulfoxide	95[a]
L-methionine-S-sulfoximine (4)	(0.10)	0.11	L-methionine-S-sulfoxide	95[a]
L-methionine-SR-sulfoximine phosphate (2,3)	(0.10)	0.11	None	c
S-methyl-L-cysteine-SR-sulfoximine (12)	(0.10)	0.11	S-methyl-L-cysteine-SR-sulfoxide	95[a]
S-methyl-L-cysteine-SR-sulfoximine	(0.10)	200		b
dimethyl sulfoximine (13)	(3000)	3300	dimethyl sulfoxide	80
methylphenyl-SR-sulfoximine (14)	(3200)	3300	methylphenyl-SR-sulfoxide	80
methylphenyl-S-sulfoximine (15)	(3200)	3300	methylphenyl-S-sulfoxide	80[d]
N,S-dimethylphenyl-SR-sulfoximine (17)	(1000)	1100	None	c

[a]Determined by automated amino acid analysis as described (4). [b]No ninhydrin positive product was obtained. [c]More than 88% of the starting material was recovered. [d]Observed, $[\alpha]_D^{28}$ -149° (c 3.4, acetone), lit. (15) $[\alpha]_D^{25}$ -142.6°. [e]The reaction volume was 1 ml for the amino acids. In the other studies, the volume was 7 ml; the mixtures were saturated with NaCl and the product was extracted with dichloromethane. The products were identified by comparison of their infrared spectra with those of the authentic materials.

References

1. R.A. Ronzio and A. Meister, Proc. Natl. Acad. Sci. U.S., 59, 164 (1968).

2. R.A. Ronzio, W.B. Rowe and A. Meister, Biochemistry 8, 1066 (1969).

3. W.B. Rowe, R.A. Ronzio and A. Meister, Biochemistry 8, 2674 (1969).

4. J.M. Manning, S. Moore, W.B. Rowe and A. Meister, Biochemistry, 8, 2681 (1969).

5. W.B. Rowe and A. Meister, Proc. Natl. Acad. Sci. U.S., 66, 500 (1970).

6. W.B. Rowe and A. Meister, Biochemistry, 12, 1578 (1973).

7. P.R. Richman, M. Orlowski and A. Meister, J. Biol. Chem., 248, 6684 (1973).

8. C.R. Johnson, Accts. Chem. Res., 6, 341 (1973).

9. T.R. Williams, A. Nudelman, R.E. Booms and D.J. Cram, J. Am. Chem. Soc., 94, 4684 (1972).

10. J.K. Whitehead and H.R. Bentley, J. Chem. Soc., 1572 (1952).

11. H.R. Bentley, R.G. Booth, E.N. Greer, J.G. Heathcote, J.B. Hutchinson and T. Moran, Nature, 161, 126 (1948).

12. L.F. Reiner, F. Misani and P. Weiss, Arch. Biochem., 27, 234 (1950).

13. D.D. Van Slyke, J. Biol. Chem., 83, 425 (1929).

14. Prepared by Dr. T. Ubuka of this laboratory.

15. Kindly provided by Dr. W.B. Rowe of this laboratory.

16. C.R. Johnson, M. Haacke and C.W. Schroeck, J. Am. Chem. Soc., 92, 6594 (1971).

17. C.W. Schroeck and C.R. Johnson, J. Am. Chem. Soc., 93, 5305 (1971).

18. D.J. Cram, J. Day, D.R. Raynor, D.M. von Schritz, D.J. Duchamp and D.C. Garwood, J. Am. Chem. Soc., 92, 7654 (1971).

19. J.P. Scannell, D.L. Pruess, T.C. Demny, H.A. Ax, F. Weiss, T. Williams, A. Stempel, in "Chemistry and Biology of Peptides", J. Meienhofer, ed., p. 415. Ann Arbor Sci., Ann Arbor, Michigan, 1972.

20. D.L. Pruess, J.P. Scannell, H.A. Ax, M. Kellett, F. Weiss, T.C. Demny and A. Stempel, J. Antibiot. 26, 261 (1973).

21. A. Stempel, personal communication.