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THE TRAPPING OF SULFENIC ACIDS FROM PENICILLIN SULFOXIDES - USE OF 2,5-DIMERCAPTO-1,3,4-THIADIAZOLE AND 2,4-DIMERCAPTOPYRIMIDINE AS TRAPPING AGENTS.

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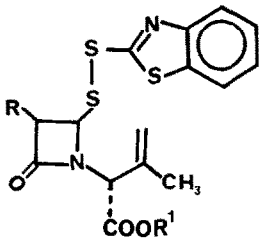
Summary: 2,5-Dimercapto-1,3,4-thiadiazole and 2,4-dimercaptopyrimidine were used to trap sulfenic acids from penicillin sulfoxides.

Kamiya et al[1] first reported the preparation of unsymmetrical azetidinone disulfides 1 from penicillin sulfoxides and utilized this disulfide 1 for the derivatization of the β-methyl group in penicillins. Since then, "Kamiya's disulfide" has found synthetic utility for the preparation of many other 2β-methylpenam derivatives including triazolyl[2], halo[1], azido[2,3] substituted amino[3], hydroxy[4], alkoxy[3] and nitroxy[5]. Though 2-mercaptobenzothiazole is a convenient thiol for the trapping of sulfenic acid from penicillin sulfoxide, our previous papers[6-8] in this series have described the use of other substituted monothiols ranging from aliphatic to aromatic to heteroaromatic. However, part of the usefulness of these unsymmetrical disulfides as synthetic intermediates greatly depend on their ability to recyclise to the five membered thiazolidine ring system of the penam nucleus.

We found the disulfides 2 in which 'B' is aliphatic (e.g., 2b) or aromatic (e.g., 2a) failed to cyclise under the experimental conditions employed with the disulfides in which 'B' is heteroaromatic (e.g., 2c). As an extension of our program in this area we decided to study dimercapto compounds, e.g.,



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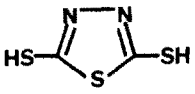

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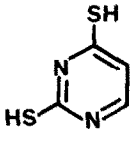

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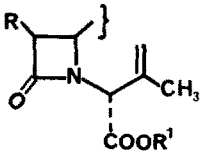
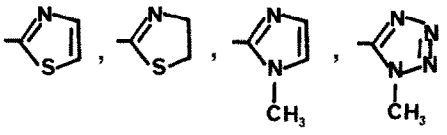
A–S–S–B

2

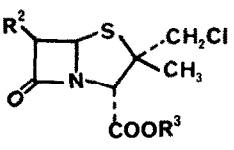
a, B =  X = H, Cl, NO_2, CH_3, OCH_3

b, B = $CH_2COOC_2H_5$

A = 

c, B = 

R = $PhOCH_2CONH$, $PhCH_2CONH$, H



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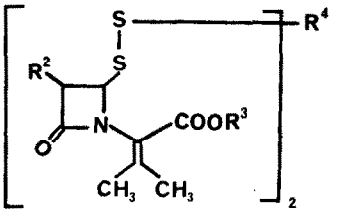
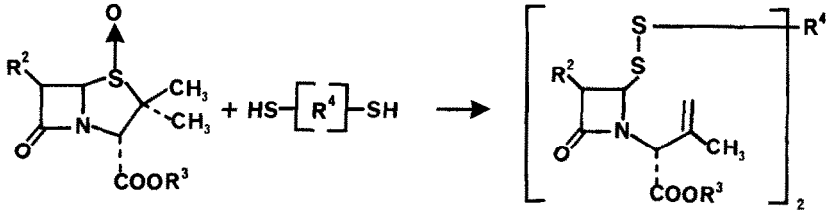
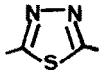
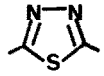
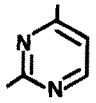
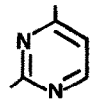
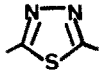
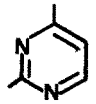
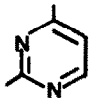


7

TABLE



5 6

Compound	R^2	R^3	R^4	Solvent	Time (h)	Yield (%)
6a	$PhOCH_2CONH$	CH_2CCl_3		Dioxane	7.5	85
6b	$PhOCH_2CONH$	CH_3		Dioxane	7	91
6c	$PhOCH_2CONH$	CH_2CCl_3		Dioxane	12	95
6d	$PhOCH_2CONH$	CH_3		Dioxane	12	87
6e	H	$CH_2.C_6H_4.NO_2$		Dioxane	7	88
6f	H	$CH_2.C_6H_4.NO_2$		Dioxane	12	90
6g	H	CH_3		Dioxane	12	90

2,5-dimercapto-1,3,4-thiadiazole 3 and 2,4-dimercaptopyrimidine 4 as trapping agents. When one equivalent of 3 was heated under reflux with two equivalents of the penicillin sulfoxide 5 in dioxane, the desired adduct 6 was obtained in almost quantitative yield after the usual work up. Similar results were obtained with 2,4-dimercaptopyrimidine 4. The table summarises some of our results.

When the crude adduct 6c dissolved in methylene chloride was stirred overnight with neutral alumina (Brockmann I) quantitative conversion to the α, β-isomer 7c occurred. Purification by silica gel chromatography and subsequent crystallization afforded the pure α,β-isomer 7c, mp 110-115°. All the adducts 6a - 6g reacted smoothly with cupric chloride to give the corresponding 2β-(chloromethyl) penicillins 8 in good yields (70-75%).

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References:

1. T. Kamiya, T. Teraji, Y. Saito, M. Hashimoto, O. Nakaguchi and T. Oku, Tetrahedron Lett., 3001 (1973).

2. T. W. Hall, S. N. Maiti, R. G. Micetich, P. Spevak, S. Yamabe, N. Ishida, M. Kajitani, M. Tanaka and T. Yamazaki in "Recent Advances in the Chemistry of β-Lactam Antibiotics", Eds., S. M. Roberts and A. G. Brown, Royal Society of Chemistry, London, pp. 242-254, 1985.

3. T. Kamiya, T. Teraji, M. Hashimoto, O. Nakaguchi, and T. Oku, U.S. Patent 3954732 (1976).

4. D. O. Spry, J. Org. Chem., 44, 3084 (1979).

5. S. Kukolja, S. R. Lammert, M. R. Gleissner, and A. I. Ellis, J. Am. Chem. Soc., 97, 3192 (1975).

6. R. G. Micetich, S. N. Maiti, M. Tanaka, T. Yamazaki and K. Ogawa, Tetrahedron Lett., 26, 3179 (1985).

7. R. G. Micetich, S. N. Maiti, M. Tanaka, T. Yamazaki and K. Ogawa, Heterocycles, 23, 1403 (1985).

8. R. G. Micetich, S. N. Maiti, M. Tanaka, T. Yamazaki and K. Ogawa, Heterocycles, 23, 325 (1985).

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