Tetrahedron Letters,Vol.26,No.27,pp 3179-3182,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

THE TRAPPING OF SULFENIC ACIDS FROM PENICILLIN SULFOXIDES. ETHYL 2-MERCAPTOACETATE

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Abstract: The thermolysis of trichloroethyl 6-phenoxyacetamido penicillanate sulfoxide and ethyl 2-mercaptoacetate in toluene gave the unsym-azetidinone disulfide (β,γ-isomer) in 65% yield. With added catalytic amounts of N,N-dimethylaniline the α,β-isomer was the major product (60%), along with a new β-lactam cleaved product, 8 (5-6%).

The oxidation of thiols to disulfides is suggested to proceed by way of sulfenic acids[1,2]. On this basis, the sulfenic acids formed by the thermal sigmatropic rearrangement of penicillin sulfoxides have been trapped intermolecularly by thiols to give unsym-azetidinone disulfides[3-5]; and intramolecularly by a C-6-thioamide substituent to provide the 1,2,4-dithiazeneazetidinones[6,7].

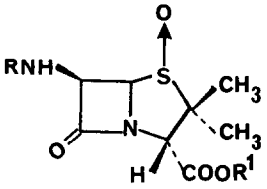
While penicillin sulfoxides reacted with 2-mercaptobenzothiazole (one mole equivalent), in a solvent such as toluene or dioxane, under reflux for about 4 hours, to give an essentially quantitative yield of the β,γ-unsaturated isomer, 3 (R^2 = 2-benzothiazole)[3]; the reaction with aliphatic mercaptans (2-methyl-propane-1-thiol or butane-1-thiol) using the mercaptan (as solvent and reagent) was slow (up to 120 hours), and gave only the α,β-unsaturated isomer, 4 (R^2 = iso-Bu or n-Bu)[4,5]. This difference in isomers formed may be a result of the long reaction time (due to the lower boiling point of the aliphatic mercaptan compared to toluene or dioxane or the relative inactivity of the alkyl thiol). We have previously prepared both the pure α,β- and the β,γ-unsaturated isomers, 3, and, 4, (R^2 = tert-Bu) by a different route from the thiazoleneazetidinones, and found that these compounds are stable to chromatographic conditions on silica gel.[8]

We expected that the use of a suitable activated high-boiling alkyl thiol, such as ethyl 2-mercaptoacetate, would reduce the reaction time and produce the β,γ-isomer, 3 (R^2 = $-CH_2COOC_2H_5$) rather than the α,β-isomer, 4. This paper describes our studies on the trapping of the sulfenic acids from penicillin sulfoxides using ethyl 2-mercaptoacetate.

When the trichloroethyl ester of 6-phenoxyacetamido penicillanate sulfoxide, 1, (R = $\emptyset OCH_2CO-$, R^1 = CH_2CCl_3) was refluxed in toluene for 20 hours with ethyl 2-mercaptoacetate (1.1 equivalent) in a nitrogen atmosphere, and the reaction mixture concentrated under vacuum, the β,γ-unsym-azetidinone disulfide, 3 (R = $\emptyset OCH_2CO$, R^1 = CH_2CCl_3, R^2 = $CH_2COOC_2H_5$) was obtained as a foam in 70% yield along with small amounts of the α,β-isomer, 4, compound 5 and 6 (from the PMR spectrum of the crude product). An attempt to purify the compound by silica gel chromatography resulted in isomerisation of the β,γ-isomer, 3, to the α,β-isomer, 4. When the crude product dissolved in methylene chloride was stirred for 4 hours with neutral alumina (Brockmann I), quantitative conversion to the α,β-isomer (purified by column chromatography) occurred. This change was accompanied by a shift in the β-lactam carbonyl infrared maximum from 1800 cm^{-1} (for 3) to 1775 cm^{-1} (for 4). The nmr ($CDCl_3$) spectrum: δ 1.3 (t, 3H, $COOCH_2CH_3$), 2.25 and 2.4 (ss, 6H, gem-CH_3), 3.35 (s, 2H, -S-CH_2-), 4.22 (q, 2H, $COOCH_2CCl_3$), 4.65 (s, 2H, -OCH_2-), 4.87 (q, 2H, CH_2CCl_3), 5.25 (q, 1H, C_3-H), 5.68 (d, 1H, C_4-H), 6.95 to 7.6 (m, C_6H_5 and NH), is consistent with structure 4. In addition, small amounts of compounds 5, 6, and 7, identical with authentic samples were also isolated by column chromatography.

When the penicillin sulfoxide, 1, was heated for 6 hours with neat ethyl 2-mercapto-acetate, the major product was the β-lactam cleaved product, 5; while addition of a catalytic amount of a Lewis acid (such as aluminum tribromide), to inhibit the formation of free thiolate anion, resulted in extensive β-lactam ring cleavage.

When the penicillin sulfoxide, 1, was heated with the thiol in refluxing toluene, in the presence of a catalytic amount of N,N-dimethylaniline, the major product (60% after chromatography) was the α,β-isomer, 4 (R = $\emptyset OCH_2CO$, R^1 = CH_2CCl_3, R^2 = $CH_2COOC_2H_5$). Also isolated (7-9%) were the non β-lactam compounds 5, 6, and 7; and a new β-lactam cleaved product (5-6%), 8 (R = $\emptyset OCH_2CO$, R^1 = CH_2CCl_3). The structure of 8 was supported by the spectral (IR, PMR, CMR, and mass) data. IR ($CHCl_3$); cm^{-1}, 1730 (unsaturated ester), 1665 (amide), 1598 (c = c). PMR ($CDCl_3$); δ 1.25 (t, 3H, $COOCH_2CH_3$), 1.95 and 2.25 (ss, 6H, gem. CH_3), 3.5 (s, 2H, -SCH_2-), 4.2 (q, 2H, $COOCH_2$), 4.6 (s, 2H, -OCH_2), 4.8 (s, 2H, -CH_2CCl_3), 6.95 to 7.4 (m, 6H, C_6H_5 and vinylic H), 7.52 (s, 1H, exchanged by D_2O, NH), 8.41 (s, 1H,



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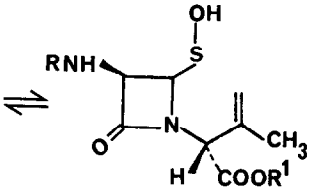

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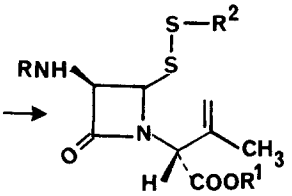

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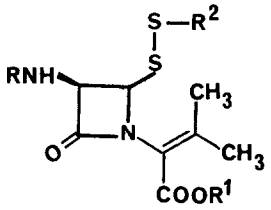

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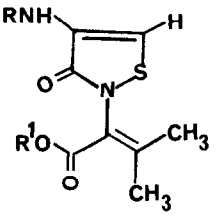

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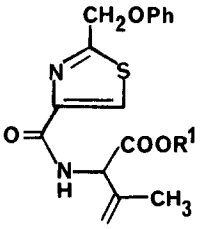

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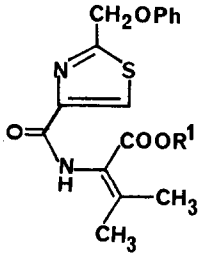

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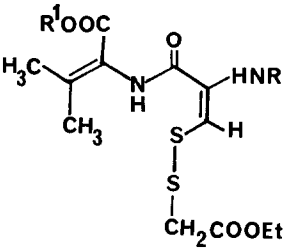

8

R = $PhOCH_2CO$

$R^1 = CH_2CCl_3$

$R^2 = CH_2COOEt$

exchanged by D_2O, NH). CMR ($CDCl_3$): δ 3 CH_3 (14.4, 22.0, 23.4), 4 CH_2 (42.0, 63.0, 68.0, 75.5), 5 CH (Aryl) (116, 123.5, 131), 1 CH (134.0), 9 tert-C (95.6, 120.8, 127.6, 152.6, 158.4, 162.8, 163.8, 168.0, 170.4). Mass Spec. m/e 480 (M^+-$SCH_2COOC_2H_5$), 303 (480-$COOCH_2CCl_3$), 135 ($\emptyset OCH_2CO^+$), 107 ($\emptyset OCH_2^+$), 77 ($C_6H_5^+$, 100%).

Compound 8 could possibly be formed by the base catalysed ring opening of 4. However when 4 was heated in toluene with N,N-dimethylaniline a mixture of 5 and 7 was formed. Also when 5 was heated with ethyl 2-mercaptoacetate and N,N-dimethylaniline, only 7 was isolated, proving that 5 is not a precursor of 8. It is hence probable that 8 is formed from the intermediate sulfenic acid 2.

Acknowledgement - The authors wish to thank Taiho Pharmaceutical Co., of Japan, for their research support which made this work possible.

REFERENCES

1. K. Sirakawa, O. Aki, T. Tsujikawa and T. Tsuda, Chem. Pharm. Bull. (Japan), 18, 235 (1970).

2. J. P. Danehy and M. Y. Oester, J. Org. Chem., 32, 1491 (1967).

3. T. Kamiya, T. Teraji, Y. Saito, M. Hashimoto, O. Nakaguchi, and T. Oku, Tetra. Letters, 3001 (1973).

4. R. D. Allan, D. H. R. Barton, M. Girijavallabhan, P. G. Sammes and M. V. Taylor, J. C. S. Perkin I, 1182 (1973).

5. D. H. R. Barton, P. G. Sammes, M. V. Taylor, C. M. Cooper, G. Hewitt, B. E. Looker and W. G. E. Underwood, Chem. Comm., 1137 (1971).

6. R. G. Micetich, C. G. Chin and R. B. Morin, Tetra. Letters, 975 (1976).

7. H. Tanida, R. Muneyuki and T. Tsushima, Tetra. Letters, 3063 (1975).

8. R. G. Micetich, R. A. Fortier and J. Liew, Can. J. Chem., 59, 1020 (1981).

(Received in USA 13 September 1984)