THE TRAPPING OF SULFENIC ACIDS FROM PENICILLIN SULFOXIDES. HETEROCYCLIC MERCAPTANS

Ronald G. Micetich*, Samarendra N. Maiti*, Motoaki Tanaka†, Tomio Yamazaki†, and Kazuo Ogawa†

*Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Alberta, Canada T6G 2N8

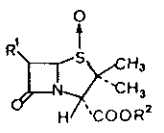
†Research Institute, Taiho Pharm. Co. Ltd., Tokushima, Japan

Abstract - Various heterocyclic thiols have been used for trapping the azetidinone sulfenic acids obtained by the thermolysis of penicillin sulfoxides. The ester function was found to be important in determining the unsym-azetidinone disulfide (α,β- or β,γ-unsaturated) isomer formed. All β,γ-isomers prepared reacted with cupric chloride to give the 2-chloromethylpenams.

There have been considerable research efforts directed towards the trapping of the reactive azetidinone sulfenic acids, 2, produced by the thermolysis of penicillin sulfoxides, 1. A variety of reagents which include olefins or acetylenes[1-4], azo compounds[5], arylsulfinic acids[6], trimethylsilyl chloride-hexamethyldisilazane[7] and imides[8], and thioamides[9], have been investigated. One of the most efficient and useful trapping methods is by the nucleophilic substitution of the sulfenic acids by 2-mercaptobenzothiazole to give the unsym-azetidinone disulfides, 3[10,11].

These intermediates, 3, lend themselves to further manipulation to produce the 2-substituted methylpenams, 4, the 3-substituted cephams, 5, and the cephems, 6, through the common episulfonium ion, 7. In addition the compounds 3 have been successfully utilized for the synthesis of other modified β-lactam antibiotics such as the azetidinone thioethers[12], sulfenylanilide [13], penems[14], oxapenems[15], 3-exomethylenecephams[16], 3-hydroxycephems[17], and 3-methoxycephems [17,18]. In spite of the considerable synthetic importance of these disulfides, there is surprisingly little data in the literature on this class of compounds -- the use being almost exclusively restricted to the 2-benzothiazole derivative, 3 (R^3=2-benzothiazole).

There are two important features that make the unsym-azetidinone disulfides, 3, useful and versatile synthetic intermediates for certain subsequent reactions. These are the reactivity



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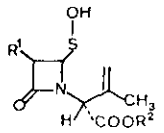

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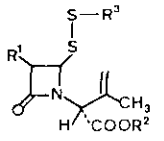

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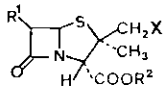

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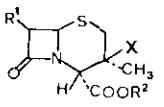

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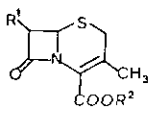

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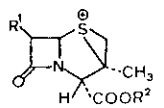
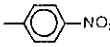


7

R^1 = $PhOCH_2CONH$, $PhCH_2CONH$, H

R^2 = CH_3 , CH_2Cl_3 , CH_2—  —NO_2 , $CHPh_2$

R^3 = Heterocyclic (monocyclic or bicyclic)

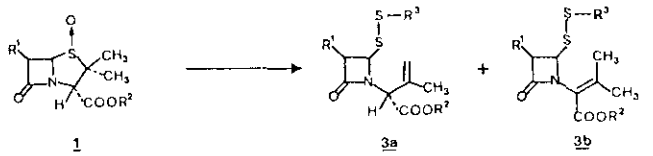
X = Cl , Br , I

of the disulfide bond to halogenation or oxygenation. As we have shown, this reactivity is determined by the nature of the R^3 group. When R^3 is alkyl (tert-butyl) or aryl (phenyl), the disulfide is inert to reagents such as cupric chloride[19]. The second factor is the location of the double bond, and this is in turn influenced by the nature of the ester group (R^2), the nature of the side chain at C-6 (R^1)[20], and the nature of the thiol used [19].

2-Mercaptobenzothiazole and 2-mercaptobenzoxazole are particularly well suited for this purpose, and 2-mercaptobenzothiazole has been utilized almost exclusively for this purpose, probably because of its ready availability and low cost. However, various other heteroaromatic thiols are equally effective, as is the nonaromatic 2-mercaptothiazoline. Table 1 summarizes the results of some of our work in this area.

TABLE 1

Conversion of Penicillin Sulfoxides to Azetidinone Disulfides



1 3a 3b

Expt. No.	R^1	R^2	R^3	Reaction Time (h)	Solvent	Products ratio[a] 3a : 3b
1	$PhOCH_2CONH$	CH_2CCl_3		2.5	toluene	100 : 0
2	H	$CH_2 \cdot C_6H_4 \cdot NO_2$		2.5	toluene	100 : 0
3	$PhOCH_2CONH$	CH_2CCl_3		2.0	toluene	100 : 0
4	H	$CH_2 \cdot C_6H_4 \cdot NO_2$		3.5	dioxane[b]	100 : 0
5	$PhOCH_2CONH$	CH_2CCl_3		2.0	toluene[c]	0 : 100
6	$PhOCH_2CONH$	CH_3		2.0	toluene	80 : 20
7	$PhOCH_2CONH$	CH_2CCl_3		2.0	toluene	65 : 35
8	$PhOCH_2CONH$	CH_3		2.0	toluene	100 : 0
9	$PhOCH_2CONH$	CH_2CCl_3		2.0	toluene[d]	0 : 100
10	$PhOCH_2CONH$	CH_3		4.0	dioxane	100 : 0

a. Estimated from the pmr spectrum of the crude product.
b. In toluene, some decomposition products were obtained.
c. Small amounts (~ 5%) of the isothiazolone was isolated after column purification.
d. The mixture was not homogeneous in refluxing toluene.

The product ratio of the β,γ-isomer 3a to the α,β-isomer, 3b, varies remarkably depending on the choice of the carboxyl protecting group, as well as the reaction conditions. The carboxyl protecting group affects the acidity of the C-3 proton. Thus, in the methyl ester series (see experiments 6, 8 and 10 in table 1) this proton, adjacent to the ester function, has low acidity. The acidity of this proton in the corresponding trichloroethyl esters (see experiments 5, 7 and 9) is high and this results in the formation of the α,β-isomer, 3b.

However, this is not the only factor responsible for this isomerisation. The nature of the R^3 moiety is also important. Thus, in the trichloroethyl ester series, when R^3 is thiazole (experiment 1) or tetrazole (experiment 3) the β,γ-isomer is the sole product; whereas with the imidazole and benzimidazole (experiments 5 and 9), the α,β-isomer is the only product. Thus with 2-mercapto-1-methylimidazole and the trichloroethyl ester of penicillin V sulfoxide, two hours reflux in toluene give complete conversion to the α,β-isomer, 3b, (experiment 5), whereas the methyl ester under identical conditions gives 80% of 3a and 20% of 3b (experiment 6). Similar results are obtained with 2-mercaptothiazoline (experiments 7 and 8). With 2-mercaptobenzimidazole 100% of the α,β-isomer, 3b, was obtained with the trichloroethyl ester in toluene after 2.0 h reflux; and 100% of the β,γ-isomer, 3a, with the methyl ester in dioxane over 4 h. However in this latter case besides the change in ester there is also a change in solvent, which could also affect the reaction, particularly since the reaction mixture in toluene was not homogeneous.

The reactions were monitored for completeness of reaction by thin layer chromatography, and by removing aliquots from the reaction mixture periodically, and after work-up, analysing the crude product by its ^1H nmr spectrum. The gem-dimethyl doublet of compounds 1, the singlet of the $\rangle\!\!-CH_3$ protons of 3a, and the doublet of the $\!\!\prec^{CH_3}_{CH_3}$ group of 3b were sufficiently separated to obtain clearly separated integrations for the analysis.

In general, toluene appears to be the solvent of choice (except as for experiment 9 where solution was not complete). The reactions in dioxane appeared to be somewhat slower. The reason is not clear but could be because of the high solubility of the water (formed in the reaction) in dioxane, and possible stabilization of the reactive sulfenic acid, 2, by complexing with the dioxane.

The products from experiments 1 to 4 and 6 to 8 (in Table 1) reacted smoothly with cupric chloride in methylene chloride to give the corresponding 2-chloromethylpenams, 4. In the case of the product from experiment 10, it was not soluble in methylene chloride or chloroform.

GENERAL PROCEDURE FOR THE PREPARATION OF THE UNSYM-AZETIDINONE DISULFIDES

An equimolar amount of the penicillin sulfoxide 1, and the respective thiol was heated to reflux in toluene using a Dean-Stark trap; or in dioxane using a Soxhlet packed with molecular sieves (4A), for 2-4 h (see Table 1). The reaction mixture was concentrated to dryness under reduced pressure. The crude product was dissolved in dichloromethane and precipitated with hexane with cooling. The residual viscous liquid could be treated with charcoal if necessary, filtered and concentrated to a white or light-yellow foam, pure enough for further reactions.

GENERAL PROCEDURE FOR THE PREPARATION OF 2-CHLOROMETHYLPENAMS, 4

The azetidinone disulfide, 3a, was dissolved in dichloromethane. To this solution was added anhydrous powdered cupric chloride (10% excess) and the mixture stirred for 4-5 h at room temp. The mixture became yellowish green to dark green which indicated the progress of the reaction. Completion of the reaction was determined by thin layer chromatography. The solid was filtered through a celite pad. The filtrate was concentrated under reduced pressure, and filtered rapidly through a small bed of silica gel, and the filtrate concentrated to give an off-white foam of the 2β-chloromethylpenam, used as such in further reactions.

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