THE TRAPPING OF SULFENIC ACIDS FROM PENICILLIN SULFOXIDES. ARYL MERCAPTANS

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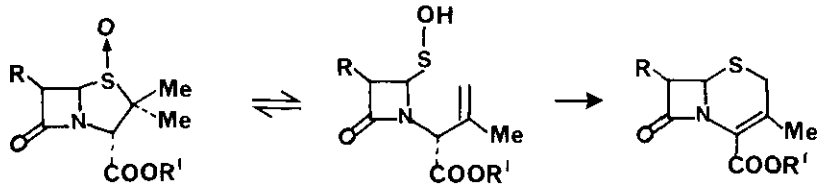
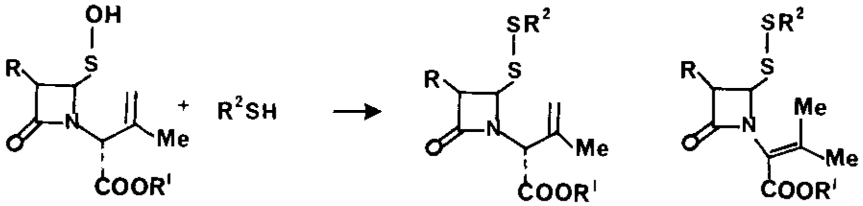
Abstract — Aryl mercaptans, unlike heterocyclic mercaptans, reacted exceptionally slowly with penicillin sulfoxides. These reactions are affected by the substituent at the C-6 position of the penam, and by the nature of the ester group at the C-3 position. The unsym-azetidinone disulfides obtained from these reactions, unlike those from heterocyclic mercaptans, did not react with halogenating agents *such as cupric chloride*.

The penicillin sulfoxides, 1, first reported some 35 years ago[1], are converted on thermolysis in the presence of suitable catalysts to the desacetoxycephalosporins, 3[2]. This reaction was suggested to proceed by way of the sulfenic acids, 2[2].



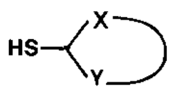
1 2 3

The existence of an equilibrium between the penicillin sulfoxides, 1, and the azetidinone sulfenic acids, 2, was substantiated by several groups[3], and the sulfenic acids have been trapped by various agents. A very efficient and widely used trapping agent, first reported by Kamiya's group at Fujisawa, is 2-mercaptobenzothiazole, which produces high yields of the azetidinone disulfides, 4 (R^2= 2-benzothiazole)[4,5].

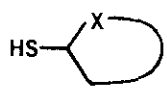


2 4 5

Other heteroaromatic thiols or even non-aromatic heterocyclic thiols, such as 2-mercapto-thiazoline, are equally effective as 2-mercaptobenzothiazole, for these trapping reactions[5,6]. Although 2-mercaptobenzothiazole has been used extensively, and a few aliphatic thiols[7–9] (see also our report on ethyl 2-mercaptoacetate[10]) have been investigated, a study of the reaction of penicillin sulfoxides, 1, with aromatic thiols has not so far been reported. When the carbon atom attached to the thiol group is flanked by two heteroatoms as in A, (for example 2-mercaptobenzothiazole), or even by only one heteroatom as in B (for example 2-mercaptopyridine), the thiols are highly reactive and the trapping reactions to produce 4, are complete within 2 to 4 h. Replacement of the heteroatoms by carbon atoms changes the



A



B

property of the thiol completely, and the trapping reactions with these types of thiols are exceptionally slow. Thus, when the penicillin sulfoxide, 1 (R=$PhOCH_2CONH$, R^1=CH_2CCl_3) was heated under reflux with an equimolar amount of 4-methyl-2-mercaptothiazole in toluene, the reaction was complete in 2.5 h giving the corresponding disulfide, 4, in quantitative yield[6]. By contrast, reaction of the same sulfoxide with two equivalents of thiophenol in toluene was complete only after 22 h. The results of our work in this area, with various substituted thiophenols, are summarised in Table 1. The progress of the reactions was monitored by working up aliquots of the reaction mixture periodically and analysing the ^1H nmr spectrum of the crude product. In the case of the trichloroethyl ester series, the *gem*-dimethyl doublet of the sulfoxide, 1, the singlet of the $\underline{CH_3}$ protons of the β,γ-

unsaturated isomer, 4, and the doublet of the isopropylidene group of the α,β-unsaturated isomer, 5, were clearly separated, so that the integration of these signals provide a convenient basis for the analysis.

TABLE 1

Expt. No.	R	R^1	Thiol	Sulfoxide:Thiol Molar Ratio[a]	Reaction Time (h)	Yield % [b,c] β,γ : α,β
1	$PhOCH_2CONH$	CH_3	C_6H_5SH	1 : 1.2	16	95 -
2.	$PhOCH_2CONH$	CH_3	p-ClC_6H_4SH	1 : 1.2	15	95 -
3.	$PhOCH_2CONH$	CH_3	p-$CH_3C_6H_4SH$	1 : 1.2	15	95 -
4.	$PhOCH_2CONH$	CH_3	p-$CH_3OC_6H_4SH$	1 : 1.2	15	95 -
5.	$PhOCH_2CONH$	CH_2CCl_3	C_6H_5SH	1 : 2	22	75 15
6.	$PhOCH_2CONH$	CH_2CCl_3	p-ClC_6H_4SH	1 : 1.5	20	75 15
7.	$PhOCH_2CONH$	CH_2CCl_3	p-$CH_3C_6H_4SH$	1 : 2	16	75 15
8.	$PhOCH_2CONH$	CH_2CCl_3	p-$CH_3OC_6H_4SH$	1 : 2	21	70 20
9.	H	CH_3	p-$CH_3C_6H_4SH$	1 : 1.2	15	No Reaction
10.	H	CH_3	p-$CH_3C_6H_4SH$	1 : 2	30	50 -

a. When a ratio of sulfoxide:thiol of 1:1 was used, the reaction time was found to be much slower than when larger amounts of the thiol was used; thus, even after 30 to 40 h starting sulfoxide was still present in these reaction mixtures.

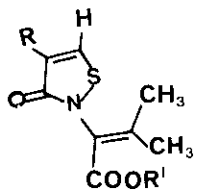
b. Estimated from the pmr spectrum of the crude product.

c. Small amounts (5 to 10%) of non β-lactam products (6 and 7) were present in the reaction mixture.

With the trichloroethyl esters the proton adjacent to the carboxyl group is more acidic than that of the corresponding methyl ester derivative. The result is that, with the long reaction times required with the aryl mercaptans, the products from the trichloroethyl ester is always a mixture of the β,γ-, 4, and α,β- , 5, unsaturated isomers. Treatment of these mixtures with neutral alumina effects complete conversion to the α,β-isomer, 5.

Because of the labile nature and low concentration of the sulfenic acid formed, these trapping reactions have to be relatively efficient in order to compete with other side reactions, such as rearrangements and β-lactam cleavage. Since the aryl mercaptans are relatively unreactive

as trapping agents, a small amount (5 to 10%) of non β-lactam products (as judged from the ^{1}H nmr spectra of the crude products) is also obtained. When a large excess of the aryl mercaptan was used, the amount of non β-lactam products (6 and 7) increases considerably.



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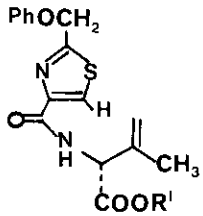

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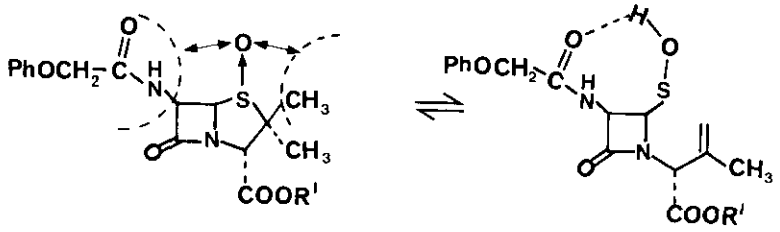
Another interesting observation in this series, emphasized by the slowness of these reactions, is the effect of the C-6 substituent of the penicillin sulfoxide on the formation of the sulfenic acid. When the methyl ester of 6β-phenoxyacetamidopenicillanate-1β-sulfoxide, 1 (R=$PhOCH_2CONH$, R^1=CH_3) - see Table 1, Expt 3 - was heated under reflux with thiocresol (1.2 equivalent) in dry toluene under nitrogen, the reaction was complete in 15 h - no starting sulfoxide, 1, being observed in the pmr spectrum of the crude product. However, when methyl 6,6-dihydropenicillanate-1β-sulfoxide, 1 (R=H, R^1=CH_3)[11] - Table 1, Expt 9- was heated with thiocresol (1.2 equivalent) under exactly the same conditions, there was NO observable reaction after 15 h - only starting sulfoxide, 1, being observed in the pmr spectrum of the crude reaction mixture. With thiocresol (2 equivalents), even after 30 h there was still about 50% of the starting sulfoxide left unreacted.

This difference in reactivity can be explained by the steric crowding effect of the 6β-phenoxyacetamido side chain (see structure 8). Since both the 6β-phenoxyacetamido and the 1β-sulfoxide groups are in the same face (the hindered β-face) of the molecue, the steric compression by the 6β-phenoxyacetamido and the syn-2β-methyl group against the 1β-sulfoxide bond leads to a more efficient opening of the thiazolidine ring to form the sulfenic acid, 2, and thus help relieve the steric strain. A similar steric buttressing effect by the C-3 carboxyl protecting group adjacent to the gem-dimethyl group has been noted previously[12]. The bulkier the acid derivative at C-3, the faster the reaction[12].

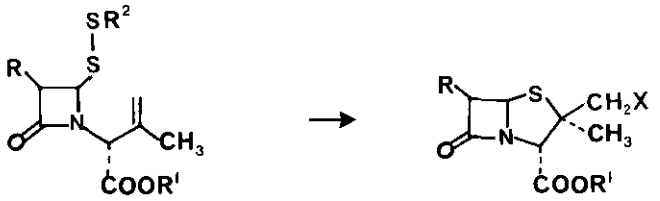


8 ⇌ 9

Another factor could be that when the penoxyacetamido or phenylacetamido side chain is present at C-6, the sulfenic acid formed is stabilised through H-bonding (see structure 9), thus favouring the reaction (8⇌9), and hence increasing the concentration of the sulfenic acid in the reaction mixture.

The trapping reaction of the sulfenic acid from 6,6-dihydropenicillanate-1β-sulfoxide with highly reactive thiols, such as 2-mercaptobenzothiazole or 4-methyl-2-mercaptothiazole, in refluxing toluene proceeds normally, and is complete in 3 to 4 h. In this case, once the sulfenic acid is formed, even in very low concentration, due to the very efficient trapping agents, the reaction is driven to completion.

Another significant observation in this series is with regard to the reaction of the unsym-azetidinone disulfides, 4 (R=$PhOCH_2CONH$, R^1=CH_3, R^2= C_6H_4X, where X=H, Cl, CH_3 and OCH_3), with chlorinating agents such as cupric chloride or sulfuryl chloride. Compounds 4 (R^2= heterocyclic ring), react readily when dissolved in methylene chloride and stirred with cupric chloride at room temperature, the product being the 2β-chloromethylpenam, 10 (X=Cl). A similar reaction occurs with sulfuryl chloride under carefully controlled conditions.



4 → 10

In contrast, the disulfides, 4 (R^2=phenyl or substituted phenyl) were exceptionally inert to cupric chloride and sulfuryl chloride - no reaction being observed.

A similar observation was made previously by us on compounds 4 where R^2= tert-butyl[13].

The nature of the R^2 group in the unsym-azetidinone disulfides, 4, thus determines the reactivity of the S-S bond towards halogenation, and formation of the sulfenyl halide.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover uni-melt melting point apparatus, and are uncorrected. IR spectra were recorded on a Nicolet DX FTIR Spectrometer - only significant maxima are reported. ^{1}H NMR spectra were obtained using a Varian Em-360 Spectrometer and are reported in ppm downfield from TMS as an internal reference. Representative examples are included.

Reaction of methyl 6β-phenoxyacetamidopenicillanate-1β-sulfoxide, 1 (R=$PhOCH_2CONH$, R^1=CH_3) with thiophenol.

A mixture of methyl 6β-phenoxyacetamidopenicillanate-1β-sulfoxide, 1 (1 g, 0.0026 mole) and thiophenol (0.3471 g, 0.0031 mole) in toluene (15 ml) was heated under reflux, in a nitrogen atmosphere, for 16 h, using a Dean-Stark trap. Toluene was then removed under reduced pressure, and the residue dissolved in a small volume of methylene chloride, and precipitated with hexane under cooling. The separated oil was retreated twice, with methylene chloride and hexane, in the same way. The resulting material was dried under vacuum to give a sticky foam. These compounds were rapidly affected by silica, so that purification by silica gel chromatography was not possible. The compound had IR ($CHCl_3$): cm^{-1} 3300(NH), 1780(β-lactam), 1740(ester), 1690(amide); NMR ($CDCl_3$): δ 6.9-7.8(m,11H,aryl and NH), 5.64 dd,1H,J=4.5,8.0Hz, 3-H), 5.4(d,1H,J=4.5Hz,4-H), 5.1 and 4.9(two br s, 2H, $C=CH_2$), 4.68(s,1H,CHCOO), 4.45 (br s, 2H,OCH_2CO), 3.72(s,3H,$COOCH_3$), 1.80(s,3H,CH_3).

Reaction of trichloroethyl 6β-phenoxyacetamidopenicillanate-1β-sulfoxide, 1 (R=$PhOCH_2CONH$, R^1=CH_2CCl_3) with p-thiocresol.

A mixture of the sulfoxide (1 g, 0.002 mole) and p-thiocresol (0.5069 g, 0.004 mole) in toluene (15 ml) was heated under reflux in a nitrogen atmosphere for 16 h. The toluene was removed under reduced pressure and the residue dissolved in methylene chloride and stirred with neutral alumina (Brockmann I), for 10 h. The mixture was filtered and concentrated in vacuum to give a white foam, 0.9 g. Chromatography on silica using ethyl acetate : hexane (3 : 2) as eluant gave 0.82 g of (3R,4R)-4-(p-methylphenyl-dithio)-1-[2-methyl-(2,2,2-trichloroethoxycarbonyl)prop-1-enyl]-3-phenoxyacetamido-azetidin-2-one as a white solid, mp 58-62°C ; IR (KBr): cm^{-1} 3300(NH), 1778(β-lactam), 1738(ester), 1689(amide) ; NMR ($CDCl_3$): δ 6.88-7.50(m,10H,aryl and NH), 5.68(d,1H,J=4.5Hz,4-H), 5.30(dd,1H,J=4.5,8.0Hz,3-H), 4.70 (ABq,2H,J=12Hz,$COOCH_2CCl_3$), 4.50(s,2H,OCH_2CO), 2.30(s,3H), 2.20(s,3H), 2.10(s,3H).

(3R,4R)-4-(p-Methoxyphenyldithio)-1-[2-methyl-1-(2,2,2-trichloroethoxycarbonyl)prop-1-enyl]-3 phenoxyacetamidoazetidin-2-one, 5 (R=$PhOCH_2CONH$, R^1=CH_2CCl_3, R^2=$C_6H_4OCH_3$), was made analogously; mp 55-60° C; IR (KBr): cm^{-1} 3353 (NH), 1780(β-lactam), 1740(ester), 1689(amide) ; NMR ($CDCl_3$):δ 6.70-7.55(m,10H,aryl and NH), 5.68(d,1H,J=5.0Hz,4-H), 5.30(dd,1H,J=5.0,8.0Hz, 3-H), 4.78(ABq,2H,J=16Hz,$COOCH_2CCl_3$), 4.45(s,2H,OCH_2CO), 3.72(s,3H,OCH_3), 2.20(s,3H), 2.05

(s,3H).

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