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DESULFURISATION OF PENICILLIN-DERIVED DISULFIDES - SYNTHESIS OF SOME 4-AZA-AZETIDINONES

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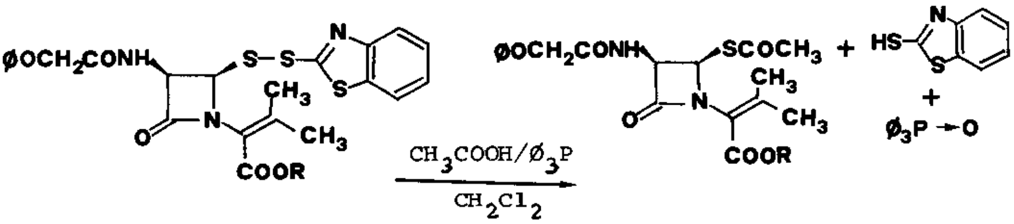
Abstract:Disulfides (1), (2) and (3) on treatment with triphenylphosphine in refluxing benzene yielded 4-aza-azetidinones (7),(8) and (9) in addition to the expected sulfides (4), (5) and (6). The structures of these compounds were determined by ^{1}H NMR and ^{13}C NMR data. Analogous products were also isolated from the reaction of azetidinone (10) with 2-mercaptobenzothiazole.

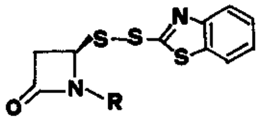
In an earlier publication[1], we described a new method of making thioesters (Scheme 1) starting from disulfides derived from penicillins using carboxylic acids and triphenylphosphine.



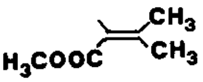
Scheme 1

This method was found to be applicable only to disulfides possessing an acylamino group in cis fashion to the disulfide function on the β-lactam nucleus. In the absence of such an acylamino group, the above reaction yielded only the sulfur extrusion products.

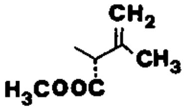
Desulfurisation[2] of penicillin-derived disulfides[3] in general is a very facile process compared to other disulfides and occurs readily under mild conditions. Compounds (1), (2) and (3) could be desulfurised to the

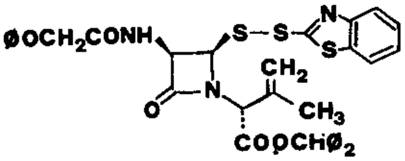


(1) R=



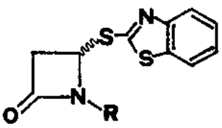
(2) R=



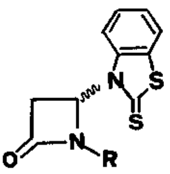


(3)

corresponding sulfides (4), (5) and (6) in high yield with triphenylphosphine in methylene chloride at 0° C. However, when the desulfurisation of the above disulfides was carried out in refluxing benzene we isolated, in addition to sulfides (4), (5) and (6), an isomeric series of products. Compound (1) upon treatment with



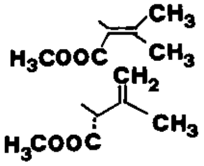
(4)



(7)

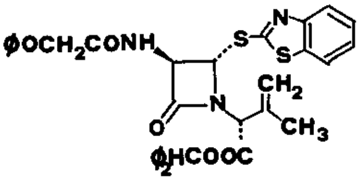
(4), (7) R =

(5), (8) R =

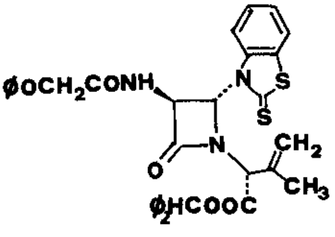


(5)

(8)



(6)



(9)

triphenylphosphine in refluxing benzene gave azetidinones (4) (55 %, IR (CH_2Cl_2): 1775 and 1725 cm^{1}) and (7) (40 %, IR (CH_2Cl_2): 1775, 1720 and 1240-1300 br cm^{-1}). Similarly, disulfide (2) gave compounds 5 (50 %, $[\alpha]_D^{20}$= -199° ($CHCl_3$), mp 54-56° C, IR (CH_2Cl_2): 1775 and 1740 cm^{-1}) and 8 (45 %, $[\alpha]_D^{20}$= -325° ($CHCl_3$), m p 122-124° C, IR (CH_2Cl_2): 1775, 1740 and 1240-1300 br cm^{-1}) and (3) gave compound(6)(oil, 40 %, $[\alpha]_D^{20}$= -35.8° ($CHCl_3$), IR (CH_2Cl_2): 3420, 1775, 1740 and 1685 cm^{-1}) and (9) (oil, 35 %, $[\alpha]_D^{20}$= -213.8° ($CHCl_3$), IR (CH_2Cl_2): 3425, 1785, 1745, 1690 and 1240-1300 cm^{-1}).

Table 1 ^{1}H NMR data 4-thioazetidinones (from SiMe$_4$, solvent CDCl$_3$)

compound	H-3 trans	H-3 cis	H-4	COOCH$_3$	CH$_3$	others
(4)	3.18 dd (J=16,2.5Hz)	3.76 dd (J=16,5Hz)	6.15 dd (J=2.5,5Hz)	3.85 (3H,s)	1.99 (3H,s) 2.16 (3H,s)	7.20-8.00 (4H,m)
(5)	3.16 dd (J=16,2.5Hz)	3.7 dd (J=16,5Hz)	5.85 dd (J=2.5,5Hz)	3.83 (3H,s)	1.90 (3H,br)	4.90(1H,br) 4.99(1H,br), 5.12(1H,br)and 7.20-8.00(4H,m)
(6)	5.15 dd (J=2.5,7Hz)		5.78 d (J=2.5Hz)		1.95 (3H,br)	4.58(2H,s) 4.96(1H,br) 5.13(2H,br) and 6.90-7.90(20H,m)
(11)	3.08 ddd (J=16,2.5, 1.3 Hz)	3.60 ddd (J=16,5, 1.8 Hz)	5.68 dd (J=5,2.5Hz)			7.20-8.00(4H,m) 8.55(1H,br)

The main feature in the ^{1}H NMR spectra (Table 1) of compounds (4) and (5)[5] is the appearance of a doublet of doublets for the three azetidinone protons showing the expected chemical shifts and coupling constants. The trans stereochemistry assigned for the two protons on the β-lactam ring in compound (6) is based on the observed coupling constant (J = 2.5 Hz).

Table 2 ^{1}H NMR data 4-Aza-azetidinones (from SiMe$_4$, solvent CDCl$_3$)

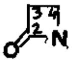
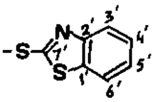
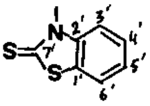
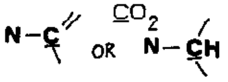
Compound	H-3 trans	H-3 cis	H-4	COOCH$_3$	CH$_3$	others
(7)	3.97 dd (J=16,2.5Hz)	3.59 dd (J=16,5Hz)	a)	3.74 (3H,s)	1.90 (3H,s) 2.14 (3H,s)	7.30-7.70(5H,m)
(8)	3.65, m	3.65, m	a)	3.47 (3H,s)	1.82 (3H,br)	4.85(1H,br) 5.20(1H,q,J=1.5Hz) 7.30-7.70(5H,m)
(9)	5.63 d [b)] (J=2.5Hz)		a)		1.76 (3H,br)	4.54(2H,s), 4.90 (1H,s),5.05(1H,br) 5.15(1H,q,J=1.5Hz) 6.80-7.60(21H,m)
(12)	3.65 m	3.65 m	a)			7.30-7.80(5H,m)
(12)+ (Eu(FOD)$_3$	6.00 dd (J=16,2.5Hz)	5.76 ddd (J=16, 5, 1.8 Hz)	8.35 dd (J=2.5,5Hz)			

[a)] overlapping with aromatic protons

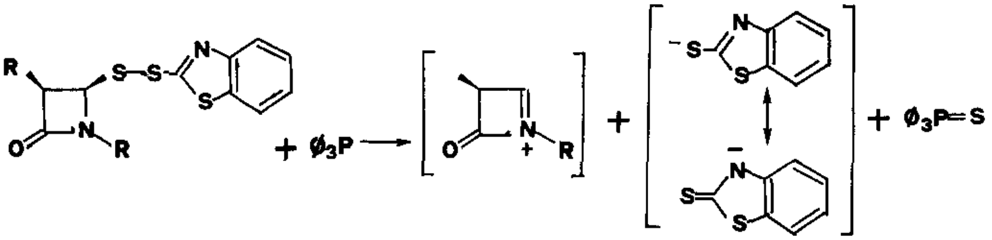
[b)] after exchange with D$_2$O

The isomeric desulfurised products are assigned structures (7), (8) and (9) on the basis of ^{1}H NMR (table 2) and ^{13}C NMR (table 3) data. In these compounds the resonance of the proton at C-4 is shifted downfield compared to its position at C-4 in compounds (4), (5) and (6). The sterochemistry of the two ß-lactam protons in aza-azetidinone (9) was found to be trans (J = 2.5 Hz), the same as in the isomeric thia-derivative (6). The ^{13}C chemical shifts of the thione carbon in compounds (7) (193 ppm) and (8) (191.6 ppm) resemble closely those reported for analogous compounds in the literature^{6}. The corresponding carbon in the thia-azetidinone (4) which is in the imine form appeared^{6} at 164.3 ppm.

Table 3 ^{13}C NMR data (from SiMe$_4$, solvent CDcl$_3$)

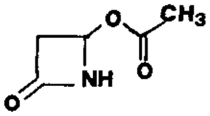
		(4)	(11)	(7)	(8)	(12)
	$\underline{C}$-2	164.3	164.8	165.4	165.7	165.6
	$\underline{C}$-3	44.1	44.6	41.2	41.9	43.8
	$\underline{C}$-4	59.6	52.8	64.5	62.6	60.0
	$\underline{C}$-1'	135.7	135.2	128.5	126.2	126.4
	$\underline{C}$-2'	153.4	153.4	139.9	139.6	139.8
	$\underline{C}$-3'	121.2	121.1	113.4	113.0	113.1
	$\underline{C}$-4'	125.1	124.7	127.1	126.9	127.2
	$\underline{C}$-5'	122.3	121.8	125.3	124.7	125.0
	$\underline{C}$-6'	126.6	126.2	121.8	121.3	121.8
	$\underline{C}$-7'	164.1	164.0	193.0	191.6	190.9
	$O\underline{C}H_3$	51.8		52.1	52.1	
	$\underline{C}O_2$	163.2		163.8	167.7	
		129.6		129.3	61.3	
	$=C-\underline{C}H_3$	21.7 and 23.8		22.0 and 23.3	20.5	
	$=\underline{C}H_2$				118.6	
	$=\underline{C}<$	154.4		153.3	136.6	

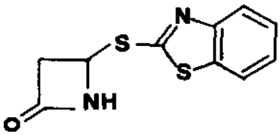
The formation of the isomeric products from the reaction of disulfides (1), (2) and (3) with triphenylphosphine could be rationalised by assuming an acyl immonium species as an intermediate (Scheme 2).

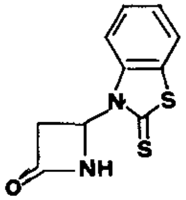


Scheme 2

Depending on the mode of attack of the ambident anion of mercaptobenzothiazole (MBT) either the 4-thia or the 4-aza azetidinones could be formed. The above results prompted us to study the reaction of MBT with 4-acetoxy azetidinone[7]. Reaction of azetidinone (10) with MBT in the presence of one equivalent of sodium *hydroxide in water*[8] *afforded* compound (11) in 98 % yield as described in the literature[9]. Compound (11) (mp 108-110^{0}C, IR (CH$_2$Cl$_2$): 3400 and 1775 cm^{-1}) was found to rearrange, on heating above its melting point, into compound (12) (mp 180-181^{0} C[10], IR (CH$_2$Cl$_2$): 3400, 1780 and 1240-1300 br cm^{-1}). Compound (11) was also found to rearrange readily into compound (12) on heating in toluene. In contrast, compounds (4) and (5) are completely stable in refluxing toluene.


(10)


(11)


(12)

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REFERENCES AND NOTES

1. K. Prasad, H. Hamberger, P. Stütz and G. Schulz, Helv. Chim. Acta, 64, 279 (1981).
2. Triphenylphosphine sulfide was formed as a byproduct in all the desulfurisation reactions.
3. Compounds (1), (2) and (3) were prepared from the esters of the corresponding penicillanic acid S-oxides using a two-step procedure of Kamiya et. al. (ref. 4).
4. T. Kamiya, T. Teraji, Y. Sato, M. Hashimoto, O. Nakaguchi and T. Oku, Tetrahedron Lett., 1973, 3001.
5. Compounds (5) and (8) appear to be a single diastereoisomer from the NMR spectra. The absolute stereochemistry of these compounds and compounds (4) and (7) is not determined.
6. E. Fujita, Y. Nagao, K. Seno, S. Takao, T. Miyasaka, M. Kimura and W.H. Watson, J. Chem Soc., Perkin I, 1981, 914.
7. K. Clauss, D. Grimm and G. Prossel, Ann., 1974, 539.
8. When the reaction was carried out in a dioxane-water mixture instead of water alone, compounds (11) and (12) were formed in 25 % and 60 % yield respectively.
9. K. Clauss and D. Grimm, DT 1945542, 1971.
10. This melting point was reported for compound (11) in ref. 9.

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