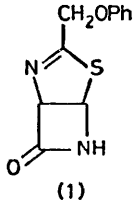
# The Chemistry of 4-Mercaptoazetidin-2-ones. Part 1. Preparation and Properties of (3*R*,4*R*)-4-Mercapto-3-phenoxyacetamidoazetidin-2-one

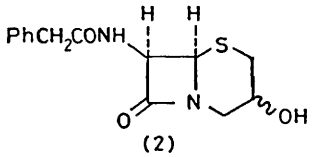
By **Neal F. Osborne**, Beecham Pharmaceuticals, Research Division, Brockham Park, Betchworth, Surrey RH3 7AJ.

(3*R*,4*R*)-4-Mercapto-3-phenoxyacetamidoazetidin-2-one (4) has been prepared in good yield from the penicillin V-derived thiazoline-azetidinone (1). Alkylation and acylation led exclusively to *S*-substituted azetidinones. Reaction with dimethyl acetylenedicarboxylate in hexamethylphosphoramide gave, in addition to the expected dimethoxycarbonylvinylthioazetidinone (15), the C-4-epimer (18). The latter probably arises *via* the intermediacy of the azetinone (16).

PREVIOUS work in this laboratory [1] has shown that the fused thiazoline-azetidinone (1), readily derived from penicillin V, may be converted by a reaction sequence involving attack by α-bromo-esters or -ketones at sulphur into analogues of penicillin in which the 2-methyl groups are replaced by alkoxycarbonyl or acetyl functions. In attempting to extend the scope of such syntheses, consideration was given to possible reaction of the thiazoline-azetidinone (1) with an epoxide. An



(1)



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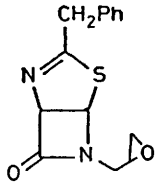

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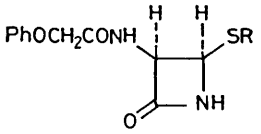
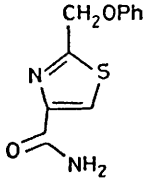


(4) R = H
(5) R = Me
(10) R = Et
(11) R = $CHMe_2$
(12) R = $CH_2CO_2Me$
(13) R = COMe



(6)

intramolecular precedent [2] for the desired intermolecular attack by the epoxide at sulphur was available in the formation of the cepham (2) from the thiazoline-azetidinone (3). When the thiazoline-azetidinone (1) was treated with ethyl 2,3-epoxy-3-methylbutyrate in aqueous acetic acid a crystalline product was obtained, but spectroscopic examination indicated that the epoxide was not involved in its formation. Subsequent experiment showed that the new compound was formed from the thiazoline-azetidinone in aqueous acetic acid alone. The product had an intact β-lactam ring ($\nu_{max.}$ 1 760 $cm^{-1}$, Nujol mull) which had retained its *cis*-stereochemistry as shown by the characteristic 5 Hz coupling of the n.m.r. signals at δ 5.10 and 5.45. The latter signal was further coupled (9 Hz) to an exchangeable proton at δ 9.09 which, together with a 2 proton singlet at δ 4.70, indicated the presence of the phenoxyacetamido-substituent on the β-lactam ring. In the absence of any other signals attributable to a sulphur substituent the $D_2O$-exchangeable singlet at δ 3.27 was assigned to the S–H proton of the 4-mercaptoazetidinone (4). Elemental analysis and mass spectrometry supported the structural assignment.

The only previously reported 4-mercaptoazetidin-2-one, unsubstituted at nitrogen, appears to be the 3-phthalimido-derivative which Sheehan [3] obtained by a different type of degradation of 6β-phthalimidopenicillanic acid. Subsequent to our work [4] a patent from the Ciba–Geigy group [5] mentioned the phenoxyacetamido-4-mercaptoazetidinone (4) but the compound was not well characterised, while other workers [6] have prepared the phenylacetamido-analogue.

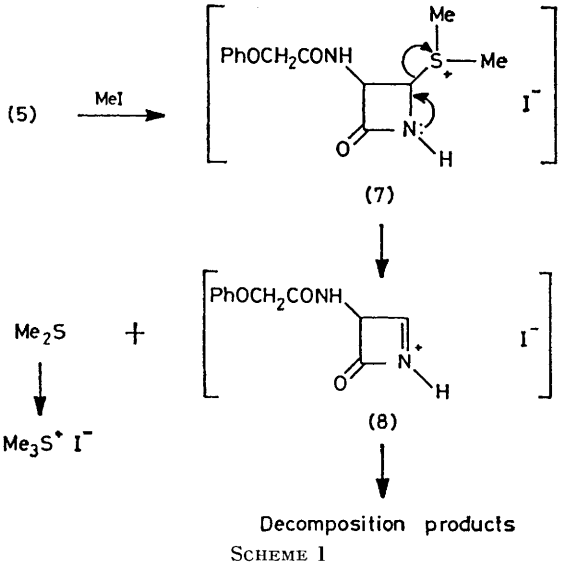
Further support for the structural assignment of the 4-mercaptoazetidinone (4) was obtained from a study of its reactions. Thus treatment with methyl iodide (1.5 equivalents) in hexamethylphosphoramide (HMPT), conditions found favourable for the alkylation of *N*-substituted mercaptoazetidinones,[7] gave rise to the expected methylthio-derivative (5) [8] in low yield. Also obtained was the thiazole (6) formed from the mercaptoazetidinone (4) by opening of the β-lactam ring and subsequent cyclisation of the intermediate ene-thiol, a reaction which has been discussed in a recent communication from Baldwin.[9] In an experiment using a ten-fold excess of methyl iodide the initially formed methylthio-derivative (5), as observed by t.l.c., was slowly consumed. The only identified product from this reaction was trimethylsulphonium iodide which is assumed to have arisen by further reaction of the methylthio-derivative (5) as shown in Scheme 1. The sulphonium salt (7) contains a good leaving group which facilitates decomposition *via* the azetinone (8), the dimethyl sulphide formed in the process giving rise to the isolated trimethylsulphonium iodide. An analogous process was invoked by Barton *et al.*[10] to account for the decomposition of the vinylic sulphoxide (9). Similar treatment of the 4-mercaptoazetidinone (4) with ethyl bromide or isopropyl iodide did not give the desired azetidinones (10) and (11). However, reaction with

methyl bromoacetate afforded the expected methoxycarbonylmethylthioazetidinone (12) in moderate yield.

Acylation of the thiol function was also possible, as exemplified by the treatment of (4) with acetyl chloride–pyridine in tetrahydrofuran to give the acetylthioazetidinone (13).[8]

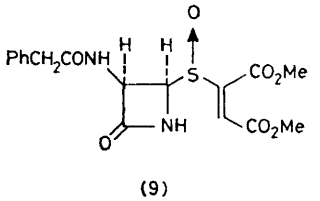
It was also anticipated that oxidation of the thiol (4) would lead to the disulphide (14). In the event this was achieved by the use of iodine in aqueous dimethyl sulphoxide.

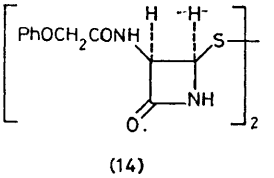
The intermolecular addition of penicillin-derived thiols to double and triple bonds is an area of penicillin chemistry which appears to have attracted little[6] attention. The isolation of the mercaptoazetidinone described here presented a good opportunity to investigate these reactions. The reaction of the mercaptoazetidinone (4) with dimethyl acetylenedicarboxylate



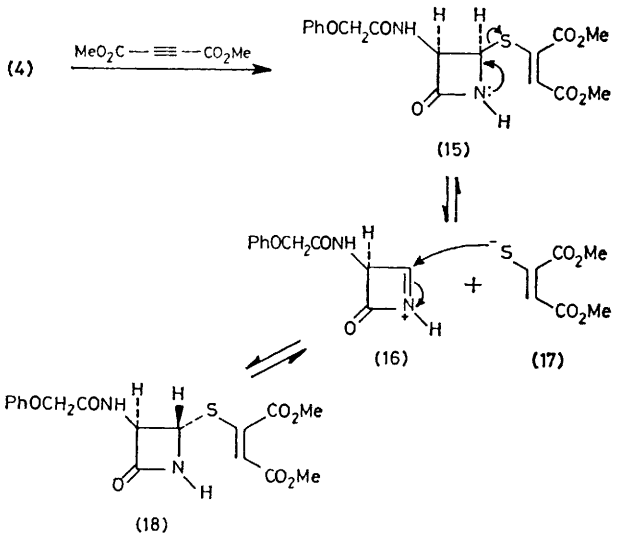

SCHEME 1

proved to be a reaction of unexpected interest. When carried out in dry HMPT two products were obtained in the ratio *ca.* 4 : 3 (Scheme 2). The less polar of these products was assigned the structure (18), based on its n.m.r. spectrum which revealed the presence of *trans*-disposed β-lactam protons (*J* 2 Hz) and a vinylic proton at δ 6.14. The more polar product was assigned the structure (15), its n.m.r. spectrum showing the normal *cis*-disposed β-lactam protons (*J* 4.5 Hz) and a vinylic



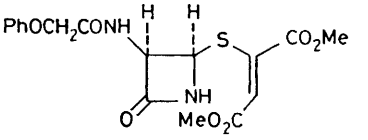

proton at δ 6.05. When the reaction was carried out in tetrahydrofuran an interesting catalytic effect was noted. T.l.c. of a mixture of the mercaptoazetidinone (4) and dimethyl acetylenedicarboxylate in tetrahydrofuran revealed the formation of a product. However, work-up of the reaction mixture gave only starting materials recovered in near quantitative yield. The suggested catalytic effect of silica gel was confirmed by its incorporation in the reaction mixture. Examination of the products of this reaction revealed none of the *trans*-β-lactam (18). In contrast a mixture of the *cis E*- and

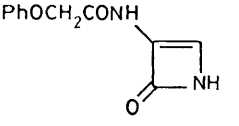



SCHEME 2

*Z*-compounds (15) and (19) was obtained in the ratio 3 : 1 (as determined from the vinylic proton signals at δ 6.05 and 6.69 respectively). The *trans* β-lactam (18) is considered to have been formed *via* an elimination process giving the azetinone (16) which then adds the ene-thiolate (17). Since compounds (15) and (18) possess optical activity the possibility of an alternative mechanism *via* the eliminated intermediate (20) can be excluded.

To conclude, the readily available 4-mercaptoazetidinone (4) has been shown to undergo a number of reactions selectively at the sulphur atom allowing the synthesis of a range of azetidinone derivatives. In addition, evidence for the existence of the azetinone (16)




has been presented. The use of the 4-mercaptoazetidinone (4) in the synthesis of a bicyclic β-lactam derivative will form the basis of a further paper.

## EXPERIMENTAL

I.r. spectra were recorded for solutions in chloroform unless stated otherwise. $^1$H N.m.r. spectra were recorded on either a Varian E.M. 360 or a Perkin-Elmer R12a 60 MHz instrument for solutions in $CDCl_3$ with tetramethylsilane as internal standard unless stated otherwise; 80 and 90 MHz spectra were obtained on Varian CFT 20 and

Perkin-Elmer R32 instruments respectively. Mass spectra were determined with an A.E.I. MS9 machine. Merck Kieselgel 60 (particle size $<0.063$ mm) was used for column chromatography, with mixtures of ethyl acetate–light petroleum (b.p. 60—80 °C) as eluant. Melting points were determined with a Kofler hot-stage apparatus. A Perkin-Elmer 141 polarimeter was used to determine specific rotations.

(3R,4R)-4-*Mercapto*-3-*phenoxyacetamidoazetidin*-2-*one* (4).—The thiazoline-azetidinone (1) (2.0 g) [8] was dissolved in a mixture of glacial acetic acid (35 ml) and water (15 ml) and the solution was stirred at room temperature for 2 h. The product which crystallised out was collected by filtration, washed with water and ether, and dried in a vacuum desiccator to give the 4-*mercaptoazetidinone* (4) (1.47 g) as a microcrystalline solid, m.p. 133—135 °C, $[\alpha]_D^{22}$ +37.5° (*c* 1 in DMF); $\nu_{max.}$ (Nujol) 3 280 (shoulder), 3 200, 1 760, and 1 660 $cm^{-1}$; δ [$(CD_3)_2SO$] 3.27 (1 H, s, exch. $D_2O$), 4.70 (2 H, s), 5.10 (1 H, d, *J* 5 Hz), 5.45 (1 H, dd, *J* 5 and 9 Hz, collapsing to d, *J* 5 Hz on exch. $D_2O$), 6.9—7.6 (5 H, m), 8.93 (1 H, s, exch. $D_2O$), and 9.09 (1 H, d, *J* 9 Hz, exch. $D_2O$) (Found: C, 52.1; H, 5.1; N, 11.1; S, 12.8%; $M^+$, 252.0540. $C_{11}H_{12}N_2O_3S$ requires C, 52.4; H, 4.8; N, 11.1; S, 12.7%; *M*, 252.0568).

(3R,4R)-4-*Methylthio*-3-*phenoxyacetamidoazetidin*-2-*one* (5).—(*a*) The mercaptoazetidinone (4) (126 mg) was dissolved in dry HMPT (1 ml) and treated with methyl iodide (107 mg). The mixture was kept at room temperature for 24 h, diluted with ethyl acetate (20 ml), and washed with brine. The dried ($MgSO_4$) organic layer was evaporated and the residue chromatographed to give two products. The less polar product, 4-*carbamoyl*-2-*phenoxymethylthiazole* (6) (13 mg) was obtained as needles, m.p. 171—172 °C (from chloroform), $\nu_{max.}$ (Nujol) 3 430, 3 120, 1 700, and 1 670 $cm^{-1}$; δ [$(CD_3)_2SO$] 5.55 (2 H, s), 6.95—8.00 (7 H, m, 2 H exch. $D_2O$), and 8.48 (1 H, s) (Found: C, 56.1; H, 4.3; N, 12.1; S, 13.7. $C_{11}H_{10}N_2O_2S$ requires C, 56.4; H, 4.3; N, 12.0; S, 13.7%). The more polar product, the desired methylthioazetidinone (5) (17 mg) was obtained as needles, m.p. 171—172 °C [from ethyl acetate–light petroleum (b.p. 60—80 °C)] (lit.,[8] m.p. 170—172 °C).

(*b*) The above experiment was repeated using a greater proportion of methyl iodide (710 mg). After a few hours at room temperature t.l.c. confirmed the presence of the methylthio-derivative (5). However, after 3 days some needles (decomp. 190—195 °C) had separated which were shown to be trimethylsulphonium iodide (lit.,[11] decomp. 203—207 °C). None of the expected methylthio-derivative (5) was isolated in this experiment.

(3R,4R)-4-*Methoxycarbonylmethylthio*-3-*phenoxyacetamidoazetidin*-2-*one* (12).—The mercaptoazetidinone (4) (252 mg) was dissolved in dry HMPT (3 ml) and treated with methyl bromoacetate (168 mg). The mixture was kept at room temperature for 20 h, diluted with ethyl acetate (20 ml), and washed with brine. The dried ($MgSO_4$) organic layer was evaporated and the residue chromatographed to give the *azetidinone* (12) (130 mg), m.p. 157—158 °C (needles from chloroform–ether), $\nu_{max.}$ 3 370, 1 780, 1 735, and 1 690 $cm^{-1}$; δ [$CDCl_3$ + $(CD_3)_2SO$] 3.38 (2 H, s), 3.75 (3 H, s), 4.65 (2 H, s), 5.18 (1 H, d, *J* 5 Hz), 5.55 (1 H, dd, *J* 5 and 9 Hz), 6.9—7.6 (5 H, m), and 8.35—8.65 (2 H, m, 1 H readily exch. $D_2O$) (Found: C, 51.8; H, 4.9; N, 8.5; S, 9.9%; $M^+$, 324.0768. $C_{14}H_{16}N_2O_5S$ requires C, 51.9; H, 4.9; N, 8.6; S, 9.9%; *M*, 324.0780).

(3R,4R)-4-*Acetylthio*-3-*phenoxyacetamidoazetidin*-2-*one* (13).—The mercaptoazetidinone (4) (50 mg) was dissolved in dry tetrahydrofuran (5 ml), cooled to 0 °C, and treated with acetyl chloride (17 mg) followed by pyridine (1 drop). The mixture was stirred at 0 °C for 20 min, diluted with ethyl acetate (20 ml), and washed with brine. The dried ($MgSO_4$) organic layer was evaporated and the residue chromatographed to give acetylthioazetidinone (13) (21 mg), needles from ethyl acetate–light petroleum (b.p. 60—80 °C), m.p. 139—140 °C (lit.,[8] 138—141 °C).

*Bis*-(3R,4R)-(3-*phenoxyacetamidoazetidin*-2-*on*-4-*yl*) *Disulphide* (14).—The mercaptoazetidinone (4) (252 mg) was dissolved in a mixture of dimethyl sulphoxide (5 ml) and water (1 ml). To this solution was added dropwise with stirring at room temperature a solution containing iodine (1.0 g) and potassium iodide (2.0 g) in water (5 ml) until the colour of iodine persisted (0.54 ml in 15 min). The mixture was diluted with ethyl acetate (25 ml) and washed with water. The dried ($MgSO_4$) organic layer was evaporated and the residue chromatographed to give the *disulphide* (14) (111 mg) as a microcrystalline solid, m.p. 139—146 °C, $\nu_{max.}$ 3 300br, 1 775, and 1 690 $cm^{-1}$; δ [$(CH_3)_2SO$] 4.70 (2 H, s), 5.09 (1 H, d, *J* 4 Hz), 5.34 (1 H, dd, *J* 4 and 8 Hz, collapsing to d, *J* 4 Hz on $D_2O$ exch.), 6.9—7.6 (5 H, m), and 8.9—9.2 (2 H, m, exch. $D_2O$) (Found: C, 52.8; H, 4.5; N, 11.2; S, 12.7. $C_{22}H_{22}N_4S_2O_6$ requires C, 52.6; H, 4.4; N, 11.2; S, 12.8%).

*Reaction of the* 4-*Mercaptoazetidinone* (4) *with Dimethyl Acetylenedicarboxylate*.—(a) *In HMPT*. The mercaptoazetidinone (4) (252 mg) was dissolved in dry HMPT (3 ml) and treated with dimethyl acetylenedicarboxylate (156 mg) when a slightly exothermic reaction took place. The mixture was stirred for 10 min, diluted with ethyl acetate (20 ml), and washed with brine. The dried ($MgSO_4$) organic layer was evaporated and the residual gum chromatographed to give two products. The less polar product, (3R,4S)-(E)-4-[1,2-*bis*(*methoxycarbonyl*)*vinylthio*]-3-*phenoxyacetamidoazetidin*-2-*one* (18) (124 mg) was obtained as an amorphous solid, $[\alpha]_D^{22}$ −54.8° (*c* 1 in $CHCl_3$); $\nu_{max.}$ 3 400, 1 790, 1 725, and 1 690 (shoulder) $cm^{-1}$; δ 3.78 (3 H, s), 3.93 (3 H, s), 4.58 (2 H, s), 5.07 (1 H, dd, *J* 2 and 8 Hz), 5.26 (1 H, d, *J* 2 Hz), 6.14 (1 H, s), 6.87—7.60 (5 H, m), 7.75 (1 H, s, exch. $D_2O$), and 8.18 (1 H, d, *J* 8 Hz) (Found: $M^+$, 394.0838. $C_{17}H_{18}N_2O_7S$ requires *M*, 394.0835). The more polar product, (3R,4R)-(E)-4-[1,2-*bis*(*methoxycarbonyl*)-*vinylthio*]-3-*phenoxyacetamidoazetidin*-2-*one* (15) (91 mg) was also obtained as an amorphous solid, $[\alpha]_D^{22}$ −1.0° (*c* 1 in $CHCl_3$); $\nu_{max.}$ 3 400, 1 790, 1 725, and 1 695 (shoulder) $cm^{-1}$; δ 3.71 (3 H, s), 3.91 (3 H, s), 4.61 (2 H, s), 5.34 (1 H, d, *J* 4.5 Hz), 5.79 (1 H, dd, *J* 4.5 and 9 Hz), 6.05 (1 H, s), 6.90—7.46 (5 H, m), 7.59 (1 H, s, exch. $D_2O$), and 8.09 (1 H, d, *J* 9 Hz) (Found: $M^+$, 394.0823. $C_{17}H_{18}N_2O_7S$ requires *M*, 394.0835).

(b) *In tetrahydrofuran*. A mixture of the mercaptoazetidinone (4) (126 mg), dimethyl acetylenedicarboxylate (78 mg), and silica gel H (Merck type 60) (200 mg) in dry tetrahydrofuran (10 ml) was stirred at room temperature for 10 min. The mixture was evaporated to give a slurry which was transferred to the top of a short column of silica gel. Elution with ethyl acetate–light petroleum (b.p. 60—80 °C) mixtures gave a 3 : 1 mixture of the (*E*)- (15) and (*Z*)- (19) isomers of (3R,4R)-4-[1,2-*bis*(*methoxycarbonyl*)-*vinylthio*]-3-*phenoxyacetamidoazetidin*-2-*one* (54 mg) as an amorphous solid, $\nu_{max.}$ 3 400, 1 790, 1 725, and 1 695 (shoulder) $cm^{-1}$; δ 3.73 and 3.80 (3 H, each s), 3.94 (3 H, s), 4.62 (2 H, s), 5.34 ($\frac{3}{4}$ H, d, *J* 4 Hz), 5.40 ($\frac{1}{4}$ H, d, *J* 4 Hz),

5.63—6.0 (1 H, m), 6.05 (¾ H, s), 6.69 (¼ H, s), 6.9—7.6 (6 H, m), and 7.84—8.16 (1 H, m).

(c) *In tetrahydrofuran in the absence of silica gel.* The above reaction, carried out in the absence of silica gel gave unchanged starting materials in near quantitative yields.

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