β-Lactam Antibiotics. Part 2.[1] New Methods of Cyclising Hydrazinothioazetidinones to Cephem Ring Systems

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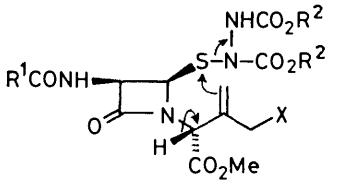
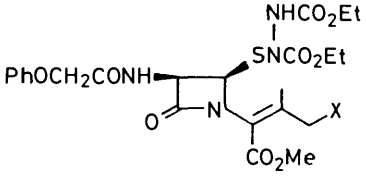
Base-induced and oxidative cyclisation of hydrazinothioazetidinones as novel routes to cephem ring systems are described together with the proposed mechanisms. General procedures for these cyclisations are reported.

In continuation of our preliminary studies [2] this paper describes the cyclisation, in different ways, of hydrazinothioazetidinones (1) [3] and (2) to cephem ring systems. Azetidinones (1a and b), which are βγ-unsaturated esters,[1,2] were easily converted to deacetoxycephalosporin (3) [4] in 80% yield simply by stirring a benzene solution with aluminium oxide or 30% aqueous potassium hydroxide at room temperature.



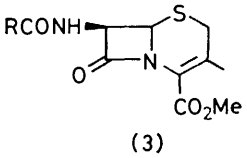
(1)

a; R^1 = $PhOCH_2$, X = H, R^2 = Me
b; R^1 = $PhOCH_2$, X = H, R^2 = Et
c; R^1 = Me, X = OAc, R^2 = Et
d; R^1 = Bu^t, X = OAc, R^2 = Et

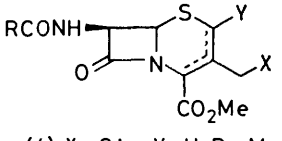


(2)

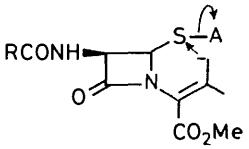
a; X = H
b; X = OAc (*E*- and *Z*-isomers)
c; X = OMe (*E*-isomer)
d; X = OBu^t (*E*-isomer)



(3)



(4) X = OAc, Y = H, R = Me
(5) X = OAc, Y = H, R = Bu^t
(6) X = Y = H, R = $PhOCH_2$
(7) X = OAc, Y = H, R = $PhOCH_2$
(8) X = H, Y = OAc, R = $PhOCH_2$
(9) X = OMe, Y = H, R = $PhOCH_2$
(10) X = H, Y = OMe, R = $PhOCH_2$
(11) X = OBu^t, Y = H, R = $PhOCH_2$



(12)

The mechanism proposed for this cyclisation involves initial abstraction of the α-proton by the base as outlined in (1).

Alternatively, oxidative cyclisation of azetidinones (1) was also obtained using a suitable halogenating agent. The reaction proceeds *via* the transient sulphenyl halide which undergoes addition to the appropriately positioned isopropenyl double bound through the episulphonium ion.[4,5] Indeed (1b) reacted with t-butyl hypochlorite yielding the corresponding 3-chlorocepham [5] which in turn was converted into deacetoxycephalosporin (3; R = $PhOCH_2$) [4] as the major product by further dehydrohalogenation under mild basic conditions in fairly good yield.

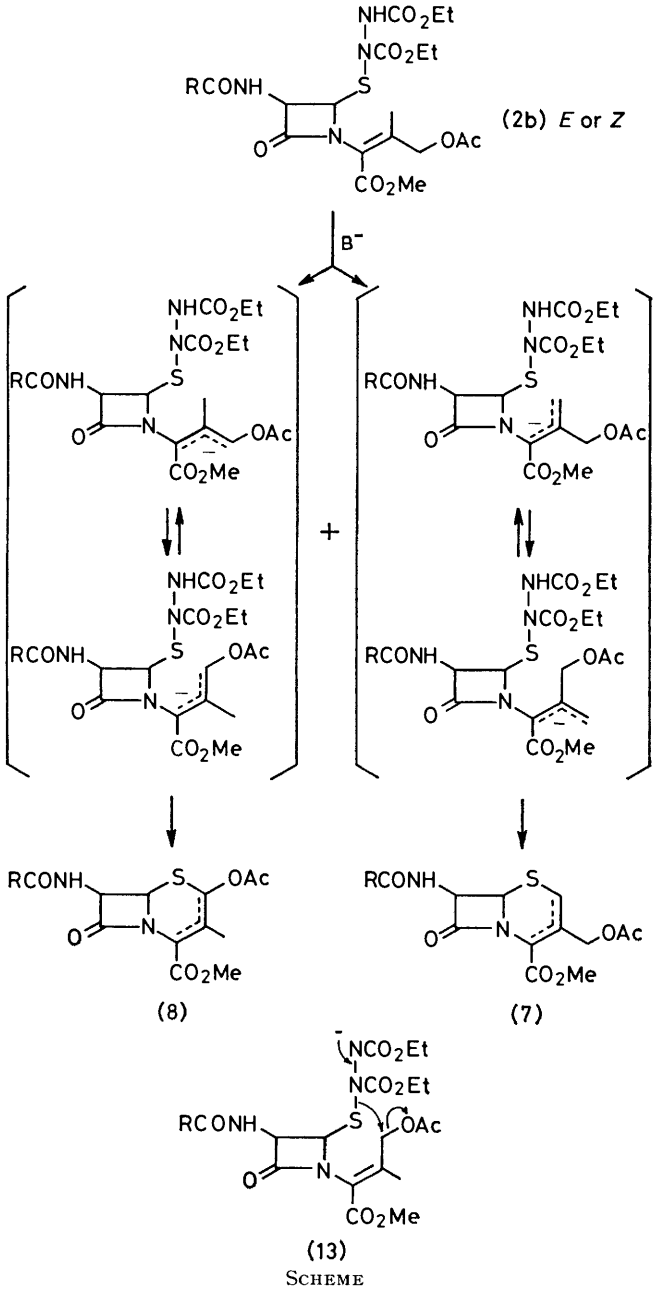
Cyclisation of (1c and d) was performed by treatment with potassium t-butoxide (1 equiv.) in tetrahydrofuran at −78 °C for 10 min to give cephalosporins (4) [6] and (5) as a Δ^2–Δ^3 mixture in 40% yield. Oxidation of the entire mixture with *m*-chloroperbenzoic acid and subsequent reduction of the sulphoxides by the acetyl chloride–sodium dithionite procedure,[7] gave the desired 3-cephem derivatives identical with authentic samples.

Attempts to cyclise (1c) with aluminium oxide or potassium hydroxide under the aforementioned mild conditions were unsuccessful affording only decomposition products.

On the other hand, ring closure of azetidinones (2), which are αβ-unsaturated esters, was successfully performed by means of a large excess (at least 4—5 equiv.) of a strong base, such as lithium di-isopropylamide or potassium t-butoxide in tetrahydrofuran at −78 °C for 30 min. In fact (2a) gave, by a similar treatment, the corresponding deacetoxycephalosporin (6) as a mixture of Δ^2–Δ^3 isomers [4] in 40% yield, confirming that azetidinones of general formula (12) are potential intermediates for the preparation of both penicillins and cephalosporins in line with the biosynthetic pathways proposed in early studies.[8,9]

Ring-closure, in a penam scheme, involving a Michael addition of a sulphur anion to the conjugated double bond has been claimed by some authors.[10,11] In our case the cyclisation of (2a) involves the formation of an allylic carbanion on one of the two isopropylidene methyl groups and concomitant nucleophilic displacement of diethyl hydrazodicarboxylate resulting in the formation of the dihydrothiazine ring as outlined in (12). Recently a similar cyclisation affording the 3-methoxy-3-cephem nucleus was reported.[12] Additionally, treatment of (2b) (*E*–*Z* mixture as well as single isomers) with lithium

di-isopropylamide in tetrahydrofuran at −78 °C for 30 min gave a complex mixture of products among which were deacetoxycephalosporin (6) (5%), cephalosporin (7) [4] (10%), and the corresponding 2-acetoxy-3-methylcephem (8) [13] (15%) as outlined in the Scheme. Obviously, all these compounds were obtained as Δ^2–Δ^3 mixtures which were carefully separated and identified by mass and ^{1}H n.m.r. spectral analysis and by comparison (t.l.c. and h.p.l.c.) with authentic specimens.



SCHEME

The formation of (8) also represents a novel synthetic route for the preparation of 2-substituted cephalosporins not involving the pre-formed dihydrothiazine ring.[13] The transformation of azetidinone (2b) to (7) and (8) should proceed through two intermediate carbanions (see Scheme), apparently with a predominant negative charge on the methylene bearing the acetoxy-group. Free rotation around the single C–C bond derived from allylic rearrangements explains why the same results were obtained when *E*- and *Z*-isomers were used separately.

Effect of base on ring closure of azetidinones (2)

Base	Solvent [a]	Product
Lithium methoxide	THF	No β-lactam products
Lithium isopropoxide	THF	(8) (Δ^3),[d] (8) (Δ^2), (7) (Δ^2)
Potassium t-butoxide	THF	(8) (Δ^3), (8) (Δ^2),(7) (Δ^3)
	DMF	(8) (Δ^3), (8) (Δ^2), (7) (Δ^3)
Lithium (8α,9*R*)-cinchonane-9-oxide	THF [b]	(8) (Δ^3),[d] (7) (Δ^2)
Lithium triphenylmethane	THF	(6) (Δ^2)
Sodium hydride	THF	(8) (Δ^3), (8) (Δ^2), (7) (Δ^2)
Lithium-2,6-di-t-butyl-4-methoxyphenoxide	THF	(8) (Δ^3), (7) (Δ^2)
Lithium di-isopropylamide	THF	(7) (Δ^2),[d] (7) (Δ^3), (6) (Δ^2), (8) (Δ^2), (8) (Δ^3)
Lithium dicycloesylamide	THF	(7) (Δ^2),[d] (7) (Δ^3), (6) (Δ^2)
Triton B	$CHCl_3$–H_2O [c]	No β-lactam products

[a] Except where otherwise indicated, all the reactions have been carried out at −78 °C. [b] Carried out at −20 °C. [c] Phase-transfer; room temperature. [d] Very major component.

On the other hand, we suggest for the formation of (6) a reductive closure arising from a nucleophilic attack of a sulphur anion on the methylene and concerted displacement of the acetoxy-group as shown in formula (13).

Many studies, using different bases, were also carried out in the hope of obtaining a less complex mixture. Some experimental details are reported in the Table. Unfortunately, none of the bases used gave better results than those obtained with lithium di-isopropylamide.

In order to decrease the formation of both deacetoxycephalosporin (6) and 2-substituted 3-methylcephem derivatives (8) we deemed that the oxymethyl ethers (2c and d) could be attractive substrates. Indeed cyclisation of (2c) carried out under the same conditions used for (2b), afforded (9; Δ^2–Δ^3 mixture) [14] in 20% yield and (10) [15] in very small amounts as a single Δ^3 isomer. Ring closure of (2d) gave, after silica gel column chromatography, (11) as the Δ^3 isomer in 10% yield and the Δ^2 isomer in 20% yield.

EXPERIMENTAL

Reactions were monitored by t.l.c. on Merck silica gel GF_{254} with benzene–light petroleum–ethyl acetate as solvents. Light petroleum refers to the fraction of boiling range 68—80 °C. H.p.l.c. conditions: column μ-Porasil (Waters), mobile phase 4 : 1 chloroform–methylene chloride.

Cyclisation Procedures of Hydrazinothioazetidinones (1).—(*a*) A 30% solution of potassium hydroxide (0.8 ml) was added, with vigorous stirring, to a benzene solution (20 ml) of 3-β-phenoxyacetamido-4-β-*NN'*-bismethoxycarbonyl-1-(1-methoxycarbonyl-2-methylprop-2-enyl)azetidin-2-one (0.510 g) (1a). The two-phase system was kept at room temperature with stirring for 30 min, ice–water was added, and the organic layer was washed with dilute hydrochloric acid and water, and dried to give, after crystallisation, methyl 7-phenoxyacetamido-3-methyl-3-cephem-4-carboxy-

late (3; R = $PhOCH_2$) (0.310 g), m.p. 141—142 °C (diethyl ether). Physico-chemical data were in accord with those in the literature.[4]

(*b*) t-Butyl hypochlorite (0.2 ml) in tetrahydrofuran (2 ml) was added dropwise to a solution of 3-β-phenoxyacetamido-4β-*NN'*-bisethoxycarbonylhydrazinothio-1-(1-methoxycarbonyl-2-methylprop-2-enyl)azetidin-2-one (1b) (0.200 g) in tetrahydrofuran (10 ml) at −78 °C.

After 40 min stirring at −78 °C an almost complete transformation into a less polar compound was noticed (t.l.c.); triethylamine (0.1 ml) was added and the mixture was left at 20 °C for 1 h. Evaporation *in vacuo* followed by column chromatography gave methyl 7-phenoxyacetamido-3-methyl-3-cephem-4-carboxylate (3) [4] (0.045 g) as the major product.

(*c*) A cooled solution (−78 °C) of 3-β-trimethylacetamido-4-β-*NN'*-bisethoxycarbonylhydrazinothio-1-(1-methoxycarbonyl-2-acetoxymethylprop-2-enyl)azetidin-2-one (1d) (0.5 g) in a mixture of dimethylformamide (15 ml) and tetrahydrofuran (3 ml) was treated with potassium t-butoxide (1.2 g). After 10 min stirring the mixture was quenched with acetic acid, diluted with water, and extracted with ethyl acetate. The organic layer, after evaporation of the solvent followed by column chromatography (4 : 1, benzene–ethyl acetate) gave methyl 7-trimethylacetamidocephalosporanate (5) (0.200 g) as a mixture of Δ^2–Δ^3 isomers.

Additional separation by preparative t.l.c. afforded the single isomers, as oils: Δ^2 isomer, δ 1.28 [9 H, s, $(CH_3)_3C$], 2.05 (3 H, s, CH_3CO), 3.83 (3 H, s, CH_3O), 4.69br (1 H, s, 4-H), 5.02br (2 H, s, CH_2O), 5.30 (1 H, d, *J* 4.0 Hz), 6-H 5.62 (1 H, dd, *J* 4.0 and 8.0 Hz, 7-H), 6.2—6.8 (2 H, m, 2-H and NH); Δ^3 isomer, δ 1.25 [9 H, s, $(CH_3)_3C$], 2.08 (3 H, s, CH_3CO), 3.41 and 3.60 (2 H, 2 × d, *J* 19 Hz, 2-H_2), 3.88 (3 H, s, CH_3O), 4.88 and 5.16 (2 H, 2 × d, *J* = 13.5 Hz, CH_2O), 5.02 (1 H, d, *J* 5.0 6-H), 5.81 (1 H, dd, *J* 5.0 and 9.0 Hz, 7-H), and 6.54 (1 H, d, *J* 9.0 Hz, NH).

Spectroscopic data were in agreement with those of authentic samples prepared from 7-aminocephalosporanic acid.

Cyclisation Procedures for Hydrazinothioazetidinones (2).—(*a*) A solution of lithium di-isopropylamide, prepared from di-isopropylamine (1.01 g, 10 mmol) in anhydrous tetrahydrofuran (15 ml) and n-butyl-lithium (4.57 ml of a 20% hexane solution), was added dropwise to a stirred solution of 3-β-phenoxyacetamido-4-β-*NN'*-bisethoxycarbonylhydrazinothio-1-(1-methoxycarbonyl-2-methylprop-1-enyl)-azetidin-2-one (2a) (1.076 g, 2 mmol) in tetrahydrofuran (5 ml) at −78 °C.

After 30 min stirring, the red-brown mixture was quenched at −78 °C with acetic acid in tetrahydrofuran, and the temperature was allowed to reach 20 °C. The mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with water and brine, dried, and evaporated *in vacuo*. The brown oily residue was chromatographed on silica gel (85 : 15 benzene–ethyl acetate) to give methyl 7-phenoxyacetamido-3-methylcephem-4-carboxylate (6) as a Δ^2–Δ^3 mixture. Single isomers were then separated by preparative t.l.c. and compared with authentic specimens.[4,5]

(*b*) A solution of di-isopropylamine (2.3 g) in tetrahydrofuran (30 ml) and butyl-lithium (11 ml of a 20% hexane solution) was added dropwise to a solution of 3-β-phenoxyacetamido-4-β-*NN'*-bisethoxycarbonylhydrazinothio-1-(1-methoxycarbonyl-2-methyl-3-acetoxyprop-1-enyl)-azetidin-2-one (2b; *E*-isomer) (2.5 g) in tetrahydrofuran (50 ml) under stirring at −78 °C. After 30 min the brown solution was quenched at −78 °C with acetic acid (5 ml) in tetrahydrofuran and allowed to reach room temperature.

Ethyl acetate and water were added, the organic layer was separated, washed with brine, and the solvent evaporated *in vacuo*. The resulting oil, which gave many spots on t.l.c., was carefully chromatographed on silica gel (benzene–ethyl acetate).

Methyl 7-phenoxyacetamido-3-methyl-3-cephem-4-carboxylate (6) [4] (0.020 g) was first eluted as a minor product; methyl 7-phenoxyacetamido-2-acetoxy-3-methyl-3-cephem-4-carboxylate (8) (0.060 g) was then obtained, δ 2.07 and 2.12 (6 H, 2 × s, $CH_3C=$ and CH_3CO), 3.74 (3 H, s, CH_3O), 4.57 (2 H, s, OCH_2CO), 5.19 (1 H, d, *J* 4.5 Hz, 6-H), 5.97 (1 H, dd, *J* 4.5 and 9.0 Hz, 7-H), 6.35 (1 H, s, 2-H), 6.8—7.6 (6 H, NH and aromatic protons). Further elution gave a mixture of two products and finally the more polar methyl 7-phenoxyacetamido-3-acetoxymethyl-2-cephem-4-carboxylate (7) (0.060 g).[4] A second column chromatography (9 : 1 benzene–ethyl acetate) of the fractions containing the mixture of the two aforementioned products gave methyl 7-phenoxyacetamido-2-acetoxy-3-methyl-2-cephem-4-carboxylate (8) (0.030 g), δ 1.78 (3 H, d, *J* < 1.0 Hz, $CH_3C=$), 2.17 (3 H, s, CH_3CO), 3.83 (3 H, s, CH_3O), 4.58 (2 H, s, OCH_2CO), 5.0 (1 H, s, 4-H), and 5.4—6.0 (2 H, m, 6- and 7-H), and methyl 7-phenoxyacetamido-3-acetoxymethyl-3-cephem-4-carboxylate (7) (0.040 g).[4]

All these compounds were compared with authentic specimens prepared from 7-aminocephalosporanic acid and 7-aminodeacetoxycephalosporanic acid and the cephalosporins obtained were isomerized to the corresponding Δ^2 isomers with triethylamine.[4]

The same results were obtained when the cyclisation was carried out starting from (2b; *Z*-isomer).

(*c*) A solution of methyl 3-β-phenoxyacetamido-4-β-*NN'*-bisethoxycarbonylhydrazinothio-1-(1-methoxycarbonyl-2-t-butoxymethylprop-1-enyl)azetidin-2-one (2d) (1.8 g) in a mixture of dimethylformamide (15 ml) and tetrahydrofuran (5 ml) was cooled at −78 °C and treated with potassium t-butoxide (3.35 g). After stirring for 0.5 h at −78 °C, the mixture was quenched with acetic acid (2.5 ml) in tetrahydrofuran and the temperature was raised to 20 °C. Ethyl acetate was added and the resulting solution washed with brine and water. The oily residue was carefully chromatographed on silica gel (9 : 1 benzene–ethyl acetate) to give methyl 7-phenoxyacetamido-3-t-butoxymethyl-3-cephem-4-carboxylate (11) (0.130 g), δ 1.27 [9 H, s, $(CH_3)_3C$], 3.56br (2 H, s, CH_2S), 3.86 (3 H, s, CH_3O), 4.36br (2 H, s, $=CCH_2O$), 4.58 (2 H, s, OCH_2CO), 5.15 (1 H, d, *J* 4.5 Hz, 6-H), 5.90 (1 H, dd, *J* 4.5 and 9.0 Hz, 7-H), and 6.8—7.6 (6 H, NH and aromatic protons), and the more polar methyl 7-phenoxyacetamido-3-t-butoxymethyl-2-cephem-4-carboxylate (11) (0.180 g), δ 1.20 [9 H, s, $(CH_3)_3C$], 3.80 (3 H, s, CH_3O), 3.98br (2 H, s, $=CCH_2O$), 4.58 (2 H, s, OCH_2CO), 5.10br (1 H, s, 4-H), 5.33 (1 H, d, *J* 4.0 Hz, 6-H), 5.75 (1 H, dd, *J* 4.0 and 9.0 Hz, 7-H), 6.33br (1 H, s, 2-H), 6.55vbr (1 H, s, NH), and 6.8—7.6 (5 H, m, aromatic protons).

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