Novel Rearrangement of a Cephalosporin into a Trisubstituted Thiazole

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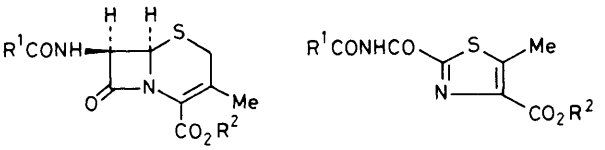
Reaction of the cephalosporin esters (**1**)—(**3**) with cerium(IV) ammonium nitrate in aqueous acetic acid gave the trisubstituted thiazoles (**4**)—(**6**).

Various methods of functionalisation of the cephalosporin nucleus have been studied in the search for novel β-lactam antibiotics.[1] As an extension of earlier work on the modification of 3-deacetoxycephalosporins,[2] the ester (**1**) in glacial acetic acid was treated with an excess of cerium(IV) ammonium nitrate (CAN) in 50% aqueous acetic acid.[3] After a work-up which incorporated a sodium hydrogen carbonate wash a viscous oil was obtained (75% by weight) which was mainly one product (t.l.c.). Purification by chromatography and crystallisation gave the trisubstituted thiazole (**4**), λ_{max} (EtOH) 282 nm (ε 10 030) and 238 nm (inflexion, ε 10 440); ν_{max} ($CHBr_3$) 1730 and 1700 cm^{-1}; δ ($CDCl_3$; 200 MHz), 2.89 (3H, s, CH_3), 4.20 (2H, s, $PhCH_2$), 5.00 (2H, s, CH_2CCl_3), 7.2—7.4 (5H, m, Ph), and 9.68 (1H, s, NH); M^+ *m/z* 433.9716. The structure of (**4**) was confirmed by *X*-ray analysis (see Figure 1).†

Under similar conditions the cephalosporins (**2**) and (**3**) gave the thiazoles (**5**) and (**6**) respectively.

The mechanism of this reaction presumably involves excision of C(2) and C(8) from the parent structures and possible pathways are outlined in Schemes 1 and 2. Thus electron-transfer from sulphur to Ce^{IV} and α-hydrogen loss[4] would give the sulphur stabilised carbonium ion (A). This would readily react with water‡ to give the hemithioacetal (B). Ring contraction *via* a Michael addition[5] (to the formally deactivated unsaturated ester unit[6]) or capture of a thiol radical by the alkene bond would provide, after protonation, the 2-formyl ester (D). Further oxidation to the 2-carboxylic acid (E),[7] followed by oxidative decarboxylation mediated by



(**1**) R^1 = $PhCH_2$; R^2 = CH_2CCl_3 (**4**)
(**2**) R^1 = $PhCH_2$; R^2 = Me (**5**)
(**3**) R^1 = $PhOCH_2$; R^2 = CH_2CCl_3 (**6**)

† *Crystal data:* $C_{16}H_{13}Cl_3N_2O_4S \cdot H_2O$, M_r = 453.7, monoclinic, space group *Cc*, *a* = 10.097(2), *b* = 10.632(2), *c* = 37.114(5) Å, β = 97.82(3)°, *U* = 3947.22 Å^3, D_c = 1.526 g cm^{-3}, *Z* = 8, μ(Mo-K_α) = 5.32 cm^{-1}, *F*(000) = 1776. The final *R* and R_w values are 0.0556 and 0.0532 respectively for 1586 observed reflections [$I > 3\sigma(I)$], measured on a Philips PW1010 four-circle diffractometer, 310 parameters were refined.

The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication. The structure factor table is available as Supplementary Publication No. SUP. 23743 (10 pp.) from the British Library. For details see Instructions for Authors, *J. Chem. Soc., Perkin Trans.* 1, 1983, Issue 1, p. xvii.

‡ The participation of other nucleophiles (*e.g.* nitrate ion, acetic acid) at this point would give similar products which could be transformed into the isolated thiazole by slight modification of the proposed mechanism.

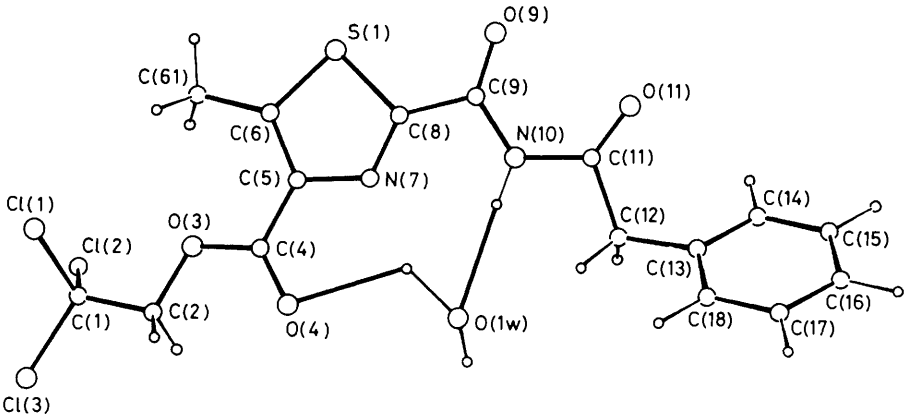
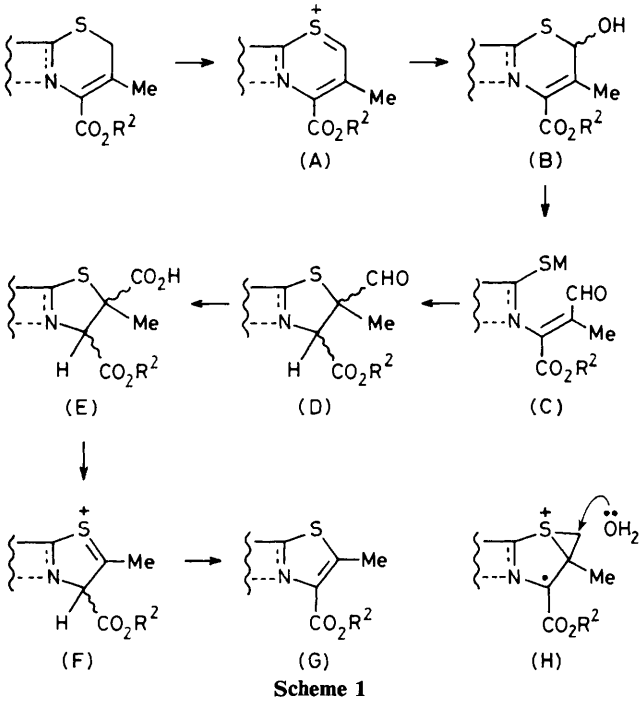
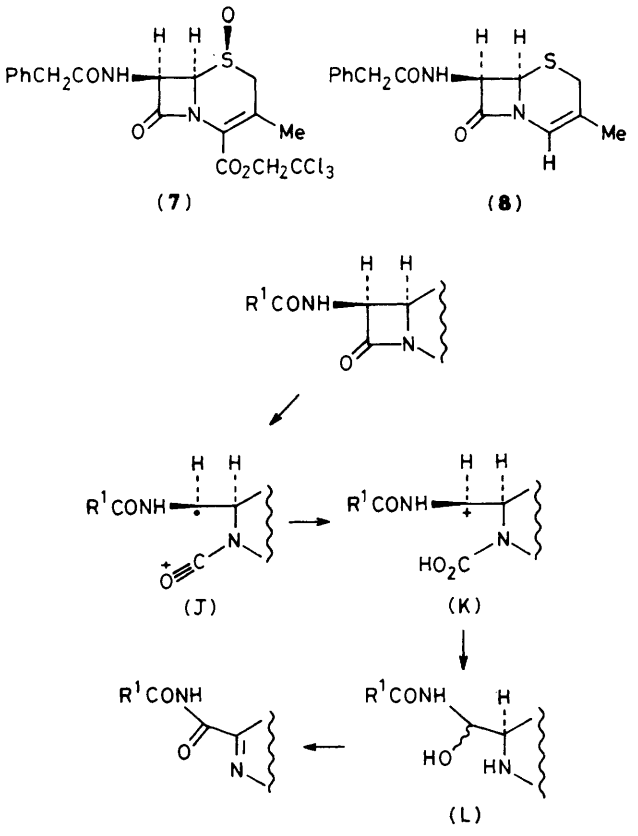


Figure 1. The structure of one of the two hydrated molecules of (**4**) which comprise the asymmetric unit is shown; the other has the same structure and conformation within experimental error. The bond-lengths (mean e.s.d. 0.016 Å) and bond-angles (mean e.s.d. 1.0°) agree with the values expected from formula (**4**). Each water molecule is hydrogen-bonded to O(4) and N(10) of one molecule, and also to O(9) of a second molecule forming infinite chains. The main skeleton, excluding the chlorine atoms and the phenyl ring, is planar within 0.25 Å, and the phenyl ring makes an angle of 43° with the main plane.



Scheme 1



Scheme 2

oxidation at sulphur (as shown), or possibly at nitrogen,[8] would lead to the sulphenium ion (F) and thence by proton loss to the required 5-membered ring system (G). The possibility that the intermediate (A) arises by way of a Pummerer-type reaction[9] is unlikely since the *S*-oxide (**7**) failed to react with CAN under the conditions described above. An essential role is also attributed to the ester function at C(4) of the starting material (**1**) by virtue of the fact that the decarboxy analogue (**8**) did not give any well-defined products when similarly treated with CAN.

A second possible mechanism for the ring contraction involves initial one electron oxidation of the sulphur atom and formation of the relatively stable radical cation (H). Attack by water as indicated would give a five-membered ring system which would suffer further oxidation in a similar way to that described in the sequence (D)→(G).

Cleavage of the β-lactam ring (Scheme 2) probably occurs by one-electron oxidation of the carbonyl group and C–C bond fission[8] to give the cation radical (J) which after reaction with water and further oxidation would yield the carbonium ion (K). This cation would be trapped by water‡ and decarboxylated to afford the hydroxyamide (L). Further facile oxidation of the side-chain and the embryonic thiazole ring system would lead to the observed product. Alternatively breakdown of the four-membered ring may take place *via* acyl–nitrogen bond cleavage and oxidative decarboxylation of the resulting amido-acid.

Whether the processes outlined in Schemes 1 and 2 are operating in series or in parallel is a moot point since no intermediates have yet been identified in this complex, but high yield, oxidation process.

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References

1 Recent examples include, M. M. Campbell and S. J. Ray, *J. Chem. Soc., Chem. Commun.*, 1980, 665; T. E. Gunda and C. Eneback, *Acta Chem. Scand., Ser. B*, 1980, **34**, 299; J. L. Pfeil, S. Kukolja, and L. A. Paquette, *J. Org. Chem.*, 1981, **46**, 827; M. M. Campbell, B. P. Connarty, J. Kemp, and S. J. Ray, *J. Chem. Soc., Chem. Commun.*, 1982, 748.
2 B. R. Cowley, D. C. Humber, B. Laundon, and A. G. Long, *Tetrahedron*, 1983, **39**, 337.
3 L. Syper, *Tetrahedron Lett.*, 1966, 4493.
4 T.-L. Ho and C. M. Wong, *Synthesis*, 1972, 561.
5 J. E. Baldwin, J. Cutting, W. Dupont, L. Kruse, L. Silberman, and R. C. Thomas, *J. Chem. Soc., Chem. Commun.*, 1976, 736.
6 This process has been shown to be difficult to achieve in analogous compounds possessing an intact β-lactam ring system, see J. E. Baldwin, M. Jung, and J. Kitchin, *J. Chem. Soc., Chem. Commun.*, 1981, 578; see also W. A. Slusarchyk, H. E. Applegate, C. M. Cimarusti, J. E. Dolfini, P. Funke, and M. Puar, *J. Am. Chem. Soc.*, 1978, **100**, 1886.
7 W. H. Richardson in 'Oxidation in Organic Chemistry,' part A, ed. K. B. Wiberg. Academic Press, New York, 1965, ch. IV.
8 T.-L. Ho, *Synthesis*, 1973, 347.
9 G. A. Koppel and L. J. McShane, *J. Am. Chem. Soc.*, 1978, **100**, 288.