

Cephalosporin Sulphoxides: Functionalization at C-2 and C-4

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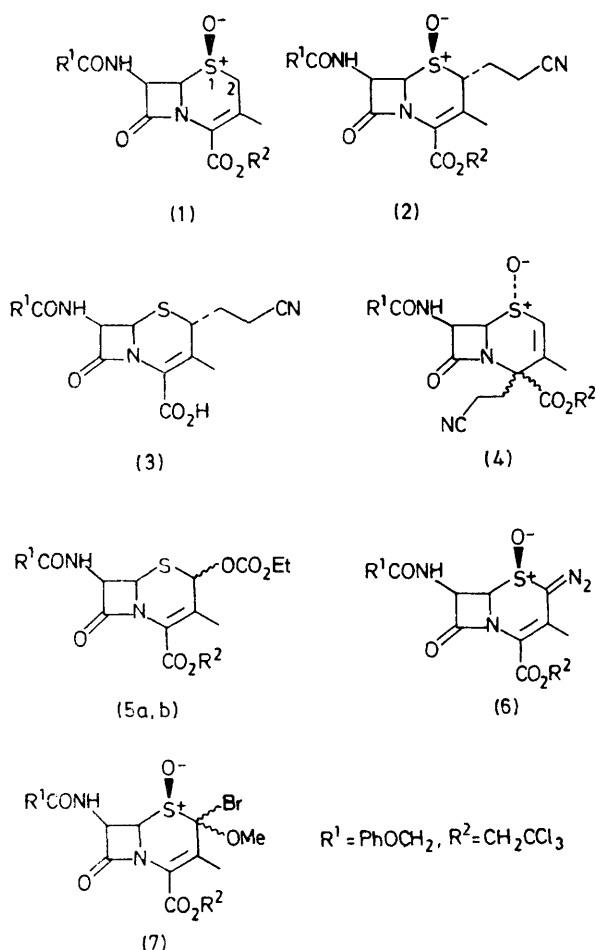
Summary Deacetoxycephalosporanate (S)-1-oxide 2-anions afforded (a) the Michael adducts with acrylonitrile, (b) Pummerer reactions with alkoxychloroformates, and (c) diazo-exchange reactions with tosyl azide, whereas the (R)-oxide under similar conditions reacted only with acrylonitrile giving a Michael adduct at C-4.

THE incorporation of substituents at C-2 of the cephem nucleus has been of considerable importance¹ in the synthesis of analogues with potential antibiotic activity. We therefore report our preliminary investigations of the use

of cephalosporin sulphoxides in effecting 2-substitution. Previous utilization of the 2-anion which should readily be generated has been limited to Mannich additions^{2a} which afforded 2-methylene adducts, and to 2-thiomethylation reactions.^{2b}

An investigation of possible Michael reactions at C-2 in cephem (S)-1-oxides showed, for example, that the (S)-1-oxide (**1**) reacted slowly with acrylonitrile in the presence of triethylamine (other bases were less efficacious) to give the adduct (**2**)† (24%), as an oil [λ_{\max} (MeOH) 267 nm; δ (CDCl₃) 3.70 (H-2)]. Deoxygenation of the sulphoxide

† New compounds had correct elemental analysis and/or molecular ion high resolution mass measurement.



‡ The corresponding (R)-1-oxide did not react under similar conditions.

¹ See, for example, D. O. Spry, *Tetrahedron Letters*, 1972, 3717; 1973, 2413; *J.C.S. Chem. Comm.*, 1973, 671; see also ref. 5, p. 138.

² (a) I. G. Wright, C. W. Ashbrook, T. Goodson, G. V. Kaiser, and E. M. Van Heyningen, *J. Medicin. Chem.*, 1971, 14, 420; (b) A. Yoshida, S. Oida, and E. Ohki, *Chem. Pharm. Bull. (Japan)*, 1975, 23, 2507.

³ P. Claes, A. Vlietinck, E. Roets, H. Vanderaheghe, and S. Toppet, *J.C.S. Perkin I*, 1973, 932.

⁴ R. R. Chauvette, P. A. Pennington, C. W. Ryan, R. D. G. Cooper, F. L. Jose, I. G. Wright, E. M. Van Heyningen, and G. W. Huffman, *J. Org. Chem.*, 1971, 36, 1259.

⁵ 'Cephalosporins and Penicillins,' ed. E. H. Flynn, Academic Press, New York, p. 183, 1972.

⁶ M. Regitz, *Angew. Chem. Internat. Edn.*, 1967, 6, 733.

by phosphorus tribromide³ followed by de-esterification (zinc-acetic acid-dimethylformamide⁴) gave the carboxylic acid (3)† (65%), as an oil [λ_{max} (MeOH) 266 nm; δ (CDCl₃) 3.50 (H-2)]. Under similar conditions the corresponding cephalosporanate (R)-1-oxide underwent quantitative reaction at C-4 yielding the Michael adduct (4)† as an amorphous solid.

Reaction of (1) with certain alkyl chloroformates and triethylamine‡ rapidly gave, for example, the 2 α -carbonate (5a)† (68%) as an oil, together with the 2 β -carbonate (5b)† (4%), m.p. 209–210 °C. A Pummerer rearrangement⁵ is presumably implicated. It is of interest that no 2-alkoxycarbonyl (S)-1-oxides were isolated. This reaction which simultaneously deoxygenates the (S)-1-oxide and gives a 2-substituted cephem did not occur with acetic anhydride or with tosyl chloride under similar conditions.

A further new reaction of the (S)-1-oxide 2-anion resulted from brief treatment of (1) with triethylamine and tosyl azide.† In a diazo-exchange reaction⁶ the 2-diazo cephem (S)-1-oxide (6)† (65%), m.p. 89–90 °C, was formed. The synthetic utility of (6) was illustrated by its reactions with halogens and pseudohalogens; N-bromosuccinimide-methanol, for example, gave a 2-bromo-2-methoxycephem (S)-1-oxide (7)† (23%), as an oil. The diazo (S)-1-oxide (6) was unreactive towards acetic and perchloric acids, which normally react with the diazo group.

It is apparent that considerable scope exists for the exploitation of the cephem (S)-1-oxide 2-anion in the modification of cephalosporins. The extent and limitations of these reactions will be described elsewhere.

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