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

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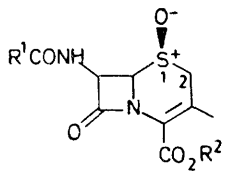
Summary Deacetoxycephalosporanate (*S*)-1-oxide 2-anions afforded (a) the Michael adducts with acrylonitrile, (b) Pummerer reactions with alkoxychloroformates, and (c) diazo-exchange reactions with tosyl azide, whereas the (*R*)-oxide under similar conditions reacted only with acrylonitrile giving a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

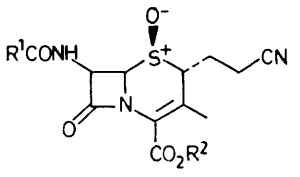
THE incorporation of substituents at C-2 of the cephem nucleus has been of considerable importance[1] in the synthesis of analogues with potential antibiotic activity. We therefore report our preliminary investigations of the use of cephalosporin sulphoxides in effecting 2-substitution. Previous utilization 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 ($CDCl_3$) 3·70 (H-2)]. Deoxygenation of the sulphoxide

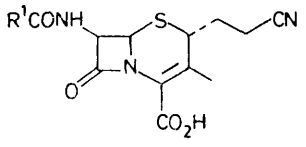
† New compounds had correct elemental analysis and/or molecular ion high resolution mass measurement.



(1)



(2)



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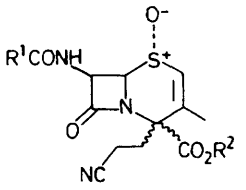

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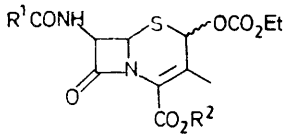
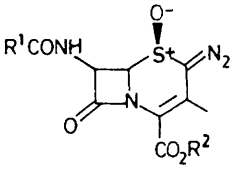


(5a, b)



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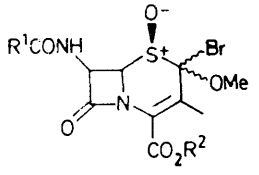

(7)

$R^1 = PhOCH_2$, $R^2 = CH_2CCl_3$

by phosphorus tribromide[3] followed by de-esterification (zinc–acetic acid–dimethylformamide[4]) gave the carboxylic acid (**3**)† (65%), as an oil [λ_{max} (MeOH) 266 nm; δ ($CDCl_3$) 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 2α-carbonate (**5a**)† (68%) as an oil, together with the 2β-carbonate (**5b**)† (4%), m.p. 209—210 °C. A Pummerer rearrangement[5] 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 reaction[6] 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.

We are grateful to the S.R.C. for a Studentship to D.H.B.

(*Received, 26th April* **1976**; *Com.* **456**.)

‡ 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.
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[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.