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REACTIONS OF CEPHALOSPORINS: NEW C-2 AND C-4 FUNCTIONALIZATION METHODS

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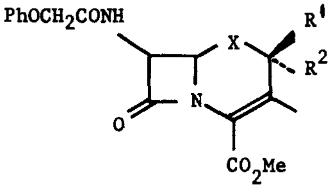
In the pursuit of cephalosporin analogues with enhanced biocidal activity there is considerable interest[1] in the introduction, either by total synthesis or by transformation of cephalosporins, of functional groups at C-2 and C-4. We have extended our studies[2] of the reactions of N-halo-N-metallo reagents with penams, and now report reactions resulting in functionalization of C-2 and C-4 of cephems.

Methyl 7β-phenoxyacetamidodesacetoxycephalosporanate (1) reacted readily with N-chloro-N-sodiourethane in methanol - acetonitrile to give the new 4-substituted 2-cephem (2)* isolated as an oil (17%), $[\alpha]_{D}^{22^{\circ}} + 198^{\circ}$ (c = 1.00, $CHCl_3$). Structure (2) was readily assigned on the basis of high resolution mass measurement of the molecular ion ($C_{20}H_{23}N_{3}O_{7}S$), which indicated incorporation of a urethane unit, together with the infrared spectrum ($\nu_{max.}$ 1784 cm^{-1}), the ultraviolet spectrum ($\lambda_{max.}$ 266 nm, ε 4,300), and the ^{1}H and ^{13}C nuclear magnetic resonance spectra (cis - β-lactam protons and the 2-cephem resonances). The stereochemistry at C-4 remains unresolved. Other workers[1b,g] have shown that alkylation reactions at C-4 apparently proceed through a β-anion, giving β-oriented adducts. However, in our case compound (2) is probably formed by a two-step process involving (a) formation of a 2-chloro or a 4β-chloro intermediate, and then (b) α-face displacement of the 2- or 4β-chloride by carbamidate anion. On these grounds, the urethane group at C-4 in (2) may therefore be α-oriented.

The second β-lactam product formed in the reaction was characterised as the 2-methoxy-3-cephem (3)* and was isolated as a crystalline solid (20%), m.p.165-167°, $[\alpha]_{D}^{22^{\circ}} + 198^{\circ}$ (c = 1.00, $CHCl_3$). Related 2-methoxy-3-cephems have been prepared[1b] by methanol-chlorine reactions of cephems.

In a similar reaction the cephem (S)-sulphoxide (4) afforded the 2,2-dichlorocephem (5)* in 40% yield as an oil. Compound (5) exhibited the correct spectroscopic features and was re-converted to (4) in zinc-acetic acid. This dichlorocephem** is presumably formed by electrophilic attack of a 2-anion on an N-chloro species derived from disproportionation of N-chloro-N-sodiourethane.

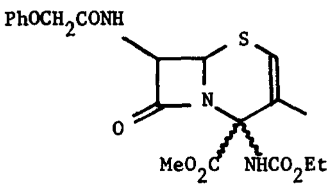


1, $R^1=R^2=H$, X=S

3, $R^1=H$, $R^2=OMe$, X=S

4, $R^1=R^2=H$, X=S-O

5, $R^1=R^2=Cl$, X=S-O



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It was of interest to compare the reactions of N-chlorourethane with those of N-chloro-N-sodiourethane. Accordingly, it was shown that excess N-chlorourethane did not react readily with (1) in dry solvent, but in wet tetrahydrofuran a mixture of the (R)-sulphoxide (64%) and the (S)-sulphoxide (4) (18%) was obtained. No 2- or 4-substituted products were isolated. This reaction thus affords a convenient synthesis of the less accessible cephalosporanate (R)-sulphoxides, and parallels a closely-related reaction of N,N-dichlorourethane[3].

The formation of the 4-urethane (2) represents an interesting new reaction mode of cephems, and the production of (3) and (5) affords alternative routes to these 2-substituted cephems. Further studies of these reactions[4] are in progress, and the synthetic utility of the 2- and 4-substituted cephems is being explored.

‡ New compounds exhibited satisfactory elemental analysis and/or high resolution mass measurements.

‡‡ A 2,2-dichlorocephem sulphoxide from a t-butylhypochlorite-methanol reaction is mentioned in a footnote in reference 1b.

1. See, for example (a) R.D.G. Cooper, P.V. Demarco, C.F. Murphy and L.A. Spangle, J.Chem.Soc.(C), 1970, 340. (b) D.O. Spry, Tetrahedron Letters, 1972, 3717; ibid, 1973, 165 and 2413. (c) J.G. Wright, C.W. Ashbrook, T. Goodson, G.V. Kaiser and E.M. Van Heyningen, J. Med. Chem., 1971, 420. (d) R. Scartazzini, H. Peter, N. Bickel, K. Heusler and R.B. Woodward, Helv. Chim. Acta, 1972, 55, 408. (e) M. Yoshimoto, S. Ishihara, E. Nakayama, E. Shoji, H. Kuwano and N. Soma, Tetrahedron Letters, 1972, 4387. (f) D.H.R. Barton, I.H. Coates, P.G. Sammes and C.M. Cooper, J.C.S. Perkin I, 1974, 1459. (g) A. Yoshida, S. Oida and E. Ohki, Chem. Pharm. Bull., 1975, 23, 2507.

2. M.M. Campbell and G. Johnson, J.C.S. Chem. Comm., 1975, 479; D.H. Bremner, M.M. Campbell and G. Johnson, Tetrahedron Letters, 1975, 2955; ibid., p. 3331.

3. M. Ochiai, O. Aki, A. Morimoto and T. Okada, Tetrahedron Letters, 1972, 3241.

4. Preliminary investigations of certain related cephems show a 3-cephem to 2-cephem rearrangement in the reaction conditions, leading to complications.