Reactions of Cephalosporins with *N*-Bromosuccinimide

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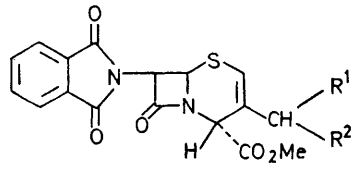
Summary A 3-acetoxymethyl-Δ^2-cephem derivative was converted into a 3-formyl-Δ^2-cephem by oxidation with *N*-bromosuccinimide; a Δ^3-deacetylcephalosporanic acid lactone formed a 2-bromo-derivative.

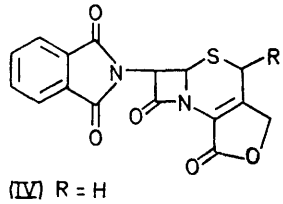
As part of our study of the chemistry of cephalosporins, we examined the reaction of 7-phthalimido-Δ^2-cephalosporanic acid, methyl ester (I)† with *N*-bromosuccinimide (NBS). A transient brownish-red colour was observed when a degassed,

† Compound (I), m.p. 210—211 °C, was prepared (*ca.* 50%) by first heating the methyl ester of 7-aminocephalosporanic acid with phthalic anhydride and triethylamine in benzene for 2 h, followed by treatment with acetic anhydride for 18 h.

ethanol-free, chloroform solution of the substrate was treated with NBS. However, only starting material was found after 24 h at 25 °C. Reaction did occur in the presence of a trace of azobisisobutyronitrile (AIBN). N.m.r. monitoring showed a decrease of the intensity of the methylene signal without the appearance of a new low-field signal, and a new material with a low-field resonance at δ 9·37 p.p.m. was isolated from the reaction mixture, which was assigned structure (III), m.p. 221—226 °C δ ($CDCl_3$)‡ 9·37 (1H, s, CHO), 7·85 (4H, m, ArH), 7·52 (d, *J* 0·5 Hz, 2-H), 5·75 (1H, d, *J* 4·4 Hz, 7-H), 5·68, (d, *J* 0·5 Hz, 4-H), 5·40 (1H, d, *J* 4·4 Hz, 6-H), and 3·82 (3H, s, OMe) p.p.m.; ν_{max} 1780, 1735, 1713, and 1670 cm^{-1}. Structure (II) seems likely for the intermediate prior to hydrolysis.



(I) R^1 = H, R^2 = OCOMe
(II) R^1 = Br, R^2 = OCOMe
(III) R^1, R^2 = O



(IV) R = H
(V) R = Br
(VI) R = OMe

The bromination does not occur in the presence of oxygen or in polar solvents and is certainly of a free-radical type related to that reported by Webber *et al.*[1]

Another free-radical reaction involving NBS occurred when the lactone (IV)§ was treated with NBS (1 equiv.) in pure chloroform, the reaction proceeded at room temperature only in the presence of AIBN and in the absence of oxygen. After 14 h, a practically quantitative yield of the 2-bromo-compound (V) was obtained, m.p. 222—224 °C. The position of the bromine atom at C-2 was confirmed by the n.m.r. spectrum [$(CD_3)_2SO$)] from which the characteristic 2H C(2)-H AB quartet had disappeared while a 1H singlet had appeared at 3·53 p.p.m.

The methanolic solution of the bromo-derivative at room temperature rapidly became acidic, and addition of triethylamine (1 equiv.) gave the 2-methoxy-compound (VI), m.p. 187—190 °C, whose n.m.r. spectrum was similar to that of (V); [δ (OMe) 3·31 p.p.m.].

Our findings suggest a new route to functionalization of the 2-position of the cephem nucleus.[2]

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‡ All n.m.r. spectra were obtained on a Varian A-60 spectrometer with Me_4Si as internal standard.

§ Compound (IV), m.p. 275 °C, was prepared by acylation of 7-aminocephalosporanic acid with phthaloyl chloride, which gave 7-phthalimidocephalosporanic acid, followed by lactonization, without purification, according to the procedure used by J. D. Cocker, *J. Chem. Soc.*, 1965, 5015.

[1] J. A. Webber, G. W. Huffman, R. E. Koehler, C. F. Murphy, C. W. Ryan, E. M. Van Heyningen, and R. T. Vasileff, *J. Medicin. Chem.*, 1971, **14**, 113.

[2] For other approaches, *cf.* I. G. Wright, C. W. Askbrook, T. Goodson, G. V Kaiser, and E. M. Van Heyningen, *J. Medicin. Chem.*, 1971, **14**, 420; 426.