Transformation of Cephalosporins: Preparation of a 3-Methyl-3-nitro-4-hydroxyiminocepham

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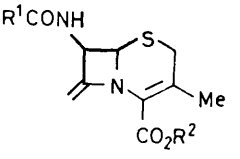
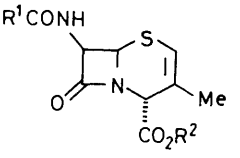
Summary The reaction of N_2O_3 with 3-methyl-7β-phenoxyacetamidoceph-3-em-4-carboxylic acid gives, by an addition–decarboxylation sequence, 3α-methyl-3β-nitro-4(*E*)-hydroxyimino-7β-phenoxyacetamidocepham-4-carboxylic acid.

ANTIBIOTIC activity in cephalosporins (**1**) and derived molecules almost invariably requires the presence of a C(3)–C(4) double bond. Isomerisation to a 2-cephem (**2**), in which C-4 becomes sp^3 hydridized and the carboxylic acid is α-oriented, results in diminished activity.[1] We have been concerned with a systematic study of functionalization and rearrangement at various points in the penicillin and cephalosporin nuclei,[2] and within this programme we now describe a new reaction mode leading to a modified cephalosporin in which C-3 is sp^3 hybridized and C-4 is sp^2 hybridized.

The acid (**1**, R^1 = $PhOCH_2$, R^2 = H) in dichloromethane was treated at room temperature with an excess of dinitrogen trioxide.[3] Following aqueous work-up, the product (**4**) (67%) was recrystallized from toluene–ethyl acetate to give pale yellow needles, m.p. 154—155 °C, $[\alpha]_D^{22}$ +88·5° (*c* 0·02 in acetone). Analysis indicated the formula $C_{15}H_{16}N_4O_6$, consistent with decarboxylation and addition of N_2O_3. Spectroscopic analysis did not permit an unambiguous structural assignment, and an *X*-ray crystallographic analysis was therefore undertaken.



(1)



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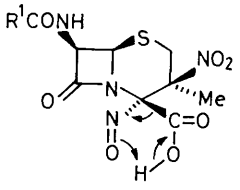

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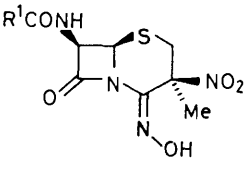

(4)

The *X*-ray analysis[4] indicated the novel cephalosporin structure (**4**). Thus the principle spectroscopic characteristics can be therefore assigned as follows: ν_{max} (KBr) 1773 (β-lactam), 1670 (NHCO), and 1565 (NO_2) cm^{-1}; δ[$(CD_3)_2SO$; 60 Mz] 1·84 (3H, s, Me-3), 3·71 (2H, dd, *J* 14 Hz, H-2), 4·64 (2H, s, $PHOCH_2$), 5·34 (1H, d, *J* 4 Hz, H-6), 5·62 (1H, dd, *J* 4 and 8 Hz, H-7), 6·8—7·4 (5H, m, Ph),

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9·16 (1H, d, *J* 8 Hz, exch NH), and 12·0 br (1H, s, exch OH) Similar spectroscopic data were obtained for the corresponding 3-acetoxymethyl ceph-3-em derivative

The addition of N_2O_3 may be either ionic or radical [3] In one possible reaction pathway an intermediate such as (**3**)‡ may undergo elimination of CO_2 to give the *E*-oxime (**4**) The addition reaction is noteworthy because of the relative lack of reactivity of the C(3)—C(4) double bond, particularly towards electrophilic reagents [5]

This new structural type is of interest because (a) an sp^2 centre has been retained at C-4 and (b) the carboxy-group has been replaced by a hydroxyimino-group Studies on further structural modifications of (**4**) and its 3-acetoxymethyl analogue, which exhibit marginal antibiotic activity against Gram-positive bacteria, are in progress

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‡ This mode of addition would contrast interestingly with other studies which show that reactions of a 4-carbanion, such as methylation and methylsulphenylation, give 4β-adducts owing to control by the N-5 lone pair which is α-oriented, A Yoshida, S Oida, and E Ohki, *Chem Pharm Bull*, 1975, **23**, 2507, 2518

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[2] M M Campbell and G Johnson, *J Chem Soc, Perkin Trans* 1, 1975, 1212, D H Bremner, M M Campbell, and G Johnson, *ibid*, 1976, 1918, D H Bremner and M M Campbell, *ibid*, 1977, 2298
[3] For a recent summary of N_2O_3 radical chemistry see J Pfab, *J Chem Soc, Chem Commun*, 1977, 767, and for discussion of equilibria involving NO, N_2O_3, and N_2O_4 see B C Challis and S A Kyrtopoulos, *J Chem Soc, Perkin Trans* 1, 1979, 299
[4] The crystallographic analysis was performed by Dr A Forbes Cameron, University of Glasgow and will be reported separately
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