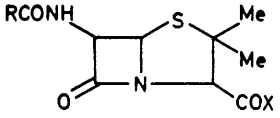
Transformations of Cephalosporanates: The Formation of 4-Alkoxyformamidoceph-2- and -3-ems

By **Malcolm M. Campbell,* Alan Henderson,** and **Stephen J. Ray,** Department of Chemistry, Heriot-Watt University, Riccarton, Currie, Edinburgh EH14 4AS

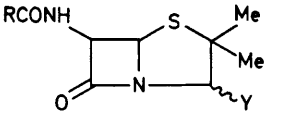
A ceph-3-emcarboxylic acid reacted with diphenylphosphoryl azide–toluene–t-butyl alcohol–triethylamine to give the 4α- and 4β-t-butoxycarbonylceph-2-ems and a 4-t-butoxyformamidoceph-2-em. Interconversion studies on the 4α- and 4β-esters were performed. Reaction in the presence of excess of sodium azide gave as the sole β-lactam product a 4-t-butoxyformamidoceph-3-em.

In continuation of our investigations [1] of new methods of chemically modifying the penicillin and cephalosporin antibiotics, we report the preparation of 4-alkoxyformamidoceph-2- and -3-ems resulting from Curtius reactions.

Penicillanic acids (1) have been transformed [2] by a multistep reaction sequence involving the acid azide (2) and subsequent Curtius rearrangement into the 3-alkoxyformamido-derivatives (3) and the 3-hydroxy-derivatives (4), which are important precursors for the synthesis of analogues of the β-lactam antibiotics. A more direct Curtius degradation sequence was effected by the reaction of diphenylphosphoryl azide (DPPA) with a penicillanic acid.[3] We have extended these studies and have developed conditions in which a cephalosporanic acid can be transformed into either a 4-alkoxyformamidoceph-2- or -3-em.



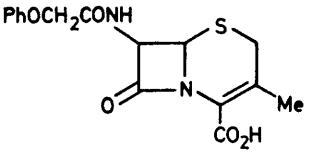
(1) X = OH
(2) X = N_3



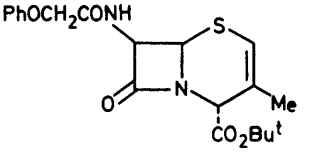
(3) Y = $NHCO_2R$
(4) Y = OH

RESULTS AND DISCUSSION

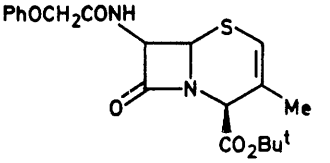
3-Methyl-7β-phenoxyacetamidoceph-3-em-4-carboxylic acid (5) was heated in toluene–t-butyl alcohol with DPPA and triethylamine. Rapid short-path pressurised column chromatography on fine-mesh silica separated the three β-lactam reaction products. The first was the 4α-ester (6) (18%),[4] formed by DPPA acting as a coupling reagent. The ^1H and ^{13}C n.m.r. spectra and the mass spectrum (*m/e* 218, retro-Diels–Alder fragment) were in accord with the assigned structure. The second β-lactam eluted was a minor product (3%), and was isomeric with (6) giving an identical i.r. and mass spectrum. The ^1H n.m.r. spectrum [δ($CDCl_3$) 1.9 (3 H, s, 3-Me), 4.38 (1 H, br d, 4-H), 4.96 (1 H, d, *J* 4 Hz, 6-H), 5.63 (1 H, m, 7-H), and 6.21 (1 H, br, s, 2-H)] was of particular interest because of the five-bond coupling (2 Hz) between H-4 and H-7 (double irradiation study), which is indicative of a 4α-hydrogen.[5] Structure (7) was therefore assigned, and to our knowledge this is the first instance of the 4β-carboxylate isomer in the ceph-2-em series being isolated. Compound (7) was transformed irreversibly on standing and in solution into the more stable isomer (6), which then equilibrated more slowly with the ceph-3-emcarboxylate (1 : 1 mixture



(5)



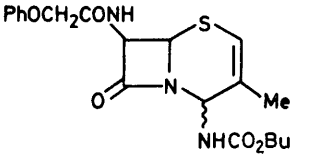
(6)



(7)

formed in triethylamine). The thermodynamically less-stable isomer (7) is presumably formed by kinetically favoured protonation from the α face of an intermediate C-2/C-4 anion.

Further elution gave the 4-t-butoxyformamidoceph-2-em (8) (11%). The structure of this new cephem was readily assigned on the basis of elemental composition and ^1H n.m.r. spectroscopy; δ($CDCl_3$) 1.9 (3 H, s, 3-Me), 5.15 (1 H, d, *J* 4 Hz, 6-H), 5.54 (1 H, s, 4-H), 5.75 (1 H, dd, *J* 4 and 10 Hz, 7-H), and 6.04 (1 H, s, 2-H). In the absence of the C-4 epimer the stereochemistry at this position cannot be assigned rigorously, but the lack of coupling between H-4 and H-7 may indicate a 4α-alkoxyformamide.



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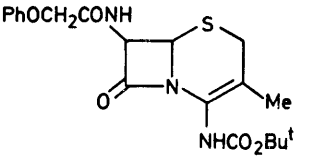

(9)

The reaction with DPPA was repeated in the presence of excess of sodium azide in an attempt to trap the intermediate isocyanate as a tetrazolone. In the presence and in the absence of triethylamine the only β-lactam product (14%) was 4-t-butoxyformamido-7β-phenoxy-

acetamidoceph-3-em (9), in contrast with the earlier reactions which had given the ceph-2-em (8). Structure (9) was assigned on the basis of the ^{1}H n.m.r. spectrum (which contained a geminal methylene unit at C-2), together with other analytical and spectroscopic data. It was of interest that the two isomers (8) and (9) were not interconvertible during control experiments involving triethylamine and/or sodium azide, implying that isomerisation to the ceph-3-em occurred at an intermediate stage. The balance of the products in each of the reactions investigated was accounted for by complex mixtures of non-β-lactams formed by alternative reaction pathways.

These new reactions therefore complement and extend our earlier studies of reactivity at different sites in the penam and cephem series, and afford urethanes which may be amenable to further structural modifications.

EXPERIMENTAL

General details are as reported previously.[1] Elemental compositions assigned on the basis of high-resolution mass spectrometry were of chromatographically pure material. No attempt was made to optimise yields of β-lactam products.

Reactions of 3-Methyl-7β-phenoxyacetamidoceph-3-em-4-carboxylic Acid with Diphenylphosphoryl Azide.—(*a*) To a solution of the ceph-3-em-4-carboxylic acid (5) (1.74 g, 5 mmol) and diphenylphosphoryl azide (1.4 g, 6 mmol) in toluene (10 ml) and t-butyl alcohol (1.5 ml) was added triethylamine (0.5 g, 5 mmol). The solution was heated on a steam-bath for 7 h, cooled, diluted with ethyl acetate (50 ml), and extracted with water (2 × 50 ml). The organic extract was dried ($MgSO_4$), evaporated *in vacuo* and chromatographed. The first product was t-butyl 7β-phenoxyacetamidoceph-2-em-4α-carboxylate[4] (6) (350 mg, 18%); $[\alpha]_D^{22}$ +379° ($CHCl_3$), $\nu_{max.}$* (Nujol) 1 780, 1 738, and 1 690 cm^{-1}; δ($CDCl_3$) 1.5 (9 H, s, Bu^t), 1.93 (3 H, s, Me), 4.62 (2 H, s, CH_2O), 4.7 (1 H, s, 4-H), 5.52 (1 H, d, *J* 4 Hz, 6-H), 5.76 (1 H, dd, *J* 4 and 10 Hz, 7-H), 5.97 (1 H, br s, 2-H), and 6.8—7.7 (6 H, m, aromatic and NH). *t-Butyl 7β-phenoxyacetamidoceph-2-em-4β-carboxylate* (7) (49 mg, 3%) was obtained as an oil, i.r. similar to that for (6), δ($CDCl_3$) 1.5 (9 H, s, Bu^t), 1.9 (3 H, s, Me), 4.38 (1 H, br d, 4-H), 4.59 (2 H, s, CH_2O), 4.96 (1 H, d, *J* 4 Hz, 6-H), 5.63 (1 H, m, 7-H), 6.21 (1 H, br s, 2-H), and 6.78—7.55 (6 H, m, aromatic and NH) (Found: M^+, 404.140 37. $C_{20}H_{24}N_2O_5S$ requires *M*, 404.141 65). This product spontaneously rearranged into (6) on standing in an inert dry atmosphere, and in dry solvent, precluding elemental analysis. The mass spectrum (M^+ 404) of a freshly-prepared sample was identical to that of (6). The third product was *4-t-butoxyformamido-7β-phenoxyacetamidoceph-2-em* (8) (224 mg, 11%), m.p. 90 °C; $[\alpha]_D^{22}$ +143° ($CHCl_3$); $\nu_{max.}$ (KBr) 1 777 and 1 690 cm^{-1}; $\lambda_{max.}$ (EtOH) 266 nm (ε 4 000), δ($CDCl_3$) 1.5 (9 H, s, Bu^t), 1.90 (3 H, s, Me), 4.59 (2 H, s, CH_2O), 5.15 (1 H, d, *J* 4 Hz, 6-H), 5.54 (1 H, s, 4-H), 5.75 (1 H, dd, *J* 4 and 10 Hz, 7-H), 6.04 (1 H, s, 2-H), and 6.8—7.7 (6 H, m, aromatic and NH) (Found: M^+, 419.151 3. $C_{20}H_{25}N_3O_5S$ requires *M*, 419.151 3).

(*b*) To a solution of (5) (5.22 g, 15 mmol) in t-butyl alcohol (90 ml) was added diphenylphosphoryl azide (4.2 g, 15 mmol) and sodium azide (6 g, 92 mmol). The suspension was heated on a steam-bath for 7 h, cooled, diluted with chloroform, and filtered to remove inorganic material. The filtrate was extracted with water (2 × 100 ml), and the organic layer dried ($MgSO_4$) and concentrated *in vacuo*. Rapid, pressurised, short-path column chromatography gave the sole β-lactam product, *4-t-butoxyformamido-7β-phenoxyacetamidoceph-3-em* (9) (0.892 g, 14%) as a yellow foam, m.p. 98—101 °C; $[\alpha]_D^{22}$ +28.70° ($CHCl_3$); $\nu_{max.}$ (Nujol) 1 770, 1 705, and 1 675 cm^{-1}, $\lambda_{max.}$ (EtOH) 273 nm (ε 4 040); δ($CDCl_3$), 1.45 (9 H, s, Bu^t), 1.75 (3 H, s, 3-Me), 3.35 (2 H, dd, *J* 14 Hz, 2-H), 4.45 (2 H, PhOCH_2), 5.1 (1 H, d, *J* 6 Hz, 6-H), 5.85 (1 H, dd, *J* 6 and 12 Hz), and 7.2 (7 H, m, aromatic and NH) (Found: M^+, 419.149 7. $C_{20}H_{25}N_3O_5S$ requires *M*, 419.151 3).

* Spectroscopic data for (6) are quoted for comparison with (7).

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