Preparation of 2-Exomethylene Penam and Penicillin-2-carboxylate Systems

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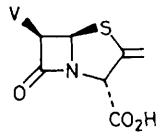
The preparation of penicillin-2-carboxylate systems and their conversion *via* a decarboxylative Pummerer reaction into the 2-methylene penam and 2-methyl penem systems is reported.

The 2-exomethylene penam system (**1**) represents a structural bridge between the penicillin framework and that of clavulanic acid. While several exoalkylidene penam systems have been prepared,[1] the parent system (**1**) was previously unknown.

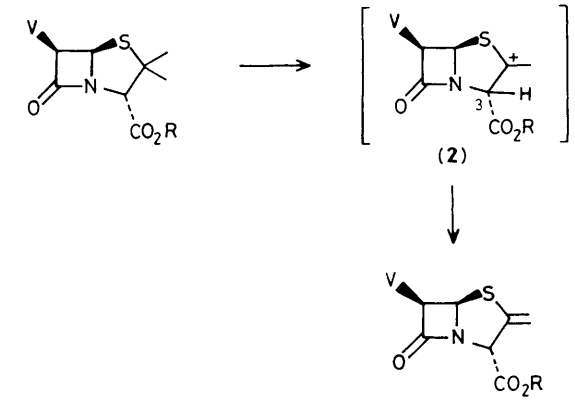
The synthesis of (**1**) was planned on the basis of Scheme 1.†



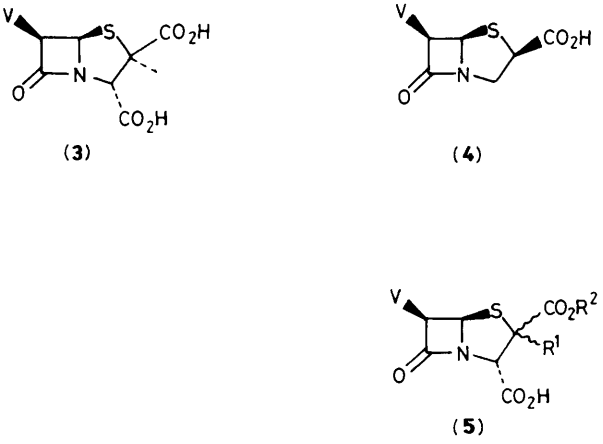
(**1**)

V = $PhOCH_2CONH$

† All new compounds have been characterised by n.m.r., mass spectral, and in some cases elemental analysis.



Scheme 1

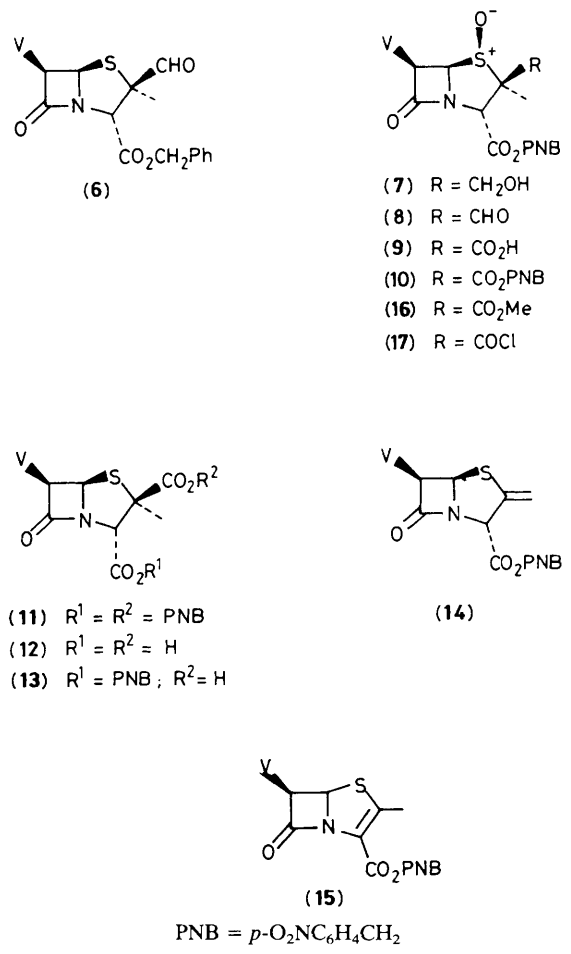


It was hoped that on generation of cation (**2**) in the presence of base, a methyl proton would be removed in preference to the more acidic, but hindered, C-3 proton. The generation of (**2**), ultimately from penicillin V, requires the heterolytic cleavage of a C–C bond. We therefore decided to examine the decarboxylative Pummerer reaction of penicillin-2-carboxylates. The 2,3-dicarboxylate system (**3**) was also recognised to be an interesting synthetic target in its own right. Long[2] has reported the synthesis of the penam-2β-carboxylate (**4**), and has stated that it possesses higher activity than penicillin V against a non-β-lactamase producing strain of *Staphylococcus aureus*. Various penicillin 2-alkoxycarbonyl-3-carboxylates (**5**) have also been previously reported.[3]

Initially it was envisaged that the aldehyde (**6**)[4] would be readily converted into the corresponding acid; however despite use of various oxidants no such conversion was achieved.

The known sulphoxide (**7**)[5] was therefore converted into the corresponding aldehyde (**8**) using Moffat oxidation [dimethyl sulphoxide (DMSO)–Ac_2O, 20 °C][6] in 85% yield. Oxidation with sodium chlorite and resorcinol in a two-phase tetrahydrofuran (THF)–pH 3.5 pyridinium acetate buffer system yielded, after chromatographic purification (SiO_2, 95:5 EtOAc:HOAc), the carboxylate sulphoxide (**9**) (90%).

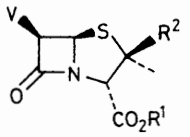
After protection of (**9**) as its PNB ester (**10**) (*p*-nitrophenyldiazomethane, 88%), treatment with phosphorus tribromide in dimethylformamide (DMF) gave the sulphide (**11**), although only in 43% yield based on recovered starting material, and then hydrogenation gave the required dicarboxylate (**12**). Protection of the C-2 carboxylate proved



Scheme 2

nowever to be unnecessary since direct deoxygenation of (**9**) with PBr_3, in DMF at 0 °C gave sulphide (**13**) (66%), which was hydrogenolysed to diacid (**12**) (62%).

Decarboxylation was achieved by way of the acid chloride. Thus treatment of acid (**9**) with oxalyl chloride–pyridine (0 °C in CH_2Cl_2 or THF followed by 16 h at room temp.) gave penam (**14**) with the known penem (**15**)[7] in ratio 4:1 (total yield 18%). Use of 2,6-lutidine in the presence of 4 Å molecular sieve in place of pyridine gave only the exomethylene-isomer (**14**) (44%), which could be completely



(**19**) R^1 = PNB, R^2 = COCl
(**20**) R^1 = PNB, R^2 = $CONMe_2$
(**21**) R^1 = H, R^2 = $CONMe_2$

isomerised to (**15**) with triethylamine. Thus this decarboxylative Pummerer reaction provides a route to exomethylene penams and also penems, in which all carbon atoms are derived from the penicillin starting material. The intermediacy of the acid chloride was demonstrated by the following experiment. After addition of the oxalyl chloride, the reaction mixture was stirred at 0 °C for 2 h, then excess of methanol added. The corresponding methyl ester (**16**) was isolated (90%), strongly implicating the acid chloride (**17**) as an intermediate in this conversion. The reaction most likely proceeds *via* the sequence involving (**18**), Scheme 2.

The acid chloride (**19**), derived from the sulphide (**13**), in the same manner (oxalyl chloride, 2,6-lutidine), on treatment with excess of dimethylamine, provided the amide (**20**) (26%) which was hydrogenolysed to the acid (**21**) (42%). Similarly the ester (**14**) was deprotected to give the required acid (**1**).

Preliminary bioassay results‡ indicate that both (**1**) and (**12**) have comparable antibacterial activity to penicillin V, while amide (**21**) has activity an order of magnitude lower.

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‡ Bioassay was carried out by holed plate assay with *S. aureus* N.C.T.C. 6571 and *Escherichia coli* E.S.S. as indicating organisms. All compounds are sensitive to β-lactamase (**1**) from *Bacillus cereus*.