Chiral Conversion of 6-Aminopenicillanic Acid into an Antibacterial Pen-2-em-3-carboxylic Acid Derivative: Absolute Structure from *X*-Ray Analysis

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Summary Sulphoxidation of the ester (**5**) and reaction of the product with 2-mercaptobenzothiazole gave the adduct (**6a**), which on ozonolysis and mesylation was converted into the ester (**7b**); stereoselective chlorinolysis and treatment of the product (**8**) with hydrogen sulphide–triethylamine gave a mixture of the enantiomeric penem esters (**3a**) and (**9a**) in which the former predominated.

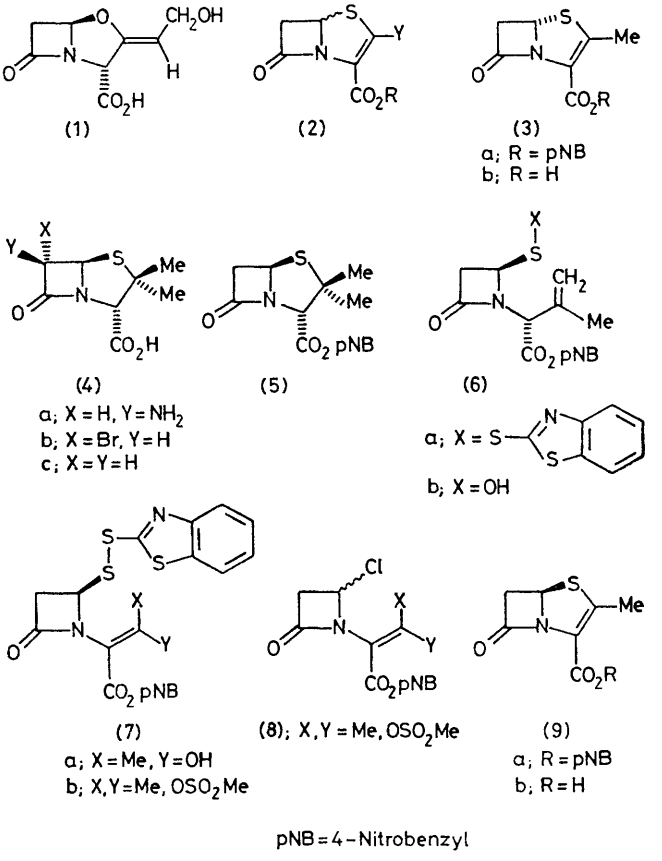
THE accompanying paper[1] describes the conversion of derivatives of clavulanic acid (**1**) into novel 2-substituted pen-2-em-3-carboxylates (**2**); these products were racemic because the chirality of the starting material was lost at an early stage in the sequence. We report that use of the more readily available penicillin nucleus as starting material, and modification of the synthesis, provide an optically active 2-substituted penem derivative (**3a**) whose absolute structure has been confirmed by *X*-ray crystallography.

(6*R*)-6-Aminopenicillanic acid (**4a**) is readily converted[2] *via* (6*S*)-6-bromopenicillanic acid (**4b**) into penicillanic acid (**4c**). Reaction of (**4c**) with *p*-nitrobenzyl bromide ($NaHCO_3$–dimethylformamide) gave† the ester (**5**), $[\alpha]_D$ + 205° ($CHCl_3$), which on treatment with peracetic acid or *m*-chloroperbenzoic acid was converted principally[3] into the β-sulphoxide, $[\alpha]_D$ + 200° ($CHCl_3$). When this was heated with 2-mercaptobenzothiazole (1 equiv., toluene, reflux 4 h), the crystalline adduct[4] (**6a**), λ_{max} (EtOH) 266 nm (ε 21,400); τ ($CDCl_3$) 4·79, 4·97, and 5·12 (1H each), and 8·08 (3H) (–CH–CMe=CH_2), was obtained in 83% yield, presumably *via* the sulphenic acid (**6b**).

On treatment with ozonised oxygen in dichloromethane at −78 °C, the disulphide (**6a**) was converted into the enolised β-oxoester[5] (**7a**), which was isolated as an amorphous solid (46%) after chromatography on silica: λ_{max} (EtOH) 274 nm (ε 33,900); ν_{max} ($CHBr_3$) 1760 (β-lactam) and 1659 cm^{-1} (3-hydroxybut-2-enoate); τ ($CDCl_3$) 7·85 (=CMe). Reaction of the enol (**7a**) with methanesulphonyl chloride and triethylamine in dichloromethane at −15 °C, followed by chromatography on silica, gave the amorphous mesylate (**7b**) (63%) as a mixture of geometrical isomers (ratio *ca.* 9:1): λ_{max} (EtOH) 267 nm (ε 25,300); ν_{max} ($CHBr_3$) 1772 (β-lactam) and 1729 cm^{-1} (ester); τ ($CDCl_3$) 6·74 (SO_2Me) and 7·46 (=CMe) (major isomer), and 6·88 and 7·74 (minor isomer).

Addition of chlorine (1·7 mol equiv.) in carbon tetrachloride to the mesylate (**7b**) in dichloromethane at −15 °C gave, after chromatography, the 4-chloroazetidin-2-one (**8**) as a gum (*ca.* 60%); again a mixture of geometrical isomers (ratio *ca.* 9:1) was shown to be present by ^1H n.m.r. spectroscopy. In one experiment the major geometrical isomer crystallised from toluene–ethyl acetate: ν_{max} ($CHBr_3$) 1780 (β-lactam) and 1727 cm^{-1} (ester); τ ($CDCl_3$) 4·10 (CHCl, dd, *J* 1·5 and 4·5 Hz), 6·74 (SO_2Me, s), and 7·36 (=CMe, s); the minor geometrical isomer was present in the mother liquors (τ 6·81 and 7·62, SO_2Me and =CMe).

When the 4-chloroazetidin-2-one mesylate (**8**) was added to a solution of triethylamine (2 mol equiv.) in tetrahydrofuran saturated with hydrogen sulphide, a mixture of the enantiomeric penem esters (**3a**) and (**9a**) was obtained. Crystallization from ether gave first the laevorotatory enantiomer (17%), $[\alpha]_D$ −128° ($CHCl_3$), λ_{max} (EtOH) 265 (ε 11,900) and 311 nm (ε 9,200); ν_{max} ($CHBr_3$) 1786 (β-lactam) and 1708 cm^{-1} (ester), and subsequently near-racemic material (17%), $[\alpha]_D$ −13° ($CHCl_3$), with similar spectral characteristics.



† Satisfactory spectroscopic data were obtained for all new compounds.

The ^{1}H n.m.r. spectra of both samples showed the expected resonances for the *p*-nitrobenzyl group together with signals at τ ($CDCl_3$) 4·37 [C(5)-H, dd, J 4 and 2 Hz], 6·20 and 6·56 [C(6)-H, 2 × dd, J 16 and 4 Hz, and J 16 and 2 Hz, respectively], and 7·63 (=CMe). Addition of an optically active shift reagent caused progressive differentiation of the resonances of the two enantiomers in the sample with small optical rotation, and indicated that the first crop was essentially a single enantiomer. This was shown to be the (5*S*)-isomer (**3a**) by *X*-ray analysis.‡

Crystal data: $C_{14}H_{12}N_2O_5S$, orthorhombic, $P2_12_12_1$, a = 14·28, b = 22·61, c = 4·460 Å. 2598 Data (θ_{max} = 70°) were collected on a STADI-2 diffractometer (Cu-K_α radiation) from the hkl and $\bar{h}kl$ octants of reciprocal space. Equivalent reflexions of the form $hk0$ and $\bar{h}k0$ were merged with a merging R of 0·016. Reflexions with $I \geqslant 3\sigma(I)$ were used in the refinement, and both $F(hkl)$ and $F(\bar{h}kl)$ were used where appropriate. 1782 Reflexions were used altogether of which 700 were of the form $F(\bar{h}kl)$. The structure was solved by direct phasing methods with the SHELX-76 crystallographic program system. Present R value is 0·0414 for absolute configuration (**3a**) [R = 0·0511 for enantiomeric configuration (**9a**)].§

This is the first reported examination of the penem system by *X*-ray crystallography. Comparison of the structural data with literature values[6,7] for penicillin and cephalosporin acids and salts shows that the penem ester (**3a**) has a significantly smaller sum of bond angles at the bridge-head nitrogen atom [333·3(5)°]; this suggests that amide resonance, already reduced in the β-lactam groups of penicillins and cephalosporins, may be even lower in the new system. The presence of the carbon–carbon double bond leads to lower flexibility and greater strain in the five-membered ring than is found in normal penicillins.

Since the penem formed was mainly the (5*S*)-enantiomer (**3a**), the last two stages in the synthetic sequence must result principally in net inversion of configuration at C(4) of the azetidin-2-one ring. We believe that chlorinolysis of the disulphide (**7b**) proceeds mainly with retention of configuration, and that treatment with H_2S–Et_3N then converts the side-chain into the β-thioxoester; cyclisation would then proceed with inversion by an S_N2 process.

Catalytic hydrogenolysis (Pd–C, EtOAc, 3 h) of the (5*S*)-penem ester (**3a**) gave the corresponding acid (**3b**) isolated as the sodium salt, $[\alpha]_D$ −152° (Me_2SO). Near-racemic ester (**3a** + **9a**), $[\alpha]_D$ −13° ($CHCl_3$), was similarly converted into the sodium salt, $[\alpha]_D$ −21° (Me_2SO), λ_{max} (pH 6 phosphate buffer) 258 (ε 4,800) and 299 nm (ε 5,800). The mixture of enantiomers (**3b** + **9b**) exhibited considerably greater broad spectrum antibacterial activity *in vitro* than clavulanic acid (**1**) or the (5*S*)-penem enantiomer (**3b**) alone.

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‡ The preparation of the (5*R*)-epimers (**9a**) ($[\alpha]_D$ + 136°, $CHCl_3$) and (**9b**), and of the racemates, by a different approach has been described recently (Ciba-Geigy AG, German OLS No. 2,819,655). Our spectral data are in agreement.

§ The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

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