Novel β-Lactamase Inhibitory and Antibacterial 6-Spiro-epoxypenicillins

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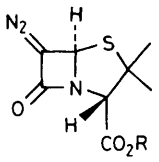
A series of novel 6-spiro-epoxypenicillins prepared by the reaction of diazopenicillanates with oxalyl halides followed by various nucleophiles is reported; these compounds exhibit notable β-lactamase inhibitory and antibacterial properties dependent on the substituents and stereochemistry of the epoxide.

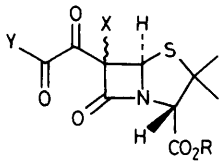
The susceptibility of classical β-lactam antibiotics to chromosomally- and plasmid-mediated β-lactamases has led to the development of a range of irreversible inhibitors for this important class of enzymes.[1] In the main the compounds are specific for β-lactamases, having considerably less affinity for the so-called penicillin-binding proteins (PBPs), the principal targets for antibacterial action.[2] However, recently a series of semi-synthetic penicillin derivatives possessing both β-lactamase inhibitory and antibacterial activity have been reported.[3] We now also describe a new class of potent penicillin-derived β-lactamase inhibitors, some members of which exhibit appreciable antibacterial activity. These inhibitors possess side-chains which are highly conformationally restricted but structurally similar to those of some active penicillins.

As an extension of our programme aimed at the introduction of novel electron withdrawing side-chains to the 6-position of the penicillin nucleus,[4] we investigated the reaction of suitably protected diazopenicillanate (**1a, b**)[5] with oxalyl chloride. It had previously been reported that the reaction of (**1a**) with methoxalyl chloride afforded the 6,6-disubstituted penicillanate (**2a**) of undefined stereochemistry.[6] In our hands the reaction of (**1a**) with oxalyl chloride, followed by quenching of the putative intermediate acid chloride (**3a**) with water and esterifying with diazomethane, yielded predominantly two isomeric compounds in the ratio 4 : 1. The ^{1}H n.m.r. and mass spectral properties of the major isomer were consistent with (**2a**) but were equally compatible with the 6-spiro-epoxides (**4a**) or (**5a**).† Similar compounds also resulted from the reaction of benzyl 6-diazopenicillanate (**1b**) with oxalyl chloride. For convenience of separation and analysis, the mixture of isomers was converted to the corresponding sulphoxides (by oxidation using *m*-chloroperbenzoic acid). The ^{13}C-n.m.r. spectrum of the major product from this reaction revealed only three carbonyl signals (δ 161.24, 165.00, and 167.23) and two signals (δ 73.60 and 73.81) which could be assigned to the quaternary carbons of the putative epoxide. The spiro structures were established by an *X*-ray crystallographic analysis of the sulphoxide of the

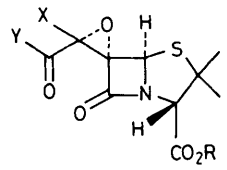
† Similar epoxides have independently been reported from the Lewis acid-catalysed reaction of aldehydes with (**1a**). These epoxides readily rearrange and lack the potential for side-chain manipulation.[7]



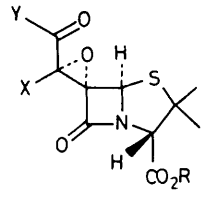
(1)



(2) X = Cl, Y = OMe
(3) X = Cl, Y = Cl

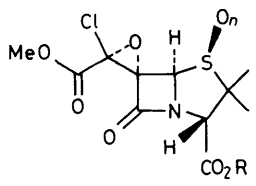


(4) X = Cl, Y = OMe
(6) X = Y = Cl
(8) X = Y = Br
(10) X = Cl, Y = NHPh
(12) X = Br, Y = NHPh
(14) X = Cl, Y = NHCH*(CO$_2$R)Ph
(16) X = H, Y = NHPh



(5) X = Cl, Y = OMe
(7) X = Y = Cl
(9) X = Y = Br
(11) X = Cl, Y = NHPh
(13) X = Br, Y = NHPh
(15) X = Cl, Y = NHCH*(CO$_2$R)Ph
(17) X = H, Y = NHPh

*(*R*) and (*S*)



(18) *n* = 1
(19) *n* = 2

a; R = CH_2CCl_3
b; R = CH_2Ph
c; R = H

major isomer (**18b**) from this series.‡ Figure 1 shows a computer-generated representation of (**18b**). The minor and major isomers could thus be assigned as (**5a, b**) and (**4a, b**), respectively.

The reaction sequence proposed in Scheme 1 is consistent with the approach of the reagent from the least hindered α-face of the penicillanate and interaction of the diazo-group predominantly with the *re*-face of one of the carbonyl groups of the oxalyl chloride; the acid chlorides (**6b**) and (**7b**) finally resulting from the displacement of nitrogen. The relative ratio of the major to minor isomers for the corresponding acid bromides (**8b**) and (**9b**), prepared analogously from oxalyl

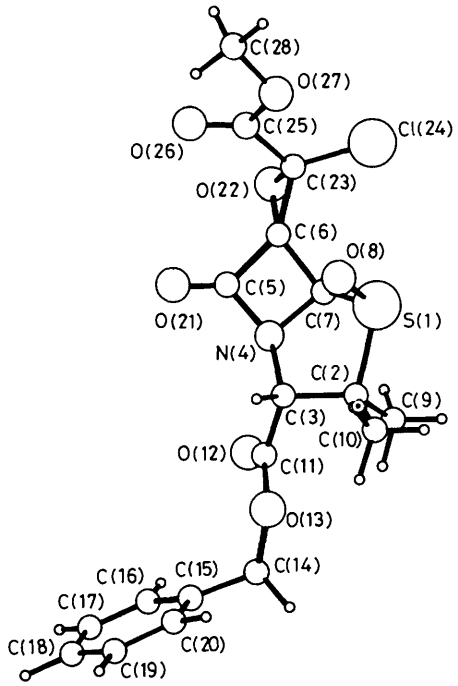


Figure 1. Computer-generated representation of (**18b**), showing the atom numbering scheme.

bromide, was increased approximately twofold to 9:1, demonstrating a further substantial steric effect. Reaction of the versatile intermediate acid halides with, for example, aniline and the benzyl esters of the (*R*) and (*S*) isomers of phenylglycine readily yielded the corresponding amides, (**10b—15b**).§

Dehalogenation at the 3-position of the epoxide was achieved in good yield by means of activated Zn–Cu[10] in aqueous tetrahydrofuran (THF) at pH 4 but only on the bromo series [*e.g.* (**12b**), (**13b**) to (**16b**), (**17b**)]. The reaction is highly stereoselective, (**12b**) leading predominantly to (**16b**), and although definitive assignment of the relative stereochemistry of the diastereoisomers (**16b**) and (**17b**) by various n.m.r. techniques has proved inconclusive, the dehalogenation is assumed to proceed with overall retention of configuration.¶ Oxidation of both halogen series to the sulphoxide, *e.g.*

‡ *Crystal data* for (**18b**): $C_{18}H_{18}ClNO_7S$, M = 427.85; orthorhombic, space group $P2_12_12_1$, a = 9.916(1), b = 10.809(1), c = 18.305(1) Å, U = 1961.9 Å^3, D_c = 1.45 g cm^{-3}, Z = 4, R = 6.13, R_w = 7.08 for 1584 reflections with θ < 76°, $I > 3\sigma(I)$, crystal size 0.5 × 0.3 × 0.15 mm, Cu-K_α radiation. The crystal structure was solved using the direct methods heavy atom difference procedure with the DIRDIF program[8] and refined using the CRYSTALS programs.[9]

Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

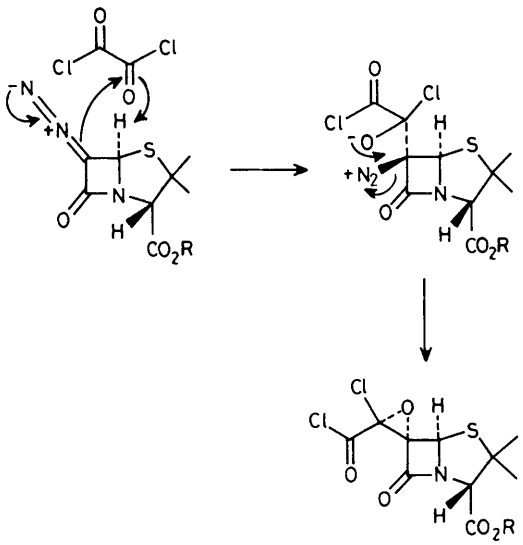
§ Selected physical data; i.r. (KBr or thin film) and ^{1}H n.m.r. ($CDCl_3$, 90 MHz) for (**11b**): I.r. 1792, 1740, 1700 cm^{-1} (C=O); ^{1}H n.m.r. δ 1.37 (3H, s), 1.55 (3H, s), 4.62 (1H, s), 5.16 (2H, s), 5.65 (1H, s), 7.10—7.60 (10H, m), 8.25 (1H, br., s).

(**14b**): M.p. 137—138 °C; i.r. 1790, 1740, 1730, 1710 cm^{-1} (C=O); ^{1}H n.m.r. δ 1.42 (3H, s), 1.55 (3H, s), 4.55 (1H, s), 5.10—5.22 (2H, ABq), 5.22 (2H, s), 5.55 (1H, d, *J* 6.7 Hz), 5.59 (1H, s), 7.13—7.40 (15H, m), 7.59 (1H, br., d, *J* 6.6 Hz).

(**16b**): M.p. 154—156 °C; i.r. 1785, 1745, 1695 cm^{-1} (C=O): ^{1}H n.m.r. δ 1.43 (3H, s), 1.52 (3H, s), 3.97 (1H, s), 4.61 (1H, s), 5.22 (2H, s), 5.61 (1H, s), 6.98—7.67 (5H, m), 7.41 (5H, s), 7.96 (1H, br., s).

(**18b**): M.p. 159—161 °C; i.r. 1810, 1760, 1745 cm^{-1} (C=O); ^{1}H n.m.r. δ 1.12 (3H, s), 1.68 (3H, s), 3.88 (3H, s), 4.62 (1H, s), 5.24 (2H, ABq), 5.11 (1H, s), 7.34 (5H, s).

¶ The reaction most likely proceeds through a metal-stabilised carbanion species at the 3-position of the epoxide. Related carbanions on cyclopropane systems are reported to retain a tetrahedral configuration with a high barrier to inversion (>15 kcal mol^{-1}, 1 kcal = 4.184 kJ).[11] By analogy, it would be expected that the corresponding putative epoxide carbanion should have similar configurational stability, and as a consequence protonation should occur from the same face thus leading to overall retention of configuration.



Scheme 1

(**18b**), and sulphone, *e.g.* (**19b**), readily proceeds under standard conditions. The exclusive formation of the S-sulphoxide (See Figure 1) is unusual but not unprecedented.[12]

Attempted deprotection of the penicillin carboxylate in (**4a**) and (**5a**) with Zn–AcOH led to extensive degradation, but hydrogenation (10% Pd/C, EtOH or EtOAc) of (**4b**), (**5b**), and (**10b—19b**) afforded the corresponding free carboxylic acids, (**4c**), (**5c**), and (**10c—19c**), quantitatively. In the case of the diprotected compounds (**14b**) and (**15b**) containing both (*R*)- and (*S*)-phenylglycine residues, hydrogenation readily liberated both carboxylic acid functionalities.

In preliminary evaluations‖ of the free acids against whole organisms and cell-free enzyme preparations, all the compounds (**4c**), (**5c**), and (**10c—19c**) with a halogen at the 3-position of the epoxide possessed, to some degree, *in vivo* and *in vitro* β-lactamase inhibitory activity. Significantly, the activity for the (3*R*)-isomers (**5c**), (**11c**), (**13c**), and (**15c**) was, in all cases, considerably enhanced over that of the corresponding (3*S*)-isomers (**4c**), (**10c**), (**12c**), and (**14c**). The esters (**4c**), (**5c**), (**18c**), and (**19c**) lacked any significant antibacterial activity, but the amide derivatives, particularly those with the (3*R*)-configuration possessed both antibacterial and β-lactamase inhibitory activity. The effect on the biological activity of the configuration at the 3-position of the epoxide is most apparent in the dehalogenated series. The (3*R*)-isomer, (**16c**), has neither β-lactamase inhibitory nor antibacterial activity, whereas the (3*S*)-isomer, (**17c**), has diminished β-lactamase inhibitory properties yet retains antibacterial activity comparable to that of (**11c**) and (**13c**).

The BTG is acknowledged for financial support of this programme.

Received, 28th August 1987; Com. 1270

‖ Full details on the *in vivo* and *in vitro* evaluation of all the compounds reported in this communication will be described elsewhere,[13] as will the correlation of biological activity with the spatial orientation and configuration of the epoxide side-chains.[14]

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