Novel Semisynthetic 7-Spiro-epoxycephalosporins

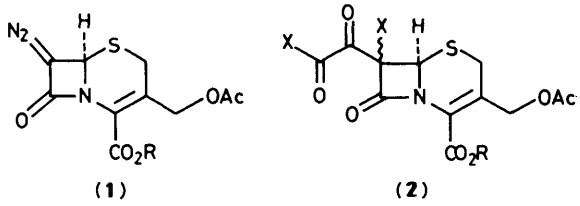
Barrie W. Bycroft,*[a] Richard E. Shute,[a] and Michael J. Begley[b]

[a] *Department of Pharmacy and* [b] *Department of Chemistry, University of Nottingham, Nottingham NG7 2RD, U.K.*

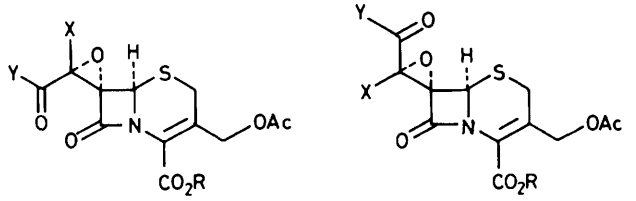
A series of novel 7-spiro-epoxycephalosporins prepared by the reaction of oxalyl halides with 7-diazocephalosporanate followed by various nucleophiles is reported: some of these compounds exhibit notable antibacterial activity which is dependent on the substituents and stereochemistry of the epoxide.

In the preceding communication[1] we described a new class of 6-spiro-epoxypenicillins arising from the reaction of 6-diazopenicillanate with oxalyl halides. This somewhat unexpected reaction of a diazo compound with an acid halide[2] afforded a convenient means of constructing novel, conformationally restricted side-chains. In order to explore the general applicability of this synthetic sequence to other β-lactam antibiotics, it was therefore of considerable interest to ascertain whether 7-diazocephalosporanate (**1**) would give a similar series of compounds or yield the alternative 7,7-chloroketone derivatives (**2**).

To this end t-butyl 7-diazocephalosporanate (**1a**)[3] was



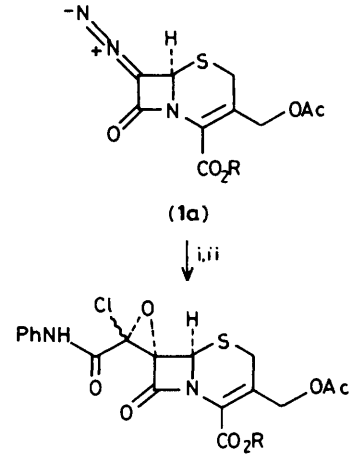
(1) (2)



(3) X = Cl, Y = NHPh
(4) X = Cl, Y = NHPh
(5) X = Y = Cl
(6) X = Y = Cl
(7) X = Y = Br
(8) X = Y = Br
(9) X = Br, Y = NHPh
(10) X = Br, Y = NHPh
(11) X = Cl, Y = $NHCH_2CN$
(12) X = Cl, Y = $NHCH_2CN$
(13) X = Cl, Y = $NHCH^*(CO_2R)Ph$
(14) X = Cl, Y = $NHCH^*(CO_2R)Ph$
(15) X = H, Y = NHPh
(16) X = H, Y = NHPh

* (*S*)- configuration

a; R = Bu^t
b; R = H



(1a)

i,ii

(3a),(4a)

Scheme 1. *Reagents*: i, $(COCl)_2$; ii, $PhNH_2$.

reacted with oxalyl chloride to yield poorly stable acid chloride intermediates which could be further reacted with aniline to give two isomeric anilide derivatives, in the ratio 4 : 1, as the only isolable products, and in yields approaching 50% (Scheme 1). The ^1H n.m.r. and mass spectra of the isomers were consistent with either the chloroketone derivatives or the alternative 7-spiro-epoxides (**3a**) or (**4a**). However the ^{13}C n.m.r. spectrum of the major isomer revealed only four carbonyl signals (δ 157.68, 158.47, 159.74, and 170.44) and two signals (δ 76.78 and 76.88) assignable, as in the pencillin series,[1] to the quaternary carbons of the spiro-epoxide. An *X*-ray crystallographic analysis of (**3a**), the major product, confirmed the assignment and again established the spiro-structure.† Figure 1 shows a computer-generated representation of (**3a**). It followed that the minor isomer, (**4a**), had the opposite configuration at the 3-position of the epoxide, and the acid chloride intermediates could be assigned the structures (**5a**) and (**6a**).

It is suggested that the reaction sequence is similar to that proposed for the penicillin derivatives, involving approach of the reagent from the least-hindered α-face of the cephalosporanate, thus accounting for the stereochemistry at the 7-position. The predominant interaction of the diazo group with the *re*-face of one of the carbonyls of the oxalyl halide appears, in this case, to be unaffected by the size of the halogen, since the relative ratio of the major to minor isomers for the corresponding bromo compounds (**7a**), (**8a**) and (**9a**), (**10a**), prepared analogously from oxalyl bromide, is comparable with that obtained for the chloro series (*i.e. ca.* 4 : 1). The reasons for this observation together with the selective formation of the spiro-epoxide structure itself are not, at this time, apparent.

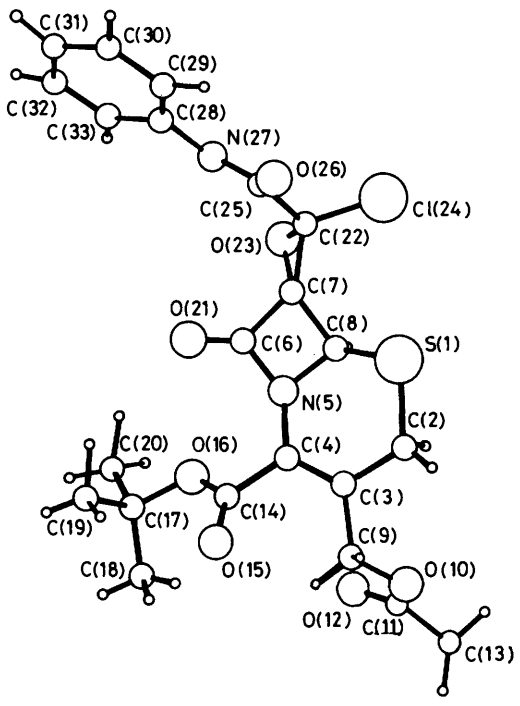


Figure 1. Computer-generated representation of (**3a**), showing the atom numbering scheme.

Reaction of the versatile intermediate acid halides with, for example, aminoacetonitrile and the t-butyl ester of the (*S*)-isomer of phenylglycine readily yielded the corresponding

† *Crystal data* for (**3a**): $C_{22}H_{23}ClN_2O_7S$, M = 494.94, monoclinic, space group $P2_1$, a = 9.888(1), b = 11.090(1), c = 11.653(1) Å, β = 111.66(1)°, U = 1187.6 Å^3, D_c = 1.38 g cm^{-3}, Z = 2, R = 4.63, R_w = 5.84 for 2307 reflections with θ < 76°, $I > 3\sigma(I)$, crystal size 0.6 × 0.35 × 0.1 mm, Cu-K_α radiation. The crystal structure of (**3a**) was solved by direct methods using the MULTAN-80 program[4] and refined with the CRYSTALS programs.[5]

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.

amides, (**11a**—**14a**).‡ Dehalogenation at the 3-position of the epoxide again could only be achieved on the bromo derivatives, thus (**9a**) and (**10a**) were readily converted to (**15a**) and (**16a**) using an activated Zn/Cu couple[6] in aqueous tetrahydrofuran (THF) at pH 4. The reaction is highly stereoselective and is assumed by analogy with the penicillins to proceed with overall retention of configuration, *i.e.* (**9a**) to (**15a**), (**10a**) to (**16a**).[1]

In all cases the cephalosporin carboxylate could be readily deprotected by treatment with trifluoroacetic acid to afford the corresponding free acids (**3b**), (**4b**) and (**9b**—**16b**). For the diprotected compounds, (**13a**) and (**14a**), this procedure liberated both carboxylic acid functionalities (**13b**) and (**14b**).

Preliminary evaluations§ of the free acids against a range of organisms revealed noteworthy activity against Gram positive bacteria. In the halogen-containing series this activity resided almost entirely with the (3*R*)-isomers (**4b**), (**10b**), (**12b**), and (**14b**). For the dehalogenated compounds, the stereochemically related (3*S*)-isomer (**16b**) was the more active, albeit to a lesser extent than the corresponding halogenated analogue (**4b**). The implications of these stereochemical constraints on the biological activity of these compounds in relation to the preferred side-chain conformations of classical β-lactam antibiotics will be discusssed elsewhere.[8]

The BTG is acknowledged for financial support, and Glaxo Pharmaceuticals for a generous gift of 7-ACA.

Received, 28th August 1987; Com. 1269

‡ Selected physical data, i.r. (KBr or thin film), and ^{1}H n.m.r. ($CDCl_3$, 90 MHz) data for (**3a**): m.p. 138—143 °C (decomp.); i.r., 1785, 1735, 1695 cm^{-1} (C=O); ^{1}H n.m.r. δ 1.60 (9H,s), 2.13 (3H, s), 3.27—3.78 (2H, ABq, *J* 18 Hz), 4.74—5.17 (2H, ABq, *J* 13 Hz), 5.38 (1H, s), 7.15—7.70 (5H, m), 8.46 (1H, br., s).

(**12a**): i.r. 2250 cm^{-1} (C≡N), 1795, 1740(sh), 1715 cm^{-1} (C=O); ^{1}H n.m.r. δ 1.60 (9H, s), 2.08 (3H, s), 3.20—3.70 (2H, ABq, *J* 18 Hz), 4.28 (2H, d, *J* 6 Hz), 4.69—5.11 (2H, ABq, *J* 13 Hz), 5.22 (1H, s), 7.63 (1H, br., tr., *J* 6 Hz).

(**13a**): m.p. 130—132 °C (decomp.): i.r. 1785, 1740, 1730, 1715 cm^{-1} (C=O); ^{1}H n.m.r. δ 1.47 (9H, s), 1.63 (9H, s), 2.13 (3H, s), 3.24—3.74 (2H, ABq, *J* 18 Hz), 4.74—5.16 (2H, ABq, *J* 14 Hz), 5.31 (1H, s), 5.43 (1H, d, *J* 6 Hz), 7.42 (5H, s), 7.63 (1H, br., d, *J* 6 Hz).

(**15a**): m.p. 163.5—164 °C; i.r. 1795, 1740, 1720, 1685 cm^{-1} (C=O); ^{1}H n.m.r. δ 1.59 (9H, s), 2.09 (3H, s), 3.21—3.71 (2H, ABq, *J* 18 Hz), 4.03 (1H, s), 4.72—5.13 (2H, ABq, *J* 13 Hz), 5.06 (1H, s), 7.05—7.60 (5H, m), 8.10 (1H, br., s).

§ Full details of the biological evaluation of these compounds will be described elsewhere.[7]

References

1 B. W. Bycroft, R. E. Shute, and M. J. Begley, preceding communication.
2 'The Chemistry of Diazonium and Diazo Groups,' ed. S. Patai, Wiley and Sons, New York, 1978; A. Schoenberg and K. Praefke, *Chem. Ber.*, 1966, **99**, 952.
3 J. C. Sheehan and T. J. Commons, *J. Org. Chem.*, 1978, **43**, 2203.
4 P. Main, S. L. Fiske, S. E. Hull, L. Lessinger, G. Germain, J. P. Declercq, and M. M. Wolfson, 'MULTAN a System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data,' University of York, U.K. and University of Louvain, Belgium.
5 J. R. Carruthers, 'CRYSTALS User Manual,' Oxford University Computing Laboratory, 1975.
6 E. LeGoff, *J. Org. Chem.*, 1964, **29**, 2048.
7 B. W. Bycroft, R. E. Shute, F. O'Grady, and B. Murphy, manuscript in preparation.
8 B. W. Bycroft, R. E. Shute, and D. E. Jackson, manuscript in preparation.