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REACTIONS AND REARRANGEMENTS OF OXAZOLINOAZETIDINONES: FORMATION OF 1,5-OXAZOCINE DERIVATIVES

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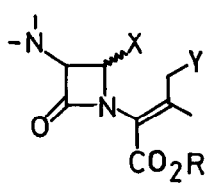
Analogues of the cephalosporins in which sulphur is replaced by oxygen, nitrogen and carbon are of considerable current interest because of their potential antibiotic activity. Recent total syntheses, involving ketene cycloadditions in the construction of the β-lactam ring may, for example, be cited[1,2] as can semi-syntheses from penams and cephems[3,4]. The latter approach utilizes intramolecular cyclization of intermediates (1) in which X is displaced by Y, leading to 3-methylcephalosporanates of structure (2). We have been



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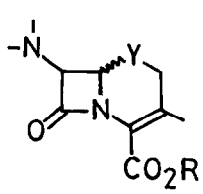

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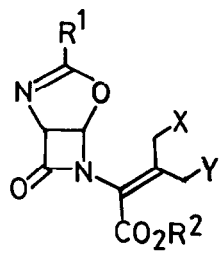


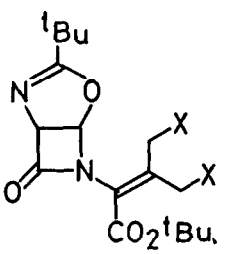
3, X=Y=H

4, X=Y=Br

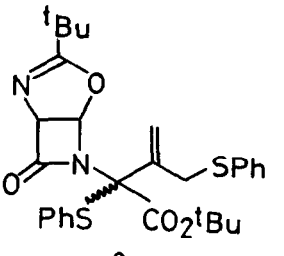
investigating the preparation and reactions of potentially useful chiral precursors such as (4) and its enantiomer[5], with the objectives of effecting nucleophilic displacement of the Z-bromide by heteronucleophiles, followed by stereospecific intramolecular cyclization to give 3-substituted cephalosporanate analogues. This preliminary note reports a range of

nucleophilic displacement reactions observed for (4) (R^1=R^2= ^{t}Bu) giving products of possible use in the construction of cephalosporin analogues, and also describes the spontaneous rearrangement of an allylic diol, derived from (4), to give substituted 1,5-oxazocines.

Several oxazolinoazetidinones (3) were investigated as precursors of the dibromides (4), but difficulties were experienced in the allylic bromination when R^1 or R^2 were alkyl or benzyl substituents, because of competing reactions. We therefore converted ^{t}butyl 6β-^{t}butylamidopenicillanate≠ into an oxazolinoazetidinone (3), (R^1=R^2=^{t}Bu) with dichloro (iodobenzene).[6] Bromination (N-bromosuccinimide, initiator, hν) gave, almost quantitatively, the dibromide (4) (R^1=R^2=^{t}Bu) which could be used directly in subsequent transformations.## There are in theory eight positions available for nucleophilic attack in (4), and it was therefore necessary to establish a reactivity profile in order that selectivity of reaction could be achieved, and undesired complications circumvented.



5, X = OCHO
6, X = N_3
7, X = SPh



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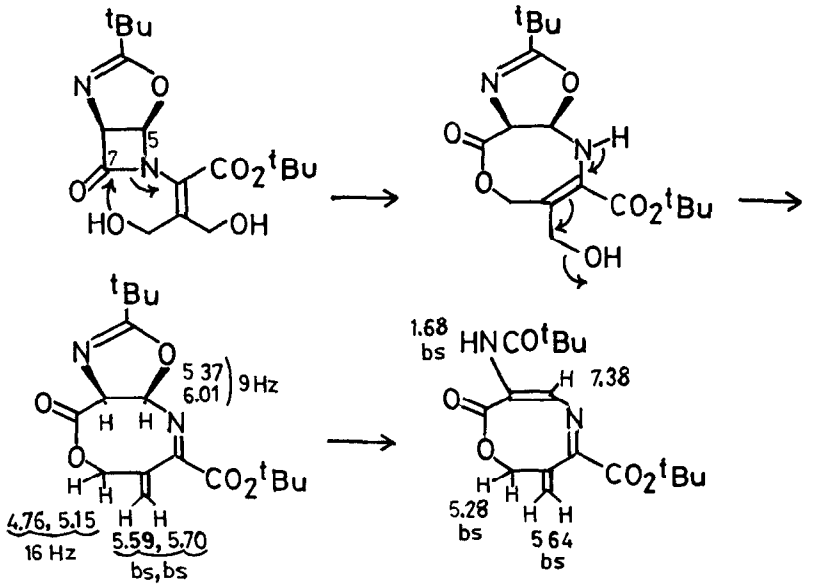
Direct displacement of bromide by hydroxide was not possible, but formate and azide ions under phase transfer conditions (C_6H_6,H_2O, tetrabutylammonium bromide) gave high yields of the bis-formate (5)≠ and the bis-azide (6)≠. Benzenethiolate anion similarly gave (7)≠, together with the diastereoisomeric allylic displacement products (8)≠ which were isolated in low yield and characterized. (Alkyl thiols react with oxazolinoazetidinones under acid catalysis to give 4-alkylthioazetidin-2-ones.[7])

≠ New compounds gave satisfactory elemental analysis and/or high resolution mass measurement, and exhibited the correct spectroscopic data.

This product, virtually pure by n.m.r., was best used immediately, without chromatographic purification which invariably resulted in on-column reactions.



9 10

Hydrolysis of the formate groups in (5) was effected by bicarbonate, but neither a diol (3) (X=Y=OH) nor a 3-hydroxymethyl 1-oxacephem could be detected in the reaction mixture. Instead, the sole non-polar reaction product (9) was isolated by pressurized, short path column chromatography as an unstable, optically active, white solid (18%), m.p. 153-154°; $[\alpha]_D$ 22° 354.8 (c, 0.62 in $CHCl_3$); $\lambda_{max.}$(EtOH) 271 nm; $\nu_{max.}$ (KBr) 1760, 1730, 1665 and 1625 cm^{-1}; δ($CDCl_3$) 1.32 (9H,s), 1.51 (9H,s), 4.76 (1H,d, J=16 Hz), 5.15 (1H,d,J=16 Hz), 5.37 (1H,d,J=9 Hz), 5.59 bs (1H), 5.70 bs (1H) and 6.01 (1H, d, J=9 Hz).

Chromatographic isolation of (9) on silica was accompanied by rearrangement (Scheme) to give an optically inactive yellow solid,(10), m.p. 210-211°, $\lambda_{max.}$ (EtOH) 270, 352 nm; $\nu_{max.}$ (KBr) 3400, 1730, 1710, 1665, 1640 and 1615 cm^{-1}; δ($CDCl_3$) 1.26 (9H,s), 1.54 (9H,s), 1.68 (1H,s, D_2O exch.), 5.28 bs (2H), 5.64 bs (2H) and 7.38 (1H,s). The substituted 1,5-oxazocine structure for (10) was unambiguously established by X-ray crystallography≠.

≠ R-factor currently 5%.

The bis-formate (5) could be directly converted to (10) in good yield on alumina.

This transformation of the bis-formate, resulting from attack by the derived allylic alcohol at C(7) rather than at C(5), thus represents an interesting mode of reaction of oxazolinoazetidinones, and leads to examples of the extremely unusual 1,5-oxazocine ring system.

1. See, for example, L.D. Cama and B.G. Christensen, J. Amer. Chem. Soc., 1974, 96, 7582; R.N. Guthikonda, L.D. Cama and B.G. Christensen, Ibid., 7584.

2. R.A. Firestone, J.L. Fahey, N.S. Maciejewicz, G.S. Patel and B.G. Christensen, J. Med. Chem., 1977, 20, 551.

3. a). S. Wolfe, S.-L. Lee, J.-B. Ducep, G. Kannengiesser and W.S. Lee, Canad. J. Chem., 1974, 497; (b) C.U. Kim and D.N. McGregor, Tetrahedron Letters, 1977, 409.

4. Shionogi Co., Ger. Offen., 2,651,771, 1977; 2,735,408,1978; 2,735,854,1978;

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6. D.H.R. Barton, F. Comer, D.G.T. Greig, P.G. Sammes, C.M. Cooper, G. Hewitt and W.G. Underwood, J. Chem. Soc. (C), 1971, 3540. A potentially useful by-product, not previously reported, which we obtained in certain reaction conditions, was tert-butyl 2- {(1S,5R)-3-tert-butyl-7-oxo-4-oxa-2,6-diazabicyclo[3.2.0]hept-2-en-6-yl} -3-chloro-3-methylbutanoate .

7. D.F. Corbett and R.J. Stoodley, J.C.S. Perkin I, 1975, 432.

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