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REACTIONS OF 6-DIAZOPENAMS AND 7-DIAZOCEPHEMS: SPIROCYCLOPROPYL AND SPIROPYRAZOLINYL β-LACTAMS

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6-Diazopenicillanates have been extensively exploited in the formation of a range of modified β-lactams related to the penicillins,[2] and antibiotic properties of derived products have been described.[3] We describe extended studies of this functional grouping in which the carbenoid and 1,3-dipolar characteristics have been utilized in cycloaddition reactions, leading to 6-spiro-substituted products from penams and 7-spiro-substituted products from ceph-3-ems. Such spiro-substitution has been of considerable recent interest,[4] particularly because of the virucidal properties disclosed for a 6-spiropyrroline.[5]

With the objectives of (a) investigating potential routes to alkoxy and hydroxy spirocyclopropyl systems sterically and electronically similar to the hydroxyethyl group at C-6 of the thienamycins and (b) preparing spiroheterocycles of potential antiviral interest, we have performed a series of model reactions in which 6-diazopenams and 7-diazoceph-3-ems were reacted with olefins including vinyl ethers, vinyl acetate, methyl acrylate and acrylamide. In this communication preliminary results are described.

Benzyl 6-diazopenicillanate (1) was reacted with ethyl vinyl ether in the presence of copper bis(acetoacetonate) to give in 73% total yield a mixture of the four possible isomers of the ethoxy-substituted spirocyclopropane (2a-d). Rapid short-path column chromatography on fine-mesh silica afforded three of the isomers as homogeneous oils.[≠] The i.r. spectra were almost identical, showing β-lactam absorption at 1790 cm^{-1} and typical cyclopropyl absorption. The n.m.r. spectra of the three isomers exhibited singlet for H-5 at δ4.57, 4.46 and 4.58 respectively. The cyclopropyl AMN systems appeared for each isomer at δ3.7 and 1.0-2.0. The mass spectra were identical, structurally diagnostic ions (3) and (4)

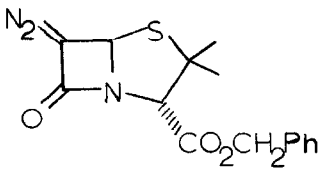
appearing at m/e 250 and 112. At this stage configuration at the spirocyclopropyl ring cannot be assigned for the three separated isomers. The 7-diazoceph-3-em (5) also reacted with ethyl vinyl ether [Cu(AcAc) catalyst] to give four isomeric spirocyclopropyl products in 53% total yield. These resisted chromatographic separation, but two pairs of isomers were obtained, the spectral features being in accord with structure (6). Reaction with vinyl acetate also led to spiro(acetoxycyclopropyl) β-lactams in low yield, but these were extremely unstable.

Methyl acrylate reacted readily with (1) and (5), with and without $Cu(AcAc)_2$. The 6-diazopenam gave a single compound (75% yield), shown to be the 1,3-dipolar addition product (7)≠ [$\nu_{max.}$ (nujol) 3315, 1790, 1745 and 1710 cm^{-1}; $\delta(CDCl_3)$ 5.30 (5-H), 3.35 (pyrazoline CH_2, ABq, J 20Hz)]. Reaction of 6-diazopenam with acrylamide similarly gave a single product (9).≠ However, reaction of 7-diazoceph-3-em with methylacrylate gave two spiropyrazolines isomeric at C-7, (8a)≠ (26%) [m.p. 198°, decomp; $\nu_{max.}$ (nujol) 1780, 1728 and 1707 cm^{-1}; $\delta(CDCl_3)$ 3.35 (2-H, ABq, J 17Hz), 3.55 (pyrazoline CH_2, ABq J 20Hz), 4.85 (6-H) and 6.99 (NH)], and (8b)≠ (38%) [$\nu_{max.}$ 1777, 1719 and 1703 cm^{-1}; $\delta(CDCl_3)$ 3.27 (2-H, ABq, J 17Hz), 3.47 (pyrazoline CH_2 ABq, J 20Hz), 4.86 (6-H), 7.67 (NH)].

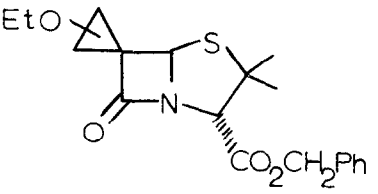
It is possible that when only one isomer is formed by (1), the 1,3-cycloaddition occurs from the sterically less-hindered α-face. In the formation of the spiropyrazolines, initial 1,3-cycloaddition affords 1-pyrazolines which undergo prototropic rearrangement to give the isomeric products (7)-(9), rather than extruding nitrogen to give spirocyclopropanes.

Diazo-β-lactams therefore react with vinyl ethers possibly through 1-pyrazoline intermediates, whereas a 1,3-dipolar cycloaddition mode predominates with derivatives of acrylic acid which give spiropyrazolines. The former process has potential in the synthesis of isosteres of the thienamycin C-6 hydroxyethyl group. The latter reactions yield a range of spiro-substituted products, a class of β-lactam derivatives which has attracted recent interest. Further studies of the chemistry and biological properties of these spiro-fused systems are in progress.

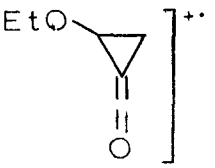
≠ New compounds gave satisfactory elemental analyses and/or high resolution mass measurement.



1



2a-d



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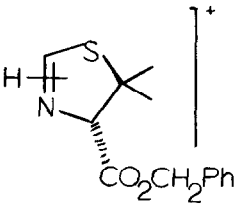

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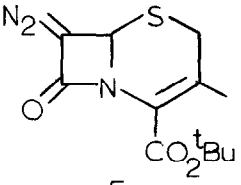

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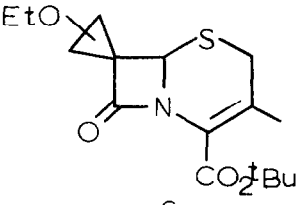

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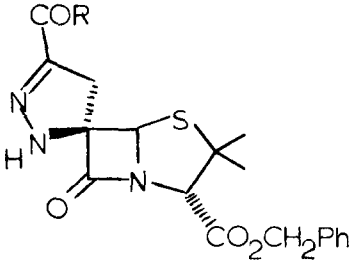
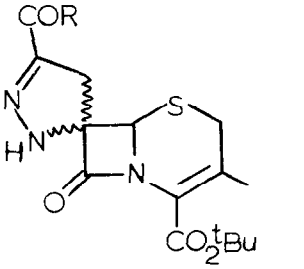


7 R = OMe

9 R = NH_2



8a, b R = NH_2

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4. See, for example, R. Reiner and P. Zeller, *Helv. Chim. Acta*, 1968, 1905; C.H. Rasmusson, G.F. Reynolds and G.E. Arth, *Tetrahedron Letters*, 1973, 145; G.A. Koppel and R.E. Koehler, *ibid.*, p. 1943; D.H. Bremner, M.M. Campbell and G. Johnson, *J.C.S. Perkin I*, 1976, 1918; K. Hirai, Y. Iwano, T. Saito, T. Hiraoka and Y. Kishida, *Tetrahedron Letters*, 1976, 1303.

5. Ger. Pat. 2702518, 1977 (*Chem. Abs.*, 1977, *87*, 152193z).

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