Novel Alkylation of Penicillanates

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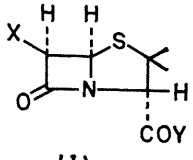
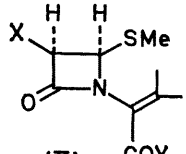
Summary Treatment of *p*-methoxybenzyl 6β-(triphenylmethylamino)penicillanate (Ia) with methyl iodide and strong anhydrous base caused selective cleavage of the thiazolidine ring to give 1-(1-*p*-methoxybenzyloxycarbonyl-2-methylprop-1-enyl)-4*R*-methylthio-3*R*-(triphenylmethylamino)azetidin-2-one (IIa) which was converted into analogues of penicillins containing a non-fused β-lactam ring.

As part of a study of compounds related to penicillins we examined the alkylation of esters of various penicillanic acids. When esters of penicillanic acid (I; X = H, Y = OH) or its 6-acylamino-derivatives were treated with methyl iodide in dry tetrahydrofuran containing a strong base (preferably sodium hydride or potassium t-butoxide) the products no longer contained the β-lactam ring. However, similar treatment of the 6-triphenylmethylamino-compound (Ia)†, m.p. 137—139°, [prepared by tritylation of (Ib)] gave the non-fused β-lactam (IIa)†, m.p. 126—128°, ν_{max} ($CHCl_3$) 1760 (β-lactam carbonyl), 1718 (αβ-unsaturated ester), and 1615 cm^{-1} (C=C). The n.m.r. spectrum‡ ([$^2H_6$]Me_2CO) showed signals at δ 1·57 (3H, s), 1·95 (3H, s), 2·17 (3H, s), 3·78 (3H, s), 4·41 (1H, d, *J* 5 Hz), 4·52 (1H, d, *J* 5 Hz), 4·87 (1H, d, *J* 12 Hz), 5·17 (1H, d, *J* 12 Hz), and 6·6—7·7 p.p.m. (19H). Formation of (IIa) involves cleavage of the 1,2-bond of the thiazolidine ring of (Ia), as in the known reactions of penam sulphoxides,[1] but the only precedent for a selective cleavage of the sulphides appears to be the base-promoted intramolecular rearrangement of the acid chlorides (Ic) or mixed anhydrides to anhydropenicillins[2] (III) and of the chloromethyl ketone (Id) or analogues thereof to (IV).[3]

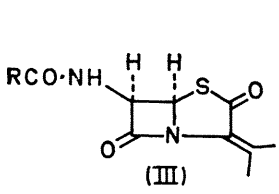


(I)

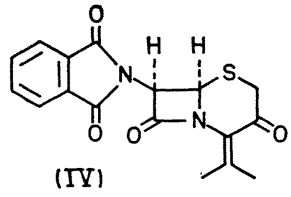


(II)

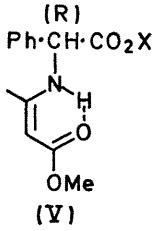
a; X = Ph_3C·NH, Y = O·CH_2·C_6H_4·OMe-*p*
b; X = NH_2, Y = O·CH_2·C_6H_4·OMe-*p*
c; X = RCO·NH, Y = Cl
d; X = phthalimido, Y = CH_2Cl
e; X = PhO·CH_2·CO·NH, Y = O·$CH_2C_6H_4$OMe-*p*
f; X = PhO·CH_2·CO·NH, Y = OH
g; X = PhCH(*R*)·CO·NH, Y = O·$CH_2C_6H_4$·OMe-*p*
NH
Me_2C:CH·CO_2Me (*R*)
h; X = PhCH(NH_2)·CO·NH, Y = OH



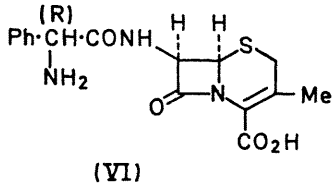
(III)



(IV)



(V)



(VI)

Since structure (II) can be regarded as a monocyclic analogue of both penams and Δ^3-cephems it was of interest to convert the ester (IIa) into acids more closely related to the biologically active penicillins and cephalosporins. Treatment of (IIa) with toluene-*p*-sulphonic acid in acetone at 0° gave the toluene-*p*-sulphonate salt of the amine (IIb),† m.p. 154—155°, ν_{max} (mull) 1805, 1722, and 1630 cm^{-1}, δ ([$^2H_6$]Me_2SO) 1·96 (3H, s), 2·06 (3H, s), 2·19 (3H, s), 2·31 (3H, s), 3·76 (3H, s), 4·88 (1H, d, *J* 5 Hz), 5·15 (1H, d,

† Satisfactory elemental analysis.
‡ N.m.r. spectra were recorded on a Varian A60 spectrometer using Me_4Si as internal reference.

J 5 Hz), 5·19 (2H, s), and 6·86—7·66 p.p.m. (8H). Acylation of the free amine (IIb)† (m.p. 78—79°) with phenoxyacetyl chloride and triethylamine in dichloromethane over 5 min at —20° gave the amide (IIe),† m.p. 120—122°, ν_{max} ($CHCl_3$) 3400, 1770, 1720, 1695, and 1615 cm^{-1}, δ ($CDCl_3$) 1·86 (3H, s), 2·00 (3H, s), 2·25 (3H, s), 3·80 (3H, s), 4·58 (2H, s,), 5·00 (1H, d, J 12 Hz), 5·06 (1H, d, J 5 Hz), 5·30 (1H, d, J 12 Hz), 5·45 (1H, q, J 5 Hz), and 6·8—7·5 p.p.m. (10H). Finally the *p*-methoxybenzyl group was removed by treatment with trifluoroacetic acid in benzene to give the analogue (IIf) of penicillin V (If) as a foam, λ_{max} (EtOH) 235 nm (ϵ 5300), ν_{max} ($CHCl_3$), 3400, 1770, 1690br, and 1630 cm^{-1}; δ ($CDCl_3$) 2·01 (3H, s), 2·07 (3H, s), 2·30 (3H, s), 4·52 (2H, s), 5·28 (1H, d, J 5 Hz), 5·56 (1H, q, collapsing to doublet J 5 Hz on addition of D_2O), and 6·8—7·7 p.p.m. (6H, Ar, NH).

Similarly the condensation product of sodium (*R*)-α-aminophenylacetate and methyl acetoacetate (V; X = Na) was converted into the mixed anhydride[4] (V; X = CO_2Et) and allowed to react with (IIb) in ethyl acetate to give the corresponding amide (IIg)† as a foam, ν_{max} ($CHCl_3$) 3390, 3250, 1770, 1720br, 1690, and 1655 cm^{-1}, δ ($CDCl_3$) 1·53 (3H, s), 1·82 (3H, s), 1·90 (3H, s), 2·22 (3H, s), 3·64 (3H, s), 2·77 (3H, s), 4·59 (1H, s), 4·92 (1H, d, J 5 Hz), 4·99 (1H, d, J 11 Hz), 5·15 (1H, d, J 7 Hz collapsing to singlet on addition of D_2O), 5·26 (1H, d, J 11 Hz), 5·45 (1H, q, collapsing to doublet J 5 Hz on addition of D_2O), 6·8—7·6 (10H, Ar, NH), and 9·45 (1H, d, exchangeable, J 7 Hz). Removal of the amine and carboxy-protecting groups with trifluoroacetic acid gave the *R*-amino-acid (IIh) as an amorphous solid, λ_{max} (EtOH) 240 nm (ϵ 4470), ν_{max} (mull) 1760 and 1680br cm^{-1}. This compound is an analogue of the important antibiotics ampicillin (Ih) and cephalexin (VI).

The β-lactam ring in the new 3*R*-acylamino-1-(1-carboxy-2-methylprop-1-enyl)-4*R*-methylthioazetidin-2-ones was less reactive than that in penicillins, giving no hydroxamic acid when treated with neutral hydroxylamine under the usual conditions of the penicillin assay procedure,[5] and neither (IIf) nor (IIh) had significant antibacterial activity.

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[1] R. B. Morin, B. G. Jackson, R. A. Mueller, E. A. Lavagnino, and W. B. Scanlon, *J. Amer. Chem. Soc.*, 1963, **85**, 1896; L. D. Hatfield, J. Fisher, F. L. Jose, and R. D. G. Cooper, *Tetrahedron Letters*, 1970, 4897; D. H. R. Barton, D. G. T. Greig, G. Lucente, P. G. Sammes, M. V. Taylor, C. M. Cooper, G. Hewitt, and W. G. E. Underwood, *Chem. Comm.*, 1970, 1683.
[2] S. Wolfe, J. C. Godfrey, C. T. Holdrege, and Y. G. Perron, *J. Amer. Chem. Soc.*, 1963, **85**, 643.
[3] B. G. Ramsay and R. J. Stoodley, *Chem. Comm.*, 1970, 1517.
[4] G. R. Fosker, J. H. C. Nayler, and J. A. Wilcox, B.P. 991,586/1965.
[5] J. H. Ford, *Ind. and Eng. Chem.* (*Analytical Edition*), 1947, **19**, 1004.