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The Removal and Displacement of the Thiazolidine Ring in Penicillin.[1] IV. Formation of a Biologically Active Cephem System

Summary: The thiazolidine ring of penicillin V (1) has been removed and replaced by a cephem system.

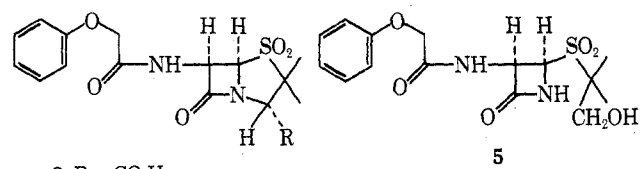
Sir: The thiazolidine ring of penicillins has been displaced for the case of 6-[2-methyl-2-(*o*-nitrophenoxy)propionamido]penicillanic acid[2] and phthalimidopenicillanic acid.[1] We now wish to report the extension of this displacement reaction to 6-phenoxyacetylaminopenicillanic acid (penicillin V, 1).

Penicillin V (1) was oxidized to the sulfone 2[3] using neutral aqueous permanganate: mp 149–151°; 94%; ir (KBr) 3450, 1800, 1735, 1675, 1600, 1530, 1325, 1240 cm^{-1}; nmr (acetone-d_6) δ 8.0 (d, 1, NH), 7.1 (m, 5, phenyl), 6.1 (dd, 1, J_1 = 5, J_2 = 11 Hz, H-6), 5.1 (d, 1, J = 5 Hz, H-5), 4.55 (s, 2, CH_2), 4.4 (s, 1, CH), 1.5, 1.3 (s, 6, CH_3). The sulfone 2 was converted to the isocyanate 3 *via* the mixed anhydride using ethyl chloroformate and pyridine, followed by treatment with sodium azide and thermal rearrangement. The use of triethylamine with the penicillin V side chain resulted in reduced yields of the isocyanate owing to loss of the β-lactam. Hydrolysis of the isocyanate afforded the "aldehyde" 4: 47%; mp 118–119°; $[\alpha]^{25}D$ 72.7° (*c* 0.5, $CHCl_3$); ir (KBr) 3400, 1805, 1675, 1600, 1530, 1315, 1245 cm^{-1}; nmr ($CDCl_3$) δ 8.6 (d, 1, NH), m at 7.1 (aromatic and benzene solvate), 6.05 (dd, 1, J_1 = 5, J_2 = 11 Hz, H-6), 5.3 (s, 1, H-3), 4.85 (d, 1, J = 5 Hz, H-5), 4.5 (s, 2, CH_2), 1.4, 1.45 (s, 6, CH_3). This compound seems to exist entirely in the ring-closed form since no aldehyde absorption is detectable by nmr.[1,2,4]

"Aldehyde" 4 was reduced to alcohol 5 with sodium borohydride: 56%; mp 142–144°; $[\alpha]^{25}D$ 28.6 (*c* 1, $CHCl_3$); mass spectrum (70 eV) *m/e* 219 [$M^+ - SO_2C(CH_3)_2CH_2OH$]; ir (KBr) 3300–3500, 1780, 1660, 1600, 1530, 1300, 1250 cm^{-1}; nmr ($CDCl_3$) δ 8.2 (d, 1, NH), 7.8 (s, 1, NH), m at 7.2 (5, phenyl), 5.95 (dd, 1, J_1 = 5, J_2 = 10 Hz, H-6), 5.25 (d, 1, J = 5 Hz, H-5), 4.55 (s, 2, CH_2), 3.75, 3.95 (overlapping s, 3, CH_2,OH), 1.4, 1.3 (s, 6, CH_3).

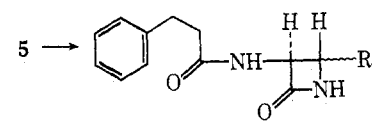
In a model reaction, compound 4 reacted with thiophenol in the presence of triethylamine to give a mixture of cis and trans (1:1) 3-(phenoxyacetamido)-4-phenylthio-2-azetidinone (6): 80%; ir (KBr) 3380, 1763, 1655, 1600, 1540; nmr (acetone-d_6) δ 8.1 (br s, 1, NH), m at 7.2 (11, aromatic and solvate), 5.65 (dd, ½, J_1 = 5, J_2 = 10 Hz, H-3 cis), 5.4 (d, ½, J = 5 Hz, H-4 cis), 5.2 (d, ½, J = 2 Hz, H-4 trans), 4.8 (m, ½, H-3 trans), 4.6 (2s, 2, CH_2).

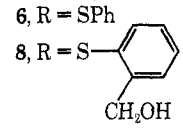
Azetidinones in which the nitrogen is substituted (7) do not react with mercaptans under these conditions. Also, if the mercaptan is sterically bulky the reaction is slow and the competing epimerization of H-4 becomes the dominant reaction route. Compound 5 reacted with isobutylmercaptan only very slowly (4 days) to give 3-(phenoxyacetamido)-4-*trans*-isobutylthio-2-azetidinone. *tert*-Butylmercaptan did not give the desired product at all; instead *trans*-5 was isolated.

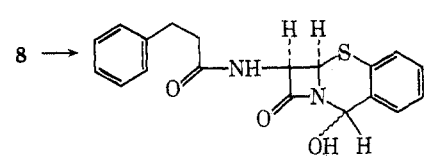


5

2, R = CO_2H
3, R = NCO
4, R = ~OH
7, R = $CO_2CH_2CH(CH_3)_2$



6, R = SPh
8, R = S– 



9

Reaction of 5 with *o*-mercaptobenzyl alcohol in the presence of triethylamine gave cis and trans (1:1) 3-(phenoxyacetamido)-4-(2-hydroxymethylphenylthio)-2-azetidinone (8): 78%; ir (CH_2Cl_2) 3300, 1755, 1690, 1540, 1500 cm^{-1}; nmr (acetone-d_6) δ 8.7-6.9 (m, NH and aromatic, 11), 5.75 (dd, ½, J_1 = 5, J_2 = 8 Hz, H-3 cis), 5.4 (d, ½, J = 5, H-4 cis), 5.2 (d, ½, J = 2, H_4 trans), 4.9 (2s, 2, CH_2), 4.7 (2s, 2, CH_2), 4.4 (dd, ½, J_1 = 2, J_2 = 7 Hz, H_3 trans), 3.7 (s, 1, OH); mp 140–142°; mass spectrum (70 eV) *m/e* 358 (M^+).

Oxidation of 8 with dimethyl sulfoxide and dicyclohexylcarbodiimide[5] gave, after column chromatography, compound 9: 20%; mp 148–150°; ir ($CHCl_3$) 3400, 1775, 1690, 1600, 1495 cm^{-1}; nmr ($CDCl_3$, cephem numbering) δ 8.0–6.9 (m, aromatic and NH), 6.0 (s, 1, H-4), 5.7 (dd, 1, J_1 = 5, J_2 = 8.5 Hz, H-7), 5.25 (d, 1, J = 5 Hz, H-6), 5.05 (s, 1, OH), 4.5 (s, 2, CH_2).

Compound 9 was tested for biological activity[6] and was shown to be active against *Diplococcus pneumoniae*, 0.4;

Streptococcus pyogenes, 1.6; and *Staphylococcus aureus*, 6.3 (minimum inhibitory concentration in μg/ml).

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