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PENICILLIN C-6 SUBSTITUTION: A NOVEL OXYGEN-BRIDGED DIMER

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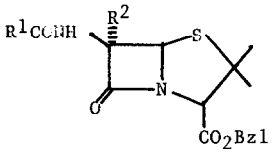
Summary.

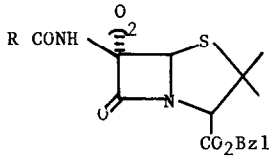
On treatment of benzyl 6α-(dimethylamino)-6β-(phenoxyacetamido)penicillanate with methyl iodide in a polar solvent a dimeric species surprisingly resulted; the anticipated 6α-quaternary ammonium salt could not be isolated. Added methanol gave the 6α-methoxypenicillin. An α-acylureido penicillin gave similar results.

One of the standard procedures for substitution at C-6 of penicillins involves the displacement of a 6α-(methylthio) group by various nucleophiles, catalysed by a heavy metal cation, usually mercury (I) or silver (I)[1]. The methylthio group is introduced by means of the Schiff's base anion procedure[2]. However, this route has some drawbacks, e.g. toxicity of the metal salts employed, especially mercury, and inability to introduce some substituents which complex strongly with the metal ions, such as cyanide[3]. A more versatile approach might be first to convert the methylthio into another good leaving group which could undergo displacement by various nucleophiles without the catalysis of metal ions. Here we describe an attempt to prepare a '6α-quaternary ammonium' penicillin for this purpose, and the isolation instead of an unexpected oxygen bridged penicillin dimer.



CO_2Bzl

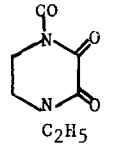
$R^1 = PhOCH_2$, R^2 = SMe, (1)
$R^1 = PhOCH_2$, $R^2 = NMe_2$, (2)
$R^1 = PhOCH_2$, R^2 = OMe, (3)
R^1 = PhCH(NHPip)*, R^2= SMe, (4)
R^1 = PhCH(NHPip)*, $R^2 = NMe_2$, (5)
R^1 = PhCH(NHPip)*, R^2 = OMe, (6)



CO_2Bzl

R = $PhOCH_2$ (7)
R = PhCH(NHPip)* (8)

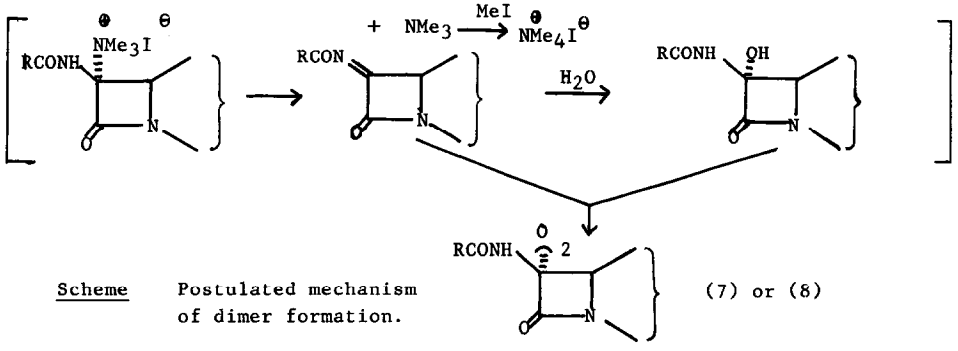
Abbreviation: *Pip =



C_2H_5

Treatment of the 6α-(methylthio)penicillin V ester (1) with dimethylamine/ethanol and silver (I) acetate in dimethylformamide gave the 6α-(dimethylamino)penicillin (2) in 96% yield[4]. Reaction of this material with excess (5-10 equivalents) of methyl iodide in acetonitrile or dimethylformamide (in less polar solvents the reaction was extremely slow) gave no trace of the anticipated 6α-quaternary ammonium salt. Instead, t.l.c. showed gradual production of a less polar material, while a crystalline by-product was also deposited. When reaction was complete, workup of the mother liquors afforded, after removal of free iodine traces, a readily crystallisable material in 44% yield, m.p. 135-136°C,

$\delta(CDCl_3)$ 1.28[6H, s, $(CH_3)_2C$], 5.69 (1H, s, 5-H). The spectroscopic and analytical data of this product, in particular m/z 894 ($M^{\oplus}$), were consistent with the dimeric 6α-oxygen bridged penicillin (7); the crystalline by-product was easily shown to be tetramethylammonium iodide. Clearly the quaternary ammonium species had undergone rapid elimination of trimethylamine, followed by reaction of the resulting acylimine with traces of water in the solvent (Scheme):



Scheme Postulated mechanism of dimer formation.

Our attempts to obtain a reactive but isolable intermediate to react with a range of nucleophiles were thus thwarted. However, other nucleophiles, provided they did not react with the methyl iodide, could themselves intercept the acylimine; thus, addition of methanol (10 eq.) to the reaction mixture generated the 6α-methoxypenicillin (3) in about 70% yield, m.p.77-78°C, $\delta(CDCl_3)$ 3.46 (3H, s, OCH_3). Also added excess water gave the 6α-hydroxy analogue, by comparison with an authentic sample. Interestingly, alkylation at sulphur[5] was not observed even with the large excess of methyl iodide used. The reaction was not restricted to the simple penicillin V side chain; a similar sequence with the 6α-(methylthio) piperacillin[6] ester (4) led to the 6α-(dimethylamino) derivative (5) (93%), the ether dimer (8) (40%) and, with added methanol, the 6α-methoxy derivative (6) (73%).

Catalytic hydrogenolysis of the dimers (7) and (8) proceeded quite smoothly to give the free di-acids, but they showed little biological activity.

The author is grateful to Dr. J. Gower of this department for obtaining the fast-atom bombardment mass spectra which were crucial in characterising the dimers.

References and Notes.

(1) T.Jen, J. Frazee and J.R.E. Hoover, J.Org. Chem., 1973, 38, 2857.
(2) Ref. 1; see also J. Stedman, J. Med. Chem., 1966, 9, 444.
(3) Unpublished results from these laboratories. J.C. Sheehan and Y.S. Lo, J.Org. Chem., 1975, 40, 191, prepared 6α-cyanopenicillin V benzyl ester by addition of HCN to the acylimine generated by an aza-Wittig reaction.
(4) This material eventually crystallised on standing at 0-5°C, m.p. 97-98°C. All new compounds gave satisfactory analytical and spectroscopic data.
(5) Cf. P.M. Denerley and E.J. Thomas, J. Chem. Soc., Perkin Trans. I, 1979, 3175.
(6) K. Ueo, Y. Fukuoka, T. Hayashi, T. Yasuda, H. Taki, M. Tai, Y. Watanabe, I. Saikawa and S. Mitsuhashi, Antimicrob. Agents Chemother., 1977, 12, 455. The piperacillin derivatives all had the R configuration of the side chain.

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