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6α-FLUOROALKYL PENICILLINS

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Abstract: Fluorination of the protected 6α-(hydroxymethyl) amine (19), deprotection and acylation afforded the fluoromethyl penicillin (8). Similar reaction with the 6α-formyl penam (13) proceeded only to the intermediate fluorohydrin (14).

In 1965 Strominger and Tipper[1] put forward the hypothesis that penicillins (and cephalosporins) are structural analogues of the terminal D-ala-D-ala residue of the acetyl muramyl pentapeptide involved in bacterial cell wall biosynthesis. Introduction of a methyl group at the 6α-position of a penicillin provides a closer structural analogy to this unit. However, the 6α-methyl penam (2) was found to be only poorly antibacterially active compared with Penicillin G(1)[2]. Since fluorine can be substituted for hydrogen with only minimal steric, but with considerable electronic effect, we reasoned that the 6α-(fluoroalkyl) derivatives (8) and (9) might possess interesting properties. Further, we had also previously described the synthesis of the antibacterially active 6α-(hydroxymethyl)[3] and 6α-formyl[4] penicillins, the latter existing as a gem diol in aqueous solution. Since there is a close physico-chemical similarity between hydroxy (C-OH) and fluorine (C-F) we hoped that preparation of the fluoromethyl and difluoromethyl penams (8) and (9) would improve the activity of these compounds.

We initially attempted to prepared the 6α-(fluoromethyl) penicillanate (5) having a simple side chain. The successful exchange of sterically hindered sulphonate esters for fluorine using tetra-n-butylammonium fluoride has been reported[5]. To this end the mesylate (4) was prepared from the hydroxymethyl penam (3) by treatment with methanesulphonyl chloride (1.5 equiv., CH_2Cl_2, 0.5h, 95% yield). However, when mesylate (4) was treated with tetra-n-butylammonium fluoride (1.5 equiv., tetrahydrofuran, 3h) degradation occurred and only the known

crystalline thiazoline (16) was isolated (32% yield). There is literature precedent for this type of reaction[7].

As we anticipated that the penicillin (8) with an acylated phenylglycyl side-chain would show the best biological activity[3] we then directed our efforts to the preparation of the ester (12).

Diethylaminosulphur trifluoride[8] (DAST) is reported to give a mild high yielding conversion of alcohols to fluorides. When 6α-(hydroxymethyl) penam (11) was treated with DAST (2 equiv., $CaCO_3$, CH_2Cl_2, -70° to -20°C, 48h) a slow reaction occurred to give only the spiro-penam (18)[9] (55% yield), by the mechanism proposed in Scheme 1.

Since activation of the hydroxymethyl group is apparently incompatible with an amide side chain the Schiff base (19)[3] was prepared and treated with DAST (1 equiv., $CaCO_3$, -20°C, CH_2Cl_2, 16h). The crude product (20) was deprotected (TsOH 1.1 equiv., Girard's T. 3 equiv., CH_2Cl_2, 0°C, 3h) to give the desired 6α-(fluoromethyl) amine (21) (19% yield). Acylation of the amine (21) with the acid chloride (17) (CH_2Cl_2, pyridine) was unsuccessful. It was found necessary to silylate (bistrimethylsilylacetamide 2 equiv., CH_2Cl_2) the amine (21) prior to reaction with acid chloride (17) in order to obtain the penicillanate (12) (59% yield). Hydrogenolysis (10% Pd/C, tetrahydrofuran) and neutralisation then afforded the sodium salt (8).

An alternative reaction of DAST is with aldehydes to give difluoroderivatives[8]. We therefore hoped that the 6α-(difluoromethyl) penicillin (9) would be accessible from the 6α-formyl penam (13)[4]. When the aldehyde (13) was treated with DAST (4.5 equiv., $CaCO_3$, CH_2Cl_2, -20°C) only the fluorohydrin (14) was isolated as a mixture of diastereoisomers, which were separable by chromatography (28% yield of each). Hydrogenation and neutralisation afforded the two salts (10) (32 and 49% yield). A fluorohydrin is the usual intermediate in this type of reaction and it was hoped that prolonged treatment of aldehyde (13) with DAST would finally give the difluoromethyl penicillanate (15). However, even after 3 weeks exposure of aldehyde (13) to excess reagent at ambient temperature no further reaction was observed.

The 6α-(fluoromethyl) penicillin (8) and the two fluorohydrin isomers (10) showed only weak antibacterial activity.

Acknowledgements

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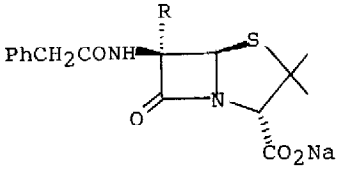
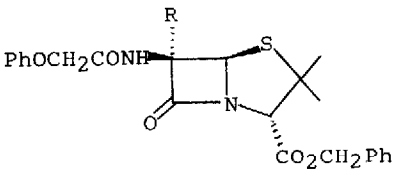
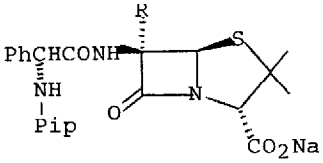


(1) R = H
(2) R = CH_3

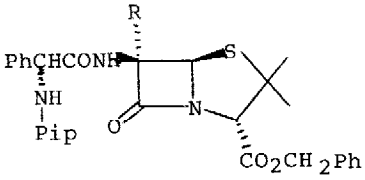


(3) R = CH_2OH
(4) R = CH_2OSO_2Me
(5) R = CH_2F



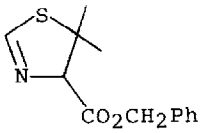
(6) R = CH_2OH
(7) R = CHO
(8) R = CH_2F

(9) R = CHF_2
(10) R = $\overset{*}{C}H(OH)F$

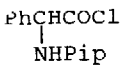


(11) R = CH_2OH
(12) R = CH_2F
(13) R = CHO

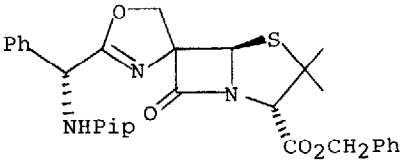
(14) R = $\overset{*}{C}H(OH)F$
(15) R = CHF_2



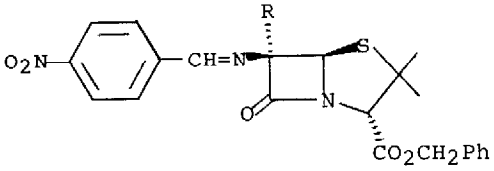
(16)



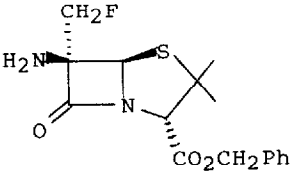
(17)



(18)

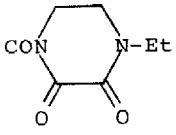


(19) R = CH_2OH (20) R = CH_2F

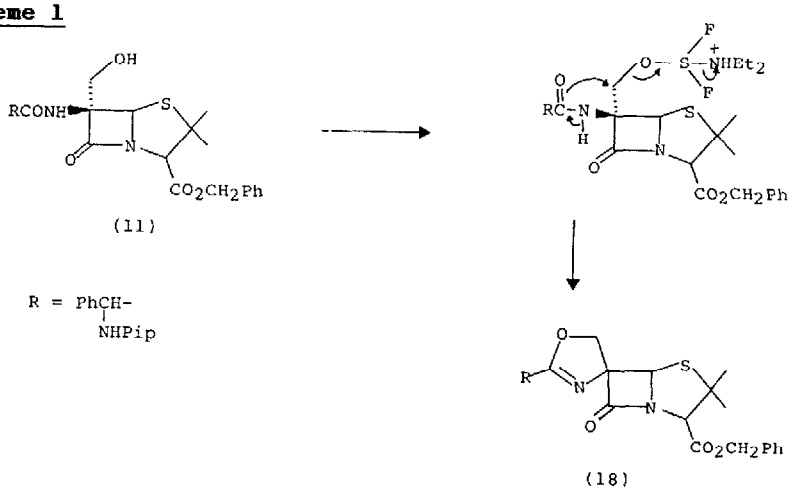


(21)

Pip =



Scheme 1



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7. M.R. Bell, J.A. Carlson, and R. Oesterlin, J. Org. Chem., 1972, 37, 2733.
8. W.J. Middleton, J. Org. Chem., 1975, 40, 574.
9. All esters were isolated by chromatography on silica gel 60, eluting with either ethyl acetate/hexane or ethyl acetate/ethanol mixtures. All compounds described were characterised by nuclear magnetic resonance, infra red, and mass spectral data. Selected physical data are as follows:
(8): ν_{max} (KBr) 1764, 1711, 1673, and 1608 cm^{-1}; δ_H [$(CD_3)_2SO$] 3.74 (1H, s, 3-H), 4.72 (2H, d, J 46.7 Hz, ABq J 9.7 Hz, CH_2F), and 5.28 (1H, s, 5-H).
(10): Isomer 1; ν_{max} (KBr) 1772, 1714, 1674, and 1609 cm^{-1}; δ_H (D_2O) 4.34 (1H, s, 3-H), 5.76 (1H, s, 5-H), and 6.69 (1H, d, J 62 Hz, CHF).
Isomer 2; ν_{max} (KBr) 1774, 1713, 1675, and 1608 cm^{-1}; δ_H (D_2O) 4.37 (1H, s, 3-H), 5.82 (1H, s, 5-H), 6.76 (1H, d, J 63 Hz, CHF).
(12): ν_{max} (CH_2Cl_2) 1780, 1715, and 1690 cm^{-1}; δ_H ($CDCl_3$) 4.03 (1H, s, 3-H), 4.82 (2H, d, J 46.6 Hz, ABq, J 9.6 Hz, CH_2F), and 5.51 (1H, s, 5-H).
(15): Isomer 1: ν_{max} (CH_2Cl_2) 1790, 1720, and 1690 cm^{-1}; δ_H ($CDCl_3$) 4.56 (1H, s, 3-H), 5.72 (1H, s, 5-H), and 6.34 (1H, d, J 64 Hz, CHF).
Isomer 2: ν_{max} (CH_2Cl_2) 1795, 1720, and 1690 cm^{-1}; δ_H ($CDCl_3$) 4.63 (1H, s, 3-H), 5.43 (1H, s, 5-H), and 6.37 (1H, d, J 63 Hz, CHF).
(19): ν_{max} (KBr) 1783, 1713, 1686, and 1647 cm^{-1}; δ_H ($CDCl_3$) 4.55 (1H, s, 3-H), 4.56 and 4.65 (2H, ABq, J 10Hz, CH_2O).
(22): ν_{max} (CH_2Cl_2) 1780 and 1725 cm^{-1}; δ_H($CDCl_3$) 4.49 (1H,s,3-H), 4.67 (2H, d, J 46.6 Hz, ABq, J 9.6 Hz, CH_2F), and 5.46 (1H, s, 5-H).

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