Tetrahedron Letters,Vol.27,No.26,pp 3049-3052,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

6α-CARBOXY AND 6α-CARBAMOYL PENICILLINS

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Abstract: Hemiacetal formation from 6α-formylpenicillins followed by oxidation has provided a series of esters of 6α-carboxypenicillins and the parent acid. Further derivatisation has afforded a 6α-carbamoylpenicillin.

In earlier communications the preparation of a range of 6α-(hydroxymethyl)[1] and 6α-formyl[2] penicillins has been described. Compounds from both series exhibited antibacterial activity, those of the former also possessing stability to β-lactamases. We were therefore interested in assessing the antibacterial activity of a 6α-carboxy analogue.

The target for our synthesis was the 6β-(acylamino)penicillin (1) since this type of derivative had proved the most biologically active in the 6α-(hydroxymethyl) and 6α-formyl series.

The 6α-carboxypenicillin (19) has been described by other workers.[3] The preparation involved substitution of the Schiff base (20) (N,N-diisopropylethylamine, benzyloxycarbonyl chloride, acetonitrile) to give the derivative (21), subsequent transformations then afforded the penicillin (19). However we were unable to isolate the desired intermediate (21) using the conditions described, or by modification using a variety of alternative bases to generate the anion of the Schiff base (20). Reaction of the anion with carbon dioxide followed by methyl iodide failed to generate the corresponding 6α-(methoxycarbonyl) Schiff base (22), but there are precedents for molecular rearrangements from this type of reaction.[4,5]

A recently published procedure describes the "one-pot" oxidation of primary alcohols to t-butyl esters.[6] When the 6α-(hydroxymethyl)-penicillanate (2) was treated in this way (t-BuOH, CrO_3.pyridine, Ac_2O, 16 h) we were gratified to obtain the 6α-(t-butoxycarbonyl)penicillanate (3) (25% yield) without any formation of the sulphoxides (23). Whilst the method[6] is restricted to esters of tertiary alcohols it proceeds *via* a hemiacetal, in this case the hemiacetal (5). We have already described hemiacetals derived

from the 6α-formyl penicillin (6)[2]. Indeed application of the oxidation conditions (CrO_3, pyridine, Ac_2O, 16h) to the methyl hemiacetal (7) gave the 6α-(methoxycarbonyl)penicillanate (8), again without sulphoxide formation (52% yield from (6)). We thus had a versatile route to a variety of penicillin carboxylates.[7]

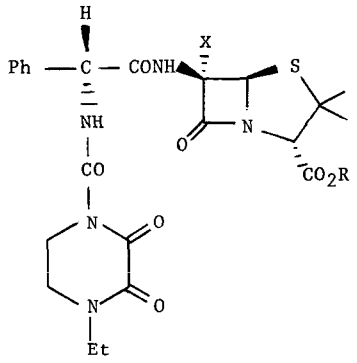
In order to obtain the 6α-carboxy penicillin (1) we needed to prepare an ester which was removable under conditions which were compatible with the penicillin nucleus. As a benzyl ester was already present at C-3 this would have seemed the obvious choice. However the need to remove all traces of benzyl alcohol from the sensitive hemiacetal prior to oxidation made this unattractive. Therefore the allyl ester (11) was chosen, and was readily obtained by generation of the allyl hemiacetal (10) using allyl alcohol/silica gel, followed by oxidation (32% yield). Treatment with Pd(0)[8] in the presence of sodium 2-ethylhexanoate gave the carboxylic acid sodium salt (12) (93% yield).

Whilst hydrogenation (10% Pd/C, tetrahydrofuran) of penicillanates (3) and (8) gave penicillins (4) and (9) isolated as sodium salts, decomposition of compound (12) occurred. Therefore the <u>in vivo</u> hydrolysable pivaloyloxymethyl C-3 ester (15) was prepared from the penicillanate (13) by the hemiacetal-oxidation-Pd(0) deprotection route.

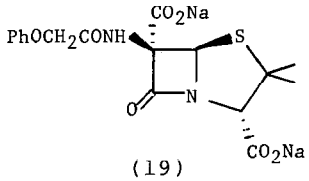
Interestingly when the methyl hemiacetal-oxidation procedure was applied to the 6β-(phenoxyacetamido)penicillanate (25) a 1:1 mixture of α- and β-sulphoxides (24) was isolated (24% yield). With a shorter reaction time, 4 h, a mixture of the sulphoxides (24) (26% yield), and sulphide (26) (27% yield) resulted. Oxidation at C-6 was found to be complete within 0.75 h with no sulphoxide formation (52% yield). We subsequently found that oxidation of the methyl hemiacetal (7) was also complete after 0.75h and a 52% yield (from (6)) of the 6β-(acylamino)penicillanate (8) was obtained.

We also wished to prepare the 6α-carbamoyl penicillin (18) since this is a structural isomer of the highly biologically active 6α-formamido penicillins.[9] The 6α-carboxy penicillanate (12) proved a useful intermediate for this purpose. None of the desired product (17) was obtained from reaction of the sodium salt (12) with oxalyl chloride followed by ammonia, or by an N,N'-dicyclohexylcarbodiimide mediated acylation of the parent acid. Preparation of the mixed anhydride (16) by treatment of the penicillanate (12) with ethoxycarbonyl chloride, followed by reaction with ammonia successfully gave the 6α-carbamoyl compound (17), albeit in low yield (20%). This was hydrogenated (10% Pd/C, tetrahydrofuran) to afford the penicillin (18).

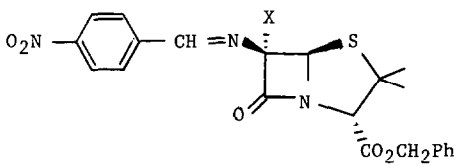
All the penicillins described were only poorly antibacterially active.



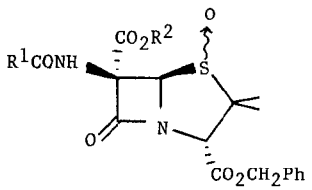
(1) X = CO_2Na, R = Na
(2) X = CH_2OH, R = CH_2Ph
(3) X = CO_2Bu^t, R = CH_2Ph
(4) X = CO_2Bu^t, R = Na
(5) X = $CH(OH)OBu^t$, R = CH_2Ph
(6) X = CHO, R = CH_2Ph
(7) X = CH(OH)OMe, R = CH_2Ph
(8) X = CO_2Me, R = CH_2Ph
(9) X = CO_2Me, R = Na
(10) X = $CH(OH)O$–⟨⟩, R = CH_2Ph
(11) X = CO_2–⟨⟩, R = CH_2Ph
(12) X = CO_2Na, R = CH_2Ph
(13) X = CHO, R = CH_2OCOBu^t
(14) X = CO_2–⟨⟩, R = CH_2OCOBu^t
(15) X = CO_2Na, R = CH_2OCOBu^t
(16) X = CO_2CO_2Et, R = CH_2Ph
(17) X = $CONH_2$, R = CH_2Ph
(18) X = $CONH_2$, R = Na



(19)

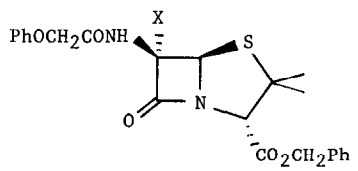


(20) X = H
(21) X = CO_2CH_2Ph
(22) X = CO_2Me



(23) R^1 = CHPh (NHCON, N-Et, O, O) R^2 = Bu^t

(24) R^1 = CH_2OPh, R^2 = Me



(25) X = CHO
(26) X = CO_2CH_3

Acknowledgements: The author wishes to thank Miss A.C. Brown for technical assistance, and Mr. C.L. Branch, Dr. P.H. Milner and Dr. T.C. Smale for helpful discussions.

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7. All diesters and ester (17) were isolated by chromatography on silica gel 60 eluting with ethyl acetate/hexane mixtures. All the compounds described were characterised by nuclear magnetic resonance, infra red, and mass spectral data. Selected physical data are as follows:
(3): $\nu_{max.}$ (CH_2Cl_2) 1785, 1740 sh, 1720, and 1690 cm^{-1}; δ_H ($CDCl_3$) 1.43 (9 H, s, Bu^t), 5.86 (1 H, s, 5-H).
(8): $\nu_{max.}$ (CH_2Cl_2) 1790, 1740, 1720, and 1690 cm^{-1}; δ_H ($CDCl_3$) 3.81 (3 H, s, CO_2Me), 5.93 (1 H, s, 5-H).
(9): $\nu_{max.}$ (KBr) 1774, 1715, 1678, and 1610 cm^{-1}; δ_H (D_2O) 3.87 (3 H, s, CO_2Me), 5.88 (1 H, s, 5-H).
(12): $\nu_{max.}$ (KBr) 1774, 1745, and 1715 cm^{-1}; δ_H (D_2O) 5.27 (2 H, s, CH_2Ph), 5.83 (1 H, s, 5-H).
(17): $\nu_{max.}$ (CH_2Cl_2) 1780, 1740, 1710, and 1690 cm^{-1}; δ_H ($CDCl_3$) 5.95 (1 H, s, 5-H), 6.26 and 7.38 (2 H, 2s, $CONH_2$).
(23): δ_H ($CDCl_3$) 1.11, 1.23, 1.63, 1.68 (6 H, 4s, 2-CH_3s), 3.86, 3.92 (3 H, 2s, CO_2Me), 4.93 and 5.40 (1 H, 2s, 5-H).
(25): δ_H ($CDCl_3$) 1.38, 1.41 (6 H, 2s, 2-CH_3s), 3.86 (3 H, s, CO_2Me), 5.96 (1 H, s, 5-H).

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(Received in UK 1 May 1986)