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6α-FORMYLPENICILLINS AND DERIVATIVES

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Abstract: Moffatt type oxidation of 6α-(hydroxymethyl)penicillins has produced a series of 6α-formylpenicillins, which were further used in chain extension reactions with Wittig reagents and diazoalkanes.

As a result of the isolation of the cephamycins[1] and the subsequent discovery of temocillin[2], the β-lactamase stability conferred on cephalosporins and penicillins by the presence of a 7α(6α)-methoxy substituent is well known. We have been interested in improving the biological activity of penicillins by the introduction of other 6α-substituents. A communication[3] from these laboratories describes the preparation and biological activity of 6α-(hydroxymethyl)penicillins and another group[4] has previously prepared 6α-formyl Penicillin V from its 6α-(hydroxymethyl) analogue. We here wish to report the preparation of a series of 6α-formylpenicillins and the derivatisation of a representative example.

The starting materials for the 6α-formylpenicillins (6) - (10) were the 6α-(hydroxymethyl) analogues (1) - (5). Using the method of Parikh and Doering[5] (5 equiv. SO_3.pyridine, Me_2SO, 11 equiv. Et_3N, 20°C, 3 h), the 6α-(hydroxymethyl)penicillins (1) - (4) were oxidised to the 6α-formyl derivatives[6] (6) - (9). However when this procedure was applied to the temocillin analogue (5) the only product isolated was the oxazolidinone (18) (58%). This structure was confirmed by preparation of an authentic sample from benzyl 6β-amino-6α-(hydroxymethyl)penicillanate (15) (1.25 equiv. 12% $COCl_2$ in toluene, 3 equiv. Et_3N, CH_2Cl_2, 0-20°C, 3.5 h). The two materials were found to possess identical physical data.

This novel side-chain cleavage was not restricted to the 6α-substituted derivative. Treatment of the ticarcillin diester (16) with the same sulphurtrioxide based reagent, and subsequent trapping of the reactive intermediate (possibly the 6β-isocyanato compound) with methanol gave the 6β-(methoxycarbonylamino)penicillanate (17).

Successful oxidation of (5) however was effected using the standard Moffatt procedure[7] (3 equiv. N,N'-dicyclohexylcarbodi-imide, 1 equiv. pyridine, 0.5 equiv. CF_3CO_2H, Me_2SO, 20°C, 3 h) to give (10) without any detectable formation of the oxazolidinone (18).

The 6α-formylpenicillin esters (6) - (9) were then converted to the sodium salts (11) - (14) by hydrogenation at atmospheric pressure (10% Pd/C, EtOH/tetrahydrofuran/H_2O mixtures), followed by treatment with sodium 2-ethylhexanoate (SEH). The proton n.m.r. spectra of the sodium salts and the esters showed them to exist mainly as gem diols in the presence of water[6].

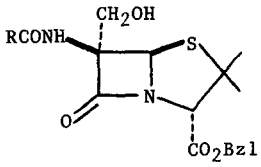
In order to extend the range of 6α-substituents the piperacillin analogue (7) was selected for derivatisation. Firstly, the reaction of (7) with various stabilised phosphoranes was investigated. From treatment of (7) with (triphenylphosphoranylidene)-acetonitrile (ca. 10 equiv., EtOAc, 20°C, 16 h) the corresponding 6α-(cyanoethenyl)-penicillin (19) was obtained. Similar reactions with (triphenylphosphoranylidene)-acetaldehyde and methyl (triphenylphosphoranylidene)acetate gave the 6α-(3-oxoprop-1-enyl) (20) and 6α-(methyoxycarbonylethenyl) (21) derivatives. Only one isomer was obtained in each case and this was assigned as E on the basis of the magnitude of the n.m.r. coupling constant for the ethenyl protons (J 15-16 Hz). Hydrogenolysis of (19) and (20) (i, 10% Pd/C, tetrahydrofuran/H_2O; ii, SEH) gave the corresponding sodium salts (26) and (27) with no detectable reduction of the ethenyl group. However when (21) was hydrogenolysed (i, 10% Pd/C, EtOH/tetrahydrofuran/H_2O; ii, SEH) the product obtained was a 1:1 mixture of the 6α-(methoxycarbonylethenyl)penicillin (28) and the dihydro derivative (29).

Meyer[8] introduced a procedure for characterisation of aldehydes by reaction with diazomethane to give methyl ketones. We have utilised this procedure to prepare the 6α-acetylpenicillin (22), which we had been unable to prepare by direct introduction routes. Thus treatment of the 6α-formylpenicillin (7) with diazomethane (ca. 3 equiv., CH_2Cl_2, -5°C, 1.5 h) gave the required product (22). Trimethylsilyldiazomethane[9] is a safe, stable substitute for diazomethane, however when (7) was treated with this reagent (excess Me_3SiCHN_2, CH_2Cl_2, 0°C, 4 h) the expected product (22) was not formed, but the silylated ketone (23) was isolated. The 6α-acetylpenicillin ester (22) was hydrogenated (i, 10% Pd/C, tetrahydrofuran/H_2O, ii, SEH) to give the sodium salt (30).

The dimethylacetal (24) was prepared by treatment of the 6α-formyl compound (7) with methanol[10] (excess MeOH, toluene-4-sulphonic acid, ground 3A molecular sieves, 20°C, 3 h), but was found to be very labile, as was the ethylhemiacetal (25), obtained by treatment of (7) with ethanol in the presence of wet silica.

All the previously mentioned 6-substituents were designated as the α-stereoisomers since they were all derived by modification of the 6α-(hydroxymethyl) analogues, the configuration of which has been determined by nuclear Overhauser studies[3].

Although compound (11) showed no antibacterial activity the other 6α-formylpenicillins (12) - (14) showed activity against a wide range of bacteria but possessed none of the expected stability to β-lactamase producing organisms. The other sodium salts (26) - (30) were devoid of activity.



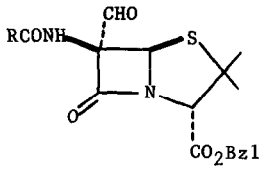
(1) R = $CH_2OC_6H_5$

(2) R = $CH(NHPip)C_6H_5$

(3) R = $CH(NHPip)C_6H_4OCO_2Bzl(4)$

(4) R = $CH(NHPip)C_6H_3(OAc)_2(3,4)$

(5) R = $CH(thien\text{-}3\text{-}yl)CO_2Bzl$



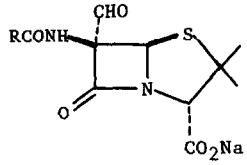
(6) R = $CH_2OC_6H_5$

(7) R = $CH(NHPip)C_6H_5$

(8) R = $CH(NHPip)C_6H_4OCO_2Bzl(4)$

(9) R = $CH(NHPip)C_6H_3(OAc)_2(3,4)$

(10) R = $CH(thien\text{-}3\text{-}yl)CO_2Bzl$

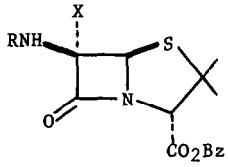


(11) R = $CH_2OC_6H_5$

(12) R = $CH(NHPip)C_6H_5$

(13) R = $CH(NHPip)C_6H_4OCO_2Bzl(4)$

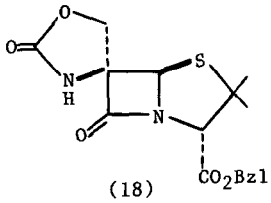
(14) R = $CH(NHPip)C_6H_3(OAc)_2(3,4)$



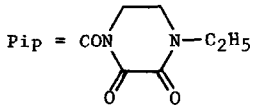
(15) R = H, X = CH_2OH

(16) R = $COCH(thien\text{-}3\text{-}yl)CO_2Bzl$, X = H

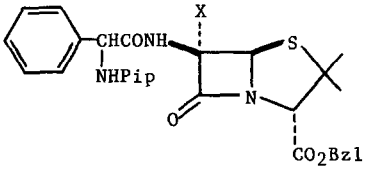
(17) R = CO_2CH_3, X = H



(18)

Pip = 

Bzl = $CH_2C_6H_5$



(19) X = CH=CHCN

(20) X = CH=CHCHO

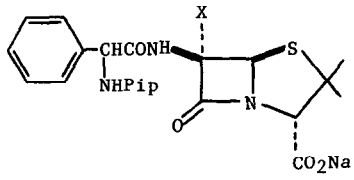
(21) X = $CH{=}CHCO_2CH_3$

(22) X = $COCH_3$

(23) X = $COCH_2SiMe_3$

(24) X = $CH(OCH_3)_2$

(25) X = $CH(OH)OC_2H_5$



(26) X = CH=CHCN

(27) X = CH=CHCHO

(28) X = $CH{=}CHCO_2CH_3$

(29) X = $CH_2CH_2CO_2CH_3$

(30) X = $COCH_3$

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6. All esters except (24) 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 microanalytical or mass spectral data. Compounds (5), (10) and (16) were diastereoisomeric mixtures, all other compounds were single enantiomers. Selected physical data are as follows:

(6): $\nu_{max.}(CH_2Cl_2)$ 1790, 1745 sh, 1730, and 1685 cm^{-1}; $\delta[(CD_3)_2CO]$ 5.84 (1 H, s, 5-H), 9.62 (1 H, s, CHO); $\delta((CD_3)_2CO+D_2O)$ 5.69 (1 H, s, C<u>H</u>$(OH)_2$), 5.73 (1 H, s, 5-H).

(7): $\nu_{max.}(CH_2Cl_2)$ 1785, 1720, and 1690 cm^{-1}; $\delta(CDCl_3)$ 5.80 (1 H, s, 5-H), 9.56 (1 H, s, CHO).

(10): $\nu_{max.}(CH_2Cl_2)$ 1790, 1745, 1730 sh, and 1680 cm^{-1}; $\delta(CDCl_3)$ 5.79, 5.81 (1 H, 2 s, 5-H diastereoisomers), 9.47, 9.51 (1 H, 2 s, CHO diastereoisomers).

(14): $\nu_{max.}$(KBr) 1767, 1712, and 1676 cm^{-1}; n.m.r. in D_2O shows reduction of signal intensity at δ8.54 (CHO) and corresponding increase at δ5.52 (C<u>H</u>$(OH)_2$).

(15): m.p. 170°C; $\nu_{max.}(CH_2Cl_2)$ 1790, 1760 sh, and 1670 cm^{-1}; $\delta(CDCl_3)$ 4.59, 4.72 (2 H, ABq, <u>J</u> 9 Hz, 6-CH_2), 5.40 (1 H, s, 5-H).

(19): $\nu_{max.}(CH_2Cl_2)$ 2230, 1785, 1740, 1715, and 1690 cm^{-1}; $\delta(CDCl_3)$ 5.48 (1 H, s, 5-H), 5.90 (1 H, d, <u>J</u> 15.8 Hz, CH=C<u>H</u>CN), 6.82 (1 H, d, <u>J</u> 15.8 Hz, C<u>H</u>=CHCN).

(20): $\delta(CDCl_3)$ 5.54 (1 H, s, 5-H), 6.40 (1 H, dd, <u>J</u> 16 and 7.5 Hz, CH=C<u>H</u>CHO), 6.98 (1 H, d, <u>J</u> 16 Hz, C<u>H</u>=CHCHO), 9.58 (1 H, d, <u>J</u> 7.5 Hz, CHO).

(21): $\delta(CDCl_3)$ 5.51 (1 H, s, 5-H), 6.14 (1 H, d, <u>J</u> 15.8 Hz, CH=C<u>H</u>CO_2CH_3), 7.09 (1 H, d, <u>J</u> 15.8 Hz, C<u>H</u>=CHCO_2CH_3).

(22): $\delta(CDCl_3)$ 2.32 (3 H, s, $COCH_3$), 5.92 (1 H, s, 5-H).

(24): $\delta(CDCl_3)$ 3.47 (6 H, s, 2xOCH_3), 4.90 (1 H, m, C<u>H</u>$(OCH_3)_2$).

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