Tetrahedron Letters,Vol.30,No.18,pp 2433-2436,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

6α-(N-SUBSTITUTED FORMAMIDO) PENICILLINS AND DERIVATIVES

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Abstract: A simple N-substituted formamido penicillin was found to differ in rate and mode of decomposition from its unsubstituted counterpart. A series of derivatives were prepared and their antibacterial properties examined.

In earlier publications we have described the preparation[1] and degradation[2] of BRL 36650 (1), a 6α-formamido penicillin with potent antibacterial activity, and have shown that the relatively rapid degradation in water at the natural pH occurs principally *via* reaction through the formamido group. We hoped to modify the rate and mode of decomposition by substitution on the nitrogen of the formamido group, thereby blocking reaction of this function. We therefore prepared the 6α-(N-methylformamido) penam (23). The corresponding ester (10) was derived from 6α-(methylthio) penicillanate (2) by treatment with ethanolic methylamine [$Hg(OAc)_2$, dimethylformamide (DMF), tetrahydrofuran (THF), 0-5°C, 1h] followed by formylation using acetic formic anhydride (AFA) (5 equiv., pyridine 10 equiv., CH_2Cl_2, 0-5°C, 2h). Hydrogenation and neutralisation then afforded the penicillin (23). A 4% aqueous solution of the compound (23) slowly decomposed over 8 days to the penillic acid (37) by participation of the 6β-amido group. There was no evidence of the breakdown products (40) and (41), whereas BRL 36650 (1) decomposes over 36h to the two components (39) and (41)[2]. We were therefore observing not only a different mode of degradation but also greater aqueous stability in the N-substituted formamido penicillin (23). However unlike the unsubstituted formamido penicillin BRL 36650 (1) the penicillin (23) has no significant antibacterial activity. Therefore a programme was initiated to prepare a series of N-substituted formamido penams to find a biologically active derivative possessing chemical stability similar to compound (23).

As representative examples in this area we chose the four types of substituent described below *viz* amino (24), methoxycarbonylmethyl (27), hydroxyl (28), and carbamoylmethyl (31).

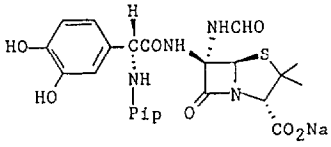
Initially we attempted to prepare the 6α-(N-aminoformamido) derivative (7) with a simple acyl side chain, by formylation of the protected hydrazine (4). Hydrazine was reacted with (4-nitrobenzyl)carbonyl chloride to give the protected hydrazine (32) as a hydrochloride (49% yield). Mercury (II) mediated displacement of the 6α-(methylthio) penicillanate (3) [$Hg(OAc)_2$, DMF, NEt_3, -30^{o} to $0^{o}C$, 0.5h) gave the protected 6α-hydrazino penam (4) (65% yield). However attempted formylation (AFA 5 equiv., pyridine 10 equiv., $0-5^{o}C$, 1h, or 3-formyl-5-methylthiadiazole-5-thione[4] (FMT), acetone, K_2CO_3, 4h) was unsuccessful. A different approach was required and introduction of the protected formylhydrazine (34) was investigated. This was prepared by formylation of benzyl carbazate (AFA 1.5 equiv., NEt_3 3 equiv., CH_2Cl_2, $0-20^{o}C$, 5h). Mercury (II) mediated displacement as before gave the desired penam (6) (32% yield). Catalytic hydrogenation (10% Pd/C, THF) followed by neutralisation afforded the sodium salt (7) (64% yield). To confirm that the product was indeed structure (7) and not the regioisomer (9) we also prepared ester (8) from 6α-(methylthio) penicillanate (3) by treatment with formyl hydrazine ($Hg(OAc)_2$, DMF, -40^{o} to $-20^{o}C$, 1h, 39% yield). Hydrogenolysis and neutralisation afforded the salt (9) (82% yield). The spectral characteristics of ester (8) and salt (9) were substantially different from those of the earlier compounds (6) and (7).

Since we expected the penicillin (24) with an acylated phenylglycine side chain to exhibit a better level of biological activity we prepared the ester (12) from 6α-(methylthio) penam (2) by the method described above (21% yield). However hydrogenolysis unexpectedly gave the 6α-hydroxy derivative (42) arising through an intramolecular expulsion of the 6α-substituent followed by trapping of the resulting acylimine (43) with water.

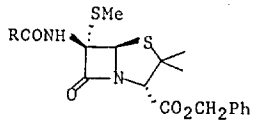
In order to confirm the structure of ester (12) the regioisomer (13) was prepared as described for (8) (31% yield) and also deprotected to give the salt (26) (82% yield).

Interestingly as with the 6α-formamido penicillins[1] the 6α-(formylhydrazo) esters (8) and (13) displayed rotameric mixtures (1:1 and 5:3 respectively) in the ^{1}H n.m.r. spectra. In one rotamer (A) coupling between NH-NHCHO was observed (J 6.3 Hz) whereas in rotamer B no coupling was observed. However in rotamer B coupling between NH-CHO was seen (J 10.6 Hz), but no such coupling was observed in rotamer A. The isomeric (N-amino formamido) compound (6) displayed none of these characteristics.

Subsequently other N-substituted penicillins were prepared only with an acylated phenylglycine type side chain as it was expected that use of this side chain would furnish the more active compounds. The penicillin (27) was

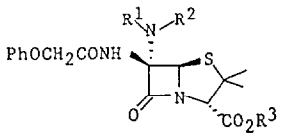


(1) BRL 36650

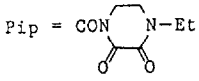


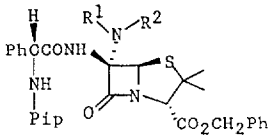
(2) R = CH(NHPip)Ph

(3) R = CH_2OPh



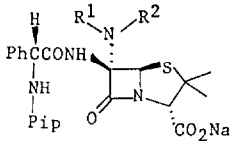
	R^1	R^2	R^3
(4)	$NHCO_2CH_2C_6H_4NO_2(4)$	H	CH_2Ph
(5)	$NHCO_2CH_2C_6H_4NO_2(4)$	CHO	CH_2Ph
(6)	$NHCO_2CH_2Ph$	CHO	CH_2Ph
(7)	NH_2	CHO	Na
(8)	NHCHO	H	CH_2Ph
(9)	NHCHO	H	Na





	R^1	R^2
(10)	Me	CHO
(11)	Me	H
(12)	$NHCO_2CH_2Ph$	CHO
(13)	NHCHO	H
(14)	CH_2CO_2Me	CHO
(15)	OCH_2Ph	CHO
(16)	$OCH_2C_6H_4NO_2(4)$	H

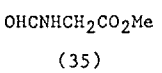
	R^1	R^2
(17)	$OCH_2C_6H_4NO_2(4)$	CHO
(18)	OH	H
(19)	OCHO	H
(20)	OH	CHO
(21)	OH	$COCH_3$
(22)	CH_2CONH_2	H



	R^1	R^2
(23)	Me	CHO
(24)	NH_2	CHO
(25)	NH_2	H
(26)	NHCHO	H
(27)	CH_2CO_2Me	CHO
(28)	OH	CHO
(29)	OCHO	H
(30)	CH_2CONH_2	H
(31)	CH_2CONH_2	CHO

$R^1NHNHCO_2R^2$

(32) R^1 = H R^2 = $CH_2C_6H_4NO_2(4)$
(33) R^1 = H R^2 = CH_2Ph
(34) R^1 = CHO R^2 = CH_2Ph



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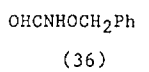

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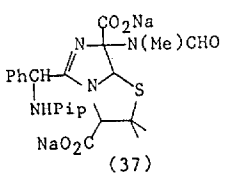

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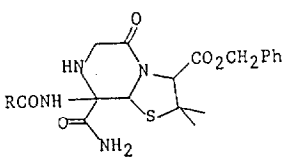
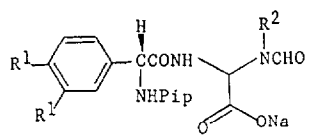
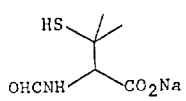


(38) R = CH(NHPip)Ph



(39) R^1 = OH R^2 = H
(40) R^1 = H R^2 = Me



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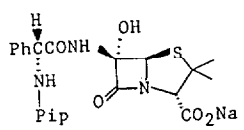

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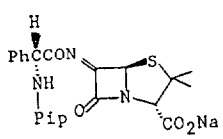

(43)

successfully prepared by reaction of penam (2) with methyl N-formylglycinate to give ester (14) followed by hydrogenolysis and neutralisation. However direct introduction of O-benzyl-N-formylhydroxylamine (36) failed to give any of the protected 6α-(N-hydroxyformamido) compound (15). We were able to introduce O-(4-nitrobenzyl)hydroxylamine to give the protected hydroxamate (16). Subsequent prolonged reaction with a large excess of AFA (60 equiv., pyridine 10 equiv., CH_2Cl_2) gave the formylated product (17) (29% yield). However attempted deprotection by hydrogenolysis resulted in decomposition. As a more direct approach the N-(hydroxyamino) penam (18) was prepared by the usual procedure from 6α-(methylthio) penicillanate (2) (49% yield). After treatment with AFA and pyridine only the N-acetylated compound (21) was isolated (54% yield).

3-Formyl-5-methyl-1,3,4-thiadiazole-S-thione (FMT) has been reported to specifically N-formylate in the presence of hydroxy groups under neutral conditions[4]. Indeed a single product was obtained after treatment of ester (18) with FMT (1 equiv., acetone), but from initial spectroscopic evidence we were unable to determine whether the product was N or O formylated (19) or (20). Surprisingly ^{15}N n.m.r. showed that the O-formylated structure was correct. Hydrogenolytic deprotection subsequently afforded the salt (29).

The use of glycinamide hydrochloride enabled us to prepare the N-(carbamoylmethyl) amino derivative (22) (42% yield). However, AFA failed to effect formylation either using pyridine as base or with prior silylation of the amide (22) using N,O-bis(trimethylsilyl) acetamide. When AFA or FMT were used in the presence of 4-(dimethylamino) pyridine, slow base catalysed rearrangement occurred to give compound (38). The rearrangement was found to occur as above with 4-(dimethylamino)pyridine alone and more quickly with DBU. The ester (22) was deprotected to give the salt (30).

None of the penicillins described here displayed significant antibacterial activity.

Acknowledgements: The authors wish to thank Drs T.C. Smale and R. Southgate for their interest and encouragement, and the members of the spectroscopy department for their assistance.

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(Received in UK 27 February 1989)