6α(7α)-Formamido Penicillins and Cephalosporins

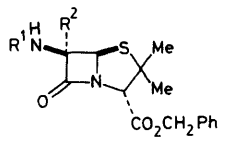
Peter H. Milner, Angela W. Guest, Frank P. Harrington, Roger J. Ponsford, Terence C. Smale,* and Andrew V. Stachulski

Beecham Pharmaceuticals, Research Division, Brockham Park, Betchworth, Surrey RH3 7AJ, U.K.

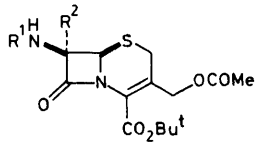
6α(7α)-(Methylthio)penicillins and cephalosporins have been converted into novel antibacterially active 6α(7α)-formamido derivatives by using either mercury(II) acetate and ammonia followed by formylation, or mercury(II) acetate and *N,N*-bis(trimethylsilyl)formamide in a single step.

The naturally occurring 7α-methoxycephalosporins (cephamycins) were discovered in 1971[1] and the consequent observation that the methoxy group stabilised the antibiotics to attack by β-lactamases stimulated considerable research into 6α(7α)-substituted penicillins and cephalosporins.[2] However, even the methoxy moiety, although conferring β-lactamase stability on cephalosporins, only rarely leads to active compounds when present at the 6α-position of penicillins.[3] Other publications have disclosed 6α-aminopenicillins[4] and 7α-aminocephalosporins[5] together with certain *N*-acylated derivatives; all having negligible activity. The formamido substituent has not previously been described, and its presentation in this communication represents a significant advance in the area of 6α(7α)-substitution.

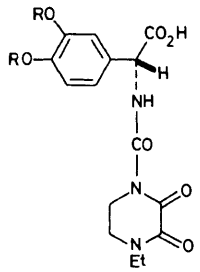
The penicillin V series was selected for initial experiments; the requisite starting material (**2**) being obtained by phenoxy-



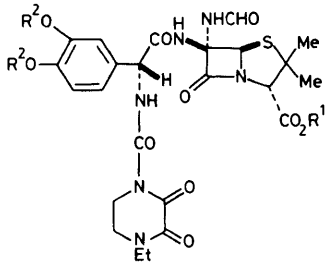
(1) R^1 = H, R^2 = SMe
(2) R^1 = $COCH_2OPh$, R^2 = SMe
(3) R^1 = $COCH_2OPh$, R^2 = NH_2
(4) R^1 = $COCH_2OPh$, R^2 = NHCHO
(5) R^1 = $CO_2CH_2CCl_3$, R^2 = SMe
(6) R^1 = $CO_2CH_2CCl_3$, R^2 = NHCHO
(7) R^1 = H, R^2 = NHCHO



(8) R^1 = H, R^2 = SMe
(9) R^1 = $CO_2CH_2CCl_3$, R^2 = SMe
(10) R^1 = $CO_2CH_2CCl_3$, R^2 = NHCHO
(11) R^1 = H, R^2 = NHCHO



(12) R = H
(13) R = COMe



(14) R^1 = CH_2Ph, R^2 = COMe
(15) R^1 = Na, R^2 = COMe
(16) R^1 = Na, R^2 = H

acetyl chloride–pyridine acylation of (**1**).[6] Reaction of (**2**) with equimolar amounts of mercury(II) acetate and ammonia in *N,N*-dimethylformamide (−40 °C warming to 0 °C over 1 h) produced the 6α-aminopenam (**3**) by the normal attack on the intermediate acylimine from the least hindered face.[2] The unpurified product (**3**) was formylated with excess of acetic formic anhydride and pyridine (CH_2Cl_2, 0 °C, 1.5 h) to give the 6α-formamido penicillin V ester (**4**) [62% from (**2**)].† It has been found that the introduction of the formamido substituent can be accomplished in a single step utilising a novel nucleophilic formamide equivalent. Thus reaction of (**2**) with a two-fold excess of *N,N*-bis(trimethylsilyl)formamide[7] [$Hg(OAc)_2$, dimethylformamide, 20 °C, 2 h] gave a 65% yield of (**4**).

The phenoxyacetyl side-chain is experimentally convenient, but one of the least interesting in terms of biological activity. Therefore a route has been devised to the 6α-formamido penicillin nucleus (**7**), which can be coupled to a wide range of different side-chains. The methylthio compound (**1**) was treated with (2,2,2-trichloroethoxy)carbonyl chloride and pyridine to give the protected derivative (**5**), which could be transformed by either the one-step or two-step process to compound (**6**), m.p. 132—134 °C. This was deprotected using zinc powder (5:1 tetrahydrofuran–1 M aqueous KH_2PO_4 at pH 4—5)[8] to give the 6α-formamido penicillin (**7**)‡ in an overall yield of up to 52% from (**1**). The 7α-(methylthio)cephalosporanate (**8**)[6] could similarly be protected as a carbamate (**9**) and subjected to a mercury(II) mediated displacement to form the 7α-formamido cephalosporin (**10**). The zinc catalysed deprotection gave in this case a crystalline amine (**11**), m.p. 166—170 °C.

Restricted rotation about the formamide N—C bond allows the two preferred planar conformations to be observed during n.m.r. spectroscopy on the various compounds. The major rotamer is *Z*, which exhibits *J* 1 Hz for N*HCHO*, and there is up to 30% of the *E*-rotamer, *J* 11 Hz.[9] A variable temperature proton n.m.r. study was carried out on the cephalosporin nucleus (**11**), and in $(CD_3)_2SO$ solution the CHO signals, which were at δ 8.05 (*Z*) and 8.39 (*E*) at 30 °C, coalesced at 100 °C.

The utility of the 6β(7β)-amino-6α(7α)-formamido compounds can be typified by the coupling to what we have found to be one of the more apt side-chains for biological activity. The D-dihydroxyphenylglycine derivative (**12**)[10] was acetylated (acetic anhydride in tetrahydrofuran–water at pH 6.5—7.0) to give (**13**) and then treated with the 6β-aminopenam (**7**) and *N,N'*-dicyclohexylcarbodiimide to give the penicillin (**14**) in a racemisation-free process. Catalytic hydrogenation (10% Pd/C, tetrahydrofuran) led to the sodium salt (**15**), which deacetylated in aqueous solution at pH 9.0—9.5 to give compound (**16**).[10] This penicillin (BRL 36650) has exceptional activity against Gram-negative bacteria including *Pseudomonas* spp. and is highly resistant to attack by β-lactamases. Full details on antibacterial activity are being published elsewhere.[11]

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Note added in proof. A recent paper[12] has described the isolation of 7α-formamido cephalosporins from fermentation of a bacterium.

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† Satisfactory spectroscopic data and mass spectrometric or elemental analyses were obtained for new compounds.

‡ Chromatographically purified (**7**) gave $\nu_{max.}$ ($CHCl_3$) 1 780, 1 745, and 1 695 cm^{-1}; δ($CDCl_3$) 5.35 (0.2 H, s, 5-H), 5.53 (0.8 H, s, 5-H), 6.70 (1 H, br., NH), 8.17 (0.8 H, d, *J* 1 Hz, CHO), and 8.38 (0.2 H, d, *J* 11 Hz, CHO). The crude material was suitable for further reaction, but was best used within a few days when in this state.