SYNTHESIS OF NOVEL 1-OXADETHIA-2-OXOCEPHEMS

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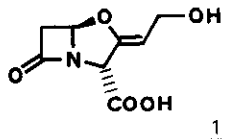
Abstract: Synthetic methods for the preparation of compounds 13, 14, and 15 are described utilising acetoxy azetidinone (4) as starting material.

Isolation of Clavulanic acid, a ß-lactamase inhibitor[1], and the potent antibacterial properties of 1-oxacephems (2)[2] sparked a major interest in the chemistry of 1-oxa-fused bicyclic ß-lactams. 7-Desamido-1-oxacephem (3) which represents an intermediate structure between the clavems and oxacephems was recently reported by Nayler and coworkers[3]. We report in this communication the synthesis of some 1-oxadethia-2-oxocephem derivatives in which the presence of an oxo group at position-2 might be expected to enhance the chemical reactivity of the ß-lactam nucleus and thus in turn the biological activity of these molecules.



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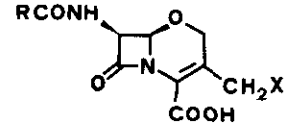

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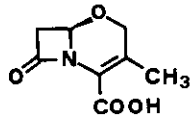

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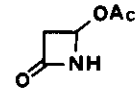

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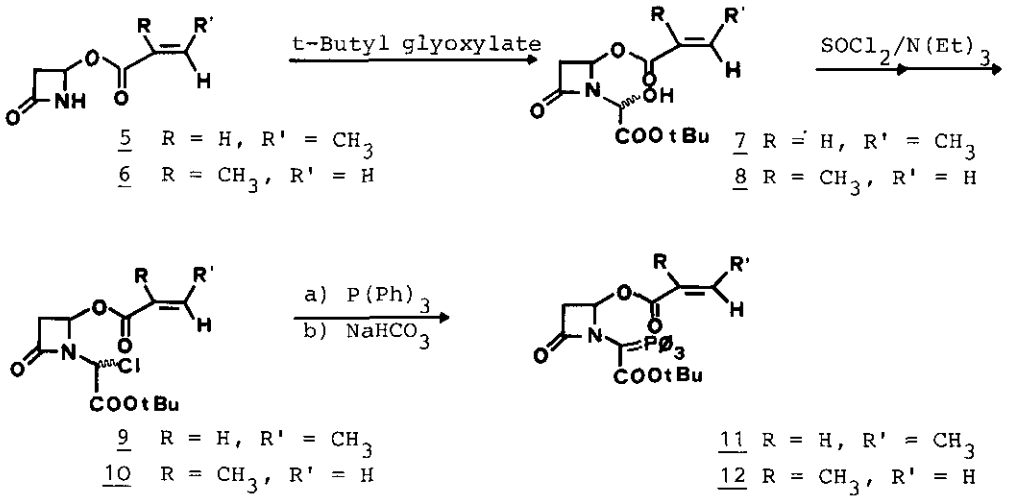
Although the displacement of the acetoxy group in 4-acetoxy azetidinone (4) by thiols, thioacids, alcohols[4] and carbon nucleophiles[5] is well documented, very little attention has been paid to the utility of carboxylic acids[6] in such reactions. In our synthetic scheme we preferred acryloyloxyazetidinones as the key intermediates for the target compounds since the corresponding acylmercapto compounds were elegantly used by Ernest for the construction of 2-oxocephems[7].

We were gratified to find that treatment of compound (4) with a four-fold excess of sodium crotonate in aqueous media readily afforded the desired azetidinone 5 as an oily derivative in 55 % yield. Compound 5: IR (CH_2Cl_2) 3450 (NH), 1785 (CO), 1720 (CO) cm^{-1}; NMR ($CDCl_3$) 1.95 (3H, dd, J_1 = 7 Hz, J_2 = 2 Hz), 3.05 (1H, m), 3.32 (1H, m), 5.70-6.00 (2H, m), 6.85-7.30 (2H, m) ppm. In a similar way, azetidinone 6 is obtained on reaction of compound (4) with sodium methacrylate. Azetidinone 6: IR (CH_2Cl_2) 3430 (NH), 1785 (CO), 1720 (CO) cm^{-1}; NMR ($CDCl_3$) 1.97 (3H, dd, J_1 = 1.5 Hz, J_2 = 1 Hz), 3.09 (1H, m, J_{gem} = 15.5 Hz, J_{trans} = 2 Hz, $J_{H,NH}$ = 1 Hz), 3.36 (1H, m, J_{gem} = 15.5 Hz, J_{cis} = 4 Hz, $J_{H,NH}$ = 2.5 Hz), 5.72 (1H, m, J_1 = 1.5 Hz, J_2 = 1.5 Hz), 5.92 (1H, dd, J_{cis} = 4 Hz, J_{trans} = 2 Hz), 6.22 (1H, m, J_1 = 1.5 Hz, J_2 = 1 Hz), 6.70 (1H, b) ppm.



5 R = H, R' = CH_3
6 R = CH_3, R' = H

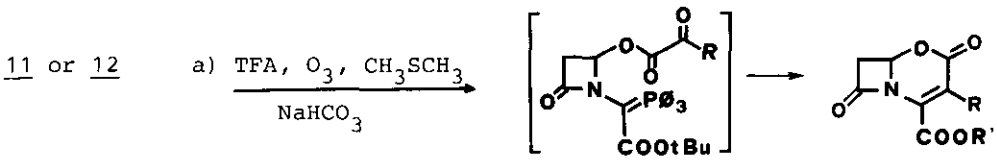
7 R = H, R' = CH_3
8 R = CH_3, R' = H

9 R = H, R' = CH_3
10 R = CH_3, R' = H

11 R = H, R' = CH_3
12 R = CH_3, R' = H

The above acyloxy-azetidinones 5 and 6 are converted into the corresponding phosphoranes utilising the three step sequence developed by Woodward et. al [8]. Thus the azetidinones 5 and 6 were reacted with t-butyl glyoxylate to give adducts 7 and 8 respectively as a mixture of diastereomers which were transformed into the corresponding chlorides 9 and 10 using thionyl chloride in the presence of triethylamine. Phosphoranes 11 and 12 were finally obtained by treating the above chlorides with triphenyl phosphine followed by deprotonation with aqueous bicarbonate.

Ozonolysis of phosphoranes 11 and 12 in CH_2Cl_2 at -40° C, in the presence of trifluoroacetic acid, followed by treatment with dimethyl sulphide and washing with aqueous bicarbonate gave the corresponding highly reactive oxo phosphoranes which spontaneously closed, in an intramolecular Wittig reaction, to the corresponding bicyclic compounds 13 and 14 respectively. Compound 13: mp 97-98° C (recrystallised from CH_2Cl_2), UV (dioxane) λ max (Σ) 297 (7700), IR (CH_2Cl_2) 1805 (CO), 1730 b (CO) cm^{-1}; NMR ($CDCl_3$) 1.57 (9H, s), 3.37 (1H, dd, J_{gem} = 16.5 Hz, J_{trans} = 1.5 Hz), 3.67 (1H, dd, J_{gem} = 16.5 Hz, J_{cis} = 3.7 Hz), 5.82 (1H, dd, J_{cis}=3.7 Hz, J_{trans} = 1.5 Hz), 6.26 (1H, s) ppm. The above compound which was stable in both protic and aprotic solvents at room temperature was found to be extremely sensitive towards bases[9]. Compound 14: mp 112-14° C (recrystallised from CH_2Cl_2/hexa-



13 R = H, R' = t-Butyl
14 R = CH_3, R' = t-Butyl
15 R = H, R' = Acetonyl

ne), UV (EtOH) λ max (Σ) 298 (5370), IR (CH_2Cl_2) 1805 (CO), 1725 (CO) cm^{-1}; NMR ($CDCl_3$) 1.57 (9H, s), 2.20 (3H, s), 3.33 (1H, dd, J_{gem} = 17 Hz, J_{trans} = 1.5 Hz), 3.63 (1H, dd, J_{gem} = 17 Hz, J_{cis} = 4 Hz), 5.80 (1H, dd, J_{cis} = 4 Hz, J_{trans} = 1.5 Hz) ppm. Use of acetonylglyoxylate[10] in place of t-butyl glyoxylate with compound 5 resulted, after the same sequence of transformations, in compound 15, mp 119-21° C (recrystallised from CH_2Cl_2/ether), UV (dioxane) λ max (Σ) 293 (6920), IR (CH_2Cl_2) 1805 (CO), 1750-1710 b (CO) cm^{-1}, NMR ($CDCl_3$) 2.23 (3H, s), 3.42 (1H, dd, J_{gem} = 17 Hz, J_{trans} = 1.5 Hz), 3.72 (1H, dd, J_{gem} = 17 Hz, J_{cis} = 4 Hz), 4.92 (2H, s), 5.90 (1H, dd, J_{cis} = 4 Hz, J_{trans} = 1.5 Hz), 6.42 (1H, s) ppm.

Attempts to make the free acid from either 13 or 15 were unsuccessful, in our hands, owing to the high lability of the product. However, the corresponding 7-acylamido-1-oxadethia-2-oxocephalosporanic acids were recently claimed in the literature [11] and were made through the deprotection of the benzyl esters. Compounds 13, 14 and 15 did not show any ß-lactamase inhibitory properties or antibacterial activity.

Acknowledgement. We are grateful to Dr. Ringrose for valuable discussions and to Mr. P. Kneussel for outstanding technical assistence.

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NMR shows the opening of the ß-lactam ring.

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Received, 5th November, 1980