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STUDIES ON 1-CARBADETHIACEPHEMS, PART I: SYNTHESIS OF 1-CARBADETHIA-2-OXOCEPHEM 4-CARBOXYLATE

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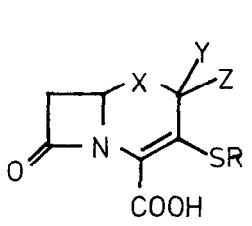
ABSTRACT. The title compound has been prepared via the novel reaction of an acylmalonic ester with 4-acetoxy-2-azetidinone followed by phosphorane ring closure. A new enol-ether cyclisation giving 1-carbadethia-4-methyl-2-oxocephems is described.

Studies on penems and carbapenems[1] have shown that an acylamino side chain at C(6) is not essential for antibacterial activity in these systems. We believed that cephem analogues 1 might mimic penems or carbapenems, and also have antibacterial activity, providng that the β-lactam was sufficiently reactive and that a suitable 3-substituent (SR) was present. Although homothienamycin[2] 2 is a very weak antibacterial agent, suitable substitution at C(2) was expected to enhance the β-lactam reactivity and, we hoped, lead to useful antibacterial activity. 1-Carbadethiacephems 1 (X = CH_2) were selected for study rather than 1-oxadethia cephems[3] (X = O) or cephems[4] (X = S) since the six membered rings of these latter classes are potentially hydrolytically labile when heterosubstituted at C(2). 7-Acylamino C(2)-functionalised 1-carbadethiacephems have been studied[5] by other workers, but our target compounds, the design of which was influenced by natural carbapenems, had a thioether substituent at C(3) and thus belong to a new structural class. This communication describes the synthesis of the novel parent nucleus 3 having a suitable substitution pattern for further elaboration to a diverse set of targets.



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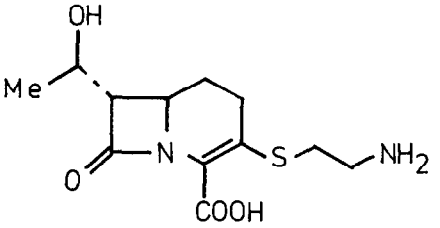

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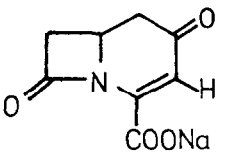

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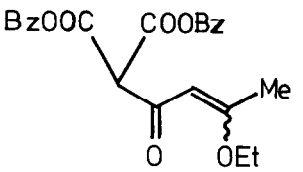
Recently we described[6] the reaction of 4-acetoxy-2-azetidinone[7] with certain tertiary carbanions and we have now extended the scope of this reaction to prepare our key β-lactam intermediate. Dibenzyl malonate was acylated with 3-ethoxycrotonyl chloride[8] to give



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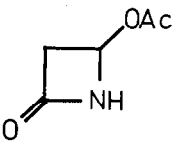

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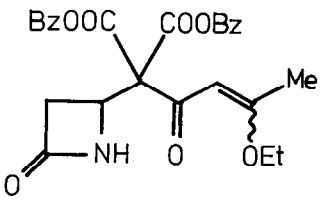

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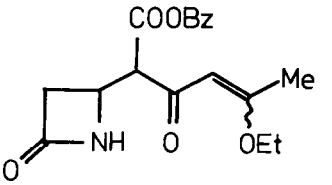

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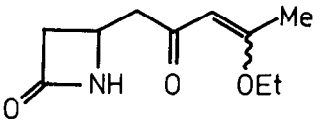

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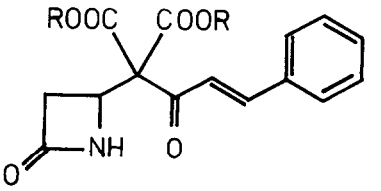

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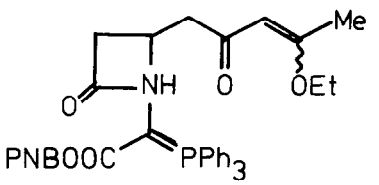

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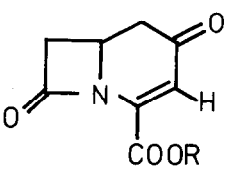
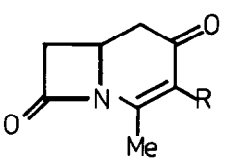


11 R=PNB

12 R=Me



13 R = H

14 R = Br

acylmalonate 4 which was isolated as the copper chelate[9] (m.p. 192-193°). This reaction was best accomplished[10] by treatment of dibenzyl malonate with magnesium methoxide in tetrahydrofuran (THF) followed by removal of the solvent. The resulting toluene-soluble malonate salt was acylated in toluene at 0° and its copper salt prepared using cupric acetate. In this way a 46% yield was obtained on a 0.7M scale. 4-Acetoxy-2-azetidinone 5 reacted with 4 (copper chelate) in THF at 50° during 2 hours to give 6[9] (83%, obtained as an oil after silicagel chromatography). Alternatively, the sodium salt of 4 reacted with 5 (NaH, THF, 0°) to give 6 in similar yield. The sodium salt method was generally more useful for other acylmalonate displacements we have studied. Hydrogenation of 6 (10% Pd/C, atmospheric pressure, THF) provided initially 7 which on continued hydrogenation gave the corresponding keto-acid which decarboxylated on warming to give azetidinone 8[9] (45%; m.p. 82-84°; λ max (EtOH) 259nm (ε15,700); ν max (KBr) 1740, 1670, 1580cm^{-1}). (There was no evidence for saturation of the enol ether under these conditions, but the related compound 9 (R=Bz), similarly prepared using the sodium salt method, was unusable as an intermediate since olefin reduction competed with benzyl ester hydrogenolysis. The alternative acid-labile malonate ester 9 (R=tBu) suffered ß-lactam cleavage during the deprotection-decarboxylation sequence).

Subsequent steps followed the approach devised for the synthesis of acylaminopenems[11], and involved reaction of 8 with p-nitrobenzyl glyoxylate (benzene, 80°, 5 hr), chlorination ($SOCl_2$,2,6-lutidine, THF, 0°, 1 hr) and treatment with triphenylphosphine (THF, 2,6-lutidine, 20°, 18 hr.). Silicagel chromatography afforded the phosphorane[9] 10, eluted with ethyl acetate (82%; m.p. 137-139°; ν max (CH_2Cl_2) 1750 cm^{-1}). Cyclisation was accomplished by ozonolysis of 10 (protected as its trifluoroacetate salt) in methylene chloride at -70° followed by reduction of the ozonide (Me_2S) and aqueous sodium bicarbonate workup to give p-nitrobenzyl 1-carbadethia-2-oxocephem-4-carboxylate[9] 11 (67%; m.p. 170-172°; λ max (EtOH) 320 nm, (ε17400); ν max (CH_2Cl_2) 1794, 1740, 1680, 1590 cm^{-1}; δ (CD_3CN) 5.44 (2H, S CH_2Ar), 6.08 (H, S, C(3)-H); m/e 316 (M^+), 275, 136, 95). An alternative, more direct preparation of 11 was subsequently devised and is described in the following communication.

Deprotection of 11 by hydrogenation (5% Pd/C, EtOAc-aqueous $NaHCO_3$, atmospheric pressure) gave the labile sodium salt 3 (m.p. 155° dec., ν max (KBr) 1760, 1635 cm^{-1}). In view of the instability of 3 it was characterised by conversion to its methyl ester 12 (MeI, DMF, 20°, 18 hr.) obtained in low yield (ν max (CH_2Cl_2) 1790, 1740, 1680, 1590 cm^{-1}; δ($CDCl_3$) 3.91 (3H,S), 6.13 (H,S); m/e 195.052, $C_9H_9NO_4$ requires 195.053).

Biological evaluation of 3 showed a very low level of Gram positive antibacterial activity.

The chemistry of the enol ether 8 was also briefly examined. Treatment of 8 with strong acids (trifluoroacetic acid or methane sulphonic acid) induced cyclisation to give the 1-carbadethia-4-methylcephem[9] 13 (43%; m.p. 62-64°; λ max (EtOH) 320nm (ε 13000); ν max (CH_2Cl_2) 1780, 1660, 1600 cm^{-1}; δ(CD_3CN) 2.21 (3H, d, J = 1, CH_3), 5.23 (H, m, C(3)-H); m/e 151 (M^+), 110). A related cyclisation occurred on treatment of 8 with pyridinium bromide

perbromide; in this case the product was the 3-bromo compound 14 (39%; oil; λ max (EtOH) 321 (ε 10500); ν max (CH_2Cl_2) 1780 cm^{-1}; δ ($CDCl_3$) 2.52 (3H, S).

Compound 11 has been a versatile precursor of our target compounds and these studies will be reported in due course.

Acknowledgement

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10. We thank Mr. D.C. Mills for devising and optimising this procedure.
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