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SYNTHESIS OF 3-HETEROSUBSTITUTED ISOCEPHEM AND ISO-OXACEPHEM ANTIBIOTICS

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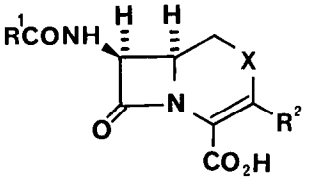
Abstract: Triethyl phosphite-induced cyclisation of 1-oxalyl-4-(alkylthio-thionocarbonyl-thiomethyl or -oxymethyl)-2-azetidinones provides novel 3-alkylthio isocephems and iso-oxacephems.

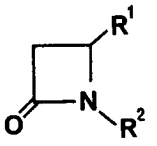
Isocephems (1) and their oxygen analogs (2) bearing H, Me or substituted Me at C-3 are known and have useful antibacterial activity when appropriately substituted[1]. During the development of the oxalimide route to the penems[2], we sought to apply this cyclisation method to the formation of dihydrothiazine and dihydro-oxazine rings, and describe herein the resulting route to novel, 3-thiosubstituted isocephem structures.

The known azetidinone[3] (3) was converted [O_3; Me_2S; $NaBH_4$ then CH_3SO_2Cl-NEt_3] to alcohol (4) and mesylate (5). Displacement [$EtSCS_2Na$-DMF] and desilylation [HCl-H_2O-THF] provided trithiocarbonate (6)[4]. The related xanthate[4] (7, mp 80-82°) was also obtained from alcohol (4) [NaH-CS_2-CH_3I then HCl-H_2O-THF]. N-Acylation of (6) and (7) with allyloxalyl chloride-$^iPr_2NEt$[2] followed by treatment of the crude oxamates (8) and (9) with $(EtO)_3P$ [2,5 eq; CH_2Cl_2, 45°, 40 h for (8) and C_6H_6, 85°, 18 h for (9)] gave after chromatography and recrystallisation the 7-unsubstituted isocephem (10)[4], mp 60-62° (68%) and the iso-oxacephem (11)[4], mp 83-85° (41%). These esters were converted to the amorphous salts (12) and (13) by homogeneous, Pd-catalysed ester exchange deprotection[5] [K-2-Et-hexanoate, 5 mol. % $Pd(PPh_3)_4$, EtOAc, 25°/1 h]. As anticipated for 7-unsubstituted cephalosporin analogs, both of these salts lacked significant antibacterial activity.



(1) X = S
(2) X = O

R^2 = H, Me or CH_2R



(3) $R^1 = CH{=}CH_2$, $R^2 = SiMe_2t\text{-}Bu$

(4) $R^1 = CH_2OH$, $R^2 = SiMe_2t\text{-}Bu$

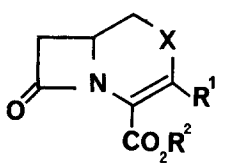
(5) $R^1 = CH_2OMs$, $R^2 = SiMe_2t\text{-}Bu$

(6) $R^1 = CH_2SCS_2Et$, $R^2 = H$

(7) $R^1 = CH_2OCS_2Me$, $R^2 = H$

(8) $R^1 = CH_2SCS_2Et$, $R^2 = COCO_2$

(9) $R^1 = CH_2OCS_2Me$, $R^2 = COCO_2$



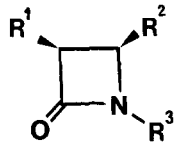
(10) $R^1 = SEt$, $R^2 =$, $X = S$

(11) $R^1 = SMe$, $R^2 =$  , $X = O$

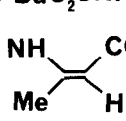
(12) $R^1 = SEt$, $R^2 = K$, $X = S$

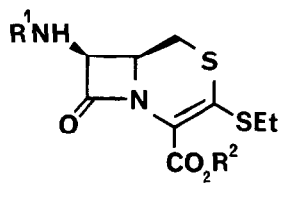
(13) $R^1 = SMe$, $R^2 = K$, $X = O$

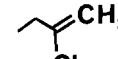
The cis-7-acylamino analogs were prepared from the iodomethyl azetidinone (14)[4], itself available from ketene-imine cycloaddition[6] to give (15), substituent manipulation[7] and final de-N-arylation with ceric ammonium nitrate[8]. Iodide (14) was converted in 72% overall yield to the differentially protected isocephem (16)[4], mp 149-151° [$NaSCS_2Et$-DMF: $CH_2 = CClCH_2OCO.COCl$-$^iPr_2NEt$[9]: $(EtO)_3P$, C_6H_6, reflux 8 h]. Despite the sensitivity of the unsubstituted compound (10) towards acid, brief treatment of (16) with CF_3CO_2H then Na_2CO_3 provided the unstable aminolactam (17)[4] cleanly, and this was quantitatively acylated with N-allyloxycarbonyl-D-phenylglycine and EEDQ[10]. Deprotection of the product [excess 2-Et-hexanoic acid, CH_2Cl_2 with catalytic $Pd(PPh_3)_4$] gave the amorphous zwitterion (18) as a mixture of diastereoisomers (for convenience, only one isomer is depicted). This material had in vitro antibacterial spectrum and potency approximately one-half that of D-phenylglycyl-desacetoxy-amino-cephalosporinic acid (Keflex). Other N-acyl derivatives of this 3-ethylthioisocephem system were generally less potent than their cephalosporin counterparts[11].

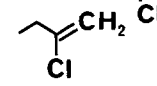


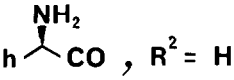
(14) R^1 = t-BuO_2CNH , R^2 = CH_2I , R^3 = H

(15) R^1 =  , R^2 =  , R^3 = 4-$MeOC_6H_4$



(16) R^1 = t-BuO_2C , R^2 = 

(17) R^1 = H, R^2 = 

(18) R^1 =  , R^2 = H

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References and Notes:

1. T. W. Doyle, J. L. Douglas, B. Belleau, T. T. Conway, C. F. Ferrari, D. E. Horning, G. Lim, B.-Y. Luh, A. Martel, M. Menard and L. R. Morris, Can. J. Chem., 1980, 58, 2508-2523 and references therein.
2. A. Afonso, F. Hon, J. Weinstein, A. K. Ganguly and A. T. McPhail, J. Am. Chem. Soc., 1982, 104, 6138-6139.
3. F. A. Bouffard and B. G. Christensen, J. Org. Chem., 1981, 46, 2208-2212.
4. All new compounds gave satisfactory combustion analyses and mass spectra consistent with the assigned structures. Selected spectroscopic data (pmr spectra were determined in $CDCl_3$, unless otherwise noted): (6), PMR: 1.37 (t, 3, J=7), 3.6-3.9 (m, 2, -CH_2S-), 3.41 (q, 2), 3.97 (m, 1, H-4) and 6.52 (br. s, 1, exch. by D_2O). (7), PMR: 2.58 (s, 3), 2.6-3.5 (m, 2), 4.11 (m, 1, H-4) 4.5-5.0 (ABX, 2, J=10.5, 7.5 and 5.0) and 6.87 (br. s, 1, exch. by D_2O). (10), IR (CH_2Cl_2 solution): max 1770 and 1725 cm^{-1}. NMR: 1.29 (t, 3, J=7.5), 2.4-3.6 (m, 6H) and 3.86 (m, 1, H-4). (11), IR (CH_2Cl_2 solution: max 1770 and 1695 cm^{-1}. PMR: 2.47 (s, 3), 2.9-3.3 (m, 3, 3-CH_2 + H-4), 2.62 and 4.75 (br. d.'s, each 1H, J=13). (14) PMR

(DMSO-d_6): 1.35 (s, 9), 3.97 (m, 1, H-4), 4.86 (dd, 1, J=11 and 5, H-3), 7.65 (d, 1, J=11, exch. by D_2O) and 8.52 (s, 1, exch. by D_2O, beta-lactam NH). (16) IR (Nujol): max 3350, 1780, 1715 and 1685 cm^{-1}. PMR: 1.32 (t, 3, J=7), 1.45 (s, 9), 3.01 (q, 2, J=7), 3.1-3.3 (m, 2), 4.04 (m, 1, H-6), 4.87 (s, 2, -OCH_2-), 5.34 (br s, H-7 + NH), 5.58 and 5.69 (both br. s, 1, olefinic-H). (17) PMR: 1.32 (s, 3, J=7), 1.62 (br. s, 2, exch. by D_2O), 2.96 (q, 2, J=7), 3.1-3.4 (m, 2), 3.96 (m, 1, H-6), 4.71 (d, 1, J=5.5, H-7), 4.80 (s, 2), 5.45 and 5.66 (both br. s, 1, olefinic H).

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6. A. K. Bose, M. S. Manhas, J. M. van der Veen, S. G. Amin, I. F. Fernandez, K. Gala, R. Gruska, J. C. Khapur, M. S. Khajavi, L. Mukkavilli, B. Ram, M. Sugiura and J. E. Vincent, Tetrahedron, 1981, 37, 2321-2334. By using 1.5 eq. of the protected glycine-K-salt, 3 eq of EtOCOCl and excess NEt_3, the yield of (15) was increased to over 90% based on starting imine.
7. Compound (15) was subjected to the following sequence: HCl-H_2O-THF; Boc_2O-NEt_3, THF; $NaIO_4$, trace OsO_4 in H_2O-Me_2CO; $NaBH_4$, H_2O-THF; MsCl-pyridine and finally NaI-Me_2CO, reflux to give the N-(4-methoxy-phenyl) derivative of (14) in good overall yield. All intermediates were isolated by crystallisation and fully characterised.
8. D. R. Kronenthal, C. Y. Han and M. K. Taylor, J. Org. Chem., 1982, 47, 2765-2768.
9. *The 2-chloro substituent on the allyl ester moiety eliminates cyclopropane formation* during the cyclisation step (compare reference 2). In contrast to the penem-forming oxalimide cyclisations, it was not essential to introduce the phosphite slowly in order to secure good yields in the isocephem-forming step.
10. B. Belleau and G. Malek, J. Am. Chem. Soc., 1968, 80, 1651-1652.
11. All compounds were tested as mixtures, being racemic in the case of achiral N-acyl groups (e.g. 2-thienylacetyl) and diastereoisomeric for acyl groups attached as the pure optical isomer (e.g. D-phenylglycyl).

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