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STEREOCHEMISTRY AND RING OPENING OF A CARBOCYCLIC ANALOGUE OF A 1-OXAPENAM

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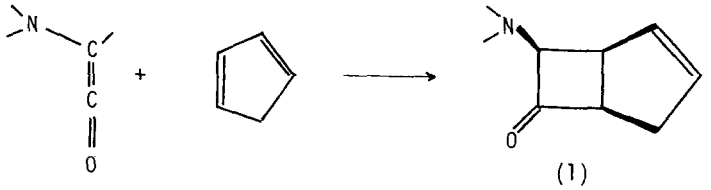
Summary: The cycloaddition of succinimido ketene to 2,3-dihydrofuran yields 7-exo-succinimido bicyclo [3.2.0] 2-oxoheptan-6-one. This unusual stereochemistry is confirmed by ^{1}H NMR and X-ray crystallography. The cyclobutanone product undergoes ring opening in concentrated hydrochloric acid to give 1-succinimido-5-chloro-2-pentanone.

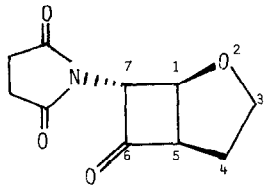
We have shown that β-lactam antibiotics do not exhibit unusual chemical reactivity and that a pyramidal nitrogen does not significantly reduce amide resonance in bicyclic β-lactams.[1,2] Consequently we have reported that cyclobutanone analogues of the β-lactams may inhibit transpeptidase and β-lactamase enzymes by formation of hemi-ketals or by ring opening of the four-membered ring using the enzymes active serine hydroxyl residue.[3]

The synthetic strategy we have previously used for introducing the required acylamino substituent into the carbocyclic analogues of penicillin is to use the addition of phthalimido- and succinimido- ketenes to C=C bonds:[3]



(1)

The stereochemistry of the product bicyclo[3.2.0] heptan-6-one (1) is with the nitrogen substituent endo.[3] Although the cycloaddition reactions of these ketenes with furan, 3-carbomethoxy 2,3-dihydrofuran and cyclopenten-3-one were unsuccessful, the cycloaddition with 2,3-dihydrofuran led to the synthesis of potential carbocyclic analogues of the oxapenams. The interesting observation of these reactions is that the nitrogen substituent is now exo, (2).



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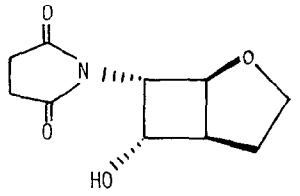

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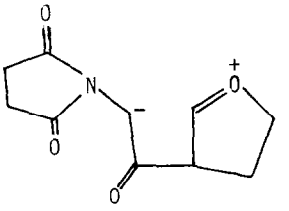
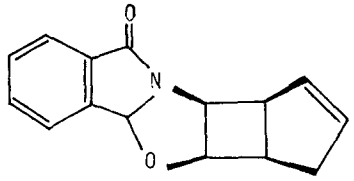


(6)

The dropwise addition of dry triethylamine to a well stirred solution of α-succinimido acetyl chloride and excess 2,3-dihydrofuran in dry dichloromethane gave the racemic mixture of (2) (m.p. 191-193°; IR (nujol) 1975, 1690 cm^{-1}; m/e 209; ^{13}C NMR (DMSO)δ:27.42 (t,C4), 28.20 (t C_9, C_{10}), 61.46 (d, C5), 65.62 (d, C7), 68.35 (t, C3), 75.12 (d, C1), 176.59 (s, C8, C11), 204.40 (s, C6); Analysis: C: 57.26 H:5.25 N:7.06%, $C_{10}H_{11}NO_4$ requires C:57.42 H:5.26 N:6.70%). The exo geometry of the succinimido substituent is evident from the ^1H NMR spectrum which shows H7 at 5.07 δ with $J_{7,1}$ = 3Hz and $J_{7,5}$ = 3Hz, H1 at 5.12 δ with $J_{1,7}$ = 3Hz and $J_{1,5}$ = 7Hz and H5 at 4.05 δ with $J_{5,1}$ = 7Hz, $J_{5,7}$ = 3Hz and $J_{5,4}$ = 3Hz. The H7, H1 coupling constant is indicative of trans hydrogens on C1 and C7. The cis coupling constant in cyclobutane derivatives is usually 4-6 Hz.[4] The proposed structure was confirmed by X-ray crystallography[5] of the product obtained from the sodium borohydride/methanol reduction of (2). The 7-exo-succinimido bicyclo [3.2.1] 2-oxoheptan-exo-6-ol (3) has the stereochemistry shown, the cyclobutane and furan rings make an angle of 118.2° and other bond angles and lengths are normal.

It is of interest to note that the sodium borohydride/me thanol reduction of 7-endo-phthalimidobicyclo [3.2.0] hept-2-ene-6-one (1) gives an oxazolidine (4) resulting from ring closure of the endo cyclobutanonol and one of the imido residues.[3] By contrast the reduction of the corresponding succinimido derivative forms 7-(3'-methoxycarbonyl-propionamido)-bicyclo [3.2.0]hept-2-ene-6-ol (5), again with an endo cyclobutanol.

However, the reduction of the oxo derivative (2) gives the exo cyclobutanol (3). The novel ring opening of the succinimide to (5) is presumably the result of neighbouring group participation but the sterically hindered endo approach of borohydride to the cyclobutanone is quite unexpected.



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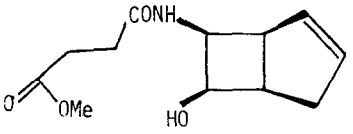
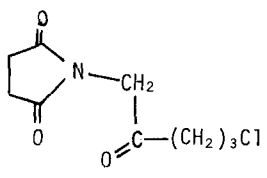


(5)

The cycloaddition of ketenes to C=C is thought to be concerted and involve a stereospecific $\pi 2s + \pi 2a$ process with a strong preference for the formation of the endo isomer.[6] It is probable that the vinyl ether used in the present reaction encourages a stepwise process with the intermediate formation of the oxocarbonium ion, (6), which could ring close to give the thermodynamically stable isomer with the substituent exo.

The cyclobutanone, (2), is readily ring opened in acid solution to give 1-succinimido 5-chloro-2-pentanone (7).[7] The rate of reaction is dependent on acid and chloride ion concentration and has a half-life of 15 mins. at 25°C in 10M HCl. A possible mechanism for the ring opening process is (8) to give (9) which can deformylate to yield the product (7).



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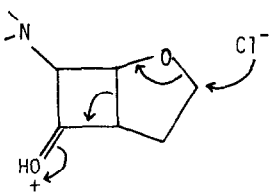

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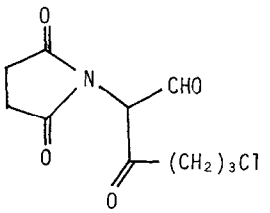

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5. B.Sheldrick, D.Akrigg, M.I.Page and D.Agathocleous unpublished observations. Mr = 211.2$_0$ orthorhombic, $P2_12_12_1$; b = 9.918(3), a = 9.748(2), c = 10.136(2) Å, V = 980.1 A^3, Z = 4, Dx = 1.43 Mg m^{-3}, λ (Cu Kα) = 1.5418 Å, μ = 0.947 mm^{-1}, F(000) = 448, T = 293K, R = 0.0685 for 894 unique observed reflections.

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7. Mp 87-89°C, IR (nujol) 1770, 1700 cm^{-1}, ^1H NMR ($CDCl_3$) 1.88 δ (2H,qn), 2.50 δ(2H, t), 2.6 δ (4H, s) 3.42 δ (2H, t), 4.18 δ (2H, s); MS m/e 219; Analysis: C:49.52, H: 5.58, Cl: 16.27, N: 6.58%, $C_9H_{12}ClNO_3$ requires C: 49.65, H: 5.52, Cl: 16.36, N: 6.44%.

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