SYNTHETIC STUDIES ON β-LACTAM ANTIBIOTICS. IV[1]. SYNTHESIS OF 1,9b-DIHYDRO-2H,4H-2-OXO-AZETO[1,2-c][1,3]BENZOXAZINE DERIVATIVES

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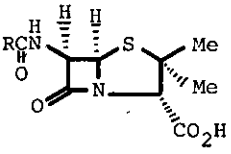
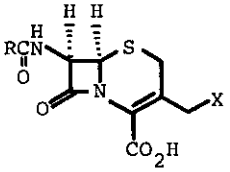
Abstract —— Synthesis of novel tricyclic β-lactams, 1,9b-dihydro-2H,4H-2-oxo-azeto[1,2-c][1,3]benzoxazines (14 and 15), was achieved by a cycloaddition reaction of 2-(4-chlorophenyl)-4-methylthio-2H-1,3-benzoxazine (12) with phenoxyketene followed by desulphurisation of the product (13).
This paper also describes a synthetic approach to an azeto-[1,2-c][1,3]benzoxazine through reaction of an acyclic imine with ketene.

It is well known that penicillins (1) and cephalosporins (2) are effective chemotherapeutics. Discovery of thienamycin[2], clavulanic acid[3], and nocardicins[4], which show interesting chemotherapeutic activities from the pharmaceutical point of view, suggests that modification of the ring part fused to the β-lactam system should provide pharmacologically active compounds, and thus many papers on the syntheses of novel β-lactams differentiating from penams and cephams have been published.[5] We have also examined the synthesis of novel β-lactams[1], and here wish to report a novel tricyclic β-lactam (cf. 3) related to cephams.

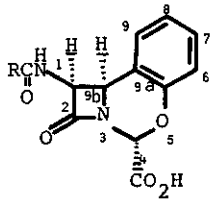
Scheme 1



(1)



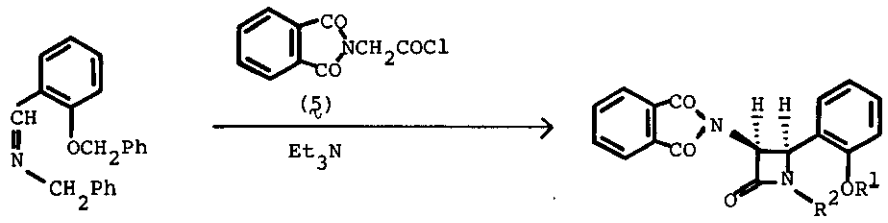
(2)



(3)

Firstly, we have investigated the synthesis of the 2-oxo-azeto[1,2-c][1,3]benzoxazinine system by cycloaddition of acyclic imines to ketene. The acyclic imine (4), obtained in 99.3 % yield [δ ($CDCl_3$) : 8.8 (s, -CH=N-)] by condensation of o-benzyloxybenzaldehyde with benzylamine in boiling benzene, was treated with phthaloylglycyl chloride (5) in methylene chloride in the presence of triethylamine at -10°C overnight to give the β-lactam (6) [mp 187 ∿ 191°C, m/c 488 (M^+), ν (KBr) 1770, 1747, 1705 cm^{-1}] in 72.4 % yield, whose cis-configuration at the C_3 and C_4 positions was shown by nmr spectral analysis (in $CDCl_3$) whereby both methine protons appeared as doublets (J = 5.0 Hz[6]) at 5.27 and 5.60. Selective debenzylation of the β-lactam (6) with boron trifluoride etherate and ethyl mercaptan in hot methylene chloride[7] proceeded smoothly to afford, in 52.8 % yield, cis-1-benzyl-4-(2-hydroxyphenyl)-3-phthalimidoazetidin-2-one (7), mp 244 - 246° [ν (KBr) 3300 cm^{-1}; δ ($CDCl_3$ + DMSO-d_6) 4.31 and 5.03 (each 1H, d, J = 15 Hz, NCH_2Ph)]. As this product could not be converted into the secondary amide (8) by reductive debenzylation with metallic sodium in liquid ammonia,[8] our attention was directed to a synthetic approach involving cycloaddition of cyclic imines containing a benzoxazine ring with ketene.

Scheme 2



(4)

(5)

Et_3N

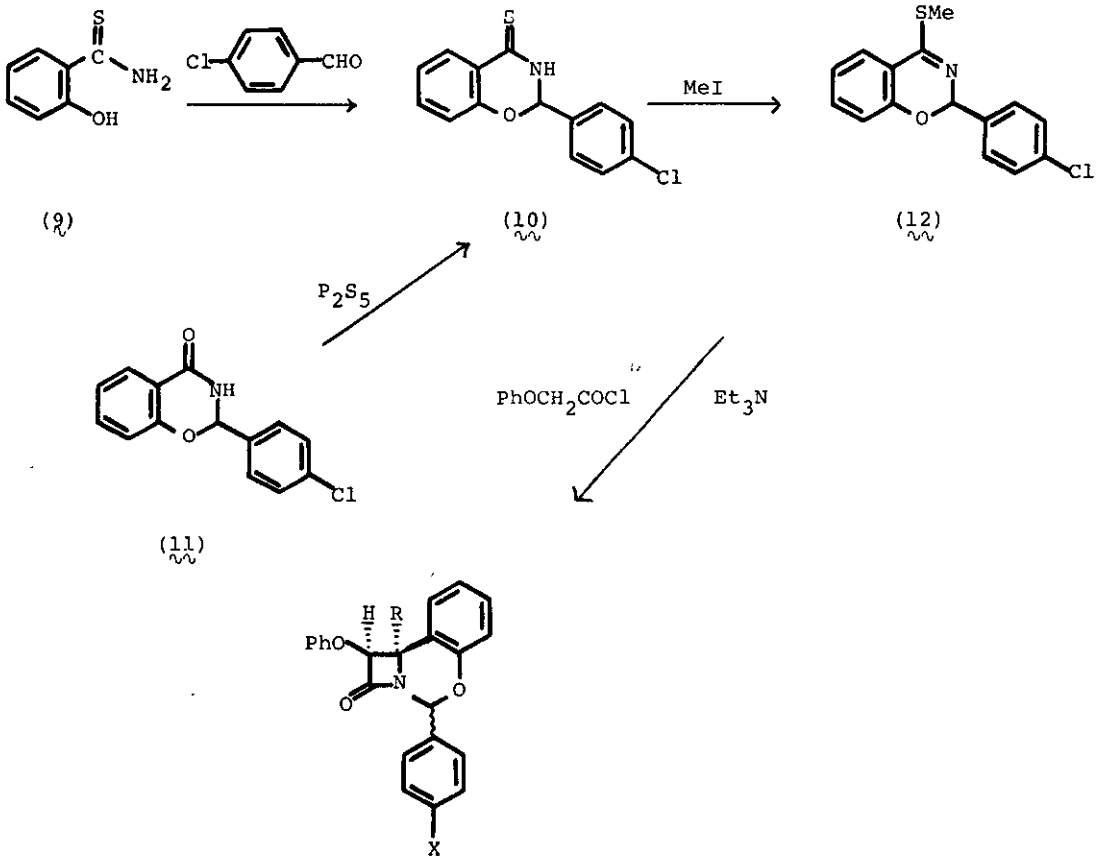
(6) $R^1=R^2=CH_2Ph$

(7) $R^1=H$, $R^2=CH_2Ph$

(8) $R^1=R^2=H$

A key compound, the cyclic imine (12), was synthesised from salicyl thioamide as follows: Salicyl thioamide (9)[9] was condensed with p-chlorobenzaldehyde in boiling benzene in the presence of p-toluenesulphonic acid using a Dean-Stark apparatus for 2 h[10] to afford, in 79.5 % yield, the 2,3-dihydro-4H-1,3-benzoxazine-4-thione (10) [mp 215 ∿ 217°C, ν (KBr) 3130 cm^{-1}; δ ($CDCl_3$ + DMSO-d_6) 6.14 (1H, d, J = 1.9 Hz, OCHNH), m/e 277 and 275 (M^+)], which was also obtained from 2,3-dihydro-4H-1,3-benzoxazin-4-one (11)[11] by reaction with phosphorous pentasulphide in carbon disulphide and methylene chloride in 21.2 % yield. Methylation of 10 with methyl iodide and potassium carbonate in dry tetrahydrofuran at 60 ∿ 70°C for 4 h afforded the thioimidate (12) [mp 91 ∿ 92°C; δ (CCl_4 + $CDCl_3$) 2.44 (3H, s, SMe)] in 96.5 % yield. This imine (12) was treated with phenoxyacetyl chloride and triethylamine in methylene chloride at room temperature overnight to furnish the expected 1,9b-dihydro-2H,4H-2-oxo-azeto[1,2-c][1,3]benzoxazine (13) [mp 128 ∿ 130.5°C, ν (KBr) 1780 cm^{-1}; δ (CCl_4 + $CDCl_3$) 1.53 (3H, s, SMe), 5.38 (1H, s, C_1-H), and 6.82 (1H, s, C_4-H); m/e 425 and 423 (M^+)] in 91.4 % yield.[12] Desulphurisation of this product (13) was carried out with Raney nickel (W_2) in boiling methanol and benzene for 15 min to give a mixture of 14 and 15, which was separated by silica gel column chromatography using benzene-n-hexane as eluent. The first fraction afforded the chloro compound (14) [mp 194 - 197°C, m/e 379 and 377 (M^+)] in 26.6 % yield, which showed the β-lactam system at 1760 cm^{-1} in its ir spectrum (KBr) and the cis-relationship between C_1-H and C_{9b}-H was shown by doublet (J = 4.8 Hz) resonances at 5.53 and 5.10 in its nmr sepctrum ($CDCl_3$).[12] The second compound (15) [mp 150 ∿ 151°C, m/e 343 (M^+)] was obtained in 25.1 % yield and showed the β-lactam system [ν (KBr) 1760 cm^{-1}] and cis-configuration at C_1 and C_{9b} positions [δ ($CDCl_3$)[12] 5.49 and 5.08 (each 1H, d, J = 4.8 Hz)]. In both compounds, the stereochemistry at C_4 position could not be determined. As Wolfe and Hasan[14] have reported that a desulphurisation reaction occurred with retention of configuration, the S-methyl group in 13 should be located in a cis-relationship to the C_1-proton.

Thus, we have developed a new and stereoselective method for the synthesis of novel tricyclic β-lactams, 1,9b-dihydro-2H,4H-2-oxo-azeto[1,2-c][1,3]benzoxazines.



(9) (10) (12)

(11)

(13) R=SMe, X=Cl

(14) R=H, X=Cl

(15) R=X=H

ACKNOWLEDGEMENTS

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