

SYNTHETIC STUDIES ON β -LACTAM ANTIBIOTICS. IV¹. SYNTHESIS
OF 1,9b-DIHYDRO-2H,4H-2-OXO-AZETO[1,2-c][1,3]BENZOXAZINE
DERIVATIVES

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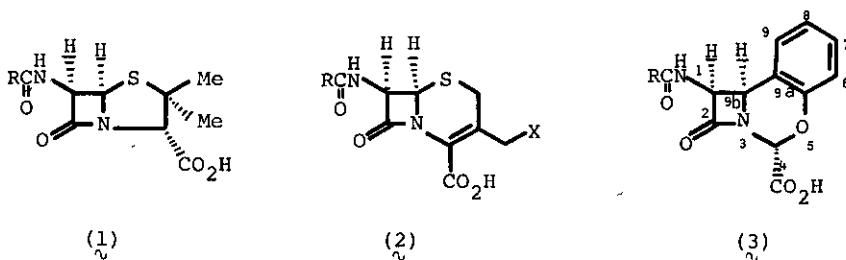
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Abstract — Synthesis of novel tricyclic β -lactams, 1,9b-di-
hydro-2H,4H-2-oxo-azeto[1,2-c][1,3]benzoxazines (14 and 15), was
achieved by a cycloaddition reaction of 2-(4-chlorophenyl)-4-
methylthio-2H-1,3-benzoxazine (12) with phenoxyketene followed 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.

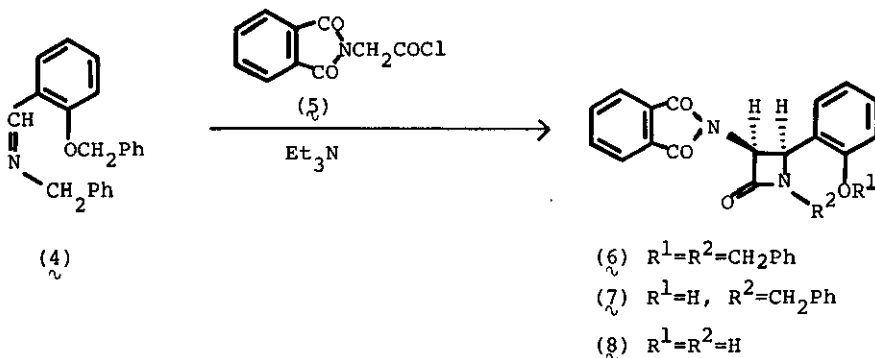
It is well known that penicillins (1) and cephalosporins (2) are effective
chemotherapeutics. Discovery of thienamycin², clavulanic acid³, and nocardicins⁴,
which show interesting chemotherapeutic activities from the pharmaceutical point
of view, suggests that modification of the ring part fused to the 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 -lactams¹, and here
wish to report a novel tricyclic β -lactam (cf. 3) related to cephams.

Scheme 1

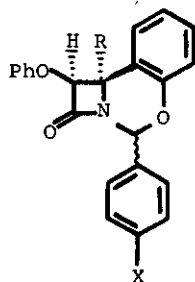
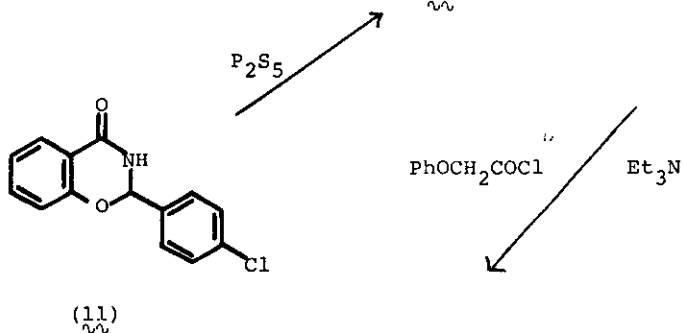
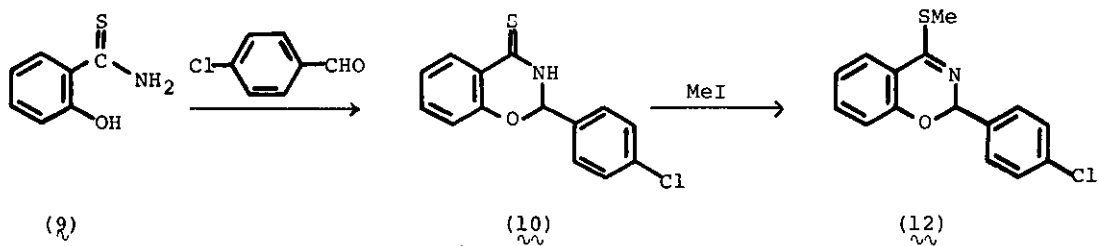


Firstly, we have investigated the synthesis of the 2-oxo-azeto[1,2-*c*][1,3]benzoxazinine system by cycloaddition of acyclic imines to ketene. The acyclic imine (4), obtained in 99.3 % yield [δ (CDCl_3) : 8.8 (s, $-\text{CH}=\text{N}-$)] by condensation of *o*-benzyl-oxybenzaldehyde with benzylamine 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 $187 \sim 191^\circ\text{C}$, 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 ($J = 5.0 \text{ Hz}$ ⁶) at 5.27 and 5.60. Selective debenzoylation of the β -lactam (6) with boron trifluoride etherate and ethyl mercaptan in hot methylene chloride⁷ proceeded smoothly to afford, in 52.8 % yield, *cis*-1-benzyl-4-(2-hydroxyphenyl)-3-phthalimidoazetid-2-one (7), mp $244 - 246^\circ$ [ν (KBr) 3300 cm^{-1} ; δ ($\text{CDCl}_3 + \text{DMSO}-d_6$) 4.31 and 5.03 (each 1H, d, $J = 15 \text{ Hz}$, NCH_2Ph)]. As this product could not be converted into the secondary amide (8) by reductive debenzoylation 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



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 h¹⁰ 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 (CDCl₃ + DMSO-d₆) 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 (CCl₄ + CDCl₃) 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 (CCl₄ + CDCl₃) 1.53 (3H, s, SMe), 5.38 (1H, s, C₁-H), and 6.82 (1H, s, C₄-H); m/e 425 and 423 (M⁺)] in 91.4 % yield.¹² Desulphurisation of this product (13) was carried out with Raney nickel (W₂) 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 C₁-H and C_{9b}-H was shown by doublet (J = 4.8 Hz) resonances at 5.53 and 5.10 in its nmr spectrum (CDCl₃).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 C₁ and C_{9b} positions [δ (CDCl₃)¹² 5.49 and 5.08 (each 1H, d, J = 4.8 Hz)]. In both compounds, the stereochemistry at C₄ position could not be determined. As Wolfe and Hasan¹⁴ 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 C₁-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.



(13) R=SMe, X=Cl

(14) R=H, X=Cl

(15) R=X=H

ACKNOWLEDGEMENTS

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