

A Key Intermediate for the Synthesis of Some Nuclear Analogues of the Penicillins and Cephalosporins

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Summary Starting with L-cysteine and using the recently developed photolytic Wolff rearrangement of 3-diazopyrrolidine-2,4-diones for the synthesis of β -lactams, an intermediate has been prepared which should allow new families of β -lactam antibiotics to be synthesised.

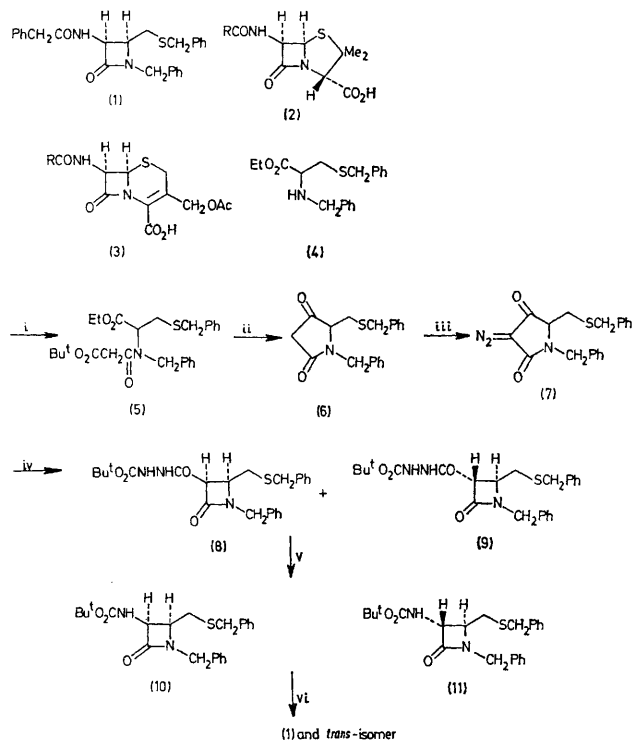
A GENERAL synthetic route has recently been developed for the conversion of α -amino-acids into β -lactams using 3-diazopyrrolidine-2,4-diones.¹ This route has now been used to prepare the *cis*- β -lactam (1) from L-cysteine. Compound (1) should be a suitable intermediate for the synthesis of a variety of nuclear analogues of the penicillins (2) and cephalosporins (3).

The chirality of the C-5(6) centre in the penicillins (cephalosporins) requires that the α -amino-acid used should have the D-configuration. However, in the synthesis of holomycin, Büchi and Lukas found that cyclisation of *N*-methyl-*N*-acetoacetyl-*S*-benzyl-L-cysteine ethyl ester with sodium ethoxide at room temperature gave a racemic pyrrolidine-2,4-dione.² The more readily available L-stereoisomer of cysteine was used therefore in the expectation that racemisation would occur during the synthesis.

S-Benzyl-L-cysteine ethyl ester was prepared,³ and converted into its *N*-benzyl derivative (4), by catalytic hydrogenation (60 atm) over 5% palladium on barium sulphate in the presence of benzaldehyde. For preparation on a large scale, it was more satisfactory to isolate the Schiff base (a mixture of *syn* and *anti*-isomers) and reduce with dimethylamine borane.⁴ *N,S*-Dibenzyl-L-cysteine ethyl ester (4) was coupled to *t*-butyl hydrogen malonate using dicyclohexylcarbodi-imide to give the crystalline amide (5), which on treatment with exactly one equivalent of potassium *t*-butoxide in benzene solution at room temperature gave racemic pyrrolidine-2,4-dione (6) in 87% yield. No *t*-butoxycarbonylpyrrolidine-2,4-dione could be detected in the n.m.r. spectrum of the product.

Diazo transfer with one equivalent of methane-sulphonyl azide and triethylamine at -18° converted the pyrrolidine-2,4-dione (6) into the diazo-compound (7) in 90% yield.

Photolysis of the diazo-compound in benzene solution for 1 h in the presence of 1.1 equivalents of *t*-butyl carbazate using a medium pressure mercury lamp in a water-cooled Pyrex vessel, gave the *cis*- and *trans*- β -lactams (8) and (9)



(i) $\text{Bu}^t\text{O}_2\text{CCH}_2\text{CO}_2\text{H}-\text{C}_6\text{H}_{11}\text{N}:\text{C}:\text{NC}_6\text{H}_{11}$

(ii) KOBu^t

(iii) $\text{MeSO}_2\text{N}_3-\text{NEt}_3$

(iv) $h\nu + \text{Bu}^t\text{O}_2\text{CNHNH}_2$

(v) (a) $\text{CF}_3\text{CO}_2\text{H}$, (b) $\text{HCl}-\text{NaNO}_2$, (c) heat, (d) Bu^tOH

(vi) (a) $\text{CF}_3\text{CO}_2\text{H}$, (b) $\text{PhCH}_2\text{COCl}-\text{NEt}_3$

[ν_{\max} (CHCl₃) 1770 cm⁻¹]. The n.m.r. spectrum showed the two stereoisomers were present in about equal amounts, but separation on silica gel caused considerable epimerisation of the *cis*-isomer (τ 6.05, J 5.5 Hz, H-3).⁵

Conversion of the mixture of stereoisomers (8) and (9) to the *cis*- and *trans*-urethanes (10) and (11) was performed by well established methods.⁶ The n.m.r. spectrum of the reaction product showed the isomer ratio to be unchanged, indicating that epimerisation, which had been a serious problem in a related synthesis,^{6b} had been avoided. The overall yield from the diazo-compound (7) to the urethanes (10) and (11) was 25%. Treatment of the urethanes with trifluoroacetic acid and phenylacetylation of the resulting

amines gave a mixture of the *cis*- and *trans*-phenylacetamido- β -lactams, from which the *cis*-isomer (1) crystallised spontaneously. Recrystallisation from ethyl acetate-light petroleum gave the pure product, [ν_{\max} (CHCl₃) 1755 cm⁻¹ (β -lactam)]; the n.m.r. spectrum contained a double doublet at τ 4.48 ($J_{\text{NH,H-3}}$ 8 Hz, $J_{\text{H-3,H-4}}$ 5 Hz) which identified it as the *cis*-stereoisomer.⁵ The transformation of this compound into nuclear analogues of penicillins and cephalosporins is in progress. We thank the National Research Development Corporation for financial support.

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