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

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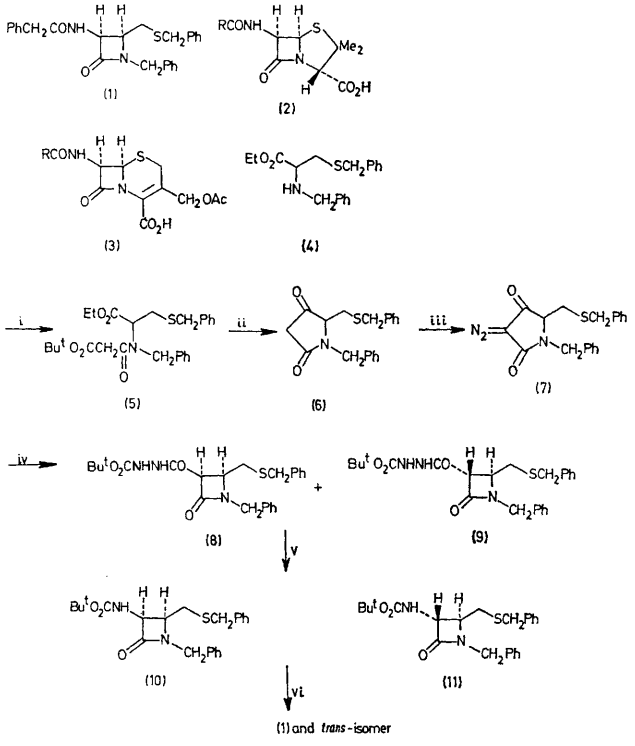
Summary Starting with L-cysteine and using the recently developed photolytic Wolff rearrangement of 3-diazopyrrolidine-2,4-diones for the synthesis of β-lactams, an intermediate has been prepared which should allow new families of β-lactam antibiotics to be synthesised.

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) $Bu^tO_2CCH_2CO_2H$–$C_6H_{11}N:C:NC_6H_{11}$
(ii) $KOBu^t$
(iii) $MeSO_2N_3$–NEt_3
(iv) $h\nu$ + $Bu^tO_2CNHNH_2$
(v) (a) CF_3CO_2H, (b) HCl–$NaNO_2$, (c) heat, (d) Bu^tOH
(vi) (a) CF_3CO_2H, (b) $PhCH_2COCl$–NEt_3

[ν_{max} ($CHCl_3$) 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} ($CHCl_3$) 1755 cm^{-1} (β-lactam)]; the n.m.r. spectrum contained a double doublet at τ 4·48 ($J_{NH,H-3}$ 8 Hz, $J_{H-3,H-4}$ 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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