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# THE STEREOCHEMISTRY OF CYCLISATION OF N-t-BUTYLDIHYDROCINNAMAMIDE TO A β-LACTAM

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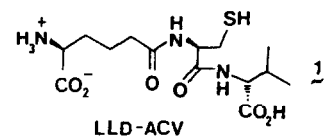
Abstract - Using a stereospecifically labelled precursor, the peroxide catalysed cyclisation of N-t-butyldihydrocinnamamide to the corresponding β-lactam was shown to proceed with complete loss of stereochemistry at the benzylic carbon atom.

The evidence which is presently available, suggests that isopenicillin N (2) is derived by oxidation cyclisation of the tripeptide δ-(L-α-aminoadipyl)-L-cysteinyl-D-valine (LLD-ACV, 1) by a mechanism which is as yet unknown but which proceeds with retention of configuration in each of the ring closures[1].

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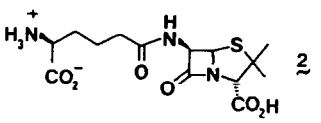
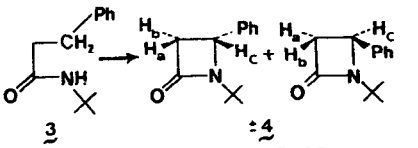


2

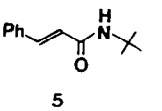
Attempts to model this reaction have been unsuccessful[2] except where artificially reactive systems have been used[3]. In a previous communication[4], we reported the cyclisation of N-t-butyldihydrocinnamamide (3) to a β-lactam (4) with di-t-butylperoxide in the presence of Cu(o-phenanthroline)$_2$Cl$_2$. Although the yield of this process was low (ca. 2%), it was the first report of a direct oxidative cyclisation of an amide to a β-lactam.



3 ± 4

δHa=3.23 ppm
δHb=2.67 ppm
δHc=4.57 ppm

N-t-Butylcinnamamide (5) and the β-chlorodihydrocinnamamide (6) were excluded as possible intermediates in the reaction by appropriate control experiments and a radical mechanism involving organocopper species was suggested.



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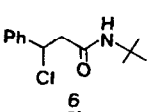
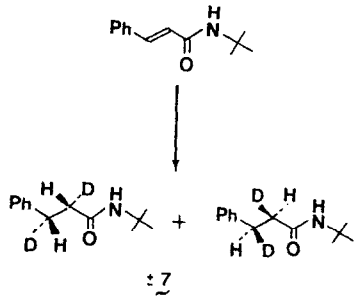


6

The biosynthesis of penicillin G from a chirally labelled cysteine precursor has been reported[5] to occur with retention of configuration at the cysteine β-carbon ie. the pro-S hydrogen at C-3 of cystein is lost stereospecifically. In continuation of our study into the mechanism of penicillin biosynthesis, we report here an investigation of the stereochemical course of the cyclisation of 3 to 4.

## RESULTS AND DISCUSSION

Racemic 2R,3R/2S,3S - dideutero-N-t-butylcinnamamide (7) was synthesised by catalytic reduction of trans-N-t-butylcinnamamide with deuterium gas and Wilkinson's catalyst.



±7

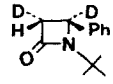
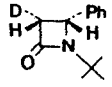
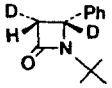
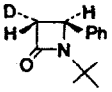
The $^1$H NMR spectrum of 7 contains two broad resonances in the methylene region (δ2.36, δ2.91 ppm, $CDCl_3$ solvent, 20°C) which resolve to an AB quartet ($J_{AB}$ = 7.0 Hz) on irradiation of $^2$H. The dideuterocinnamic acids obtained on hydrolysis of 7 exhibit a vicinal H-H coupling constant of 6.6 Hz as reported[6] for the threo isomers.

±7 was treated with di-t-butyl-peroxide and $Cu(o\text{-phen})_2Cl_2$ in chlorobenzene at reflux for 96 hours. The β-lactam products were isolated from the reaction mixture by preparative GLC and unreacted ±7 was recovered unchanged ie. without loss of stereochemical integrity.

Each of the possible stereospecific cylisations of 7 yields a β-lactam product which can be identified uniquely by $^1$H NMR spectroscopy, by virtue of the characteristic cis and trans vicinal H-H coupling constants in the β-lactam ring (Table 1).

TABLE 1

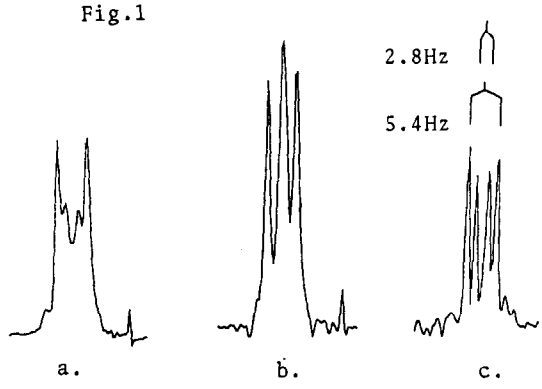
Products[a] from stereospecific cyclisation of ±7.

| Reaction Course | Product | | Predicted NMR[b] |
|---|---|---|---|
| Inv. (-H) |  | ±8 | δ2.67(s) |
| Inv. (-D) |  | ±9 | δ3.23,δ4.57 $J_{AB}$=5.4 Hz |
| Ret. (-H) |  | ±10 | δ3.23(s) |
| Ret. (-D) |  | ±11 | δ2.67,δ4.57 $J_{AB}$=2.8 Hz |

a. only one enantiomer is shown in each case.
b. β-lactam ring protons only, ppm from TMS with irradiation of $^2$H.

Integration of the $^1$H NMR spectrum of the isolated β-lactam products indicated a preferential loss of hydrogen over deuterium (ca. 2.4:1) during the cyclisation. The resonances of the benzylic protons (δ4.57 ppm) appeared as a superposition of two doublets (J = 5.4Hz, J = 2.8Hz) which were assigned to the benzylic protons of 9 and 11 by $^1$H and $^2$H decoupling experiments (Figure 1).

Fig.1




$^1$H NMR spectrum of the benzylic protons (δ4,57 ppm) of β-lactam products.

a. $CDCl_3$ solvent, 20°C.
b. with irradiation at δ2.67 ppm.
c. with irradiation of $^2$H.

The observation that two doublets of equal intensity were obtained at δ4.57 upon irradiation of $^2$H (Figure 1) is only consistent with complete loss of stereochemistry at the benzylic carbon of 7 during the cyclisation to β-lactam products.

Clearly, the observed reaction products are not in accord with the reported retention of configuration in the biosynthesis of the penam nucleus. However, in our experiments, any stereochemical preferences which may have arisen from small differences in activation energy between alternative reaction pathways (retention, inversion, racemisation) would have been obscured by the harsh reaction conditions required for the cyclisation.

In the biosynthesis of isopenicillin N from LLD-ACV, each ring closure involves a stereospecific cyclisation at an unactivated carbon atom. Coordinatively unsaturated metal complexes are a class of compounds with a capacity to react with C-H σ-bonds[7] under relatively mild conditions and such compounds have not, as yet, been considered as possible catalysts in penicillin biosynthesis.

The reaction of coordinatively unsaturated complexes at σ-bonds is most favoured when the bond is constrained in close proximity to the metal centre[8] eg. C-H bonds in coordinated ligands. In an enzyme-bound ACV substrate, the oxidative addition of a metal to the β-carbon of the cysteine residue or the β-carbon of the valine residue would yield an organometallic species, effectively activating these positions towards subsequent reactions eg. nucleophilic attack, reductive elimination.

In cases where it has been studied, oxidative addition (and reductive elimination) of coordinatively unsaturated metals to C-H bonds often occurs with retention of stereochemistry[9]. It is attractive to speculate that a metalloprotein containing a coordinatively unsaturated metal center could be the catalyst responsible for the oxidative cyclisations which occur in penicillin biosynthesis.

## EXPERIMENTAL

NMR spectra were recorded on a Bruker WH300 spectrometer in $CDCl_3$ solution at 20°C and chemical shifts (δ) are presented in ppm from internal TMS. IR spectra were recorded on a Pye-Unicam SP3-200 spectrometer and elemental analyses were performed by Dr F. Strauss (Oxford). M.ps. were recorded on a Kofler hot stage and are uncorrected.

(±)-N-t-Butyl-2-phenylazetidinone (4)

Zinc dust (1.5g, 23mmol) and ammonium hydroxide (2.2mls, 20M) were added to a solution of 3,3'-dichloro-N-t-butyl-2-phenylazetidinone[10] (124 mg, 0.46mmol) in methanol (5mls). The mixture was heated at 73°C for 24 hours, cooled, and dilute hydrochloric acid (40mls, 2M) was added. The mixture was extracted with ether (2 x 40mls) and the combined extracts were dried ($MgSO_4$), filtered and concentrated in vacuo. The crude product was purified by distillation (50-60°, 0.01 mmHg, Kugelrohr) to give (±)-N-t-butyl-2-phenylazetidinone (4) as a white crystalline solid (90mg, 96%). Recrystallisation from light petroleum (40-60°C) afforded an analytical sample mp. 62.5-63.5°C. Anal. expected: C, 76.8%; H, 8.4%; N, 6.9%; found: C, 76.5%; H, 8.4%; N, 6.9%. $\delta^1$H: 1.24(9H, s, $-CMe_3$), 2.67(1H, dd, H-3, $J_{23(trans)}$ = 2.8Hz, $J_{33'(gem)}$ = -14.6Hz), 3.23(1H, dd, H-3', $J_{23'(cis)}$ = 5.4Hz), 4.57(1H, dd, H-2), 7.2-7.4(5H,m, Ar-H) ppm; $\nu_{max}(CHCl_3)$ 1735 $cm^{-1}$.

(±)-2,3-Dideutero-N-t-butylcinnamamide (7)

N-t-Butylcinnamamide (12.5g 62mmol) and tris-triphenylphosphinerhodium chloride (2.1g, 2.3mmol) were dissolved in dry benzene (250mls) and stirred under a deuterium atmosphere for 48 hours. The solvent was removed and the residue triturated with ether (300 mls) for 48 hours. The mixture was filtered and the solvent removed to give a crude product (13.4g) which was distilled (to 200°C, 0.1mm Hg, Kugelrohr) and recrystallised from hexane to yield racemic 2R,3R/2S,3S-dideutero-N-t-butylcinnamamide (7) as a white crystalline solid (11.2g, 87%) mp.88-89°C. $\delta^1$H: 1.29(9H,s, $-CMe_3$), 2.38 (1H, m, -CHD-CO-), 2.94(1H, m, -CHD-Ar), 5.20(1H, bs, -NH), 7.2-7.4(5H, m, Ar-H) ppm. Irradiation of $^2$H simplified the resonances at δ2.38 and δ2.94 to an AB spin system with $J_{AB}$=7.0Hz.

Cyclisation of 7 to N-t-butyl-2-phenylazetidinone products

A mixture of (±)-7 (10g, 48mmol), $Cu(o\text{-phen})_2Cl_2$ (240mg, 0.5mmol) and di-t-butylperoxide was heated in dry chlorobenzene at reflux for 96 hours. The volatiles were removed in vacuo and the residue was distilled (to 150°C, 0.2mm, Kugelrohr). The distillation residue was purified by flash column chromatography (silica eluted with ethyl acetate/dichloromethane, 5:95) followed by preparative GLC (OV225, 210°C) to yield a mixture of N-t-butyl-2-phenylazetidinone products. $\delta^1$H: 1.24(9H, s, $-CMe_3$), 2.67(1H, m, H-3) 3.23(1H, m, H-3'), 4.57(0.58H, m, H-2), 7.2-7.4 (5H, m, Ar-H)ppm.

Acknowledgements

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