Synthesis and Absolute Configuration of the *p*-Nitrobenzyl Ester of SQ 27860

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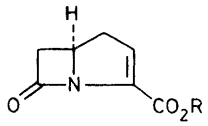
Transformation of D-glucosamine into the *p*-nitrobenzyl ester (**2**) of SQ 27860 is described, revealing the absolute configuration of this carbapenem antibiotic as (**1**).

SQ 27860 (**1**) was recently reported to be the first carbapenem antibiotic produced by bacteria and it shows a wide antibacterial spectrum.[1] While this unstable carbapenem has been characterised as its *p*-nitrobenzyl ester, its absolute configuration has not yet been elucidated.

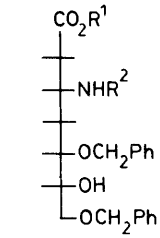
We describe herein the synthesis of (**2**) from the β-amino acid (**3**),[2] derived previously from D-glucosamine, and the assignment of the absolute configuration of (**1**) as depicted.[3]

The amino group in (**3**) was protected by conversion into a t-butylcarbamate [$(Bu^tOCO)_2O$, 2 M NaOH] and this was followed by esterification with diazomethane. The resulting hydroxy ester (**4**), $[\alpha]_D^{21}$ +10.0° ($CHCl_3$), obtained in 90% yield, was converted into a methanesulphonate ($MeSO_2Cl$, pyridine), which was then treated with *N,N*-diisopropylethylamine [dimethylformamide (DMF), 90–100 °C] to give the pyrrolidine derivative (**5**)† in 88% yield. After quantitative removal of the benzyl groups in (**5**) by hydrogenolysis [H_2, $Pd(OH)_2$–C, EtOH], the primary hydroxy group in the product (**6**),† $[\alpha]_D^{23}$ +49.9° ($CHCl_3$), was benzoylated (PhCOCl, pyridine) to yield the benzoate (**7**),† $[\alpha]_D^{15}$ +63.1° ($CHCl_3$), with high regioselectivity (84% yield). The secondary hydroxy group remaining in (**7**) was quantitatively protected as a (2-methoxyethoxy)methyl ether [MeO-$[CH_2]_2OCH_2Cl$, Pr^i_2NEt] and the benzoyl group in the product was then deprotected with sodium methoxide. This was followed by Jones oxidation and esterification with *p*-nitrobenzyl bromide ($NaHCO_3$, DMF[4]), to afford the nitrobenzyl ester (**8**),†‡ $[\alpha]_D^{23}$ −14.8° ($CHCl_3$), in good yield (81%). Since alkaline hydrolysis of the *p*-nitrobenzyl ester group in (**8**) was expected to be slow owing to steric congestion, (**8**) was treated with lithium hydroxide in aqueous methanol at room temperature, and the crude product was then hydrolysed with 2 M hydrochloric acid to regenerate the amino and hydroxy groups. The resulting hydrochloride of the β-amino acid (**9**) was suspended in dichloromethane and treated with excess of triethylamine to give a mixture of the free amino acid (**9**) and triethylamine hydrochloride. Removal of the triethylamine salt from the mixture by silica gel column chromatography (eluted with 70% ethanol) afforded crude (**9**)



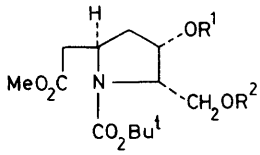
(**1**) R = H

(**2**) R = $CH_2C_6H_4NO_2$-*p*



(**3**) $R^1 = R^2 = H$

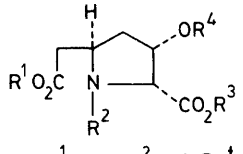
(**4**) R^1 = Me, $R^2 = CO_2Bu^t$



(**5**) $R^1 = R^2 = CH_2Ph$

(**6**) $R^1 = R^2 = H$

(**7**) $R^1 = H$, R^2 = COPh



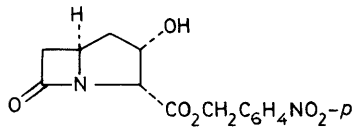
(**8**) R^1 = Me, $R^2 = CO_2Bu^t$

$R^3 = CH_2C_6H_4NO_2$-*p*

$R^4 = CH_2O[CH_2]_2OMe$

(**9**) $R^1 = R^2 = R^4 = H$

$R^3 = CH_2C_6H_4NO_2$-*p*



(**10**)

† Syrupy product.

‡ Some signals in the ^1H n.m.r. spectrum of this compound were observed as pairs (*ca.* 1:1) at room temperature. Since the pairs unified at *ca.* 80 °C, the splitting of the signals is probably due to conformers based on restricted free rotation of the t-butoxycarbonyl group. A similar observation has been reported (ref. 6).

as a crystalline mass. Without further purification, (**9**) suspended in acetonitrile–water (95 : 5)§ was treated with 2,2′-dipyridyl disulphide and triphenylphosphine[5] to give the β-lactam (**10**), $[\alpha]_D^{17}$ +163° ($CHCl_3$) as an amorphous solid in 58% overall yield from (**8**). The β-lactam (**10**) was mesylated ($MeSO_2Cl$, pyridine) and then treated with triethylamine in dichloromethane. Purification of the product by Florisil column chromatography provided (**2**), m.p. 119—121.5 °C, $[\alpha]_D^{16}$ +99.0° (toluene) in 80% yield, which was identified as SQ 27860 *p*-nitrobenzyl ester by spectral comparison (i.r. and ^{1}H n.m.r.) and optical rotation.¶

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§ This reaction was sluggish in dry acetonitrile.

¶ Lit.[1] m.p. 119—121 °C, $[\alpha]_D^{22}$ +104° (toluene).

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