Equilibration of Penicillanic Acid Derivatives

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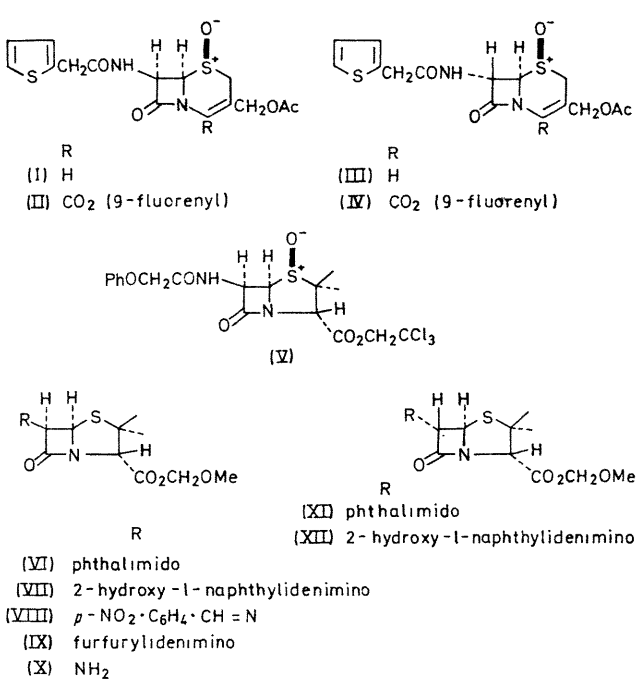
Summary Certain 6β-substituted penicillanic acid esters undergo equilibration with the corresponding 6α-isomers in the presence of 1,5-diazabicyclo[4,3,0]non-5-ene at room temperature: the equilibrium constant depends upon the steric requirement of the 6-substituent and upon the solvent.

RECENTLY there has been considerable interest in the epimerisation of penicillanic acid derivatives at position 6.[1–6] The process is usually base-catalysed and occurs when a diacylamino, an acylalkylamino, or a trialkylammonium substituent is present. Both alkali-metal salts and esters of penicillanic acids undergo epimerisation although the salts appear to require a stronger base than the esters. The position of the equilibrium has not been established in the above cases although it is generally agreed that little of the 6β-isomer is present.

Penicillins fail to epimerise under the above conditions[3] suggesting that an acylamino substituent increases the activation energy for the reaction. However, the cephalosporin derivatives (I and II) are converted into the corresponding 6α-isomers (III and IV) even with a weak base,[7] while the penicillin derivative (V) is epimerised under essentially neutral conditions with *NO*-bis(trimethylsilyl)-acetamide.[8] These results indicate that the sulphoxide function can dramatically lower the activation energy for the epimerisation process. Furthermore, in the latter example *ca.* 20% of the 6β-isomer is present at equilibrium.

The higher free energies of the β-isomers of penicillanic acid derivatives may be attributed to a *cis*-interaction between the 6-substituent and the sulphur atom and, perhaps also, to a compressional interaction involving the former substituent and the 2β-methyl group. A variation in the steric requirement of the 6-substituent is expected, therefore, to alter the position of the equilibrium. In the case of simple β-lactams such an effect has already been



(I) R = H
(II) R = CO_2 (9-fluorenyl)
(III) R = H
(IV) R = CO_2 (9-fluorenyl)
(V)
(VI) R = phthalimido
(VII) R = 2-hydroxy-1-naphthylidenimino
(VIII) R = *p*-$NO_2 \cdot C_6H_4 \cdot CH=N$
(IX) R = furfurylidenimino
(X) R = NH_2
(XI) R = phthalimido
(XII) R = 2-hydroxy-1-naphthylidenimino

observed. Thus, although *cis*-1,4-diphenyl-3-phthalimidoazetidin-2-one undergoes complete epimerisation to the *trans*-isomer, *cis*- or *trans*-3-bromo-1,4-diphenylazetidin-2-one is converted into an equilibrium mixture containing 30% of the *cis*-isomer with 1,5-diazabicyclo[4,3,0]non-5-ene (DBN) in benzene solution.[9]

We have examined the reaction of methoxymethyl 6β-phthalimidopenicillanate† (VI), m.p. 124—125°, $[\alpha]_D$ +267° ($CHCl_3$), with a trace of DBN in dichloromethane solution at room temperature. Epimerisation occurred rapidly to yield the 6α-isomer (XI) as the sole product on the basis of n.m.r. spectroscopy [under conditions in which the presence of 1% of (VI) could have been detected]. The 6α-isomer (XI), m.p. 174—176°, $[\alpha]_D$ + 181° ($CHCl_3$), which was isolated in 70% yield after recrystallisation, was characterised by microanalysis and spectroscopy. In particular, n.m.r. spectroscopy ($CDCl_3$) revealed the *trans*-stereochemistry of the β-lactam protons,[11] which appeared as doublets at τ 4·36 and 4·57 (*J* 2 Hz). The 6α-isomer (XI) is more stable than the 6β-isomer, therefore, by > 11·2kJ mol^{-1} (at 293 °K).

Under similar conditions methoxymethyl 6β-(2-hydroxy-1-naphthylidenimino)penicillanate‡ (VII), m.p. 106—107°, $[\alpha]_D$ + 24° ($CHCl_3$), also underwent very rapid epimerisation. However, in contrast to the above example, the product contained 61% of the 6α-isomer (XII) and 39% of the 6β-isomer (VII) on the basis of n.m.r. spectroscopy.

The mixture was fractionated by silica gel chromatography to afford (XII) as a yellow syrup (31%), $[\alpha]_D$ + 337° ($CHCl_3$), τ ($CDCl_3$) 4·90 and 4·35 (*J* 2 Hz, *trans*-β-lactam protons[11]). The 6β-isomer (VII), m.p. 106—107°, was also recovered (24%).

In the presence of DBN in dichloromethane, (XII) was converted into an equilibrium mixture containing 39% of (VII). It is evident, therefore, that a true equilibrium has been established in which (XII) is preferred to (VII) by only 1·0 kJ mol^{-1}.

Similar results were obtained with the methoxymethyl esters of other Schiff bases of 6β-aminopenicillanic acid. The results (see Table) are in accord with the suggestion that the equilibrium constant reflects the steric requirement of the 6-substituent, since an aldimino group is expected to be smaller than the phthalimido group. It is evident in the case of (VII) and of methoxymethyl 6β-*p*-nitrobenzylideniminopenicillanate[13] (VIII) that solvent can also influence the equilibrium constant.

Equilibration of penicillanic acid derivatives with DBN at room temperature

Derivative	Solvent	6α-Isomer	6β-Isomer
(VI)	CH_2Cl_2	>99	<1
(VII) and (XII) ..	CH_2Cl_2	61	39
(VII)	C_6D_6	53	47
(VIII)	CH_2Cl_2	81	19
(VIII)	C_6D_6	70	30
(VIII)	$MeNO_2$	85	15
(VIII)	Me_2SO	76	24
(IX)[a]	CH_2Cl_2	80	20

[a] This compound was isolated as a syrup (85%) from the reaction of chloromethyl methyl ether, triethylamine, and 6β-furfurylideniminopenicillanic acid [obtained as an unstable crystalline solid (63%) from 6β-aminopenicillanic acid and freshly-distilled furfural in dry methanol].

We consider that the above results are significant in two respects. Firstly, while it has not yet been possible to epimerise an unmodified penicillin, we feel that the aldimino group provides a reasonable steric model for the acylamino group. Therefore, the overwhelming thermodynamic preference for the α-isomer which has been reported for 6-phthalimido-,[1] 6-acylalkylamino-,[2,3] and 6-trialkylammonium-penicillanic acid[3] derivatives should not be extrapolated to penicillins.

Secondly, the results provide a method for inverting the stereochemistry at position 6 of methyl 6α-aminopenicillanate, which has been synthesised by Bose and his co-workers,[14] and they enable, therefore, a total chemical synthesis of penicillins to be achieved. In this respect, (VII) readily afforded the crystalline tolyl-*p*-sulphonate salt of (X)[13] (58%) with tolyl-*p*-sulphonic acid in acetone–ether.

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† This compound was prepared (87%) by the reaction of chloromethyl methyl ether with the triethylamine salt of 6β-phthalimidopenicillanic acid.[10]

‡ This compound was obtained (95%) from the reaction of the triethylamine salt of 6β-(2-hydroxy-1-naphthylidenimino)penicillanic acid[12] with chloromethyl methyl ether.

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