Epimerisation of a *trans*-β-Lactam[1]

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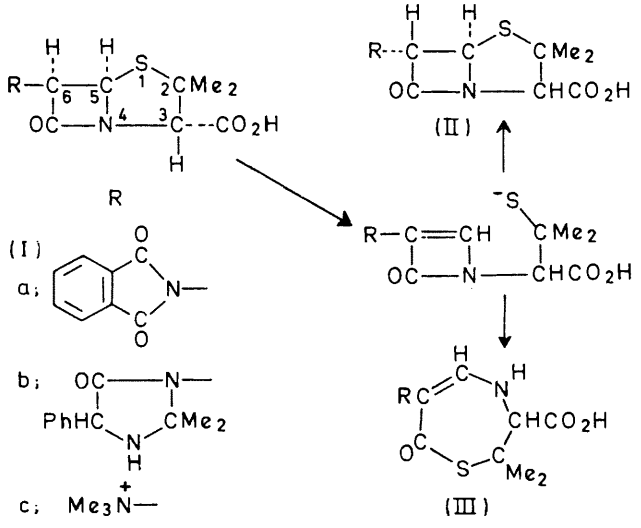
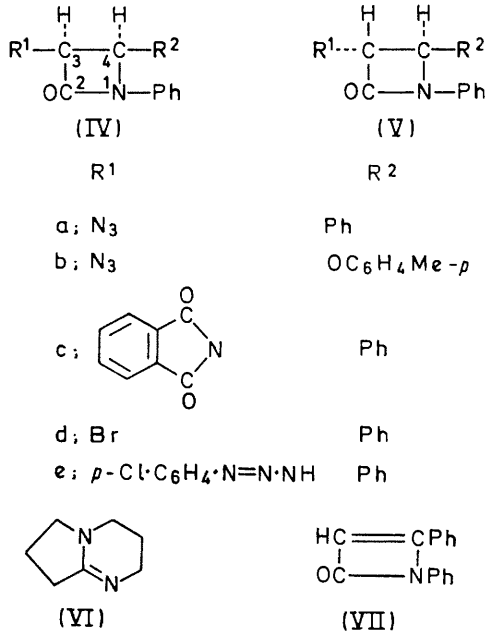
Summary *cis*-1,4-Diphenyl-3-phthalimidoazetidin-2-one was epimerised completely to the corresponding *trans*-β-lactam in presence of 1,5-diazabicyclo[4,3,0]non-5-ene in benzene solution at 100° in about 22 h but the *trans*-isomer was unchanged on similar treatment: an equilibrium mixture containing 30% of the *cis*-isomer was obtained when either the *cis*- or the *trans*-3-bromo-1,4-diphenylazetidin-2-one was heated on a steam bath with the same base in benzene solution or treated with a solution of the base in Me_2SO at room temperature.

RECENTLY the epimerisation of some 5,6-*cis*-penicillin derivatives [*e.g.* (Ia—c)] to the 5,6-*trans*-isomer has been reported.[2-4] A few cephalosporin sulphoxides have also



been shown[5] to undergo epimerisation to give the *trans*-isomer. Wolfe and Lee[2] have suggested that the isomerisation to the 6-epimer (II) of a penicillin (I) involves the scission and the subsequent recyclization of the thiazolidine system. The formation of a rearrangement product (III) during the epimerisation of (I) has been construed[6] as an indirect evidence in support of this mechanism. A remarkable aspect of the isomerisation of penicillins and cephalosporins reported so far, is the 100% conversion of the *cis*-derivative into the *trans*-derivative (except for side reactions such as β-lactam ring scission). The *trans*-bromo-compound (II; R = Br) readily incorporated deuterium at C-6—apparently through the formation of an anion at C-6—but no epimerisation occurred.[4] Some of these unusual features have been ascribed to the steric compression in a fused β-lactam system.[4]

We have examined the epimerisability of monocyclic β-lactams which cannot fit the mechanism suggested by Wolfe and Lee.[2] Previously[7] it was reported that both *cis*- and *trans*-3-azido-1,4-diphenylazetidin-2-one (IVa and Va) are unaffected by prolonged heating in benzene with triethylamine. The corresponding 3-phthalimido-compounds (IVc and Vc) were also unchanged under the influence of triethylamine in benzene or dimethyl sulphoxide. However, when (IVc) was heated on a steam bath with 1,5-diazabicyclo[4,3,0]non-5-ene (VI) in deuteriated benzene and the reaction monitored by observing changes in the n.m.r. spectrum, a new AB pattern (J 2·5 Hz) characteristic of (Vc) appeared while the AB pattern J 5 Hz) characteristic of (IVc) disappeared progressively. The epimerisation was essentially 100% complete in 24 h. The product of this reaction was identified by direct comparison with an authentic sample of (Vc). Under similar conditions the *trans*-isomer (Vc) remained unaffected even after 48 h of heating on a steam bath. The base (VI) which



is stronger than triethylamine failed to isomerise 1,4-diphenyl-3-methoxyazetidin-2-one and it led to the decomposition of the azide (IVb).

The β-lactam (IVd) described by Russian workers[8] was found by us to be 3,4-*cis* on the basis of its n.m.r. spectrum. The *trans*-β-lactam (Vd) was obtained in poor yield by the treatment of benzylideneaniline with bromoacetyl bromide and triethylamine.[9] These two bromo-β-lactams could be interconverted under the influence of (VI) but not triethylamine. Epimerisation was conveniently followed by monitoring the n.m.r. spectrum. When deuteriated benzene was used as the solvent for the *cis*-β-lactam, equilibrium (*cis*: 30; *trans*: 70) was reached in about 22 h on heating on a steam bath. That a true equilibrium was attained was shown by the formation of the same mixture when the pure *trans*-compound (Vd) was used as the starting material. The *trans*-isomer reached equilibrium in about 2 h—much faster than the *cis*-isomer. In Me_2SO solution at room temperature and in presence of (VI), equilibrium was reached by (Vd) in 15 min and (IVd) in 20 h.

It is obvious that epimerisability depends on the functional group at C-3 and the organic base used while the solvent plays a smaller role. In view of our observations and those of Clayton *et al.*,[4] the pathway suggested by Wolfe and Lee[2] for epimerisation could be operative in some instances but is not obligatory.

On the basis of data at hand it is not possible to rule out a mechanism involving dehydrobromination and hydrobromination. It is noteworthy that Henery-Logan and Rodricks[10] were unable to prepare (VII) by the dehydrobromination of the corresponding 3-bromoazetidin-2-one (Vd) but when they cleaved the triazene (Ve) with boron trifluoride etherate, they obtained (VII) in 20% yield. The possibility of debromination and rebromination as the mechanism of epimerization has been suggested. Further work will be necessary to determine which of the various pathways operate. Irrespective of the exact mechanism, the epimerisation of a *trans*-β-lactam to its *cis*-isomer under mild conditions is of special interest because the total synthesis of *trans*-penicillin V methyl ester and related penam and cepham derivatives have been described.[11,12] Natural and semi-synthetic penicillins in clinical use belong exclusively to the 5,6-*cis*-series.

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