Epimerisation of Penicillanic Acid Derivatives and their Rearrangement to 1,4-Thiazepines: Evidence for an *E1cB* Mechanism

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Summary A common enolate-like intermediate is implicated in the weak base-catalysed conversion of methyl 6β-phthalimidohomopenicillanate into methyl 6α-phthalimidohomopenicillanate and methyl 2,3,4,7-tetrahydro-2,2-dimethyl-7-oxo-6-phthalimido-1,4-thiazepine-3(*S*)-acetate.

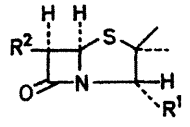
THERE has been considerable recent interest in the epimerisation of penicillanic acid derivatives at position 6,[1-4] and different intermediates have been postulated to account for this process. Wolf and Lee[1] noted that methyl 6β-phthalimidopenicillanate (I) was epimerised to the 6α-isomer (VI) in the presence of a variety of bases and, on the basis of some deuterium-labelling experiments, they considered that the enethiolate (XI) was a better model for the transition state of the reaction than the enolate (XIII). Nayler and his co-workers[3] investigated the epimerisation of hetacillin (II) in alkaline deuterium oxide and they accounted for their results in terms of an enolate intermediate.

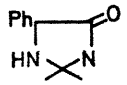
The reaction of methyl 6β-phthalimidopenicillanate (I) with triethylamine in dichloromethane was re-examined by Kovacs *et al.*[5] and the 1,4-thiazepine (XV) was isolated in addition to (VI). We have obtained the 1,4-thiazepine (XVI) from methoxymethyl 6β-*p*-nitrobenzaldiminopenicillanate (III) under similar conditions.[6] These results provide some support for the intervention of the enethiolate although it is not necessarily involved in the rate-determining step of the epimerisation.

We became interested in the mechanism of epimerisation of penicillanic acid derivatives while attempting to equilibrate methyl 6β-phthalimidohomopenicillanate[7] (IV), m.p. 152—154°, $[\alpha]_D$ + 251° ($CHCl_3$) with its isomer (XVIII). With triethylamine in dichloromethane, (IV) was converted into two products which were separated readily by silica gel chromatography. Both substances were isomeric with the starting material on the basis of micro-analysis and mass spectrometry. The major isomer (40%), m.p. 201—203°, $[\alpha]_D$ + 169° ($CHCl_3$), τ ($CDCl_3$) 4·74 (centre of ABq, *J* 2Hz, *trans*-β-lactam protons[8]), was considered to be methyl 6α-phthalimidohomopenicillanate (IX). The minor isomer (32%), m.p. 258—260°, $[\alpha]_D$ −233° (C_5H_5N), τ (CD_3SOCD_3) 1·0 br (q, separation 15 Hz, N*H*), 2·86 (d, *J* 9 Hz, C-5-vinylic H), 6·04 (m, H-3) (addition of D_2O to the solution caused the signal at 1·0 to disappear, that at 2·86 to collapse to a singlet, and that at 6·04 to simplify to a quartet) was believed to be methyl 2,3,4,5-tetrahydro-2,2-dimethyl-7-oxo-6-phthalimido-1,4-thiazepine-3(*S*)-acetate (XVII). Both substances were stable under the reaction conditions.

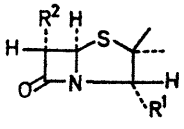
Recently, Wolfe and his co-workers have examined further the reaction of (I) with base.[9] They conclude that epimerisation occurs *via* a carbanionic intermediate in the presence of a strong base. A common rate-determining

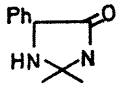
step is implicated in the formation of (VI) and (XV) when triethylamine is used, and it is considered that the enethiolate (XI) is produced in this step by an *E*2 process.

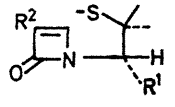


(I) $R^1 = CO_2Me$; R^2 = phthalimido
(III) $R^1 = CO_2H$; R^2 

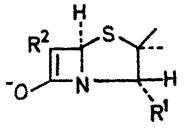
(III) $R^1 = CO_2CH_2OMe$; $R^2 = p\text{-}NO_2\cdot C_6H_4\cdot CH{=}N$
(IV) $R^1 = CH_2CO_2Me$; R^2 = phthalimido
(V) $R^1 = CO_2CH_2OMe$; R^2 = phthalimido



(VI) $R^1 = CO_2Me$; R^2 = phthalimido
(VII) $R^1 = CO_2H$; R^2 = 
(IX) $R^1 = CH_2CO_2Me$; R^2 = phthalimido
(X) $R^1 = CO_2CH_2OMe$; R^2 = phthalimido



(XI) $R^1 = CO_2Me$; R^2 = phthalimido
(XII) $R^1 = CH_2CO_2Me$; R^2 = phthalimido

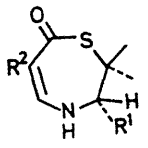


(XIII) $R^1 = CO_2Me$; R^2 = phthalimido
(XIV) $R^1 = CH_2CO_2Me$; R^2 = phthalimido

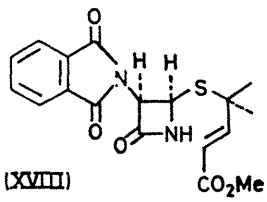
Furthermore, it is suggested that in the formation of (VI) the SH group of the enethiol adds to the double bond in a concerted *syn*-manner. According to this unusual postulate the conjugate acid is not involved in the slow step of reprotonation.

We now comment on some of these suggestions. In particular, we consider that the case in favour of the *E*2 pathway is unconvincing and we suggest that an *E*1*cB* process (in which an "anionic" intermediate intervenes in the slow step) provides a more satisfactory explanation.

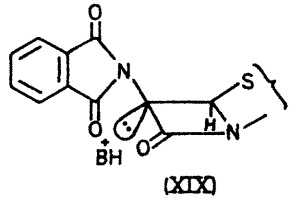
The main objection raised against the *E*1*cB* mechanism was the failure of (VI) to undergo thiazepine formation in the presence of triethylamine.[9] We have observed that (IX) behaves similarly and, indeed, under conditions in which (IV) is transformed to a mixture of (IX) and (XVII) in 4 days, (IX) may be recovered unchanged after 5 months. These results indicate that the free energy of activation for removal of the *endo*-proton of (VI) or (IX) is substantially greater than that for removal of the *exo*-proton of (I) or (IV). It has been inferred, therefore, that an *anti*-arrangement of the C-6 proton and the S atom is a transition state requirement for epimerisation in the presence of a weak base (*i.e.*, an *E*2 mechanism is involved).[9] We consider, however, that the results are also consistent with an enolate-like intermediate in which the transition states for *exo*- and *endo*- protonation are similar in energy and in which the α- and β-isomers are separated by a large free energy difference. In this respect we have noted that <1% of (V) was present under conditions in which an equilibrium between (V) and (X) was believed to have been established.[10]



(XV) $R^1 = CO_2Me$; R^2 = phthalimido
(XVI) $R^1 = CO_2CH_2OMe$; $R^2 = p\cdot NO_2\cdot C_6H_4\cdot CH{=}N$
(XVIII) $R^1 = CH_2CO_2Me$; R^2 = phthalimido



(XVIII)



(XIX)

With 1,5-diazabicyclo[4,3,0]non-5-ene in pyridine containing 5% deuterium oxide, (IV) afforded (IX) which, on the basis of mass spectroscopy, contained 42·5% $^2H_0$ and 55·9% $^2H_1$ after 2 m, 29·5% $^2H_0$ and 69·5% $^2H_1$ after 10 m, and 29·2% $^2H_0$ and 69·0% $^2H_1$ after 20 m. Under identical reaction conditions, (IX) contained 94% $^2H_0$ and 4·3% $^2H_1$ after 2 m and 78·4% $^2H_0$ and 20·8% $^2H_1$ after 10 m. Therefore, (IX) undergoes deuterium exchange at position 6 (inferred by n.m.r. spectroscopy) *ca.* 14 times more slowly than (IV) is converted into (IX). Consequently, the free energy of activation for removal of the *exo*-proton of (IV) or the *endo*-proton of (IX) differ only by *ca.* 6·7 kJ mol^{-1} in the presence of a strong base. These results parallel those reported for (II) and (VII) in the presence of alkaline deuterium oxide.[3]

More proton transfer is expected at the transition state of a reaction involving a carbon acid and a weak base than in the corresponding reaction involving a strong base. We suggest, therefore, that while the enolate provides a satisfactory model for the transition state of the reaction in the former case, the ion-pairs, [*e.g.*, (XIX)], which approximate ground state geometry, are more appropriate models in the latter case.

We have investigated the influence of base on the rate of disappearance of (IV) and on the ratio of (IX) to (XVII) formed. The results (see Table) show that the rate of disappearance of (IV) is sensitive to both the strength of the base and its steric requirement. The ratio of (IX) to (XVII) reflects the relative rate constants for protonation and rearrangement of the common intermediate. Even though the pK_a of the base, determined in aqueous solution,[11] may provide only an approximate guide to its value in deuteriochloroform, it is clear that the amount of α-isomer formed increases with the strength of the base employed.

At first sight this appears to be a puzzling result. The transition state leading from the intermediate to 6α-isomer is likely to involve a proton-transfer process. However,

the conjugate acid is not expected to be involved in the slow step of thiazepine formation. Since more rapid proton transfer is to be expected as the strength of the conjugate acid increases, more 6α-isomer should be formed as the strength of the base decreases.

triethylamine in $CHCl_3$–Bu^tOD, yielded epimer which contained no deuterium. They have suggested that this result provides an experimental criterion for epimerisation by the β-elimination pathway.[9] We dispute this interpretation since (IV), with 1-methylpiperidine in CD_3SOCD_3

Reaction of (IV) *with organic bases in* $CDCl_3$ *solution at* 33°

Base	pK_a	Relative rate disappearance of of (IV)[a]	Product composition[b] % (IX)	% (XVII)
1-Methylmorpholine	7·4	1·0	15	85
Dimethylbenzylamine	8·9	2·2	20	80
1-Methylpiperidine	10·1	14	35	65
1-Ethylpiperidine	10·5	11·8	65	35
1-Isopropylpiperidine	—	5·0	55	45
1-t-Butylpiperidine	—	1·1	45	55
Triethylamine	10·8	8·2	50	50
1,2,2,6,6-Pentamethylpiperidine ..	11·2	1·1	80	20
NNN'N'-Tetramethylguanidine ..	13·6	$3·4 \times 10^3$	>95	<5
1,5-Diazabicyclo[4,3,0]non-5-ene ..	—	$40·5 \times 10^3$	>95	<5

[a] Reactions were followed until at least 80% completion by n.m.r. spectroscopy and satisfactory pseudo-first order plots were obtained.
[b] Estimated by n.m.r. spectroscopy.

We consider that the results are consistent with the rate-determining formation of an "anionic" intermediate which, in the presence of the conjugate acid of a weak base undergoes competitive protonation and rearrangement to thiazepine. We postulate that the conversion of the "anionic" intermediate into the enethiolate is the rate-determining step for thiazepine formation. The enolate and enethiolate possess certain geometrical similarities and we suggest that these species are close in energy. Accordingly, as the energy of the "anionic" intermediate is lowered, *i.e.*, it becomes less enolate-like and closer in geometry to one of the ion-pairs, more re-organisation and, therefore, more energy is necessary to convert it into the enethiolate.

Wolfe and his co-workers have reported that the conversion of (I) into (VI) and (XV), when performed with containing 5% D_2O was converted into a mixture of 60% (IX) and 40% (XVII). The epimer was 71% monodeuteriated on the basis of mass spectroscopy and the deuterium was shown to be located in one of the β-lactam protons (assumed to be that at position 6) on the basis of n.m.r. spectroscopy.

We consider that there is little evidence for the epimerisation of penicillanic acid derivatives at position 6 *via* an *E*2 mechanism, even in the presence of a weak base.

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[1] S. Wolfe and W. S. Lee, *Chem. Comm.*, 1968, 242.
[2] D. A. Johnson, D. Mania, C. A. Panetta, and H. H. Silvestri, *Tetrahedron Letters*, 1968, 1903.
[3] J. P. Clayton, J. H. C. Nayler, R. Southgate, and E. R. Stove, *Chem. Comm.*, 1969, 130.
[4] D. A. Johnson and D. Mania, *Tetrahedron Letters*, 1969, 267; R. D. G. Cooper, P. V. DeMarco, and D. O. Spry, *J. Amer. Chem. Soc.*, 1969, **91**, 1528; G. E. Gutowski, *Tetrahedron Letters*, 1970, 1779; B. G. Ramsay and R. J. Stoodley, *Chem. Comm.*, 1970, 1517.
[5] O. K. J. Kovacs, B. Ekström, and B. Sjöberg, *Tetrahedron Letters*, 1969, 1863.
[6] J. R. Jackson and R. J. Stoodley, *Chem. Comm.*, 1970, 14.
[7] B. G. Ramsay and R. J. Stoodley, *J. Chem. Soc.* (*C*), 1969, 1319.
[8] E. J. Corey and A. M. Felix, *J. Amer. Chem. Soc.*, 1965, **87**, 2518; I. McMillan and R. J. Stoodley, *Tetrahedron Letters*, 1966, 1205; *J. Chem. Soc.* (*C*), 1968, 2533.
[9] S. Wolfe, W. S. Lee, and R. Misra, *Chem. Comm.*, 1970, 1067.
[10] J. R. Jackson and R. J. Stoodley, unpublished work.
[11] D. D. Perrin, "Dissociation Constants of Organic Bases in Aqueous Solution," Butterworths, London, 1965.