On the Conditions for C-6 Epimerization of the Penicillin Nucleus by a β-Elimination Mechanism

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Summary The effects of temperature, the substitution pattern at C-5 and C-6, and the base are employed to delineate the conditions for proton abstraction from C-6 of the penicillin nucleus by carbanion or β-elimination pathways.

IN our initial account of C-6 epimerization of a penicillanic acid derivative (**1** → **2**),[1] the suggestion was made that the reaction could take place by the β-elimination route (**1** → **3** → **2**). Although data were obtained which permitted this speculation to be presented, attempts to trap the unsaturated thiol (**3**) by intermolecular reactions were unsuccessful. Subsequently, it was found[2] that, in D_2O at pH 5·9, both (**4a**) and (**5a**) undergo hydrogen–deuterium exchange at C-6, exchange of the former being the more rapid of the two and that, above pH 7, (**4a**) is converted quantitatively into deuteriated (**5a**). Similar observations were made at pH 9·5 for the conversion of (**4b**) into (**5b**).[2,3] These facts are consistent with the reversible formation of *carbanionic* intermediates in the conversions (**4**) → (**5**), and the preponderance of (**5**) at equilibrium can be understood when the kinetic equations are examined:

$$(4) \underset{k_{-c}}{\overset{k_c}{\rightleftharpoons}} \underset{(6)}{\text{anion}} \underset{k_{-t}}{\overset{k_t}{\rightleftharpoons}} (5)$$

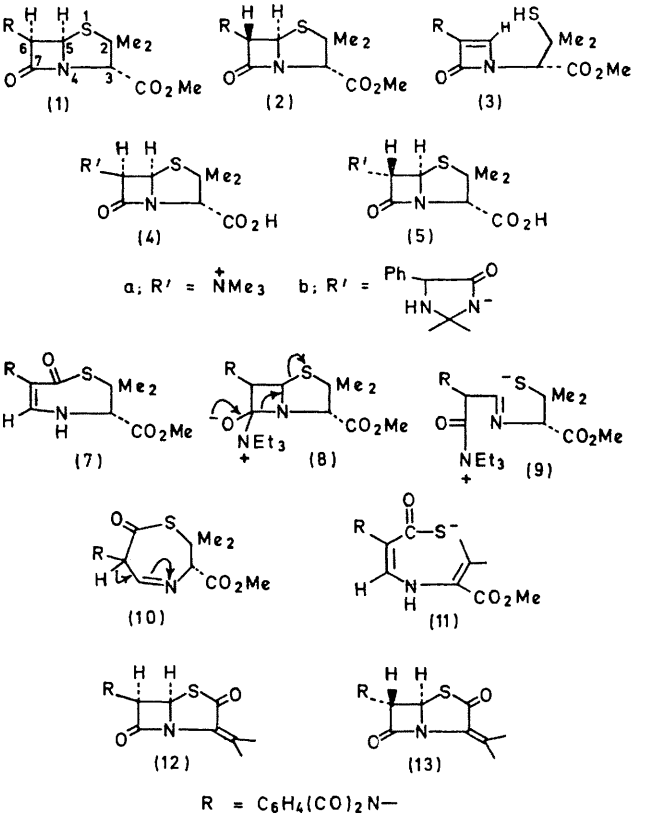
At equilibrium,

$$K = [5]/[4] = (k_c/k_t)(k_{-t}/k_{-c})$$

the equilibrium constant being expressed as the product of two ratios,[4] one (k_c/k_t) associated with the reactivities of (**4**) and (**5**), and the other (k_{-t}/k_{-c}) associated with the partitioning of (**6**) in the two directions. Since $k_c > k_t$ and $k_{-t} >> k_{-c}$, it follows that $K >> 1$.

Following the appearance of the above reports, a careful re-examination of the epimerizationof (**1**) with triethylamine in methylene chloride led to the isolation of a new compound which was shown to have structure (**7**);[5] and it was argued that (**7**) could have arisen only by intramolecular attack of the thiol function of (**3**) on the carbonyl group of the β-lactam ring. If this were correct, occurrence of β-elimination under the conditions of C-6 epimerization would be proved, but it would not follow that (**3**) is a necessary precursor of (**2**). For this reason and because it is possible to suggest a pathway for the conversion of (**1**) into (**7**) which does not involve (**3**), *viz.*, (**8** → **9** → **10** → **7**), it seemed desirable to provide additional support for a β-elimination route in the epimerization of (**1**).

The conversion of (**1**) (0·075 M, $[\alpha]^{28}$ + 257°, *c* 2·5, Et_3N–$CHCl_3$–Bu^tOH) into the mixture of (**2**) ($[\alpha]_D^{28}$ + 199°, *c* 2·25, Et_3N–$CHCl_3$–Bu^tOH) and (**7**) ($[\alpha]_D^{28}$ − 183°, *c* 1, Et_3N–$CHCl_3$–Bu^tOH) with triethylamine (0·094 M) in $CHCl_3$–Bu^tOH (1 : 1) was studied polarimetrically at 25·0° and 50·0°. The conversions were complete after 69·0 and 25·0 hr, respectively, and the rotations at these times were $[\alpha]_D$ + 6·4° and $[\alpha]_D$ + 1°. The difference between these values was found to be the result of a slow conversion of (**7**) under the experimental conditions into optically inactive products (see below; at 50·0° the loss of optical activity from a solution of (**7**) in $CHCl_3$–Bu^tOH containing a ten-fold excess of triethylamine required over 200 hr for completion), and it can be concluded, therefore, that the ratio of (**2**) to (**7**) (1 : 1) at the two temperatures is the same.



On the assumption that the entropies of activation are not temperature-dependent, it follows that the reactions which produce (**2**) and (**7**) have the same energy of activation. In terms of the mechanistic suggestions discussed above, this result rules out the sequence (**8** → **9** → **10** → **7**) and must mean that the two reactions have the same rate-determining step. The intermediate formed in this step is either a carbanion or the unsaturated thiol (**3**). If the intermediate is the carbanion, then (**3**), the precursor of (**7**), must be formed from this carbanion, *i.e.*, in an *ElcB* process. But this would imply that C–S cleavage can compete successfully with protonation of the carbanion, a reaction whose rate constant will be in excess of 10^{10} M^{-1} sec^{-1}.[6] This seems unlikely and, indeed, the analogues of (**7**) were not observed in the reactions (**4** → **5**), in which carbanionic

intermediates do intervene. A more significant objection to a carbanionic intermediate in the present system is that a carbanion is the product of a reversible acid–base reaction and ought to be accessible from *either* (**1**) *or* (**2**). This implies that if (**3**), the precursor of (**7**), were formed by an *E1cB* route, both (**1**) and (**2**) should be convertible into (**7**). In fact, (**2**) is stable under these experimental conditions; a 0·075 M solution of (**2**) in $CHCl_3$–Bu^tOH (1 : 1) containing triethylamine (0·094 M) showed no change in rotation and no change in its u.v. spectrum after 48 hr at 25°. The common intermediate for the products (**2**) and (**7**) must, therefore, be (**3**), the product of the β-elimination.

As reported earlier,[1] treatment of (**1**) with Bu^tOK–Bu^tOD affords deuteriated (**2**) and it has now been checked that (**7**) is not produced under these conditions. When the conversion of (**1**) into (**2**) and (**7**) was performed with triethylamine in CH_2Cl_2–Bu^tOD, the epimer was found to contain *no* deuterium. It is suggested that formation of (**7**) and lack of deuterium incorporation into (**2**) are complementary experimental criteria for epimerization by the β-elimination route. An interpretation of the deuteriation result is that cyclization of (**3**) is a concerted *cis*-addition of S–H to the β-face of the C-5–C-6 double bond. Because a free thiolate anion would acquire deuterium in preference to hydrogen, and hydrogen exchange of a free S–H group or a free triethylammonium ion with the solvent can be expected to be rapid,[7] the hydrogen of this S–H group has apparently been transferred to sulphur from the triethylammonium cation prior to separation of the ions, so that the 6α-proton of (**1**) has become the 6β-proton of (**2**).

The data now available indicate that in a competition between β-elimination and carbanion formation at C-6 of the penicillin nucleus, the latter process, as expected,[8] is facilitated by an appropriate combination of acid-strengthening substituent at C-6 [Br, $\overset{+}{N}Me_3$, $C_6H_4(CO)_2N$] and strong base (OH^-, NaH, $NaNH_2$, Bu^tO^-). The β-elimination route is favoured when the base is triethylamine.[5,9] It was of interest to determine how the competition between the two routes depends upon the nature of the (potential) leaving group at C-5, and the epimerization of an anhydropenicillin was, therefore, examined. Although, in basic media, alkyl–sulphur cleavage seems to be more difficult for a thiol ester than for a sulphide,[10] (**7**)[5] and related compounds[9,11] undergo virtually instantaneous β-elimination (*e.g.*, **7** → **11**) upon treatment with NaOMe–MeOH.

Reaction of anhydro-6-phthalimidopenicillin (**12**), m.p. 236—238°[12] with sodium hydride in tetrahydrofuran ("carbanion conditions") or with triethylamine in methylene chloride ("β-elimination conditions") afforded in each case anhydro-6-*epi*phthalimidopenicillin (**13**), m.p. 200—201° as the sole product; but with triethylamine in CH_2Cl_2–Bu^tOD, the conversion of (**12**) into (**13**) proceeded *without* incorporation of deuterium. Structural identification of (**13**) was facilitated by observation of the characteristic change in the β-lactam region of the n.m.r. spectrum, from δ 5·60 and 5·90 (*J* 4·2 Hz) in (**12**) to δ 5·58 and 5·62 (*J* 1·8 Hz) in (**13**).

As noted above, (**7**) reacts slowly with triethylamine. Treatment of (**1**) (0·5 g) at 28° for 60 hr with triethylamine (0·3 g) in CH_2Cl_2 (20 ml) yielded (**2**) (0·23 g), (**7**) (0·10 g), and a new compound $C_{18}H_{17}ClN_2O_5S$, m.p. 158—160° (0·091 g). The structure of this new compound [which is derived from (**7**)] and its mode of formation are of some interest and will be the subject of a separate communication.[13]

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