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INTERCONVERSION OF THE THIAZINE AND THIAZOLIDINE SYSTEM OF β-LACTAM ANTIBIOTICS. ELECTROCHEMICAL CLEAVAGE OF KAMIYA'S DISULPHIDE PROMOTED BY BROMIDE ION

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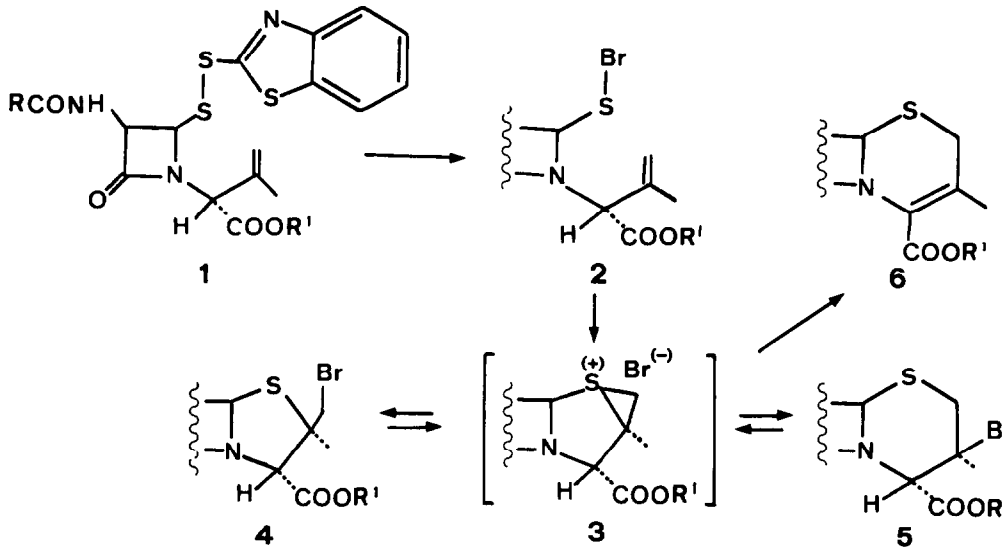
SUMMARY *A new transformation of Kamiya's disulphide (1) into the bromopenam derivative (4) has been carried out by electrolysing the disulphide (1) in protic solvents in the presence of Me_4NBr The transformation occurs through an intermediate episulphonium-bromide ion pair in which the bromide appears to be tightly linked to the sulphur*

Several recent reports on β-lactam antibiotics have been devoted to the interconversion reactions of penam and cepham systems. These reactions, which usually proceed through the intermediate formation of an episulphonium ion, can offer alternative routes to simple cephems starting from penicillins, or afford newly substituted penicillins and cephems.[1,2]

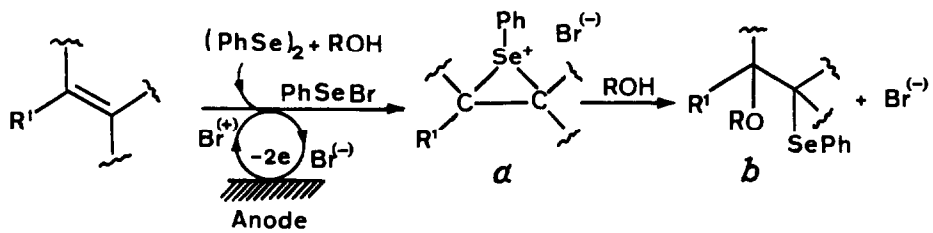
The asymmetrical azetidinone disulphides (1), easily available from penicillin sulphoxides through Kamiya's method,[3] are considered important key intermediates for the synthesis of penicillins substituted on the 2β-methyl, or of 3β-substituted cephams and desacetoxy-cephalosporins. For example, their bromination, under carefully controlled conditions, lead to the 2β-bromomethylpenam (4), which can rearrange to the 3β-bromocepham (5) or can be converted into the corresponding desacetoxy-cephalosporin (6).[3] This reaction presumably proceeds through the cleavage of the S–S bond by the bromine to yield a sulphenyl bromide (2),[4] the latter intermediate is transformed, through intramolecular addition to the olefinic double bond, into the episulphonium ion (3) which gives the reaction product by attack of a nucleophile [3,4]

Recently, the electrochemical solvo-selenenylation of olefins by symmetric



diselenides in the presence of a trace amount of halide ions (e.g. bromide ions) has been reported.[5] (See Scheme 1)

Scheme 1

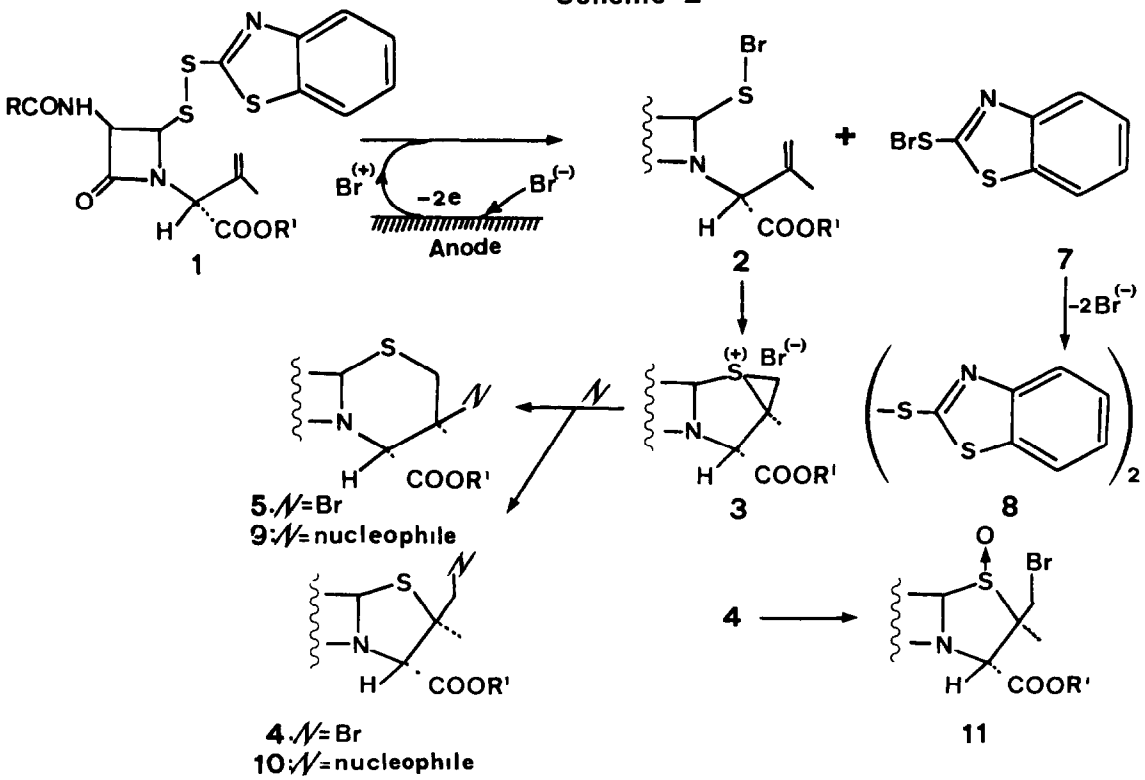


These results prompted us to examine the possibility of transferring this kind of reaction to structurally analogous systems such as the disulphides, and in particular to Kamiya's disulphides (1), with the aim of getting substituted penicillins and cephems under very mild reaction conditions. These studies are to be related to our previous research on interconversion of the thiazine and thiazolidine system of β-lactam antibiotics.[2]

We therefore examined the electrolysis of the azetidinone disulphides (1) (a: R=$PhCH_2$, R'=CCl_3CH_2; b: R=$PhOCH_2$, R'=p-NO_2-$C_6H_4CH_2$) in the presence of bromide ions in protic solvents The reaction of the bromonium ion (Br^+) or of the bromine with the disulphide 1 (see Scheme 2), was expected to give the episulphonium bromide 3, through an intramolecular cyclization of the intermediate sulphenyl bromide 2. 3 would give derivatives of type 9 and 10 by attack of a nucleophile.

The electrolyses of solutions of the disulphides 1 in MeCN in an undivided cell using Pt foils (4 cm^2) under a constant current of 8 mA (4.8 F/mol) in the

Scheme 2



presence of $ClCH_2COOH$ and of a stoichiometrical amount of Me_4NBr dissolved in the minimum amount of water, exclusively yield the 2β-bromopenam derivatives 4 accompanied by 2-benzothiazolyl disulphide (8). Attempts to purify the bromo-derivatives 4 by chromatographic techniques, led to recovery of 3β-bromocepham derivatives 5 together with small amounts of the Δ^3-cephem derivatives 6 (40-45% of 5b and 4-6% of 6b starting from 1b, and 18-22% of 5a and 8-12% of 6a starting from 1a). 4 and 5 are identical to the products prepared through Kamiya's method,[3] by treatment of the disulphides 1 with bromine in CH_2Cl_2 at very low temperature. Also the dissolution of crude 4 in some solvents (e.g. DMF) yields the rearranged products 5. The easy conversion of 4 into 5 should involve the formation of epi-sulphonium ion (3).[3] In order to prevent rearrangement and dehydrohalogenation processes during the purification, the crude penams 4 were oxidized by *m*-chloro-peroxybenzoic acid, to the corresponding (S) sulphoxides 11 which were isolated by preparative TLC (38-42% of 11b starting from 1b, and 22-25% of 11a starting from 1a).

Several electrolyses of 1 carried out under modified reaction conditions (e.g without monochloroacetic acid in the presence of catalytic amount of H_2SO_4,

or without monochloroacetic acid in the presence of acetic acid, or in the total absence of acids) led only to decomposition products or to recovery of the starting disulphides 1. When performing the electrolyses of 1 in the presence of monochloroacetic acid the use of a stoichiometric amount of Me_4NBr, together with a large excess of different electrophiles ($ClCH_2COO^-$, MeOH, MeCOOH, H_2O/MeCN), leads to recovery of the bromopenam derivatives 4 as the only β-lactam products. Attempts carried out by adding the disulphides 1 to a solution of the other previously electrolyzed reagents, led to recovery of the starting material; further electrolysis of the reaction mixture gave the same result. When the electrolyses were carried out in the presence of a stoichiometric amount of chloride ions $[C_6H_5CH_2N(Cl)(Me)_3]$, only decomposition products were obtained. The electrolytic reactions take place neither in the presence of catalytic amounts nor in the absence of bromide ions.

The results so far obtained confirm the possibility of getting the electrochemical cleavage of disulphides in the presence of halide ions. Furthermore, these data support the mechanistic scheme hypothesized above for the reaction of Kamiya's disulphide, which implies the intermediate formation of the episulphonium bromide (3) (see Scheme 2). However, the sole formation of bromoderivative (4) and therefore the non incorporation by the episulphonium ion of nucleophiles other than bromide, even if present in a large excess in the reaction medium, suggests, for the intermediate episulphonium bromide (3), ion pair structures in which the bromide is tightly linked to the sulphur.[6] Therefore the attack of a nucleophile on the electrophilic carbon of the episulphonium ion must take place preferentially by the bromide ion rather than by a nucleophile external to the ion pair 3.

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