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EPIMERIZATION OF PENICILLIN SULFOXIDES AND THEIR CONVERSION TO ISOTHIAZOLONES. DUAL PATHWAY ON TREATMENT WITH BASES

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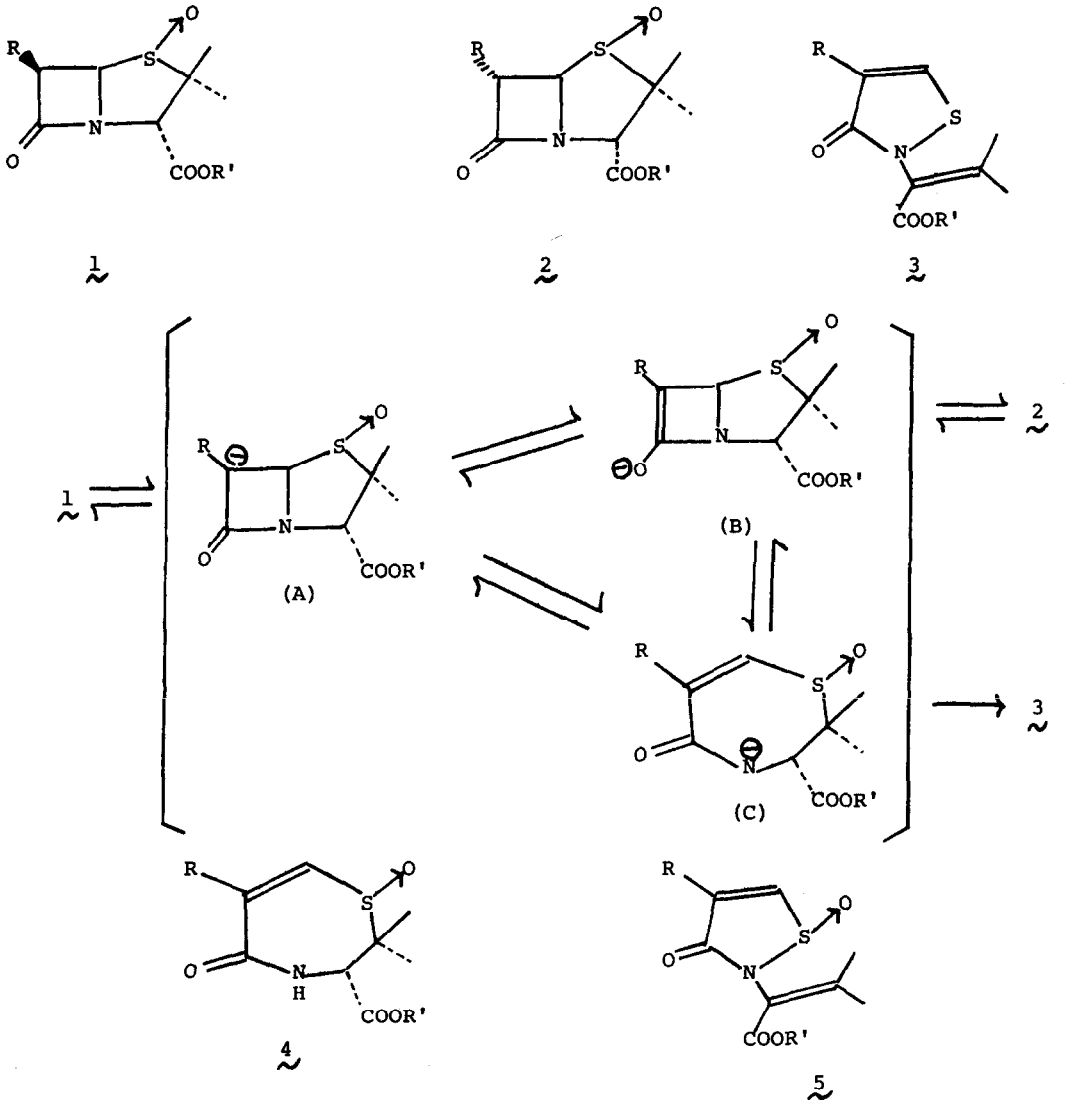
Base-catalized epimerization of penicillins and their sulfoxides has been reported recently (1,2). The reactivity of penicillin with base is also an important problem to introduce substituents at C-6 (3,4,5). In penicillins which contain no amino hydrogen atom, such as 6β-phthalimido derivatives, facile epimerization proceeds under basic conditions, and the rearrangement to 1,4-thiazepine via β-elimination concomitantly occurs as the side reaction (6). In secondary acylamidopenicillins, the first proton to be removed by base may be the N-H proton, and the resulting negative charge prevents the formation of the C-6 carbanion (7). Only recently, Koppel succeeded in the direct epimerization of phenoxymethylpenicillin methyl ester by the treatment with lithium diisopropyl amide (8). In contrast, penicillin sulfoxides, even if containing a secondary amide side chain, epimerize easily to their C-6 epimers by the treatment with bases (2,9). We found that in the epimerization reaction of penicillin sulfoxides in the presence of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), an additional compound isothiazolone 3 was isolated. The formation of this compound requires the occurrence of the β-elimination. The purpose of this paper is to describe the possible role of isothiazolone in epimerization reaction.

When the benzyl ester of 6β-phenylacetamidopenicillin (S)-sulfoxide 1ax was treated with one equivalent of DBN in CH_2Cl_2 at 0° for 10 min. according to Claes et al. (2), a mixture of 1ax and its C-6 epimer 2ax was obtained in the ratio of 4 to 6. No isothiazolone 3ax could be detected. In contrast, when the *p*-nitrobenzyl ester 1ay was treated with DBN under the same conditions, 3ay was formed in addition to 2ay. Inspection of the n.m.r. spectrum revealed that the product ratio of 1ay to 2ay to 3ay is 6 to 4 to 1. Furthermore, the β,β,β-trichloroethyl ester 1az was transformed to a mixture of 1az and 3az in the ratio of 7 to 4 under the same conditions. Compound 3az was isolated by column chromatography over silica gel using $CHCl_3$ as eluant: m.p. 198-201° n.m.r. ($CDCl_3$) δ 1.92 (3H,s), 2.33 (3H,s), 3.75 (2H,s), 4.67 (2H,s), 7.33 (5H,s), 8.62 (1H,brs), 8.73 (1H,s). No C-6 epimer could be detected. Similar isothiazolone 3 (R=$PhOCH_2CONH$-, R'=CH_3) has been obtained in refluxing pyridine by Morin et al. (10), and the mechanism of the formation proposed by Cooper (11).

These facts suggest that the first proton to be removed by base in penicillin sulfoxides may not be the N-H proton but the C-6 proton, and penicillin sulfoxide is competitively transformed to the C-6 epimer and isothiazolone by the following mechanism.



R		R'	
a	: $PhCH_2CONH-$	x	: $-CH_2Ph$
b	: $C_6H_4(CO)_2N-$	y	: $-CH_2Ph-p-NO_2$
c	: $(CH_3O)_2PONH-$	z	: $-CH_2CCl_3$

In a competition between β-elimination and carbanion formation at C-6 of the penicillin nucleus, the former process is facilitated by an electron withdrawing ester group at C-6. The occurrence of β-elimination under the conditions of C-6 epimerization would suggest that intermediate (C) is a possible precursor of 2. The reversibility between (A) and (C), although not confirmative, suggests the possibility of the transannular reaction of 1,4-thiazepine sulfoxide 4 in the synthesis of penicillin ring system (12). In 6β-phthalimidopenicillin (R)-sulfoxide, not only 1bz but also 1bx were transformed to the corresponding isothiazolone almost quantitatively without formation of the 6α-epimer under the same conditions: 3bx; m.p. 210-212°, n.m.r. ($CDCl_3$) δ 1.95(3H,s), 2.37(3H,s), 5.18(2H,s), 7.32(5H,s), 7.82(4H,m), 8.37(1H,s) ; 3bz; m.p. 164-168°, n.m.r. ($CDCl_3$) δ 2.03(3H,s), 2.45(3H,s), 4.78(2H,s), 7.84(4H,m), 8.40(1H,s). It is quite interesting that not only (S)-sulfoxide of 1 but also (R)-sulfoxide were converted to 3. In contrast, it has been known that 1,4-thiazepine (S)-sulfoxide 4 (R = $PhCH_2CONH$-, R' = CH_3) was converted to isothiazolone in refluxing acetone, whereas (R)-sulfoxide underwent no reaction (11). Furthermore, it is of interest that in 6β-phthalimidopenicillins, the carbanionic process is favoured on treatment with DBN (13), whereas in 6β-phthalimidopenicillin sulfoxide, β-elimination is predominated. In 6β-phosphoramidopenicillin (S)-sulfoxides (14), which possess a nonenolizable secondary amide side chain, the reactivity of 1cx and 1cy with DBN was similar to 1ax and 1ay. However, 1cz was transformed to a mixture of 1cz, 3cz, and 5cz in the ratio of 3 to 2 to 1. Compounds 3cz and 5cz were separated by column chromatography over silica gel using $CHCl_3$ as eluant: 3cz; colorless needles, m.p. 131-132°, m/e 452, n.m.r. ($CDCl_3$) δ 1.97(3H,s), 2.43(3H,s), 3.80(6H,d,J=12Hz), 4.72(2H,s), 5.68(1H,d,J=12 Hz),7.52(1H,s); 5cz; amorphous solid, m/e 468, n.m.r.($CDCl_3$) δ 2.13(3H,s), 2.48 (3H,s), 3.85(6H,d,J=12Hz), 4.70(2H,s), 6.32(1H,d,J=12Hz), 6.80(1H,s). No C-6 epimer 2cz could be detected. Compound 5cz was also obtained by the oxidation of 3cz with *m*-chloroperbenzoic acid. When the same reaction was conducted under nitrogen stream, 5cz was not formed. Furthermore, by the treatment with DBN under the same conditions, 3cz was transformed to a mixture of 3cz and 5cz in the ratio of 1 to 1. In contrast, neither 1az nor 3az gave 5az under the same conditions. Compound 5cz must be produced by the atmospheric oxidation of 3cz, because the sulfur atom of 3cz is electron-sufficient by the nonenolizability of N-anion of 3cz produced by the treatment with DBN.

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