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STUDIES ON β-LACTAM ANTIBIOTICS. I.
A NOVEL CONVERSION OF PENICILLINS INTO CEPHALOSPORINS

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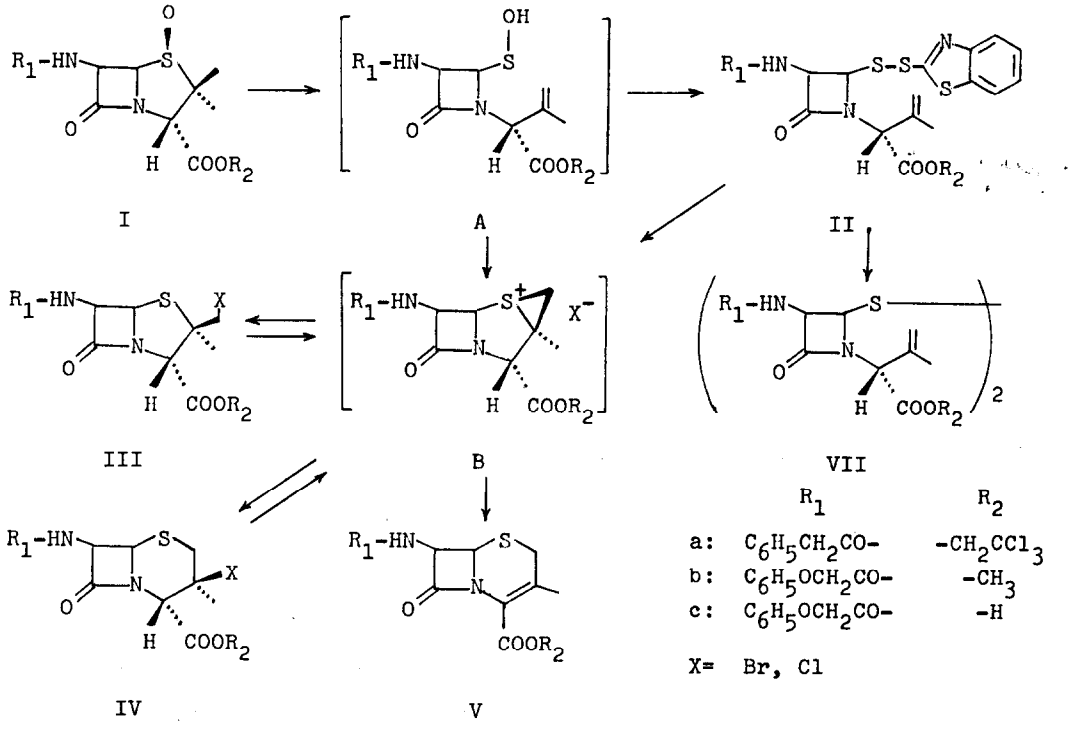
The sulfenic acid intermediate (A) formed by a thermal sigmatropic rearrangement of penicillin sulfoxides (I) has been trapped either intramolecularly or intermolecularly by several methods.[1] Our efforts have been directed to the preparation of a key intermediate useful for syntheses of modified β-lactam antibiotics. We found that dithioazetidinones (II),[2] easily obtained from reactions of penicillin sulfoxides (I) with heteroaromatic thiols, are the key intermediates for preparing 2-halomethyl-penams (III) and cephams (IV) derivatives. This paper reports a novel conversion of penicillins into cephalosporins through these important key intermediates.

Treatment of a penicillin sulfoxide (Ia) with 2-mercaptobenzothiazole in refluxing toluene for 4 hours afforded the crystalline disulfide (IIa), m.p. 140-1°; $[\alpha]_D^{25}$-103.9° (c=1.01, $CHCl_3$); nmr ($CDCl_3$,δ):1.98 (3H,br.s,-CH_3), 5.15 and 5.23 (2H, two br.s, C=C$\underline{H}_2$), 5.33 (1H, dd, J=8, 4.5Hz, 3-$\underline{H}$), 5.52 (1H, d, J=4.5Hz, 4-$\underline{H}$), 5.07 (1H, br.s, -C$\underline{H}$-COO-); in over 90 % yield. In a similar manner, the free acid (Ic) reacted smoothly with 2-mercaptobenzothiazole and gave the disulfide (IIc); m.p. 146-8° (dec); $[\alpha]_D^{25}$-75.5° (c=1.00, EtOH); without decarboxylation. When the disulfide (IIa) was treated with base, the isolated double bond was moved to the conjugation (VIa), oil; nmr ($CDCl_3$,δ): 2.22 and 2.25 (6H, two s, 2 χ -C$\underline{H}_3$), 5.00 (1H, dd, J=7.5, 5Hz, 3-$\underline{H}$), 5.68 (1H, d, J=5Hz, 4-$\underline{H}$). The acid (IIc) was not isomerized under the same conditions. On the contrary,



when this acid (IIc) was dissolved in aq. $NaHCO_3$, a symmetrical disulfide of 2-azetidinone (VIIc), m.p. 189-190° (dec); nmr (d_6-DMSO,δ): 1.84 (6H, s, $-CH_3$), 5.0-5.3 (4H, m, $C=C\underline{H}_2$, 3-$\underline{H}$, 4-$\underline{H}$), 4.75 (1H, s, $-C\underline{H}-COOH$), and bis-2-benzothiazolyl disulfide were obtained almost quantitatively. This mechanism can be explained by the initial attack of its carboxylate anion to the disulfide function followed by disproportionation of the thiol anions.[3)]

It has been found that the disulfides (II) give 2-halomethyl-penicillins (III) by halogenation, and the position of the double bond plays an important role in achieving recyclization. Treatment of the disulfide (IIa) with bromine in CH_2Cl_2 afforded 2β-bromomethyl-penicillin (IIIa; X=Br), m.p. 90-3° (dec); $[\alpha]_D^{25}$ + 137.6° (c=1.76, $CHCl_3$); nmr ($CDCl_3$,δ): 1.65 (3H, s, 2-$C\underline{H}_3$), 3.32 (2H, s, 2-$C\underline{H}_2Br$), 5.10 (1H, s, 3-$\underline{H}$), 5.45-5.75 (2H, m, 5-$\underline{H}$, 6-$\underline{H}$), as the sole product in almost quantitative yield. Similarly, 2β-chloro-penam (IIIa; X=Cl), m.p. 107-8° (dec); $[\alpha]_D^{25}$+ 133.6° (c=1.39, $CHCl_3$); nmr ($CDCl_3$,δ) : 1.62 (3H, s, 2-$C\underline{H}_3$), 3.37

(2H, s, 2-C$\underline{H}_2$Cl), 5.02 (1H, s, 3-$\underline{H}$), 5.45-5.70 (2H, m, 5-$\underline{H}$, 6-$\underline{H}$) was obtained by this procedure. The conjugated disulfide (VIa), however, gave no halogenated products under the same conditions as above. The configuration of these products was confirmed by measuring their internal nuclear Overhauser effect and a solvent-induced shift.[4),5)] This recyclization should proceed via an episulfonium halide (B),[6)] which could be formed by the addition of the initially formed sulfenyl halide to the appropriately positioned double bond.[7)] This intermediate must be β-orientated and subsequently opened by a nucleophilic attack by the halogen ion.

The 2β-bromomethyl derivative (IIIa) is relatively stable in the solid state When this compound was dissolved in dimethylformamide and allowed to stand overnight at room temperature, it gave quantitatively a 3β-bromo-cepham derivative (IVa); m.p. 135-6° ; $[\alpha]_D^{25}$ + 0.8° (c=10.75, $CHCl_3$); nmr ($CDCl_3$,δ): 1.97 (3H, s, 3-C$\underline{H}_3$), 2.78 and 3.52 (2H, ABq, J=14Hz, 2-C$\underline{H}_2$), 4.97 (1H, s, 4-H), 5.28 (1H, d, J=4.5Hz, 6-$\underline{H}$), 5.62 (1H, dd, J=9, 4.5Hz, 7-$\underline{H}$). The 2β-chloro derivative (IIIa; X=Cl) gave similarly the 3β-chloro-cepham derivative (IVa), oil; nmr ($CDCl_3$,δ): 1.77 (3H, s, 3-C$\underline{H}_3$), 2.75 and 3.65 (2H, ABq, J=14.5Hz, 2-C$\underline{H}_2$), 4.87 (1H, s, 4-$\underline{H}$), 5.30 (1H, d, J=4.5Hz, 6-$\underline{H}$), 5.67 (1H, dd, J=9, 4.5Hz, 7-$\underline{H}$). The halogen groups are assumed to be β-orientated by mechanistic consideration. This rearrangement should also involve initial formation of the episulfonium ion (B), which is subsequently opened by the halogen anions to give the thermodynamically favored cepham derivatives (IV).

The 2β-halomethyl-penams (III) and the 3β-halo-cephams (IV) were readily converted into the cephems (V) by treating them with bases. Treatment of the 2β-halomethyl-penams (IIIa,b) and the 3β-halo-cephams (IVa,b) with pyridine in benzene at the refluxing temperature afforded the cephem derivatives (Va,b), by a spontaneous ring enlargement of penicillin nucleus in good yield. This conversion can be also explained by the formation of the episulfonium ion (B) from both (III) and (IV) in the initial step. This intermediate (B) is easily transformed to the cephems (V) by the abstraction of the α-proton with bases. The sequence of reactions described above provides a novel and useful procedure for preparing deacetoxy-cephalosporins (V).

The mechanistic consideration described above suggests the possibility of the direct conversion of the sulfoxides (I) to the 2-halomethyl-penams (III). When sulfoxide (Ia) was heated with pyridine hydrochloride and pyridine in tetrachloroethane, a mixture of (Va) and (IIIa; X=Cl) was obtained in moderate yield. This reaction also provides a simple and useful method for preparing 2-halomethyl-penicillins (III) and deacetoxy-cephalosporins (V). Synthesis of other new β-lactam antibiotics by the use of key intermediates (II,III,IV) will be reported in the future.

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