

REARRANGEMENT OF CEPHALOSPORINS TO A PENICILLIN NUCLEUS BY THE REACTION WITH
BENZYL SULFONYL CHLORIDE THROUGH A NEW EXTRUSION REACTION OF SULFUR DIOXIDE

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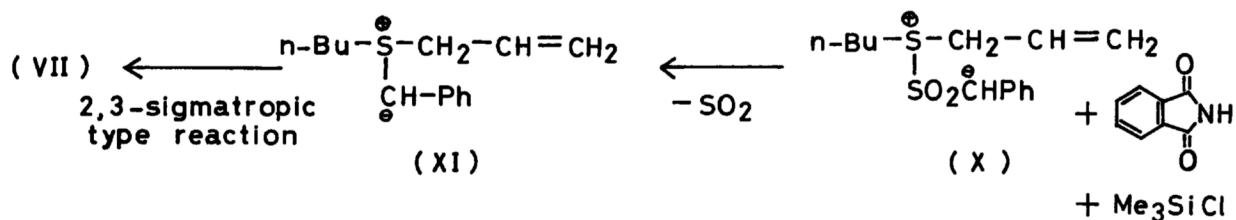
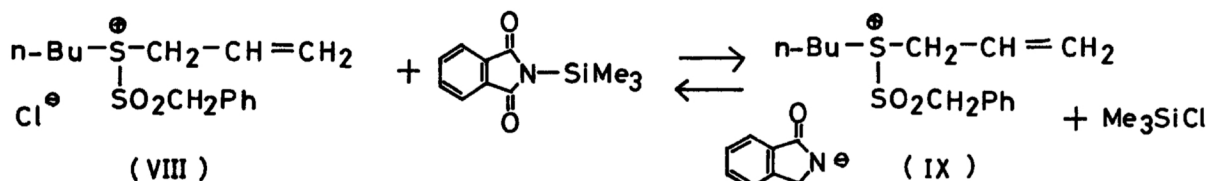
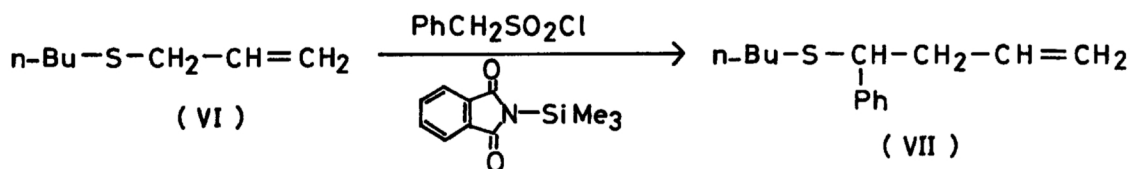
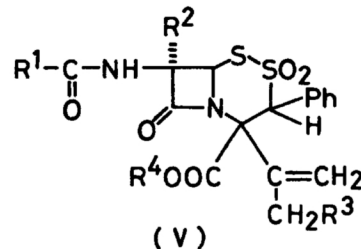
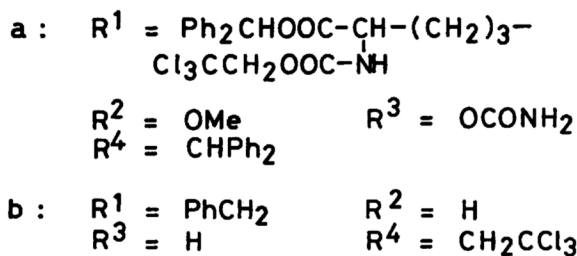
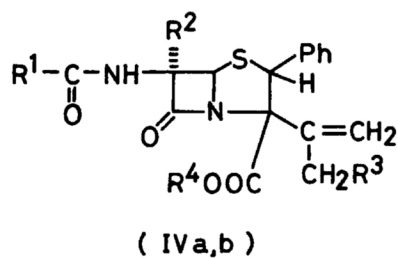
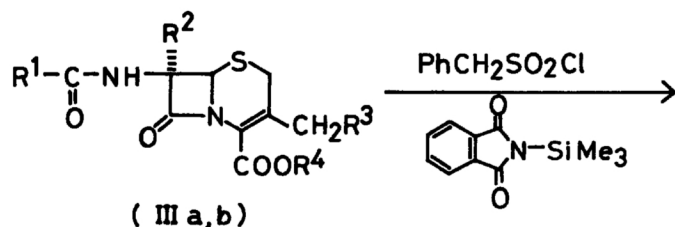
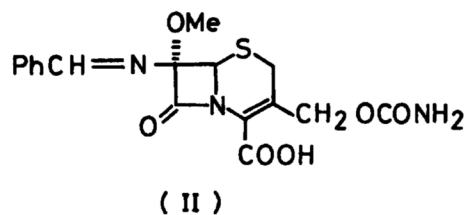
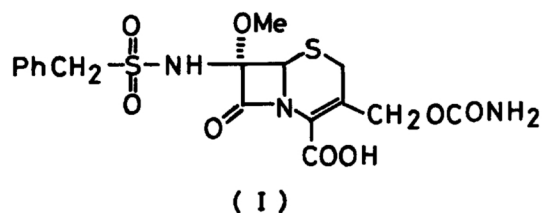
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Cephalosporins rearranged to penicillin derivatives on treatment with α -toluenesulfonyl chloride in the presence of a silylating reagent via 2,3-sigmatropic type reaction after extrusion of sulfur dioxide. This reaction also proceeded in the case of alkyl allyl-sulfide.

During the course of our investigation to obtain free amine derivatives of cephamycins¹⁾ we have found a rearrangement of cephalosporins to a penicillin nucleus involving a new extrusion reaction of sulfur dioxide.

Our planned methodology comprises exchange of the acyl group of cephamycins with α -toluenesulfonyl moiety according to a Merck's method²⁾ to the sulfonamide (I) which might be converted into the Schiff base (II) by elimination of sulfur dioxide.³⁾ Thus, the cephamycin-C derivative (IIIa) was treated with α -toluenesulfonyl chloride in the presence of N-trimethylsilylphthalimide in acetonitrile at 40° for 20 hr to give an unexpected penicillin derivative (IVa) in 40% yield after silica gel chromatography. The structure of IVa was determined on the basis of elemental analysis and NMR decoupling experiments: NMR(100 Mc) (CDCl₃) δ ppm 1.40-2.20(6H, m), 3.45(3H, s), 4.38(1H, m), 4.59(2H+2H, broad s), 4.69(2H, broad s), 5.28(1H, s), 5.32(1H, s), 5.41(1H, s), 5.45(1H, s), 5.98(1H, d, J=8 Hz), 6.85(1H, broad s), 6.80(1H, s), 6.90(1H, s), 6.95-7.50(25H, m); IR: 1790 cm⁻¹(Nujol). At first sight this rearrangement seemed to be curious and a reasonable structure deduced from the reaction mechanism was speculated to be a cyclic thiol sulfonate (V), however, the structure of V was excluded by elemental analysis, mass spectrum, and an experiment starting from non-cyclic sulfide (VI) (vide infra). A similar



rearrangement of cephalosporins to the corresponding penicillin derivatives by treatment with diazo compounds was reported by Yoshimoto et al.⁴⁾ and examination of their NMR spectra confirmed the structure (IVa). Analogously, 7H-cephalosporins (IIIb) afforded the rearranged product (IVb) in 37% yield; NMR(CDCl₃) (100 Mc) δ ppm: 1.76(3H, s), 3.55(2H, s), 4.72 and 4.90(2H, AB-q, J=12 Hz), 5.23(1H, s), 5.29(1H, d, J=4 Hz), 5.37(1H, s), 5.52(1H, q, J=4 and 8.5 Hz), 5.57(1H, s), 5.82(1H, d, J=8.5 Hz), 6.95-7.35(10H, m).

In order to clarify the mechanism of the reaction and to confirm the structure (IVa) and (IVb) an analogous reaction was conducted with acyclic allyl sulfide (VI). A mixture of the sulfide (VI), α -toluenesulfonyl chloride and N-trimethylsilyl chloride in acetonitrile was heated at 40° for 5 hr to afford the sulfide (VII) as an oil in 64% yield upon silica gel chromatography. The structure of the sulfide (VII) was identified from its NMR spectrum and elemental analysis, and the analogous rearranged product was obtained from allyl benzyl ethylsulfonium tetrafluoroborate on treatment with sodium ethoxide through 2,3-sigmatropic reaction.⁵⁾ The mechanism of the formation of IV and VII from the allyl sulfides (III) and (VI) is considered as follows. The sulfonium salt (VIII) is equilibrated with the salt (IX) in the presence of trimethylsilylphthalimide, and also the sulfonium salt (IX) is in an equilibrium with the inner salt (X), which loses sulfur dioxide as in the case of Ramberg-Bäcklund rearrangement⁶⁾ to give the ylide (XI). 2,3-Sigmatropic-type reaction of this ylide furnishes the final product (VII). At present it is not clear whether a true concerted 2,3-sigmatropic reaction is operative or a cage recombination through a radical anion⁷⁾ is involved. It is interesting to note that this new rearrangement did not occur without trimethylsilylphthalimide, and in the presence of an organic base such as triethylamine instead of the silylating reagent no rearrangement was observed due to formation of α -toluenesulfene from α -toluenesulfonyl chloride. In the case of 2-propenesulfonyl chloride no clear-cut result was obtained.

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