CHEMISTRY LETTERS, pp. 1399-1402, 1977. Published by the Chemical Society of Japan

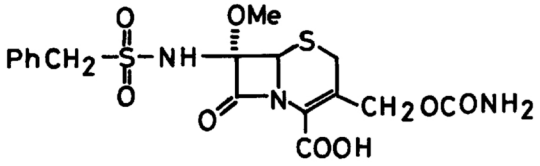
REARRANGEMENT OF CEPHALOSPORINS TO A PENICILLIN NUCLEUS BY THE REACTION WITH BENZYLSULFONYL CHLORIDE THROUGH A NEW EXTRUSION REACTION OF SULFUR DIOXIDE

Takeo KOBAYASHI and Tetsuo HIRAOKA
Central Research Laboratories, Sankyo Co., Ltd.
1-2-58, Hiromachi, Shinagawa-ku, Tokyo 140

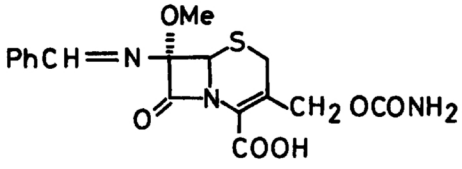
Cephalosporins rearranged to penicillin derivatives on treatment with α-toluenesulfonyl chloride in the presence of a silylating reagent via 2,3-sigmatropic type reaction after extrusion of sulfur dioxide. This reaction also proceeded in the case of alkyl allyl-sulfide.

During the course of our investigation to obtain free amine derivatives of cephamycins[1] we have found a rearrangement of cephalosporins to a penicillin nucleus involving a new extrusion reaction of sulfur dioxide.

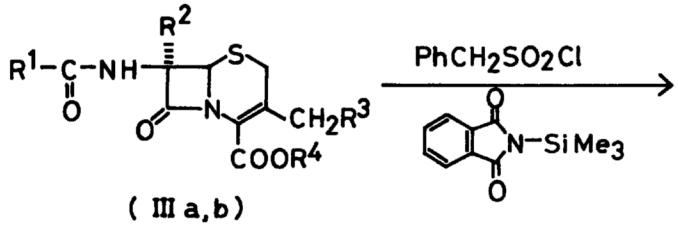
Our planned methodology comprises exchange of the acyl group of cephamycins with α-toluenesulfonyl moiety according to a Merck's method[2] to the sulfonamide (I) which might be converted into the Schiff base (II) by elimination of sulfur dioxide.[3] Thus, the cephamycin-C derivative (IIIa) was treated 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) ($CDCl_3$) 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



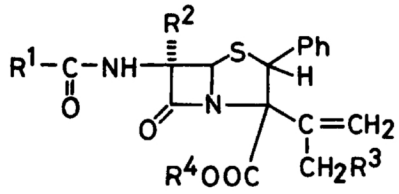
(I)



(II)



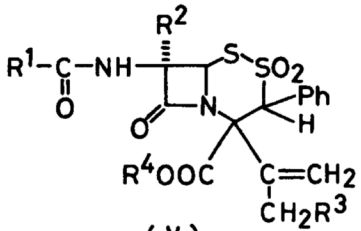
(IIIa,b)



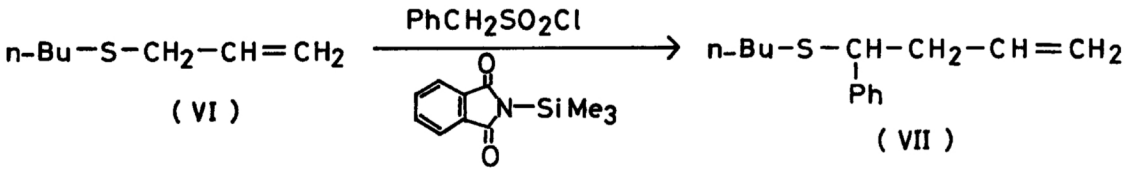
(IVa,b)

a : R^1 = $Ph_2CHOOC-CH-(CH_2)_3-$
$Cl_3CCH_2OOC-NH$
R^2 = OMe R^3 = $OCONH_2$
R^4 = $CHPh_2$

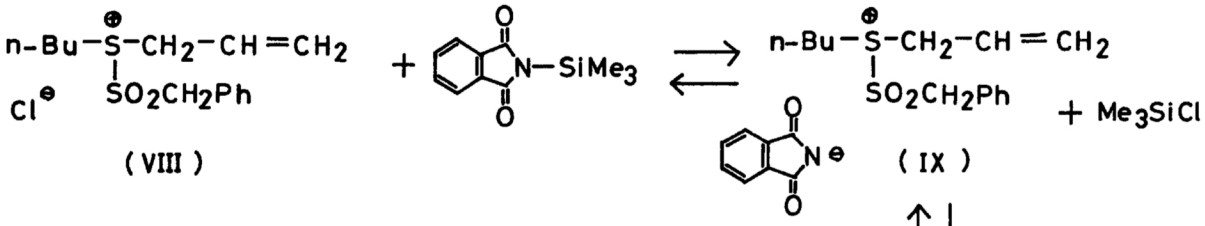
b : R^1 = $PhCH_2$ R^2 = H
R^3 = H R^4 = CH_2CCl_3



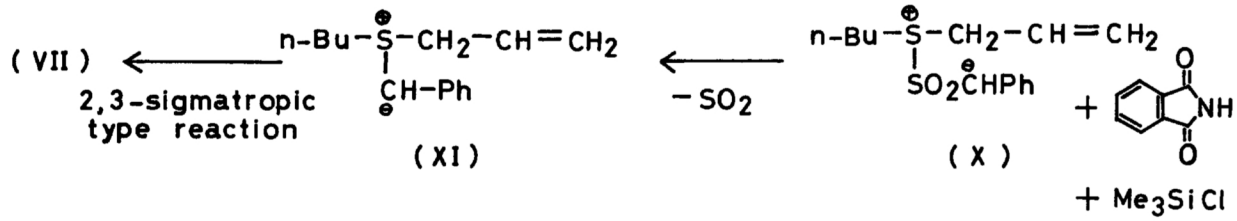
(V)



(VI) (VII)



(VIII) (IX)



(VII) (XI) (X)

rearrangement of cephalosporins to the corresponding penicillin derivatives by treatment with diazo compunds 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($CDCl_3$) (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 rearrangement[6] 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 anion[7] 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.

Acknowledgement. The authors are grateful to Mr. H. Kuwano for decoupling experiments in NMR. Thanks are also due to Dr. K. Arima, the director of our Research Laboratories, and to Dr. Y. Kishida, the director of Chemical Research for their interest and discussion throughout this work.

References

1) (a) R. Nagarajan, L. D. Boeck, M. Gorman, R. L. Hamill, C. E. Higgens, M. M. Hoehn, W. M. Stark, and J. G. Whitney, J. Am. Chem. Soc., 93, 2308 (1971); (b) E. O. Stapley, M. Jackson, S. Hernandez, S. B. Zimmerman, S. A. Currie, S. Mochales, J. M. Mata, H. B. Woodruff, and D. Hendlin, Antimicrob. Agents Chemother. 2, 122 (1972); (c) T. W. Miller, R. T. Goegelman, R. G. Weston, I. Putter, and F. J. Wolf, ibid. 2, 132 (1972).

2) S. Karady, S. H. Pines, L. M. Weinstock, F. E. Roberts, G. S. Brenner, A. M. Hoinowski, T. Y. Cheng, and M. Sletzinger, J. Amer. Chem. Soc., 94, 1410 (1972).

3) (a) T. Kobayashi and T. Hiraoka, presented at the 25th annaul meeting of the Chemical Society of Japan (Oct. 11-14, 1971); see the abstracts of the meeting, p 542 (1971). This result will be published in a journal; (b) J. C. Sheehan, U. Zoller, and D. Ben-Ishai, J. Org. Chem., 39, 1817 (1974).

4) M. Yoshimoto, S. Ishihara, E. Nakayama, and N. Soma, Tetrahedron Lett., 2923 (1972).

5) (a) R. W. C. Cose, A. M. Davies, W. D. Ollis, C. Smith, and I. O. Sutherland, Chem. Commun., 293 (1969); (b) B. M. Trost and L. S. Melvin, Jr., "Sulfur Ylides", Academic Press, New York, 1975, p 108.

6) L. A. Paquette, Accounts Chem. Res., 1, 209 (1968), and references cited therein.

7) J. E. Baldwin, W. F. Erickson, R. E. Hackler, and R. M. Scott, Chem. Commun., 576 (1970).

(Received August 31, 1977)