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TRANSFORMATION OF PENICILLIN SULFOXIDE ESTER INTO 2-HALOGEN-SUBSTITUTED PENICILLIN ESTER, INTERMEDIATE TO CEPHAM SYSTEM

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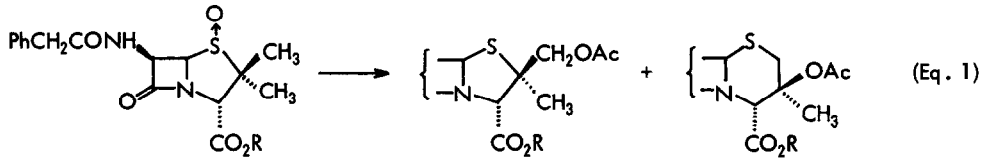
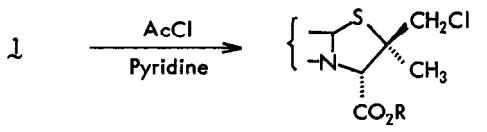
One of the most important approaches to the conversion of a penicillin nucleus into a cephalosporin structure is due to Morin and coworkers[1] who found that treatment of a penam sulfoxide ester (1) with acetic anhydride affords two principal products, a 2-acetoxy-substituted penicillin (2) and a 3-acetoxycepham (3) (Eq. 1). Although several modified methods have been reported,[2-4] we wish to present here a simple procedure leading entirely to a 2-halogen-substituted penam. It is also found that this penam can be transformed into a 3-substituted cepham or a deacetoxycephem derivative.

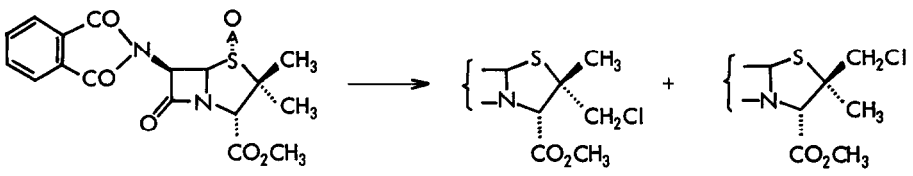


1 2 3 (Eq. 1)

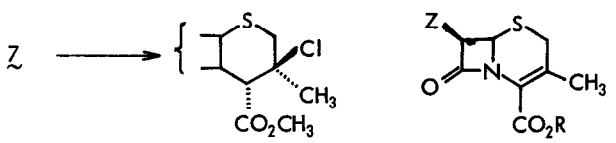
When a toluene solution of a penicillin G (S)-sulfoxide ester (1) (or an analogue bearing a secondary amide side chain at C-6) and one equivalent of each of acyl halide (or aroyl halide) and pyridine was refluxed for 1-2 hrs, it was found that a sort of β-lactam derivative was formed, the structure of which was established as the 2β-chloromethyl penam (4) (Eq. 2), e.g., 2β-chloro derivative of penicillin G benzhydryl ester, m.p. 116-117°: $\nu_{max}^{CHCl_3}$ 1788, 1745, and 1680 cm^{-1}: ^1H NMR δ($CDCl_3$) 1.25 (CH_3), 3.25 (CH_2Cl), 3.62 (CH_2Ph), 4.95 (3-H), ~5.6 (5- and 6-H, and NH), and 6.93 ($CHPh_2$). The yield varied in a range of 30-70% depending upon the C-6 amide chain and the acyl halide employed.[5] Evidence for the structure of 4 was obtained from ^{13}C and ^1H NMR[6] as well as other spectroscopic methods.



4 (Eq. 2)



5 6 7 (Eq. 3)



8 9

When the reaction was carried out with phthalimidopenicillin (R)-sulfoxide methyl ester (5), a 53:47 mixture of two β-lactam derivatives was obtained in a total yield of 67%; their structures were unequivocally established by ^{13}C and ^{1}H NMR studies[6] as the 2α-chloromethylpenam derivative (6), m.p. 163-165°: $[\alpha]^{23.5}D$ 205 ± 2.5° (c 0.996 in CH_3CN): ^{1}H NMR (Table), for the major product and as the 2β-chloromethylpenam derivative (7), m.p. 107-108°: $[\alpha]^{23.5}D$ 253.7 ± 3.1° (c 0.996 in CH_3CN): ^{1}H NMR (Table), for the minor one (Eq. 3). It appeared from the physical data that 7 is identical with the major product obtained from the reported reaction of 5 with thionyl chloride and triethylamine, although a different structure of a 3β-chlorocepham (8) has been proposed for that.[7] However, this was recently corrected to structure 7.[8,9] In fact, the formation of 8, m.p. 194-196°: $[\alpha]^{24}D$ 125.3 ± 5.5° (c 0.304 in CH_3CN): ^{1}H NMR (the Table),[6] was realized on heating 7 in a solvent of a high dielectric constant, for example, in dimethylsulfoxide at 100° for 1 hr.

Preparation of a corresponding cephem derivative (9) by eliminating hydrogen chloride was achieved in a satisfactory yield directly from a penam chloride or via a cepham chloride by warming at 130° in dimethylsulfoxide in the presence of a weak base, e.g., urea.

TABLE ^1H Chemical Shifts, δ[a]

Compound	Solvent	3β-H	5α-H	6α-H	2α-CH_2X	2β-CH_2X	CO_2CH_3
Methyl phthalimido-penicillanate	$CDCl_3$[b]	4.68	5.61	5.69	1.52	1.83	3.80
	C_6D_6[c]	4.72	5.35	5.42	1.29	1.69	3.29
6	$CDCl_3$	4.78	5.62	5.67	3.80 3.87	1.93	3.81
	C_6D_6	4.77	5.26	5.34	3.48 3.67	1.79	3.31
7	$CDCl_3$	5.13	5.73	5.73	1.60	3.72 4.50	3.83
	C_6D_6	5.22	5.53	5.39	1.42	3.65 4.65	3.28

		4β-H	6α-H	7α-H	2α-H	2β-H	3-CH_3	CO_2CH_3
8	$CDCl_3$	4.96	5.39	5.61	3.42	3.09	1.78	3.83
	C_6D_6	5.04	4.95	5.24	2.91	2.21	1.35	3.15

[a] ^1H NMR spectra were taken with a Varian A-60A spectrometer at 38°; precisions of δ_H are ±0.02. [b] Identical with the reported values.[10] [c] Considerably differ from the reported values.[10]

REFERENCES

(1) R. B. Morin, B. G. Jackson, R. A. Mueller, E. R. Lavagnino, W. B. Scanlon and S. L. Andrews, J. Amer. Chem. Soc. 85, 1869 (1963); 91, 1401 (1969).

(2) R. D. G. Cooper and D. O. Spry, "Cephalosporins and Penicillins. Chemistry and Biology," Ed. E. H. Flynn, Chapter 5, Academic Press, New York (1972).

(3) D. H. R. Barton and P. G. Sammes, Proc. Roy. Soc. B179, 345 (1971); D. H. R. Barton, Pure Appl. Chem. 33, 1 (1973).

(4) T. Kamiya, J. Synthetic Org. Chem. Japan 33, 24 (1975).

(5) Experimental Procedure for Penicillin V (S)-sulfoxide methyl ester (1). A solution of 380 mg of the ester, 140 mg of benzoyl chloride, and 79 mg of pyridin in 20 ml of toluene was refluxed for 80 min and cooled to room temperature. The mixture was poured into a 3% aq $NaHCO_3$ solution and extracted with ethyl acetate. The extract solution was washed with water, dilute HCl, and water, dried over Na_2SO_4, and evaporated. The residue was purified by TLC (Merk-silica gel, benzene-ethyl acetate). The yield of 4 was 180 mg.

(6) Some details of structural assignments of isomeric 2-halogenomethylpenams and 3-halogenocephams using ^{13}C and ^1H NMR spectroscopy are presented in the following communication, since they could not simply be distinguished. See, K. Tori, T. Tsushima, Y. Tamura, H. Shigemoto, H. Ishitobi, T. Tsuji, and H. Tanida, the following paper. After completing the assignment, however, a simple method for diagnosing the structure of such a chloride as above by ^1H NMR could be derived as follows: 3-H of a penicillin ester is deshielded by about +0.1 and +0.5 ppm by its respective change

into a 2α- and 2β-chloro-substituted derivative (see the Table); if it is a cepham derivative, the ^2J value for geminal CH_2 should be ca. 14.5 Hz (^2J for CH_2Cl should be ca. 12 Hz).[6]

(7) S. Kukolja and S. R. Lammert, J. Amer. Chem. Soc. 94, 7169 (1972).

(8) S. Kukolja, S. R. Lammert, M. R. Gleissner and A. I. Ellis, Ibid. 97, 3192 (1975).

(9) X-ray analyses by Dr. H. Koyama and coworkers of this laboratory unequivocally proved the structures of 7 and 8, for which we thank them.

(10) R. D. G. Cooper, P. V. Demarco and D. O. Spry, J. Amer. Chem. Soc. 91, 1528 (1969).