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The Conversion of Penicillin *S*-Oxides into Cephalosporin *S*-Oxides

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Synopsis. The reaction of penicillin *S*-oxides (**1a,b**) with *N*-bromosuccinimide afforded sulfinyl bromides (**2a,b**) in high yields. The bromides were converted into cephalosporin *S*-oxides (**4a**, **4b**, **6a**, and **7a**) in fairly good yields.

It is well known that sulfenic acid is generated by a thermal sigmatropic rearrangement of penicillin *S*-oxide. The highly reactive sulfenic acid has been trapped by several methods.[1,2] We have also investigated a method for trapping sulfenic acid with the objective of the preparation of a useful intermediate for the synthesis of cephalosporin analogues. In this paper the reaction of penicillin *S*-oxides with *N*-bromosuccinimide (NBS) is described and a few examples of the conversion of the produced sulfinyl bromides into cephalosporin *S*-oxides are noted.

The reaction of methyl 6-phthalimidopenicillinate 1-oxide (**1a**) with 1 equivalent of NBS in boiling CCl_4 afforded sulfinyl bromide (**2a**) in high yield. The NMR spectrum of **2a** resembles closely that of the corresponding sulfinyl chloride, prepared by the reaction of **1a** with sulfuryl chloride according to the method of Kukolja *et al.*[3] The structural assignment of **2a** is also supported by the reaction of **2** with aniline; readily reacted with 2 equivalents of aniline to give sulfinamide (**3a**).

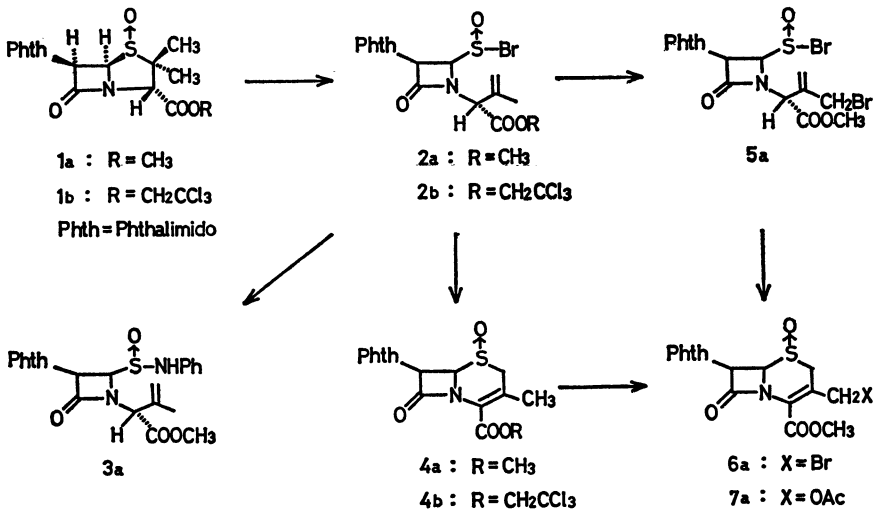
A noteworthy fact is that **2a** was successfully converted into cephem *S*-oxide by the action of 1 equivalent of tertiary amine. When **2a** was treated with triethylamine in CCl_4, the ring-closed product **4a** was obtained in 47% yield. In a similar manner, trichloroethyl ester *S*-oxide (**1b**) was transformed into the corresponding cephem *S*-oxide (**4b**).

In connection with the above results, we examined the preparation of 3-bromomethyl cephem *S*-oxide (**6a**) and 3-acetoxymethyl cephem *S*-oxide (**7a**). The reaction of **2a** with NBS in the presence of benzoyl peroxide (BPO) in boiling CCl_4 provided **5a** (not isolated), which, on subsequent treatment with triethylamine, gave **6a** in 33% yield. The direct bromination of **4a** with excess NBS in the presence of BPO in boiling benzene also afforded **6a**. The bromide **6a** was then acetoxylated by the action of AgOAc in AcOH to give **7a** in 45% yield.

Experimental

Preparation of Methyl 3-Methyl-2-(2-bromosulfinyl-4-oxo-3-phthalimido-1-azetidinyl)-3-butenoate (2a). A mixture of methyl 6-phthalimidopenicillinate 1-oxide (**1a**) (376 mg, 1 mmol) and NBS (178 mg, 1 mmol) in 15 ml of CCl_4 was refluxed for 1.5 hr under N_2. The precipitated succinimide was removed by filtration and the filtrate was evaporated to afford a yellow amorphous solid. This product was found from its NMR spectrum to be a 2 : 1 mixture of the two diastereomers of the compound **2a** which were epimeric at sulfur.[4] Yield, 442 mg (97%). NMR ($CDCl_3$): major component, δ 1.96 (3H, br. s), 3.84 (3H, s), 5.03 (2H, br. s), 5.20 (1H, br. s), 5.85 (1H, d, J=5 Hz), 6.08 (1H, d, J=5 Hz), 7.83 (4H, m); minor component, δ 2.00 (3H, br. s), 3.84 (3H, s), 4.90 (2H, br. s), 5.12 (1H, br. s), 5.82 (1H, d, J=5 Hz), 6.08 (1H, d, J=5 Hz), 7.83 (4H, m).

Reaction of 2a with Anilline. Into the solution of **2a** in CCl_4, prepared from 1 mmol of **1a** by the above procedure, anilline (232 mg, 2.5 mmol) was added with stirring at 0 °C. The mixture was then diluted with CH_2Cl_2, washed with water, and dried ($MgSO_4$). The evaporated residue was purified by silica gel chromatography using C_6H_6–AcOEt (2 : 1) as the eluent to give the pale yellow amorphous solid of methyl 3-methyl-2-(2-anilinosulfinyl-4-oxo-3-phthalimido-1-azetidinyl)-3-butenoate (**3a**) (389 mg, 83% yield). Softening point 100—120 °C. UV (EtOH): λ_{max} 207 nm (ε 40700), 221 (50400), and 290 (2400). IR (KBr): 1790 (β-lactam) and 1065 cm^{-1} (S=O). NMR ($CDCl_3$): δ 1.92 (3H, br. s),



3.59 (3H, s), 4.73 (1H, br. s), 4.82 (1H, br. s), 5.02 (1H, br. s), 5.86 (1H, d, J=5 Hz), 6.29 (1H, d, J=5 Hz), 6.80 (5H, m), 7.63 (1H, s), 7.81 (4H, m). Found: C, 59.21; H, 4.67; N, 8.52%. Calcd for $C_{23}H_{21}N_3O_6S$: C, 59.09; H, 4.53; N, 8.99%.

*Reaction of **2a** with Triethylamine.* Into the solution of **2a** in CCl_4, prepared from 1 mmol of **1a** by the above procedure, triethylamine (120 mg, 1.2 mmol) was added at 0 °C. After stirring for 20 min, the mixture was diluted with CH_2Cl_2, washed with water, and dried ($MgSO_4$). The evaporated residue was chromatographed on silica gel using AcOEt as the eluent to afford methyl 3-methyl-7-phthalimido-3-cephem-4-carboxylate 1-oxide (**4a**) (175 mg, 47% yield); mp 212—214 °C (dec) (from MeOH) (lit,[3] 215 °C (dec)). UV (EtOH): λ_{max} 221 nm (ε 40700) and 264 (4900). IR (KBr): 1795 (β-lactam) and 1055 cm^{-1} (S=O). NMR ($CDCl_3$): δ 2.35 (3H, s), 3.49 (1H, d, J=16 Hz), 3.84 (3H, s), 4.13 (1H, d, J=16 Hz), 4.65 (1H, d, J=5 Hz), 6.03 (1H, d, J=5 Hz), 7.79 (4H, m). Found: C, 54.34; H, 3.75; N, 7.37%. Calcd for $C_{17}H_{14}N_2SO_6$: C, 54.54; H, 3.77; N, 7.48%.

*Preparation of Trichloroethyl 3-Methyl-7-phthalimido-3-cephem-4-carboxylate 1-Oxide (**4b**).* In a procedure similar to that described above, **4b** was obtained in 54% yield. Mp 200—202 °C (dec) (from MeOH). UV (EtOH): λ_{max} 221 nm (ε 50900) and 271 (5700). IR (KBr): 1800 (β-lactam) and 1055 cm^{-1} (S=O). NMR ($CDCl_3$): δ 2.44 (3H, s), 3.67 (1H, d, J=16 Hz), 4.19 (1H, d, J=16 Hz), 4.68 (1H, d, J=5 Hz), 4.90 (2H, s) 6.07 (1H, d, J=5 Hz), 7.81 (4H, m). Found: C, 44.20; H, 2.72; N, 5.97%. Calcd for $C_{18}H_{13}N_2O_6SCl_3$: C, 43.96; H, 2.66; N, 5.70%.

*Preparation of Methyl 3-Bromomethyl-7-phthalimido-3-cephem-4-carboxylate 1-Oxide (**6a**).* *Method A*: A mixture of **1a** (3.76 g, 10 mmol) and NBS (1.78 g, 10 mmol) in 150 ml of CCl_4 was heated at refluxing temperature for 1.5 hr under N_2. After cooling to room temperature, NBS (2.67 g, 15 mmol) and BPO (300 mg) were added and the mixture was refluxed for 3 hr under N_2. The reaction mixture was then chilled in an ice bath, and triethylamine (1.50 g, 15 mmol) was added. After stirring for 20 min, the mixture was diluted with CH_2Cl_2, washed with water, and dried ($MgSO_4$). The evaporated residue was purified repeatedly by chromotography on silica gel using C_6H_6-AcOEt (2 : 1) as the eluent to give the amorphous solid of **6a** (1.40 g, 33% yield). Softening point 130—140 °C. UV (EtOH): λ_{max} 221 nm (ε 43200) and 278 (8500). IR (KBr): 1800 (β-lactam) and 1045 cm^{-1} (S=O). NMR ($CDCl_3$): δ 3.68 (1H, d, J=16 Hz), 3.92 (3H, s), 4.23 (1H, d, J=16 Hz), 4.55 (2H, s), 4.73 (1H, d, J=5 Hz), 6.08 (1H, d, J=5 Hz), 7.85 (4H, m). Found: C, 45.29; H, 2.94; N, 6.26%. Calcd for $C_{17}H_{13}N_2O_6SBr$: C, 45.05; H, 2.89; N, 6.18%.

Method B: A solution of **4a** (374 mg, 1 mmol), NBS (445 mg, 2.5 mmol), and BPO (50 mg) in 20 ml of benzene was refluxed for 3 hr. The reaction mixture was worked up in a similar procedure to that described above to give **6a** (80 mg, 18% yield).

*Preparation of Methyl 3-Acetoxymethyl-7-phthalimido-3-cephem-4-carboxylate 1-Oxide (**7a**).* To a solution of **6a** (453 mg, 1 mmol) in 4 ml of AcOH, a suspension of AgOAc (200 mg, 1.2 mmol) in 4 ml of AcOH was added with stirring; the stirring was continued for 1 hr. The reaction mixture was filtered to remove the silver salts, and the filtrate was diluted with AcOEt. The solution was then washed successively with water, 3% $NaHCO_3$, and water. After drying over $MgSO_4$, the solvent was evaporated and the residue was purified by chromatography on silica gel using C_6H_6-AcOEt (1 : 1) as the eluent to give the colorless amorphous solid of **8a** (178 mg, 45% yield). Softening point 105—125 °C. UV (EtOH): λ_{max} 221 nm (ε 45100) and 267 (5600). IR (KBr): 1800 (β-lactam) and 1045 cm^{-1} (S=O). NMR ($CDCl_3$): δ 2.10 (3H, s), 3.58 (1H, d, J=16 Hz), 3.89 (3H, s), 4.14 (1H, d, J=16 Hz), 4.68 (1H, d, J=5 Hz), 4.91 (1H, d, J=14 Hz), 5.79 (1H, d, J=14 Hz), 6.06 (1H, d, J=5 Hz), 7.82 (4H, m). Found: C, 52.92; H, 3.77; N, 6.46%. Calcd for $C_{19}H_{16}N_2O_8S$: C, 52.77; H, 3.73; N, 6.48%.

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3) S. Kukolja and S. R. Lammert, *Angew. Chem.*, **85**, 40 (1973); *Angew Chem. Int. Ed., Engl.* **12**, 67 (1973).

4) The reaction of **1a** with 1 equivalent of *N*-chlorosuccinimide in boiling CCl_4 for 1.5 hr afforded the corresponding sulfinyl chloride in quantitative yield. The NMR spectrum of this product was completely superimposable on that of the chloride prepared from **1a** and SO_2Cl_2 according to the method described in Ref. 3). This result indicates that two diastereomers were produced in the same ratio (2 : 1) in both reactions.