New Rearrangement of Penicillin Sulfoxide

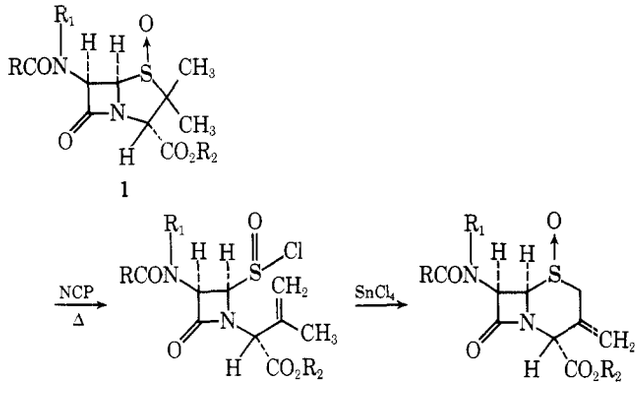
T. S. Chou,* W. A. Spitzer,* D. E. Dorman, S. Kukolja,
I. G. Wright, N. D. Jones, and M. O. Chaney

The Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46206

Received June 27, 1978

A new rearrangement resulting from cleavage of the S–C_5 bond of penicillin sulfoxide is reported. An episulfonium ion, D, is suggested as a possible intermediate. Both the six-membered ring products **4**, **5** and **6** and a five-membered ring compound, **7**, arise from the same intermediate D. Understanding the mechanism of the new rearrangement was an important step in learning how to control reaction conditions so that the desired S–C_2 cleavage reaction occurs with minimum contamination by the competing S–C_5 cleavage process.

The key intermediate in the conversion of penicillin sulfoxide **1** to *exo*-methylenecepham sulfoxide **3** is sulfinyl chloride **2**.[1] In a typical example, the synthesis of sulfinyl chloride **2** is carried out by reacting penicillin sulfoxide with *N*-chlorophthalimide (NCP) in refluxing toluene. Where R,R_1 is phthaloyl, the formation of sulfinyl chloride **2** is uneventful



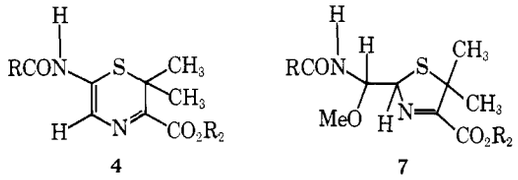
1 **2** **3**

R_2 = CH_3, *p*-NO_2PhCH_2-

and proceeds in high yield.[1] However, when R is an amide function (for example, phenoxyacetyl) and R_1 is H, a capricious side reaction often intervenes in which the reaction mixture rapidly turns dark with concomitant evolution of quantities of HCl gas. The frequency and rapidity of the side reaction increase dramatically with increasing reaction size and concentration. In the most striking examples, all of the penicillin sulfoxide is consumed in a few minutes, and two new yellow-colored products, **5** and **6**, are formed and comprise the majority of the reaction product.

Early in our investigation of this side reaction we noted that the ratio of **5** to **6** varied with time. It was subsequently demonstrated that when **5** was refluxed in toluene for a few hours, it was converted quantitatively to **6**. Furthermore, we found that trace amounts of acid greatly accelerated the conversion of penicillin sulfoxide **1** to **5** and **6** and that this side reaction could be minimized by carefully avoiding the introduction of acid and by using acid scavengers.[2]

An important clue to the mechanism of the reaction was provided by the observation that pencillin sulfoxide **1** reacts with NCP on standing in methylene chloride at room temperature (again the reaction is accelerated by the addition of acid). The product of this reaction was obtained as a yellow solid and identified as an HCl salt of compound **4**. It was crystallized from acetone as yellow needles, mp 148–150 °C.



4 **7**

R = $PhOCH_2$-; R_2 = *p*-NO_2PhCH_2-

Later, compound **4** was found to be a minor component of the crude reaction mixtures in which **5** and **6** were the major products, and compound **4** was subsequently isolated from these mixtures by silica gel chromatography. When the HCl salt of **4** was suspended in a toluene solution saturated with Cl_2 and heated to reflux, compounds **5** and **6** were formed, thus establishing an important link in the rearrangement.

When the HCl salt of **4** was dissolved in methanol at room temperature, the color was discharged and **7** was obtained in high yield as a white crystalline solid. Interestingly, **4** as the free imine did not react with methanol under similar conditions.

Compound **7** crystallized from methanol as white prisms, mp 119–120 °C. Elemental analysis and high-resolution mass measurements indicated a composition of $C_{23}H_{25}N_3O_7S$. Its proton NMR spectrum showed signals corresponding to an OCH_3 and an AMX system (–NH–CH(OCH_3)–CH–), in addition to the gem-dimethyl group, the phenoxyacetamido side chain, and the *p*-nitrobenzyl ester. The final structure was determined by ^{13}C NMR spectroscopy and NOE studies of the proton NMR spectrum, as well as by X-ray analysis as follows.

The unit cell of compound **7**, as determined by X-ray diffraction, contained four molecules and had the dimensions a = 23.154 (4) Å, b = 11.032 (2) Å, c = 9.659 (2) Å, and β = 98.88 (1)°, with the space group $P2_1/a$. The density calculated for $C_{23}H_{25}N_3O_7S$ was 1.328 g cm^{-3}, which was exactly the density determined by flotation. A total of 2681 reflections, of which 244 were considered unobserved, were measured on a four-angle automated diffractometer using monochromatic copper radiation. The structure was solved by phasing on the sulfur atom, located from an $E^2 - 1$ map, followed by refinement using the tangent formula. Further refinement by the the least-squares method, including anisotropic temperature factors for all heavy atoms and isotropic hydrogen atoms at assumed positions, gave a final R value of 0.068. The final heavy atom positional and thermal parameters (Table I) and the bond distances and angles (Table II) are included in the supplementary material. Figure 1 shows the extended conformation of the molecule.

The proton NMR spectrum of **4** indicated that the phenoxyacetamido side chain and the *p*-nitrobenzyl ester function were still intact; however, the proton signals corresponding to the AMX system in **7** were gone. Instead, a vinyl proton singlet at δ 7.52 and two exchangeable resonances at δ 11.0 (s, 1 H, amide NH) and ca. 11.3 (brd s of variable position) appeared. The upfield 6 H singlet at δ 1.44 indicated that the gem dimethyl groups were adjacent to a divalent sulfur such as in penicillins. In fact, examining the proton and ^{13}C spectra revealed that the partial structure shown below was

0022-3263/78/1943-3835$01.00/0

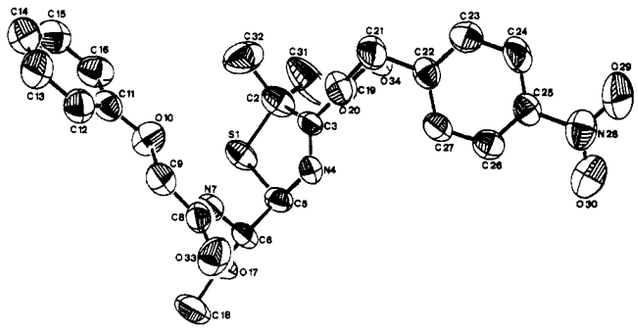
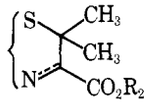
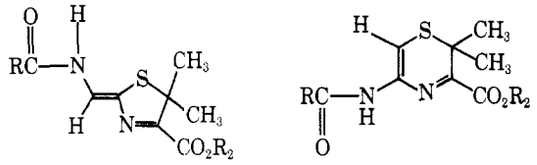


Figure 1. ORTEP drawing of 7.

present in all other products (4, 5, and 6) in this series. In view of this evidence, only two structures (I and II) in addition to structure 4 met the structural requirements.



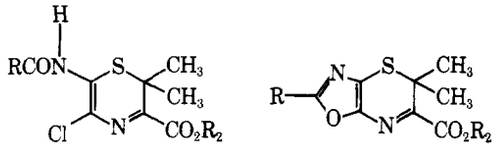
Of the two similar structures I and II, the latter seemed less probable since it would require N–C_5 cleavage rather than the more likely S–C_5 cleavage. We favored structure 4 of the two remaining alternatives. As described above, the proton NMR spectrum showed two discrete exchangeable proton resonances. This implies strongly that the exchange rate of the NH was quite slow. Thus, rapid chemical exchange cannot be invoked to explain an absence of vicinal coupling as in structure I. Therefore, the NH and the vinyl proton of 4 cannot be adjacent.



I II

R = $PhOCH_2$–; R_2 = p-NO_2PhCH_2–

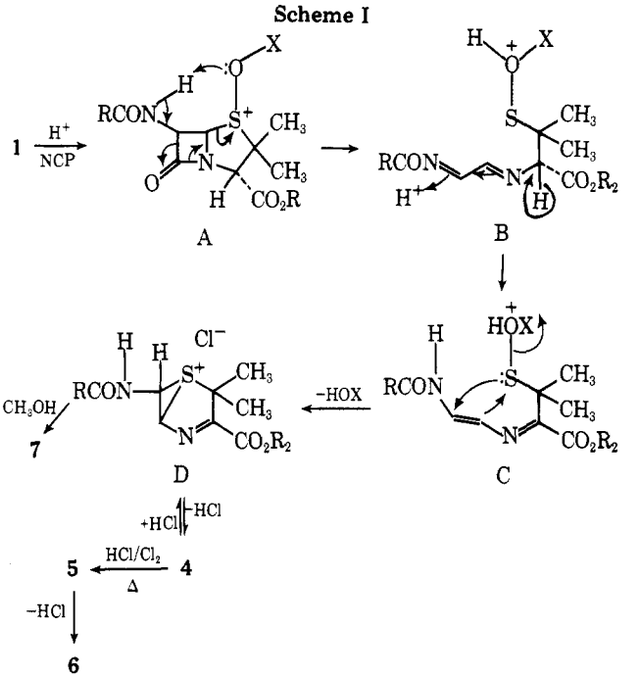
Having determined the structure of 4 and having established the link between 4, 5 and 6, their physical data were compared. Compounds 5 and 6 were readily separated and purified by silica gel column chromatography. Compound 5, isolated as a yellow oil, had a composition of $C_{22}H_{20}N_3O_6SCl$ as determined by elemental analysis and high-resolution mass measurement. Compound 6, crystallized from chloroform as yellow plates, mp 92–93 °C, had a composition of $C_{22}H_{19}N_3O_6S$, which amounted to the loss of HCl from 5. The proton NMR spectrum of 5 was almost identical with that of 4 except for the vinyl proton signal which was missing from 5. In addition, the following changes were observed in the NMR spectra of 5 and 6. The chemical shift of the methylene protons in the side chain showed a downfield shift from δ 4.59 in 5 to δ 5.16 in 6, and a similar change in the ^{13}C NMR spectra from δ 66.8 to 62.4 was observed. The carbonyl carbon of the side chain also shifted from δ 167.0 in 5 to δ 160.3 in 6. These changes are consistent with a change from a phenoxyacetamido side chain in 5 to $PhOCH_2$–C(O–)=N– in 6, and, therefore the following structures are proposed.



5 6

R = $PhOCH_2$–; R_2 = p-NO_2PhCH_2–

Scheme I



X = –Cl, $-COCH_2C_6H_5$, or $-SOC_6H_5R$ = $C_6H_5OCH_2$–;

R_2 = p-$NO_2C_6H_4CH_2$–

Based on the information in hand, we believe that the rearrangement occurs as outlined in Scheme I. First, NCP activated by a trace of acid reacts with penicillin sulfoxide 1 to form intermediate A, which suffers S–C_5 bond cleavage followed by loss of CO to give intermediate B. Elimination of a proton to give C is followed by ring enclosure to give episulfonium ion D. Loss of HCl from D gives compound 4. As described earlier, the HCl salt of 4 reacts with Cl_2 (generated in situ by the reaction of HCl and NCP) to give compound 5, which on heating loses HCl to give 6 as the final product.

The S–C_5 bond cleavage of penicillin sulfoxide followed by loss of CO and reclosure to a six-membered ring compound as outlined in Scheme I is not unprecedented. Thomas and Williams have demonstrated a similar reaction between penicillin sulfoxide and phenylacetyl chloride in the presence of aqueous acetone (in this example, ring enclosure to a six-membered ring bicyclic acetonide occurred).[3] Likewise, we found that both phenylsulfinyl chloride and phenylacetyl chloride reacted rapidly at room temperature with penicillin sulfoxide ester 1 to give the HCl salt of 4 in a manner entirely analogous to the reaction with NCP.

It is possible that the HCl salt of 4 reacts with methanol via intermediate D to give compound 7.[4] Evidence that an episulfonium ion such as D may intervene is obtained when the reaction is carried out in deuterated methanol (MeOD). Exclusive incorporation of deuterium occurs in compound 7 at the carbon bearing the methoxy function. This result excludes a five-membered ring intermediate I as a possible precursor.

Our results indicate that the S–C_5 bond cleavage is a major (yet relatively unexplored) rearrangement pathway of penicillin sulfoxide. In addition, the unusual rearrangements which ensue offer further testimony to the wealth of chemistry which resides in the pencillin molecule.

Experimental Section

Proton NMR spectra were determined with a Varian HA-100 spectrometer and ^{13}C NMR spectra with a Jeol PFT-100 spectrometer. All solvents were spectrophotometric grade. Melting points were measured using a Thomas-Hoover capillary melting point apparatus and were uncorrected.

General Procedure for the Preparation of 4. The *p*-nitrobenzyl ester of penicillinV sulfoxide (1; R = $PhOCH_2$–, R_2 = *p*-NO_2PhCH_2–) (10 g, 20 mmol) and *N*-chlorophthalimide (4 g, 22 mmol) were mixed in 50 mL of unstabilized methylene chloride, and the suspension was stirred at room temperature until the starting materials dissolved and yellow-colored precipitate formed (about 5–6 h). The yellow precipitate was filtered, suspended in 30 mL of acetone (1 h), and filtered again to remove the soluble phthalimide. Treatment with acetone gave yellow needle-like crystals, mp 148–150 °C, in high yield. Elemental analysis showed a composition of $C_{22}H_{21}N_3O_6S$·HCl, and 7% of chlorine was free chloride. Its proton NMR spectrum showed the following signals: (Me_2SO–d_6, 100 MHz) δ 1.44 (s, 6 H, dimethyl), 4.73 (s, 2 H, $-CH_2$–OPh), 5.42 (s, 2 H, $-CH_2$–Ph-*p*-NO_2), 6.9–8.3 (9 H, characteristic of the phenoxyacetyl and *p*-nitrobenzyl aromatic protons), 7.52 (s, 1 H, vinyl proton), and exchangeable resonances at δ 11.0 (s, 1 H, amide NH) and ca. 11.3 (brd s of variable position, 1 H, apparently HCl). Irradiation of the CH_2 group of $-CH_2$–OPh led to an NOE (7%) at one of the exchangeable proton resonances, and irradiation of the above exchangeable proton resonances led to a 13% NOE in the vinyl proton resonance. The ^{13}C NMR (Me_2SO-d_6) spectrum indicated the presence of 2 CH_3 (δ 23.4), 4 carbons of the dihydrothiazine ring (δ 38.6, 120.1, 128.8, and 143.3), and 2 ester carbons (δ 162.8 and 166.9).

General Procedure for the Preparation of 5 and 6. The *p*-nitrobenzyl ester of pencillinV sulfoxide (1; 25 g, 50 mmol) and *N*-chlorosuccinimide (10 g, 67 mmol) were heated to reflux for 20 min in 250 mL of 1,1,2-trichloroethane. At this time, the reaction mixture was very dark and no starting material remained by TLC. A large quantity of HCl gas can be seen (NH_4OH) evolving from the condenser. The reaction mixture was extracted three times with 500 mL of saturated NaCl solution and dried ($MgSO_4$), and the solvent was removed by rotary vacuum evaporation. Thin-layer chromatography showed that the mixture was mostly compound **5**, and it was isolated by column chromatography (750 g of silica gel eluted with 40% ethyl acetate–hexane). Heating **5** in toluene for ca. 3 h gave **6** in high yield.

Alternately, instead of isolating **5**, the crude reaction mixture from above was redissolved in toluene and refluxed overnight. Purification was carried out by column chromatography as before to give compound **6** as a gum which can be crystallized by the addition of a small amount of chloroform.

Compound **5**, isolated as a yellow oil, analyzed for $C_{22}H_{20}N_3O_6SCl$, and FDMS showed a molecular ion at *m/e* 489. Its proton NMR spectrum showed the following signals: ($CDCl_3$, 60 MHz) δ 1.56 (s, 6 H, dimethyl), 4.59 (s, 2 H, $-CH_2$–OPh), 5.38 (s, 2 H, $-CH_2$–Ph*p*-NO_2), and 6.9–8.3 (9 H, characteristic of phenoxyacetyl and *p*-nitrobenzyl aromatic protons). The ^{13}C NMR spectrum (Me_2SO-d_6) indicated the presence of 2 CH_3 (δ 23.6), 4 carbons on the dihydrothiazine ring (δ 40.6, 119.5, 123.6, and 146.1), and 2 ester carbons (δ 161.9 and 167.0).

Compound **6**, crystallized from $CHCl_3$ as yellow plates, mp 92–93 °C, analyzed for $C_{22}H_{19}N_3O_6S$, and FDMS showed a molecular ion at *m/e* 453. Its proton NMR spectrum showed the following signals: ($CDCl_3$, 100 MHz) δ 1.66 (s, 6 H, dimethyl), 5.16 (s, 2 H, $-CH_2$–OPh), 5.40 (s, 2 H, $-CH_2$–Ph-*p*-NO_2), and 6.9–8.3 (9 H, characteristic of the phenoxyacetyl and *p*-nitrobenzyl aromatic protons). The ^{13}C NMR spectrum (Me_2SO-d_6) indicated the presence of 2 CH_3 (δ 25.5), 4 carbons on the thiazine ring (δ 44.9, 127.3, 145.3, and 148.4), 1 carbon on the oxazole ring (δ 160.3), and 1 ester carbon (δ 162.3).

Conversion of Compound 4 to 7. The thiazine derivative **4** (2 g) was dissolved in methanol (10 mL), and if a small amount of phthalimide remained it was removed by filtration. Gradually the yellow color of the filtrate disappeared, and colorless crystals formed in high yield. The product was filtered off and dried to give tetrahydrothiazoline **7** as white prisms, mp 119–120 °C, microanalyzed for $C_{23}H_{25}N_3O_7S$, and FDMS showed a molecular ion at *m/e* 487 and also *m/e* 293 and 194, corresponding to the fragments cleaved between the carbon holding OCH_3 and the thiazine ring. Its proton NMR spectrum showed the following signals: (Me_2SO, 100 MHz) δ 1.64 (s, 6 H, dimethyl), 3.26 (s, 3 H, $-OCH_3$), 4.58 (s, 2 H, $-CH_2OPh$), 5.44 (s, 2 H, $-CH_2$–Ph-*p*-NO_2), 5.41 (dd, *J* = 9.5 and 4.5 Hz, 1 H, –CH–OCH_3), 6.02 (d, *J* = 4.5 Hz, 1 H, –CH–S), 8.04 (d, *J* = 9.5 Hz, 1 H, –NH), and 6.8–8.3 (9 H, characteristic of phenoxacetyl and *p*-nitrobenzyl aromatic protons). Irradiation of the CH_2 group of the phenoxyacetamido side chain and the *p*-nitrobenzyl ester function led to sharpening of the ortho protons of the respective aromatic rings. However, irradiation of the protons of the OCH_3 group leads to no NOE anywhere in the AMX system, indicating a confirmation which maintains the OCH_3 group distant from the AMX protons. The ^{13}C NMR spectrum showed 2 CH_3 (δ 29.1 and 29.6), 1 Me_2C– (δ 64.1), 1 –C(N)H–S (δ 80.8), 1 C(OMe)H–N ((Me_2SO-d_6) δ 80.3), 1 OCH_3 (δ 161.0), and 2 ester carbons (δ 168.6 and 168.4).

Reaction of 1 with Benzenesulfinyl Chloride. To a suspension of 20 g of **1** in 300 mL of acetone was added 10 mL of benzenesulfinyl chloride. After stirring for 30 min, all of the solid material had dissolved and shortly afterwards a yellow product started to precipitate. Stirring at room temperature was continued for a total of 2 h, and 6.2 g of yellow crystalline product was filtered off. The crystals (650 mg) were recrystallized from 50 mL of boiling acetonitrile. Next morning tiny needles of the HCl salt of **4**, mp 148–150 °C, were collected. Anal. Calcd for $C_{22}H_{22}N_3O_6SCl$: C, 53.82; H, 4.31; N, 8.56; S, 6.53; Cl, 7.22. Found: C, 54.05; H, 4.56; N, 8.69; S, 6.76; Cl, 6.88.

Acknowledgment. The authors wish to thank J. L. Occolowitz for the mass spectra analysis and J. W. Paschal and T. K. Elzey for NMR measurements. We express our appreciation to Professor J. E. Baldwin for useful discussions during the course of this work.

Registry No.—1 (R = $PhOCH_2$–; R_2 = *p*-NO_2PhCH_2–), 29707-62-8; **4**, 67194-57-4; **4** HCl, 67194-58-5; **5**, 67194-59-6; **6**, 67194-60-9; **7**, 67194-61-0.

Supplementary Material Available: Tables I and II of atomic parameters and bond distances and angles for **7** (4 pages). Ordering information is given on any current masthead page.

References and Notes

(1) S. Kukolja, S. R. Lammert, M. R. Gleissner, and A. I. Ellis, *J. Am. Chem. Soc.*, **98**, 5040 (1976); S. Kukolja, *Chem. Soc., Spec. Publ.*, No. **28**, 181 (1977).
(2) Acid scavengers such as propylene oxide greatly improve the yield of the desired sulfinyl chloride: S. Kukolja, Belgium Patent 837 040, 1976.
(3) R. Thomas and D. J. Williams, *J. Chem. Soc., Chem. Commun.*, 226 (1973).
(4) An alternate mechanism would involve the addition of methanol to the protonated enol ester of compound **4** followed by rearrangement to the observed five-membered ring product **7**.