Regiospecific Thermolysis of Two Diastereomeric β-Lactam Sulfoxides

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(3*R*,4*R*,5*R*)-4-[[2-(methoxycarbonyl)ethyl]sulfinyl]-3-phthalimido-2-azetidinone (**5b**) and its epimeric (*S*)-oxide **5c** were prepared, and their absolute chirality at the sulfur atom was determined by X-ray crystallographic analysis. The regiospecificity of the thermolysis of each of the two sulfoxides was deduced from analyzing the adducts of their primary thermolytic products and 2-mercaptobenzothiazole. the difference in the reaction patterns of the two isomers is rationalized on the grounds of differences in steric nonbonding intramolecular compression in two alternative conceivable transition states.

β-Lactam sulfoxides are useful intermediate compounds in the synthesis of β-lactam antibiotics and nuclear analogues thereof.[1] In a previous paper from this laboratory[2] the thermal rearrangement of the 4-[[2-(methoxycarbonyl)ethyl]sulfinyl]-2-azetidinone (**1**; Chart I) and similar compounds to 4-thioxo-2-azetidinones like **3** was described. This transformation, which involves, in the first step, the fragmentation of the sulfoxide into a sulfenic acid (**2**) and methyl acrylate, occurred with both diastereomeric sulfoxides **1**. We now describe the thermolysis of the two diastereoisomeric β-lactam sulfoxides **5b** and **5c** which are unsubstituted at position 1.

The starting material for the preparation of these compounds was the β-lactam **1**, which was obtained from penicillin sulfoxide as a 2:1 mixture of two diastereoisomers.[2] To unmask the nitrogen atom of the β-lactam, compounds **1** were ozonized (in methylene dichloride at −78 °C), and the methoxyalyl derivatives **4** thus formed were subjected, without purification, to methanolysis (methanol–methyl acetate at ambient temperature).[3] By this procedure, which does not affect any of the chiral centers, a mixture of two diastereoisomeric β-lactams of **5a** was obtained with approximately the same ratio as in the starting material. Chromatography of this mixture afforded 61% of the major isomer and 27% of the minor isomer. Since the nature of the thermolysis of sulfoxides depends, inter alia, upon the chirality at the sulfur atom,[4] it was necessary to determine its absolute configuration in each one of the two diastereoisomers **5a**. These compounds were obtained in an amorphous form unsuitable for a direct X-ray crystallographic analysis. Therefore, the analysis was undertaken on the minor isomer of the precursor **1**, which was available in a crystalline form.[2] The postulate that the major and minor isomers of **5a** derive respectively from the major and minor isomers of **1** was corroborated by deprotection of two separated isomerically pure samples of **1**.

Crystal data for the minor isomer of **1** (mp 128–130 °C; $[\alpha]^{26}_D$ +30.3°) are given in the Experimental Section. A stereoscopic view of the molecule is shown in Figure 1. The crystallographic analysis indicates that the sulfur atom is in the opposite configuration to that of the C-3 and C-4 β-lactam atoms. The absolute configuration of these two centers is *R*, as in the corresponding positions in the natural penicillin[5] from which compound **1** was obtained;[2] therefore,the sulfur atom must be of the *S* configuration. On this ground, structure **5b** with the *R* configuration at sulfur, and structure **5c**, with the *S* configuration at sulfur, were assigned, respectively, to the major and minor isomers of **5a**.

Chart I

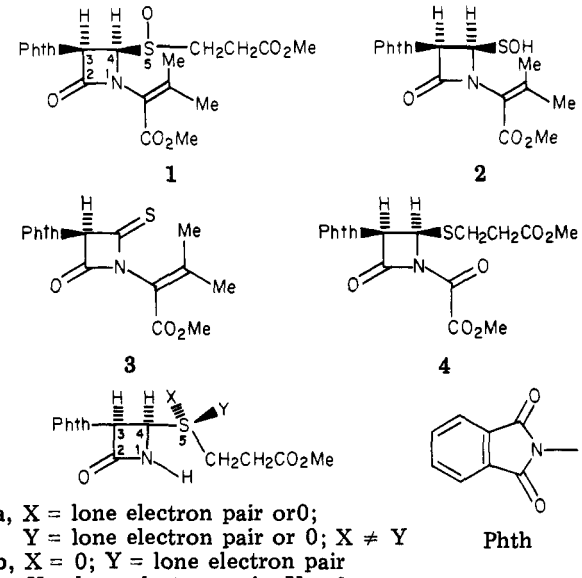
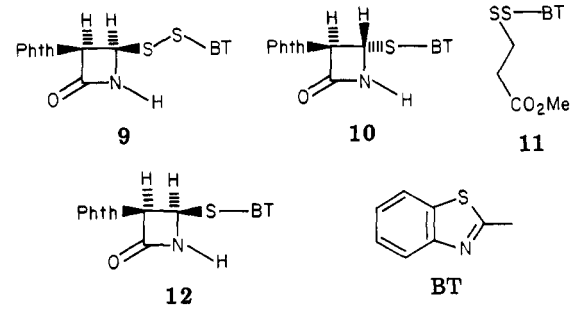
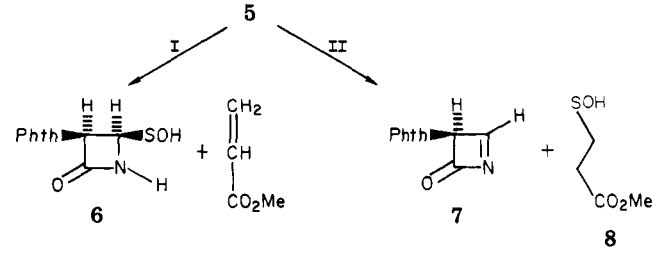


Chart II



Scheme I



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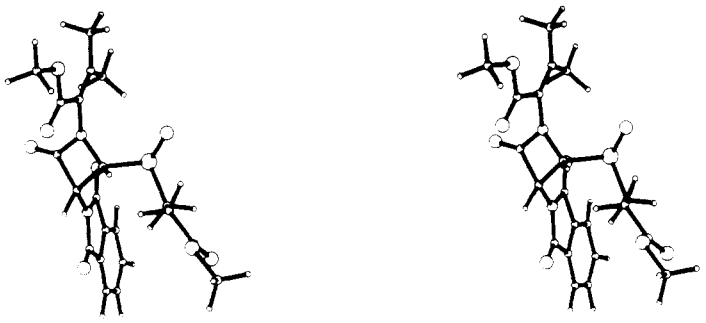

Figure 1. Stereoscopic drawing of (3*R*,4*R*,5*S*)-4-[[2-(methoxycarbonyl)ethyl]sulfinyl]-1-[1-(methoxycarbonyl)-2-methylprop-1-enyl]-3-phthalimido-2-azetidinone.

It is conceivable that the thermolysis of the sulfoxides **5** may proceed through syn elimination, either via path I (Scheme I) to give the sulfenic acid **6** and methyl acrylate or via path II to generate the azetinone **7** and the sulfenic acid **8**.[6] In order to investigate the regiospecificity of the dehydrosulfenylation, we performed the thermolysis in the presence of 2-mercaptobenzothiazole. This mercaptan was considered to be a suitable trapping agent for all three of the expected reactive primary reaction products, **6**–**8**.[7-9]

Heating the (*R*)-sulfoxide **5b** with 2 equiv. of 2-mercaptobenzothiazole in refluxing chloroform afforded, as the major product, the disulfide **9** (62%) which was accompanied by the *trans*-azetidinone **10** (31%) and the disulfide **11** (35%) (Chart II). When the (*S*)-sulfoxide **5c** was treated with 2-mercaptobenzothiazole under the same conditions, different results were observed. While none of the disulfide **9** was detected, the *trans*-azetidinone **10** became the major lactamic product (71%); it was accompanied by its cis isomer **12** (*ca.* 10%) and the disulfide **11** (86%). This distribution of products indicates that the thermolysis of the (*R*)-sulfoxide **5b** proceeded through both pathways I and II with a considerable preference to the former, while thermolysis of the (*S*)-sulfoxide **5c** proceeded exclusively through path II. The addition of 2-mercaptobenzothiazole to the azetinone **7** resulted in a mixture of trans β-lactam **10** and its cis isomer **12**, but the latter isomerized to the former on storage at room temperature. Condensation of the sulfenic acids **6** and **8** with 2-mercaptobenzothiazole afforded, respectively, the disulfides **9** and **11**.

The syn cycloelimination of a sulfenic acid on thermolysis of sulfoxides bearing one or more hydrogen substituents at a β-carbon atom is markedly enhanced as the acidity of the migrating hydrogen atom is increased.[10,11]

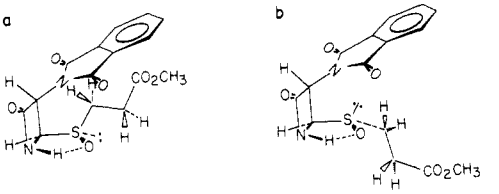

Figure 2. Transition state for the elimination of 8 from **5b** (a) and from **5c** (b).

It might, therefore, have been reasonable to expect that the thermolysis of the sulfoxides **5b** and **5c** would proceed exclusively through path II, involving the migration of the hydrogen atom linked to the nitrogen atom which is the most acidic. While this transformation indeed occurred on thermolysis of the (*S*)-sulfoxide **5c**, the β elimination of a sulfenic acid from the epimeric (*R*)-sulfoxide **5b** proceeded preferentially through path I, involving the extraction of a more strongly bonded hydrogen atom. The dependance of the regiospecificity of the thermal elimination on the chirality of the sulfur atom is rationalized in terms of differences in steric interaction in the cyclic transition state. The concerted electrocyclic syn elimination of the sulfenic acid **8**, which involves the extraction of the more acidic N-1 hydrogen atom, requires a planar disposition of all the participating atoms, as shown in Figure 2. While in the case of the (*S*)-sulfoxide (Figure 2b), all the substituents which do not participate in the reaction can be accommodated in a conformation devoid of any appreciable nonbonding interaction, in the case of the (*R*)-sulfoxide (Figure 2a), repulsion between a methylene group and the phthalimido group is taking place. This steric hindrance causes an increase in the energy level of the transition state to such a degree that the competitive elimination through path I, which is not involved with any appreciable nonbonding intramolecular compression, becomes favorable. The thermolysis of the sulfoxides **5b** and **5c** were thus found to be highly regiospecific, the direction of dehydrosulfenylation being determined by the chirality of the sulfoxide. a similar phenomenon was observed in the pyrolysis of certain methylsulfinyl steroids.[4]

Experimental Section

IR spectra were recorded with a Perkin-Elmer 237 spectrophotometer. Proton NMR data were determined on a 90-MHz Bruker FT-HFX-10 or a 60-MHz Varian A-60 instrument. Low- and high-resolution mass spectra were recorded on a Varian MAT-731 (double focusing) spectrometer. Optical rotations were measured with a Perkin-Elmer 141 polarimeter. Melting points were measured using a Büchi apparatus and are uncorrected. Reactions were performed in dry solvents under argon. Chro-

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matographies were carried out on columns with Merck silica gel 60 (70–230 mesh).

Preparation of the Two Diastereomeric Sulfoxides 1. The sulfoxide 1 was obtained as a 2:1 mixture of two isomers from methyl 6-phthalimidopenicillanate 1-oxide as previously described.[2] Chromatography of the mixture afforded the major isomer of 1 [less polar; mp 135–136 °C (from CH_2Cl_2–hexane); $[\alpha]^{26}_D$ +77.3° (*c* 1.0, $CHCl_3$)] followed by the minor isomer of 1: more polar; mp 128–130 °C (from CH_2Cl_2–hexane); $[\alpha]^{26}_D$ +30.3° (*c* 1.0, $CHCl_3$). For full characterization see ref 2. On the basis of the X-ray diffraction analysis (see the next section and Figure 1) and the known absolute configurations at the C-3 and C-4 β-lactam atoms,[2] the minor isomer of 1 was assigned as (3*R*,4*R*,5*S*)-4-[[2-(methoxycarbonyl)ethyl]sulfinyl]-1-[1-(methoxycarbonyl)-2-methylprop-1-enyl]-3-phthalimido-2-azetidinone.

X-ray Diffraction Analysis of (3*R*,4*R*,5*S*)-4-[[2-(Methoxycarbonyl)ethyl]sulfinyl]-1-[1-(methoxycarbonyl)-2-methylprop-1-enyl]-3-phthalimido-2-azetidinone. Single crystals of the title compound were orthorombic, space group $P2_12_12_1$, with a = 10.745 (3) Å, b = 13.874 (3) Å, c = 14.934 (2) Å, d_{calcd} = 1.38 g cm^{-3}, and d_{meas} = 1.375 g cm^{-3} for Z = 4 ($C_{21}H_{22}N_2O_8S$, M_r = 462.40). The intensity data were collected on a computer-controlled Enraf-Nonius CAD-4 diffractometer, with graphite-monochromated Mo Kα radiation, by using a crystal of 0.1 × 0.2 × 0.4 mm dimensions. The integrated intensities of 2771 reflections ($\theta < 27°$) were processed in the usual way, yielding 2500 reflections with $F_o > 3\sigma(F_o)$. The structure was solved by direct methods[12] and refined by the full-matrix least-squares procedure.[13] All nonhydrogen atoms were refined anisotropically, and the positions of all hydrogen atoms were calculated and constrained to a reasonable geometry. The final discrepancy indices are R = 0.09 and R_w = 0.07. The final difference map shows only randomly distributed peaks (maximum of 0.3 e Å^{-3}).[14]

(3*R*,4*R*,5*R*)-4-[[2-(Methoxycarbonyl)ethyl]sulfinyl]-3-phthalimido-2-azetidinone (5b) and Its Epimeric (*S*)-Oxide 5c. Ozone was passed through a solution of a 2:1 mixture, respectively, of the (*R*)- and the (*S*)-sulfoxides 1[2] (3.0 g, 6.5 mmol) in CH_2Cl_2 (250 mL) at −78 °C until the solution was permeated by a deep blue color. Excess ozone was removed by a stream of nitrogen. The reaction mixture was washed with cold aquous 3% $NaHSO_3$ and brine, dried, and evaporated. The crude residue which contained the methoxalyl derivatives 4[3] was dissolved in a mixture of ethyl acetate (90 mL), methanol (270 mL), and water (0.6 mL) and left at room temperature for 20 h. The solvent was evaporated, and the residue was chromatographed on silica gel (ethyl acetate) to afford the following. (a) The (*R*)-sulfoxide **5b**: 1.38 g (61%); colorless foam; $[\alpha]^{26}_D$ +9.1° (*c* 0.9, $CHCl_3$); IR ($CHCl_3$) 3410, 1805, 1775, 1735 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 2.95–2.84 and 3.22–3.14 (2 m, $S(O)CH_2CH_2CO_2$), 3.68 (s, OMe), 4.79 (d, J = 4.7 Hz, 4-H), 5.85 (dd, J = 4.7, 1.2 Hz, 3-H), 7.83 (m, Phth), 8.08 (br, NH). Anal. Calcd for $C_{15}H_{14}N_2O_6S$: C, 51.43; H, 4.03; N, 8.00; S, 9.14. Found: C, 51.45; H, 4.12; N, 8.23; S, 9.55. (b) The (*S*)-sulfoxide **5c**: 613 mg (27%); colorless foam; $[\alpha]^{26}_D$ +37.7° (*c* 0.9, $CHCl_3$); IR ($CHCl_3$) 3410, 1805, 1775, 1735 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 2.8–3.0 (m, $S(O)CH_2CH_2CO_2$), 3.42 (s, OMe), 5.01 (d, J = 5.0 Hz, 4-H), 5.69 (d, J = 5 Hz, 3-H), 7.82 (m, Phth), 8.33 (br, NH); mass spectrum, m/e 214 (M^+ − $HOSCH_2CH_2CO_2CH_3$). Anal. Calcd for $C_{15}H_{14}N_2O_6S$: C, 51.43; H, 4.03; N, 8.00; S, 9.14. Found: C, 51.22; H, 4.09; N, 8.25; S, 9.29.

Authentic samples of **5b** and **5c** were obtained, respectively, from pure samples of the (*R*)-sulfoxide 1 and (*S*)-sulfoxide 1.

Thermolysis of the (*R*)-Sulfoxide 5b in the Presence of 2-Mercaptobenzothiazole. A solution of the (*R*)-sulfoxide **5b** (900 mg, 2.6 mmol) and 2-mercaptobenzothiazole (900 mg, 5.4 mmol) in dry ethanol-free chloroform (20 mL), was heated at reflux for 18 h. After evaporation of the solvent, the reaction mixture was chromatographed on silica gel (toluene–ethyl acetate, 9:1) to give the following. (a) The disulfide **11**: 256 mg (35%); mp 70–71 °C (from CH_2Cl_2–hexane); IR ($CHCl_3$) 1740, 1735 cm^{-1}; NMR (60 MHz, $CDCl_3$) δ 2.65–2.9 and 3.1–3.35 (2 m, $SCH_2CH_2CO_2$), 3.7 (s, OMe), 7.25–7.5 and 7.7–8.0 (2 m, aromatic); high-resolution mass spectrum, calcd for $C_{11}H_{11}NO_2S_3$ m/e 284.9918, found m/e 284.9954; m/e 285 (M^+), 254 ($M^+ - OCH_3$), 199 ($M^+ - CH_2{=}CHCO_2CH_3$), 167 ($C_6H_4SNCSH^+$). (b) The *trans*-azetidinone **10**: 304 mg (31%); mp 192–195 °C; $[\alpha]^{26}_D$ −47.2° (*c* 1.0, DMF); IR (KBr) 3270, 1795, 1765, 1715 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 5.51 (d, J = 2.6 Hz, azetidine H), 6.02 (d, J = 2.6 Hz, azetidine H), 6.92 (br, NH), 7.2–7.5 (m, benzothiazole), 7.7–8.0 (m, Phth and benzothiazole); high-resolution mass spectrum, calcd for $C_{11}H_6N_2O_3$ 214.0378, found m/e 214.0415; m/e 214 (M^+ - C_6H_4SNCSH), 167 ($C_6H_4SNCSH^+$); the low-resolution mass spectrum shows a weak peak at 381 (M^+). Anal. Calcd for $C_{18}H_{11}N_3O_3S_2$: C, 56.68; H, 2.91; N, 11.02. Found: C, 56.72; H, 2.91; N, 11.13. (c) The disulfide **9**: 658 mg (62%); mp 187–189 °C (from CH_2Cl_2–hexane) (lit.[15] mp 184–187 °C); $[\alpha]^{26}_D$ −135.0° (*c*, 1.0, CH_2Cl_2); IR ($CHCl_3$) 3410, 1800, 1780, 1730, 1720 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 5.43 (d, J = 5 Hz, 4-H), 5.78 (dd, J = 5, 1 Hz, 3-H), 6.86 (br, NH), 7.3–8.0 (m, Phth and benzothiazole); high-resolution mass spectrum, calcd for $C_{11}H_6N_2O_3S$ m/e 246.0099, found m/e 246.0098; m/e 246 (M^+ - C_6H_4SNCSH), 214 (M^+ - $C_6H_4SNCSSH$), 167 ($C_6H_4SNCSH^+$); the low-resolution mass spectrum shows a weak peak at m/e 413 (M^+).

Thermolysis of the (*S*)-Sulfoxide 5c in the Presence of 2-Mercaptobenzothiazole. A solution of the (*S*)-sulfoxide **5c** (800 mg, 2.3 mmol) and 2-mercaptobenzothiazole (800 mg, 4.8 mmol) in dry, ethanol-free chloroform (20 mL) was heated under reflux for 4.5 h. After evaporation of the solvent, the reaction mixture was chromatographed on silica gel (toluene–ethyl acetate, 9:1) to give (a) the disulfide **11** (560 mg, 86%; for characterization see the previous paragraph), (b) the *trans*-azetidinone **10** (618 mg, 71%; for characterization see the previous paragraph), and (c) the *cis*-azetidinone **12** (ca. 10%). This product was not stable in solution at room temperature and, as observed by TLC and NMR monitoring, it isomerized to the *trans*-azetidinone **10**. Characteristic peaks in the NMR (90 MHz, $CDCl_3$) of **12**: δ 5.88 (dd, J = 5.0, 1 Hz, 3-H), 6.32 (d, J = 5.0 Hz, 4-H).

Supplementary Material Available: A drawing and tables containing atom coordinates, anisotropic temperature factors, hydrogen atom coordinates, bond lengths, and bond angles of (3*R*,4*R*,5*S*)-4-[[2-(methoxycarbonyl)ethyl]sulfinyl]-1-[1-(methoxycarbonyl)-2-methylprop-1-enyl]-3-phthalimido-2-azetidinone (1) (6 pages). Ordering information is given on any current masthead page.

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