THE CHLORINOLYSIS OF AZETIDINONE DISULFIDES[1]

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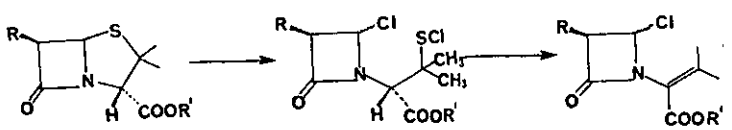
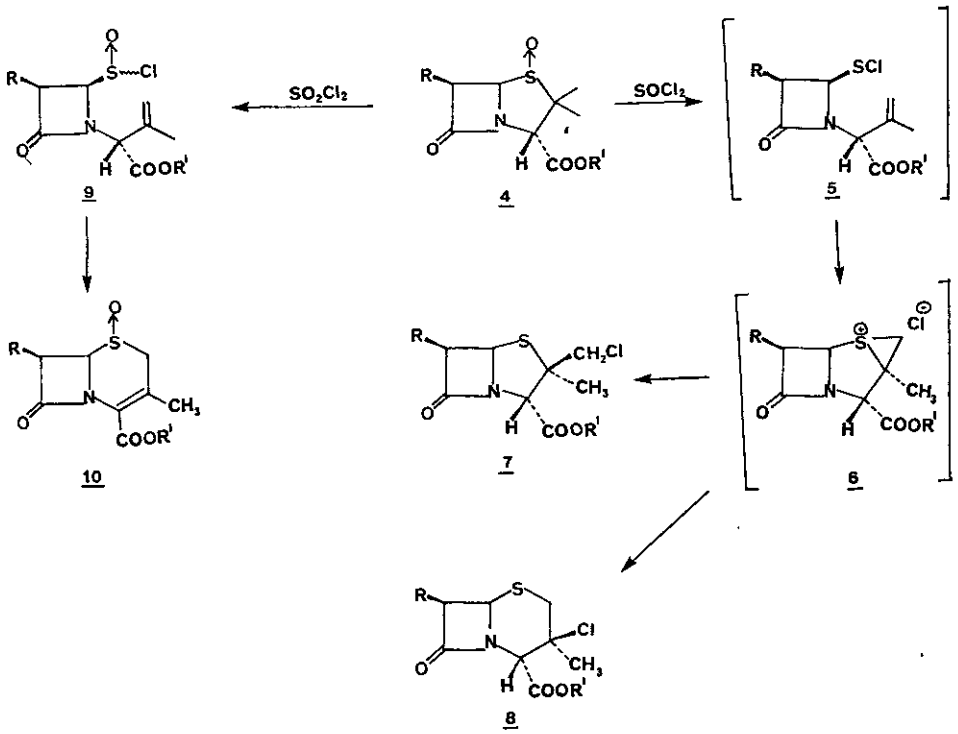
Abstract - The chlorinolysis of dithiazeneazetidinones, unsym-azetidinone disulfides, and 2-chloromethylpenams, with sulfuryl chloride produce the 2-[2'(R and S)-chloro-4'-oxoazetidin-1'-yl]-3-chloromethyl-3-chloro-sulfenylbutyric acid ester isomers in which the S-isomer predominates. Treatment of this compound (R and S isomers) with pyridine results in elimination of HSCl and formation of the Z and E isomers in which the Z isomer predominates.

Penicillins[4-9], penicillin sulfoxides[10-14], anhydropenicillins[15,16], and cephams[17,18], undergo electrophilic ring opening with chlorine, thionyl chloride, sulfuryl chloride, and 1-chlorobenzotriazole, in suitable solvents such as carbon tetrachloride or methylene chloride. In the case of the penicillins, 1, the initial product formed, the 2-[2'(R and S)-chloro-4'-oxo-3'S-phthalimino-doazetidin-1'-yl]-3-chlorosulfenyl-3-methylbutyrate ester 2, is readily converted by excess of the chlorinating agent, or with triethylamine, to the 2-[2'(R and S)-chloro-4'-oxo-3'S-phthalimido-azetidin-1'-yl]-3-methylbut-2-enoate ester, 3[4].

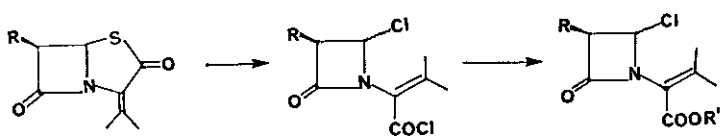


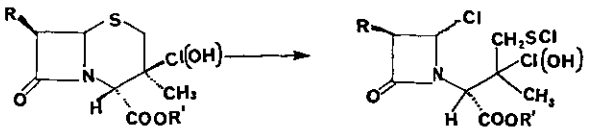
1 2 3

Penicillin sulfoxides, 4, on heating in the presence of thionyl chloride, are converted to the 3-chloro-3-methylcephams, 8, and the 2-chloromethyl-2-methylpenams, 7, by way of the azetidinone



thiiranium chlorides, 6, which are in turn formed from the 2-[2'S-chlorosulfenyl-4'-oxo-3'S-phthalimidoazetidin-1'-yl]-3-methylenebutyrate esters, 5[10]. In the presence of sulfuryl chloride in place of thionyl chloride, the product is the isomeric mixture of the 2-[2'S-chlorosulfinyl-4'-oxo-3'S-phthalimidoazetidin-1'-yl]-3-methylenebutyrate esters, 9, isomeric about the sulfinyl center. The compounds, 9, with triethylamine form the 3-methyl-7-phthalimidoceph-3-em sulfoxides, 10[11]. Chlorination of anhydropenicillins, 11, produce the sulfur-free 2-[2'(R and S)-chloro-4'-oxo-3'S-phthalimido or amidoazetidin-1'-yl]-3-methylbut-2-enoyl chlorides, 12, which are readily converted to the acids, 13 (R'=H) or esters, 13[15,16].

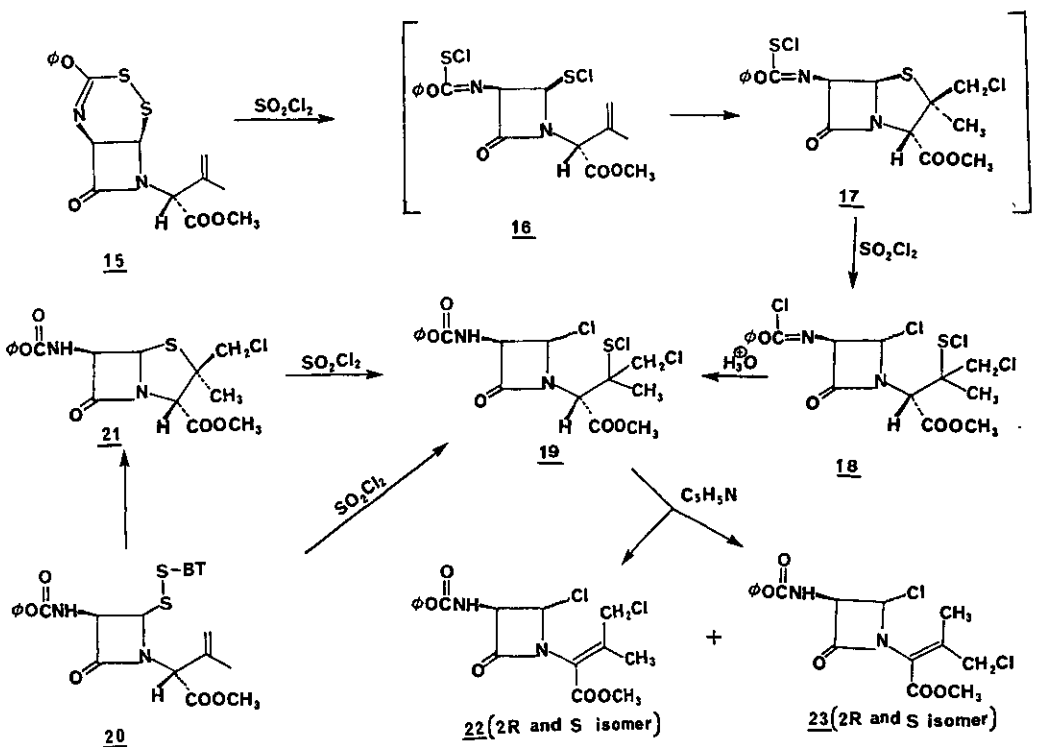




8 14

Direct chlorination of cephams such as 8, produce the 2[2'(R and S)-chloro-4'-oxo-3'S-phthalimido or amidoazetidin-1'-yl]-3-chlorosulfenylmethyl-3-chloro (or hydroxy) butyrate esters, 14[17,18]. These products of chlorinolysis have been used for the preparation of 5-epipenicillins[19], 2-halomethylpenicillins, 1,2-disulfide analogues of cephalosporins[20], penems[21,22], 1-oxapenams, 6-epi-1-azacephalosporins[23], and 1-oxacephalosporins[24]. Many of these products were found to be bioactive.

This paper describes our work on the chlorinolysis of the 1,2,4-dithiazeneazetidinones, 15,[25] and the unsym-azetidinone disulfides, 20[26,27].



15 16 17 18 19 20 21 22(2R and S isomer) 23(2R and S isomer)

Unsym-Azetidinone disulfides of type 20 have been described by Kamiya and co-workers[26,27]. When these compounds are treated with the stoichiometric amount (0.5 mole equivalent) of chlorine or sulfuryl chloride, in a suitable solvent such as methylene chloride or carbon tetrachloride, at a low temperature (about -40°C), excellent yields of the 2β-chloromethyl-2 -methylpenams, 21, are obtained. This reaction proceeds by way of the (unisolated) sulfenyl chloride, 5, and the thiiranium chloride, 6[27].

The unsym-azetidinone disulfide, 20, when dissolved in excess sulfuryl chloride (reagent and solvent), undergoes an immediate reaction to give essentially quantitative yields of methyl 2-[2'(R and S)-chloro-4'-oxo-3'S-phenoxycarbonylaminoazetidin-1'-yl]-3-chloromethyl-3-chlorosulfenylbutanoate, 19, in an isomer [2'R and S-chloro isomers, determined from the 300 MHz NMR spectrum] ratio of R:S of 1:4. This same product, 19, is also obtained, in the same isomer (R:S) ratio, by the chlorinolysis, in the same way, of the 2β-chloromethylpenam, 21.

The 3-phenoxy-1,2,4-dithiazeneazetidinone, 15[25], reacted very slowly with sulfuryl chloride (1 or 2 mole equivalent) in methylene chloride, at room temperature. After one hour, at room temperature, the NMR spectra and thin layer chromatograms indicated the presence of considerable amounts of the starting material, 15, along with other products. However, when the 3-phenoxy-1,2,4-dithiazene-azetidinone, 15, was dissolved in sulfuryl chloride (reagent and solvent), an immediate reaction occurred (as shown by the nmr spectrum, run on the reaction mixture). The product of this reaction is methyl 2-[2'(R and S)-chloro-4'-oxo-3'S-α-phenoxy-α-chloromethyleneiminoazetidin-1'-yl]-3-chloro-methyl-3-chlorosulfenylbutanoate, 18, probably formed via the sulfenyl chloride, 16, and the 2β-chloromethylpenam, 17, (which were not isolated). This product, 18, obtained in quantitative yield, consisted of the isomeric mixture at C-2, the ratio of R:S isomers being 1:4, as determined from the NMR (300 MHz) spectrum. The compound, 18, is fairly stable in solutions, and a solution in benzene can be washed rapidly with water, to remove excess sulfuryl chloride. The NMR spectrum of the washed sample is identical to that of the crude sample. On stirring with ice water, this compound, 18, is hydrolyzed to methyl 2-[2'(R and S)-chloro-4'-oxo-3'S-phenoxycarbonylaminoazetidin-1'-yl]-3-chloromethyl-3-chlorosulfenylbutanoate, 19, identical with the samples obtained from the unsym-azetidinone disulfide, 20, and from the 2β-chloromethylpenam, 21.

Compound 19, on treatment with pyridine (reactant and solvent), in an ice-bath, gave a mixture of both the Z ($COOCH_3$ cis to CH_3-compound 22), and the E ($COOCH_3$ trans to CH_3-compound 23) geometric isomers, in a ratio of 4:1; each of these geometric isomers also consisting of the chiral R and S isomers. The structural assignments of these compounds were made on the basis of the NMR (300 MHz) spectrum of the product obtained from the treatment with pyridine. The CH_3 singlet of the Z isomer, 22, thus appeared at δ 2.33, while the CH_3 singlet of the E isomer, 23, was at δ 2.11.

When compound 19, was treated with pyridine, in methylene chloride as solvent, the ratio of the Z:E isomers changed from 4:1 to 2:1.

The chemistry of compounds 18, 19, 22, and 23, is under study and will be reported in subsequent

publications.

EXPERIMENTAL

IR spectra were recorded on a Nicolet DX-FTIR spectrophotometer. NMR spectra were recorded on a Varian EM-360A, and a Brucker AM-300 spectrometer, using tetramethylsilane as an internal reference.

Methyl 2-[2'(R and S)-chloro-4'-oxo-3'S-α-phenoxy-α-chloromethyleneiminoazetidin-1'-yl]-3-chloro-methyl-3-chlorosulfenylbutanoate, 18.

Methyl 3-phenoxy-4,5-dithia-2,7-diazabicyclo[4.2.0]oct-2-ene-8-one-7-isopropenyl acetate, 15, (1.0 g) was dissolved in distilled sulfuryl chloride (5 ml). There was an immediate reaction with production of the title compound as was evident from the nmr spectrum (SO_2Cl_2)[28]: Major product (2'S-isomer) δ 1.73 (3H, s, CH_3), 3.8 (3H, s, $COOCH_3$), 4.10 (2H, s, CH_2Cl), 4.63 (1H, s, $CHCOOCH_3$), 5.06 (1H, d, J=1.8Hz), 5.50 (1H, d, J=1.8Hz-trans-β-lactam protons), 7.33 (5H, m, C_6H_5); Minor product (2'R-isomer) δ 1.66 (3H, s, CH_3), 3.82 (3H, s, $COOCH_3$), 4.18 (2H, s, CH_2Cl), 4.5 (1H, s, $CHCOOCH_3$), 5.20 (1H, d, J=4Hz), 6.17 (1H, d, J=4Hz-cis-β-lactam protons), 7.33 (5H, m, C_6H_5). The excess sulfuryl chloride was removed under reduced pressure and the resulting oil was dried under high vacuum. The resulting oil was dissolved in benzene and this solution washed rapidly with water. The organic layer was dried over sodium sulfate, filtered and concentrated. The nmr spectrum of the residual oil (in $CDCl_3$) was identical to that of the reaction product (in SO_2Cl_2), and showed the presence of the S- and R-isomers in a ratio of 4:1. This compound, although comparatively stable in solution in the absence of air and moisture, changes rapidly on isolation and on attempted purification, and should be used as soon as possible. A high resolution mass spectral analysis of this compound gave a measured mass of 436.9890, while that calculated for $C_{16}H_{16}N_2O_4S^{32}Cl_3{}^{35}$ (M-35) is 436.9898.

Methyl-2-[2'(R and S)-chloro-4'-oxo-3'S-phenoxycarbonylaminoazetidin-1'-yl]-3-chloromethyl-3-chloro-sulfenylbutanoate, 19.

Methyl 2-[2'S-(benzothiazol-2-yl)dithia-4'-oxo-3'S-phenoxycarbonylaminoazetidin-1'-yl]-3-methylene-butanoate, 20, (1.0 g) was stirred with distilled sulfuryl chloride (15 ml). There was an immediate reaction, the compound dissolved to a yellow solution and very quickly a yellow solid separated. The reaction mixture after filtration was concentrated to give a yellow syrup. This syrup was stirred with ether, filtered, and the ether evaporated to give a yellow oil with an nmr ($CDCl_3$) spectrum: Major product (2'S isomer) δ 1.73 (3H, s, CH_3), 3.80 (3H, s, $COOCH_3$), 4.10 (2H, s, CH_2Cl), 4.73 (1H, s, $CHCOOCH_3$), 4.90 (1H, dd, J_1=8Hz, J_2=2Hz, 3-H), 5.80 (1H, d, J=2Hz, 2-H), 6.56 (1H, d, J=8Hz, NH), 7.26 (m, C_6H_5); Minor product (2'R isomers) δ 1.63 (3H, s, CH_3), 3.80 (3H, s, $COOCH_3$), 4.23 (2H, s, CH_2Cl), 4.53 (1H, s, $CHCOOCH_3$), 4.90 (1H, dd, J_1=8Hz, J_2=4Hz, 3-HO, 6.20 (1H, d, J=4Hz, 2-H), 6.56 (1H, d, J=8Hz, NH), 7.26 (m, C_6H_5). This nmr spectrum shows that the major product is

the S-isomer, and the minor the R-isomer in a ratio of 4:1.

The same compound, with essentially the same isomer distribution is obtained by treating the 2-chloromethylpenam, 21, with sulfuryl chloride in a similar way, or by stirring compound 18 with ice water (acidic) for 0.5 h. The nmr spectra of the products obtained from 21 and 18, were identical to that of the product from 20.

Methyl 2-[2'(R and S)-chloro-4'-oxo-3'S-phenoxycarbonylaminoazetidin-1'-yl]-3-chloromethyl-but-2-enoate, 22 and 23.

Compound 19 (1.2 g) was dissolved in pyridine (10 ml) cooled in an ice bath. Immediately after solution was complete, the pyridine was removed under vacuum, using benzene as a chaser. The resulting brown gum was dissolved in benzene and the resulting solution was washed with 1 normal HCl and water. The benzene solution was then dried over anhyd. Na_2SO_4, filtered, and concentrated to a brown foam. The nmr spectrum (integration of the methyl and β-lactam protons) of the product showed a mixture of the four products 22S:22R:23S:23R in the ratio 12:4:3:1. Chromatography on silica gel using ethyl acetate-hexane (3:17) as eluant gave 350 mg (35%) of compound 22S. NMR ($CDCl_3$) spectrum: δ 2.33 (3H, s, CH_3), 3.83 (3H, s, $COOCH_3$), 4.27 (2H, d, J=6Hz, CH_2Cl), 4.97 (1H, dd, J_1=8Hz, J_2=2Hz, 3-H), 6.00 (1H, d, J=2Hz, 2-H), 6.40 (1H, d, J=8Hz, NH), 7.27 (5H, m, C_6H_5). IR (KBr) 3377, 2951, 1790, 1731, 1529, 1491, 1324, 1266, 1220, 1208 cm^{-1}.

A second fraction (150 mg) consisted of a mixture of 22R:23S:23R in the ratio of 7:2:1 from the nmr spectrum. The nmr ($CDCl_3$) spectrum for compound 22R: δ 2.31 (3H, s, CH_3), 3.83 (3H, s, $COOCH_3$), 4.23 (2H, d, J=6Hz, CH_2Cl), 5.20 (1H, dd, J_1=8Hz, NH), 7.33 (5H, m, C_6H_5). The nmr spectrum of compound 23 (both S and R isomers) differs from that of compound 22, in that the CH_3 singlet appears at 2.11 and the CH_2Cl appears as a doublet at 4.67 with J=1Hz.

The analysis of compound 22S, obtained as described above, is within acceptable limits.

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