THE CHEMISTRY OF THE 6β-THIOAMIDOPENAM 1β-SULFOXIDES. THE 1,2,4-DITHIAZINEAZETIDINONES AND THIAZOLINEAZETIDINONES

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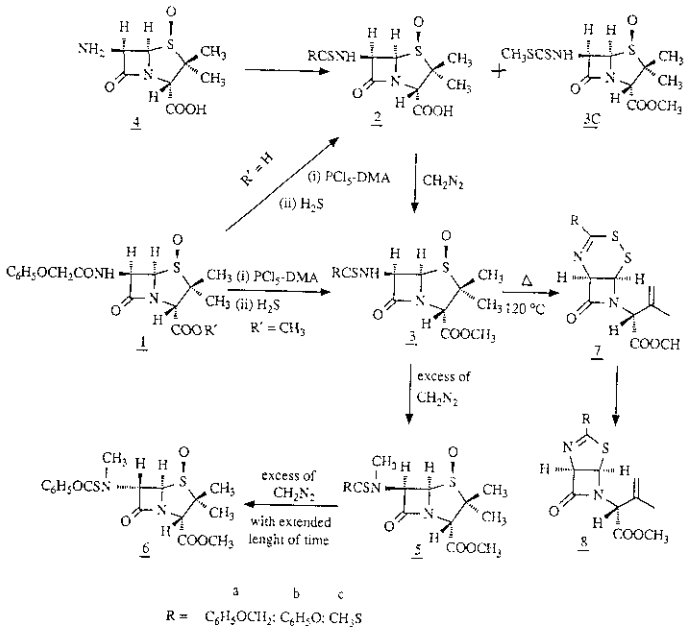
Abstract - 6β-Thioamidopenam 1β-sulfoxides on thermolysis gave methyl 2-(3-substituted 4,5-dithia-2,7-diazabicyclo[4.2.0]oct-2-en-8-one-7-yl)-3-methyl-but-3-enoate (1,2,4-dithiazineazetidinones). The reaction of these compounds with halogenating agents is discussed.

The sulfenic acid intermediate obtained by the thermal sigmatropic rearrangement of penicillin sulfoxides have been trapped either intermolecularly (with olefins or acetylenes,[1-4] azocompounds,[5,6] arylsulfonic acids,[7] silylated amides,[8] imides[9] and mercaptans[10-13]) or intramolecularly (with trimethylphosphite).[14,15] Many of these products are utilized for the preparation of cephalosporins and modified penicillins.[10-13,16]

Tanida and co-workers reported that 6β-thioamidopenam 1β-sulfoxides,[17] 3, on heating in D_2O-toluene, gave the thiazolineazetidinones, 8, by way of the (unisolated) intermediate 1,2,4-dithiazineazetidinone, 7, which we have isolated

in good yield.[18] Some aspects of the chemistry of the 1,2,4-dithiazineazetinones are reported in this paper.

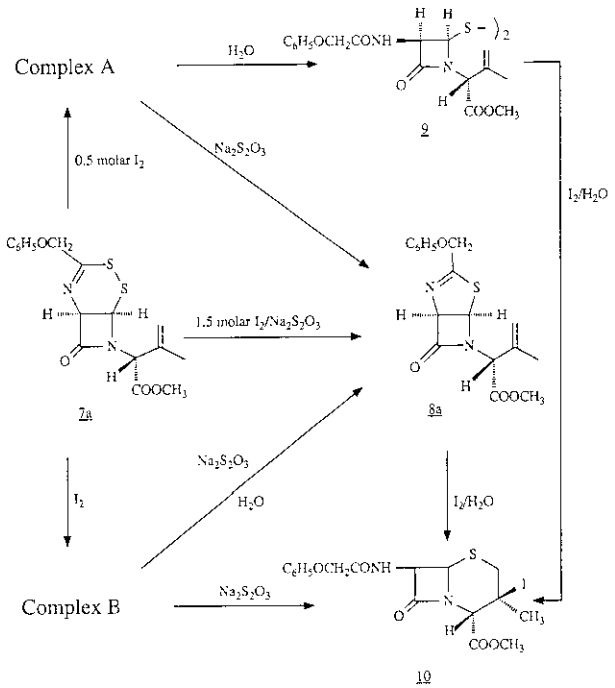
The 6β-thioamidopenam 1β-sulfoxides 3[19] required as starting material were prepared from the 6β-phenoxyacetamidopenam 1β-sulfoxide 1 by treatment with PCl_5 in the presence of a base followed by H_2S. The 6β-thiocarbamidopenam 1β-sulf-



Scheme 1

oxides 2 were prepared by either coupling 6β-aminopenam 1β-sulfoxide 4 with phenyl chlorothioformate or by the reaction of compound 4 with CS_2 in the presence of triethylamine and methyl iodide. Compound 2 was esterified to its methyl ester 3 with one equivalent of diazomethane. In excess of diazomethane compound 2 or 3 gave the N-methyl derivative 5 which readily epimerized at C6 either by treatment with a base such as triethylamine or by standing with silica gel or when left in contact with diazomethane solution in THF for an extended period of time. Thus, compound 2b, treated with an excess of diazomethane for over 17 hours at 0°C, was converted almost completely to compound 6 which was obtained as an amorphous white powder, nmr ($CDCl_3$)δ : 1.26 and 1.73(s, s, 6H, gem-CH_3), 3.62(s, 3H, N-CH_3), 3.90(s, 3H, OCH_3), 4.63(s, 1H, C_3-H), 5.12(d, J=2Hz, C_5-H), 6.01(d, J=2Hz, C_6-H), 7.06-7.53(m, 5H, C_6H_5).

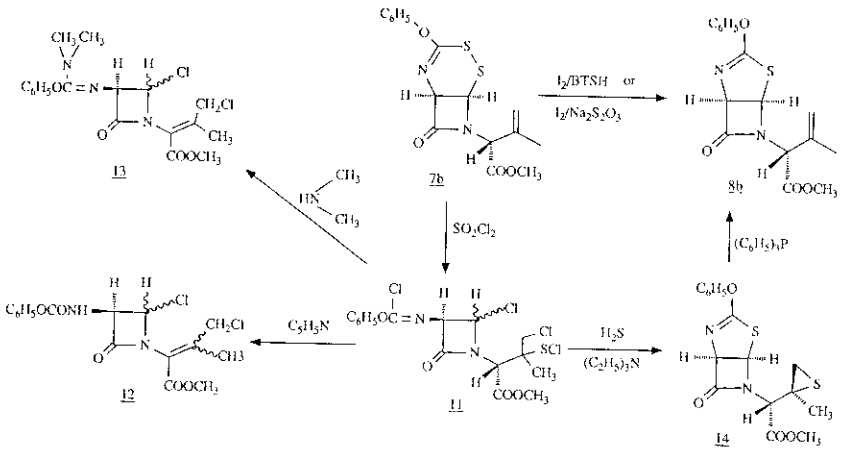
The 6β-thioamidopenam 1β-sulfoxides 3 on thermolysis at 120°C in a suitable solvent like toluene or dioxane in a nitrogen atmosphere for 2-4 h (reaction time depends on the nature of R) gave the 1,2,4-dithiazineazetidinones 7. The thermolysis reaction required carefully controlled reaction conditions. The stability of compounds 7 and their further reactions were dependent on the nature of the R group. Compound 7b and 7c were quite stable whereas compound 7a was unstable and rapidly converted to compound 8 with other unidentified products on exposure to light, moisture and air.



Scheme 2

The conversion of the thiazolineazetidinones 8 and azetidinone disulfides to the 3-iodocephams 10 and 2-iodomethylpenams in high yields have been reported.[20,21] The 1,2,4-dithiazineazetidinone 7a reacted with iodine in solvents such as toluene, dioxane and methylene chloride to form the complex A (with 1 atomic equivalent of I_2) or complex B (with 1 molar equivalent of I_2). The nmr and ir spectra and tlc of these complexes were different to each other. The complexes were comparatively stable in the absence of moisture. On addition of water, complex A gave high yields of the symmetrical azetidinone disulfide 9 which on further treatment with I_2 and water gave 3-iodocepham 10,[22] while complex B gave the 3-iodocepham 10 (a small amount of the 2-iodomethylpenam was detected in the nmr

spectrum of the crude product). Complex A and complex B, on treatment with aqueous sodium thiosulfate gave the thiazolineazetidinone 8a. Compound 7b was more stable and did not behave in the same way as 7a. However, compound 7b on treatment with iodine itself or iodine in presence of mercaptan, followed by washing with sodium thiosulfate gave the thiazolineazetidinone 8b. The reaction with chlorine or sulfuryl chloride did not proceed in the same way as iodine.



Scheme 3

3-Phenoxy-1,2,4-dithiazineazetidinone 7b reacted very slowly with sulfuryl chloride (one or two mole) in dichloromethane at room temperature. After one hour the nmr and tlc indicate the presence of a considerable amount of starting material. However, when 3-phenoxy-1,2,4-dithiazineazetidinone 7b was dissolved in sulfuryl chloride, an immediate reaction occurred and produced methyl 2-[2'(R and S)-chloro-4'-oxo-3'S-(-phenoxy- -chloromethyleneimino)azetidin-1'-yl]-3-chloromethyl-3-chlorosulfenyl butanoate (11),[23] an isomeric mixture at C_2 in a ratio of 1:4 (R:S). Compound 11, on stirring with water and working up followed by treatment with pyridine in an ice bath gave compound 12 as a mixture of geometrical isomers Z ($COOCH_3$ cis to CH_3) and E (-$COOCH_3$ trans to CH_3) in a ratio of 4:1. Compound 11, on reaction with dimethylamine in CH_2Cl_2 at -60°C gave compound 13 whereas with excess of H_2S in the presence of triethylamine at -60°C the thiazoline azetidinone episulfide 14 whose structure was determined by its nmr spectrum. Further confirmation of structure 14 was obtained by converting the compound 14 to the thiazoline-azetidinone 8b by reaction with triphenyl-

phosphine. Presumably the mechanism of formation of compound 14 involves the initial formation of the thioamide from chloroimine followed by the formation of the thiazoline ring; and the replacement of -SCl by mercaptan followed by the formation of the episulfide ring. The spectral data of compound 14 indicate that the stereochemistry of the episulfide is similar to that reported for the oxazoline azetidinone episulfide.[24]

EXPERIMENTAL

Ir spectra were recorded on a Perkin Elmer 267 and Nicolet DX-FTIR spectrophotometer. Nmr spectra were recorded on a Varian EM-360A and a Brucker AM-300 spectrometer using tetramethylsilane as an internal standard.

Methyl 6β-phenoxythioacetamidopenicillanate 1β-sulfoxide (3a):

Phosphorous pentachloride (26.4 g, 0.126 mol) was added in one lot to a stirred cold (-70°C) solution of methyl 6β-phenoxyacetamidopenicillanate 1β-sulfoxide (1.45 g, 0.1185 mol) and dimethylaniline (36.3 g, 0.3 mol) in methylene chloride (600 ml). After stirring the reaction mixture for 0.5 h, H_2S gas was bubbled for 1.5 h at -70°C and for an additional 1.5 h at 0°C. The reaction mixture was poured onto ice cold aqueous $NaHCO_3$ (750 ml) solution. The organic layer was separated and washed with water, dil. HCl and brine solution, dried over Na_2SO_4 and gave a yellow powder which was purified by column chromatography on silica gel using chloroform as eluant to give 23.0 g (49%) of the pure thioamide, mp 144-145°; nmr ($CDCl_3$) δ : 1.25 and 1.75(brs, 6H, gem-$C\underline{H}_3$), 3.88(s, 3H, $COOC\underline{H}_3$), 4.78(s, 1H, C_3-H), 4.99(s, 2H, $OC\underline{H}_2$), 5.23(d, J=4Hz, 1H, C_5-H), 6.73 - 7.52(m, 6H, $C_6\underline{H}_5$ and C_6-H), 9.88(d, J=10Hz, 1H, NH).

6β-Phenoxythioacetamidopenicillanic acid 1β-Sulfoxide (2a):

Chlorotrimethylsilane (0.148 ml, 3.3 mmol) was added to a stirred solution of anhydrous 6β-phenoxyacetamidopenicillanic acid 1β-sulfoxide and dimethylaniline (1.14 ml, 9 mmol) in dry CH_2Cl_2 (20 ml). After stirring the yellow solution for 30 min at 0°C, it was cooled to -30°C and PCl_5 (0.605 g, 3.3 mmol) was added. The resulting mixture was stirred for 3 h at -30°C, and H_2S gas was bubbled through the dark green colored mixture for 1 h keeping the temperature between

-25°C to 0°C. The mixture was poured onto ice cold saturated $NaHCO_3$ solution which was then extracted with ether. The alkaline aqueous layer was acidified with dil. HCl and extracted with ethyl acetate (3 x 50 ml). The combined ethyl acetate extract was washed with water, dried over Na_2SO_4 and concentrated to give 0.73 g of a yellow solid which was purified by column chromatography on silica gel to give 460 mg (40%) of the product; mp 145-149°(dec); nmr(DMSO-d_6) δ: 1.20 and 1.53(s, s, 6H, gem-$C\underline{H}_3$), 3.52(s, 1H, $COO\underline{H}$), 4.43(s, 1H, C_3-H), 4.92(s, 2H, $OC\underline{H}_2$), 5.58(d, J=4Hz, 1H, C_5-H), 6.56(dd, J_1=9Hz, J_2=4Hz, 1H, C_6-H), 6.90-7.49(m, 5H, $C_6\underline{H}_5$), 10.16(d, J=9Hz, 1H, $N\underline{H}$).

6β-Phenoxythiocarbamidopenicillanic acid 1β-Sulfoxide (**2b**):

To an ice cold basic solution (pH 8 made by addition of 2N-KOH) of 6β-aminopenicillanic acid 1β-sulfoxide (23.2 g, 0.1 mol) in a mixture of water (275 ml) and THF (125 ml), a solution of phenoxythiocarbonyl chloride (17.2 g, 0.1 mol) in THF (50 ml) and an aqueous solution of KOH (2N) was added simultaneously by dropping funnels at such a rate that maintained the pH of the reaction mixture at 8. After the complete addition, the reaction mixture was stirred for 1 h, stored in a refrigerator overnight and extracted with ethyl acetate. The aqueous layer was acidified with dil. HCl and extracted with ethyl acetate. The combined ethyl acetate extract was washed with water, dried over Na_2SO_4 and concentrated, to give a yellow brown solid which was recrystallized with ether, to give 18.0 g (49%) of a white solid, mp 153-156°C (dec); nmr(DMSO-d_6) δ: 1.29 and 1.60(s, s, 6H, gem-$C\underline{H}_3$), 4.47(s, 1H, C_3-H), 5.50(d, J=4Hz, 1H, C_5-H), 6.05 (dd, J_1=7Hz, J_2=4Hz, 1H, C_6-H), 7.10-7.55(m, 5H, $C_6\underline{H}_5$), 9.90(d, J=7Hz, 1H, $N\underline{H}$).

Methyl 6β-methyldithiocarbamidopenicillanate 1β-sulfoxide (**3c**) and 6β-methyldithiocarbamidopenicillanic acid 1β-sulfoxide (**2c**)

Carbon disulfide (3.35 g, 0.044 mol) was added to an ice cold stirred solution of 6β-aminopenicillanic acid-1β-sulfoxide (9.28 g, 0.04 mol) and triethylamine (8.5 g, 0.084 mol) in dry DMF (25 ml). After 15 h of stirring in the ice bath, methyl iodide (12.4 g, 0.088 mol) was added and the mixture was stirred for an additional 0.5 h in the ice bath followed by overnight at room temperature. The solution was diluted with water and extracted with chloroform (3 x 50 ml), the chloroform solution was dried over Na_2SO_4 and concentrated to give 8.6 g of

brown foam. The crude product was purified by chromatography on silica gel using ether as eluant, to give 4.6 g (33%) of white crystals whose nmr spectrum indicates that it is a mixture of compound 3c and 2c in a ratio of 2:1. The compound 3c was obtained by washing chloroform solution of the mixture with aqueous $NaHCO_3$. The chloroform layer was dried over Na_2SO_4 and concentrated to give compound 3c as a white solid. mp 138-142°C; nmr($CDCl_3$) δ : 1.22 and 1.70(s, s, 6H, gem-CH_3), 2.63(s, 3H, S-CH_3), 3.85(s, 3H, $COOCH_3$), 4.75(s, 1H, C_3-H), 5.21 (d, J=4Hz, 1H, C_5-H), 6.75(dd, J_1=9Hz, J_2=4Hz, 1H, C_6-H), 8.68(d, J=9Hz, 1H, NH).

Reaction of Diazomethane with 6β-Phenoxythiocarbamidopenicillanic acid 1β- sulfoxide (2b)

A solution of diazomethane (obtained from 3.5 g of N-methyl-N-nitroso-p-toluenesulfonamide) in ether was added to a 6β-phenoxythiocarbamidopenicillanic acid 1β-sulfoxide 2b (5 g, 13.6 mmol)in tetrahydrofuran (50 ml) at 0°C and left for 1 h. The excess of diazomethane was decomposed with acetic acid and the reaction mixture was concentrated. The residue was dissolved in dichloromethane and washed successively with water (3 x 50 ml) and brine. The organic phase was dried over Na_2SO_4 and concentrated to give a yellowish brown foam which was recrystallized with methanol to give the pure compound 3b. Yield 3.0g (58%) mp 148-150°C; nmr($CDCl_3$) δ : 1.22 and 1.78(s, s, 6H, gem-CH_3), 3.88(s, 3H, $COOCH_3$), 4.8(s, 1H, C_3-H), 5.27(d, J=4Hz, 1H, C_5-H), 6.55(dd, J_1=10Hz, J_2=4Hz, 1H, C_6-H), 7.10 - 7.51(m, 5H, C_6H_5), 8.22(d, J=10Hz, 1H, NH). Similarly, 2a and a mixture of 2c and 3c were treated with diazomethane to give the respective methyl esters 3a and 3c. With excess (at least 2-3 equivalents) of diazomethane and a longer reaction time, compounds 2 were converted to the N-methyl derivatives 5. In case of 2b and 2c quantitative yields of 5b and 5c were obtained after 4-5 h at 0°C; while under similar conditions 2a gave a 1:1 mixture of 3a and 5a. Nmr($CDCl_3$) δ : 5a: 1.18 and 1.62(ss, 6H, gem-CH_3), 3.60(s, 3H, N-CH_3), 3.85(s, 3H, OCH_3), 4.67(s, 1H, C_3-H), 5.05(s, 2H, OCH_2), 5.48(d, J=4Hz, 1H, C_5H), 5.62(d, J=4Hz, 1H, C_6-H), 6.90-7.40(m, 5H, C_6H_5). 5b: 1.22 and 1.70(s, s, 6H, gem-CH_3), 3.52 (s, 3H, N-CH_3), 3.85(s, 3H, OCH_3), 4.72(s, 1H, C_3-H), 5.42(d, J=4Hz, 1H, C_5-H), 5.63(d, J=4Hz, 1H, C_6-H), 7.10-7.58(m, 5H, C_6H_5). 5c: 1.28 and 1.70(s, s, 6H, gem-CH_3), 2.70(s, 3H, S-CH_3), 3.52(s, 3H, N-CH_3), 3.88(s, 3H, OCH_3), 4.69(s, 1H, C_3-H), 5.53(d, J=4Hz, 1H, C_5-H), 5.82(d, J=4Hz, 1H, C_6-H).

Methyl 2-(3-phenoxymethyl-4,5-dithia-2,7-diazabicyclo[4.2.0]oct-2-en-8-one-7-yl)-3-methylbut-3-enoate (7a)

A mixture of methyl 6-phenoxythioacetamidopenicillanate 1β-sulfoxide (3a, 0.5 g, 1.35 mmol) and dimethylaniline (4.5 drops) in purified toluene (60 ml) was refluxed under stirring using a Dean Stark trap in a N_2 atmosphere at 120°C for 1.5 h. The reaction mixture was concentrated under high vacuum and the residue was dissolved in chloroform and washed successively with dil. HCl and water, dried over Na_2SO_4 and concentrated to give 300 mg the title compound. The title compound is not very stable and it is advisable to use it as quickly as possible preferably without purification. Nmr($CDCl_3$) δ : 1.90(s, 3H, CH_3), 3.80(s, 3H, $COOCH_3$), 4.85(s, 2H, OCH_2), 4.95-5.20(m, 3H, $CHCOOCH_3$ and CH_2), 5.60(d, J=5Hz, 1H, C_6-H), 5.70(d, J=5Hz, 1H, C_1-H), 6.92-7.50(m, 5H, C_6H_5). Other related 7b and 7c dithiazineazetidinone have been prepared and isolated. 7b: Yield 52%, nmr($CDCl_3$) δ : 1.97(s, 3H, CH_3), 3.80(s, 3H, $COOCH_3$), 4.99-5.20(m, 3H, CH and CH_2), 5.45(d, J=5Hz, 1H, C_6-H), 5.69(d, J=5Hz, 1H, C_1-H), 7.15-7.50(m, C_6H_5). 7c: Yield 45%, nmr($CDCl_3$) δ : 1.91(s, 3H, CH_3), 2.47(s, 3H, S-CH_3), 3.80(s, 3H, $COOCH_3$), 4.93-5.20(m, 3H, CH and CH_2), 5.62(d, J=5Hz, 1H, C_6-H), 5.82(d, J=5Hz, 1H, C_1-H).

Reaction of Iodine with Dithiazineazetidinone 7a

(a) With 1 atomic equivalent of I_2: A mixture of the dithiazineazetidinone 7a (378 mg, 1 mmol) and iodine (127 mg, 0.5 mmole) in dry dioxane (30 ml) was stirred at 0°C for 15 min. Moist air was bubbled through the reaction mixture which was stirred at room temperature for 16 h. The reaction mixture was diluted with water and extracted with methylene chloride. The organic phase was washed with water and brine, dried over Na_2SO_4 and concentrated to give 290 mg of the symazetidinone 9. Nmr($CDCl_3$) δ : 1.73(s, 6H, CH_3), 3.74(s, 6H, $COOCH_3$), 4.60(s, 4H, CH_2), 4.77-5.63(m, 10H, CH and CH_2), 7.10(m, 10H, C_6H_5), 7.03(d, J=8Hz, 2H, NH).

(b) With 1 molar equivalent of Iodine: A mixture of the dithiazineazetidinone 7a (378 mg, 1 mmol) and iodine (254 mg, 1 mmol) in dry dioxane (30 ml) was stirred at 0°C for 15 min. Moist air was bubbled through the reaction mixture which was stirred at room temperature for 16 h. The reaction mixture was diluted with water and extracted with methylene chloride. The organic phase was washed with sodium thiosulfate, water and brine solution, dried over Na_2SO_4 and concentrated and purified by flash chromatography on silica gel using ether: hexane (3:1) as

eluant to give 150 mg (30%) of the 3-iodocepham 10. The yield of 10 was improved to 80% by the addition of thiourea or 2-mercaptobenzothiazole (1 equivalent) in the initial reaction mixture. The 3-iodocepham 10 was purified by flash chromatography on silica gel using ether: hexane (3:1) as eluant to give a yellow solid. mp 118-120°C; nmr($CDCl_3$): 2.22(s, 3H, CH_3), 2.98(ABq, J=15Hz, 2H, C_2-CH_2), 3.85(s, 3H, $COOCH_3$), 4.70(s, 2H, CH_2), 4.95(s, 1H, CH), 5.42(d, J=4Hz, 1H, C_6-H), 5.70 and 5.88 (dd, J_1=9Hz, J_2=4Hz, 1H, C_7-H), 7.85-6.92(m,6H,C_6H_5 and NH).

(c) With 3 atomic equivalent of Iodine: The reaction was done in the same way as described above. The organic phase was washed with sodium thiosulfate, water and brine, dried over Na_2SO_4 and concentrated. The residue was chromatographed over silica gel using ethyl acetate:hexane as gradient eluant, to give compound 8a in 48% yield; nmr($CDCl_3$) δ : 1.80(s, 3H, CH_3), 3.80(s, 3H, $COOCH_3$), 4.87-5.13(m, 5H, CH and CH_2S), 5.90(d, J=4Hz, 1H, CH), 6.03(d, J=4Hz, 1H, CH), 7.20 (m, 5H, C_6H_5). The yield was improved by the addition of 2-mercaptobenzothiazole (1.5 equivalents) in the initial reaction mixture. Similarly, compound 8b was obtained from 6b in 54% yield; mp 108-110°C; ir(KBr)cm^{-1}: 3081, 2907, 1763, 1731, 1623; nmr($CDCl_3$) δ : 1.96(s, 3H, CH_3), 3.80(s, 3H, $COOCH_3$), 5.02(d, 2H, CH_2), 5.20(s, 1H, CH), 5.72(d, J=4.5Hz, 1H, CH), 6.08(d, J=4.5Hz, 1H, CH), 7.32 (m, 5H, C_6H_5).

Methyl 2-[2'(R and S)-chloro-4'-oxo-3'S-[illegible]-phenoxy-[illegible]-chloromethyleneiminoazetidin-1'-yl]-3-chloromethyl-3-chlorosulfenyl butanoate (11):

Methyl 2-(3-phenoxy-4,5-dithia-2,7-diazabicyclo[4.2.0]oct-2-en-8-one-7-yl)-3-methyl-but-3-enoate (7b) (1.0 g, 2.7 mmol) was dissolved in distilled sulfuryl chloride (5 ml). There was an immediate reaction with the production of the title compound as was evident from the nmr spectrum in sulfuryl chloride: Major product (2'S-isomer) δ : 1.73(s, 3H, CH_3), 3.80(s, 3H, $COOCH_3$), 4.10(s, 2H, CH_2Cl), 4.63 (s, 1H, CH), 5.06(d, J=1.8Hz, 1H, 3-H), 5.50(d, J=1.8Hz, 1H, trans β-lactam proton 2-H), 7.33(5H, m, C_6H_5); Minor product (2'-R-isomer) δ : 1.66(s, 3H, CH_3), 3.82(s, 3H, $COOCH_3$), 4.18(s, 2H, CH_2Cl), 4.50(s, 1H, CH), 5.70(d, J=4Hz, 1H, C_3-H), 6.17(d, 1H, J=4Hz, cis β-lactam proton C_2-H), 7.33(m, 5H, C_6H_5) in a ratio of 4:1.

Reaction of Compound 11 with dimethylamine

To a cold solution of 11 (obtained by treatment of 500 mg of the diathiazine-azetidinone with sulfuryl chloride (3 ml), followed by washing with $NaHCO_3$ and water) in methylene chloride (20 ml) at -60°C under nitrogen, 1.84 ml of 7% dimethylamine solution in methylene chloride (10 ml) were added and the mixture was stirred at the same temperature for 30 min, followed at -10°C for an additional 30 min. The solvent was removed under vacuo and the residue was dissolved in benzene, washed with water and brine. The organic phase was dried over Na_2SO_4 and concentrated to give a brown oil which was purified by preparative thin layer chromatography on silica gel using ethyl acetate: hexane (1:2) as solvent, to give compound 13 in 45% (160 mg) yield as an oil. Ir(neat)cm^{-1}: 2943, 1787, 1728, 1645, 1595; and nmr($CDCl_3$) δ: 2.08(s, 3H, $C\underline{H}_3$), 2.96(s, 6H, $N(C\underline{H}_3)_2$), 3.88(s, 3H, $COOC\underline{H}_3$), 4.56 and 4.80(ABq, J=12Hz, 2H, $C\underline{H}_2$), 4.98(d, J=1.2Hz, 1H, C_2-H), 5.72(d, J=1.2Hz, 1H, C_3-H), 7.30-7.40(m, 5H, $C_6\underline{H}_5$).

Reaction of Compound 11 with Hydrogen Sulfide

Through a cold solution of compound 11 (obtained by treatment of 500 mg of dithiazineazetidinone with sulfuryl chloride (3 ml), followed by washing with $NaHCO_3$ and water) in THF (15 ml) at -60°C, H_2S gas was bubbled under nitrogen for 5 min. After stirring for 30 min at the same temperature, 0.72 ml of triethylamine was added to the reaction mixture which was stirred at 0°C for 0.5 h. The pH of the reaction mixture was adjusted to 6 by addition of acetic acid followed by concentration. The residue was diluted with benzene and washed with water, the benzene solution was dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel using ethyl acetate : hexane (3:17) as eluant. Yield 140 mg (55%), mp 99-101°C; Ir(KBr)cm^{-1}: 1763, 1732; nmr($CDCl_3$) δ : 1.72(s, 3H, CH_3), 2.50 and 2.80 (ABq, J=1.5Hz, 2H), 3.74(s, 3H, $COOCH_3$), 4.58(s, 1H, C$\underline{H}$), 5.70(d, J=4.25Hz, 1H, C$\underline{H}$), 6.08(d, J=4.25Hz, 1H, C$\underline{H}$), 7.30(m, 3H), 7.40(m, 2H). The ^{13}C nmr spectrum shows two CH_3 carbons at 24.65 and 52.42, one CH_2 carbon at 32.55, three CH carbons at 61.80, 70.18 and 85.69, phenyl carbons at 120.67, 126.15 and 129.54, and tert carbons at 41.05, 153.91, 165.12, 166.71 and 167.51.

Treatment of Compound 14 with triphenylphosphine

A solution of compound 14 (400 mg, 1.095 mmol) and triphenylphosphine (287 mg, 1.1 mmol) in toluene (15 ml) was heated in a nitrogen atmosphere at 50°C for 3h.

The solvent was removed in vacuo and gave the crude product which was purified on silica gel column using ethyl acetate : hexane as gradient eluant, to give 231 mg (77%) of compound 8b, mp 109-110°C.

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