A NOVEL INTRAMOLECULAR ACYLATION OF UNSYM-DIACYLAMINOAZETIDINONE DISULFIDES. THE 3,8-DIOXO-5-THIA-2,7-DIAZABICYCLO[4.2.0]OCTANES

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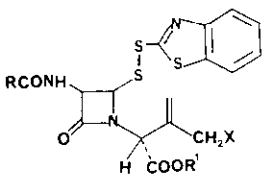
Abstract - unsym-Diacylaminoazetidinone disulfides on treatment with triethylamine produce the 3,8-dioxo-5-thia-2,7-diazabicyclo[4.2.0]octanes.

Penicillin sulfoxide esters, on heating with 2-mercaptobenzothiazole in solvents such as toluene or dioxane produce the unsym-azetidinone disulfides 1 in high yields[1]. On treatment with a base such as triethylamine, these compounds 1, are rapidly isomerised to the more stable isomers 2, in which the double bond is conjugated with the ester carbonyl moiety[1]. In the case of the unsym-azetidinone disulfide free acids 1 (R = X = H), however, treatment with aqueous $NaHCO_3$ gave the sym-azetidinone disulfides 3, in near quantitative yields[1]. The unsym-azetidinone disulfides 1b on treatment with ammonia in DMF at -35°C provide the 3-chloromethylcephems 4[2].



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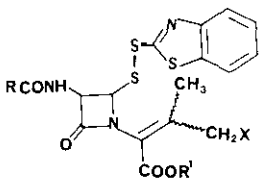

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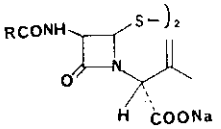

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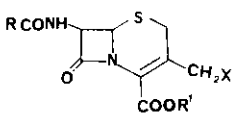
X = H
X = Cl



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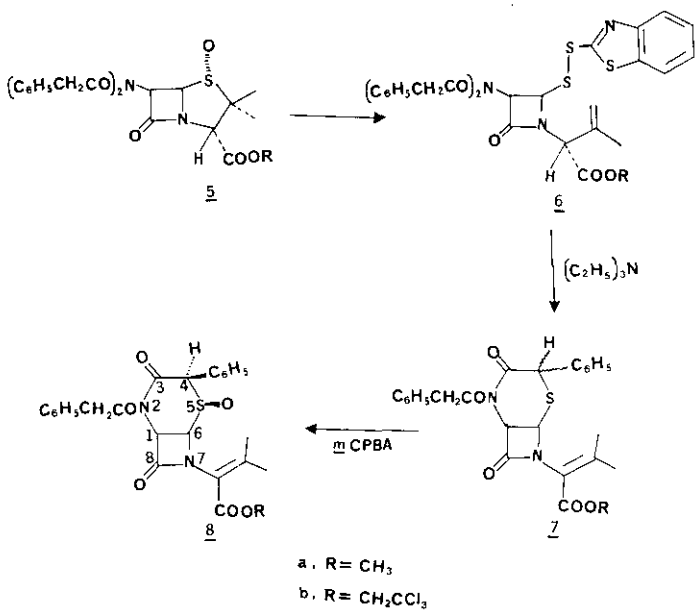
We have found that the reaction of the unsym-diacylaminoazetidinone disulfides 6 with a base, gives the 3,8-dioxo-5-thia-2,7-diazabicyclo[4.2.0]octanes 7, and in the case of the chloro substituted compounds 11, the compounds 12 are formed. Related bicyclic ring systems have been reported using idfferent methods[3,4].

Scheme–1



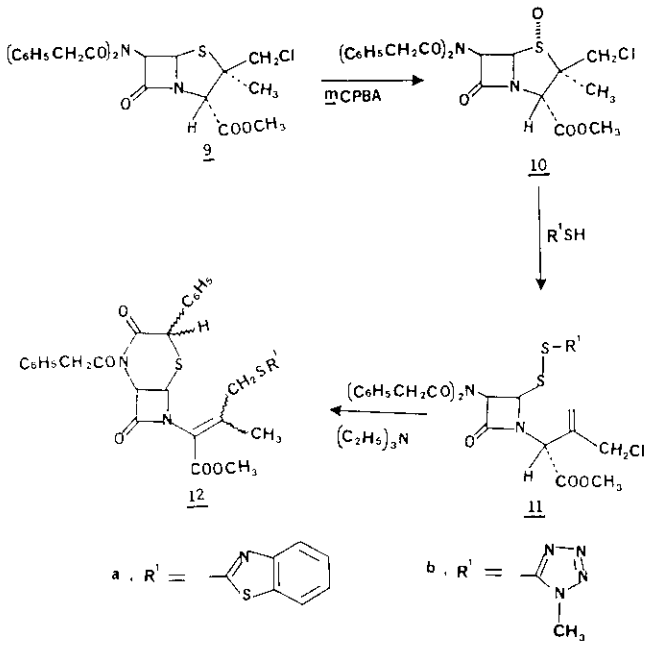
The 6β-diacylaminopenicillin-1R-sulfoxides 5[5] on heating under reflux with 2-mercaptobenzothiazole in benzene for 1.5 h have the unsym-azetidinone disulfides 6 in about 70% yields. Treatment of 6 with triethylamine (excess) in dichloromethane at room temp for 2 h gave compounds 7 as amorphous solids in about 75% yields after purification by silica gel chromatography. Spectral (IR, PMR, CMR and high resolution mass) and microanalytical data (C H N O S) are in agreement with the proposed structure; and indicated that a mixture of the C-4 isomers in a ratio of 9:1 is formed in the case of 5a.

The stereochemistry at C-4 of the major isomer of 7a has been assigned the structure indicated on the basis of the PMR spectrum of the oxidation product 8a. Oxidation of 7a with m-CPBA in dichloromethane at 0°C for 1 h, gave a 78% yield (after chromatography) of one isomer 8a with the spectral data given in the experimental section.

Oxidation of 7a to produce the sulfoxide 8a influences the chemical shifts of the protons at C-1, C-4 and C-6. The signal of the C-1 proton moves to low field, while that at C-6 moves to high field, similar to what is observed in the conversion of the penicillins and cephalosporins to their 1β-sulfoxides[6]. It is hence assumed that 8a is the β-sulfoxide. The two

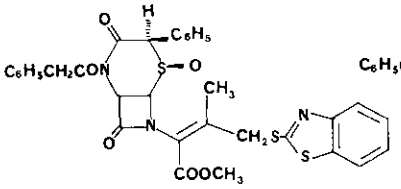
ortho protons of the C-4 phenyl group have also moved to low field, probably as a result of these protons falling in the deshielding cone of the oxygen of the sulfoxide. This is only possible (borne out by examination of the Drieding model), when the sulfoxide oxygen and the phenyl ring are periplanar to each other. The structure of the major isomer is hence as indicated in 8a.

Scheme–2



The 2β-chloromethyl-6β-diacylaminopenicillin 1R-sulfoxide 10 on refluxing with 2-mercaptobenzothiazole in benzene, gave the unsym-diacylaminoazetidinone disulfide 11 which on treatment with base gave a compound with the same bicyclic skeleton as described above. In addition, the chlorine of the chloromethyl group is replaced by the 2-benzothiazole thioether group; compound 12. Thus compound 11a (R^1 = 2-benzothiazole), on treatment with excess treithylamine in dichloromethane gave 12a, which was a mixture of both the Z (-$COOCH_3$ cis to -CH_3) and E (-$COOCH_3$ trans to -CH_3) geometric isomers in the ratio 7:3[7]. Each of these geometric isomers also consisted of the chiral R (92-94%) and S (8-6%) isomers at C-4 (based on the NMR spectra). The crude product was purified by column chromatography, and gave the mixture of the geometric isomers of the C-4 R isomer. The microanalytical and high resolution mass spectral data agreed with $C_{32}H_{27}N_3O_5S_3$. The PMR and CMR spectra agree with the assigned structure of 12a (mixture of geometric isomers). This structure 12a was confirmed by oxidation with m-CPBA (1.0 equivalent) in dichloromethane at 0°C, when a mixture of the geometric isomer E and Z sulfoxides 13 and 14, and the disulfoxides of the E isomer (only) 15 were

isolated. The PMR and CMR data on these compounds are given in the experimental section.



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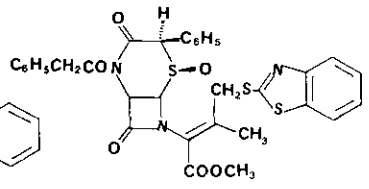

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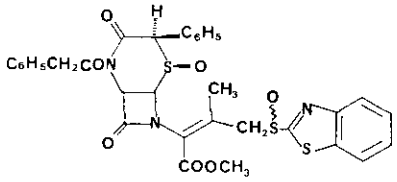

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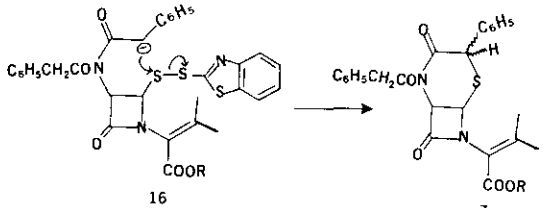
In a similar manner the 2,2,2-trichloroethyl ester 6b, and the 1-methyltetrazole compound 11b, also undergo this reaction to give 7b and 12b respectively.

The formation of these types of compounds can be explained by the formation of the anion 16, on treatment with base, followed by reaction with the disulfide bond, to produce 7. The stereoselectivity may be explained as due to the bulky phenyl group adjacent to the CH anion controlling the cyclisation reaction.



16 7

EXPERIMENTAL

All IR spectra were recorded as KBr discs, on a Nicolet DX-FTIR spectrophotometer. The NMR and CMR spectra were obtained using a Brucker AM-300 spectrometer. Microanalysis (C, H, N and S) of all new compounds were within 0.5% of the calculated values.

Methyl 2-[2-Oxo-3β(diphenylacetyl)amino-4-(benzothiazol-2-yl)azetidin-1-yl]-2-(prop-2-en-2-yl)-acetate (6a): A solution of methyl 6β-(diphenylacetyl)aminopenicillanate 1R-sulfoxide 5 (0.705 g, 1.46 mmol), was heated under reflux with 2-mercaptobenzothiazole (0.244 g, 1.46 mmol) in benzene (50 ml), for 2 h. Approximately 25 ml of benzene was distilled off, and the residue diluted with hexane. The resulting oily residue was separated, dissolved in dichloromethane, and concentrated under reduced pressure to give 640 mg (69%) of a light yellow foam; IR: 3386,

3050, 2951, 1780, 1742, 1700, 1678, 1428 cm^{-1}; PMR ($CDCl_3$)δ: 2.04(s,3H), 3.70 and 3.82(ABq, J=19.70Hz,2H), 5.22(s,1H), 5.48(d,J=4.63Hz,1H), 5.78(d,J=4.63Hz,1H), 6.90(bs,1H), 7.30(m,11H), 7.78 (d,J=6Hz,1H), 7.90(d,J=6Hz,1H).

Similarly 2,2,2-trichloroethyl 6β-(diphenylacetyl)aminopenicillanate 1R-sulfoxide (5b) with 2-mercaptobenzothiazole gave compound 6b *in 67% yield.*

Methyl 2-[2-Oxo-3β(diphenylacetyl)amino-4-(benzothiazol-2-yldithio)-azetidin-1-yl]-2-(1-chloroprop-2-en-2-yl)acetate (11a): This compound was prepared by a similar method as described above using methyl 2β-chloromethyl-6β(diphenylacetyl)*aminopenicillanate 1R-sulfoxide* (10a, 2.56g, 4.95 mmol), and 2-mercaptobenzothiazole (0.844g, 5.05 mmol). Yield 2.46g (75%); IR: 3343, 2984, 1783 and 1741 cm^{-1}; PMR ($CDCl_3$)δ: 3.80(m,7H), 4.24 and 4.44(ABq,J=12.12Hz, 2H), 5.28 and 5.42(ABq,J=16.17Hz,2H), 5.50(d,J=4.70Hz,1H), 5.61(s,1H), 5.78(d,J=4.70Hz,1H), 6.94(bs,1H), 7.34(m,11H), 7.74(d,J=6Hz,1H), 7.90(d,J=6Hz,1H). Similarly compound 10b, on refluxing with 5-mercapto-1-methyltetrazole in benzene gave the unsym-azetidinone disulfide 11b, in 72% yield.

Reaction of unsym-Diacylaminoazetidinone Disulfides with Triethylamine: Triethylamine (0.41 mL) was added to a stirred solution of the unsym-diacylaminoazetidinone disulfide (700 mg) in dichloromethane (30 ml), and the resulting solution stirred for 2 h. The reaction mixture was washed successively with dil HCl, water and brine, and dried over Na_2SO_4. Concentration of the filtrate, followed by gradient elution column chromatography over silica gel using hexane-ethyl acetate, gave the pure compound. The yield, IR, NMR and microanalytical data of these compounds are given below:

Compound 7a: Yield 77%; IR: 2962, 1778, 1719 and 1377 cm^{-1}: PMR ($CDCl_3$)δ: 2.00(s,3H); 2.21 (s,3H), 3.74(s,2.7H), 3.77(s,0.3H), 5.00(s,0.9H), 4.76(s,0.1H), 4.28 and 4.42(ABq,J=16.41Hz,2H), 5.40(d,J=6.15Hz,0.9H), 5.48(d,J=6.15Hz,0.1H), 6.74(d,J=6.15Hz,0.9H), 6.96(d,J=6.15Hz,0.1H), 7.34(m,10H); CMR: three methyl signals at 22.10, 23.54 and 52.33; one methylene at 45.55; three methine signals at 45.56 (43.70), 60.13 (63.32) and 63.55 (64.42); ten phenyl CH carbon signals between 127.08 to 129.74 and eight tertiary carbons at 119.50, 132.11, 133.91, 154.10, 163.86, 164.70, 169.91 and 174.80; EIMS: M^+ 464.1406 for $C_{25}H_{24}N_2O_5S$, calcd. 464.1437; Anal: Found C, 64.52; H, 5.21; N, 6.08; S, 7.09; Calcd. for $C_{25}H_{24}N_2O_5S$,C, 64.65; H, 5.17; N, 6.03; S, 6.89.

Compound 7b: Yield 45%; IR: 2992, 1782, 1718, 1380 cm^{-1}; PMR ($CDCl_3$)δ: 2.20(s,3H), 2.38 (s,3H), 4.33 and 4.45(ABq,J=17.14Hz,2H), 4.74 and 4.97(ABq,J=11.56Hz,2H), 5.00(s,0.9H), 4.89 (s,0.1H), 5.62(d,J=5.99Hz,0.9H), 5.68(d,J=5.99Hz,0.1H), 6.95(d,J=5.99Hz,1H), 7.36(m,10H); CMR: two methyl signals at 22.55 and 23.99; two methylene signals at 45.52 and 74.27; three methine signals at 45.67 (43.93), 60.62 (63.52) and 63.87 (64.77); ten phenyl CH carbons between 112.16-129.97 and nine tertiary carbons at 94.64, 118.58, 132.05, 133.94, 158.83, 161.48, 165.24,

169.64, 174.04; EIMS: M^+ 582.0364 calcd. for $C_{26}H_{23}N_2O_5SCl_3$ 582.0354.

Compound 12a: Yield 58%; IR: 2992, 1777, 1719, 1426 cm^{-1}; PMR ($CDCl_3$)δ: 2.12(s,2.1H), 2.28 (s,0.9H), 3.72 (s,0.9H), 3.80(s,2.1H), 4.40 and 4.71(ABq,J=13.21Hz,1.4H), 4.32(m,2.6H) 5.06 (s,0.7H), 5.12(s,0.3H), 5.36(d,J=6.60Hz,0.7H), 5.58(d,J=6.60Hz,0.3H), 6.76(d,J=6.60Hz,0.7H), 6.88(d,J=6.60Hz,0.3H), 7.28(m,12H), 7.78(m,2H); CMR: two methyl signals at 20.63 (19.51) and 52.77 (52.63); two methylene signals at 36.21 (37.53) and 45.38; three methine signals at 45.45 (40.82), 60.33 (60.57) and 63.58 (64.40); fourteen phenyl CH carbons between 120.98-129.71; tertiary carbons at 122.65 (122.03), 132.15, 133.94 (135.62), 148.84 (148.58), 152.90, 163.30 (163.59), 164.24 (164.56), 164.98 (165.15), 169.86 and 174.00; EIMS: M^+ 629.113 for $C_{32}H_{27}N_3O_5S_3$ Calcd. 629.1141. Anal: Found C, 60.74; H, 4.38; N, 6.30; S, 15.03 Calcd. for $C_{32}H_{27}N_3O_5S_3$ C, 61.04; H, 4.29; N, 6.67; N, 15.26.

Compound 12b: Yield 60%; IR: 2992, 1777, 1719, 1385 cm^{-1}; PMR ($CDCl_3$)δ: 2.20(s,2.1H), 2.24(s,0.9H), 3.70(s,0.9H), 3.80(s,2.1H), 3.82(s,0.9H), 3.88(s,2.1H), 4.44 and 4.96(ABq,J=11.81Hz, 1.4H), 4.40(m,2.6H), 4.94(s,0.7H), 5.30(s,0.3H), 5.50(d,J=5.96Hz,0.7H), 5.72(d,J=5.96Hz,0.3H), 6.78(d,J=5.96Hz,0.7H), 6.90(d,J=5.96Hz,0.3H), 7.36(m,10H). CMR: Three methyl signals at 20.42 (18.91), 33.41 and 52.76 (52.52); two methylene signals at 36.74 (37.67) and 45.25; three methine signals at 45.43 (45.51), 60.60 (60.89) and 63.58 (64.25); ten phenyl CH carbons between 126.09-129.60; tertiary carbons at 122.98 (123.42), 132.02 (133), 133.90, 148.20, 153.80, 162.99 (163.19), 164.04, 169.55 and 173.90; EIMS: M^+ 578.1406 for $C_{27}H_{26}N_6O_5S_2$ Calcd. 578.1393; Anal: Found C, 56.22; H, 4.57; N, 14.31; S, 10.92 Calcd. for $C_{27}H_{26}N_6O_5S_2$ C, 56.05; H, 4.49; N, 14.52; S, 11.07.

Oxidation of Compound 7a with m-Chloroperbenzoic Acid.

m-CPBA (80%, 158 mg, 0.73 mmol) was added to an ice cold solution of compound 7a (340 mg, 0.73 mmol), in dichloromethane (15 mL) and the mixture stirred for 1 h and filtered. The filtrate was successively washed with aq. $NaHCO_3$, water and brine solution, dried over Na_2SO_4 and concentrated. The residue was chromatographed over silica gel using EtOAc:hexane as eluant. Yield 275 mg (78%). IR: 3432, 2966, 1786, 1721, 1629 cm^{-1}; PMR ($CDCl_3$)δ: 1.97(s,3H), 2.28(s,3H), 3.68(s,3H), 4.35 and 4.42(ABq,J=18.5Hz,2H), 4.96(d,J=5.3Hz,1H), 5.24(s,1H), 7.00(d,J=5.3Hz,1H), 7.30(m,5H), 7.52(m,3H), 7.60(m,2H); CMR: Three methyl signals at 22.24, 23.66 and 52.52; one methylene signal at 45.54, three methine signals at 59.60, 63.72 and 70.24; ten phenyl CH carbons between 127.11 to 130.55 and tertiary carbons at 120.00, 133.72, 156.22, 164.86, 164.98 and 173.41. MS-FAB: 481(MH^+) for $C_{25}H_{24}N_2O_6S$ Calcd. 480.

Oxidation of Compound 12a with m-Chloroperbenzoic Acid.

The compound 12a (900 mg, 1.43 mmol) was oxidized with m-CPBA (80%, 310 mg, 1.43 mmol) in the same manner as described above for compound 7a. The crude product, chromatographed over silica gel using EtOAc:hexane as eluant gave three fractions.

Fraction A: Yield 135 mg (14.6%); IR: 3435, 2943, 1786, 1728, 1622 cm^{-1}; PMR: ($CDCl_3$)δ: 2.38(s,3H), 3.68(s,3H), 4.00 and 4.52(ABq,J=13.67Hz,2H), 4.38 and 4.44(ABq,J=18.13Hz,2H), 5.28(s,1H), 5.52(d,J=5.35Hz,1H), 7.24(d,J=5.35Hz,1H), 7.32(m,7H), 7.44(m,3H), 7.60(m,2H), 7.78(d,J=7.71Hz,1H), 7.92(d,J=7.71Hz,1H); CMR: two methyl signals at 20.09 and 52.83; two methylene signals at 37.55 and 45.46; three methine signals at 60.04, 63.85 and 70.52; ten phenyl CH carbons between 121.60-130.77; tertiary carbons at 133.64, 135.34, 152.14, 152.69, 163.57, 163.86, 164.92, 165.21 and 173.30. MS-FAB: 646(MH^+) for $C_{32}H_{27}N_3O_6S_3$ Calcd. 645. This spectral data confirms the structure as shown for 14.

Fraction B: Yield 330 mg (35.75%); IR: 3436, 2968, 1788, 1721, 1624 cm^{-1}; PMR: ($CDCl_3$)δ: 2.16(s,3H), 3.42(s,3H), 4.28 and 4.90(ABq,J=13.67Hz,2H), 4.34 and 4.40(ABq,J=18.11Hz,2H), 5.04 (d,J=5.12Hz,1H), 5.28(s,1H), 7.00(d,J=5.12Hz,1H), 7.32(m,7H), 7.60(m,6H), 7.74(d,J=6.77Hz,1H); CMR: two methyl signals at 20.76 and 53.10; two methylene signals at 36.13 and 45.50; three methine signals at 59.78, 63.89 and 69.90; fourteen phenyl CH carbons between 121.07-130.65; tertiary carbon signals at 122.71, 133.62, 135.60, 150.64, 152.87, 163.36, 164.47, 164.81 and 173.34. MS-FAB: 646(MH^+) for $C_{32}H_{27}N_3O_6S_3$ Calcd. 645. This data confirms the structure as shown for 13.

Fraction C: Yield 100 mg (10.57%); IR: 3443, 2951, 1789, 1723, 1625 cm^{-1}; PMR ($CDCl_3$)δ: 1.91(s,1.65H), 2.02(s,1.35H), 3.60(s,1.65H), 3.72(s,1.35H), 4.34 and 4.96(ABq,J=12.40Hz,1.10H), 4.50 and 4.80(ABq,J=12.40Hz,0.90H), 4.36(m,2H), 5.02(d,J=5.72Hz,0.55H), 5.04(d,J=5.72Hz,0.45H), 5.06(s,0.55H), 5.12(s,0.45H), 6.96(d,J=5.72Hz,0.55H), 6.98(d,J=5.72Hz,0.45H), 7.30(m,5H), 7.54 (m,7H), 7.96(m,2H). CMR: two methyl signals at 23.21(23.05) and 53.04; two methylene signals at 45.44 and 61.72 (60.44); three methine signals at 59.79, 63.81 (63.71) and 69.95; fourteen phenyl CH carbons between 122.23-130.62; tertiary carbons at 125.20 (124.80), 133.60, 136.03, 143.17 (142.97), 153.74, 162.79 (162.60), 164.19, 164.72, 173.30. MS-FAB: 662(MH^+) for $C_{32}H_{27}N_3O_7S_3$ Calcd. 661. This data confirms the structure as shown for compound 15.

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