A 5-Methylthiopenicillin Analog and its Transformation to Novel Bicyclic β-Lactams (1)

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Reaction of methoxyacetyl chloride with 2-methylthio-2-thiazoline resulted in the stereoselective production of one isomer of 6-methoxy-5-methylthiopenam which underwent rearrangement to 6-methoxy-7-methylthio-5-oxo-2,3,4,5-tetrahydro-1,4-thiazepine when treated with trifluoroacetic acid. Subsequent thioamidation and alkylation with methyl iodide provided 5,7-bismethylthio-6-methoxy-2,3-dihydro-1,4-thiazepine which reacted with methoxyacetyl chloride and triethylamine to give a novel 1,4-thiazabicyclo[5.2.0]non-5-ene. Other substituted bicyclic β-lactams of similar structure have also been synthesized.

In the continuing search for medicinally useful β-lactam antibacterials attention was directed at first in many laboratories to the modification of the side chain; in recent years transformation of the heterocycle fused to the β-lactam ring has been of interest (2). Most recently, substitution of the β-lactam ring, particularly at the position α to the β-lactam carbonyl, has become the focus of attention (3,4). In the course of our search for synthetic approaches to novel analogs of β-lactam antibiotics we have reported previously the preparation of various substituted β-lactams (5). We wish to describe now a convenient route to 5-alkylthiopenam derivatives and their rearrangement to intermediates for new bicyclic β-lactam systems.

In our earlier studies we utilized the "acid-chloride-imine" method for synthesizing variously substituted β-lactams (5). In the present investigation we have examined the suitability of 2-methylthio-2-thiazoline (**1**) as the imine component. The reaction of methoxyacetyl chloride and triethylamine with this imine led to the stereospecific formation of 6-methoxy-5-methylthiopenam (**2**) in 73% yield. The pmr spectrum of (**2**) shows one sharp absorption at δ 4.70 for the β-lactam proton indicating that a single isomer had been formed. The pmr spectrum also shows that one of the protons on the methylene group adjacent to the nitrogen atom is significantly deshielded (δ 3.9-4.4) due to the *syn*-periplanar relationship of that proton with the nitrogen lone pair. On the basis of spectral information alone it was not possible to unequivocally assign the relative stereochemistry of the substituents at C_5 and C_6 of the penam (**2**). This could be accomplished when **2** was converted to the corresponding 6-methoxy-5-methylsulfoxide-penam **3** with *m*-chloroperoxybenzoic acid. Comparison of the pmr spectra of **2** and **3** shows that the methylthio resonance undergoes a downfield shift of *ca.* 30 Hz on oxidation thus establishing the site of oxidation at the substituent sulfur rather than at the ring sulfur. The strongly dipolar nature of the sulfoxide bond is expected to directly influence the absorption positions of any neighboring protons in the proton spectrum. It was observed that the resonance position for the methoxyl absorption is virtually unchanged but that the β-lactam proton experiences a deshielding of *ca.* 16 Hz upon sulfoxide formation. This anisotropic deshielding effect indicates that the β-lactam proton is *cis* to the 5-methylsulfoxide substituent in **3** and hence *cis* to the 5-methylthio substituent in **2**.

The stability of penam **2** under normal atmospheric conditions is remarkable in view of the unusual feature that the molecule possesses three heteroatoms connected by single bonds to the same carbon atom. Under the influence of trifluoroacetic acid, however, **2** underwent a rapid molecular rearrangement. The product which was obtained in 85% yield has been assigned the 1,4-thiazepine structure **4** on the basis of spectral and analytical data. Presumably the protonation of the amide nitrogen of **2** followed by the abstraction of the β-lactam proton and concomitant rearrangement results in the formation of **4**.

The rearrangement of the penam (**2**) to the 1,4-thiazepine (**4**) under the influence of trifluoroacetic acid is noteworthy. It contrasts with recent reports (6,7) that penicillin G methyl ester (**5**) under similar conditions is degraded to thiazoline-4-carboxylate (**6**). The formation of the thiazoline ester (**6**) in this reaction is indicative of the simultaneous cleavage of both the amide and the C_5-C_6 bonds in (**5**). This mode of cleavage of penams has also

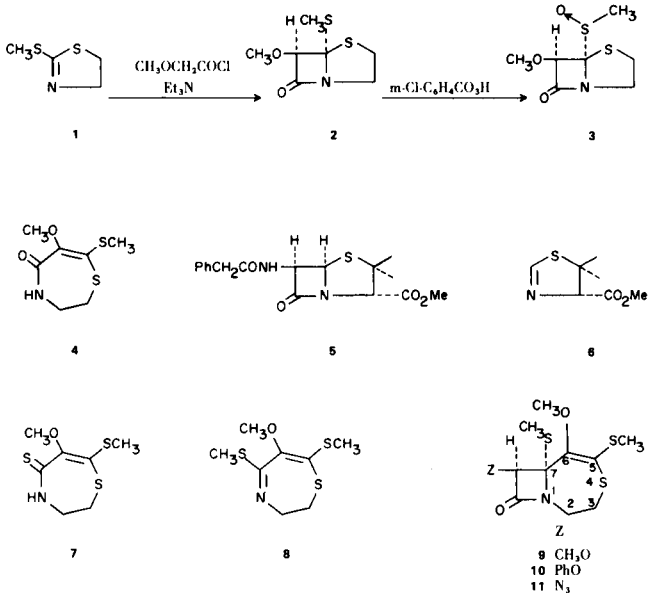
been observed by other workers under photolytic (8) as well as hydrogenolysis (9) conditions. The formation of 1,4-thiazepines from penicillins (10) and their sulfoxides (11) has also been noticed; but this type of rearrangement has been reported to occur under basic conditions.

The thiazepine (**4**) was converted to the corresponding thioamide analog **7** by reaction with a stoichiometric quantity of phosphorus pentasulfide in refluxing pyridine. Further reaction with methyl iodide produced a 2,3-dihydro-1,4-thiazepine hydroiodide (**8**). The free base was isolated by neutralization with triethylamine and extraction with dichloromethane. The methylthio resonance position for each of the methylthio substituents in the free base occurred at δ 2.23 in the nmr spectrum. Treatment of this methylthio imine with substituted acetyl chlorides produced novel bicyclic-β-lactams: **9**, **10**, **11**.

The resonance signal at δ 2.2 which integrates for three protons in the nmr spectra of **9**, **10** and **11** has been assigned to the methylthio group directly attached to the β-lactam nucleus. We have observed a similar chemical shift for the methylthio protons in a number of other compounds when methylthio cyclic imines are converted to the bicyclic β-lactams *via* cycloaddition reactions (1b). In the thiazabicyclo[5.2.0]non-5-enes **10** and **11** the methoxyl resonance in their pmr spectra is shifted downfield when compared to the substrate imine. In the case of **9** therefore it was presumed reasonable to assign the δ 3.63 absorption to the β-lactam methoxyl and the δ 3.84 absorption to the C-6 substituent.

The assignment of the C-7 methylthio substituent *cis* to the C-8 β-lactam proton is based upon lanthanide induced shift data (1b). Examination of the proton spectra of bicyclic-β-lactams such as **2**, **3**, **9**, **10** and **11** reveals that the protons of the methylene alpha to the nitrogen are absorbing in the spectrum with a shift difference of 30 to 40 Hz. This is the anisotropic effect of a ring nitrogen lone pair on an adjacent methylene group (12). Thus the low field proton has been deshielded by virtue of its *syn*-periplanar orientation to the nitrogen lone pair electrons. Upon incremental addition of Eu(FOD)$_3$ to **9** it is found that the deshielded proton and the β-lactam proton undergo pronounced shifts when compared to the rest of the protons in the molecule. A topological examination of a molecular model of **9** makes it clear that the deshielded proton and the β-lactam proton are restricted to the same face of the molecule. The N-1, C-7 ring junction of the [5.2.0] non-5-ene fixes the nitrogen lone pair and the methylthio substituent on the same side of the molecule (again *syn*-periplanar) and thus the C-7 methylthio substituent and the β-lactam substituent are *cis* to each other.

The introduction of the azido group α to the β-lactam carbonyl in **11** assumes a particular strategic importance since we have shown that the azide group may serve as a precursor to the naturally occurring amido side chains found in the penicillins and cephalosporins (5).



EXPERIMENTAL

Melting points were determined in open capillary tubes using a "Mel-Temp" apparatus and are uncorrected. Infrared spectra were obtained with a Perkin Elmer Infracord. Pmr spectra were recorded on a Varian A-60A spectrometer operating at 60 MHz in deuteriochloroform solution containing tetramethylsilane as an internal standard with chemical shifts (δ) expressed in ppm downfield from TMS. Mass spectra were obtained with a Perkin-Elmer RMU-7 mass spectrometer. Elemental analyses were performed by Bernhardt, Max-Planck Institute, Mülheim, West Germany. Florisil obtained from Fischer Scientific Company was used for chromatography. All solvents used were reagent grade. Distilled solvents were purified by distillation from phosphorus pentoxide. Dichloromethane and chloroform extracts were dried over anhydrous sodium sulfate or magnesium sulfate.

2-Methylthio-2-thiazoline (**1**).

A solution of 2-mercaptothiazoline (119 g., 1.00 mole), methyl iodide (142 g., 1.00 mole) and methanol (600 ml.) was heated under reflux for one hour. The solvent was removed to give the product hydroiodide as a white crystalline mass, m.p. 122-125°. The solid was dissolved in water (700 ml.) and neutralized with 50% sodium hydroxide (80 ml.), extracted with dichloromethane, dried, evaporated and distilled to give thiazoline **1**, 81.4 g., 73%, b.p. (1 mm) 70-71°; ir: ν max (film) 1560 (C=N) cm^{-1}; nmr (deuteriochloroform): δ 2.5 (s, 3H, CH_3), 3.4 (t, 2H, J = 7 Hz, CH_2), 4.2 (t, 2H, J = 7 Hz, CH_2).

6-Methoxy-5-methylthio-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane (**2**).

A solution of 2-methylthio-2-thiazoline (12.3 g., 0.093 mole), triethylamine (20.0 g., 0.20 mole) and distilled dichloromethane (150 ml.) was stirred at room temperature while a solution of

methoxyacetyl chloride (10.0 g., 0.093 mole) in distilled dichloromethane (150 ml.) was added dropwise over a one and a half hour period. The pale yellow reaction mixture was stirred under nitrogen at room temperature overnight. The reaction mixture was washed several times with 20% aqueous hydrochloric acid, four times with saturated aqueous sodium bicarbonate, once with water, dried and evaporated to give a pale yellow oil, 13.8 g., 73%. The oil was dissolved in benzene and passed through a column of Florisil. The oil purified in this way was placed under vacuum (0.1 mm) for several days but crystallization was not observed; ir: ν max (film) 1780 (beta-lactam C=O) cm^{-1}; nmr (deuteriochloroform): δ 2.30 (s, 3H, CH_3S), 2.8-3.6 (m, 3H, CH_2 and CH), 3.63 (s, 3H, CH_3O), 3.9-4.4 (m, 1H, CH), 4.7 (s, 1H, beta-lactam proton); mass spectrum: M^+ at m/e 205.

Anal. Calcd. for $C_7H_{11}NO_2S_2$: C, 40.96; H, 5.40; N, 6.82. Found: C, 40.81; H, 5.39; N, 6.96.

6-Methoxy-7-methylthio-5-oxo-2,3,4,5-tetrahydro-1,4-thiazepine (**4**).

A mixture of 6-methoxy-5-methylthio-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane (**2**, 2.0 g., 0.01 mole) and trifluoroacetic acid (10 ml.) was stirred together for 15 minutes. The solvent was removed and the oil triturated with ether to give a white solid product, (1.7 g., 85%), m.p. 161-162° (ethyl acetate); ir: (nujol) ν max, 3300, 3200 (NH), 1645 (C=O), 1560 (C=C) cm^{-1}; nmr: (d_6-DMSO) δ, 2.33 (s, 3H, CH_3), 2.98 (t, 2H, J = 6 Hz, CH_2), 3.30 (t, 2H, J = 6 Hz, CH_2), 3.65 (s, 3H, CH_3O), 8.0-8.6 (broad, 1H, NH). Mass spectrum: M^+ at m/e 205.

Anal. Calcd. for $C_7H_{11}NO_2S_2$: C, 40.96; H, 5.40; N, 6.82. Found: C, 41.20; H, 5.58; N, 6.95.

6-Methoxy-7-methylthio-5-thiono-2,3,4,5-tetrahydro-1,4-thiazepine (**7**).

A suspension of 6-methoxy-7-methylthio-5-oxo-2,3,4,5-tetrahydro-1,4-thiazine (**4**, 1.6 g., 0.008 mole), phosphorus pentasulfide (0.40 g., 0.002 mole) and pyridine (15 ml.) was heated under reflux for 2 hours and poured hot through filter paper into water (200 ml.). A crystalline yellow precipitate was collected after 30 minutes, 0.9 g., (52%), m.p. 137-139°. Mass spectrum: M^+ at m/e 221; ir: (nujol) ν max (3250 (NH), 1640 (C=C) cm^{-1}. Nmr (deuteriochloroform): δ 2.50 (s, 3H, CH_3S), 3.0-3.5 (m, 2H, CH_2), 3.5-4.0 (m, 2H, CH_2), 3.75 (s, 3H, CH_3O), 8.0-8.5 (broad, 1H, NH).

Anal. Calcd. for $C_7H_{11}NOS_3$: C, 37.98; H, 5.01; N, 6.33. Found: C, 38.13; H, 5.06; N, 6.38.

6-Methoxy-5,7-bismethylthio-2,3-dihydro-1,4-thiazepine Hydroiodide (**8**).

A solution of 6-methoxy-5-methylthio-7-thiono-1,2,3,7-tetrahydro-1,4-thiazine (**7**, 5.0 g., 0.022 mole), methyl iodide (3.4 g., 0.024 mole) and tetrahydrofuran (120 ml.) was refluxed for 30 minutes. After cooling to room temperature a yellow crystalline solid was collected, 5.5 g., 66%, m.p. 155-157°. A small sample was neutralized with triethylamine and the free base extracted with dichloromethane to provide material for the spectral data. The analysis was performed on the hydroiodide; ir: (nujol) ν max, 1580 (C=C), 1550 (C=N) cm^{-1}; nmr (deuteriochloroform): δ 2.23 (s, 6H, CH_3S), 3.35 (t, 2H, J = 6 Hz, CH_2), 3.68 (s, 3H, CH_3O), 3.85 (t, 2H, J = 6 Hz, CH_2).

Anal. Calcd. for $C_8H_{13}NOS_3$·HI: C, 26.45; H, 3.88; N, 3.86. Found: C, 26.56; H, 4.01; N, 3.85.

6,8-Dimethoxy-5,7-bismethylthio-9-oxo-1,4-thiazabicyclo[5.2.0]-non-5-ene (**9**).

A solution of 6-methoxy-5,7-dimethylthio-2,3-dihydro-1,4-thiazepine hydroiodide (**8**, 7.3 g., 0.020 mole), triethylamine (4.04 g., 0.040 mole) and dichloromethane (160 ml.) was stirred at room temperature under a nitrogen atmosphere while a solution of methoxyacetyl chloride (2.2 g., 0.20 mole) and dichloromethane (80 ml.) was added dropwise over a one hour period. The reaction mixture was stirred overnight under nitrogen, washed with 20% aqueous hydrochloric acid, aqueous sodium bicarbonate, water, dried and evaporated to give a pale yellow oil that was crystallized from ether/hexane (5:1) to give 1.5 g., 25%, of cream crystals, m.p. 54-56°; ir: (nujol) ν max, 1760 (beta-lactam C=O), 1585 (C=C) cm^{-1}; nmr (deuteriochloroform): δ 2.20 (s, 3H, beta-lactam CH_3S), 2.35 (s, 3H, CH_2S), 2.5-3.6 (m, 3H, CH_2 and CH), 3.63 (s, 3H, methoxyl), 3.84 (s, 3H, methoxyl), 3.7-4.3 (m, 1H, CH), 4.56 (s, 1H, beta-lactam proton).

Anal. Calcd. for $C_{11}H_{17}NO_3S_3$: C, 42.97; H, 5.58; N, 4.56. Found: C, 43.09; H, 5.69; N, 4.56.

6-Methoxy-5,7-bismethylthio-9-oxo-8-phenoxy-1,4-thiazabicyclo-[5.2.0]non-5-ene (**10**).

This compound was prepared in 62% yield from 5.4 g. of **8** and 2.8 g. of phenoxyacetyl chloride by the method described under **9**, m.p. 100-101°; mass spectrum: M^+ at m/e 369; ir: (nujol) ν max 1755 (beta-lactam C=O), 1590 (C=C) cm^{-1}; nmr (deuteriochloroform): 2.21 (s, 3H, beta-lactam CH_3O), 3.7-4.3 (m, 1H, CH), 5.38 (s, 1H, beta-lactam proton), 6.9-7.3 (m, 5H, phenyl).

Anal. Calcd. for $C_{16}H_{19}NO_3S_3$: C, 52.01; H, 5.18; N, 3.79. Found: C, 51.93; H, 5.10; N, 3.82.

8-Azido-6-methoxy-5,7-bismethylthio-9-oxo-1,4-thiazabicyclo-[5.2.0]non-5-ene (**11**).

This compound was prepared in 31% yield from **8** and azidoacetyl chloride, m.p. 86-87°; ir: (nujol) ν max 2100 (azido), 1780 (beta-lactam C=O), 1560 (C=C) cm^{-1}; nmr δ 2.20 (s, 3H, beta-lactam CH_3S), 2.33 (s, 3H, CH_3S), 2.6-3.6 (m, 3H, CH_2 and CH), 3.85 (s, 3H, methoxyl), 3.8-4.2 (m, 1H, CH), 4.98 (s, 1H, beta-lactam proton).

Anal. Calcd. for $C_{10}H_{14}N_4O_2S_3$: C, 37.71; H, 4.43; N, 17.60. Found: C, 37.88; H, 4.32; N, 17.46.

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REFERENCES

(1a) Part XXXII of "Studies on Lactams." For part XXXI see A. K. Bose, J. L. Fahey and M. S. Manhas, *Tetrahedron*, 000 (1973). (b) Abstracted in part from the Ph.D. Thesis of J. L. Fahey, Stevens Institute of Technology, Hoboken, New Jersey (1972).

(2) M. S. Manhas and A. K. Bose, "Beta-Lactams: Natural and Synthetic," Part I Wiley-Interscience, New York, New York (1973), Chapter Three.

(3) R. A. Firestone and B. G. Christensen, *J. Org. Chem.*, 38, 1436 (1973).

(4) J. E. Baldwin, F. J. Urban, R. D. G. Cooper and F. L. Jose, *J. Am. Chem. Soc.*, 95, 2401 (1973).

(5) A. K. Bose, B. Anjaneyulu, S. K. Bhattacharya and M. S. Manhas, *Tetrahedron*, **23**, 4769 (1967) and subsequent papers in this series.

(6) M. R. Bell, J. A. Carlson and R. Oesterlin, *J. Am. Chem. Soc.*, **92**, 2177 (1970).

(7) M. R. Bell, J. A. Carlson and R. Oesterlin, *J. Org. Chem.*, **37**, 2733 (1972).

(8) W. O. Godtfredsen, W. von Daehne and S. Vangedal, *Experientia*, **23**, 280 (1967).

(9) M. S. Manhas, J. S. Chib and A. K. Bose, *J. Org. Chem.*, **38**, 1238 (1973).

(10a) O. K. J. Kovacs, B. Ekstrom, and B. Sjoberg, *Tetrahedron Letters*, 1863 (1969); (b) B. G. Ramsay and R. J. Stoodley, *Chem. Commun.*, 450 (1973); (c) A. Vlietinck, E. Roets, P. Claes and H. Vanderhaege, *Tetrahedron Letters*, 285 (1972).

(11) A. K. Bose, unpublished results.

(12) J. B. Lambert, R. G. Kasge, R. E. Carhart and A. P. Jovanovich, *J. Am. Chem. Soc.*, **89**, 3761 (1967).