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# Studies on Fused β-Lactams: Synthesis of 1-Aza Analogs of Cephem

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Annelation of 2-methylthio-3,4-dihydropyrimidine (**3**) with two moles of phenoxyacetyl chloride in presence of triethylamine did not yield the expected β-lactam (**6**) and instead the *N*-acylated compound **5a** was obtained. Various *N*-acylated pyrimidines **5a**—**d** also failed to yield any β-lactam. However, β-lactam ring has been conveniently grafted on to 2-methylthio-3,6-dihydropyrimidines **9a**—**d**, **12** by annelating them with in situ prepared aryloxyketenes to furnish novel 1-aza analogs of cephem **10a**—**e** and **13**.

β-Lactam antibiotics today play a key role in bacterial chemotherapy. Most of the work on β-lactam antibiotics has dealt with structural modifications of penicillins and cephalosporins. One such modification is the replacement of sulfur by other heteroatoms.[1-5] Our earlier efforts in the replacement of sulfur atom in the cephalosporin system with nitrogen[6-8] and also at different position[9] results in various β-lactams which are of interest both from structural as well as biological point of view. The incorporation of one or more nitrogen atoms into the ring fused to the β-lactam has been investigated by various groups.[10-14] Inspired by these findings, we decided to synthesize some 1-aza analogs of cephem through cycloaddition of in situ prepared ketenes to appropriate 2-methylthio-3,4/3,6-dihydropyrimidines.

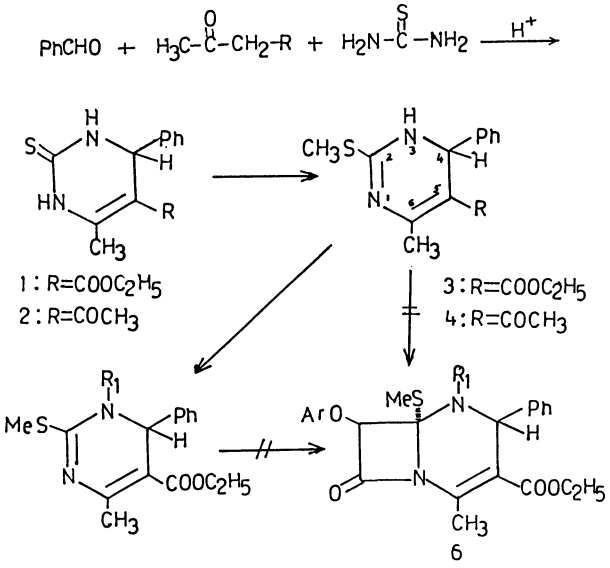
## Results and Discussion

The interesting 5-ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydro-2(1*H*)-pyrimidinethione[15,16] (**1**) was prepared by the acid-catalyzed reaction of benzaldehyde, ethyl acetoacetate, and thiourea in 80% yield. Compound **2** was also prepared in a similar manner except that acetylacetone was used in place of ethyl acetoacetate (Scheme 1). Compounds **1**, **2** were considered as suitable starting materials for the synthesis of 1-aza cephem analogs. The thione **1** was converted into 2-(methylthio)-3,4-dihydropyrimidine derivative **3** on refluxing with dimethyl sulfate in dry methanol for 2 h in 65% yield [IR (nujol) 1660 $cm^{-1}$ (C=N): $^1H$ NMR ($CDCl_3$) δ=2.70 (3H, s, H-2), 5.95 (1H, d, H-4); the latter signal collapses to a singlet after $D_2O$ exchange due to coupling with NH.

Various attempts were made to convert **3** into β-lactams **6** by annelating with 2 moles of phenoxyacetyl chloride/triethylamine or 2-naphthoxyacetic acid/phosphoryl chloride/triethylamine in dichloromethane at 5 °C for 7—10 h. However, under these conditions **3** failed to produce any β-lactam and instead the *N*-acetylated compound **5a** and **5b** were recovered in 60% and 50% yields respectively.

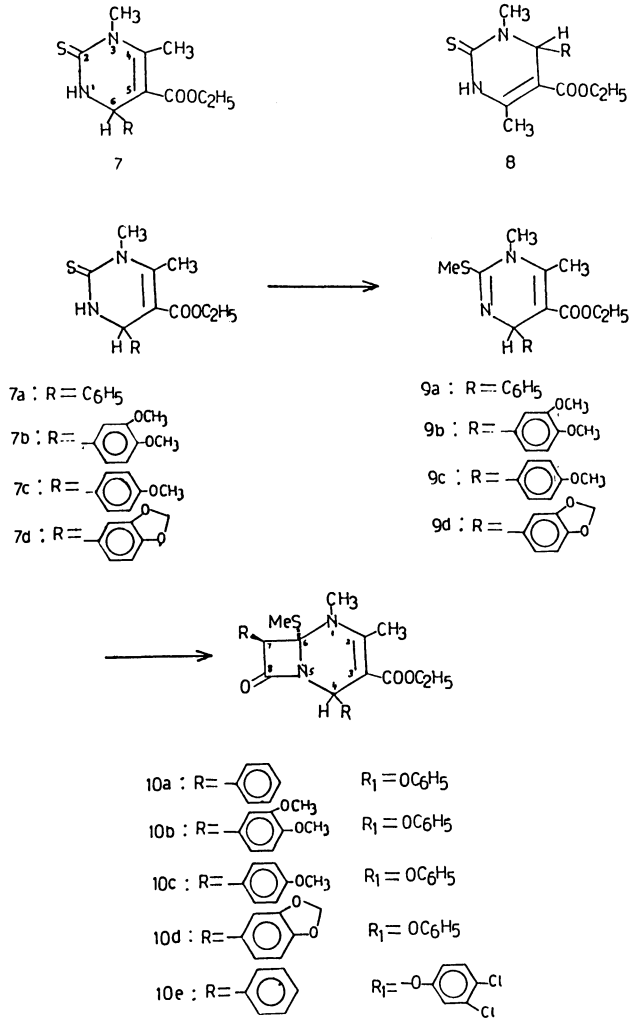
**5a:** IR (nujol) 1640 $cm^{-1}$ (C=N): $^1H$ NMR ($CDCl_3$) δ=4.95 (1H, d, $J_{gem}$=15 Hz, H-3), 5.30 (1H, d, $J_{gem}$=15 Hz, H-3);

**5b:** IR (nujol) 1710, 1690 $cm^{-1}$ (C=O and $COOC_2H_5$): $^1H$ NMR ($CDCl_3$) δ=4.85 (1H, d, $J_{gem}$=16 Hz, H-3), 5.20 (1H, d, $J_{gem}$=16 Hz, H-3). Then, we thought of acylating imino group of **3** with non-ketene-generating acyl halides prior to subjecting it to β-lactam formation. Compound **3** was reacted with benzoyl chloride/triethylamine and also with ethyl chloroformate/triethylamine in dichloromethane and was converted to *N*-substituted derivatives **5c** and **5d** in 70 and 60% yields respectively. The compounds **5a**—**d** when subjected to β-lactam formation with phenoxyacetyl chloride in presence of triethylamine in dichloromethane–benzene did not yield any β-lactam **6**. Similarly the *N*-methyl derivative **5e** procured by methylation of **3** with methyl iodide/sodium hydride in dry tetrahydrofuran also did not yield

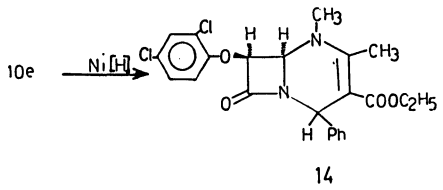



Scheme 1.

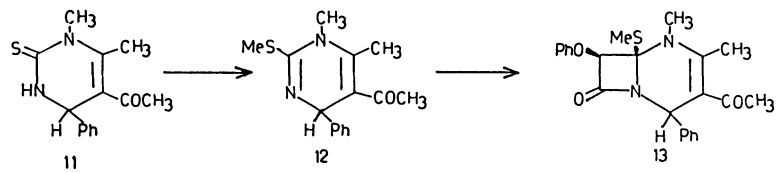
any β-lactam on cycloaddition with phenoxyketene. Using similar reaction conditions (Scheme 1), attempts were made to prepare the pyrimidine derivatives using *N*-methylthiourea in place of thiourea. This reaction went smoothly and regioselectively. Out of the two possible thiones **7** and **8**, the product corresponded to **7a** [$^1$H NMR ($CDCl_3$) $\delta$=5.45 (1H, d, $J$=3 Hz, collapsed into singlet after $D_2O$ exchange)]. Thione **7a** on refluxing with dimethyl sulfate in dry methanol yielded **9a** in 62% yield. The [2+2] cycloaddition using compound **9a** and phenoxyketene furnished the corresponding 1-aza cephem analog **10a** in 70% yield (Scheme 2). Compounds **7b**—**d** were prepared by the method similar to **7a** using different aldehydes. All these compounds produced the corresponding β-lactams **10b**—**e** in appreciable yields. The $^1$H NMR of these compounds exhibited all the resonances at the expected positions. Replacing ethyl acetoacetate with acetylacetone, the thione **11** could be prepared by the condensation of *N*-methylthiourea and benzaldehyde. *S*-Methylation of **11** produced **12** which on annelation furnished the 1-aza cephem analog **13** (Scheme 3). It is worthnoting that whereas the 2-methylthio-3,6-dihydropyrimidines **9a**—**d**, **12** undergo [2+2] cycloaddition to produce the corresponding β-lactam compounds, the 2-methylthio-3,4-dihydropyrimidines **5a**—**e** fail to do so under similar conditions. The non-reactivity of latter towards annelation can perhaps be attributed to the decreased double bond character of C=N due to its strong conjugation with the ester at C-5 (Fig. A). The 1-aza cephem analogs **10a**—**e**, **13** were obtained as single stereoisomers (TLC) and to ascertain the cis orientation of $C_6$–$SCH_3$ and $C_7$–H, one of the 1-aza cephem analogs **10e** was subjected to desulfurization with Ni[H] which has been reported to proceed with retention of configuration.[17] This reaction provided the expected cis 1-aza cephem analog **14**




Scheme 2.




Scheme 4.




Scheme 3.

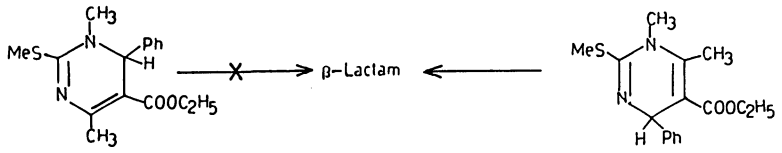



Fig. A.

in 50% yield (Scheme 4) clearly establishing the indicated orientation of the groups at $C_6$ and $C_7$. However, all the $\beta$-lactams reported in this paper are (±) with respect to their stereochemistry at C(4,6,7) chiral centers.

## Experimental

All melting points are uncorrected. IR spectra were recorded on Perkin-Elmer Model 377 spectrophotometer with sodium chloride optics using a thin liquid film or a mull of compound in Nujol. $^1$H NMR spectra were recorded on Varian EM-390, 90 MHz instrument in $CDCl_3$ solution containing tetramethylsilane as an internal standard. Thin-layer chromatography was performed on silica gel impregnated with 15% calcined gypsum and was developed in atmosphere of iodine vapors.

**5-Ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydro-2(1*H*)-pyrimidinethione (1).**[18] A solution of benzaldehyde (3.18 g, 30 mmol), ethyl acetoacetate (3.9 g, 30 mmol), thiourea (2.28 g, 30 mmol), 2 M HCl solution (20 mL) and methanol-water (1 : 1, 30 mL) were stirred for 24 h at room temperature. A white solid separated out which was washed with water, dried and recrystallized from methanol to give **1** (6.62 g, 80%): Mp 188—190 °C, IR (Nujol) 1670, 3190 cm$^{-1}$; $^1$H NMR ($CDCl_3$+DMSO) $\delta$=1.18 (3H, t), 2.4 (3H, s), 4.15 (2H, q), 5.4 (1H, d, $J$=3 Hz), 7.5 (5H, s), 7.75 (1H, br), 8.5 (1H, br). Found C, 60.80; H, 5.73; N, 10.03%. Calcd for $C_{14}H_{16}N_2O_2S$: C, 60.88; H, 5.79; N, 10.13%.

**5-Acetyl-6-methyl-4-phenyl-3,4-dihydro-2(1*H*)pyrimidinethione (2).** The same procedure was followed as detailed for compound **1** except acetylacetone was used in place of ethyl acetoacetate. Compound **2**: Yield 5.5 g (70%); mp 185 °C decomposed; IR (Nujol) 1630, 3190 cm$^{-1}$; $^1$H NMR ($CDCl_3$+DMSO) $\delta$=2.35 (3H, s), 2.60 (3H, s), 5.65 (1H, d, $J$=4 Hz), 7.50 (5H, s), 8.45 (1H, br), 9.20 (1H, br). Found: C, 63.31; H, 5.70; N, 11.40%. Calcd for $C_{13}H_{14}N_2OS$: C, 63.40; H, 5.73; N, 11.38%.

**5-Ethoxycarbonyl-6-methyl-4-phenyl-2-methylthio-3,4-dihydropyrimidine (3).** A solution of thiolactam **1** (5.52 g, 20 mmol), dimethyl sulfate (2.52 g, 20 mmol) and anhydrous methanol were refluxed for 3 h. The solvent was distilled off under reduced pressure and the residue was dissolved in water (100 mL). Then an oil was liberated on addition of 5 M NaOH (1 M=1 mol dm$^{-3}$) (50 mL) to the residue which was extracted with $CH_2Cl_2$ (40 mL×3). The organic layer was dried and removal of the solvent under reduced pressure afforded solid which was recrystallized from ethanol to give the desired compound **3** (3.76 g, 65%); mp 162—163 °C; IR (Nujol) 1660 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$=1.15 (3H, t), 2.60 (3H, s), 2.70 (3H, s), 4.15 (2H, q), 5.95 (1H, d, $J$=3 Hz), 7.40 (6H, br). Found C, 62.01; H, 6.17; N, 9.44%. Calcd for $C_{15}H_{18}N_2O_2S$: C, 62.8; H, 6.25; N, 9.65%.

**5-Acetyl-6-methyl-4-phenyl-2-methylthio-3,4-dihydropyrimidine (4).** This compound was prepared from **2** by procedure as described for compound **3**. Compound **4**: Yield 3.37 g (65%); mp 128—129 °C; IR (Nujol) 1645, 1625 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$=2.10 (3H, s), 2.30 (3H, s), 2.40 (3H, s), 5.75 (1H, d, $J$=3 Hz), 7.35—7.50 (6H, m). Found: C, 64.51; H, 6.07; N, 10.71%. Calcd for $C_{14}H_{16}N_2OS$: C, 64.60; H, 6.20; N, 10.76%.

**5-Ethoxycarbonyl-6-methyl-4-phenyl-3-phenoxyacetyl-2-methylthio-3,4-dihydropyrimidine (5a).** A solution of phenoxyacetyl chloride (1.71 g, 10 mmol) in dry $CH_2Cl_2$ (20 mL) was added dropwise to a well-stirred mixture of **3** (2.9 g, 10 mmol) and triethylamine (1.51 g, 15 mmol) in dry $CH_2Cl_2$ (30 mL) at 5 °C. Stirring was continued for 7 h and then mixture was washed with 10% $NaHCO_3$ (30 mL), brine (30 mL×2) and dried. Removal of solvent under reduced pressure afforded an oil which was purified by column chromatography on neutral alumina (eluent : $CH_2Cl_2$) to gave **5a** (2.54 g, 60%); oil, IR (Nujol) 1640 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$=1.20 (3H, t), 2.35 (3H, s), 2.45 (3H, s), 4.15 (2H, q), 4.95 (1H, d, $J_{gem}$=15 Hz), 5.30 (1H, d $J_{gem}$=15 Hz), 6.0 (1H, s), 6.90—7.40 (10H, m). Found: C, 65.01; H, 5.58; N, 6.51%. Calcd for $C_{23}H_{24}N_2O_4S$: C, 65.08; H, 5.70; N, 6.60%.

**5-Ethoxycarbonyl-6-methyl-3(2-naphthyloxyacetyl)-4-phenyl-2-methylthio-3,4-dihydropyrimidine (5b).** A solution of $POCl_3$ (1.535 g, 10 mmol) in dry dichloromethane (10 mL) was added dropwise to a well-stirred mixture of **3** (2.9 g, 10 mmol), 2-naphthyloxyacetic acid (2.02 g, 10 mmol) and triethylamine (2.22 g, 22 mmol) in dry dichloromethane (40 mL) at low temperature (5 °C). The contents were stirred at room temperature for 10 h and mixture was refluxed for 2 h. The resulting mixture was washed with saturated $NaHCO_3$ solution (40 mL×2) and brine (30 mL×2). The organic layer was separated and dried. The solvent was removed under reduced pressure and residue was purified by column chromatography on neutral alumina (eluent: ethylacetate-petroleum ether; 1 : 10) to give **5b** (2.36 g, 50%); oil, IR (Nujol) 1710, 1690 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$=1.05 (3H, t), 2.1 (3H, s), 2.35 (3H, s), 3.90 (2H, q), 4.85 (1H, d, $J_{gem}$=16 Hz), 5.20 (1H, d, $J_{gem}$=16 Hz), 6.30 (1H, s), 6.85—7.75 (12H, m). Found: C, 68.30; H, 5.50; N, 5.73%. Calcd for $C_{27}H_{26}N_2O_4S$: C, 69.34; H, 5.25; N, 5.90%.

**5-Ethoxycarbonyl-6-methyl-4-phenyl-3-benzoyl-2-methylthio-3,4-dihydropyrimidine (5c); 3,5-Bis(ethoxycarbonyl)-6-methyl-4-phenyl-2-methylthio-3,4-dihydropyrimidine (5d).** Compounds **5c** and **5d** were prepared according to procedure as for **5a** using benzoyl chloride and ethyl chloroformate respectively in place of phenoxyacetyl chloride. Compound **5c**: Yield 2.75 g (70%), oil, IR (Nujol) 1640 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$=1.25 (3H, t), 2.35 (3H, s), 2.65 (3H, s), 4.30 (2H, q), 6.60 (1H, s), 7.35—7.75 (10H, m). Found: C, 66.93; H, 5.51; N, 7.05%. Calcd for $C_{22}H_{22}N_2O_3S$: C, 66.99; H, 5.62; N, 7.10%. Compound **5d**: Yield 2.17 g (60%), oil, IR (Nujol) 1650 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$=1.25 (6H, t), 2.35 (3H, s), 2.45 (3H, s), 4.20 (4H, q), 5.70 (1H, s), 7.45 (5H, s). Found: C, 59.60; H, 6.03; N, 7.71%. Calcd for $C_{18}H_{22}N_2O_4S$: C, 59.66; H, 6.12; N, 7.73%.

**5-Ethoxycarbonyl-6-methyl-4-phenyl-3-methyl-2-methylthio-3,4-dihydropyrimidine (5e).** NaH (4.0 g) washed in *n*-hexane was added to compound **3** (2.9 g, 10 mmol) in dry THF (40 mL) at 5 °C. After the mixture was stirred for 15 min; methyl iodide (15 mmol) was added dropwise with continued stirring. The solution was stirred for 3 h and was refluxed for 2 h. THF was removed under reduced pressure and contents were diluted with water (15 mL), extracted with $CH_2Cl_2$ (30 mL×2) and dried. Removal of the solvent under reduced pressure gave solid which was recrystallized from methanol to give **5e** (1.97 g, 65%); mp 102—103 °C; IR (Nujol) 1660 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$=1.26 (3H, t), 2.4 (3H, s), 2.6 (3H, s), 3.03 (3H, s), 4.16 (2H, q), 5.26 (1H, s), 7.33 (5H, s). Found: C, 63.06; H, 6.56; N, 9.18%. Calcd for $C_{16}H_{20}N_2O_2S$: C, 63.14; H, 6.62; N, 9.21%.

**5-Ethoxycarbonyl-3,4-dimethyl-6-phenyl-3,6-dihydro-**

**2(1*H*)-pyrimidinethione (7a).** This was prepared according to procedure as described for **1** using *N*-methylthiourea in place of urea. Compound **7a**: Yield 6.0 g (70%); mp 130—131 °C; IR (Nujol) 1640, 1705, 3190 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$=1.25 (3H, t), 2.55 (3H, s), 3.65 (3H, s), 4.25 (2H, q), 5.45 (1H, d, $J$=3 Hz), 7.30 (5H, s), 8.05 (1H, br). Found: C, 62.01; H, 6.07; N, 9.51%. Calcd for $C_{15}H_{18}N_2O_2S$: C, 62.08; H, 6.25; N, 9.65%.

Compounds **7b**, **7c**, and **7d** were prepared similarly as **7a** using different aldehydes.

Compound **7b**: Yield 7.34 g (70%); mp 132—133 °C; IR (Nujol) 1705, 3190 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$=1.15 (3H, t), 2.55 (3H, s), 3.70 (3H, s), 3.90 (6H, s), 4.25 (2H, q), 5.45 (1H, d, $J$=3 Hz), 6.85 (3H, s), 8.15 (1H, br). Found: C, 58.26; H, 6.30; N, 7.88%. Calcd for $C_{17}H_{22}N_2O_4S$: C, 58.27; H, 6.33; N, 8.00%.

Compound **7c**: Yield 6.9 g (72%); mp 147—148 °C; IR (Nujol) 1705, 3195 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$=1.25 (3H, t), 2.35 (3H, s), 3.10 (3H, s), 3.70 (3H, s), 4.10 (2H, q), 5.70 (2H, d, $J$=4 Hz), 6.70—7.25 (4H, m). Found: C, 59.95; H, 6.20; N, 8.74%. Calcd for $C_{16}H_{20}N_2O_3S$: C, 59.99; H, 6.29; N, 8.75%.

Compound **7d**: Yield 7.5 g (75%); mp 129—130 °C; IR (Nujol) 1700, 3190 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$=1.20 (3H, t), 2.35 (3H, s), 3.20 (3H, s), 4.15 (2H, q), 5.95 (2H, s), 6.05 (1H, d, $J$=4 Hz), 6.75 (3H, m), 8.15 (1H, br). Found: C, 57.42; H, 5.42; N, 8.23%. Calcd for $C_{16}H_{18}N_2O_4S$: C, 57.48; H, 5.43; N, 8.38%.

**5-Ethoxycarbonyl-3,4-dimethyl-6-phenyl-2-methylthio-3,6-dihydropyrimidine (9a).** This compound was prepared similarly as described for **3**.

Compound **9a**: Yield 3.76 g (62%); mp 137—138 °C; IR (Nujol) 1650, 1700 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$=1.30 (3H, t), 2.45 (3H, s), 2.50 (3H, s), 3.25 (3H, s), 4.20 (2H, q), 5.85 (1H, s), 7.30 (5H, s). Found: C, 63.00; H, 6.61; N, 9.10%. Calcd for $C_{16}H_{20}N_2O_2S$: C, 63.14; H, 6.62; N, 9.21%.

Compounds **9b**, **9c**, and **9d** were also prepared similarly as **9a**.

Compound **9b**: Yield 4.9 g (68%); mp 98—99 °C; IR (Nujol) 1640, 1695 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$=1.20 (3H, t), 2.35 (3H, s), 2.40 (3H, s), 3.15 (3H, s), 3.75 (6H, s), 4.10 (2H, q), 5.60 (6H, s), 6.75 (3H, m). Found: C, 59.27; H, 6.58; N, 7.59%. Calcd for $C_{18}H_{24}N_2O_4S$: C, 59.33; H, 6.64; N, 7.69%.

Compound **9c**: Yield 4.4 g (66%); oil, IR (Nujol) 1645, 1705 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$=1.25 (3H, t), 2.35 (3H, s), 2.45 (3H, s), 3.15 (3H, s), 3.70 (3H, s), 4.10 (2H, q), 5.7 (1H, s), 6.7—7.25 (4H, m). Found: C, 60.93; H, 6.61; N, 8.33%. Calcd for $C_{17}H_{22}N_2O_3S$: C, 61.06; H, 6.63; N, 8.38%.

Compound **9d**: Yield 4.47 g (70%); oil, IR (Nujol) 1645, 1700 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$=1.20 (3H, t), 2.35 (3H, s), 2.45 (3H, s), 3.20 (3H, s), 4.15 (2H, q), 5.95 (2H, s), 6.05 (1H, s), 6.75 (3H, m). Found: C, 58.57; H, 5.84; N, 8.00%. Calcd for $C_{17}H_{20}N_2O_4S$: C, 58.61; H, 5.79; N, 8.04%.

**3-Ethoxycarbonyl-1,2-dimethyl-4-phenyl-7-phenoxy-6-methylthio-1,5-diazabicyclo[4.2.0]oct-2-en-8-one (10a).** Same procedure as for **5a**. β-Lactam **10a**: Yield 3.06 g (70%); mp 144—145 °C; IR (Nujol) 1685, 1780 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$=0.95 (3H, t), 1.55 (3H, s), 2.60 (3H, s), 3.05 (3H, s), 4.0 (2H, q), 5.25 (1H, s), 6.0 (1H, s), 7.1—7.7 (10H, m). Found: C, 65.71; H, 5.92; N, 6.50%. Calcd for $C_{24}H_{26}N_2O_4S$: C, 65.74; H, 5.98; N, 6.39%.

For β-lactams **10b**, **10c**, and **10d**, same procedure as for **10a**.

β-Lactam **10b**: Yield 3.33 g (67%); mp 120—121 °C; IR (Nujol) 1685, 1775 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$=1.0 (3H, t), 1.60 (3H, s), 2.55 (3H, s), 3.0 (3H, s), 3.95 (8H, m), 5.20 (1H, s), 5.90 (1H, s), 6.70—7.40 (8H, m). Found: C, 62.57; H, 5.89; N, 5.56%. Calcd for $C_{26}H_{30}N_2O_6S$: C, 62.64; H, 6.07; N, 5.62%.

β-Lactam **10c**: Yield 2.86 g (65%); mp 157—158 °C; IR (Nujol) 1680, 1770 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$=1.05 (3H, t), 1.55 (3H, s), 2.60 (3H, s), 3.05 (3H, s), 4.00 (5H, m), 5.15 (1H, s), 5.90 (1H, s), 6.80—7.4 (9H, m). Found: C, 63.97; H, 5.97; N, 5.91%. Calcd for $C_{25}H_{28}N_2O_5S$: C, 64.09; H, 6.02; N, 5.98%.

β-Lactam **10d**: Yeild 3.37 g (70%); mp 138—139 °C; IR (Nujol) 1680, 1775 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$=1.0 (3H, t), 1.65 (3H, s), 2.55 (3H, s), 3.0 (3H, s), 4.05 (2H, q), 5.20 (1H, s), 5.85 (1H, s), 5.95 (2H, s), 6.75—7.45 (8H, m). Found: C, 62.19; H, 5.39; N, 5.80%. Calcd for $C_{25}H_{26}N_2O_6S$: C, 62.23; H, 5.43; N, 5.81%.

**3-Ethoxycarbonyl-7-(2,4-dichlorophenoxy)-1,2-dimethyl-4-phenyl-6-methylthio-1,5-diazabicyclo[4.2.0]oct-2-en-8-one (10e).** A solution of $POCl_3$ (1.535 g, 10 mmol) in dry dichloromethane (10 mL) was added dropwise to a well-stirred mixture of **9a** (3.040 g, 10 mmol), 2,4-dichlorophenoxyacetic acid (2.21 g, 10 mmol) and triethylamine (2.22 g, 20 mmol) in dry dichloromethane (50 mL) at low temperature (5 °C). The contents were stirred at room temperature for 8 h. The reaction mixture was then washed with aq $NaHCO_3$ (10%) and brine. The organic layer was dried and evaporated under reduced pressure, the residue recovered was chromatographed over neutral alumina using dichloromethane–petroleum ether (2 : 1) as eluent to give β-lactam **10e**: Yield 3.14 g (62%); mp 148—149 °C; IR (Nujol) 1680, 1780 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$=0.90 (3H, t), 1.55 (3H, s), 2.55 (3H, s), 3.05 (3H, s), 3.90 (2H, q), 5.10 (1H, s), 5.98 (1H, s), 7.25—7.60 (8H, m). Found: C, 56.79; H, 4.72; N, 5.49%. Calcd for $C_{24}H_{24}N_2O_4SCl_2$: C, 56.83; H, 4.73; N, 5.52%.

**5-Acetyl-3,4-dimethyl-6-phenyl-3,6-dihydro-2(1*H*)-pyrimidinethione (11).** This compound was prepared in the same manner as **7**, by replacing ethyl acetoacetate with acetylacetone. Compound **11**: Yield 5.6 g (72%); mp 190—191 °C; IR (Nujol) 1640, 1705, 3190 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$=2.15 (3H, s), 2.45 (3H, s), 3.0 (3H, s), 5.35 (1H, d, $J$=4 Hz), 7.30 (5H, s), 8.25 (1H, br). Found: C, 64.51; H, 6.17; N, 10.71%. Calcd for $C_{14}H_{16}N_2OS$: C, 64.60; H, 6.20; N, 10.76%.

**5-Acetyl-3,4-dimethyl-6-phenyl-2-methylthio-3,6-dihydropyrimidine (12).** Same procedure as for **9**. Compound **12**: Yield 3.28 g (60%); mp 117—118 °C; IR (Nujol) 1650, 1700 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$=2.05 (3H, s), 2.15 (3H, s), 2.34 (3H, s), 2.45 (3H, s), 5.75 (1H, s), 7.40 (5H, s). Found: C, 65.70; H, 6.60; N, 10.11%. Calcd for $C_{15}H_{18}N_2OS$: C, 65.67; H, 6.61; N, 10.21%.

**3-Acetyl-1,2-dimethyl-4-phenyl-7-phenoxy-6-methylthio-1,5-diazabicyclo[4.2.0]oct-2-en-8-one (13).** Same procedure as that for **10a**. β-Lactam **13**: Yield 2.24 g (55%); oil, IR (Nujol) 1660, 1770 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$=2.05 (3H, s), 2.15 (3H, s), 2.35 (3H, s), 2.45 (3H, s), 5.15 (1H, s), 5.70 (1H, s), 7.20—7.7 (10H, m). Found: C, 67.59; H, 5.87; N, 6.84%. Calcd for $C_{23}H_{24}N_2O_3S$: C, 67.63; H, 5.92; N, 6.86%.

**3-Ethoxycarbonyl-7-(2,4-dichlorophenoxy)-1,2-dimethyl-4-phenyl-1,5-diazabicyclo[4.2.0]oct-2-en-8-one (14).** A solution of β-lactam **10e** (5 mmol) in acetone (50 mL) was refluxed for 2 h with Raney Ni catalyst (50 g). The catalyst was filtered off and washed with acetone (50 mL). The solvent was evaporated and residue recrystallized from ethanol to afford the pure *cis* β-lactam **14**: Yield 1.13 g (50%); mp 137—138 °C; IR (Nujol) 1680, 1780 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$=0.90 (3H, t), 1.6 (3H, s), 3.15 (3H, s), 3.85 (2H, q), 4.75 (1H, d, $J$=3

Hz), 5.10 (1H, d, $J$=3 Hz), 5.35 (1H, s), 7.0—7.45 (8H, m). Found: C, 59.87; H, 4.75; N, 5.85%. Calcd for $C_{23}H_{22}N_2O_4Cl_2$: C, 59.90; H, 4.77; N, 6.07%.

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