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Synthesis of 1,4-Diazines by Ring Expansion of 1,3-Diazines

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Received November 23, 2002

Fully saturated piperazin-3-one and quinoxalin-3-one derivatives were prepared by reactions of 2-anilino-2-ethoxy-3-oxothiobutanoic acid anilide with aliphatic 1,2-diamines. An unusual ring expansion of the intermediate 1,3-diazines leads to 1,4-diazines. Moreover, quinoxalin-3-one derivatives from chiral *trans*-1,2-diaminocyclohexane were obtained with diastereoselectivity >95%.

Introduction

The piperazinone derivatives are a well-known class of farnesyl transferase inhibitors[1−3] that show antitumor activity. They exemplify the new kind of biologically active compounds such as tachykinin inhibitors[4−6] that are useful in the treatment of a variety of human diseases, including asthma and bronchitis. Piperazinone derivatives exhibit activity on the central nervous system,[7−9] and have been used as potassium channels openers.[10] Some derivatives of this type have significant industrial applications, such as antioxidants for plastics[11−13] and saturated quinoxaline derivatives used in the photographic process.[14]

Results and Discusion

We now wish to report the efficient synthesis of piperazin-3-one and quinoxalin-3-one derivatives by novel ring expansion of the heterocyclic five-membered rings of 1,3-diazine (imidazolidine) to six-membered rings of 1,4-diazine (piperazine).

Studies[15,16] on the synthesis of heterocyclic systems obtained in the reactions of 3-oxothiobutanoic acid derivatives with various diamines have been our subject of interest. The method based on the binucleophilic attack of an appropriate diamine on C-2 of 2-anilino-2-ethoxy-3-oxothiobutanoic acid anilide **1** with ring closure of heterocyclic systems is particularly interesting. Recently, we have found that good leaving groups at C-2 of compounds **1** offer entry[17] to formation of six- and seven-membered rings, by the treatment with aliphatic 1,3- and 1,4-diamines, respectively. We have reported[17] a novel and convenient route to synthesize zwitterionic derivatives **3** of saturated pyrimidinylium and 1,3-diazepinylium derivatives (Scheme 1).

This heterocyclization process, by binucleophilic attack of appropriate aliphatic 1,3- or 1,4-diamines on C-2 of 2-anilino-2-ethoxy-3-oxothiobutanoic acid anilides, followed by novel sigmatropic rearrangement of the intermediate **2** leads to zwitterionic compounds **3** (Scheme 1). X-ray analysis[17] of compound **3** indicated that stereoelectronic stabilization of diaminocarbenium ions at position 2 of saturated pyrimidine **3** is most favorable in six-membered systems (sofa conformation) as well as in the seven-membered 1,3-diazepine ring. Analogous zwitterionic derivatives of the five-membered imidazolidine system **4** with aliphatic 1,2-diamine were not obtained. Probably anything smaller than a six-membered ring implies a different pathway of reaction.

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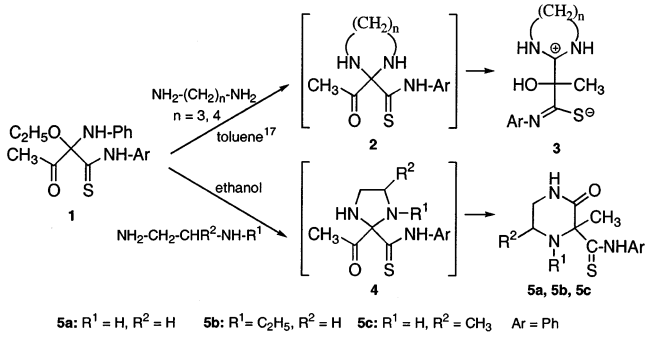
10.1021/jo026756t CCC: $25.00
Published on Web 02/21/2003

SCHEME 1



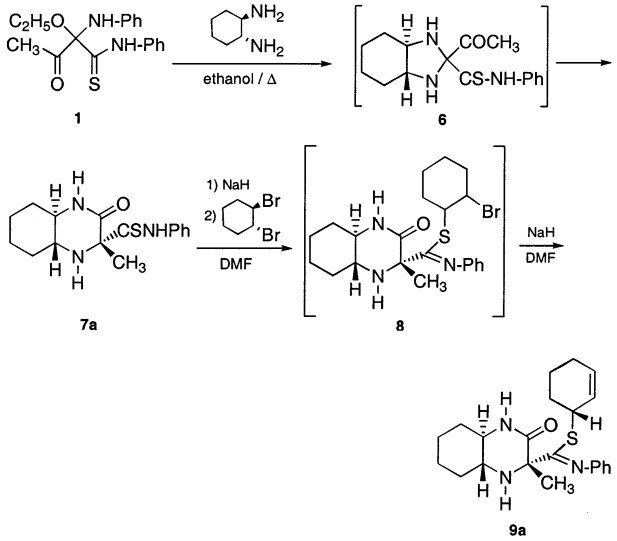
Surprisingly, the reactions of 2-anilino-2-ethoxy-3-oxothiobutanoic acid anilide **1** with aliphatic 1,2-diamines led to unexpected 1,4-diazine derivatives **5** (Scheme 1). The X-ray analysis of product **5b** confirmed the general structure of the molecules. Their isolation indicated a different mechanism of formation than with aliphatic 1,3- and 1,4-diamines or with aromatic 1,2-diamines[17] (namely attack on C-2 and C-3 of **1**).

Compound **5b**, with empirical formula $C_{14}H_{19}N_3OS$ and molecular weight 277.384, crystallizes in the monoclinic crystal system, space group $P2_1/a$. The diffraction experiment was carried out on a sample 0.25 × 0.2 × 0.15 mm^3 in size, at room temperature, using a Kappa CCD diffractometer and Mo Kα radiation. The unit cell parameters were determined as a = 13.8549(2) Å, b = 6.3197(1) Å, c = 16.6171(4) Å, β = 96.12(1)°, cell volume 1446.69(4) Å^3, and Z = 4. A total of 12 407 reflections were collected up to 2θ equal 60.09° and merged to give 4205 independent reflections with R(int) = 0.0237. The structure was solved with SHELXS97 and refined with the full-matrix least-squares method against F^2 with the SHELXL97 program system. Final discrepancy indices were R1 = 0.0441, wR2 = 0.1275 for $I > 2\sigma(I)$ and R1 = 0.0589 for all 4205 data and 249 refined parameters, with a goodness-of-fit of 1.063. The final electron density difference Fourier map was featureless with the largest peak and hole equal to 0.33 and −0.28 e·Å^{-3}, respectively.

The six-membered heteroring has a sofa conformation with slight distortion caused by unequal C−N bond lengths within the ring: the bond length at the carbonyl group is 1.34 Å, whereas the remaining bonds are longer (about 1.46 Å). The vicinity of the carbonyl group is planar (the sum of valence angles equal to 360.0(3)°), while the ethyl-substituted nitrogen atom is nonplanar with the sum of valence angles equal to 338.8(3)°. The ethyl group orientation is periplanar with respect to the sofa cusp (C8). The double bond C=S is rather short (1.64 Å). The intramolecular hydrogen bond N13−N9 (2.582 Å) stabilizes the value of the torsion angle N13−C2−C3−N9 to 35.1°. The medium-strength intermolecular hydrogen bond N6···O5 (2.903 Å) joins molecules into dimeric forms.

The ^{1}H and ^{13}C NMR and mass spectra of compounds **5a**−**c** were consistent with the structure determined by X-ray diffraction of compound **5b**. The ^{1}H NMR spectra of derivatives **5** show signals different from those of zwitterionic compounds **3**. Compounds **5a**,**c** exhibit two separate NH signals from the heterocyclic system (δ_H 3.44−3.92 and 6.21−6.56 ppm), whereas **5b** shows only one signal, at 7.05 ppm, from the CONH group, which

SCHEME 2



confirms the presence of the substituent at position N-1 of piperazine **5b**. Moreover the signal at δ_H 11.22−12.10 ppm confirms the presence of a thioanilide −NHCS− fragment at C-2 of piperazines **5a**−**c**. A signal at δ_H 8.50−9.00 ppm, typical of the two equivalent polar NH groups of heterocyclic systems of zwitterionic derivatives **3**, was not observed. The ^{13}C NMR spectra also confirm that the heterocyclization reaction of **1** with aliphatic 1,2-diamines gave piperazine derivatives **5**. A significant change in the electron density of the thiocarbonyl carbon atom is reflected in its chemical shift, δ_C 200.10−201.62 ppm in **5**, whereas the value of δ_{CS} for zwitterionic compounds **3** is in the range of 187.42−189.19 ppm.

The results presented above indicate the possibility that reaction of 2-anilino-2-ethoxy-3-oxothiobutanoic acid anilide **1a**−**d** with *trans*-1,2-diaminocyclohexane could have given quinoxaline derivatives rather than previously reported[16] perhydrobenzimidazolidine derivatives **6** (Scheme 2). We have reinvestigated the products of these reactions. The NMR data of compounds **7a**−**d** indicated the presence of the quinoxaline system. In support of this hypothesis, we have obtained *S*-alkylated product **9a**. Quinoxaline derivative **7a** treated with *trans*-1,2-dibromocyclohexane in DMF allows one to obtain, through intermediate **8**, the crystalline form of one of two diastereoisomeric forms of compound **9a** (*R*-cyclohexenyl) (Scheme 2).

Crystals of **9a** have been subjected to X-ray diffraction study. Compound **9a**, with empirical formula $C_{22}H_{29}N_3OS$ and molecular weight 383.54, crystallized in a triclinic crystal system with space group $P\bar{1}$. The diffraction experiment was carried out on a sample 0.25 × 0.15 × 0.1 mm^3 in size, at room temperature, using a Kappa CCD diffractometer with Mo Kα radiation. The unit cell parameters were determined as a = 9.4700(2) Å, b = 9.7190(2) Å, c = 12.9690(3) Å, α = 71.2330(10)°, β = 75.7190(10)°, γ = 68.7990(10)°, cell volume 1042.15(4) Å^3, and Z = 2. A total of 10828 reflections were collected in the θ range 3.07 to 31.98° and merged to give 7165 independent reflections with R(int) = 0.0214. The structure was solved with SHELXS97 and refined with the full-matrix least-squares method against F^2 with the SHELXL97 program system. Final discrepancy indices

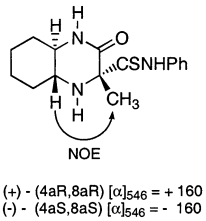


FIGURE 1.

were R1 = 0.0455, wR2 = 0.1026 for $I > \sigma(I)$ and R1 = 0.0733, wR2 = 0.1152 for all 7165 data and 360 refined parameters, with a goodness-of-fit of 1.037. The final electron density difference Fourier map was featureless with the largest peak and hole equal to 0.304 and −0.301 e·Å^{-3}, respectively.

Similar to **5b**, the six-membered heteroring of **9a** has a sofa conformation: the root-mean-square distance of both rings superimposed has a value of 0.06 Å. The hydrogen atom attached to C12 (H3) is in the trans position with respect to the hydrogen atom attached to C7, and in the cis position with respect to the methyl group (C14). The relevant torsion angle, C14−C3−C12−H3, is equal to 27.5(1)° and the cis configuration of C14 and H3 is preserved in the other molecule within the unit cell (by symmetry operation).

The agreement between the X-ray results of **5b** and **9a** proves that heterocyclization with chain as well as cyclic aliphatic 1,2-diamines, contrary to previously published results,[16] proceeds with ring expansion of the 1,3-diazine ring to a 1,4-diazine ring.

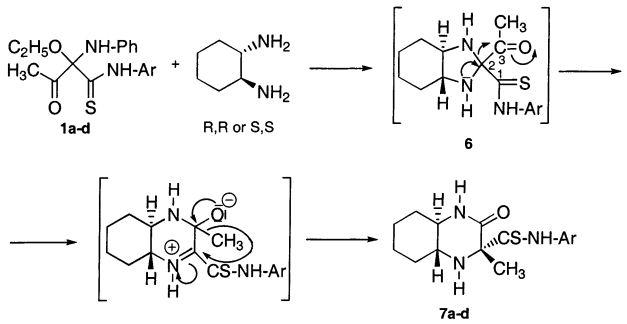
Furthermore, when chiral (*R*,*R*)- or (*S*,*S*)-*trans*-1,2-diaminocyclohexane was used in heterocyclization with 2-anilino-2-ethoxy-3-oxothiobutanoic acid anilide **1a**, the final products **7a′** and **7a″** were isolated as single diastereoisomers (Figure 1).

The position C-2 of the (4*aR*,8*aR*)- or (4*aS*,8*aS*)-2-phenylthiocarbamoyl-2-methyl-*trans*-perhydroquinoxalin-3-one **7a′** and **7a″** becomes a new stereogenic center (Figure 1). The relative configuration at positions C-2 and C-8a was determined by NOE experiment: when the peak of the CH_3 group was irradiated, a significant NOE effect was observed for 8aH. These results prove the cis orientation of 8aH and the CH_3 group and are in agreement with X-ray analysis, confirming the fact that chiral diamine reagents such as 1,2-*trans*-diaminocyclohexane control the diasteroselectivity of the rearrangement of the imidazolidine ring to the piperazine system (Scheme 3).

Additional measurement of NMR spectra of optically active compound **7a′** with the shift reagent, tris[3-(trifluoromethylhydroxymethylene)-d-camphorato]europium(III), Eu(tfc)$_3$, was carried out. For all signals of the complex, split lines from the other enantiomer could not be observed above the noise level. It was deduced that enantiomeric purity is better than 95%. Remarkably, the ring expansion can occur with high levels of diastereoselectivity, leading exclusively to one of the two possible diastereoisomers of the quinoxaline derivatives.

We propose the following mechanism for ring expansion of intermediate 1,3-diazine derivatives. Initially, binucleophilic attack of the appropriate aliphatic 1,2-diamine on the electrophilic C-2 center of compound **1** leads to the five-membered ring of a 1,3-diazine (imidazolidine). This resulting intermediate **4** (Scheme 1) or **6** (Scheme 3) with sterically congested C-2 undergoes sigmatropic rearrangement with enlargement of the five-membered imidazolidine ring to the six-membered piperazine ring. Moreover, when a chiral 1,2-diamine was used, migration of the methylide group was stereocontrolled.

SCHEME 3



Conclusions

We have developed a simple and efficient route to piperazin-3-ones and fused 1,4-diazines, such as quinoxalin-3-ones. Novel rearrangement following heterocyclizations with chiral *trans*-1,2-diaminocyclohexane demonstrates the concept of using 2-anilino-2-ethoxy-3-oxothiobutanoic acid anilide **1** as an excellent synthon for construction of optically active heterocyclic systems. The chiral quinoxaline derivative **7** has potential application as a chiral auxiliary.

Experimental Section

Melting points were determined on a digital melting point apparatus and are uncorrected. Column chromatographic separations were performed with silica gel 60 (35−70 mesh ASTM). Centrifugal chromatography was performed with a 2 mm sorbent layer (silica gel 60 PF-254), with visualization by UV light. The IR spectra were obtained at room temperature. ^{1}H and ^{13}C NMR spectra were recorded with TMS as internal standard. Chemical shifts are reported in ppm downfield from TMS.

General Procedure for the Preparation of 5a, 5b, and 5c. A solution of 4.58 mmol of appropriate aliphatic 1,2-diamine and 3.06 mmol of 2-anilino-2-ethoxy-3-oxothiobutanoic acid anilide **1** in 20 mL of anhydrous ethanol was refluxed for 5 min. Removal of the solvent gave a dark residue that was purified by crystallization from ethanol.

2-Phenylthiocarbamoyl-2-methyl-piperazin-3-one (5a). Yield 45%; colorless crystals; mp 135 °C; IR (KBr) 3293, 3174, 1661 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 11.44 (s, 1H), 7.81 (d, J = 8.7 Hz, 2H), 7.40 (t, J = 7.5 Hz, 2H), 7.26 (t, J = 6.0 Hz, 1H), 6.56 (s, 1H), 3.9 (s, 1H), AA′BB′ spin system: 3.56−3.62 (m, 1H), 3.19−3.23 (m, 1H), 2.89−2.96 (m, 2H), 1.65 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 201.6, 173.1, 139.1, 128.8, 126.7, 122.9, 68.3, 42.9, 39.4, 30.8. Anal. Calcd for $C_{12}H_{15}N_3OS$ (249.33): C, 57.80; H, 6.06; N, 16.85; S, 12.86. Found: C, 57.46; H, 6.01; N, 16.59; S, 12.76. EIMS: *m*/*z* (%) 136 (PhNHCS, 40), 113 (M^+ − PhNHCS, 38), 85.1 (16), 77 (12).

1-*N*-Ethyl-2-phenylthiocarbamoyl-2-methyl-piperazin-3-one (5b). Yield 60%; yellow crystals; mp 187 °C; IR (KBr) 3299, 3186, 1659 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 11.22 (s, 1H), 7.79 (d, J = 7.9 Hz, 2H), 7.38 (t, J = 7.6 Hz, 2H), 7.22 (t, J = 7.5 Hz, 1H), 7.05 (s, 1H), 3.57 (m, 1H), 3.36 (m, 1H), 3.12 (d, 1H),

2.80 (m, 1H), 2.54, 2.41 (qq, 2 H, J = 6.4 Hz), 1.74 (s, 3H), 1.56 (t, 3 H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 200.5, 169.8, 138.8, 128.9, 126.3, 122.6, 75.7, 44.5, 42.1, 41.5, 16.3, 13.9; Anal. Calcd for $C_{14}H_{19}N_3OS$ (277.39): C, 60.62; H, 6.90; N, 15.14; S, 11.56. Found: C, 60.66; H, 7.04; N, 15.14; S, 11.49. EIMS: *m*/*z* (%) 141 (M^+ − PhNHCS, 100), 135 (PhNCS, 2.3), 113 (10.95), 42 (8).

2-Phenylthiocarbamoyl-2,6-dimethyl-piperazin-3-one (5c). Yield 51%; colorless crystals; mp 201 °C; IR (KBr) 3218, 3205, 1681, 1164 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 12.1 (s, 1H), 7.78 (d, J = 7.7 Hz, 2H), 7.40 (t, J = 7.6 Hz, 2H), 7.26 (t, J = 7.5 Hz, 1H), 6.22 (s, 1H), 3.44 (s, 1H), 3.27 (m, 1H), 3.10 (m, 2H), 1.79 (s, 3H), 1.27 (d, J = 6.3 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 200.1, 173.1, 138.9, 128.8, 126.7, 126.3, 123.1, 66.3, 49.1, 45.1, 29.6, 19.3. Anal. Calcd for $C_{13}H_{17}N_3OS$ (263.36): C, 53.28; H, 6.50; N, 15.95; S, 12.17. Found: C, 53.07; H, 6.62; N, 15.88; S, 12.48. EIMS: *m*/*z* (%) 136 (PhNHCS, 41), 128 (M^+ − PhNHCS, 100), 99.1 (11), 77 (14), 28 (3).

General Procedure for the Preparation of 7a−d.[16] A solution of 0.55 mL of *trans*-(±)-1,2-diaminocyclohexane (4.58 mmol) and 3.06 mmol of the corresponding 2-anilino-2-ethoxy-3-oxothiobutanoic acid anilide **1a**−**d** in 20 mL of anhydrous ethanol was refluxed for 5 min. Removal of the solvent gave a dark residue that was purified by crystallization from benzene.

(±)-2-Phenylthiocarbamoyl-2-methyl-*trans*-perhydroquinoxalin-3-one (7a). Yield 54%; colorless needles; mp 220 °C; IR (KBr) 3366, 3177, 1684, 1120 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 11.86 (s, 1H), 7.81 (d, 2H, J = 7.7 Hz), 7.41 (t, 2H, J = 7.8 Hz), 7.25 (t, 2H, J = 7.5 Hz), 6.08 (s, 1H), 3.03 (m, 1H), 2.95 (d, J = 6.78 Hz, 1H), 2.75 (dt, 1H, J_1 = 3.8 Hz, J_2 = 10.2 Hz), 2.01 (m, 1H), 1.87 (m, 1H), 1.86 (m, 1H), 1.78 (s, 3H); 1.77 (m, 1H), 1.38 (t, 2H, J = 10.3 Hz), 1.28 (t, 2H, J = 11.1 Hz); ^{13}C NMR ($CDCl_3$) δ 200.5, 172.4, 138.8, 128.9, 126.6, 122.3, 68.2, 56.6, 56.3, 31.5, 31.0, 24.6, 23.6, 29.1. Anal. Calcd for $C_{16}H_{21}N_3OS$ (303.42): C, 63.36; H, 6.90; N, 13.86; S, 10.41. Found: C, 63.01; H, 7.41; N, 14.01; S, 10.29. EIMS: *m*/*z* (%) 304 (MH^+, 1), 167 (M^+ − PhNHCS, 100), 135 (PhNCS, 4), 98 (8), 41 (9).

(+)-(2*R*,4*aR*,8*aR*)-2-Phenylthiocarbamoyl-2-methyl-*trans*-perhydroquinoxalin-3-one (7a′). Yield 74%; mp 186 °C; $[\alpha]_{546}$ +160 (*c* 1, ethanol).

(−)-(2*S*,4*aS*,8*aS*)-2-Phenylthiocarbamoyl-2-methyl-*trans*-perhydroquinoxalin-3-one (7a″). Yield 78%; mp 186 °C; $[\alpha]_{546}$ −160 (*c* 1, ethanol).

The shift reagent tris[3-(trifluoromethylhydroxymethylene)-d-camphorato]europium(III), Eu(tfc)$_3$, was used. Eu(tfc)$_3$ was chosen for its solubility in $CDCl_3$, good Lewis acid properties, and nice effect in similar works.[18] Spectra were recorded on a 500.13 MHz (^{1}H) or 125.76 (^{13}C) spectrometer equipped with a 5-mm QNP probe. Typical conditions for recording one-dimensional spectra were as follows: spectral width 13 (^{1}H) or 35 kHz (^{13}C), data point 128K or 64K words, flip angle 45° or 30°, and pulse repetition 6 or 2 s. Resolution enhancement was performed by using exponential or Lorentzian to Gaussian windows for carbon and proton, respectively.

All measurements were carried out at a probe temperature of 24.0 ± 0.1 °C and the chemical shifts were initially referenced to the TMS (proton) and the solvent values of 77 ppm (carbon).

For the gradient method, a solution containing 0.026 mmol of compound (+)-**7a′** or (−)-**7a″** in 0.8 mL of $CDCl_3$ was prepared and the corresponding spectra (^{1}H, ^{13}C) were recorded. Then a known amount (ca. 4 mg) of shift reagent was added to the solution and the spectra were recorded again. This procedure was repeated several times: The $\Delta\delta$ (in ppm) values ($\Delta\delta = \delta_{obs} - \delta_0$) were determined for $\rho \leq 1$ (ρ = [Eu(tfc)$_3$]/[compound]).

For all signals of the complex, split lines from other enantiomers or its intensity were less then noise. In this case the enantiomeric purity of compound **7a** is better then 95%.

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(±)-2-(4-Methylphenylthiocarbamoyl)-2-methyl-*trans*-perhydroquinoxalin-3-one (7b). Yield 77%; colorless needles; mp 223 °C; IR (KBr) 3366, 3190, 1685, 1112 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 11.76 (s, 1H), 7.65 (d, J = 8.3 Hz), 7.20 (d, 2H, J = 8.2 Hz), 6.28 (s, 1H), 3.01 (m, 1H), 2.96 (d, J = 6.8 Hz, 1H), 2.74 (dt, 1H, J_1 = 3.7 Hz, J_2 = 9.8 Hz), 2.36 (s, 3H), 2.01 (m, 1H), 1.87 (m, 1H), 1.82 (m, 1H), 1.77 (s, 3H), 1.76 (m, 1H), 1.35 (t, 2H, J = 10.8 Hz), 1.27 (t, 2H, J = 8.8 Hz); ^{13}C NMR ($CDCl_3$) δ 200.3, 172.5, 136.5, 136.3, 129.4, 122.7, 68.1, 56.7, 56.2, 31.6, 31.0, 24.6, 23.6, 29.1, 21.1. Anal. Calcd for $C_{17}H_{23}N_3OS$ (317.44): C, 64.35; H, 7.20; N, 13.24; S, 10.10. Found: C, 64.25; H, 6.90; N, 13.47; S, 9.90.

(±)-2-(4-Methoxyphenylthiocarbamoyl)-2-methyl-*trans*-perhydroquinoxalin-3-one (7c). Yield 25%; colorless needles; mp 222 °C; IR (KBr) 3362, 3193, 1674, 1110 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 11.71 (s, 1H), 7.67 (d, 2H, J_1 = 8.9 Hz), 6.91 (d, 2H, J_1 = 8.9 Hz), 6.03 (s, 1H), 3.82 (s, 3H), 3.02 (m, 1H), 2.96 (d, J = 6.8 Hz, 1H), 2.75 (dt, 1H, J_1 = 3.8 Hz, J_2 = 9.8 Hz), 2.01 (m, 1H), 1.86 (m, 1H), 1.83 (m, 1H), 1.78 (s, 3H), 1.77 (m, 1H), 1.37 (t, 2H, J = 10.7 Hz), 1.28 (t, 2H, J = 11.6 Hz); ^{13}C NMR ($CDCl_3$) δ 200.1, 172.5, 157.9, 131.9, 124.5, 114.0, 67.9, 56.9, 56.1, 32.1, 31.5, 24.6, 23.7, 55.5, 29.1. Anal. Calcd for $C_{17}H_{23}N_3O_2S$ (333.44): C, 61.26; H, 6.90; N, 12.60; S, 9.60. Found: C, 61.41; H, 7.04; N, 12.60; S, 9.21.

(±)-2-(4-Chlorophenylthiocarbamoyl)-2-methyl-*trans*-perhydroquinoxalin-3-one (7d). Yield 55%; colorless needles; mp 223 °C; IR (KBr) 3362, 3180, 1687, 1113 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 11.94 (s, 1H), 7.77 (d, 2H, J = 8.8 Hz), 7.36 (d, 2H, J = 8.7 Hz), 6.29 (s, 1H), 3.02 (m, 1H), 2.92 (d, J = 6.0 Hz, 1H), 2.75 (dt, 1H, J_1 = 3.8 Hz, J_2 = 10.4 Hz), 2.01 (m, 1H), 1.87 (m, 1H), 1.85 (m, 1H), 1.77 (s, 3H), 1.76 (m, 1H), 1.38 (t, 2H, J = 8.3 Hz), 1.28 (t, 2H, J = 9.3 Hz); ^{13}C NMR ($CDCl_3$) δ 200.9, 172.4, 137.3, 131.6, 128.9, 124.1, 68.1, 56.9, 56.1, 31.5, 30.9, 24.6, 23.6, 29.3. Anal. Calcd for $C_{16}H_{20}N_3OSCl$ (337.86): C, 56.9; H, 5.90; N, 12.44; S, 9.48. Found: C, 57.4; H, 6.14; N, 12.45; S, 9.62.

Procedure for the Preparation of 9a. To a solution of 1 g (3.3 mmol) of 2-phenythiocarbamoyl-2-methyl-*trans*-perhydroquinoxalin-3-one **7a** in 25 mL of anhydrous DMF was added 0.237 g (9.87 mmol) of sodium hydride at 0 °C with stirring. The solution was stirred for an hour and then 0.44 mL (3.3 mmol) of *trans*-1,2-dibromocyclohexane was added. The resulting mixture was stirred for 24 h at room temperature. Removal of the solvent gave a residue that was purified by column chromatography eluting with a gradient solvent of $CHCl_3$ through 30% $CH_3COCH_3/CHCl_3$. The last fraction gave a residue that was purified by centrifugal chromatography eluting with a gradient solvent of $CHCl_3$ through 30% $CH_3COCH_3/CHCl_3$. The last fraction was concentrated giving a residue that was purified by crystallization from ethanol.

***S*-(3-Cyclohexenyl)-2-phenylthiocarbamoyl-2-methyl-*trans*-perhydroquinoxalin-3-one (9a).** Yield 20%; colorless needles; mp 213 °C; IR (KBr) 3331, 3180, 1669, 1632 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.29 (t, 1H, J = 7.3 Hz), 7.05 (d, 2H, J = 8.2 Hz), 7.03 (d, 2H, J = 6.5 Hz), 5.76 (s, 1H), 5.66 (m, 1H, J_1 = 5.1 Hz, J_2 = 10.1 Hz), 5.25 (d, 1H, J = 7.6 Hz), 3.26 (m, 1H), 3.05 (m, 1H), 2.75 (m, 1H), 1.73−1.81 (m, 7H), 1.72 (s, 1H), 1.28−1.48 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 170.9, 164.1, 130.9, 125.7, 148.7, 129.0, 123.8, 118.9, 70.1, 57.3, 55.2, 39.9, 31.0, 30.8, 24.8, 23.7, 18.7, 23.9. Anal. Calcd for $C_{22}H_{29}N_3OS$ (383.55): C, 68.89; H, 7.62; N, 10.95; S, 8.36. Found: C, 68.60; H, 7.72; N, 10.75; S, 8.40. EIMS: *m*/*z* (%) 383.2 (M^+, 1), 167 (100), 149 (5), 79 (11).

Supporting Information Available: X-ray molecular structures, crystal data tables, and Ortep figures for **5b** and **9a**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO026756T