Synthesis and Reactions of Heterocyclic Dithiocarbamates

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(Alkylthio)thiocarbonylimino-1-methyl-1,2-dihydropyridine derivatives (3a—c) were prepared by the reaction of 2-amino-1-methylpyridinium iodide (1a—c or d) with carbon disulfide in the presence of sodium hydride and subsequent methylation with dimethyl sulfate in good yields. Similarly, 1-methyl-4-(methylthio)thiocarbonyl-1,4-dihydropyridine (3i), 1-methyl-2-(methylthio)thiocarbonyl-1,2-dihydrothiazole (3g), and 1-methyl-2-(methylthio)thiocarbonyl-1,2-dihydrobenzothiazole (3h) were synthesized by the reaction of the corresponding 2-imino- and 4-imino-N-methyl heterocyclic compounds with carbon disulfide.

The reaction of 3a—e with dimethyl acetylenedicarboxylate afforded the 2- or 4-[1,2-bis(methoxy)carbonyl]-2-thioxoethylidene]-1,2- or 1,4-dihydropyridine derivatives (8a—d). The reaction of 3i with dimethyl acetylenedicarboxylate (2 mol) gave cyclobuta[7]azocine (9). The reaction of 3h with dimethyl acetylenedicarboxylate afforded 2,3-dihydrobenzothiazole-2-spiro-2'(2H-pyrrole) (10).

2-[N-bis(methylthio)methylenec amino-N-methylpyridinium and benzothiazolium iodide (11b, c), which were prepared by the methylation of 3a and h with methyl iodide, reacted with nucloephiles to yield the corresponding products substituted on one or two methylthio groups.

**Keywords**—heterocyclic dithiocarbamate; Diels-Alder reaction; 1,4-cycloaddition reaction; 1,2-dihydropyridine; thiocarbonyl; imidazoline

We reported previously that the reaction of heterocyclic enamine derivatives with carbon disulfide in the presence of a base gave the corresponding enaminodithiocarboxylates, which are very useful synthetic intermediates for the synthesis of heterocyclic compounds. For example, enaminodithiocarboxylates react with amines to give the corresponding thioamide derivatives in good yields, and also react with dienophiles, such as dimethyl acetylenedicarboxylate (DMAD), to yield 1,4-cycloaddition products.

The present paper deals with the synthesis and reactions of heterocyclic dithiocarbamates.

**Synthesis of Alkyl Dithiocarbamates**

The reaction of 2-amino-1-methylpyridinium iodide (1a) with carbon disulfide in the presence of sodium hydride in tetrahydrofuran (THF) under reflux gave the sodium dithio-
carbamate (2a), which was methylated with dimethyl sulfate to afford 1-methyl-2-(methyl-
thio)thiocarbonylimino-1,2-dihydropyridine (3a). Using the same method, other dithiocarba-
bamates (3b–d) were prepared from the corresponding 2-amino-1-methylpyrindinium iodide
derivatives (1b–d) in good yields. With benzyl chloride instead of dimethyl sulfate as the
alkylating reagent in the reaction of 1c with carbon disulfide, 2-(benzylthio)thiocarbonylimino-
1,5-dimethyl-1,2-dihydropyridine (3e) was obtained. Similarly, other heterocyclic dithiocarba-
bamates (3f, g) were prepared by the reaction of 2-amino-1-methylpyrindinium iodide (1e) and
2-amino-3-methylthiazolium iodide (1f) with carbon disulfide in good yields. The reaction of
2-amino-3-methylbenzothiazolium iodide (1g) with carbon disulfide under similar reaction
conditions afforded the stable dithiocarboxylic acid derivative (4). It is interesting that
compound 4 is stable and shows no acid character, presumably because of the betaine structure
4’. Methylation of 4 with dimethyl sulfate in the presence of potassium carbonate in dimethyl
sulfoxide (DMSO) yielded the desired methyl dithiocarbamate (3b).

When 4-amino-1-methylpyrindinium iodide (1h) was reacted with carbon disulfide in a
similar manner, 1-methyl-4-thioxo-1,4-dihydropyridine (5a) was obtained in 50% yield. In
a similar manner, the reaction of 4-amino-1,2-dimethylquinolinium iodide (1i) and 9-amino-
10-methylacridinium iodide (1j) with carbon disulfide also gave thioxo derivatives (5b and c).3
Since the desired corresponding dithiocarbamates were not obtained under these reaction
conditions, the following conditions were examined. The use of potassium carbonate and
DMSO instead of sodium hydride and THF gave the desired dithiocarbamate, 1-methyl-
4-(methylthio)thiocarbonylimino-1,4-dihydropyridine (3i). However, the reaction of 1i with
carbon disulfide under similar conditions gave two products, 5b and 1-methyl-4-methylthio-
2-(methylthio)thiocarbonylmethylene-1,2-dihydroquinoline (6), in 5 and 20% yields, respec-
tively. On the other hand, when a mixture of carbon disulfide and dimethyl sulfate in DMSO
was added to a solution of 1i and potassium carbonate in DMSO, 5b and 7 were obtained
7 and 35% yields, respectively. The formation of 7 can be regarded as a result of attack of
the dithiocarbamate anion because of the preferential methylation of the dithiocarboxylic
acid group by dimethyl sulfate co-existing in the reaction mixture. Compounds 6 and 7 were
identified from their spectral data and elemental analyses. (see “Experimental”)

1,4-Cycloaddition Reaction

Conjugated dienes and their heteroanalogs have been thoroughly investigated in organic
chemistry. However, few studies have been reported on diheterodienes having a thiocarbonyl
group and a carbon-nitrogen double bond.4) The methyl dithiocarbamate derivatives described
above have a conjugated diheterodiene system.

Reaction of 3a with DMAD gave yellow needles of mp 217—218° (dec.). This compound,
8a, was found to be 1-methyl-2-[1,2-bis(methoxycarbonyl)-2-thioxoethylidene]-1,2-dihydropy-
ridine on the basis of infrared (IR), ultraviolet (UV), nuclear magnetic resonance (NMR)
and mass spectral data, and elemental analysis. In a similar manner, treatment of other
methyl dithiocarbamate derivatives (3b–e) with DMAD afforded the corresponding 2-(2-thi-
oxoethylidene)-1,2- or 1,4-dihydropyridine derivatives (8b–e), accompanied by the elimina-
tion of methylthiocyanate, in fairly good yields. However, the reaction of 3f with DMAD
did not occur under similar conditions. To investigate the reaction mechanism, the reaction of
3e with DMAD was examined under similar conditions, and two products, 8c and benzyl-
thiocyanate, were obtained. This benzylthiocyanate was identical with the original sample.5

3) a) K. Gleu and R. Schaarschmidt, Chem. Ber., 72, 1246 (1939); b) E. Campagne, R.E. Cline, and C.E.
4) a) J.C. Meslin and H. Quiniou, Synthesis, 1974, 298; b) J.C. Meslin and H. Quiniou, Tetrahedron, 31,
3055 (1975); c) K. Burger, J. Albanauer, and W. Foag, Angew. Chem., 87, 816 (1975); d) K. Burger,
R. Oettinger, and J. Albanauer, Chem. Ber., 110, 2114 (1977); e) R. Okazaki, M. O-oka, and N. Inamoto,
When a solution of 3i and 2 molar equivalents DMAD in dimethylformamide was stirred at room temperature for 72 hr, white needles of mp 183—184° were obtained. On the basis of IR, UV, NMR, and mass spectral data and elemental analysis, this compound was assigned as 1,6,6a,8a-tetrahydro-1',2',3,4,7,8-hexakis(methoxycarbonyl)-1-methyl-6-(2-thioxoethyldiene)cyclobuta[b]jazocine (9).

The reactions of 3h with DMAD at 150° for 5 hr afforded 3-methyl-2,3-dihydrobenzo-thiazole-2-spiro-2'-[3',4'-methoxycarbonyl]-5'-methylthio-2H-pyrrole (10). This reaction did not give the 1,4-cycloaddition product at room temperature. It has been reported that the analogous 1,4-cycloaddition reaction of an enaminodithiocarboxylate with DMAD gave the corresponding spiro(benzothiazolincyclopentadiene) derivative by mono-desulfurization.²⁹

\[
3a - e + \begin{array}{c}
\text{C-COO\text{Me}} \\
\text{C-COO\text{Me}} \\
\text{DMAD}
\end{array} \rightarrow \begin{array}{c}
\text{R}^1 \\
\text{R}^2 \\
\text{R}^3 \\
\text{R}^4
\end{array} \begin{array}{c}
\text{N} \\
\text{S} \\
\text{Me}
\end{array} \begin{array}{c}
\text{C-COO\text{Me}} \\
\text{S}
\end{array} \rightarrow \begin{array}{c}
\text{R}^1 \\
\text{R}^2 \\
\text{R}^3 \\
\text{R}^4
\end{array} \begin{array}{c}
\text{N} \\
\text{S}
\end{array} \begin{array}{c}
\text{C-COO\text{Me}} \\
\text{S}
\end{array} + \begin{array}{c}
\text{RSCN}
\end{array}
\]

\[
R = \text{Me} \\
\text{CH}_2 - \text{Ph}
\]

\[
3i + \text{DMAD} \rightarrow \begin{array}{c}
\text{MeOOC-C} \\
\text{C-COO\text{Me}} \\
\text{DMAD}
\end{array} \begin{array}{c}
\text{N} \\
\text{Me}
\end{array} \begin{array}{c}
\text{MeOOC-C} \\
\text{C-COO\text{Me}}
\end{array} \rightarrow \begin{array}{c}
\text{MeOOC-C} \\
\text{C-COO\text{Me}}
\end{array} \begin{array}{c}
\text{N} \\
\text{Me}
\end{array} \begin{array}{c}
\text{MeOOC-C} \\
\text{C-COO\text{Me}}
\end{array}
\]

\[
3h + \text{DMAD} \rightarrow \begin{array}{c}
\text{N} \\
\text{S}
\end{array} \begin{array}{c}
\text{C-COO\text{Me}} \\
\text{SMe}
\end{array} \rightarrow \begin{array}{c}
\text{N} \\
\text{S}
\end{array} \begin{array}{c}
\text{C-COO\text{Me}} \\
\text{SMe}
\end{array}
\]

Chart 2

Methylation and the Reactions of Methyl Dithiocarbamates

The treatment of 3a with methyl iodide gave 1-methyl-2-[N-bis(methylthio)methylene]-aminopyridinium iodide (11a) in 90% yield. In a similar manner, 1-methyl-2-[N-bis(methylthio)methylene]aminobenzothiazolium iodide (11c) was readily obtained from 3f and h, in 97 and 95% yields, respectively. Compound 11c was easily hydrolyzed in methanol on heating to give the thioamide (12). The chemical reactivity of the methylthio group of 11a, b, and c can be investigated by reacting 11 with amines or active methylene compounds.

The reaction of 11a with morpholine gave the dimorpholine derivative (13). However, 11c reacted with morpholine to afford the amide derivative (14), which was also obtained by the reaction of 12 with morpholine. The reaction of 11a with hydrazine hydrate in ethanol gave the dihydrazine derivative (15a). In the same way, 11c reacted with hydrazine hydrate to give 15b. In a similar manner, the reaction of 11a with ethylenediamine or ethanolamine under reflux in methanol gave the corresponding imidazoline (16a) and oxazoline (16b) derivatives in good yields. The reaction of 11b and c with these amines also afforded the corresponding 16c—e in good yields.
Chart 3
Compounds 11a and c readily reacted with active methylene compounds (malononitrile, methyl cyanoacetate, nitromethane, oxindole, acetylacetonc, rhodanine) to give the corresponding methylthiosubstituted products (17a—g) in good yields.

Experimental

All melting points were determined in a capillary tube and are uncorrected. IR spectra were recorded in KBr pellets on a Jasco IRA-2 spectrometer, UV absorption spectra were determined on a Hitachi EP-S2 spectrometer in 95% EtOH, and NMR spectra were obtained using a JNM-PS-100 (100 MHz) spectrometer with tetramethylsilane as an internal standard, unless otherwise indicated. Mass spectra were recorded on a JEOL JMS-01SG double-focus mass spectrometer.

2-(Alkylthio)thiocarboxylinino-1-methyl-1,2-dihydropyridines (3a—c) — Sodium hydride (1.5 g of a 50% mineral oil dispersion, 0.03 mol) was freed from mineral oil by washing and decanting three times with petroleum ether (bp 40—60°). Next, 100 ml of THF was added to the resulting gray solid, and 0.01 mol of 2-amino-l-methylpyridinium iodide (1a—c or d) and 0.02 mol of CS₂ were added together. The mixture was heated to reflux with rapid evolution of hydrogen at first. After 1.5—2 hr, THF and the excess CS₂ were removed by evaporation to give a yellow solid. The solid was added to 100 ml of H₂O and stirring was continued until all of the solid was dissolved, then 1.3 g of Me₃SO₄ or 1.3 g of benzyl chloride (for 3e from 1e) was slowly added dropwise to the solution with stirring at room temperature. After 1 hr, the precipitate was collected,
washed with H2O, and recrystallized from MeOH or acetone to give the corresponding dithiocarbamate derivative (3a—d or e).

1-Methyl-2-(methylthio)thiocarbonylimino-1,2-dihydropyrimidine (3f)—This compound was obtained from 1e by the procedure described for 3a, and was purified by recrystallization from MeOH to give yellow needles, mp 135°, in 55% yield. *Anal. Calcd. for C9H6N2S2: C, 42.18; H, 4.55; N, 21.09; S, 32.18. Found: C, 41.89; H, 4.60; N, 21.21; S, 32.42. UV 380 nm (log ε) 220 (3.06), 256 (3.92), 310 (4.13). IR 3455 cm⁻¹: 1320, 1548, 1500, 1455, 1430, 1402. NMR (CDCl3) δ: 2.60 (3H, s, S-Me), 3.66 (3H, s, N-Me), 6.50 (1H, dd, J = 2, 6 Hz, 4-H), 7.34 (1H, dd, J = 2, 6 Hz, 6-H), 8.64 (1H, dd, J = 2, 4 Hz, 3-H).

3-Methyl-2-(methylthio)thiocarbonylimino-2,3-dihydropyrazole (3g)—This compound was obtained from 1f by the procedure described for 3a, and was purified by recrystallization from MeOH to give yellow needles, mp 165°, in 85% yield. *Anal. Calcd. for C9H6N2S2: C, 35.27; H, 3.85; N, 13.71; S, 47.07. Found: C, 35.28; H, 3.94; N, 13.89; S, 47.52. UV 380 nm (log ε) 221 (4.30), 314 (4.00), 359 (4.31). NMR (CDCl3) δ: 2.64 (3H, s, S-Me), 3.86 (3H, s, N-Me), 6.78 (1H, d, J = 5 Hz, 5-H), 7.14 (1H, d, J = 5 Hz, 4-H). IR 3455 cm⁻¹: 1550, 1480, 1400, 1360, 1250.

3-Methyl-2-imino-2,3-dihydropyrazole N-Dithiocarbonyl Acid (4)—Free sodium hydride was prepared by the method described above. THF (100 ml) was added to the resulting gray solid, then 0.01 mol of 1g and 0.02 mol of CS2 were added together. The mixture was heated to reflux for 1.5—2 hr. THF and the excess CS2 were then removed by evaporation to give a yellow solid. The solid was added to 200 ml of H2O and the whole was stirred for 1 hr. The resulting yellow precipitate was collected by filtration, washed with H2O, and recrystallized from acetone to give yellow needles, mp 142°, in 93% yield. *Anal. Calcd. for C8H13N2S2: C, 44.97; H, 3.35; N, 11.66; S, 40.02. Found: C, 44.98; H, 3.27; N, 11.45; S, 40.29. IR 3455 cm⁻¹: 1715, 1660, 1405, 1425, 1325, 1200.

3-Methyl-2-(methylthio)thiocarbonylimino-2,3-dihydropyrazole (3h)—a) Me2SO4 (1.5 g) was slowly added dropwise to a solution of 2.5 g of 4 and 2 g of K2CO3 in 50 ml of DMSO at room temperature. After 2 hr, the reaction mixture was poured into 100 ml of ice-water. The yellow precipitate was collected by filtration, washed with H2O, and recrystallized from acetone to give yellow needles, mp 142°, in 93% yield.  
b) To a solution of 0.01 mol of 1g in 30 ml of DMSO, 0.04 mol of CS2 and 0.04 mol of K2CO3 were added together. The mixture was stirred for 15—20 min at room temperature. The color of the solvent became red. The reaction mixture was poured into 200 ml of ice-water, and the precipitate was collected by filtration, washed with H2O, and recrystallized from acetone to give yellow needles, mp 142°, in 72% yield. *Anal. Calcd. for C9H16N2S2: C, 47.21; H, 3.96; N, 11.01; S, 37.81. Found: C, 47.23; H, 4.06; N, 11.07; S, 37.65. UV 380 nm 240, 1490, 1460, 1400, 1350, 1270, 1225. NMR (CDCl3) δ: 2.60 (3H, s, S-Me).

Thiazole Derivatives (5a—c)—Free sodium hydride was prepared by the method described above. THF (50 ml) was added to the resulting gray solid, then 0.01 mol of 1(b—j) and 0.02 mol of CS2 were added together. The mixture was heated to reflux for 1.5—2 hr. THF and excess CS2 were then removed by evaporation to give a yellow solid. The solid was added to 100 ml of H2O and stirring was continued for 1 hr. The resulting yellow precipitate was collected by filtration, washed with H2O, and recrystallized from MeOH to give 5a—c.  
a) mp 150°, Yield 50%, yellow needles. *Anal. Calcd. for C8H15N2S: C, 57.56; H, 5.46; N, 11.19; S, 25.61. Found: C, 57.40; H, 5.50; N, 11.00; S, 25.49.  
c) mp 224°, yield 20%, red needles. *Anal. Calcd. for C12H11NS: C, 69.80; H, 5.86; N, 7.40; S, 16.94. Found: C, 69.58; H, 5.84; N, 7.18; S, 16.91.

1-Methyl-4-(methylthio)thiocarbonylimino-1,4-dihydropyridine (3i)—K2CO3 (7 g) was added slowly with stirring to a solution of 2.38 g of 1h and 1.5 g of CS2 in 50 ml of DMSO, while the temperature of the mixture was maintained at 5—10°. The mixture was stirred at 10° for 1 hr, and 1.5 g of Me2SO4 was added dropwise with cooling over a period of 20 min. The mixture was stirred for 2 hr, then poured into 300 ml of ice-water. The reaction mixture was extracted with CHCl3, then the extract was dried over Na2SO4 and concentrated. The residue was recrystallized from MeOH to give yellow needles, mp 149—150°, in 40% yield. *Anal. Calcd. for C9H14N2S2: C, 48.45; H, 5.08; N, 14.13; S, 32.34. Found: C, 48.61; H, 5.19; N, 14.11; S, 31.94. IR 3455 cm⁻¹: 1825, 1490, 1340, 1250, 1280. UV 380 nm (log ε) 220 (4.18), 318 (4.01), 384 (4.23). NMR (CF3COOH) δ: 2.64 (3H, s, S-Me), 4.20 (6H, s, N-Me), 8.16 (2H, d, J = 7 Hz, 3 and 5-H), 8.76 (2H, d, J = 7 Hz, 2 and 6-H).

1-Methyl-4-methylthio-2-(methylthio)thiocarbonylmethylene-1,2-dihydroquinoline (6)—K2CO3 (7 g) was added to a solution of 3 g of H2, 3 g of CS2, and 1.9 g of Me2SO4 in 50 ml of DMSO with stirring at room temperature. The initially pale yellow solution slowly became red. After stirring for 1 hr, the reaction mixture was poured into 200 ml of ice-water. The precipitate was collected by filtration, washed with H2O, and recrystallized from MeOH to give the thioxo derivative, mp 266° in 20% yield. The filtrate was extracted with CHCl3. The organic extracts were washed with H2O and dried over Na2SO4. Removal of the solvent under reduced pressure left a residue, which was chromatographed over Al2O3 with benzene to afford red needles, mp 211°, in 20% yield. This compound was recrystallized from benzene. *Anal. Calcd. for C9H15N2S2: C, 57.30; H, 5.15; N, 4.77; S, 32.78. Found: C, 57.58; H, 5.11; N, 4.63; S, 32.80. IR 3455 cm⁻¹: 1590, 1545, 1480, 1280. UV 380 nm 233, 346, 495; 380 nm 296, 305. NMR (CDCl3) δ: 2.66 (6H, s, S-Me), 3.69 (3H, s, N-Me), 6.54 (1H, s, =CH), 7.24—7.92 (4H, m, aromatic H), 10.10 (1H, s, 3-H).
1-Methyl-4-[(N-bis(methylthio)methylene)amino]-2-(methylthio)thiocarboxymethylene-1,2-dihydroquinoline (7)—$K_2CO_3$ (7 g) was added to a solution of 3 g of 11, 3 g of Cs$_2$, and 3.8 g of Me$_2$SO$_2$ in 50 ml of DMSO with stirring at room temperature. The initially oily yellow solution slowly became red. After stirring for 1 hr, the reaction mixture was poured into 200 ml of ice-water. The precipitate was collected by filtration, washed with H$_2$O, and recrystallized from MeOH to give the thioxo derivative, 5b, in 7% yield. The filtrate was extracted with CHCl$_3$. The organic extracts were washed with H$_2$O and dried over Na$_2$SO$_4$. Removal of the solvent under reduced pressure left a residue, which was chromatographed over Al$_2$O$_3$ with benzene to afford red needles, mp 198°C, in 36% yield. This compound was recrystallized from acetone. Anal. Calcd. for C$_{11}H_{16}N$_2S$_2$: C, 52.42; H, 4.93; N, 7.41; S, 35.20. Found: C, 52.58; H, 4.93; N, 7.41; S, 35.20. NMR (CDCl$_3$) $\delta$: 2.60 (H, s, 2×t-Me), 2.68 (H, s, S-Me), 3.78 (3H, s, N-Me), 6.85 (1H, s, =CH−), 7.40−7.80 (4H, m, aromatic H), 9.60 (1H, s, 3-H).

1-Methyl-2-[1,2-bis(methoxycarbonyl)-2-thioethylidene]-1,2-dihydropyridine (8a-c)—A solution of 0.01 mol of 3a-c or d and 0.015 mol of DMAD in 50−80 ml of dioxane was stirred for 2−4 hr at room temperature. The precipitate was collected by filtration and recrystallized from methanol to give 8a-c or d. The filtrate was concentrated and the residue was recrystallized from MeOH to give 8a-c or d in 2−3% yield. When the benzylthio derivative, 3e, was reacted with DMAD in dioxane, benzylthiocyanate was obtained. After this reaction, the removal of dioxane gave a dark residue which was chromatographed over Al$_2$O$_3$ with benzene to give benzylthiocyanate, mp 43°C.

![Table II](Image)

<table>
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<tr>
<th>R$^1$</th>
<th>R$^2$</th>
<th>R$^3$</th>
<th>Yield (%)</th>
<th>mp (°C)</th>
<th>Appearance (Recrystol, solvent)</th>
<th>Formula</th>
<th>Analysis (%) Calcd. (Found)</th>
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<td>8a</td>
<td>H</td>
<td>H</td>
<td>80</td>
<td>217−218</td>
<td>Yellow needles (MeOH)</td>
<td>C$<em>{13}$H$</em>{14}$NO$_2$S</td>
<td>53.92 (53.78) 4.90 (4.77) 5.24 (5.11) 12.00 (11.92)</td>
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<tr>
<td>8b</td>
<td>Me</td>
<td>H</td>
<td>50</td>
<td>214−215</td>
<td>Yellow needles (MeOH)</td>
<td>C$<em>{13}$H$</em>{14}$NO$_2$S</td>
<td>55.50 (55.11) 5.37 (5.28) 4.98 (4.99) 11.40 (11.29)</td>
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<tr>
<td>8c</td>
<td>H</td>
<td>Me</td>
<td>98</td>
<td>230−232</td>
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<td>C$<em>{13}$H$</em>{14}$NO$_2$S</td>
<td>55.50 (55.51) 5.37 (5.36) 4.72 (4.72) 11.40 (11.33)</td>
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<td>8d</td>
<td>H</td>
<td>H</td>
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<td>239−240</td>
<td>Pale yellow needles (MeOH)</td>
<td>C$<em>{13}$H$</em>{14}$NO$_2$S</td>
<td>55.50 (55.15) 5.37 (5.32) 4.84 (4.84) 11.40 (11.83)</td>
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NMR (CD$_3$SO) $\delta$

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1,6a,8a-Tetrahydro-1',2',3',4,7,8-hexakis(methoxycarbonyl)-1-methyl-6-(2-thioethylidene)cyclobuta[5]azocine (9)—A solution of 0.01 mol of 3i and 0.03 mol of DMAD in 30 ml of DMF was stirred for 72 hr at room temperature. After the removal of DMF, the resulting dark red oil was chromatographed over Al$_2$O$_3$ (benzene: acetone 50:1) to give a crystalline product. This product was recrystallized from MeOH to give colorless needles, mp 183−184°C, in 40% yield. Anal. Calcd. for C$_{24}$H$_{34}$NO$_{14}$S: C, 52.27; H, 4.57; N,
2.54; S, 5.80. Found: C, 52.14; H, 4.56; N, 2.31; S, 5.58. IR $\nu_{\text{max}}$ cm$^{-1}$: 1708, 1728—1742. UV $\lambda_{\text{max}}$ nm (log $\varepsilon$): 220 (4.54), 298 (3.80). NMR (CDCl$_3$) $\delta$: 3.12 (1H, d, $J=6$ Hz, 6a-H), 3.76 (3H, s, O-Me), 3.84 (6H, s, 2xOMe), 3.88 (6H, s, 2xOMe), 4.05 (1H, d, $J=6$ Hz, 8a-H), 5.90 (1H, d, $J=1$ Hz, 2-H). MS m/z: 551 ($^{13}$C). 3-Methyl-2,3-dihydrobenzothiazole-2-spiro-2,3'-3,4'-bis(methoxy carbonyl)-5- methylthio-2H-pyrrole (10) —— A solution of 0.001 mol of 3h and 0.002 mol of DMAD was heated at 150° for 5 hr. After cooling, 5 ml of MeOH was added to the reaction mixture and the was collected by filtration, washed with a small amount of MeOH, and recrystallized from acetone to give yellow crystals, mp 245°, in 80% yield. Anal. Calcd. for C$_{12}$H$_{16}$N$_{2}$O$_{2}$S: C, 52.73; H, 4.43; N, 7.69; S, 17.50. Found: C, 52.56; H, 4.32; N, 7.50; S, 17.60. IR $\nu_{\text{max}}$ cm$^{-1}$: 1670, 1750. UV $\lambda_{\text{max}}$ nm (log $\varepsilon$): 220 (4.23), 254 (4.53), 286 (4.42), 300 (4.27), 405 (3.78). NMR (CD$_3$N) $\delta$: 2.60 (3H, s, S-Me), 3.92 (3H, s, S-Me), 3.92 (3H, s, O-Me), 3.92 (3H, s, O-Me).

1-Methyl-2-(N-bis(methylthio)methylene)aminopyrimidinium iodide (11a) —— A solution of 1.89 g of 3a and 2 ml of MeI in 50 ml of acetone was refluxed for 1 hr. After cooling, the precipitate was collected by filtration and recrystallized from MeOH to give colorless needles, mp 120—122°, in 90% yield. Anal. Calcd. for C$_{12}$H$_{16}$N$_{2}$S$_{2}$: C, 31.78; H, 3.85; N, 8.24; S, 18.82. Found: C, 32.07; H, 3.83; N, 8.12; S, 19.18. IR $\nu_{\text{max}}$ cm$^{-1}$: 1620, 1530, 1420, 1300, 1250. UV $\lambda_{\text{max}}$ nm (log $\varepsilon$): 220 (4.30), 325 (3.99). NMR (CF$_3$COOH) $\delta$: 2.74 (6H, s, S-Me).

1-Methyl-2-(N-bis(methylthio)methylene)aminopyrimidinium iodide (11b) —— A solution of 2 g of 3f and 2 ml of MeI in 50 ml of THF was allowed to stand for 24 hr. The resulting crystals were recrystallized from MeOH to give 11b, mp 208°, in 95% yield. Anal. Calcd. for C$_{12}$H$_{16}$N$_{2}$S$_{2}$: C, 28.18; H, 3.49; N, 12.44; S, 19.49. IR $\nu_{\text{max}}$ cm$^{-1}$: 1590, 1470, 1390, 1285. UV $\lambda_{\text{max}}$ nm (log $\varepsilon$): 300 (4.12), 338 (4.30). NMR (CF$_3$COOH) $\delta$: 2.81 (6H, s, S-Me), 4.20 (3H, s, N-Me), 7.47 (1H, d, $J=5$, 7 Hz, 5-H), 8.78 (1H, dd, $J=2$, 7 Hz, 4 or 6-H), 9.14 (1H, dd, $J=2$, 5 Hz, 4 or 6-H).

1-Methyl-2-(N-bis(methylthio)methylene)aminobenzothiazolium iodide (11c) —— This compound was also obtained from 3h by the procedure described for 11a: yellow needles, mp 127—130°, yield 95%. Anal. Calcd. for C$_{12}$H$_{16}$N$_{2}$S$_{2}$: C, 33.35; H, 3.31; N, 7.67; S, 24.23. Found: C, 33.11; H, 3.22; N, 7.68; S, 24.00. UV $\lambda_{\text{max}}$ nm (log $\varepsilon$): 220 (4.61), 280 (3.90), 288 (3.92), 306 (4.05), 320 (3.74), 370 (3.86). NMR (CF$_3$COOH) $\delta$: 2.80 (6H, s, S-Me).

3-Methyl-2-(N-(methylthio)carbonyl)iminoo-2,3-dihydrobenzothiazole (12) —— A solution of 3.95 g of 11c and 0.5 ml of H$_2$O in 50 ml of MeOH was refluxed on a boiling water bath for 3 hr. After removal of the solvent, the residue was recrystallized from MeOH to give yellow needles, mp 172—173°, in 95% yield. Anal. Calcd. for C$_{12}$H$_{16}$N$_{2}$O$_{2}$S: C, 50.39; H, 4.23; N, 11.76; S, 26.91. Found: C, 50.20; H, 4.10; N, 11.90; S, 26.48. IR $\nu_{\text{max}}$ cm$^{-1}$: 1600, 1495, 1455, 1440, 1340, 1170. UV $\lambda_{\text{max}}$ nm (log $\varepsilon$): 283 (3.68), 319 (4.55). NMR (CDCl$_3$) $\delta$: 2.40 (3H, s, S-Me), 3.80 (3H, s, N-Me), 7.24—7.72 (4H, m, aromatic H).

1-Methyl-2-(N-dimorpholinomethylene)aminopyrimidinium iodide (13) —— A mixture of 1.7 g of 11a and 1.5 g of morpholine was heated at 130° for 10 min. After cooling, 30 ml of acetone was added to the reaction mixture, and the whole was allowed to stand for 2 hr. The precipitate was collected by filtration, washed with ether, and recrystallized from MeOH to give colorless needles, mp 222°, in 80% yield. Anal. Calcd. for C$_{12}$H$_{16}$N$_{2}$O$_{2}$S: C, 43.06; H, 5.54; N, 13.39. Found: C, 42.82; H, 5.59; N, 13.15. IR $\nu_{\text{max}}$ cm$^{-1}$: 1620, 1500, 1430. UV $\lambda_{\text{max}}$ nm (log $\varepsilon$): 278 (4.08), 327 (4.23).

3-Methyl-2-(morpholinocarbonyl)iminoo-2,3-dihydrobenzothiazole (14) —— A mixture of 2 g of 11c and 1.5 g of morpholine was heated at 100° for 30 min. After cooling 5 ml of MeOH was added to the

<table>
<thead>
<tr>
<th>X</th>
<th>mp (°C)</th>
<th>Yield (%)</th>
<th>Appearance (Recrystall. solvent)</th>
<th>Formula</th>
<th>Analysis (%) Calcul.</th>
<th>IR $\nu_{\text{max}}$ cm$^{-1}$</th>
<th>UV $\lambda_{\text{max}}$ nm (log $\varepsilon$)</th>
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<tbody>
<tr>
<td>16a</td>
<td>NH</td>
<td>176—177</td>
<td>90</td>
<td>Colorless needles (MeOH+ MeCOOEt)</td>
<td>C$<em>{10}$H$</em>{12}$N$_{4}$</td>
<td>35.54 4.31 18.42</td>
<td>3200 220(4.28)</td>
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<td>16a</td>
<td>O</td>
<td>156—158</td>
<td>93</td>
<td>Colorless needles (MeOH+ MeCOOEt)</td>
<td>C$<em>{10}$H$</em>{12}$N$_{4}$</td>
<td>35.42 3.96 13.77</td>
<td>220(4.23)</td>
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<tr>
<td>16e</td>
<td>NH</td>
<td>283—284</td>
<td>95</td>
<td>Colorless needles (MeOH)</td>
<td>C$<em>{9}$H$</em>{12}$N$_{2}$</td>
<td>31.48 3.96 22.95</td>
<td>3210 220(4.22)</td>
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<tr>
<td>16d</td>
<td>NH</td>
<td>253—254</td>
<td>65</td>
<td>Colorless needles (MeOH)</td>
<td>C$<em>{9}$H$</em>{12}$N$_{2}$</td>
<td>36.68 3.64 15.56</td>
<td>320(4.56)</td>
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<tr>
<td>16e</td>
<td>O</td>
<td>214</td>
<td>85</td>
<td>Pale yellow needles (MeOH)</td>
<td>C$<em>{9}$H$</em>{12}$N$_{2}$</td>
<td>36.57 3.43 11.63</td>
<td>257(3.90)</td>
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Table III
| X       | Y       | Yield (%) | mp (°C) | Appearance (Recrystall. solvent) | Formula           | Analysis (%)
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<td>UV λₓ(log ε)</td>
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| 17a     | CN      | 70        | 163—165 | Yellow needles (MeOH)           | C₁₂H₁₂N₂S        | 57.37 4.38 24.33 13.92 |
|         | CN      |           |         |                                 |                   | (57.37 4.27 24.55 13.95) |
|         |         |           |         |                                 |                   | 2.28 (3H, s, S-Me) |
|         |         |           |         |                                 |                   | 2190 (CN)       |
| 17b     | CN      | 90        | 154—156 | Pale yellow crystals (MeOH)     | C₁₂H₁₂N₂O₂S      | 54.74 4.98 15.96 12.18 |
|         | COOMe   |           |         |                                 |                   | (54.61 4.95 15.85 12.06) |
|         |         |           |         |                                 |                   | 2.28 (3H, s, S-Me) |
|         |         |           |         |                                 |                   | 3.70 (3H, s, O-Me) |
|         |         |           |         |                                 |                   | 2190 (CN)       |
|         |         |           |         |                                 |                   | 1760 (CO)       |
| 17c     | H       | 55        | 187—188 | Yellow needles (acetone)        | C₈H₁₄N₂O₂S       | 47.99 4.92 18.65 14.23 |
|         | NO₂     |           |         |                                 |                   | (47.90 4.98 18.40 14.19) |
|         |         |           |         |                                 |                   | 2.60 (3H, s, S-Me) |
|         |         |           |         |                                 |                   | 2200 (H₂0)      |
| 17d     | N       | 85        | >280    | Yellow crystals (MeOH)          | C₁₂H₁₂N₂O₂S      | 64.62 5.08 14.13 10.78 |
|         |         |           |         |                                 |                   | (64.72 5.05 13.94 10.80) |
|         |         |           |         |                                 |                   | 2.46 (3H, s, S-Me) |
|         |         |           |         |                                 |                   | 3100 (NH)       |
|         |         |           |         |                                 |                   | 1645 (CO)       |
| 17e     | CMe     | 87        | 156—157 | Pale yellow crystals (MeOH)     | C₁₂H₁₄N₂O₂S₂     | 56.22 5.03 8.74 20.01 |
|         | COMe    |           |         |                                 |                   | (56.06 5.15 8.71 20.66) |
|         |         |           |         |                                 |                   | 2.15 (3H, s, S-Me) |
|         |         |           |         |                                 |                   | 2.28 (6H, s, S-Me) |
|         |         |           |         |                                 |                   | 1680 (CO)       |
|         |         |           |         |                                 |                   | 1625 (CO)       |
| 17f     | H       | 65        | 176—178 | Yellow needles (acetone)        | C₁₁H₁₄N₂O₂S₂     | 46.96 3.94 14.94 22.79 |
|         | NO₂     |           |         |                                 |                   | (47.02 3.88 14.97 22.73) |
|         |         |           |         |                                 |                   | 2.30 (3H, s, S-Me) |
|         |         |           |         |                                 |                   | 1520 (NO₂)      |
|         |         |           |         |                                 |                   | 1369 (NO₂)      |
| 17g     | S       | 50        | 143     | Yellow needles (MeOH)           | C₁₂H₁₄N₂O₄S₁     | 47.21 3.91 11.01 33.62 |
|         | S       |           |         |                                 |                   | (47.05 4.14 11.07 33.78) |
|         | O       |         |         |                                 |                   | 2.36 (3H, s, S-Me) |
|         | Et      |           |         |                                 |                   | 1680 (CO)       |

a) Concentrations could not be determined because of insufficient solubility.
reaction mixture and the whole was allowed to stand for 1 hr. The precipitate was collected by filtration, washed with ether, and recrystallized from MeOH to give colorless needles, mp 181°, in 70% yield.

b) A solution of 1.2 g of 12 and 0.7 g of MeOH was heated in a boiling water bath. After removal of the solvent, the residue was recrystallized from MeOH to give colorless needles, mp 181°, in 97% yield. Anal. Calcd. for C_{12}H_{12}N_{2}O_{2}: C, 56.30; H, 5.46; N, 15.15; S, 11.56. Found: C, 56.30; H, 5.45; N, 15.29; S, 11.46. IR ν_{max} cm^{-1}: 1600, 1530, 1400, 1265, 1208. UV λ_{max} nm (log ε): 270 (4.08), 305 (4.45), 310 (4.57).

The Reaction of 11a and 11c with Hydrazine Hydrate——A mixture of 0.01 mol of 11a or 11c and 3 ml of hydrazine hydrate was heated at 130° for 30 min. After cooling, 10 ml of MeOH was added to the reaction mixture. The precipitate was collected by filtration, washed with MeOH, and recrystallized from benzene + DMF. 15a: yellow crystals, mp 282°, Yield 70%. Anal. Calcd. for C_{12}H_{12}N_{2}S_{2}: C, 53.31; H, 5.59; N, 23.13; S, 17.79. Found: C, 53.17; H, 5.59; N, 23.47; S, 17.75. MS m/e: 390 (M^+). IR ν_{max} cm^{-1}: 1635, 1535, 1510, 1370. UV λ_{max} nm: 260, 305, 364; λ_{max} nm: 285, 326. 15b: pale yellow needles, mp 270°. Yield 87%. Anal. Calcd. for C_{12}H_{12}N_{2}S_{2}: C, 50.82; H, 4.27; N, 17.78; S, 27.13. Found: C, 50.70; H, 4.35; N, 17.70; S, 26.92. MS m/e: 472 (M^+). IR ν_{max} cm^{-1}: 1580, 1550, 1520, 1460, 1395, 1225. UV λ_{max} nm: 235, 295, 390; λ_{max} nm: 250, 300. NMR (CD_{3}COOH) δ: 2.90 (6H, s, 2×S-Me), 4.08 (6H, s, 2×N-Me).

Reaction of 11a—c with Ethylenediamine and Ethanolamine——A solution of 0.001 mol of 11(a, b or c) and 0.012 mol of amine (ethylenediamine or ethanolamine) in 50 ml of EtOH was heated under reflux for 2 hr. After removal of the solvent, the residue was recrystallized from EtOH to give the corresponding imidazoline (16a, c, d) and oxazoline (16b, e) derivatives.

Reaction of 11a and 11b with Active Methylene Compounds——Compound 11(a or c) (0.01 mol) was added to a solution of 0.011 mol of an active methylene compound (malononitrile, methyl cyanoacetate, oxindole, acetyacetone, nitromethane, or rhodanine) and 0.03 mol of K_{2}CO_{3} in 30 ml of DMSO with stirring at room temperature for 3 hr. The color of the reaction mixture became reddish-brown. The mixture was poured into ice-water and acidified with 10% HCl solution. The precipitate was collected by filtration, washed with H_{2}O, and recrystallized from MeOH to give the corresponding products substituted in the methylthio group. The results are shown in Table IV.