Rearrangement of 4-(Aminothiocarbonyl)oxazoles to 5-Aminothiazoles. Synthetic and MINDO/3 MO Studies

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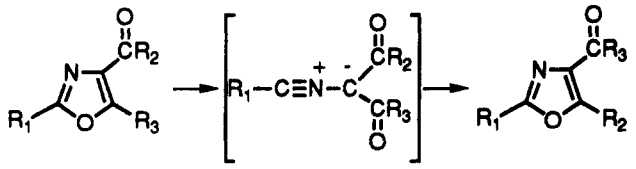
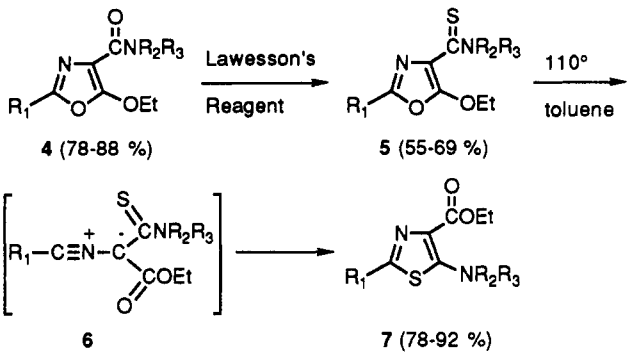
One of the most intriguing aspects of heterocyclic chemistry is the conversion of one heterocyclic system to another.[1] These processes occur via ring opening of the heterocycle under acidic, basic, thermal, or photochemical conditions followed by recyclization of an acyclic intermediate. Cycloadditions can also provide an approach to heterocyclic ring transformations. Because of its reactivity toward acids, bases, heat, dienophiles, and dipolarophiles, the oxazole ring system is an attractive starting point for a variety of ring transformations.[2]

Over 30 years ago, Cornforth reported the thermal rearrangement of 4-carbonyl-substituted oxazoles **1** to the isomeric oxazoles **3**.[3] This rearrangement has been applied to syntheses of 5-halo-,[3] 5-amino-,[3-5] 5-(arylthio)-,[5] 5-alkyl-, and 5-aryloxazoles[6] and an imidazole[5] and has been used as a key step in the synthesis of oxazolo[5,4-*d*]pyrimidin-7-ones.[7] The mechanism involves the electrocyclic opening of the oxazole ring **1**, leading to the formation of the nonisolable nitrile ylide **2**, which undergoes a 1,5-dipolar electrocyclization[8] to the rearranged oxazole **3**.



1 **2** **3**

Despite the many reported ring transformations of oxazoles, oxazole to thiazole interconversions have received little attention.[2] We now report the thermal rearrangement of 4-(aminothiocarbonyl)-5-ethoxyoxazoles **5** to 5-aminothiazoles **7**. This process is a simple, relatively general route to thiazoles **7** from readily available starting materials.[3-5] 4-(Ethoxycarbonyl)-5-aminothiazoles have been prepared by the reaction of ethyl 2-(acylamino)-2-cyanoacetate with Lawesson's reagent, but this synthesis necessarily yields only the primary aminothiazoles.[9] The optimized yield of thioamides **5** by the reaction of amides **4** with Lawesson's reagent is modest (55–69%); however, the yield of thiazoles **7** is excellent. This procedure appears



4 (78-88 %) **5** (55-69 %)

6 **7** (78-92 %)

a	R_1 = Me	$R_2 = R_3$ = H
b	R_1 = Me	R_2 = Me, R_3 = H
c	R_1 = Me	R_2 - R_3 = -$(CH_2)_4$-
d	R_1 = Ph	$R_2 = R_3$ = H
e	R_1 = Ph	R_2 = Me, R_3 = H
f	R_1 = Ph	R_2 = CH_2Ph, R_3 = H
g	R_1 = Ph	R_2 - R_3 = -$(CH_2)_5$-
h	R_1 = Ph	R_2 - R_3 = -$(CH_2)_2$-O-$(CH_2)_2$-

applicable to the synthesis of any 2-alkyl- or 2-aryl-4-(alkoxycarbonyl)-5-aminothiazoles. In our hands, under a variety of thiation conditions, the reaction of 4-[(*N*-arylamino)carbonyl]-5-ethoxyoxazoles has failed to give the desired 4-[(*N*-arylamino)thiocarbonyl]-5-ethoxyoxazoles, however.

The relative rates of the thermal rearrangement of **5** to **7** parallel qualitatively the rates of rearrangement of the 4-(aminocarbonyl)-5-alkoxyoxazoles **4** to the corresponding 5-aminooxazoles;[4] i.e., the 2-methyloxazoles rearrange faster than the 2-phenyl derivatives, and the primary thioamides rearrange faster than the secondary, which are faster than the tertiary. In the case of the reaction of 2-methyl-4-(aminocarbonyl)-5-ethoxyoxazole (**4a**) with Lawesson's reagent (refluxing THF, 2 h), only 5-aminothiazole **7a** could be isolated, while 2-methyl-4-[(*N*-methylamino)carbonyl]-5-ethoxyoxazole (**4b**) provided a mixture of thioamide **5b** and thiazole **7b** with Lawesson's reagent (1.75:1, refluxing THF, 2 h). Compounds **5b** and **7b** were separated by flash chromatography. When oxazole **5b** was heated under reflux in toluene for 2 h, thiazole **7b** was obtained in 78% yield.

The results of MINDO/3 MO[10] calculations support the proposed mechanism for the rearrangement of the 4-(aminocarbonyl)-5-alkoxyoxazoles **1** (R_2 = NH_2, R_3 = OMe) to the 4-(alkoxycarbonyl)-5-aminooxazoles **3** as well as providing insight into the nature of the nitrile ylide intermediate **2**.[11] We have carried out MINDO/3 calculations on the rearrangement of 2-methyl-4-(aminothiocarbonyl)-5-ethoxyoxazole (**5a**) to 2-methyl-4-(ethoxycarbonyl)-5-aminothiazole (**7a**). The O1–C2 bond distance (*r*, Å) in the oxazole ring was chosen as the reaction coordinate. The fact that the forward and backward reaction paths (S1–C2 bond distance of the thiazole) were similar suggests that *r* is a satisfactory reaction coordinate.[12] The corresponding minimum energy reaction path is shown in Figure 1 as a plot of calculated heats of formation (ΔH_f) vs *r*. The transition states were optimized by the use of

(1) Van Der Plas, H. C. *Ring Transformations of Heterocycles*; Academic Press: New York, 1973.
(2) (a) Turchi, I. J. Oxazoles. In *Oxazoles*; Turchi, I. J., Ed.; Wiley: New York, 1986; Chapter 1. (b) Turchi, I. J. *Ind. Eng. Chem. Prod. Res. Dev.* **1981**, *20*, 32. (c) Turchi, I. J.; Dewar, M. J. S. *Chem. Rev.* **1975**, *75*, 389.
(3) Cornforth, J. W. In *The Chemistry of Penicillin*; Princeton University Press: Princeton, NJ, 1948; p 700.
(4) Dewar, M. J. S.; Turchi, I. J. *J. Am. Chem. Soc.* **1974**, *96*, 6148.
(5) Dewar, M. J. S.; Turchi, I. J. *J. Org. Chem.* **1975**, *40*, 1521.
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(8) For reviews of 1,5-dipolar electrocyclizations, see: (a) Taylor, E. C.; Turchi, I. J. *Chem. Rev.* **1979**, *79*, 181. (b) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 947. (c) Durr, H. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 413.
(9) Golankiewicz, B.; Januszczyk, P.; Gdaniec, M.; Kosturkiewicz, Z. *Tetrahedron* **1985**, *41*, 5989.
(10) Bingham, R. C.; Dewar, M. J. S.; Lo, D. H. *J. Am. Chem. Soc.* **1975**, *97*, 1285, 1294, 1302.
(11) Dewar, M. J. S.; Turchi, I. J. *J. Chem. Soc., Perkin Trans. 2* **1977**, 724.
(12) Dewar, M. J. S.; Kirschner, S. *J. Am. Chem. Soc.* **1971**, *93*, 4291.

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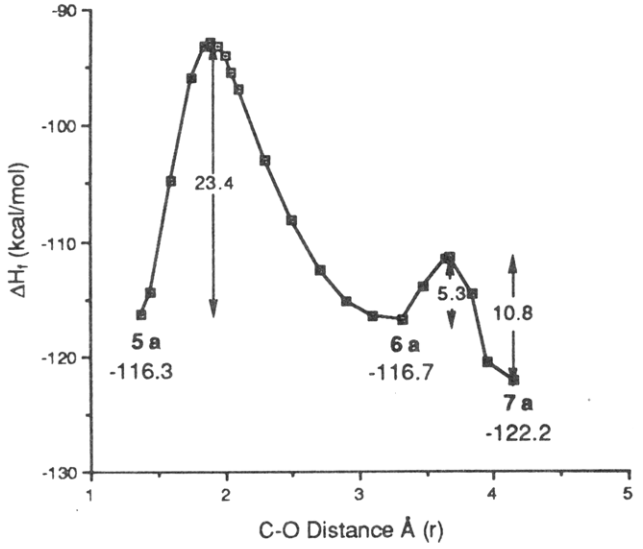
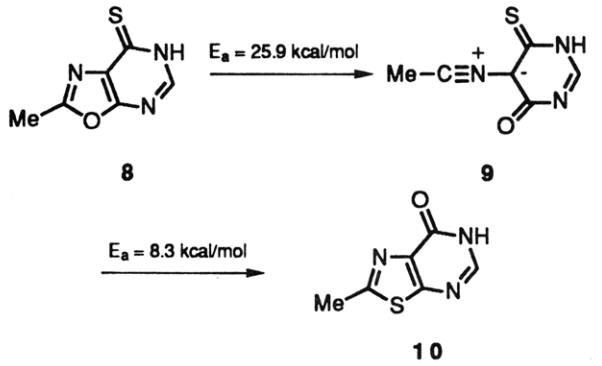


Figure 1. Energy (kcal/mol) vs reaction coordinate (r, Å) for the interconversion of **5a** to **7a**.

the SADDLE option in MOPAC Version 4.0.[13] The transition state for the overall reaction corresponds to the opening of the oxazole ring and has an activation energy of 23.4 kcal/mol. This result is consistent with the observation that the rearrangement of **5a** to **7a** occurs at a reasonable rate (60 °C, refluxing THF, 2 h). Nitrile ylide **6a** is a minimum on the reaction path and thus should be a stable intermediate; however, the activation energy for its ring closure to thiazole **7a** is very low (5.3 kcal/mol). The conversion of oxazole **5a** to thiazole **7a** is exothermic by 5.9 kcal/mol, in agreement with the observed irreversibility of the rearrangement. In view of the success of the MINDO/3 MO method in describing the path of the Cornforth rearrangement,[11] we expect that this and the AM1[14] molecular orbital methods will allow us to make predictions involving the thermal behavior of various oxazoles possessing unsaturated substituents at the 4-position.[15,16]

Two publications have appeared describing the acid-induced and thermal rearrangement of oxazolo[5,4-*d*]pyrimidine-7-thiones **8** to thiazolo[5,4-*d*]pyrimidin-7-ones **10**.[17] The authors failed to postulate a mechanism for the *thermal* rearrangement, and as this process appears to be related to ours, we carried out MINDO/3 MO calculations on this heterocyclic ring transformation. The results of these calculations support a mechanism involving electrocyclic opening of the oxazole ring in **8** (ΔH_f = −44.5 kcal/mol) leading to the formation of nitrile ylide **9** (ΔH_f = −46.0 kcal/mol) followed by electrocyclic ring closure of **9** to give the observed thiazolo[5,4-*d*]pyrimidin-7-one **10** (ΔH_f = −49.5 kcal/mol).[18]



Experimental Section

General Methods. Melting points were obtained on a Thomas-Hoover Unimelt capillary apparatus and are uncorrected. IR spectra were recorded in KBr pellets or neat on a Perkin-Elmer 683 infrared spectrometer. NMR spectra were recorded on an IBM AF-270 spectrometer and with tetramethylsilane as an internal standard. Electron impact mass spectra were recorded on a Hewlett-Packard 5995 GC–MS using a direct-insertion probe. Thin-layer chromatography (TLC) was carried out on prescored silica gel GF plates (Analtech). For flash chromatography, silica gel 60 (230–400 mesh; ASTM, E. Merck) was used. Columns were eluted with a positive nitrogen pressure. Microanalyses were determined by The BOC Group Technical Center Microanalytical Service under the direction of Allan Ellgren. Satisfactory elemental analyses (C, H, N; ±0.4%) were obtained for all new compounds.

Oxalyl chloride (Gold Label) and the starting amines were purchased from Aldrich Chemical Co., and Lawesson's reagent was purchased from Fluka Chemical Co.

2-Methyl-5-ethoxyoxazole-4-carboxylic Acid. Ethyl 2-methyl-5-ethoxyoxazole-4-carboxylate[2a] (19.9 g, 100 mmol) was stirred and heated gently in an aqueous solution of sodium hydroxide (4.4 g, 110 mmol in 25 mL of water) until a clear solution resulted (5–10 min). The solution was cooled to 5 °C, and dilute sulfuric acid was added until the solution became acidic. The precipitated acid (12.8 g, 75%) was collected by filtration, washed with water, dried under reduced pressure, and used without further purification in the preparation of the 2-methyl-4-(chlorocarbonyl)-5-ethoxyoxazole. A small sample was recrystallized from benzene for elemental analysis: mp 141–142 °C; ^{1}H NMR (DMSO-d_6) δ 12.37 (s, 1 H), 4.38 (q, J = 7.0 Hz, 2 H), 2.26 (s, 3 H), 1.32 (t, J = 7.0 Hz, 3 H).

2-Phenyl-5-ethoxyoxazole-4-carboxylic acid was prepared by hydrolysis of ethyl 2-phenyl-5-ethoxyoxazole-4-carboxylate;[3] mp 147–148 °C (lit.[3] mp 148 °C).

2-Methyl-4-(chlorocarbonyl)-5-ethoxyoxazole. A solution of oxalyl chloride (1.78 g, 13 mmol) in dichloromethane (50 mL) was added dropwise with stirring to a mixture of 2-methyl-5-ethoxyoxazole-4-carboxylic acid (1.71 g, 10 mmol) and dimethylformamide (0.03 mL) in dichloromethane (150 mL) at room temperature. The mixture was allowed to stir for 2 h; the solvent was removed under reduced pressure at room temperature. To facilitate the removal of excess oxalyl chloride, dichloromethane (100 mL) was added and then removed under reduced pressure at room temperature. The resulting solid was dried under vacuum (2 mm) for 1 h and then used immediately without purification in the preparation of the 4-(aminocarbonyl)-5-ethoxyoxazoles.

2-Phenyl-4-(chlorocarbonyl)-5-ethoxyoxazole[3] was prepared by the above procedure from 2-phenyl-5-ethoxyoxazole-4-carboxylic acid.[3]

(13) Stewart, J. J. P.; Seiler, F. J. *MOPAC: A General Molecular Orbital Package*, Version 4.0; QCPE Program No. 455; Quantum Chemistry Program Exchange: Indiana University, Bloomington, IN, 1987.

(14) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.

(15) MNDO calculations (Dewar, M. J. S.; Thiel, W. *J. Am. Chem. Soc.* **1977**, *99*, 4899) generally lead to a much higher (by 15–20 kcal/mol) activation energy for the ring opening of the 4-carbonyl-substituted oxazoles than MINDO/3 or AM1. For this reason we have abandoned MNDO calculations in the present work.

(16) For example, we have carried out MINDO/3 and AM1 calculations on 4-nitrooxazole. These calculations allow us to predict that 4-nitrooxazole will undergo cleavage of the O1–C2 bond leading to a nitroformyl-substituted nitrile ylide that will subsequently cyclize to 3-formyl-1,2,4-oxadiazole 2-oxide. The calculations also suggest that the oxadiazole will be unstable under the thermal reaction conditions and ring open to a nitroso compound by O1–C2 bond cleavage. We are presently investigating the thermal chemistry of nitrooxazoles experimentally, and the results of this study will be the subject of a future publication.

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(18) MINDO/3 calculations on the tautomeric forms of **8–10** where N3 of the pyrimidine ring bears the proton give similar results. The tautomeric form of **8** where the proton is on sulfur is approximately 8.5 kcal/mol higher in energy than either of the ring-nitrogen-protonated forms.

2-Phenyl-4-(aminocarbonyl)-5-ethoxyoxazole (4d).[3] Solid 2-phenyl-4-(chlorocarbonyl)-5-ethoxyoxazole (2.52 g, 10 mmol) was added in portions with stirring to cold concentrated aqueous ammonia (50 mL). The mixture was allowed to stir at room temperature for 30 min, and then the resulting amide was collected by filtration and dried under reduced pressure to give **4d**: 2.04 g, 88%; mp 118–119 °C (lit.[3] mp 118–119 °C). Oxazolecarboxamide **4a** was prepared in an analogous fashion, and amides **4b** and **4e** were prepared from aqueous methylamine (40%). These amides were converted to the thioamides without further purification.

2-Methyl-4-(aminocarbonyl)-5-ethoxyoxazole (4a): yield 78%; analytical sample was recrystallized from ethanol, showing mp 149–151 °C; ^{1}H NMR (DMSO-d_6) δ 7.13 (b, 2 H), 4.43 (q, J = 7.2 Hz, 2 H), 2.29 (s, 3 H), 1.32 (t, J = 7.2 Hz, 3 H). This compound is too insoluble to obtain the ^{13}C NMR spectrum.

2-Methyl-4-[(*N*-methylamino)carbonyl]-5-ethoxyoxazole (4b): yield 82%; analytical sample was recrystallized from cyclohexane, showing mp 100–102 °C. ^{1}H NMR ($CDCl_3$) δ 6.68 (b, 1 H), 4.57 (q, J = 7.0 Hz, 2 H), 3.00 (d, J = 5.1 Hz, 3 H), 2.39 (s, 3 H), 1.52 (t, J = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 161.5, 158.3, 150.1, 109.8, 70.3, 25.2, 14.7, 13.5.

2-Phenyl-4-[(*N*-methylamino)carbonyl]-5-ethoxyoxazole (4e): yield 81%; analytical sample was recrystallized from ethanol, showing mp 85–86 °C; ^{1}H NMR ($CDCl_3$) δ 7.93 (m, 2 H), 7.44 (m, 3 H), 6.87 (b, 1 H), 4.67 (q, J = 7.1 Hz, 2 H), 2.98 (d, J = 5.1 Hz, 3 H), 1.52 (t, J = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 161.5, 158.6, 150.3, 130.1, 128.6, 126.6, 125.5, 111.4, 70.7, 25.4, 14.9.

2-Phenyl-4-[(*N*-benzylamino)carbonyl]-5-ethoxyoxazole (4f). To a stirred solution of benzylamine (1.07 g, 10 mmol) and triethylamine (1.12 g, 11 mmol) in dichloromethane (100 mL) at 5 °C was added dropwise a solution of 2-phenyl-4-(chlorocarbonyl)-5-ethoxyoxazole (2.51 g, 10 mmol) in dichloromethane (50 mL). The mixture was allowed to stir at room temperature for 17 h, washed with dilute hydrochloric acid and water, and then dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residual solid was recrystallized from cyclohexane: yield 81%; mp 48–51 °C; ^{1}H NMR ($CDCl_3$) δ 7.90 (m, 2 H), 7.42 (m, 3 H), 7.32 (m, 5 H), 7.20 (b, 1 H), 4.69 (d, J = 4.5 Hz, 2 H), 4.66 (q, J = 7.1 Hz, 2 H), 1.53 (t, J = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 161.0, 159.1, 150.5, 138.6, 130.3, 128.8, 128.7, 127.9, 127.4, 126.8, 125.8, 111.2, 70.8, 42.9, 15.1.

4-(Aminocarbonyl)-5-ethoxyoxazoles **4c, g,** and **h** were prepared by the same procedure and were recrystallized from cyclohexane.

2-Methyl-4-(1-pyrrolidinocarbonyl)-5-ethoxyoxazole (4c): yield 76%; oil; ^{1}H NMR ($CDCl_3$) δ 4.40 (q, J = 7.1 Hz, 2 H), 3.78 (t, J = 6.3 Hz, 2 H), 3.57 (t, J = 6.3 Hz, 2 H), 2.34 (s, 3 H), 1.87 (m, 4 H), 1.46 (t, J = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 160.8, 158.7, 149.4, 110.9, 69.5, 47.8, 45.9, 26.1, 23.6, 14.6, 13.6.

2-Phenyl-4-(1-piperidinocarbonyl)-5-ethoxyoxazole (4g): yield 82%; mp 45–47 °C; ^{1}H NMR ($CDCl_3$) δ 7.95 (m, 2 H), 7.45 (m, 3 H), 4.50 (q, J = 7.0 Hz, 2 H), 3.75, 3.65 (2 overlapping m, 4 H), 1.65 (m, 6 H), 1.49 (t, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 161.4, 158.5, 150.2, 129.8, 128.5, 127.0, 125.5, 111.7, 69.9, 47.9, 43.3, 26.4, 25.7, 24.6, 14.8.

2-Phenyl-4-(1-morpholinocarbonyl)-5-ethoxyoxazole (4h): yield 82% mp 85–86 °C (lit.[5] mp 85–86 °C).

2-Phenyl-4-(aminothiocarbonyl)-5-ethoxyoxazole (5d). A mixture of 2-phenyl-4-(aminocarbonyl)-5-ethoxyoxazole (**4d**) (4.64 g, 2.0 mmol) and 2,4-bis(methoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide (Lawesson's reagent)[19] (8.09 g, 2.0 mmol, 2 equiv) in tetrahydrofuran (50 mL) was heated under reflux for 2 h. The solvent was removed under reduced pressure. Flash chromatography of the residue on silica gel (hexane:ethyl acetate = 4:1, also for the 2-phenyl derivatives **5d–h**, and hexane:ethyl acetate = 2:1 for the 2-methyl derivatives **5b** and **c**) afforded an oil that solidified under vacuum: 3.27 g, 66%; recrystallized from cyclohexane; mp 117–119 °C; ^{1}H NMR ($CDCl_3$) δ 8.07 (b, 1 H), 7.94 (m, 2 H), 7.47 (m, 3 H), 7.13 (b, 1 H), 4.68 (q, J = 7.1 Hz, 2 H), 1.60 (t, J = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 188.3, 160.5, 149.1, 130.4, 128.8, 127.3, 125.8, 115.5, 70.4, 15.0.

4-(Aminothiocarbonyl)-5-ethoxyoxazoles **5c** and **e–h** were prepared in this manner and recrystallized from cyclohexane.

(19) Andersen, T. P.; Ghattas, A.-B. A. G.; Lawesson, S.-O. *Tetrahedron* **1983**, *39*, 3419 and references therein.

2-Methyl-4-(1-pyrrolidinothiocarbonyl)-5-ethoxyoxazole (5c): yield 69%; yellow oil; ^{1}H NMR ($CDCl_3$) δ 4.38 (q, J = 7.1 Hz, 2 H), 3.93 (m, 2 H), 3.80 (m, 2 H), 2.37 (s, 3 H), 2.01 (m, 4 H), 1.44 (t, J = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 184.0, 155.7, 150.0, 116.7, 69.8, 53.3, 52.9, 26.3, 24.0, 14.9, 13.8.

2-Phenyl-4-[(*N*-methylamino)thiocarbonyl]-5-ethoxyoxazole (5e): yield 61%; mp 102–103 °C; ^{1}H NMR ($CDCl_3$) δ 8.70 (b, 1 H), 7.93 (m, 2 H), 7.47 (m, 3 H), 4.63 (q, J = 7.1 Hz, 2 H), 3.32 (d, J = 5.1 Hz, 3 H), 1.56 (t, J = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 185.1, 159.3, 149.2, 130.3, 129.7, 126.3, 125.6, 116.6, 70.3, 30.9, 14.9.

2-Phenyl-4-[(*N*-benzylamino)thiocarbonyl]-5-ethoxyoxazole (5f): yield 60%; mp 56–58 °C; ^{1}H NMR ($CDCl_3$) δ 8.85 (b, 1 H), 7.90 (m, 2 H), 7.35 (m, 8 H), 5.05 (d, J = 5.6 Hz, 2 H), 4.65 (q, J = 7.1 Hz, 2 H), 1.60 (t, J = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 184.3, 159.7, 149.3, 136.9, 130.4, 128.7, 128.1, 127.7, 127.4, 126.1, 125.7, 116.4, 70.3, 47.9, 15.0.

2-Phenyl-4-(1-piperidinothiocarbonyl)-5-ethoxyoxazole (5g): yield 55%; mp 69–71 °C; ^{1}H NMR (DMSO-d_6) δ 7.90 (m, 2 H), 7.55 (m, 3 H), 4.45 (q, J = 7.1 Hz, 2 H), 4.30 (m, 2 H), 3.82 (m, 2 H), 1.65 (m, 6 H), 1.40 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (DMSO-d_6) δ 185.4, 154.9, 149.7, 130.2, 128.9, 126.4, 125.1, 117.5, 70.1, 52.8, 49.6, 26.5, 25.2, 23.4, 14.7.

2-Phenyl-4-(1-morpholinothiocarbonyl)-5-ethoxyoxazole (5h): yield 59%; mp 68–70 °C; ^{1}H NMR ($CDCl_3$) δ 7.90 (m, 2 H), 7.45 (m, 3 H), 4.52 (q, J = 7.1 Hz, 2 H), 4.35 (b, 2 H), 4.00 (b, 2 H), 3.85 (bd, 4 H), 1.50 (t, J = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 187.9, 157.3, 150.5, 130.1, 128.7, 127.0, 125.7, 117.6, 70.5, 66.7, 51.9, 14.9.

2-Methyl-4-(ethoxycarbonyl)-5-aminothiazole (7a; 0.99 g, 53%) was obtained when 2-methyl-4-(aminocarbonyl)-5-ethoxyoxazole (**4a**; 1.70 g, 10 mmol) was subjected to the conditions described above and was recrystallized from cyclohexane/ether: mp 151–153 °C (lit.[9] mp 156–157 °C); ^{1}H NMR ($CDCl_3$) δ 6.18 (b, 2 H), 4.37 (q, J = 7.1 Hz, 2 H), 2.48 (s, 3 H), 1.40 (t, J = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 164.2, 159.5, 147.3, 120.3, 60.1, 18.8, 14.3.

A mixture of 2-methyl-4-[(*N*-methylamino)thiocarbonyl]-5-ethoxyoxazole (**5b**; 0.76 g, 38%) and 2-methyl-4-(ethoxycarbonyl)-5-(*N*-methylamino)thiazole (**7b**; 0.56 g, 28%) (1.75:1; overall yield 1.32 g, 66%) was isolated when 2-methyl-4-[(*N*-methylamino)carbonyl]-5-ethoxyoxazole (**4b**; 1.84 g, 10 mmol) was subjected to the above conditions. These compounds were separated by flash chromatography on silica gel (hexane:ethyl acetate = 2:1).

2-Methyl-4-[(*N*-methylamino)thiocarbonyl]-5-ethoxyoxazole (5b): yield 38%; mp 83–84 °C; ^{1}H NMR ($CDCl_3$) δ 8.43 (b, 1 H), 4.47 (q, J = 7.1 Hz, 2 H), 3.26 (d, J = 5.1 Hz, 3 H), 2.33 (s, 3 H), 1.49 (t, J = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 185.3, 158.8, 149.4, 115.3, 70.0, 30.9, 14.9, 13.7.

General Procedure for the Synthesis of 4-(Ethoxycarbonyl)-5-aminothiazoles 7b–h. A solution of the 4-(aminothiocarbonyl)-5-ethoxyoxazole (1 mmol) in toluene (50 mL) was heated under reflux with stirring for 17 h. The solvent was removed under reduced pressure, and the residue was recrystallized from cyclohexane.

2-Methyl-4-(ethoxycarbonyl)-5-(*N*-methylamino)thiazole (7b): yield 78%; mp 67–68 °C; ^{1}H NMR ($CDCl_3$) δ 7.23 (b, 1 H), 4.38 (q, J = 7.0 Hz, 2 H), 3.02 (d, J = 4.7 Hz, 3 H), 2.57 (s, 3 H), 1.39 (t, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 164.8, 164.0, 146.1, 118.0, 60.2, 35.2, 19.2, 14.6.

2-Methyl-4-(ethoxycarbonyl)-5-(*N*-pyrrolidino)thiazole (7c): yield 85%; mp 68–70 °C; ^{1}H NMR ($CDCl_3$) δ 4.32 (q, J = 7.1 Hz, 2 H), 3.34 (m, 4 H), 2.48 (s, 3 H), 1.94 (m, 4 H), 1.35 (t, J = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 161.9, 159.8, 147.1, 120.5, 59.7, 54.7, 25.7, 18.8, 14.2.

2-Phenyl-4-(ethoxycarbonyl)-5-aminothiazole (7d): yield 87%; mp 134–135 °C (lit.[9] mp 136 °C); ^{1}H NMR ($CDCl_3$) δ 7.80 (m, 2 H), 7.38 (m, 3 H), 6.12 (b, 2 H), 4.43 (q, J = 7.1 Hz, 2 H), 1.44 (t, J = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 164.8, 159.5, 149.4, 133.3, 129.4, 128.7, 126.1, 122.9, 60.6, 14.5.

2-Phenyl-4-(ethoxycarbonyl)-5-(*N*-methylamino)thiazole (7e): yield 88%; mp 118–119 °C; ^{1}H NMR ($CDCl_3$) δ 7.83 (m, 2 H), 7.43 (b, 1 H), 7.37 (m, 3 H), 4.42 (q, J = 7.1 Hz, 2 H), 3.10 (d, J = 5.1 Hz, 3 H), 1.43 (t, 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 165.1, 164.0, 147.7, 133.5, 128.9, 128.6, 125.7, 119.8, 60.3, 35.2, 14.5.

2-Phenyl-4-(ethoxycarbonyl)-5-(*N*-benzylamino)thiazole (7f): yield 85%; mp 97–98 °C; ^{1}H NMR ($CDCl_3$) δ 7.95 (b, 1 H), 7.80 (m, 2 H), 7.35 (m, 8 H), 4.55 (d, J = 5.8 Hz, 2 H), 4.40 (q, J = 7.0 Hz, 2 H), 1.45 (t, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 165.2, 162.5, 159.4, 148.4, 136.4, 129.1, 128.9, 128.6, 128.0, 127.4, 125.9, 61.8, 60.5, 53.0, 14.5.

2-Phenyl-4-(ethoxycarbonyl)-5-(1-piperidino)thiazole (7g): yield 85%; mp 76–78 °C; ^{1}H NMR ($CDCl_3$) δ 7.75 (m, 2 H), 7.30 (m, 3 H), 4.35 (q, J = 7.1 Hz, 2 H), 3.10 (t, J = 5.3 Hz, 4 H), 1.70 (m, 4 H), 1.50 (m, 2 H), 1.35 (t, J = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 164.0, 162.0, 153.8, 133.5, 129.3, 128.6, 125.9, 111.5, 60.5, 55.7, 26.7, 25.4, 24.1, 23.5, 14.4.

2-Phenyl-4-(ethoxycarbonyl)-5-(1-morpholino)thiazole (7h): yield 92%; mp 83–85 °C. ^{1}H NMR ($CDCl_3$) δ 7.88 (m, 2 H), 7.42 (m, 3 H), 4.43 (q, J = 7.2 Hz, 2 H), 3.90 (m, 4 H), 3.28 (m, 4 H), 1.43 (t, J = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 162.6, 161.9, 155.2, 133.5, 130.2, 129.7, 128.7, 126.2, 66.4, 60.7, 54.2, 14.4.

Supplementary Material Available: Tables containing the crystal structure, MNDO, and MINDO/3 geometries for 4-(ethoxycarbonyl)-5-aminothiazole, MINDO/3 geometries and charge densities for oxazole **5a**, nitrile ylide **6a**, thiazole **7a**, oxazolo[5,4-*d*]pyrimidine-7-thione **8**, nitrile ylide **9**, and thiazolo[5,4-*d*]pyrimidin-7-one **10**, MINDO/3 charge densities and frontier MO energies and coefficients for nitrile ylide **6a**, and IR, mass spectral, and elemental analysis data (13 pages). Ordering information is given on any current masthead page.

Calixarenes. 24. Complexation by Water-Soluble Calixarenes

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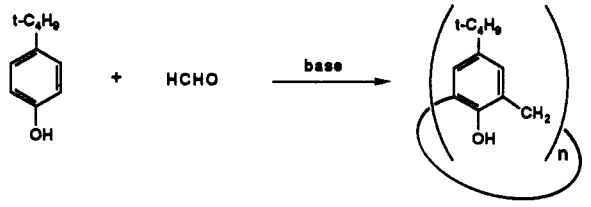
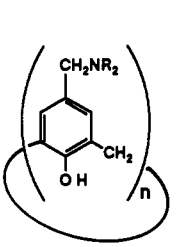
Calixarenes (**1**), which are [1_n] metacyclophanes comprising para-substituted phenolic units and methylene groups, are most readily obtained from the base-induced condensation of *p-tert*-butylphenol and formaldehyde.[1]

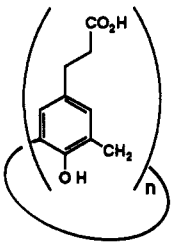


1

Because they have been made easily accessible, the calixarenes have become popular substrates for complexation studies, especially for the sequestration of inorganic ions.[2] That they also have the capacity for forming complexes with organic molecules has been demonstrated by Shinkai and co-workers[3] as well as by the results reported in the previous paper in this series[4] involving the interaction of various aromatic hydrocarbons with *p*-(dialkylamino)calixarenes (**2**, n = 4–8) and *p*-(2-carboxyethyl)calixarenes (**3**, n = 4–8). The present paper is a continuation of these earlier studies and extends the list of host molecules to include various relatives of **3**.



2

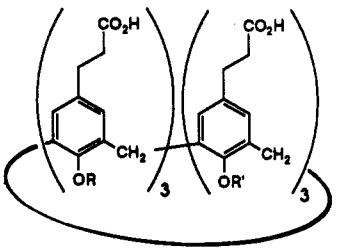


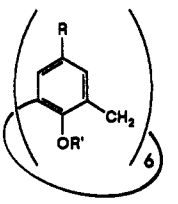
3a (n = 6)

3b (n = 8)

Synthesis of Host Molecules

Calixarenes **3a** and **3b** were synthesized by the *p*-quinonemethide procedure described in the previous paper involving treatment of the quaternary salt of **2** with 2 equiv of sodio diethyl malonate followed by hydrolysis and decarboxylation of the resulting polyester.[4] Calixarenes **4a**, **4b**, and **4c** were prepared by alkylation of **3a** following the general procedures that Shinkai et al.[3] used with the *p*-sulfonatocalixarenes. To our surprise, however, the elemental analyses for the *n*-hexyl ether (**4b**) and carboxymethyl ether (**4c**) agreed more closely with trisubstituted than with hexasubstituted compounds, and an inspection of the ratio of the areas for the ^{1}H NMR resonances of the aromatic protons vs the protons in the ether substituents provided reasonable support for this conclusion. Similar observations have been reported by Aoyama et al.[5] Calixarenes **5a**, **5b**, **6a**, and **6b** were prepared by carboxymethylation of calix[6]arene, *p-tert*-butylcalix[6]arene, calix[8]arene, and *p-tert*-butylcalix[8]arene, respectively, by the procedure described by Chang and Cho.[6]





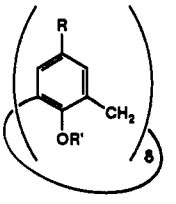
4a (R = CH_3, R' = CH_3)

4b (R = n-C_6H_{13}, R' = H)

4c (R = CH_2CO_2H, R' = H)

5a (R = H, R' = CH_2CO_2H)

5b (R = t-C_4H_9, R' = CH_2CO_2H)



6a (R = H, R' = CH_2CO_2H)

6b (R = t-C_4H_9, R' = CH_2CO_2H)

(1) For summaries of calixarene chemistry, cf.: (a) Gutsche, C. D. *Monographs in Supramolecular Chemistry*: *Calixarenes*; Stoddart, J. F., Ed.; Royal Society of Chemistry: London, 1989. (b) Gutsche, C. D. Calixarenes and the Art of Molecular Basketmaking. In *Synthesis of Macrocycles*: *The Design of Selective Complexing Agents*; Izatt, R. M., Christensen, J. J., Eds.; John Wiley & Sons: New York, 1987; p 93. (c) Gutsche, C. D. The Calixarenes. In *Host Guest Complex Chemistry*; Vögtle, F., Weber, E. Eds.; Springer-Verlag: New York, 1985; p 375.

(2) For a compilation of pertinent references, cf.; Arnaud-Neu, F.; Collins, E. M.; Deasy, M.; Ferguson, G.; Harris, S. J.; Kaitner, B.; Lough, A. J.; McKervey, M. A.; Marques, E. B.; Ruhl, B. L.; Schwing-Weill, M. J.; Seward, E. M. *J. Am. Chem. Soc.* **1989**, *111*, 8681.

(3) Shinkai, S.; Mori, S.; Koreishi, H.; Subaki, T.; Manabe, O. *J. Am. Chem. Soc.* **1986**, *108*, 2409.

(4) Gutsche, C. D.; Alam, I. *Tetrahedron* **1988**, *44*, 4689.

(5) Aoyama, Y.; Nonaka, Y.; Tanaka, Y.; Toi, H.; Ogoshi, H. *J. Chem. Soc., Perkin Trans. 2*, **1989**, 1025.

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