runs were carried out in duplicate, with a precision of ±2 mV.

Acknowledgment. Financial support from the Robert A. Welch Foundation and the Petroleum Research Fund, administered by the American Chemical Society, is gratefully acknowledged. We thank Dr. Harold Kohn for use of the recording titration system and Ms. Helga Cohen for obtaining the 400-MHz NMR spectra at the South Carolina Magnetic Resonance Laboratory supported by NSF Grant CHE 82-07445.

Registry No. **2a**, 69110-33-4; **2b**, 89691-16-7; **3a**, 89709-52-4; **3b**, 89691-11-2; **3c**, 89691-12-3; **4a**, 56488-13-2; **4b**, 89691-13-4; **4c**, 89691-14-5; **4d**, 89691-15-6; **5**, 7521-41-7; **6a**, 31170-78-2; **6b**, 56826-69-8; **6c**, 41043-13-4; **7a**, 533-37-9; **7b**, 10500-57-9; **7c**, 7197-96-8; **8a**, 74701-35-2; **8b**, 28707-60-0; **8c**, 89691-10-1; **9a**, 765-87-7; **9b**, 3008-39-7; **9c**, 3008-37-5; **9d**, 3008-41-1; benzaldehyde, 100-52-7; 2,3-butanedione, 431-03-8; 3,4-hexanedione, 4437-51-8.

5-Aryl-4-hydroxy-3(2*H*)-isothiazolone 1,1-Dioxide Derivatives. Synthesis and ^{13}C NMR Characterization

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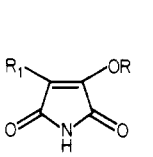
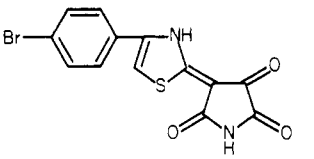
5-Phenyl- and 5-thiazolyl-4-hydroxy-3(2*H*)-isothiazolone 1,1-dioxide derivatives have been prepared by base-catalyzed cyclocondensation of diethyl oxalate with an arylmethanesulfonamide, as well as by reaction of an arylmethanesulfonamide with methyl or ethyl oxalyl chloride followed by base-catalyzed intramolecular cyclization. To verify that the preferred tautomeric structure of this until recently unexplored type of derivative was as indicated in the title, ^{13}C NMR spectral data were determined for four members of the isothiazolone 1,1-dioxide class, as well as for seven derivatives in the closely related 4-substituted-3-hydroxy-1*H*-pyrrole-2,5-dione series. The ^{13}C NMR evidence served to confirm the correctness of the structural assignments in both series for all compounds except those in which either acidic five-membered ring system was attached to the 2-position of a thiazole ring. In these instances the favored tautomer is the diketo form in which a proton resides on the thiazole ring nitrogen, with a double bond connecting the two rings.

In a search for novel inhibitors of glycolic acid oxidase (glycolate:O_2 oxidoreductase, EC 1.1.3.1) (GAO),[1] we have investigated a number of diacidic systems containing lipophilic moieties.[2,3] A key series consisted of 4-substituted-3-hydroxy-1*H*-pyrrole-2,5-dione derivatives[2] including **1a–f** and **4** (Scheme I). Examples of the closely analogous 5-substituted-4-hydroxy-3(2*H*)-isothiazolone 1,1-dioxide ring system (e.g., **2a–c**) were then prepared to determine if members of this system would exhibit comparable enzyme inhibitory activities. Although examples of the 3(2*H*)-isothiazolone 1,1-dioxide ring system have been described,[4] derivatives with a 4-hydroxyl substituent appear to have been prepared for the first time in these laboratories.[5] We report two synthetic methods to compounds of this class, where the 5-position substituent is a phenyl or substituted thiazole moiety. The ^{13}C chemical shifts and C–H couplings presented and assigned in this work for **1a–f**, **2a–c**, **3**, and **4** are the first reported for either of these two heterocyclic ring systems. Analysis of this data showed that when either of the five-membered, diacidic heterocyclic ring systems is attached to the 2-position of a thiazole nucleus (as in **3** and **4**), the keto tautomer, with a proton residing on the thiazole nitrogen and a double bond connecting the two rings, is preferred over the hydroxy tautomer. The latter is the tautomeric form which we observed for all remaining members of both heterocyclic series investigated.

Scheme I. 4-Substituted-3-hydroxy-1*H*-pyrrole-2,5-dione Derivatives for which ^{13}C NMR Spectral Data are Reported



1a–f



4

	R	R_1
1a	H	*n*-dodecyl
1b	H	[1,1′-biphenyl]-4-yl
1c	H	4′-bromo-[1,1′-biphenyl]-4-yl
1d	CH_3	[1,1′-biphenyl]-4-yl
1e	H	2-(3,4-dichlorophenyl)thiazol-4-yl
1f	H	2-(4-pyridyl)thiazol-4-yl

Results

A standard synthetic route to compounds of structure 1, where the 4-position substituent is aryl or heteroaryl, involves reaction of an arylacetamide with dialkyl oxalate and 2 mol of strong base in either protic or aprotic sol-

(1) This flavoenzyme catalyzes the oxidation of glycolic acid to glyoxylic acid, and glyoxylic acid to oxalic acid. The name in parentheses is that recommended by the Nomenclature Committee of the International Union of Biochemistry (see: "Enzyme Nomenclature 1978"; Academic Press: New York, 1979; p 55). Inhibitors of this enzyme are of interest for study in diseases, such as the primary hyperoxalurias and calcium oxalate renal lithiasis, as an approach to preventing calcium oxalate crystallization in the kidney (see ref 2).

(2) Rooney, C. S.; Randall, W. C.; Streeter, K. B.; Ziegler, C.; Cragoe, E. J., Jr.; Schwam, H.; Michelson, S. R.; Williams, H. W. R.; Eichler, E.; Duggan, D. E.; Ulm, E. H.; Noll, R. M. *J. Med. Chem.* **1983**, *26*, 700.

(3) Williams, H. W. R.; Eichler, E.; Randall, W. C.; Rooney, C. S.; Cragoe, E. J., Jr.; Streeter, K. B.; Schwam, H.; Michelson, S. R.; Patchett, A. A.; Taub, D. *J. Med. Chem.* **1983**, *26*, 1196.

(4) Lewis, S. N.; Miller, G. A.; Hausman, M.; Szamborski, E. C. *J. Heterocycl. Chem.* **1971**, *8*, 591.

(5) Colleagues in this department in the course of an unrelated research project have independently achieved the synthesis of a 5-substituted-4-hydroxy-3(2*H*)-isothiazolone 1,1-dioxide by the direct reaction of (ethoxycarbonyl)methanesulfonamide, diethyl oxalate, and base: Britcher, S. F.; Cochran, D. W.; Phillips, B. T.; Springer, J. P.; Lumma, W. C., Jr. *J. Org. Chem.* **1983**, *48*, 763.

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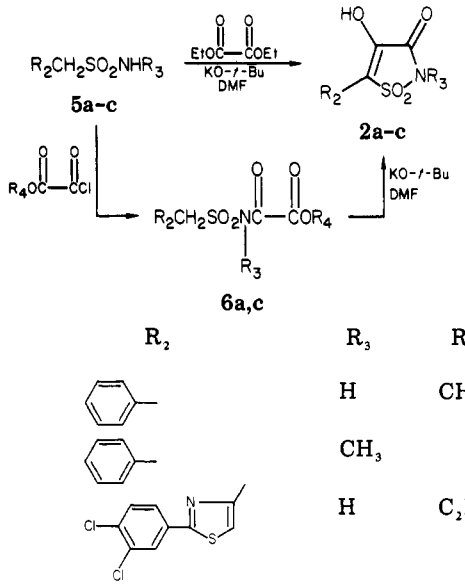
Table I. ^{13}C Chemical Shift Data of Diacidic and Thiazole Moieties[a]

	3-hydroxy-1*H*-pyrrole-2,5-dione				thiazole nucleus		
	C-2	C-3	C-4	C-5	C-2	C-4	C-5
1a	168.8	152.8	111.8	173.6			
1b	167.8	153.2	106.3	172.3			
1c	167.7	153.4	105.9	172.2			
1d	166.8	152.1	112.3	170.7			
1e	167.7	152.7	103.3	170.9	163.8	144.5	118.9
1f	167.8	154.3	102.4	171.1	163.5	146.5	119.5
4	169.8	165.8	92.5	177.3	161.0	141.0	109.5

	4-hydroxy-3(2*H*)-isothiazolone 1,1-dioxide			thiazole nucleus		
	C-3	C-4	C-5	C-2	C-4	C-5
2a	160.8	146.0	118.1			
2b	159.2	146.6	116.5			
2c	160.1	147.5	114.8	164.4	142.1	121.3
3	161.9	158.4	107.3	156.6	150.0	112.4

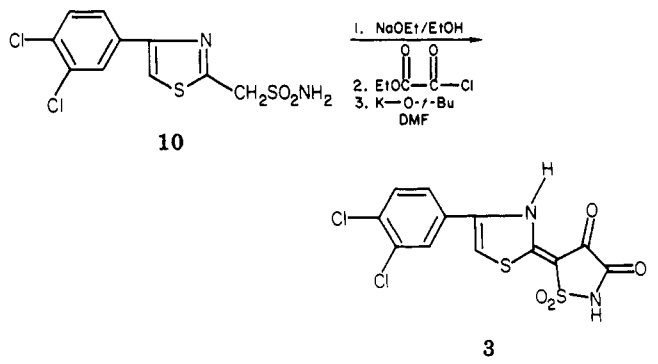
[a] ^{13}C chemical shifts determined in Me_2SO-d_6 are in ppm relative to internal Me_4Si. Chemical shift values for the remaining carbons of each of these compounds are included in the supplementary material.

Scheme II



	R_2	R_3	R_4
a		H	CH_3
b		CH_3	
c		H	C_2H_5

Scheme III



vents.[2,6] When phenylmethanesulfonamide (**5a**) was subjected to similar conditions (DMF and 2 mol of potassium *tert*-butoxide) rapid formation of the DMF-insoluble dipotassium salt of 5-phenyl-4-hydroxy-3(2*H*)-isothiazolone 1,1-dioxide (**2a**) ensued. Acidification with mineral acid gave **2a** in an overall yield of 69% (Scheme II). That **2a** possessed the expected structure was supported by all analytical data: elemental analysis, IR, mass spectroscopy, ^1H and ^{13}C NMR, and p*K*a determination (p$K_{a_{1,2}}$ 3.3, 4.9). The *N*-methyl derivative **2b**, prepared in a similar way from *N*-methyl phenylmethanesulfonamide (**5b**), exhibited a single p*K*a value of 3.72, as measured in 50% EtOH. A two-step procedure for the synthesis of **2a** was also devised. Heating **5a** in excess methyl oxalyl chloride at about 100 °C resulted in the rapid formation of *N*-[(phenylmethyl)sulfonyl]oxamic acid methyl ester, **6a**, in 83% yield. Smooth cyclization of **6a** to **2a** occurred on reaction with 2 mol of potassium *tert*-butoxide in DMF (Scheme II). The stabilities to aqueous base of **2a** and **2b** were markedly different. When **2b** was dissolved in excess sodium hydroxide solution at room temperature, rapid cleavage to generate **5b** occurred. Compound **2a**, in contrast, could be recovered unchanged after exposure to similar conditions. Since the ^{13}C chemical shifts for **2a** and **2b** are so similar (Table I), implying similar solution tautomers for the neutral species, the chemical instability of **2b** must reside in some feature of the monoanion of **2b**, i.e., the dianion formed from **2a** affords increased protection to attack by hydroxide ion.

The finding that **2a** was comparable to its pyrrole-2,5-dione counterpart in its potency as an inhibitor of porcine liver GAO encouraged us to attempt the synthesis of more complex analogues. Compound **2c**, possessing a 2-(3,4-dichlorophenyl)-4-thiazolyl substituent, was prepared as follows. Hantzsch cyclization of 3,4-dichlorothiobenzamide with 1,3-dichloroacetone gave 2-(3,4-dichlorophenyl)-4-(chloromethyl)thiazole (**7**), which was converted via the isothiouronium intermediate **8** to [2-(3,4-dichlorophenyl)thiazol-4-yl]methanesulfonyl chloride (**9**).[7] This compound reacted with ammonia to give **5c**. Reaction of the sodium salt of **5c** with ethyl oxalyl chloride to give the sulfonyloxamic ester intermediate **6c**, followed by base treatment in DMF, resulted in the formation of the cyclized product **2c**. Comparison of ^{13}C NMR chemical shift data (Table I) as well as p*K*a values and carbonyl bands in the solid-state IR spectra[8] for **2a–c** strongly suggested

(6) (a) Wiley, R. H.; Slaymaker, S. C. *J. Am. Chem. Soc.* **1958**, *80*, 1385. (b) Skinner, G. S.; Miller, C. B. *Ibid.* **1953**, *75*, 977. (c) Skinner, G. S.; Ludwig, R. E. *Ibid.* **1953**, *78*, 4656.

(7) Johnson, T. B.; Sprague, J. M. *J. Am. Chem. Soc.* **1936**, *58*, 1348.

(8) Conclusions based on solid-state IR spectral data may be erroneous because the crystal structure of tautomeric compounds may not correspond to the solution structure. However, in this work, because of the extreme insolubility of compounds such as **2a**, **2c**, and **3** in $CHCl_3$ and other solvents, it was impossible to obtain solution IR spectra. The one exception was **2b**. The carbonyl absorption in $CHCl_3$ solution for **2b** occurred at 1725 cm^{-1}, compared to that in the solid state (KBr pellet) at 1715 cm^{-1}.

Table II. ^{13}C–^{1}H Coupling Constants of Diacidic and Thiazole Moieties[a]

	3-hydroxy-1*H*-pyrrole-2,5-dione				thiazole nucleus		
	C-2	C-3	C-4	C-5	C-2	C-4	C-5
1b[b]	d (3)	d (7.5)	q (3.5)	d (2)			
1d[b]	d (2)	d, q (7, 5)	q (3)	d (2)			
1e	d (2)	d (7)	d (4)	d (2)	m	d (5)	d (194)
4	s	s	d (3)	s	d (6.5)	d, t (6.5, 3)	d (196.5)

	4-hydroxy-3(2*H*)-isothiazolone 1,1-dioxide			thiazole nucleus		
	C-3	C-4	C-5	C-2	C-4	C-5
2a	s	s	t (4.5)			
2b	q (2.5)	s	t (4)			
2c	s	s	s	d, t (4.5, 7.5)	d (5)	d (196)
3	s	s	s	d (8)	q (4.5)	d (189.5)

[a] Observed multiplicities are reported; measured coupling constants (in Hz) are in parentheses. Data for remaining carbons of these compounds are included in the supplementary material. [b] Multiplicity of all four carbons decreased by 1 after addition of D_2O.

that all three compounds were derivatives of the 4-hydroxy-3(2*H*)-isothiazolone 1,1-dioxide ring system.

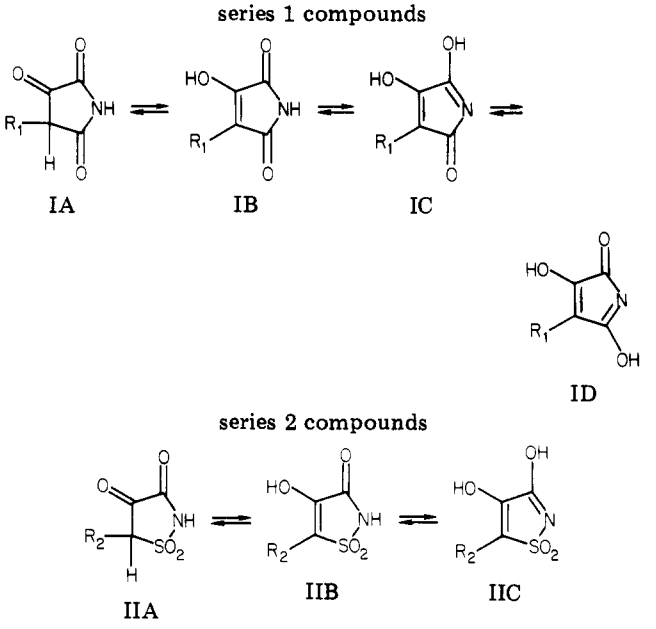
A fourth compound of interest in this series was the isomer of **2c** in which the positions of the two substituents on the thiazole ring of **2c** were reversed. Synthesis of this compound was approached by the following route. Reaction of 2-bromo-1-(3,4-dichlorophenyl)ethanone with 2-(aminosulfonyl)thioacetamide in refluxing ethanol gave the methanesulfonamide **10**. When **10** was subjected to the sequence of reactions followed in the synthesis of **2c** from **5c**, the product **3** (Scheme III), which was isolated as a crystalline solid, gave the elemental analysis, mass spectral, and ^{1}H NMR data consistent with the expected structure. However, the ^{13}C NMR chemical shift data, the p*K*a values (4.37 and 9.65), the carbonyl absorption in the solid-state IR spectrum, and the UV spectrum in EtOH all showed significant differences when compared to those of **2a–c**. These discrepancies prompted us to carry out more detailed ^{13}C NMR studies on **2a–c** and **3**.

The availability of ^{13}C NMR chemical shift and ^{13}C–^{1}H coupling constant data proved crucial in assigning unequivocally the structures of **2a–c** and **3**. Detailed ^{13}C NMR studies were also carried out on seven members of the 3-hydroxy-1*H*-pyrrole-2,5-dione series (**1a–f**, **4**). The assignments of ^{13}C resonances and ^{13}C–^{1}H coupling constants for the acidic ring and thiazole moieties in both series are presented in Tables I and II. The detailed explanation of these assignments is available in the supplementary material section.

Discussion

In assigning detailed structures to **2a–c** and **3**, it is necessary to take into account the different tautomeric forms possible for these diacidic nuclei (Scheme IV). Representation of **2a** and **2b** as the 5-phenyl-4-hydroxy-3(2*H*)-isothiazolone 1,1-dioxide derivatives was supported by the observation of hydroxyl and carbonyl absorptions in their solid-state IR spectra[8] (3340 and 1710 cm^{-1} for **2a**, and 3240 and 1715 cm^{-1} for **2b**). For **2c** a strong carbonyl absorption at 1710 cm^{-1} as well as p*K*a values of 3.12 and 4.20 (similar to those of **2a**) indicated a similar preference. Significant differences were clearly evident in the properties of **3** as compared to those of **2a–c**. The carbonyl absorption in the IR (solid state)[8] was weaker and its position was shifted to 1750 cm^{-1}. The absorbance in the UV spectrum was extended to longer wave lengths. In addition, the second of the two p*K*a values (3.7 and 9.65) was considerably higher than expected. Since elemental analysis and mass and ^{1}H NMR spectral data indicated that cyclization to a five-membered ring had occurred, it

Scheme IV. Possible Tautomeric Forms for Acidic Ring Systems of Series 1 and 2 Compounds



was postulated that **3** might exist in a different tautomeric form.[9] For **2a,c** three reasonable tautomeric structures can be drawn when the isothiazolone moiety alone is considered (IIA–C in Scheme IV). For **2b** the number of possibilities is reduced to two (IIA and IIB). Tautomer IIC is eliminated from consideration for **2b** because of the presence of the *N*-methyl substituent. As neither ^{13}C nor ^{1}H NMR spectra of **2a–c** or **3** show any resonance that can be ascribed to a sp^3 methine, tautomer IIA is not a significant contributor in this series. Accordingly, tautomer IIB is the only remaining possibility for **2b**. The similarities in the ^{13}C NMR chemical shift values (Table I) for the isothiazolone moieties (as well as similarities in the IR, UV, and p*K*a data) of **2a** and **2c**, when compared to **2b**, strongly support the conclusion that these two derivatives also exist as IIB tautomers. On the other hand, the ^{13}C NMR spectral data for **3** in Table I show significant differences in the chemical shift values for C-4 and C-5 of the isothiazole ring as compared to those of **2a–c**. Thus the

(9) An alternative seven-membered ring size for **3** in which intramolecular cyclization might have occurred on the thiazole ring nitrogen seemed highly unlikely on the basis of the ^{1}H NMR and IR spectra, as well as on the fact that **2c** and **3** showed similar fragmentations in their low resolution mass spectra.

structure of **3** is clearly not that represented by the IIB tautomer. The increased chemical shift value observed for C-4 of **3** (158.4 ppm vs. 146–147.5 ppm for **2a–c**) is indicative of a carbonyl group at that position. Since tautomer IIA has been eliminated from consideration (and IIC would not fit this data), a more involved change than simple enol–keto tautomerism must have occurred. The most reasonable explanation must invoke a protomeric shift to the thiazole ring nitrogen leading to an exocyclic double bond connecting the thiazole and isothiazole rings as shown in structure **3**. While the observed ^{13}C chemical shift values for the thiazole carbons in **2c** and **3** are difficult to interpret, an unexpected upfield chemical shift in the ^1H NMR spectrum for the thiazole H-5 was observed on cyclization of the oxamate precursor **11** to **3**. This change (from δ 8.41 to 8.02) is consistent with the loss of the aromatic bond structure from the thiazole ring as proposed for **3**.

At this point it became of interest to carry out a similar ^{13}C NMR investigation of compounds in the 3-hydroxy-1*H*-pyrrole-2,5-dione series to determine if an analogous tautomeric difference existed for 2- and 4-thiazolyl-substituted derivatives. (Irregularities had been apparent in the spectral and p*K*a data for **4**, when compared to other derivatives (**1a–f**) of that ring system.) For structure **1**, four reasonable tautomeric forms may be drawn (IA–D in Scheme IV). As in the **2** series, structure IA can be eliminated as a significant contributor since neither ^{13}C nor ^1H NMR showed a resonance for a sp^3 methine. Additional support for this conclusion derives from the similarity of ^{13}C NMR chemical shifts of the pyrrole-2,5-dione moieties in **1b** and **1d**. In the latter, methylation of the C-3 hydroxyl group has precluded any contribution from tautomer 1A. The observed coupling between the amide NH proton and all four ring carbons in **1b** rules out any contribution from tautomers IC or ID. Since only one set of resonances is observed, any exchange between tautomeric forms is fast on the NMR time scale ($>10^{-5}$ s). Any contribution from IC or ID, for which coupling to all four ring carbons would not be expected, would be equivalent to saturating the amide NH resonance, erasing any observable coupling between the ring carbons and the amide NH proton. The major tautomeric contributor to **1a–f** must therefore be IB.[10] The ^{13}C chemical shift values for C-3 (165.8 ppm) and C-4 (92.5 ppm) of **4** are significantly different from those in **1a–f** (152.1–154.3 ppm for C-3 and 102.4–112.3 ppm for C-4). The C-3 value for **4** indicates the presence of a carbonyl group (as observed for C-4 of **3**). As tautomer IA has been eliminated as a possibility, the only reasonable alternative is the structure shown for **4** (Scheme III), with a double bond separating the two rings and a proton residing on the thiazole ring nitrogen. The increased shielding observed for the C-4 carbon in **4** is consistent with this proposal and is expected on the basis of the observation of increased shielding of C-5 in **3**.

Thus, evidence from ^{13}C NMR, taken together with ^1H NMR, IR, UV, and p*K*a data, provides strong support for the assignment of the tautomeric structures shown for **3** and **4**. In both series this unusual tautomeric preference was seen only when the respective acidic rings were attached to the 2-position of a thiazole nucleus. The existence of 2-substituted thiazole derivatives in a protomeric form in which the double bond at the 2-position is exo rather than endo is well-known when the 2-position substituents are heteroatoms. In contrast, reports of this type of tautomer where the 2-position substituents are connected through a carbon atom to the thiazole ring are relatively rare.[11] As a general rule, two strongly electron-withdrawing substituents attached to a 2-position methine appear to be essential if the 2,3-dihydrothiazol-2-ylidene arrangement of double bonds is to be favored.[12,13] In **3** and **4**, the two requisite electron-withdrawing groups, plus the α-carbon, form part of an acidic ring substituent.

Experimental Section

Capillary melting points were determined by using a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses, pK_a, and UV spectral data were provided by Dr. W. C. Randall and associates. Mass spectral determinations were effected by Mr. R. E. Rhodes and Dr. H. Ramjit using the MM7035 mass spectrometer (VG Instruments Inc.). ^1H NMR spectra were determined on Varian Associates T-60 and EM-390 spectrometers and a Nicolet 360 MHz instrument. ^{13}C NMR spectra were obtained on a Varian CFT-20 spectrometer operating at 20 MHz for carbon. Collecting 4000 Hz FIDs in 8K data points yielded chemical shifts accurate to ±0.1 ppm. Coupled spectra were obtained by using a 2000-Hz spectral width, and hence coupling constants are ±1 Hz.

4-Hydroxy-5-phenyl-3(2*H*)-isothiazolone 1,1-Dioxide (2a) (One-Step Procedure). To a solution of phenylmethanesulfonamide (**5a**) (3.42 g, 0.02 mol) and diethyl oxalate (3.20 g, 0.022 mol) in DMF at room temperature was added potassium *tert*-butoxide (4.92 g, 0.044 mol). After stirring overnight, the colorless solids were removed by filtration and washed first with a small volume of DMF and then with diethyl ether. The dried product (6.76 g) had the following: mp >300 °C; ^1H NMR ($CDCl_3$) δ 2.84 (s, 3 H), 2.99 (s, 3 H), 4.80 (s, 2 H), 7.2–7.6 (m, 3 H), 7.8–8.0 (m, 3 H). Anal. Calcd for $C_9H_5K_2NO_4S{\cdot}0.8C_3H_7NO$: C, 38.05; H, 2.97; N, 7.01. Found: C, 37.44; H, 3.09; N, 7.01.

The crude dried dipotassium salt–DMF complex (6.59 g) was stirred in 6 N HCl (40 mL) for 1 h. The fine white solid was filtered to give 3.40 g (69.2% overall) of **2a**: mp 262–264 °C. The IR and ^1H NMR spectra were identical with those for the sample of **2a** prepared from intermediate **6a** in the two-step procedure below. Anal. Calcd for $C_9H_7NO_4S$: C, 48.00; H, 3.13; N, 6.22. Found: C, 47.93; H, 3.16; N, 6.27.

Methyl *N*-[(Phenylmethyl)sulfonyl]oxamate (6a). A mixture of **5a** (6.0 g, 0.035 mol) and methyl oxalyl chloride (15 mL, 0.16 mol) was heated at 100 °C for 1.3 h. Following removal of the excess methyl oxalyl chloride by vacuum evaporation, the crystalline residue was stirred with Et_2O. Filtration afforded 7.73 g (85.9%): mp 117–122 °C; IR (KBr) 3240, 1725, 1440, 1355, 1275, 1170, 1120, 900, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.90 (s, 3 H), 4.66 (s, 2 H), 7.30 (s, 5 H); MS, *m/e* 257 (M^+), 193, 154. Anal. Calcd for $C_{10}H_{11}NO_5S$: C, 46.69; H, 4.31; N, 5.44. Found: C, 47.06; H, 4.32; N, 5.41.

4-Hydroxy-5-phenyl-3(2*H*)-isothiazolone 1,1-Dioxide (2a). To a solution of **6a** (2.0 g, 0.0077 mol) in DMF (15 mL) was added in portions potassium *tert*-butoxide (1.74 g, 0.016 mol). After stirring overnight, the solids were removed by filtration and washed well with Et_2O. The filtrate was concentrated to dryness. The solid residue, combined with the DMF-insoluble fraction, was dissolved in a small volume of water, and the solution was made strongly acidic by the addition of concentrated HCl. After cooling at 0 °C for 1 h, there was obtained on filtration 0.51 g (29.4%): mp 249–256 °C; IR (KBr) 3340, 3140, 2705, 1710, 1655, 1490, 1440, 1385 1340, 1265, 1180, 1155, 1025, 975, 920, 845, 755 cm^{-1}; UV (EtOH) λ_{max} 224.5 nm (ϵ 11 600), 306 (10 300); ^1H NMR (Me_2SO-d_6) δ 7.38–7.55 (m, 3 H), 7.79–7.85 (m, 2 H), 11.03 (s, 2 H, exchangeable with D_2O); MS, *m/e* 225 (M^+), 160, 132; exact mass, calcd *m/e* 225.0094, found *m/e* 225.0071; p*K*a (H_2O) 3.32, 4.92. Anal. Calcd for $C_9H_7NO_4S$: C, 48.00; H, 3.13; N, 6.22.

(10) In **2a,c** and **3** the lack of any observed coupling of the three ring carbons to the amide NH is probably explained by the much higher amide acidity in this series.

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Found: C, 48.00; H, 3.12; N, 6.45.

4-Hydroxy-2-methyl-5-phenyl-3(2*H*)-isothiazolone 1,1-Dioxide (2b). To a solution of *N*-methyl phenylmethanesulfonamide (**5b**) (4.82 g, 0.026 mol) and diethyl oxalate (4.76 g, 0.029 mol) in DMF (40 mL) was added potassium *tert*-butoxide (3.65 g, 0.033 mol). After stirring overnight at room temperature, most of the solvent was removed by vacuum evaporation. Dropwise addition 6 N HCl (40 mL) to the clear solution at ice temperature resulted in the appearance of colorless solid, which after filtration and drying weighed 5.16 g (83%); mp 188–198 °C. Recrystallization of a 0.5-g sample from CH_2Cl_2–hexane gave 0.24 g; mp 209–214 °C; IR (KBr) 3245, 1715, 1655, 1445, 1420, 1380, 1320, 1300, 1180, 1160, 1150, 1020, 935, 800 cm^{-1}; IR ($CHCl_3$) 1725, 1660, 1385, 1325, 1160, 1025; UV (EtOH) λ_{max} 231 nm (ϵ 13 300), 316 (9300); ^1H NMR (Me_2SO-d_6) δ 3.1 (s, 3 H), 7.35–7.6 (m, 3 H), 7.7–7.9 (m, 2 H); MS, *m/e* 239 (M^+), 174, 147, 132, 118; exact mass calcd *m/e* 239.0252, found 239.0264; p*K*a (50% EtOH) 3.72. Anal. Calcd for $C_{10}H_9NO_4S$: C, 50.20; H, 3.79; N, 5.85. Found: C, 50.21; H, 3.80; N, 5.95.

Stabilities of 2a and 2b to Base. A solution of **2b** (0.24 g, 0.001 mol) in 1.0 N NaOH (3 mL, 0.003 mol) was allowed to stand at room temperature for 20 min. Acidification with concentrated HCl followed by filtration and drying gave 0.10 g (0.00054 mol) of **5b**; mp 108–112 °C. When a solution of **2a** (0.22 g, 0.001 mol) in 1.0 N NaOH (4 mL, 0.004 mol) was treated in a similar manner there was recovered 0.12 g (55%) of **2a** unchanged; mp 259–265 °C dec.

4-(Chloromethyl)-2-(3,4-dichlorophenyl)thiazole (7). A mixture of 3,4-dichlorothiobenzamide (8.24 g, 0.04 mol) and 1,3-dichloroacetone (5.1 g, 0.04 mol) in acetone (150 mL) was stirred at room temperature overnight. After removal of the solvent under reduced pressure, the residue was dissolved in MeOH (150 mL) and the solution was refluxed for 1.5 h to eliminate water from the initially formed carbinolamine. After cooling and removal of the MeOH under vacuum, a small quantity of MeOH was added to the oily residue whereupon crystallization occurred. The solids obtained on filtration (6.05 g, 54.3%) had mp 93–96 °C. Recrystallization from EtOH gave an analytical sample: mp 95–98 °C; IR (KBr) 3105, 1480, 1440, 1425, 1365, 1255, 1240, 1125, 1010, 955, 860, 835, 780, 735, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.74 (s, 2 H), 7.46 (s, 1 H), 7.62 (d, J = 9.0 Hz, 1 H), 7.77 (dd, J = 9.0, 2.0 Hz, 1 H), 8.08 (d, J = 2.0 Hz, 1 H). Anal. Calcd for $C_{10}H_6Cl_3$ NS: C, 43.11; H, 2.17; N, 5.03. Found: C, 43.31; H, 2.11; N, 4.94.

***S*-[2-(3,4-Dichlorophenyl)thiazol-4-yl]methylisothiouronium Hydrochloride (8).** A mixture of **7** (17.8 g, 0.062 mol), thiourea (5.4 g, 0.062 mol), and EtOH (150 mL) was heated under reflux for 3.5 h, and then allowed to stand at room temperature overnight. After vacuum evaporation of the solvent a small volume of acetone was added to the residue. Filtration gave 13.3 g of solid; mp 163–170 °C. Recrystallization from EtOH gave 11.1 g (64.3%): mp 163–176 °C; IR (KBr) 3250–2970, 1620, 1505, 1480, 1425, 1375, 1320, 1240, 1115, 1025, 1010 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 4.67 (s, 2 H), 7.77 (d, J = 7.0 Hz, 1 H), 7.85–7.97 (m, 2 H), 8.12 (d, J = 2.1 Hz, 1 H), 9.43 (s, 4 H, exchangeable with D_2O). Anal. Calcd for $C_{11}H_9Cl_2N_3S_2$·HCl: C, 37.25; H, 2.84; N, 11.85. Found: C, 37.42; H, 2.66; N, 11.64.

[2-(3,4-Dichlorophenyl)thiazol-4-yl]methanesulfonyl Chloride (9). Chlorine gas was passed for 20 min into a solution of **8** (6.0 g, 0.017 mol) in glacial acetic acid (120 mL) at ice-bath temperature. After being stirred for another 20 min, the mixture was filtered to give 4.8 g (90.9%); mp 124–127 °C. An analytical sample, recrystallized from Et_2O–petroleum ether, had mp 128–130 °C; IR (KBr) 3120, 3000, 1540, 1480, 1440, 1385, 1360, 1260, 1225, 1160, 1130, 1025, 955, 900, 860, 820, 775 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.14 (s, 2 H), 7.54 (d, J = 9.0, 1 H), 7.65 (s, 1 H), 7.78 (dd, J = 9.0, 2.1 Hz, 1 H), 8.18 (d, J = 2.1 Hz, 1 H). Anal. Calcd for $C_{10}H_6Cl_3NO_2S_2$: C, 35.05; H, 1.77; N, 4.09. Found: C, 35.03; H, 1.82; N, 3.86.

[2-(3,4-Dichlorophenyl)thiazol-4-yl]methanesulfonamide (5c). A mixture of **9** (15.3 g, 0.049 mol) and concentrated NH_4OH (150 mL) was allowed to stand for 10 min. On filtration there was obtained 8.75 g (55.3%), mp 165–167 °C. An analytical sample, obtained by recrystallization from THF–Et_2O–petroleum ether, had mp 168–170 °C: IR (KBr) 3310, 3250, 3100, 2975, 1550, 1500, 1480, 1440, 1365, 1325, 1255, 1235, 1155, 1130, 1010, 920 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 4.53 (s, 2 H), 6.99 (s, 2 H), 7.79 (d, J = 9.0 Hz, 1 H), 7.80 (s, 1 H), 7.94 (dd, J = 9.0, 2.1 Hz, 1 H), 8.19 (d, J = 2.1 Hz, 1 H). Anal. Calcd for $C_{10}H_8Cl_2N_2O_2S_2$: C, 37.16; H, 2.49; N, 8.67. Found: C, 37.13; H, 2.36; N, 8.36.

Ethyl *N*-[[[2-(3,4-Dichlorophenyl)thiazol-4-yl]methyl]sulfonyl]oxamate (6c). To a suspension of **5c** (6.5 g, 0.02 mol) in THF (100 mL) and toluene (60 mL) was added sodium hydride (50% suspension in oil, 1.6 g, 0.034 mol). After stirring for 0.5 h there was added ethyl oxalyl chloride (4.0 g, 0.03 mol). The mixture was heated on a steam bath for 0.25 h. After cooling there was added Et_2O (400 mL) and saturated $NaHCO_3$ solution (200 mL). The white solid that formed was removed by filtration. The solids were suspended in H_2O, and the mixture was acidified with 6 N HCl. The solid **6c** was filtered and recrystallized from EtOH to give 5.4 g (69.1%): mp 153–155 °C; IR (KBr) 3350, 3250, 3120, 2970, 2920, 1725, 1430, 1385, 1350, 1275, 1180, 1115, 1025, 1005, 845 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.21 (t, J = 7.0 Hz, 3 H), 4.22 (q, J = 7.0 Hz, 2 H), 4.97 (s, 2 H), 7.48–7.81 (m, 3 H), 7.95 (d, J = 2.0 Hz, 1 H). Anal. Calcd for $C_{14}H_{12}Cl_2N_2O_5S_2$: C, 39.72; H, 2.86; N, 6.62. Found: C, 39.50; H, 2.66; N, 6.51.

5-[2-(3,4-Dichlorophenyl)thiazol-4-yl]-4-hydroxy-3(2*H*)-isothiazolone 1,1-Dioxide (2c). To a solution of **6c** (4.4 g, 0.01 mol) in DMF (26 mL) was added potassium *tert*-butoxide (3.5 g, 0.032 mol) in portions over 0.25 h. After stirring overnight, the mixture was poured into H_2O (250 mL). Acidification with 6 N HCl, followed by filtration, gave 3.5 g of crude **2c**. Recrystallization from THF–Et_2O–petroleum ether gave 1.74 g (46.2%) of off-white colored crystals: mp 301 °C dec; IR (KBr) 3080, 1710, 1640, 1545, 1480, 1450, 1325, 1280, 1220, 1160, 1130, 1040, 1020, 1000 cm^{-1}; UV (EtOH) λ_{max} 245 nm (ϵ 19 100), 320.5 (19 400); ^1H NMR (Me_2SO-d_6) δ 7.83 (d, J = 9.0 Hz, 1 H), 7.96 (dd, J = 9.0, 2.1 Hz, 1 H), 8.12 (s, 1 H), 8.17 (d, J = 2.1 Hz, 1 H), 10.1 (s, 2 H, exchangeable with D_2O); MS, *m/e* 376 (M^+), 269; exact mass calcd *m/e* 375.9146, found 375.9160, p*K*a (H_2O) 3.12, 4.30. Anal. Calcd for $C_{12}H_6Cl_2N_2O_4S_2$: C, 38.20; H, 1.60; N, 7.42. Found: C, 38.46; H, 1.68; N, 7.47.

[4-(3,4-Dichlorophenyl)thiazol-2-yl]methanesulfonamide (10). A mixture of 2-(aminosulfonyl)thioacetamide (7.7 g, 0.05 mol) and 2-bromo-1-(3,4-dichlorophenyl)ethanone (13.4 g, 0.05 mol) in EtOH (50 mL) was heated at reflux for 2 h. After cooling and filtration, there was obtained 11.5 g (71.2%): mp 187–190 °C; IR (KBr) 3350, 3250, 3105, 2990, 1545, 1475, 1440, 1330, 1265, 1185, 1140, 1105, 1020, 930, 870, 740 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 4.82 (s, 2 H), 7.22 (s, 2 H), 7.73 (d, J = 9.0 Hz, 1 H), 7.97 (dd, J = 9.0, 2.1 Hz, 1 H), 8.24 (d, J = 2.1 Hz, 1 H), 8.39 (s, 1 H). Anal. Calcd for $C_{10}H_8Cl_2N_2O_2S_2$: C, 37.16; H, 2.49; N, 8.67. Found: C, 37.38; H, 2.45; N, 8.46.

Ethyl *N*-[[[4-(3,4-Dichlorophenyl)thiazol-2-yl]methyl]sulfonyl]oxamate (11). To a solution of **10** (3.2 g, 0.01 mol) in a mixture of THF (25 mL) and toluene (15 mL) there was added a suspension of sodium hydride (50% in oil, 0.5 g, 0.01 mol) in toluene (15 mL). The mixture was heated at reflux for 0.25 h. While hot, a solution of ethyl oxalyl chloride (2.5 g, 0.02 mol) in toluene (10 mL) was added. After being heated on the steam bath for another 0.25 h, the mixture was cooled and then extracted with saturated $NaHCO_3$ solution (2× 150 mL). Acidification of the aqueous phase gave 3.1 g (73.3%); mp 180–182 °C. The analytical sample recrystallized from EtOH had mp 182–184 °C; IR (KBr) 3250, 3100, 2905, 1725, 1480, 1440, 1400, 1365, 1355, 1295, 1155, 1120, 1060, 1025, 1005 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.24 (t, J = 6.9 Hz, 3 H), 4.24 (q, J = 6.9 Hz, 2 H), 5.27 (s, 2 H), 7.73 (d, J = 9.0 Hz, 1 H), 7.94 (dd, J = 9.0, 2.1 Hz, 1 H), 8.18 (d, J = 2.1 Hz, 1 H), 8.41 (s, 1 H), 10.1 (s, 1 H). Anal. Calcd for $C_{14}H_{12}Cl_2N_2O_5S_2$: C, 39.72; H, 2.86; N, 6.62. Found: C, 40.16; H, 2.85; N, 6.41.

5-[4-(3,4-Dichlorophenyl)thiazol-2-yl]-4-hydroxy-3(2*H*)-isothiazolone 1,1-Dioxide (3). To a solution of **11** (1.0 g, 0.0024 mol) in DMF (5 mL) was added potassium *tert*-butoxide (0.55 g, 0.0048 mol) in several portions over 0.25 h. The mixture was stirred at room temperature for 24 h. After diluting with H_2O (30 mL) and acidifying with concentrated HCl (congo red indicator paper), a yellow gum was obtained. The crude product was triturated with MeCN, and the solids were filtered to give a yellow solid (0.6 g, 66.3%), mp 250 °C dec. An analytical sample obtained by evaporative crystallization from a large volume of Et_2O had mp 283–290 °C dec: IR (KBr) 1745, 1605, 1575, 1520, 1370, 1310,

1290, 1260, 1140, 1125, cm^{-1}; UV (EtOH) λ_{max} 246 nm (ϵ 20300), 357 (10500); ^1H NMR δ 7.72 (d, J = 9.0 Hz, 1 H), 7.96 (dd, J = 9.0 2.1 Hz, 1 H), 8.02 (s, 1 H), 8.19 (d, J = 2.1 Hz, 1 H), 10.1 (s, 2 H, exchangeable with D_2O); MS, m/e 376 (M^+), 269; exact mass calcd m/e 375.9146, found 375.9139; pKa (H_2O) 3.7, 9.65. Anal. Calcd for $C_{12}H_6Cl_2N_2O_4S_2$; C, 38.20; H, 1.60; N, 7.43. Found, C, 38.41; H, 1.55; N, 7.50.

2-(Aminosulfonyl)thioacetamide. A solution of 2-(aminosulfonyl)acetonitrile[14] (24 g, 0.2 mol) and triethylamine (50 mL) in pyridine (100 mL) was saturated with hydrogen sulfide gas over a period of 1 h. After removal of the volatile components by vacuum evaporation, the residue was dissolved in dioxane (50 mL). On standing at room temperature the product crystallized to give, after filtration and washing with Et_2O, 22.4 g (73%), mp 110–113 °C. An analytical sample, obtained by evaporative crystallization from Et_2O, had mp 115–117 °C. Anal. Calcd for $C_2H_6N_2O_2S_2$: C, 15.58; H, 3.92; N, 18.17. Found: C, 15.97; H, 3.80; N, 17.97.

UV Spectral Data for 1b, 1e, and 4. 1b: UV (EtOH) λ_{max} 272 nm (ϵ 22500), 370 (6700). **1e**: UV (EtOH) λ_{max} 262 nm (ϵ 24400), 365 (6900); **4**: UV (EtOH) λ_{max} 245 nm (ϵ 23500), 281.5 (22400).

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Registry No. 2a, 89566-24-5; **2a** (dipotassium salt), 89873-47-2; **2b**, 89873-37-0; **2c**, 89873-38-1; **3**, 89873-39-2; **5a**, 4563-33-1; **5b**, 19299-41-3; **5c**, 89873-40-5; **6a**, 85195-24-0; **6c**, 89873-41-6; **7**, 89873-42-7; **8**, 89873-43-8; **9**, 89873-44-9; **10**, 89873-45-0; **11**, 89873-46-1; diethyl oxalate, 95-92-1; methyl oxalyl chloride, 5781-53-3; 3,4-dichlorothiobenzamide, 22179-73-3; 1,3-dichloroacetone, 534-07-6; thiourea, 62-56-6; ammonia, 7664-41-7; ethyl oxalyl chloride, 4755-77-5; 2-(aminosulfonyl)thioacetamide, 89873-48-3; 2-bromo-1-(3,4-dichlorophenyl)ethanone, 2632-10-2; 2-(aminosulfonyl)acetonitrile, 41827-87-6; hydrogen sulfide, 7783-06-4; potassium *tert*-butoxide, 865-47-4.

Supplementary Material Available: ^{13}C chemical shift and coupling constant data for substituents other than thiazole in structures **1a–f**, **2a–c**, **3**, and **4**, along with ^{13}C NMR data for **5c** and **10** (4 pages). Ordering information is given on any current masthead page.

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Stereo- and Regioselective Total Synthesis of the Hydropyrido[2,1,6-*de*]quinolizine Ladybug Defensive Alkaloids[1a]

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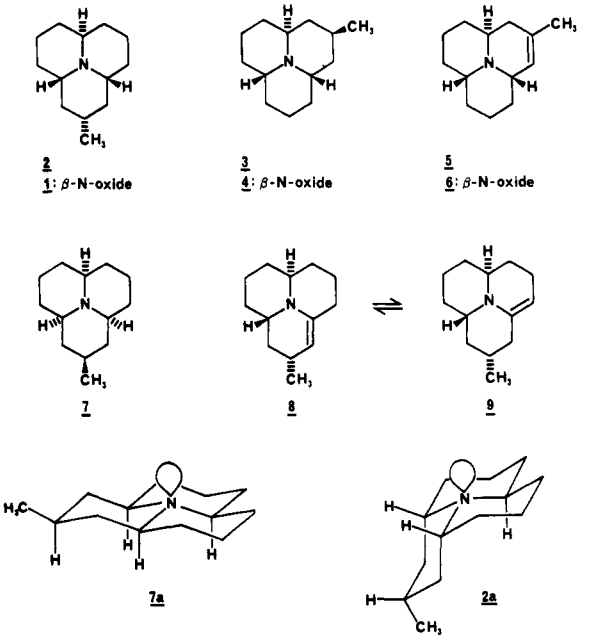
The stereo- and regioselective syntheses of the ladybug defensive alkaloids coccinelline (**1**), precoccinelline (**2**), (±)-hippodamine (**3**), (±)-convergine (**4**), (±)-hippocasine (**5**), (±)-hippocasine oxide (**6**), myrrhine (**7**), (±)-propyleine (**8**), and (±)-isopropyleine (**9**) are described starting from perhydroboraphenalene.

Ladybugs are well-known for their voracious appetites for such agricultural pests as aphids and scale insects;[2] in fact, they are commercially available for just this purpose.[3] Interestingly, ladybugs have few natural enemies, a fact suggested by the bright coloration of many ladybug species; this "aposematic coloration" warns potential predators of the existence of a chemical defense system.[4] When threatened, ladybugs secrete an oily, bitter tasting fluid from their joints which repulses ants, quail, and other creatures which might otherwise consume them. This phenomenon, referred to as "reflex bleeding", serves the ladybug as a highly effective means of protection.[5]

The first studies directed toward characterization of the actual ladybug defensive agents were reported by Tursch and co-workers in 1971.[6,7] A white, crystalline solid was isolated from methanol extracts of the European ladybug *Coccinella septempunctata*; this substance was shown to repel the ant *Myrmica rubra* at concentrations as low as 0.1–0.5% in water.[8] Spectral[9] and crystallographic[10]

Scheme I



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