of **7c** (66%) and **15c** (11%). A NMR sample of **6c** in $CDCl_3$ was also heated with Dabco to give **15c** (δ 4.55) in quantitative yield. The benzothiazole **15c** has been isolated (mp 166–167 °C) and identified by comparison with an authentic sample.[14]

Reaction of *p*-Tolyl Isothiocyanate with Benzyl Azide. *p*-Tolyl isothiocyanate (5.96 g, 0.04 mol) was allowed to react with benzyl azide (2.66 g, 0.02 mol) at 60 °C for 7 weeks. The reaction mixture was crystallized from ether to give **7d** (2.13 g) and the mother liquor was subjected to column chromatography on silica with *n*-hexane–ethyl acetate as the eluent. This furnished starting materials, a fraction (0.15 g) composed of **5d** (66%, δ 5.46), **6d** (30%, δ 5.56), and **7d** (4%, δ 5.38), and a third fraction of **15d** (0.1 g, mp 176–178 °C from acetone). Crystallization of the second fraction from *n*-hexane–chloroform furnished pure **5d** (15 mg), mp 90–90.5 °C, δ 5.55.

In order to isolate **6d**, the reaction was repeated and the mixture worked up after 12 days (conversion 30%). Column chromatography on silica with *n*-hexane as the eluent furnished starting materials (6.3 g), **7d** (0.7 g, 8.7%), and **6d** (0.84 g, 10.4%).

6d (mp 116–118 °C). Anal. Calcd for $M^{\cdot+}$: 403.11768. Found: 403.12095.

7d (mp 178–180 °C). Anal. Calcd for $C_{23}H_{21}N_3S_2$ (403): C, 68.48; H, 5.21; N, 10.42; S. 15.88. Found: C, 68.33; H, 5.14; N, 10.55; S, 15.77.

Reaction of 4-Methyl-5-phenylimino-1,2,3,4-thiatriazoline (16) with Phenyl Isothiocyanate. The procedure of Neidlein and Tauber[12] for the reaction of 5-phenylamino-1,2,3,4-thiatriazoline with an excess of diazomethane furnished, after column chromatography on silica gel with hexane–ether (70:30) as eluent, 38% of **16** (mp 68–70 °C, δ 3.95 for CH_3) and 36% of **17** (mp 56–58 °C, δ 3.7 for CH_3). Compound **16** (5×10^{-3} mol) was allowed to react with 3 equiv of phenyl isothiocyanate at room temperature for 22 h, followed by warming at 40 °C for another 2 h. The excess of phenyl isothiocyanate and crude benzothiazole **20** (2.5%)[12] were removed by column chromatography on silica gel using *n*-hexane as the eluent. The remaining fraction was crystallized from *n*-hexane–petroleum ether to give **18a** in 57% yield. The filtrate, which contained **18a** and **19** in a ratio of 40:60, was then treated with Dabco in order to isomerize **18a** completely into **19**. Crystallization from chloroform–ether furnished pure **19** in 27% yield.

18a (mp 86–88 °C). Anal. Calcd for $M^{\cdot+}$: 299.05508. Found: 299.05338.

19 (mp 134–135 °C). Anal. Calcd for $M^{\cdot+}$: 299.05508. Found: 299.05564.

Reaction of 16 with Benzyl Isothiocyanate. When compound **16** (5×10^{-3} mol) was allowed to react with 3 equiv of benzyl isothiocyanate at room temperature for 7 days, 1 equiv of nitrogen had evolved. Column chromatography of the reaction mixture on silica gel with *n*-hexane–ethyl acetate as the eluent furnished sulfur (10 mg), starting benzyl isothiocyanate (1.66 g), **18b** (1.1 g, 70.3%), and 4-methyl-2-phenyl-5-phenylimino-1,2,4-thiadiazolidin-3-one [0.1 g, mp 78–79 °C, C=O at 1703 cm^{-1}, CH_3 at δ 3.40, $M^{\cdot+}$ at 283.07939 (calcd, 283.07793)].

18b (mp 97–98 °C). Anal. Calcd for $M^{\cdot+}$: 313.07073. Found: 313.069504.

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Registry No.—**5a,** 61249-30-7; **5b,** 61249-31-8; **5c,** 61249-32-9; **5d,** 61249-33-0; **6a,** 56406-09-8; **6b,** 56406-12-3; **6c,** 50506-90-6; **6d,** 61249-34-1; **7a,** 56406-08-7; **7b,** 56406-11-2; **7c,** 55000-06-1; **7d,** 56406-13-4; **8a,** 61249-35-2; **9a,** 56406-10-1; **10,** 61249-36-3; **15b,** 61249-37-4; **15c,** 21816-82-0; **15d,** 56406-14-5; **16,** 34551-29-6; **17,** 34551-25-2; **18a,** 50506-86-0; **18b,** 61249-38-5; **19,** 61249-39-6; *p*-nitrophenyl isothiocyanate, 2131-61-5; benzyl azide, 622-79-7; *p*-chlorophenyl isothiocyanate, 2131-55-7; phenyl isothiocyanate, 103-72-0; P_2S_5, 1314-80-3; *p*-tolyl isothiocyanate, 622-59-3; benzyl isothiocyanate, 622-78-6; 4-methyl-2-phenyl-5-phenylimino-1,2,4-thiadiazolidin-3-one, 61249-40-9.

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Novel Heterocyclic Synthons, Synthesis and Properties of Thia- and Oxacyclohexane-3,5-diones

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Novel thia- (**1**) and oxacyclohexane-3,5-diones (**2**), as useful starting materials for the total synthesis of steroid S- and O-heterocycles, have been prepared and their physical properties are described. Both series of the heterodiones were prepared by a versatile synthetic route involving base-catalyzed cyclization of methyl 2-(3-alkylacetonylthio)acetates (**4**) and methyl 2-(3-alkylacetonyloxy)acetates (**5**), readily available from thiodiacetic and diglycolic anhydrides, respectively. The IR, NMR, UV, and pK_a data are discussed in terms of the heteroatom and compared to those of cyclohexane-1,3-diones (**3**).

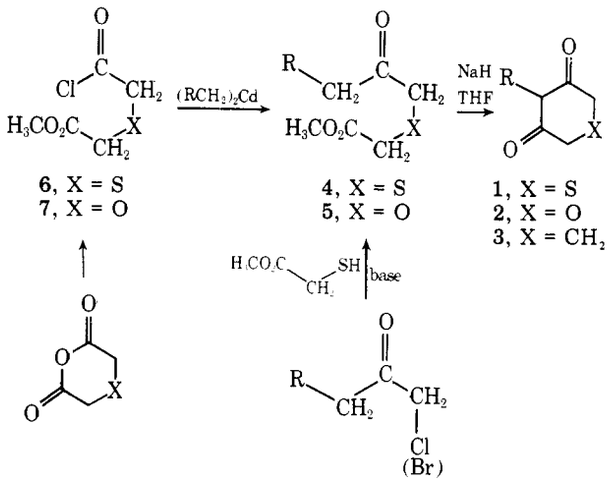
At the outset of our studies directed toward the total synthesis of steroid S- and O-heterocycles, we considered as useful starting materials compounds of types **1** and **2**, isosteres of cyclohexane-1,3-diones (**3**) which have been widely used in the synthesis of natural products. Such novel types of heterodiones may not only be utilized as expedient building blocks

for construction of other heterocyclic compounds but also serve as potentially valuable synthetic fragments in organic synthesis.

Thus, we have examined the preparative synthesis of thia- (1) and oxacyclohexane-3,5-diones (2), and their physical properties, which are described in this paper.

Synthesis

Thiacyclohexane-3,5-dione[1] (**1a**) and its 2-methyl derivative[2] have been synthesized by the base-catalyzed cyclization of **4a** and **4b**, respectively. We initially attempted following this procedure to supply both series of compounds, **4** and **5**,



as our requisite substrates. Base-induced condensation of methyl thioglycolate with ethyl chloro- (or bromo-) methyl ketone in place of chloro- (or bromo-) acetone gave similarly **4b** in 80–90% yield.

However, some difficulties were encountered in preparing higher alkyl homologues of the proposed α-halo ketones.[3] For instance, direct bromination of unsymmetrical ketones often necessitated troublesome and tedious separation of isomeric monobromo ketones. An alternate method[4] via diazo ketones from corresponding acyl halides and diazomethane was not suitable for a large-scale work. In addition, the halo ketone procedure could not be successfully applied to the oxa series (**5**) because of the reduced nucleophilicity of the glycolate anion.

These problems prompted us to devise a more convenient and versatile synthetic route applicable to the synthesis of both **4** and **5**. The approach involved the reaction of organocadmium reagents with **6** and **7**, which were prepared nearly quantitatively by methanolysis and successive treatment with thionyl chloride from readily available thiodiacetic and diglycolic anhydrides,[5] respectively.

The reaction of acyl chlorides with dialkylcadmium was carried out according to the improved procedure of Cason.[6] When methyl-, ethyl-, propyl-, and benzylmagnesium bromides were used as respective sources of the organocadmium, a series of the reaction with **6** afforded **4a–d** in a distilled yield of 50–60%. Similar results were obtained with **7**. However, the reaction of **7** with dimethylcadmium gave no reproducible results. Although various conditions were tried with methylmagnesium bromide, most of the experiments led to exclusive formation of hydroxylic polar compounds, presumably arising from overalkylation. By chance, when methylmagnesium iodide was employed instead of its bromide, poor yield of **5a** was obtained in only one of several trials but the follow-up experiments proved to be unpromising. The exceptional reaction behavior was considered to be due to increased reactivity of **7** relative to **6**, coupled with a smaller bulk of the reagent species.

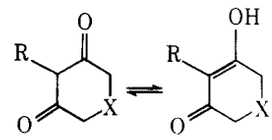
An alternative preparation of **5a** was carried out by the reaction of **7** with diazomethane and subsequent reduction of the resulting diazo ketone with hydriodic acid and/or zinc dust in acetic acid, resulting in 58% yield. Other approaches to **4** and **5**, for example, direct Grignard reaction of the anhydrides,[7] proved unpromising.

While the previous investigators used sodium methoxide in benzene solution at the condensation agent in the cyclization of **4a** into **1a**, our exploratory experiments indicated sodium hydride in tetrahydrofuran to be a more effective base–solvent combination. In the general procedure, the cyclization to **1** and **2** could be achieved by adding **4** and **5**, respectively, to a slurry of sodium hydride dispersion in tetrahydrofuran at room temperature. Under these conditions, **1a–c** were obtained as crystalline solids in 50–80% yield, while lower yields of less than 50% were obtained for **2** as well as **1d**. Decreased yields of **1a–c** were sometimes experienced, even under the same conditions, and it appears that isolated yields of the diones depend on subtle effects in workup procedure and properties including polarity, solubility, and stability. The oxadiones (**2**) tend to be somewhat labile during isolation compared with thiadiones (**1**).

Physical Properties

The detailed IR, NMR, and UV spectral data as well as pK_a values are summarized in Tables I and II.

The spectra of cyclic β-diketones which can be enolized show in general both types of bands or signals belonging to the diketo and enol forms.



X = CH_2, S, O

Inspection of the spectra gives valuable information on the problem of keto–enol tautomerism of cyclic β-diketones. In this regard, it is of considerable interest to compare the characteristics of the heterodiones with those of the corresponding carbocyclic diones.

IR Spectra. In chloroform, compounds **3a** and **6** exhibit a split band at 1700–1750 cm^{-1} and a broad, relatively intense band at 1600–1650 cm^{-1}, which are attributed to the diketo and enol forms, respectively. The spectral features are consistent with the previous results[9b,c] which show that the enol forms of **3** are moderately stable even in less polar solvents. The spectra of oxadiones **2a–c** resemble very closely those of **3**, showing clearly that the former compounds also exist preferentially in the enol forms. In sharp contrast, the spectra of thiadiones **1a–c** indicate that the high-frequency bands predominate, showing that **1a–c** in chloroform are exclusively stable in the diketo forms. On the other hand, all the diones discussed above are fully enolized in solid state (or Nujol suspension). The spectra display consistently only broad absorptions in the range of 1530–1650 cm^{-1}, which correspond to a mixture of monomeric and dimeric forms of the enols. The 4-phenyl derivatives **1d** and **2d**, even in chloroform as well as in Nujol suspension, are both enolized much more strongly based on a conjugation effect with the phenyl ring. However, weak absorption bands associated with the diketo forms in addition to bands characteristic for the enol forms are still detected only in the spectra of **1d**. This is further evidence

Table I. pK_a, IR, and UV Spectral Data

Registry no.	Compd (mp, °C)	pK_a	IR, ν cm^{-1}		UV, λ_{max} nm (ϵ)		
			$CHCl_3$	Nujol	95% EtOH	+NHCl	+NNaOH
6881-49-8	**1a**	4.27	1740 (sh)	1593	261	260.5	279
	(76–78)		1731	1547	(10 400)	(10 600)	(14 000)
			1714		304.5		304.5
			1606		(1400)		(10 700)
61363-53-9	**1b**	4.62	1737	1635	275	272	289
	(132.5–133.0)		1705	1553	(9500)	(9900)	(11 600)
			1632		315		316
					(2400)		(12 900)
61363-54-0	**1c**	3.53	1736	1570	273	272	289.5
	(108.5–109.5)		1703		(9600)	(9500)	(11 500)
			1623		317		317
					(1200)		(12 200)
61363-55-1	**1d**	4.29	1735 1619	1625	233.5	234	284
	(187–188)		1713 1599	1603	(7000)	(9400)	(11 300)
			1649 1491	1561	278	277	317.5
				1496	(7900)	(7600)	(9400)
61363-56-2	**2a**	3.76	1750 (sh)	1642	256	252.5	278.5
	(127–129)		1732	1617	(14 000)	(16 200)	(23 000)
			1650 (sh)	1605 (sh)	282 (sh)		
			1607	1543	(6700)		
61363-57-3	**2b**	3.99	1755	1653	261.5	260.5	290
	(178–180)		1725	1570	(15 700)	(17 100)	(24 800)
			1642		291 (sh)		
					(4000)		
61363-58-4	**2c**	4.20	1756	1617 (sh)	261.5	261.5	291
	(117–119)		1721	1570	(12 200)	(12 300)	(21 300)
			1626				
61363-59-5	**2d**	3.66	1664	1631	229	232	288.5
	(177–179)		1631	1615	(8300)	(9200)	(18 200)
			1598	1570–1595	269	267	
			1492	1496	(11 400)	(11 100)	

Table II. NMR Spectral Data

Compd	Solvent	NMR, δ, ppm (J, Hz)
1a	$CDCl_3$	3.40 (s, 4 H, 2-H_2, 6-H_2), 3.58 (s, 2 H, 4-H_2)
	CD_3OH	3.31 (s, 4 H, 2-H_2, 6-H_2), 5.38 (s, 1 H, 4-olefinic H)
1b	$CDCl_3$	1.28 (d, 3 H, J = 7, 4-CH_3), 3.44 (s, 4 H, 2-H_2, 6-H_2), 3.73 (q, 1 H, J = 7, 4-H)
	CD_3OD	1.69 (bs, 3 H, 4-vinylic CH_3), 3.34 (bs, 4 H, 2-H_2, 6-H_2)
1c	$CDCl_3$	0.95 (t, 3 H, J = 7.5, 4-CH_2CH_3), 1.93 (b quint, 2 H, J = 7.5, 4-CH_2CH_3), 3.41 (s, 4 H, 2-H_2, 6-H_2)
	CD_3OD	0.92 (t, 3 H, J = 7.5, 4-vinylic CH_2CH_3), 1.84 (bq, 0.42 H, J = 7.5, 4-CH_2), 2.32 (q, 1.58 H, J = 7.5, 4-vinylic CH_2), 3.34 (s, 4 H, 2-H_2, 6-H_2)
1d	$CDCl_3$	3.46, 3.51 (bs, s, 4 H, 2-H_2, 6-H_2), 7.33 (m, 5 H, aromatic H)
	CD_3OH	3.38 (s, 4 H, 2-H_2, 6-H_2), 7.35 (m, 5 H, aromatic H)
2a	$CDCl_3$–CD_3OH (98:2)	3.69 (bs, 0.56 H, 4-H_2), 4.18 (s, 4 H, 2-H_2, 6-H_2), 5.53 (s, 0.72 H, 4-olefinic H)
	CD_3OH	4.15 (s, 4 H, 2-H_2, 6-H_2), 5.46 (s, 1 H, 4-olefinic H)
2b	$CDCl_3$–CD_3OH (98:2)	1.26 (d, 0.825 H, J = 7, 4-CH_3), 1.74 (bs, 2.175 H, 4-vinylic CH_3), 4.21 (bs, 4 H, 2-H_2, 6-H_2)
	CD_3OD	1.70 (bs, 3 H, 4-vinylic CH_3), 4.18 (bs, 4 H, 2-H_2, 6-H_2)
2c	$CDCl_3$	1.01 (t, 3 H, J = 8, 4-CH_2CH_3), 1.85 (quint, 0.28 H, J = 7.5, 4-CH_2CH_3), 2.35 (q, 1.72 H, J = 8, 4-vinylic CH_2), 4.27 (s, 4 H, 2-H_2, 6-H_2)
2d	$CDCl_3$–CD_3OH (98:2)	4.28 (s, 4 H, 2-H_2, 6-H_2), 7.33 (m, 5 H, aromatic H)
	CD_3OD	4.31 (s, 4 H, 2-H_2, 6-H_2), 7.28 (bs, 5 H, aromatic H)

supporting the foregoing observation that the diketo forms are more favored for **1** relative to **2**.[10]

NMR Spectra. The NMR spectra are expected to give more detailed information on the keto–enol tautomerism. Nevertheless, no systematic studies have as yet been reported on those of cyclic β-diketones.

The spectra of **1a, 2a,** and **3a** in less polar solvents (chloroform-d_6 containing 0–5% methanol-d_3) show two characteristic signals attributed to the C-4 methylene protons (δ 3.4–3.6) in the diketo form and the 4-olefinic proton (δ 5.4–5.6) in the enol form. The keto–enol equilibria in **1b, 2b,** and **3b** can be recognized more easily from the methyl signals. The signal appears as a doublet (δ 1.2–1.3) in the diketo form and a singlet (δ 1.7–1.8) in the enol form. The spectral patterns of **2a** and **2b** are similar to those of **3a** and **3b,** respectively, demonstrating the low-field signals to be predominant. The high-field signals predominate in **1a** and **1b.** Similar signal behaviors can be observed in the cases of **1c** and **2c** but with somewhat uncertainty in the signal analysis. On the other hand, the NMR spectra of the diones mentioned above in a more polar solvent such as methanol no longer exhibit signals due to the diketo forms but only those responsible for the enol

Table III. Estimated Keto–Enol Contents of Cyclic β-Diketones

	Solvents	1, %		2, %		3, %	
		Diketo	Enol	Diketo	Enol	Diketo	Enol
a	$CDCl_3$	~100				20	80
	$CDCl_3$–CD_3OH (98:2)			28	72[e]		
	$CDCl_3$–CD_3OH (95:5)	71	29[a]				
	CD_3COCD_3				~100		
	CD_3OH		~100		~100		~100
b	$CDCl_3$	100					
	$CDCl_3$–CD_3OH (98:2)	85	15[b]	28	72[f]	7	93
	$CDCl_3$–CD_3OH (95:5)	71	29	8	92		
	$CDCl_3$–CD_3OH (75:25)				~100		
	CD_3OH		100		100		~100
c	$CDCl_3$	100		14	86[g]		
	CD_3OD	21	79[c]				
d	$CDCl_3$		~100[d]				
	$CDCl_3$–CD_3OH (98:2)				~100[h]		
	$CDCl_3$–CD_3OD (95:5)				~100		
	CD_3OD		~100		100		

[a] Registry no., 61363-71-1. [b] Registry no., 61363-72-2. [c] Registry no., 61363-73-3. [d] Registry no., 61363-74-4. [e] Registry no., 61363-75-5. [f] Registry no., 61363-76-6. [g] Registry no., 61363-77-7. [h] Registry no., 61363-78-8.

forms at the positions slightly displaced to a higher field. No signals associated with the diketo forms are indeed detectable also in the spectra of **1d** and **2d** so far as the solvent studied is concerned.

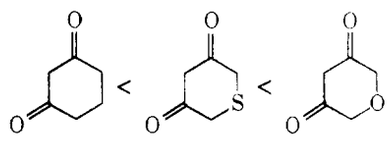
Thus, on the basis of relative integrated intensities of the respective signals belonging to the tautomeric forms, the diketo–enol content of the cyclic β-diketones in solvents with different polarities can be estimated.[11] These results are listed in Table III. From these data, it follows that all the diones exist in the enol forms to a great extent in more polar solvents, while the diketo–enol mixtures are present in less polar solvents and their content ratios depend on the types of diones. For instance, **1b** exists predominantly in the diketo form (85%) in $CDCl_3$–CD_3OH (98:2), whereas **2b** and **3b** are preferentially in the enol forms (72 and 93%, respectively) in the same solvent. This is also the case for **1a** vs. **2a** and **1c** vs. **2c**. In addition, the fact that more than 20% of **1c** is still present as the diketo form in methanol where **1a** and **1b** are completely enolized may somewhat reflect the steric hindrance of a bulkier alkyl group attached to C-4. These findings are in agreement with those obtained from the IR spectra, representing predominance of the diketo over the enol form in **1**, in contrast to **2**.

UV Spectra. Our interest in the UV spectral study of cyclic β-diketones is focused on enol–enolate equilibria of the enol forms, since the diketo forms show only very weak absorptions at 290–300 nm.

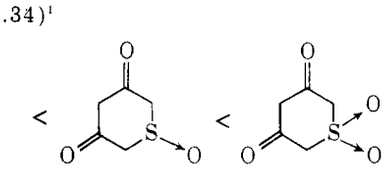
In 95% ethanol, the spectra of **2a–c** are very similar to those[9a,b] of **3**, exhibiting an intense absorption maximum at 250–265 nm under acid and neutral conditions. The maximum is shifted bathochromically[12] by 5–15 nm in the spectra of **1a–c**. The alkyl substituent at C-4 effects a bathochromic shift by 8–10 nm. A more striking feature of the spectra can be seen in aqueous basic solution. **1a–c** show two absorption maxima at 280–290 and 300–320 nm, whereas **2** and **3** only exhibit the former absorption. Such two-maximum absorptions are not found also for either the 1,1-dioxide or the enol ethyl ether of **1b**. No reasonable explanation of this unusual spectral behavior is available. However, we have observed that a well-defined isosbestic point appears at 280 nm in the spectra of **1b** in neutral to various alkaline solutions, as shown in Figure 1. Since the isosbestic point can be obtained usually only in the case of equilibrium between two species, no more enolate structures than indicated in the figure would be responsible for the equilibrium in **1** despite the appearance of two separate maxima in alkaline solution. Substitution of a phenyl substituent at C-4 for the alkyl would be expected to affect the spectra. In fact, the spectra of **1d** and **2d** in neutral and acid media show a couple of absorption maxima at 225–235 and 265–280 nm. The latter maxima correspond to those observed for the 4-alkyl compounds with a bathochromic shift of 5–8 nm, whereas the former ones newly appear, probably due to a styrene-type chromophore. Under alkaline media, no more significant differences are visible between the 4-phenyl and 4-alkyl compounds.

Acidity. All of these heterodiones dissolve with effervescence in aqueous sodium hydrogen carbonate and show a red-brown coloration with aqueous ferric chloride. They are monobasic acids stronger than not only the corresponding carbocyclic diones but also acetic acid.

As can be seen from the pK_a data in Table I, compounds **2** have a relatively stronger acidity than **1**. The 10- to 30-fold increase in acid strength occurs when the C-5 methylene function of **3a** is replaced by a sulfur or oxygen atom. The



	3a	**1a**	**2a**
pK_a	5.20 (5.26)[1]	4.27 (4.34)[1]	3.76



	(3.12)[1]	(2.72)[1]
pK_a		

observed order of acid strengths in this series of cyclic β-diketones parallels variation in the inductive electron-attracting power of the hetero groups, as further evidenced by the comparative data[1] of the sulfinyl and sulfonyl derivatives.

Alkyl substitution at C-4 has a tendency to slightly weaken the acidity in the same series of these heterodiones, probably as a result of sterically hindered conjugation effect, that is, reduced stabilization of the negative charges in the enolate anions by distribution over conjugated systems. When a

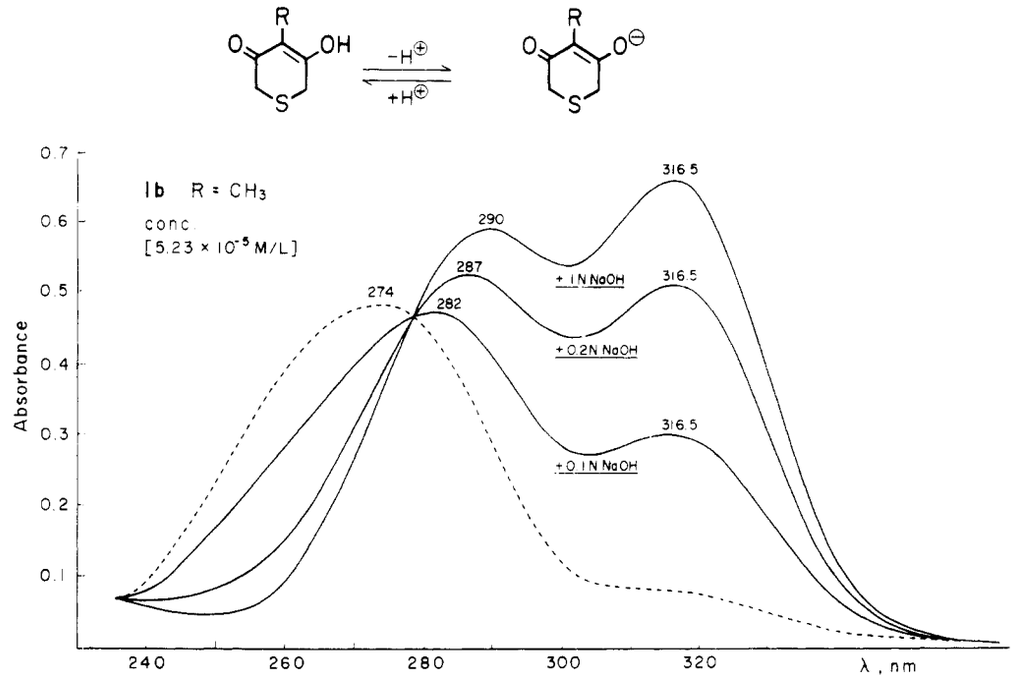


Figure 1. UV absorption of thiadione (**1b**) under neutral (- - -) and alkaline (—) conditions in 95% ethanol.

phenyl group is alternately substituted, however, the conjugation effect would not be lowered because the steric effect may be outweighed by an additional aromatic conjugation. Consequently, it seems to be reasonable that **1d** and **2d** have a strong acidity comparable to that of **1a** and **2a**, respectively.

Experimental Section

Melting points were determined on a calibrated Kofler hot-stage apparatus. Boiling points are uncorrected. Infrared (IR) spectra were recorded on a JASCO-DS-403G spectrophotometer and ultraviolet (UV) spectra were recorded on a Hitachi EPS-3T spectrophotometer. Nuclear magnetic resonance (NMR) spectra were taken on a Varian A-60 instrument using Me_4Si as the internal standard. The pK_a values of the diones were measured at 25 °C in water (CO_2 free) potentiometrically using a combined glass calomel electrodes system in conjunction with a Metrohm potentiograph E436. Preparative thin layer chromatography (preparative TLC) was carried out on 20 × 20 × 0.2 cm precoated glass plates. All new compounds gave satisfactory elemental analyses.

Materials. Diglycolic (mp 96–97 °C) and thiodiacetic anhydrides (mp 90–91 °C) were prepared[5] from commercially available diglycolic and thiodiacetic acids in improved yields of 95.3 and 79.7%, respectively. Bromomethyl [bp 68–70 °C (33 mm)] and chloromethyl ethyl ketones [bp 67.5–68 °C (57 mm)] were prepared[4] by the diazomethane reaction with propionyl bromide and chlorides in yields of 61.8 and 93.2%, respectively. Bromo- and chloroacetones and methyl thioglycolate were commercially obtained and freshly distilled prior to use: bp 136–138, 119–121, and 48–49 °C (15–16 mm), respectively.

For comparative purposes on physical properties, commercially available cyclohexane-1,3-dione (**3a**) was purified (mp 106–108 °C) and its 2-methyl derivative (**3b**) (mp 208–209.5 °C) was prepared[13] by methylation of **3a**. The 1,1-dioxide (mp 195/215–218 °C)[14] and the enol ethyl ether of **1b** (mp 68.5–69 °C)[14] were prepared from **1b** by peroxide oxidation and acid-catalyzed ethanolysis, respectively in a usual manner.

Preparation of Methyl 2-(Chloroformylmethylthio)acetate (6). A mixture of 82.8 g (0.63 mol) of thiodiacetic anhydride and 20.2 g (0.63 mol) of methanol was heated at 60–70 °C for 1 h. To the resultant homogeneous liquid, 91 mL (1.25 mol) of thionyl chloride was added dropwise under stirring, while hydrogen chloride and sulfur dioxide evolved were trapped continuously through an aqueous sodium hydroxide solution. The solution was allowed to stand at room temperature overnight until the gas evolution ceased. The excess thionyl chloride was removed under reduced pressure and the residual liquid was distilled, giving 105.8 g (92.4%) of **6**, bp 129–130 °C (17 mm) [lit.[5] bp 133 °C (24 mm)]. Redistillation yielded 99.0 g (86.5%) of the pure material: bp 125–126 °C (13 mm); IR (neat) 1800 and 1740 cm^{-1}; IR ($CHCl_3$) 1797 and 1742 cm^{-1}; NMR ($CDCl_3$) δ 3.38 (s, 2 H, CH_2COO), 3.75 (s, 3 H, $COOCH_3$), and 3.93 (s, 2 H, CH_2COCl).

Preparation of Methyl 2-(Chloroformylmethoxy)acetate (7). This preparation was carried out in the same manner as described above using 42.0 g (0.36 mol) of diglycolic anhydride, 11.6 g (0.36 mol) of methanol, and 39.5 mL (0.54 mol) of thionyl chloride. Distillation of the crude reaction product yielded 59.1 g (98.0%) of **7**, bp 123–126 °C (24 mm). Redistillation gave 56.3 g (93.4%) of the pure material: bp 121–123 °C (25 mm); IR (neat) 1806 and 1757 cm^{-1}; IR ($CHCl_3$) 1803 and 1755 cm^{-1}; NMR ($CDCl_3$) δ 3.77 (s, 3 H, $COOCH_3$), 4.25 (s, 2 H, CH_2COO), and 4.59 (s, 2 H, CH_2COCl).

Preparation of Methyl 2-(3-Alkylacetonylthio)acetate (4). I. General Procedure. This procedure was based upon the reaction of **6** with dialkylcadmium. All reactions were performed in an atmosphere of nitrogen. To a stirred ice-cold ethereal solution (ca. 300–500 mL) containing 0.56 mol of corresponding alkylmagnesium bromide, 51.3 g (0.28 mol) of dry, powdered cadmium chloride was added in small portions. Stirring was continued without heating for 5 min, followed by refluxing for 30–45 min until a negative Gilman test was obtained, and then 500 mL of dry benzene was added. After mixing was complete, the resultant cadmium reagent was cooled below 0 °C (inner temperature, usually −10 to 0 °C). Under vigorous stirring, 91.3 g (0.5 mol) of **6** in 500 mL of dry benzene was added as rapidly as consistent with control of the exothermic reaction. The reaction mixture was stirred at room temperature for 3–5 h, then decomposed by addition of cold 6 N sulfuric acid, and extracted three times with ether. The organic extracts were combined, washed successively with aqueous sodium bicarbonate solution and saturated brine, and then dried (Na_2SO_4). The solvent was evaporated and the residual liquid was distilled at a reduced pressure. The following compounds were obtained using the Grignard reagents prepared from methyl, ethyl, propyl, and benzyl bromides, respectively.

Methyl acetonylthioacetate (4a), bp 80–84 °C (0.4 mm), was obtained in 57.2% yield. The spectral data were virtually identical with those of an authentic sample described below.

Methyl 2-(3-methylacetonylthio)acetate (4b), bp 137–140 °C (13 mm), was obtained in 60.9% yield. This compound was identical in the spectral data with a specimen prepared by the procedure described below.

Methyl 2-(3-ethylacetonylthio)acetate (4c), bp 102–103 °C (2 mm), was obtained in 51.8% yield. This material was redistilled for an analytical use: bp 99–100 °C (0.9 mm); IR (neat) 1737 and 1706 cm^{-1}; IR ($CHCl_3$) 1740 and 1710 cm^{-1} (sh); NMR ($CDCl_3$) δ 0.94 (t, 3 H, J = 7 Hz, CH_2CH_3), 2.57 (t, 2 H, J = 6 Hz, $COCH_2CH_2$), 3.27 (s, 2 H, SCH_2COO), 3.42 (s, 2 H, SCH_2CO), and 3.73 (s, 3 H, $COOCH_3$).

Methyl 2-(3-phenylacetonylthio)acetate (4d), bp 147–150 °C (0.65 mm), was obtained in 47.5% yield. This material was purified by redistillation for an analytical use: bp 147–148 °C (0.6 mm); IR (neat) 1738 and 1710–1720 cm^{-1} (sh); IR ($CHCl_3$) 1735 and 1720 cm^{-1} (sh); NMR ($CDCl_3$) δ 3.23 (s, 2 H, SCH_2COO), 3.43 (s, 2 H, SCH_2CO), 3.69 (s, 3 H, $COOCH_3$), 3.88 (s, 2 H, $COCH_2C_6H_5$), and 7.28 (m, 5 H, C_6H_5).

II. Alternative Procedure. A. With Sodium Methoxide. To an ice-cold solution of sodium methoxide, prepared from 2.3 g (0.1 mol) of sodium and 43 mL of methanol, there was added under vigorous stirring 10.6 g (0.1 mol) of methyl thioglycolate and subsequently 0.1 mol of chloromethyl alkyl ketone over a period of 20 min. The resulting mixture was stirred at room temperature for 15–30 min and then at 50–60 °C for an additional 15–30 min. The reaction mixture was filtered to remove the precipitates (NaCl). After removal of the solvent, the residue was poured into cold water and then extracted with ether. The extract was washed with aqueous sodium bicarbonate solution and saturated brine and dried (Na_2SO_4). The solvent was removed and the residual liquid was distilled at a reduced pressure.

Methyl acetonylthioacetate (4a), bp 78–80 °C (0.3 mm) [lit.[1] bp 110–115 °C (5 mm) or 124–129 °C (10 mm)], was prepared following this procedure using chloroacetone in 72.6% yield. This material was redistilled for analysis: bp 93 °C (1.2 mm) [lit.[1] bp 143 °C (24 mm)]; IR (neat) 1740 and 1712 cm^{-1}; IR ($CHCl_3$) 1739 and 1712 cm^{-1}; NMR ($CDCl_3$) δ 2.30 (s, 3 H, $COCH_3$), 3.27 (s, 2 H, SCH_2COO), 3.44 (s, 2 H, SCH_2CO), and 3.73 (s, 3 H, $COOCH_3$).

Methyl 2-(3-methylacetonylthio)acetate (4b), bp 79–80 °C (0.3–0.35 mm), was obtained similarly using chloromethyl (or bromomethyl) ethyl ketone in 89.5% yield. This material was redistilled for analysis: bp 93.5–94.5 °C (0.8 mm); IR (neat) 1740 and 1711 cm^{-1}; IR ($CHCl_3$) 1737 and 1712 cm^{-1} (sh); NMR ($CDCl_3$) δ 1.10 (t, 3 H, J = 7 Hz, CH_2CH_3), 2.62 (q, 2 H, J = 7 Hz, $COCH_2CH_3$), 3.28 (s, 2 H, SCH_2COO), 3.43 (s, 2 H, SCH_2CO), and 3.73 (s, 3 H, $COOCH_3$).

B. With Triethylamine. A mixture of 10.6 g (0.1 mol) of methyl thioglycolate, 10.7 g (0.1 mol) of chloromethyl ethyl ketone, and 240 mL of methylene chloride containing 15.2 g (0.15 mol) of triethylamine was stirred at room temperature for 3–4 h. The reaction mixture was poured into ice-water, and the organic phase was separated. The aqueous phase was extracted again with methylene chloride. The combined organic extracts were washed with water and dried (Na_2SO_4), and the solvent was evaporated in vacuo. The residual liquid was purified through a short column of neutral alumina (Woelm, activity I) by eluting with 1:1 petroleum ether–ether and then distilled at a reduced pressure to give 15.1 g (85.9%) of **4b,** bp 103–104 °C (2 mm).

Preparation of Methyl 2-(3-Alkylacetonyloxy)acetate (5). General Procedure. All reactions were carried out under the same experimental condition as in the general procedure for the thia compounds (4) described above using 83.3 g (0.5 mol) of **7.** The Grignard reagents prepared from methyl iodide and ethyl, propyl, and benzyl bromides were used for the following compounds, respectively.

Methyl acetonyloxyacetate (5a), bp 113–115 °C (19 mm), was obtained in 17.7% yield. Although this material contained some impurities and could not be purified by redistillation, its spectra were essentially identical with those of a specimen obtained by the alternative preparation (vide infra).

Methyl 2-(3-methylacetonyloxy)acetate (5b), bp 134–137.5 °C (30 mm), was prepared in 58.0% yield. The analytical sample was obtained by redistillation: bp 115–117 °C (10 mm); IR (neat) 1755, 1738 (sh), and 1720 cm^{-1} (sh); IR ($CHCl_3$) 1751 and 1745 cm^{-1} (sh); NMR ($CDCl_3$) δ 1.08 (t, 3 H, J = 7 Hz, CH_2CH_3), 2.51 (q, 2 H, J = 7 Hz, CH_2CH_3), 3.76 (s, 3 H, $COOCH_3$), and 4.20 (s, 4 H, CH_2OCH_2); NMR (C_6D_6) δ 0.91 (t, 3 H, J = 7 Hz, CH_2CH_3), 2.17 (q, 2 H, J = 7 Hz, CH_2CH_3), 3.32 (s, 3 H, $COOCH_3$), 3.84 (s, 4 H, CH_2OCH_2).

Methyl 2-(3-ethylacetonyloxy)acetate (5c), bp 124–127 °C (13 mm), was prepared in 51.2% yield. The analytical sample was obtained by redistillation: bp 119–121 °C (11 mm); IR (neat) 1755, 1740 (sh), 1720 cm^{-1} (sh); IR ($CHCl_3$) 1754, 1740 (sh), 1721 cm^{-1} (sh); NMR ($CDCl_3$) δ 0.93 (t, 3 H, J = 7 Hz, CH_2CH_3), 2.46 (t, 2 H, J = 7, $COCH_2CH_2$), 3.75 (s, 3 H, $COOCH_3$), 4.18 (s, 4 H, $CHOCH_2$).

Methyl 2-(3-phenylacetonyloxy)acetate (5d), bp 131–133 °C (0.3 mm), was prepared in 50.7% yield. The analytical sample was obtained by redistillation: bp 138–139 °C (0.5 mm); IR (neat) 1752, 1739 (sh), and 1734 cm^{-1} (sh); IR ($CHCl_3$) 1753, 1732 cm^{-1} (sh); NMR ($CDCl_3$) δ 3.72 (s, 3H, $COOCH_3$), 3.78 (s, 2 H, $COCH_2C_6H_5$), 4.13 (s, 2 H, OCH_2COO), 4.23 (s, 2 H, OCH_2CO), and 7.26 (bs, 5 H, C_6H_5).

Alternative Preparation of Methyl Acetonyloxyacetate (5a). This preparation was carried out essentially as described.[15] A solution of 16.7 g (0.1 mol) of **7** in 30 mL of dry ether was added during 15 min to a well-stirred ice-cold solution of 5.0 g (0.12 mol) of diazomethane and 10.1 g (0.1 mol) of triethylamine in 240 mL of dry ether. A crystalline precipitate of triethylamine hydrochloride separated. After stirring in the cold for 1 h and at room temperature for 2 h, the precipitate was collected by filtration and washed with dry ether. The solvent was evaporated in vacuo from the combined filtrate and washings to afford 17.2 g (98.3%) of the crude oily diazo ketone. To a cold solution of the diazo ketone in 130 mL of chloroform, 30 mL of 57% hydriodic acid was added, and stirring was continued for 15 min. After evolution of nitrogen had ceased, 200 mL of water was added, and the chloroform layer was separated. The aqueous layer was extracted again with chloroform. The combined organic extracts were shaken with aqueous sodium thiosulfate solution to remove iodine liberated, washed successively with aqueous sodium bicarbonate and aqueous brine, and dried (Na_2SO_4). Evaporation of the solvent left 11.3 g of a light yellow liquid, which was distilled at a reduced pressure to give 7.73 g of **5a,** bp 74–76 °C (0.9–1.0 mm). The distillation residue (ca. 4.0 g), which showed a positive Beilstein's test (presumably iodated product), was dissolved in 50 mL of acetic acid, and subsequently 8 g of zinc powder was added. Stirring was continued for 2 days at room temperature. The solids were filtered off, and the filtrate was concentrated to dryness in vacuo. The residue was extracted with methylene chloride, and the extract was worked up as described above. The residual liquid (ca. 2.6 g) was distilled at a reduced pressure, giving additional 0.63 g of **5a,** bp 75–76 °C (1 mm), total yield 8.4 g (57.5%). A portion of this material was redistilled for analysis: bp 78 °C (1.2 mm); IR (neat) 1754, 1737, and 1720 cm^{-1} (sh); IR ($CHCl_3$) 1753, 1736, and 1720 cm^{-1} (sh); NMR ($CDCl_3$) δ 2.19 (s, 3 H, $COCH_3$), 3.77 (s, 3 H, $COOCH_3$), and 4.20 (bs, 4 H, CH_2OCH_2); NMR (C_6D_6) δ 1.78 (s, 3 H, $COCH_3$), 3.30 (s, 3 H, $COOCH_3$), and 3.77, 3.82 (s, s, 4 H, CH_2OCH_2).

Preparation of Thiacyclohexane-3,5-diones (1). 4-Methylthiacyclohexane-3,5-dione (1b). A solution of 101.3 g (0.57 mol) of **4b** in 2.3 L of dry tetrahydrofuran was added dropwise over a period of 3 h to a stirred suspension of 0.57 mol of sodium hydride (27.4 g of 50% mineral oil suspension) in 1.1 L of dry tetrahydrofuran at room temperature under nitrogen. Stirring was continued for an additional 3 h. The resulting reaction mixture was concentrated to a small volume below 40 °C under a reduced pressure, poured into ice-cold water, and then extracted with ether. The aqueous layer was separated, acidified (pH 2–3) with dilute hydrochloric acid, and extracted several times with chloroform. The extracts were washed with a small portion of saturated brine and dried (Na_2SO_4). The solvent was removed in vacuo and the residue was crystallized from dichloromethane–ether, giving 62.7 g (75.6%) of **1b,** mp 131–133 °C. Recrystallization from acetone–ether provided an analytical sample, mp 132.5–133 °C.

4-Ethylthiacyclohexane-3,5-dione (1c). The reaction was carried out using 2.20 g (0.0125 mol) of **4c,** 0.0125 mol of sodium hydride (0.6 g of 50% mineral oil suspension), and total 100 mL of dry tetrahydrofuran according to the same procedure as described above, except that the addition was complete in a 1.5-h period. The yield of **1c** was 1.07 g (53.8%), mp 107–109 °C (dichloromethane–ether). The analytical sample was obtained by recrystallization from the same solvent, mp 108.5–109.5 °C.

Thiacyclohexane-3,5-dione (1a). A solution of 57.1 g (0.35 mol) of **4a** in 1.4 L of dry tetrahydrofuran was added to a stirred suspension of 0.35 mol of sodium hydride (16.9 g of 50% mineral oil suspension) in 1.1 L of dry tetrahydrofuran. The reaction was carried out and worked up by the same procedure as described above. The semicrystalline residue was crystallized from dichloromethane–ether to yield 26.6 g (58.0%) of **1a,** mp 70–74 °C. Recrystallization from acetone–ether or dichloromethane–ether gave an analytical specimen, mp 76–78 °C [lit.[1] mp 80–81 °C].

4-Phenylthiacyclohexane-3,5-dione (1d). To a stirred suspension of 0.005 mol of sodium hydride (0.48 g of 50% mineral oil suspension) in 10 mL of dry tetrahydrofuran, there was added dropwise over a 2-h period at room temperature under nitrogen a solution of 1.19 g (0.005 mol) of **4d** in 30 mL of dry tetrahydrofuran. Stirring was continued for 1.5 h at room temperature followed by 2.5 h at 60 °C. The reaction mixture was concentrated to dryness in vacuo. The residual solid was dissolved into a small volume of aqueous sodium bicarbonate solution and extracted with ether. The aqueous phase was separated, acidified with 2 N hydrochloric acid, and extracted several times with chloroform containing a little methanol or ethyl acetate. The extracts were combined, washed with a small amount of saturated brine, and dried (Na_2SO_4), and the solvent was evaporated in vacuo. The crude noncrystalline residue was purified by preparative TLC (Merck, Kieselgel GF_{254}, 98:2 chloroform–acetic acid with double development) to give 0.178 g (17.3%) of **1d** as a crystalline solid, mp 181–186 °C. The ana-

lytical sample was obtained by recrystallization from chloroform (3% of ethanol)–ether, mp 187–188 °C.

Preparation of Oxacyclohexane-3,5-diones (2). 4-Methyloxacyclohexane-3,5-dione (2b). A solution of 25.05 g (0.156 mol) of **5b** in 430 mL of dry tetrahydrofuran was added dropwise over a 2.5-h period at room temperature under nitrogen to a stirred suspension of 0.312 mol of sodium hydride (14.98 g of 50% mineral oil suspension) in 430 mL of dry tetrahydrofuran. Stirring was continued for an additional 4.5 h. The reaction mixture was concentrated to a small volume below 40 °C under reduced pressure, poured into ice-cold water, and then extracted with ether. The separated aqueous layer was acidified (pH 2–3) with 4 N hydrochloric acid and extracted with chloroform–methanol (95:5) continuously using a modified Soxhlet extractor. The extracts were combined and dried (Na_2SO_4), and the solvent was evaporated in vacuo to yield total 10.28 g (51.3%) of **2b**, mp 173–176 °C. Recrystallization from chloroform (2% of methanol)–ether gave the analytical sample, mp 178–180 °C.

4-Ethyloxacyclohexane-3,5-dione (2c). The reaction was carried out using 10.22 g (0.0587 mol) of **5c**, 0.117 mol of sodium hydride (2.82 g of 50% mineral oil suspension), and total 350 mL of dry tetrahydrofuran following the same procedure as described above, except that 3.5 h was required for the addition followed by an additional 4-h stirring. The continuous extraction using chloroform gave a total of 2.34 g (28.1%) of **2c**, mp 114–115 °C. This material was purified by recrystallization from dichloromethane–ether for an analytical use, mp 117–119 °C.

Oxacyclohexane-3,5-dione (2a). A solution of 4.62 g (0.0316 mol) of **5a** in 40 mL of dry tetrahydrofuran was added dropwise over a 1.5-h period at 0–3 °C under nitrogen to a stirred suspension of 0.0474 mol of sodium hydride (2.28 g of 50% mineral oil suspension) in 20 mL of dry tetrahydrofuran. The reaction mixture was stirred at 0–3 °C for an additional 0.5 h and then allowed to stand overnight in a refrigerator (0 °C). After concentration to a small volume below 35 °C, the reaction mixture was poured into ice-cold water and extracted with ether. The aqueous phase was separated, acidified with 2 N hydrochloric acid, and then extracted several times with ethyl acetate. The combined extracts were dried (Na_2SO_4), and the solvent was evaporated in vacuo leaving a tan paste. Trituration with dichloromethane and/or ether gave a total of 1.72 g (47.8%) of **2a**, mp 122–125 °C. The analytical sample was obtained by recrystallization from chloroform (3% of methanol)–ether, mp 127–129 °C.

4-Phenyloxacyclohexane-3,5-dione (2d). A solution of 2.22 g (0.01 mol) of **5d** in 20 mL of dry tetrahydrofuran was added dropwise over a 40-min period at 0–3 °C under nitrogen to a stirred suspension of 0.015 mol of sodium hydride (0.72 g of 50% mineral oil suspension) in 40 mL of dry tetrahydrofuran. Stirring was continued for an additional 1 h at the same temperature. After standing overnight in a refrigerator (0 °C), the reaction mixture was left stand at room temperature for 2 h and then worked up as described above. The crude product, obtained as an oil, was purified by preparative TLC (Merck, Kieselgel GF_{254}, 95:5 chloroform–acetic acid with double development), giving 0.43 g (22.5%) of **2d**, mp 175–177 °C. The analytical sample was obtained by recrystallization from chloroform–ether, mp 177–179 °C.

Acknowledgment. The authors wish to thank Dr. T. Kubota for his interest and helpful discussions and suggestions on the ultraviolet spectral data of the heterocyclic diones.

Registry No.—**1b** 1,1-dioxide, 61363-60-8; **1b** enol ethyl ether, 61363-61-9; **4a**, 61363-62-0; **4b**, 61363-63-1; **4c**, 61363-64-2; **4d**, 61363-65-3; **5a**, 61363-66-4; **5b**, 61363-67-5; **5c**, 19688-72-3; **5d**, 61363-68-6; **6**, 61363-69-7; **7**, 61363-70-0; diglycolic anhydride, 4480-83-5; thiodiacetic anhydride, 3261-87-8; thionyl chloride, 7719-09-7; methyl thioglycolate, 2365-48-2; chloroacetone, 78-95-5; chloromethyl ethyl ketone, 616-27-3; diazomethane, 334-88-3; dimethylcadmium, 506-82-1; diethylcadmium, 592-02-9; dipropylcadmium, 5905-48-6; dibenzylcadmium, 17051-04-6; bromomethyl ethyl ketone, 816-40-9; methyl iodide, 74-88-4; ethyl bromide, 74-96-4; propyl bromide, 106-94-5; benzyl bromide, 100-39-0.

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(10) One of the important factors responsible for preference of the diketo forms in **1** over those in **2** must be the ring strain. Introduction of a 4,5 double bond in the six-membered ring in going from the diketo to enol forms tends to open outside the bond angle at the position occupied by the heteroatom. The angle strain leading to increase in ring strain would be greater in **1** than in **2** judging from their valence angles (98.5, 109.5, and 110° for C–X–C when X is S, CH_2, and O, respectively). It appears to contribute to a lower stability of the enol than diketo form in **1** compared to **2**.
(11) Actually, a wide variety of solvents with different polarities could not necessarily be employed in the spectral study of the diones because of their limited solubility in organic solvents.
(12) The bathochromic shift of **1** over **2** and **3** may be rationalized, presumably as a result of the contribution of hyperconjugation and direct interaction through the space between the sulfur atom (smaller ionization potential) and the conjugated system in the enol of **1**.
(13) A. B. Mekler, S. Ramachandran, S. Swaminathan, and M. S. Newman, *Org. Synth.*, **41**, 56 (1961), and references cited therein.
(14) The following physical data are given for the 1,1-dioxide and the enol ethyl ether of **1b**. The 1,1-dioxide: IR (Nujol) ~3200 and 1600 cm^{-1}; NMR ($CDCl_3$) δ 1.79 (s, 3 H, 4-vinylic CH_3) and 4.18 (bs, 4 H, 2-H_2, 6-H_2); NMR (CD_3OD) δ 1.68 (s, 3 H, 4-vinylic CH_3) and 4.27 (s, 4 H, 2-H_2, 6-H_2); UV (95% EtOH) 270.5 nm (ε 11 300) and 296 (sh) (7500); UV (95% EtOH + 1 N HCl) 268 nm (ε 13 900); UV (95% EtOH + 1 N NaOH) 300 nm (ε 23 300). The ethyl ether: IR ($CHCl_3$) 1612 and 1643 cm^{-1}; NMR ($CDCl_3$) δ 1.36 (t, 3 H, J = 7 Hz, OC_2CH_3), 1.76 (t, 3 H, J = 1.5 Hz, 4-vinylic CH_3), 3.21, 3.50 (bs, m, 4 H, 2-H_2, 6-H_2), and 4.06 (q, 2 H, J = 7 Hz, OCH_2CH_3); UV (95% EtOH) 276 nm (ε 11 300), and no significant change in the absorption band with varying conditions.
(15) M. S. Newman and P. Beal, III, *J. Am. Chem. Soc.*, **71**, 1506 (1949).