Lactone Chemistry. Synthesis of β-Substituted, γ-Functionalized Butanolides and Butenolides and Succinaldehydic Acids from Glyoxylic Acid

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The Mannich-type aminoalkylation reaction of enolizable aldehydes with morpholine and glyoxylic acid instead of formaldehyde was investigated: in basic and neutral media were obtained α,γ-dimorpholinobutanolides **2** and α-morpholino-γ-hydroxybutanolides **1**, respectively. In acidic medium the spontaneous elimination of the α-morpholino group afforded the γ-hydroxybutenolide **8**. The reaction pathways were suggested from the isolation and characterization of some intermediates of the Mannich reaction. These lactone structures constitute versatile synthetic intermediates for the preparation of β-substituted succinaldehydic acids **15** and 5-substituted 3-(2*H*)-pyridazinones **13** and **14**.

Enzymes of the catabolism of γ-aminobutyric acid (GABA) have been shown to play an important role in the central nervous system. In order to have a better insight into the enzymatic mechanisms which are implicated, and in continuation with previous work on succinaldehydic acid (SSA),[1] a metabolite of GABA, we turned our attention to substituted SSA's and particularly to β-substituted SSA's as hypothetical substrates or inhibitors of SSA dehydrogenase or SSA reductases. Our synthetic approach was based on aminoalkylation reactions of enolizable aldehydes with glyoxylic acid. Indeed, in a previous work involving various ketones,[2] the use of glyoxylic acid, instead of formaldehyde, in the Mannich reaction led us to an easy route to γ-keto acids and to related lactonic systems. In analogous manner, the replacement of the ketones by enolizable aldehydes in this modified Mannich reaction might constitute an extension allowing the synthesis of γ-aldehydic acids and of the corresponding lactols.

Aminoalkylation of Enolizable Aldehydes

(1) In Basic or Neutral Media. In the classical Mannich reaction, the three reactive partners (carbon acid, formaldehyde, secondary amine) are present in a 1:1:1 ratio. In addition to our initial operating conditions, we added an additional 1 equiv of morpholine in order to neutralize the acidic hydrogen of glyoxylic acid. In ethanol as the solvent the reaction mixture was at first homogeneous but gave rise after some hours at 4 °C to a crystalline precipitate of the α,γ-dimorpholinobutanolide **2**. This compound resulted from the lactonization of the open form of **1** followed by the substitution of its γ-hydroxy group (Scheme I).

In two cases (R = Me or Ph), we observed a spontaneous elimination or morpholine and formation of the γ-morpholinobutenolides **3**. The characteristics of the morpholino lactones **2** and **3** are summarized in Table I.

By analogy with the mechanisms proposed for the Mannich reaction in basic medium with formaldehyde,[3,4] we can postulate either the classical S_N2 mechanism involving attack by the ionized carbon acid (Scheme II, mechanism a) or the formation of a cyclic hydrogen bonded complex (mechanism b). In both cases glyoxylic acid is supposed to be present as a monoamino derivative.

In fact, glyoxylic acid in the presence of 2 equiv of morpholine can exist as a monor or diamino compound,

Scheme I

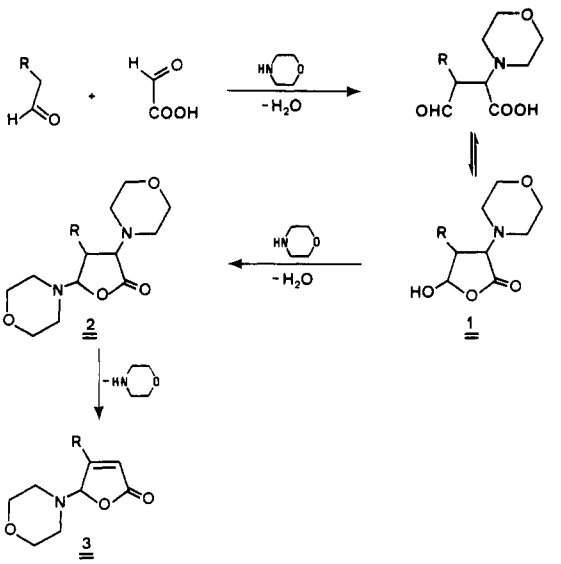

Table I. γ-Morpholinobutanolides and -butenolides 2 and 3

compd	R	yield, %	mp, °C	^{1}H NMR ($CDCl_3$), δ
2a[a]	Me	60	140.3	1.05 (d, 3 H), 4.81 (d, 3 H)
2b	Et	55	129.3	1.0 (t, 3 H), 3.05 (q, 2 H), 4.75 (d, 1 H)
2c	*n*-Pr	59	152.6	1.5-0.95 (m, 7 H), 4.75 (d, 1 H)
2d	*i*-Pr	80	133.8	1.0 (d, 6 H), 4.81 (d, 1 H)
2e	Bz	72	148.5	7.25 (m, 5 H), 4.75 (d, 1 H)
3a	Me	70	124	1.0 (s, 3 H), 5.45 (s, 1 H), 5.9 (m, 1 H)
3f	Ph	70	134.8	7.5 (m, 5 H), 6.05 (d, 1 H), 6.50 (d, 1 H)

[a] Reaction time 30 min.

either one being present as a zwitterion, or as an ammonium salt. With our experimental conditions, we probably have a complex system (Scheme III). This prompted us to study the behavior of glyoxylic acid in the presence of increasing amounts of morpholine. (a) Neutralization of an ice-cooled ethanolic solution of glyoxylic acid with 1 equiv of morpholine led to a quantitative precipitation of the zwitterionic monoaminal **4** (2-morpholino-2-hydroxyethanoic acid). The structure of this compound was sup-

(1) C. G. Wermuth, *J. Org. Chem.*, 44, 2406 (1979).
(2) J. Schreiber, C. G. Wermuth, and A. Meyer, *Bull. Soc. Chim. Fr.* 625 (1973).
(3) B. B. Thompson, *J. Pharm. Sci.*, 57, 715 (1968).
(4) M. Tramontini, *Synthesis*, 703 (1973).

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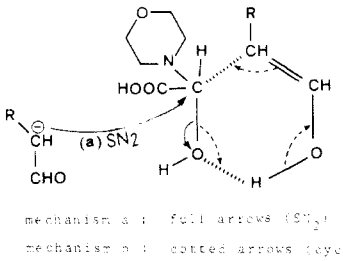
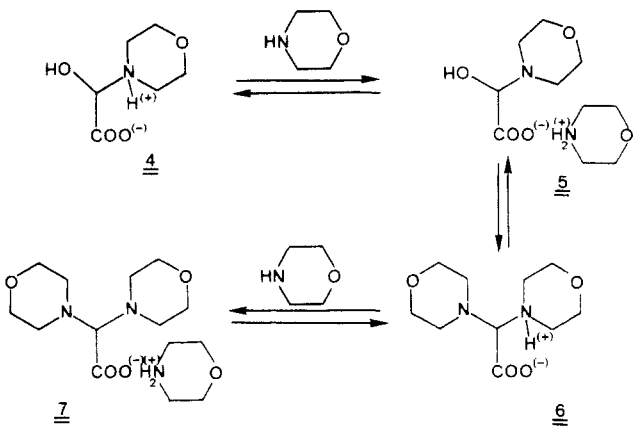
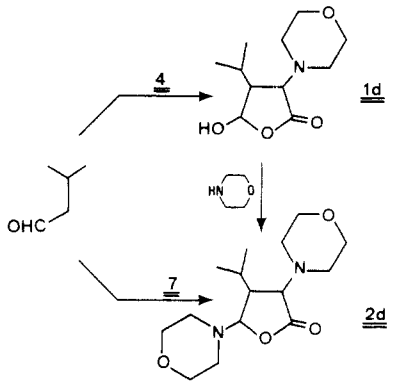
Scheme II



Scheme III



Scheme IV

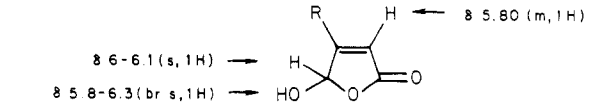


ported by its ^1H NMR spectrum (D_2O), which exhibits a singlet at 5.0 ppm (methine proton) and a multiplet at 3.3 ppm, a characteristic of a protonated aminomethylene group. Additional evidence for a zwitterionic structure of 4 was given by the IR carboxylate band at 1625 cm^{-1}. (b) Treatment of glyoxylic acid in ethanol with 2 equiv of morpholine gave a homogeneous, viscous solution, from which we were unable to isolate any definite products. (c) However, in the presence of 3 equiv of morpholine, we succeeded in isolating the morpholinium salt of glyoxylic acid aminal **7** (dimorpholinoethanoic acid). The ^1H NMR spectrum ($CDCl_3$) of this salt exhibits a downfield resonance (δ ~9.6, exchangeable with D_2O) for the morpholinium protons and a singlet at 3.2 ppm assigned to the methine proton.

It seemed interesting to us to investigate the reactivity of the isolated hemiaminal **4** and aminal **7** as aminoalkylating agents toward a given aldehyde, isovaleraldehyde (see Scheme IV).

The condensation of 2-morpholino-2-hydroxyethanoic acid **4** with isovaleraldehyde at room temperature afforded the γ-hydroxy lactone **1d** (3-morpholino-4-isopropyl-5-hydroxy-4,5-dihydro-2(3*H*)-furanone). Under the same conditions, the reaction of isovaleraldehyde with the

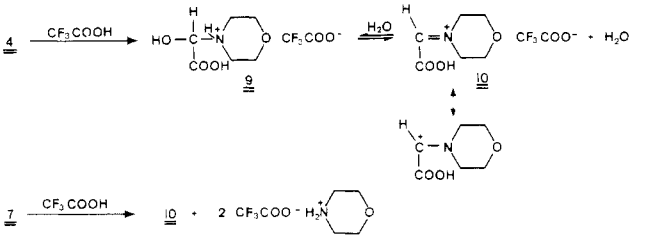
Table II. γ-Hydroxybutenolides 8



compd	R	yield, %	mp or bp (mm), °C	^1H NMR ($CDCl_3$), δ
8a	Me	76	113 (0.05)	2.10 (d, 3 H)
8b	Et	80	81.3	2.35 (m, 2 H), 1.18 (t, 3 H)
8c	*n*-Pr	70	115 (0.01)	2.35 (m, 2 H), 1.60 (m, 2 H), 0.95 (m, 3 H)
8d	*i*-Pr	84	80.0	2.70 (q, 1 H), 1.15 (dd, 6 H)
8e	Ph	83	159.0	7.5-7.7 (m, 5 H), 6.68 (s, 2 H)[a]

[a] Me_2SO-d_6.

Scheme V



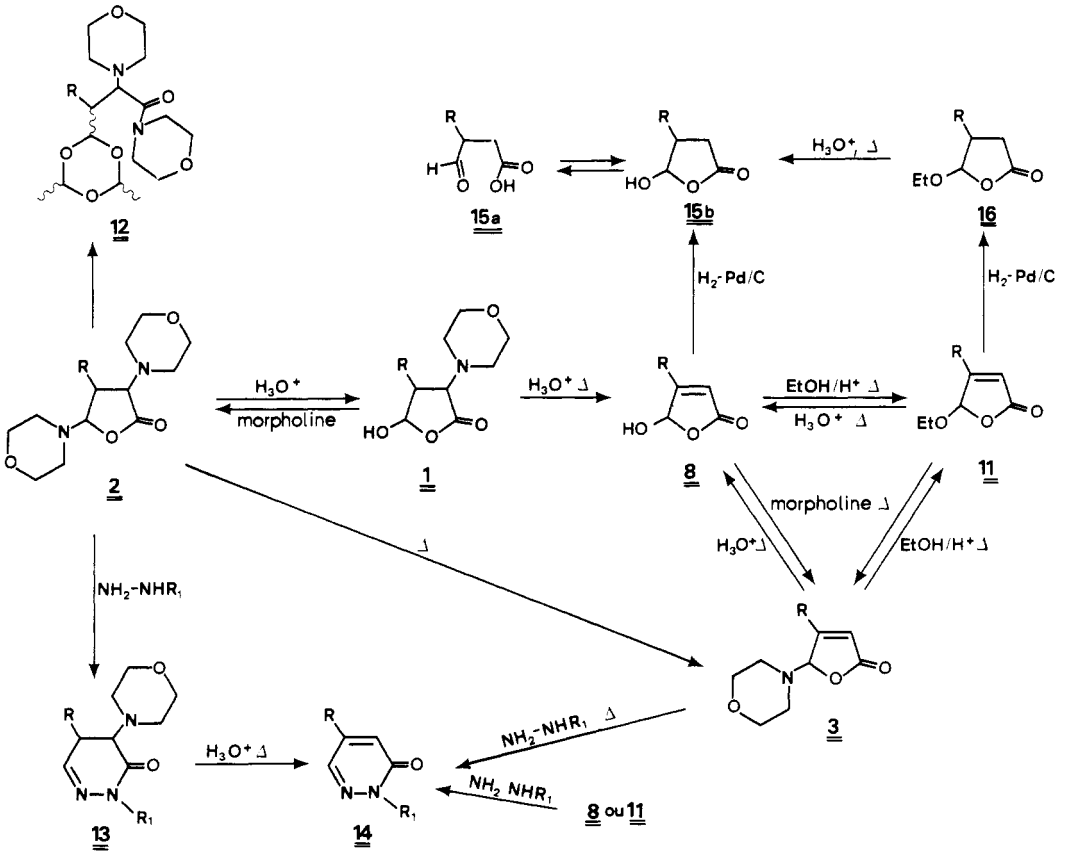
morpholinium salt of the dimorpholinoethanoic acid **7** led to the α,γ-dimorpholinobutanolide **2d**. The solubility of the starting morpholinium salt in chloroform allowed the Mannich reaction to proceed in aprotic conditions with similar yields. In addition, treatment of the lactol **1d** with 1 equiv of morpholine in ethanol afforded the dimorpholino lactone **2d** quantitatively. These observations led us to the conclusion that the Mannich reaction with 2 equiv of morpholine to give the α,γ-dimorpholinobutanolides **2** can proceed equally well via hemiaminal **4** or aminal **7**. The possibility of realizing the aminoalkylation under very mild conditions at neutral pH with the hemiaminal **4** constitutes evidence in favor of the concerted cyclic mechanism b (Scheme II).

(2) Acid Catalysis. The aminoalkylation in acidic medium was performed by condensing an equimolar amount of glyoxylic acid and enolizable aldehyde with 1 equiv of morpholinium hydrochloride. The reaction led directly and with satisfactory yields to the 4-substituted 5-hydroxy-2(5*H*)-furanones **8** (Table II). By analogy with the classical Mannich reaction intermediates, we suggest the formation of an immonium salt derived from glyoxylic acid and morpholinium hydrochloride. The existence of an equilibrium (see Scheme V) under our operating conditions (aqueous medium) was supported by ^1H NMR analysis.

The spectrum of **7** in CF_3COOH clearly exhibits the presence of a deshielded proton at 8.65 ppm, which was assigned to the immonium ion **10**,[5] while the spectrum of **4** in CF_3COOH allows the characterization of the equilibrium between the two species **9** and **10** (characterized by signals at 5.40 and 8.65 ppm, respectively). When a large amount of D_2O was added to this sample, the spectrum shows the disappearance of the singlet at 8.65 ppm but not the signal of the methine proton of **9** at 5.40 ppm.

(5) Y. Jasor, M. Gaudry, M. J. Luche, and A. Marquet, *Tetrahedron*, 33, 295 (1977).

Scheme VI



A direct aldol reaction between the aldehyde and glyoxylic acid catalyzed by the acid and without any participation of morpholine could have been an alternative explanation for the formation of the γ-hydroxybutenolide 8. Such a condensation reaction was performed in a mixture of acetic and chlorhydric acids with a substituted cyclohexylacetaldehyde and glyoxylic acid.[6] In our case this hypothesis can be discarded because the reaction of an aldehyde like propanal with glyoxylic acid and 1 equiv of HCl under our operating conditions but without morpholine led to a complex mixture containing only 8% of distillable **8a**.

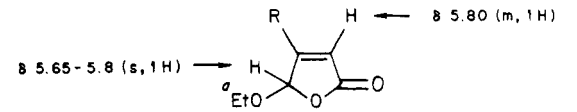
Due to their hemiacetalic hydroxyl group, the lactols 8 are easily converted to their corresponding γ-alkoxybutenolides by treatment with an appropriate alcohol containing gaseous HCl (Scheme VI). The γ-alkoxybutenolides can also be prepared by a one-pot, modified acidic aminoalkylation reaction carried out in a given alcoholic solvent (MeOH, EtOH). The characteristics of a series of γ-ethoxybutenolides 11 are summarized in Table III. The main product is usually accompanied by a small amount (less than 5%) of ethyl glyoxylate diethyl acetal.

Chemistry of γ-Morpholino Lactones and Interconversion Reactions

The chemical behavior of the α,γ-dimorpholinobutanolides 2 is the consequence of the β-elimination reactions of the Mannich base derivative, the mobility of the semiaminal group in γ-position of the lactone ring, and the reactivity of the γ-oxo carboxylic acid system (see Scheme VI).

(1) β-Elimination Reactions. The ability of Mannich bases to undergo β-elimination reactions is well-known in the literature. Similar behavior could be expected for the lactones 1 and 2. Indeed, β elimination occurred for 2 spontaneously at room temperature (R = Me and Ph) or at the melting point temperature (R = *i*-Pr, Bz). The thermal treatment of **2e**, however, by heating it in refluxing *n*-butanol or dioxane for one night, gave a complex mixture from which the trioxanic amide 12 was isolated with a 35% yield. The structure of 12 is supported by a strong amide absorption band at 1635 cm^{-1} and the disappearance of the lactonic carbonyl band at 1750 cm^{-1}. The absence of any absorption beyond 1635 cm^{-1}, as well as the characteristic resonance of morpholino amide group and the disparition of the signal of the deshielded CH aldehydic moiety in the NMR ($CDCl_3$), favors the cyclic trimeric structure. The polymeric structure of 12 was confirmed by mass spec-

Table III. γ-Ethoxybutenolides 11

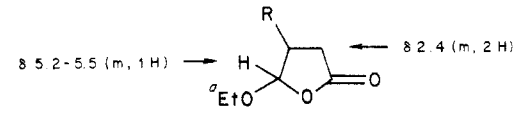


compd	R	yield, %	bp (mm), °C	^1H NMR ($CDCl_3$), δ
11a	Me	59	114 (15)	2.0 (d, 3 H)
11b	Et	53	73 (0.05)	2.3 (m, 2 H), 1.18 (t, 3 H)
11c	*n*-Pr	65	72 (0.05)	2.3 (m, 2 H), 1.0-1.7 (m, 5 H)
11d	*i*-Pr	58	63 (0.05)	1.15 (dd, 6 H), 2.70 (q, 1 H)
11e	Ph	75	138 (0.05)	7.5 (m, 5 H), 6.4 (s, 1 H), 6.3 (s, 1 H)
11f	Bz	83	136 (0.05)	7.30 (m, 5 H), 3.70 (m, 2 H)

[a] δ 1.25 (t, 3 H), 3.8 (m, 2 H), ABX_3 system.

(6) H. H. Inhoffen, W. Kreiser, and M. Nazir, *J. Liebigs Ann. Chem.* **755**, 1 (1972).

Table IV. γ-Ethoxybutyrolactones 16 from 11



compd	R	yield, %	bp (mm), °C	^{1}H NMR ($CDCl_3$), δ
16a	Me	90	114 (15)	1.05 (d, 3 H)
16b	Et	88	65 (0.02)	0.8-1.6 (m, 5 H)
16c	*n*-Pr	88	79 (0.15)	0.8-1.6 (m, 7H)
16d	*i*-Pr	85	87 (0.15)	0.9 (dd, 6 H)
16e	Ph	80	120 (0.05)	7.25 (s, 5 H)
16f	Bz	86	132 (0.10)	7.20 (s, 5 H), 2.8 (m, 2 H)

[a] δ 1.2 (t, 3 H), 3.7 (m, 2 H), ABX_3 system.

trometric analysis: because of its thermic instability, it was not possible to prove the trimeric structure. Nevertheless, methane chemical ionization methods gave a mixture of thermolysis products, which led to the identification of the dimeric intermediate (MH^+, mol wt 693).

Acidic catalysis is more suitable for the β-elimination reaction: boiling **2d** with concentrated hydrochloric acid for 2 h afforded the γ-hydroxybutenolide **8d** quantitatively. The first step of this reaction is nucleophilic displacement of the γ-morpholino group; the intermediate compound **1d** can be trapped after a short reflux period (10 min).

(2) Nucleophilic Displacement of the γ-Substituent. Substitution of the γ-hemiacetal group is easy in the saturated lactonic systems **1** and **2** as well as in the α,β-unsaturated butenolides **3**, **8**, and **11**. This behavior allows a lot of interconversion reactions such as a facile hydrolysis of the γ-morpholino compounds (**2** → **1**, **3** → **8**) and the γ-ethoxy compound (**11** → **8**). Interconversion reactions also occurred by starting from γ-hydroxy compounds (**1** → **2**, **8** → **11**, **8** → **3**).

(3) Reactivity of the γ-Oxo Carboxylic Acid Systems. The masked γ-oxo carboxylic acid in the lactones **2** and **3** was revealed in their reactions with hydrazines: treatment of **2d** with methylhydrazine afforded quantitatively the 2-methyl-4-morpholino-5-isopropyl-4,5-dihydro-3(2*H*)-pyridazinone (**13d**; R = *i*-Pr, R_1 = Me), which under acidic conditions led to the 2-methyl-5-isopropyl-3(2*H*)-pyridazinone (**14d**). Similar pyridazinones can be also obtained directly from **3**.

Conversion to the saturated succinaldehydic acid system **15** can be achieved through catalytic hydrogenation of γ-hydroxybutenolides **8** (method a) or by hydrolysis of the precursor γ-ethoxybutanolides **16** (method b), which themselves result from catalytic hydrogenation of the corresponding butenolides **11** (Table IV).

These compounds are stable, protected forms of β-substituted SSA's. It is interesting to note that we never observed the formation of an ethyl ester of a β-substituted SSA.

For two β-substituted SSA's (R = Me and Ph), we have investigated the ring–chain tautomerism (**15a** ⇄ **15b**) using ^{1}H NMR and IR spectroscopy: while the open structure of SSA was visualized by the characteristic signal of the aldehydic proton at nearly 9 ppm in $CDCl_3$ or toluene solutions,[1] the β substitution of SSA (R = Me and Ph) led to a system which was marked by a faster chemical exchange between the two structures **15a** and **15b**, and the ^{1}H NMR spectrum ($CDCl_3$, Me_2SO-d_6 or D_2O) showed just a very broad coalescence for the γ-methine proton of **15** for which the position depends upon the population of the two sites. Nevertheless, the existence of the two isomers was supported by IR spectroscopy: the absorption of the aldehydic carbonyl group at 1720 cm^{-1} assigns the open structure **15a**, while the 1780-cm^{-1} band is characteristic of the lactonic structure for β-Me-SSA, the only one β-substituted SSA described in the literature.[7] The authors have shown the existence of an equilibrium by esterification reactions with diazomethane to obtain the ethyl ester of substituted SSA; this fact involves the presence of a fraction of β-Me-SSA in the open tautomer **15a**.

Conclusion

Among the various syntheses of γ-oxo carboxylic acids or their esters, the aldol condensation of glyoxylic acid with carbonyl compounds appears as a possible route to such systems,[8-10] but this approach presents some drawbacks such as the formation of methylene bis compounds[10] or self-adolization when an aldehydic partner is used. Nevertheless, two applications can be found in the literature: (a) the condensation of glyoxylic acid with substituted cyclohexylacetaldehyde in a mixture of acetic and chlorhydric acids yielded a mixture of the free and acetylated aldol;[6] (b) using methanolic sodium hydroxide in condensing glyoxylic acid and cyclopentylacetaldehyde, Weiler et al. obtained a mixture of the aldol and the crotonized derivative.[11] We found that aminoalkylation of enolizable aldehydes with glyoxylic acid is a versatile alternative for preparing β-alkyl and β-aryl γ-functionalized lactones under mild and various experimental conditions. The compounds may also constitute valuable synthetic intermediates in the lactone chemistry as well as for the synthesis of original β-substituted SSA's.

Experimental Section

General Methods. Melting points (uncorrected) were determined on a Mettler FP_1 capillary melting point apparatus. ^{1}H NMR spectra were recorded with a Perkin-Elmer R 12A spectrometer by using the δ scale with reference to Me_4Si for $CDCl_3$ solutions and to 2,2,3,3-tetradeuterio-3-(trimethylsilyl)propionic acid sodium salt for D_2O solutions. IR spectra were taken with a Beckman Acculab 4 spectrophotometer using $CHCl_3$ solutions or KBr disks. Gas chromatography was performed with a Girdel 30 chromatograph equipped with a 10% SE-30 column at a temperature of 140 °C and using nitrogen as the carrier gas. Glyoxylic acid hydrate was purchased from Aldrich Chemical Co.

Glyoxylic Acid Derivatives. (a) Morpholinohydroxyethanoic Acid 4. Morpholine (9 mL, 0.103 mol) dissolved in 10 mL of absolute ethanol was slowly added to glyoxylic acid hydrate (9.2 g, 0.10 mol) in 50 mL of absolute ethanol, and the mixture was maintained at 4 °C (ice bath). After being stirred a few minutes, the reaction medium was refrigerated for 3 h. The precipitate was collected and thoroughly washed first with 20 mL of absolute ethanol and then three times with dry ethyl ether. The product (white powder) was dried under vacuum in a desiccator containing silica gel. The crude product (14.5 g, yield 90%) was analytically pure without further purification: mp 95 °C; NMR (D_2O) δ 3.25 (m, 4 H, NCH_2), 3.90 (m, 4 H, OCH_2), 5.05 (s, 1 H, CH); IR (KBr) 1625 cm^{-1} (ionized carboxyl group). Anal. Calcd for $C_6H_{11}NO_4$: C, 44.71; H, 6.68; N, 8.69. Found: C, 44.70; H, 6.81; N, 8.80.

(b) Morpholinium Salt of Dimorpholinoethanoic Acid 7. Under the same conditions as for **4**, but with excess of morpholine (29.8 mL, 3.5 equiv), the salt **7** precipitated in the reaction medium. The solid was filtered and thoroughly washed, first with THF and then with dry ethyl ether, and treated as above for **4**.

(7) P. Pino, G. Gaudiano, M. Cecchetti, and F. Piacenti, *Ann. Chim. (Rome)*, **51**, 785 (1961).
(8) M. A. Bielefeld and P. Kurath, *J. Org. Chem.*, **34**, 237 (1969).
(9) M. Debono, R. M. Molloy, and L. E. Patterson, *J. Org. Chem.*, **34**, 3032 (1969).
(10) G. R. Pettit, B. Green, and G. L. Dunn, *J. Org. Chem.*, **35**, 1367 (1970).
(11) F. W. Sum and L. Weiler, *J. Org. Chem.*, **44**, 1012 (1979).

The white solid (27 g, yield 84%) was analytically pure: mp 110 °C; NMR ($CDCl_3$) δ 2.80 (m, 12 H, NCH_2), 3.25 (s, 1 H, CH), 3.80 (m, 12 H, OCH_2), 9.60 (s, 2 H, exchangeable protons by D_2O, NH_2^+); IR ($CHCl_3$) 1630 cm^{-1} (C=O carboxylate). Anal. Calcd for $C_{14}H_{27}N_3O_5$: C, 52.98; H, 8.58; N, 13.32. Found: C, 52.93; H, 8.66; N, 13.35.

The compound **7** may be obtained from **4** in the heterogeneous phase (THF) with 2.1 equiv of morpholine (yield 76%).

(c) Immonium Salt from 4 and 7. Treating 3.82 g (0.01 mol) of **7** in 25 mL of dry THF with 3.35 g (0.0294 mol) of slowly added CF_3COOH afforded a mixture of the immonium salt **10** and morpholinium trifluoroacetate (1:2) as a pale yellow solution, which was used directly for synthetic purposes. The ^1H NMR of **7** in CF_3COOH characterized **10**: δ 8.65 (s, 1 H), 7.85 (large s, 4 H), 3.55 (m, 8 H), 4.20 (m, 16 H); after exchange with D_2O δ 5.40 (s, 1 H), 3.90 (m, 12 H), 3.30 (m, 12 H). A 15% solution of **4** in CF_3COOH afforded a mixture of **9** and **10** (ratio of 2:3).

General Procedure for the Mannich Reaction in Basic Medium. Glyoxylic acid hydrate (9.2 g, 0.10 mol) was dissolved in 20 mL of 95% ethanol and maintained at 4 °C (ice bath). To the homogeneous solution was slowly added 17.5 mL (0.20 mol) of morpholine under vigorous stirring followed by 0.105 mol of freshly distilled aldehyde. The stirring was continued at room temperature for 2–5 h, and then the flask was stored in refrigerator for 1 or 2 days. The product crystallized in the medium and was filtered, washed, and recrystallized from appropriate solvent.

(a) 4-Substituted 3,5-Dimorpholino-4,5-dihydro-2(3*H*)-furanones (2). These were recrystallized from a mixture of chloroform/diisopropyl ether. Characterization of **2e** (R = Bz): IR ($CHCl_3$) 1760 cm^{-1} (C=O stretching of lactone ring). Anal. Calcd for $C_{19}H_{26}N_2O_4$: C, 65.87; H, 7.57; N, 8.09. Found: C, 65.70; H, 7.71; N, 7.99.

(b) 4-Substituted 5-Morpholino-2(5*H*)-furanones (3). These were recrystallized from absolute ethanol. Characterization of **3a** (R = Me): IR ($CHCl_3$) 1760, 1660 cm^{-1} (α,β-unsaturated lactone ring). Anal. Calcd for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65. Found: C, 59.13; H, 7.24; N, 7.66.

Mannich Reaction in Neutral Medium. 3-Morpholino-4-isopropyl-5-hydroxy-4,5-dihydro-2(3*H*)-furanone (1d). To a suspension of **4** (1.60 g, 0.01 mol) in 10 mL of 95% ethanol was added 3-methylbutanal (0.862 g, 0.01 mol) at 4 °C, and stirring was continued for 2 h at room temperature. The mixture was evaporated under vacuum, and the crude oil was dissolved in 50 mL of ethyl ether. The organic layer was washed with water, and the hydrochloride of **1d** was formed by passing HCl gas carefully through the ethereal solution. The solid was collected and recrystallized from absolute ethanol, affording white crystals: 1.8 g (69% yield); mp 154 °C; IR (KBr) 3350–3400 cm^{-1} (OH group), 1760 cm^{-1} (C=O lactone); NMR (Me_2SO-d_6) δ 7.9 (br, 2 H exchangeable by D_2O, OH, NH^+), 5.60 (d, 1 H), 4.25 (d, 1 H), 3.2–3.4 (m, 4 H, CH_2N^+), 2.15 (m, 1 H, $CH(Me)_2$), 0.95 (dd, 6 H).

General Procedure for Acid Catalysis. (a) In Aqueous Medium: 4-Substituted 5-Hydroxy-2(5*H*)-furanones (8). Glyoxylic acid hydrate (9.2 g, 0.10 mol) and powdered morpholinium hydrochloride (13.6 g, 0.11 mol) were dispersed in 40 mL of dioxane. Water (5 mL) was added dropwise to the medium, which became homogeneous. Then 0.105 mol of freshly distilled aldehyde was added to the solution, and the mixture was maintained at room temperature for 1 h and then refluxed during 24 h. The progress of the reaction was followed by TLC in ethyl acetate/hexane (1:1). The solvent was evaporated to dryness, and the residue was extracted with ethyl ether (3 × 80 mL). The organic layer was dried over anhydrous $MgSO_4$, and the solvent was evaporated. The crude oil was purified by distillation under reduced pressure (**8a,c**) or by recrystallization from isopropyl ether (**8b**), isopropyl ether/hexane (**8d**), or acetone/chloroform (**8e**). Anal. Calcd for $C_{10}H_8O_3$ (**8e**): C, 68.17; H, 4.58. Found: C, 68 22; H, 4.42. IR ($CHCl_3$) for **8d** 1760 cm^{-1} (lactone ring), 1640, 2980 (C=CH), 3350 cm^{-1} (OH).

(b) In Ethanolic Medium: 4-Substituted 5-Ethoxy-2-(5*H*)-furanones (11). Glyoxylic acid hydrate (9.2 g, 0.10 mol) was dissolved in 50 mL absolute ethanol at 4 °C (ice bath), and 0.105 mol of freshly distilled aldehyde was added to the solution. Then powdered morpholinium hydrochloride (13.6 g, 0.11 mol) was dispersed in the medium. The mixture was allowed to stand at room temperature for 1 h and was then refluxed for 12 h. Absolute ethanol containing HCl gas (7 g of HCl in 150 mL of absolute ethanol) was added dropwise, and the mixture was refluxed for another 12 h (controlled by TLC). Then the water was removed by azeotropic distillation with toluene. The solvent was evaporated, and the residue was triturated with dry ethyl ether (3 × 80 mL). The combined ethereal extracts were washed with 50 mL of 10% potassium bicarbonate solution and 20 mL water and dried. After removal of the solvent, the crude material was distilled under reduced pressure with a Claisen flask fitted with a Vigreux column. For **11a**: IR ($CHCl_3$) 1770, 1660 cm^{-1} (unsaturated lactone ring). Anal. Calcd for $C_7H_{10}O_3$: C, 59.14; H, 7.09. Found: C, 59.21; H, 7.17.

Thermal Treatment of α,γ-Dimorpholinobutanolides 2. (a) In the Melted State (β-Elimination). A sample of **2e** was maintained at 155 °C for 15 min in an open dish. The residual oil was characterized by ^1H NMR (DCl_3): δ 7.20 (m, 5 H), 5.75 (m, 1 H), 5.40 (s, 1 H), 3.6 (m, 4 H, and s, 2 H), 2.7 (m, 4 H).

Formation of the 1,3,5-Trioxane of the α-Morpholino-β-substituted Succinaldehydic Morpholinoamide 12. The refluxing of **2e** (17.32 g, 0.05 mol) in ethanol (or THF) for one night gave, after removal of the solvent, a crude material, which was recrystallized from diisopropyl alcohol to give 6 g (34.6% yield) of crystals: mp 119.4 °C; IR (KBr) 1630 cm^{-1} (C=O amide); NMR ($CDCl_3$) δ 7.20 (s, 5 H), 2.2–3.5 (m, 21 H). Anal. Calcd for $(C_{19}H_{26}N_2O_4)_3$: C, 65.87; H, 7.57; N, 8.09. Found: C, 65.70; H, 7.71; N, 7.99.

Interconversion Reactions. (a) Hydrolysis. Refluxing **3** or **11** with concentrated HCl (2 mL/g of product) for 15 min gave quantitatively the corresponding γ-hydroxybutenolide **8**. From **2**, the same reaction conditions gave first **1** and after an additional period of refluxing (2 h) afforded the awaited **8**. For recovery of **1d**, compound **2d** (7 g, 0.0234 mol) was refluxed with 15 mL concentrated HCl for 15 min. The reaction medium was neutralized with potassium bicarbonate solution, concentrated, and extracted with $CHCl_3$. The organic layer was washed with water, dried, and evaporated to give 5 g of an oil. This oil was dissolved in 100 mL of dry ethyl ether, and the hydrochloride was precipitated by passing HCl gas carefully through the ethereal solution. The white solid was collected, washed with ethyl ether and dried in a desiccator to give 3.5 g of hydrochloride of **1d** (56% yield).

(b) Ethanolysis. A solution of 0.05 mol of **8** in 150 mL of absolute ethanol containing 7 g of HCl gas was refluxed for 12 h. After removal of the solvent, **11** was recovered as described earlier.

(c) Aminolysis. Treatment of **8a** with 1.05 equiv of morpholine in refluxing THF for 4 h gave the pure γ-morpholinobutenolide **3a** quantitatively.

3(2*H*)-Pyridazinones from 5-Functionalized 2(3*H*)-4,5-Dihydrofuranones and 2(5*H*)-furanones. (a) 2-Methyl-4-morpholino-5-isopropyl-3(2*H*)-pyridazinone (13d, R_1 = Me). To 25 mL of *n*-butanol containing **2d** (2.98 g, 0.010 mol) was added dropwise pure methylhydrazine (0.51 g, 0.011 mol), and the solution was refluxed for 12 h. The medium was evaporated to dryness to give quantitatively **13d** (R_1 = Me) as a yellow oil. The crude compound was chromatographically and spectroscopically pure: NMR ($CDCl_3$) δ 7.05 (d, 1 H), 3.60 (t, 4 H), 3.30 (s, 3 H), 3.00 (d, 1 H), 2.55 (m, 4 H), 2.0 (m, 1 H), 0.95 (dd, 6 H).

(b) 2-Methyl-5-isopropyl-3(2*H*)-pyridazinone (14d, R_1 = Me). Crude **13d** (R_1 = Me) was heated at 80 °C in concentrated HCl (1 g of solid/2 mL) for 15 min. After evaporation to dryness, the residue was extracted with $CHCl_3$. The organic layer was washed with saturated potassium bicarbonate and water, dried over anhydrous $MgSO_4$, and evaporated in vacuo, giving crude **14d** (R_1 = Me): NMR ($CDCl_3$) δ 7.75 (d, 1 H), 6.75 (d, 1 H), 3.75 (s, 3 H), 1.15 (d, 6 H).

(c) 5-Phenyl-3(2*H*)-pyridazinone (14f, R_1 = H). A solution of **3f** (1.0 g, 4 mmol) and hydrazine hydrate (0.28 g, 55 mmol) in 20 mL MeOH was refluxed for 12 h and allowed to stand at room temperature. Crude **14f** crystallized. Recrystallization from ethanol afforded white crystals: yield 75%); mp 194 °C; IR (KBr) 1670 cm^{-1} (unsaturated C=O); NMR (Me_2SO-d_6) δ 7.20 (d, 1 H), 7.4–7.9 (m, 5 H), 8.35 (d, 1 H), 9.2 (br, s, NH).

(d) 5-Methyl-3(2*H*)-pyridazinone (14a, R_1 = H). Treatment of **11a** (7.1 g, 0.05 mol) in 50 mL of 95% ethanol with hydrazine hydrate (2.5 mL, 0.05 mol) afforded crude **14a** (R_1 = H) after the

mixture was refluxed for 3 h, and this was recrystallized in water: yield 60%; ^{1}H NMR (Me_2SO-d_6) δ 7.65 (d, 1 H), 6.55 (m, 1 H), 3.25 (exchangeable by D_2O, NH), 2.05 (s, 3 H).

β-Substituted Succinaldehydic Acids. Method a: Catalytic Hydrogenation of 8. A solution of **8e** in ethyl acetate (3.5 g, 0.02 mol) was well stirred under 1 atm of hydrogen pressure with Pd as a catalyst (Engelhard, 10% Pd/C, 1 g of catalyst for 10 g of product). H_2 (1 equiv) was absorbed over a 3–4-h period. The catalyst suspension was removed by filtration. The organic layer was evaporated, and the residual oil was distilled at 190 °C under reduced pressure (0.05 mm) with a Kugelrohr distillation apparatus, giving 3 g of oil which crystallized: yield 86%; mp 77 °C; IR ($CHCl_3$) 3020 (Ph), 1780 (C=O lactone ring) 1715 cm^{-1} (C=O aldehyde); NMR ($CDCl_3$) δ 7.30 (m, 5 H), 5.9 (s, exchangeable with D_2O, OH), 3.25 (td, 1 H), 2.85 (d, 2 H).

Method b: Catalytic Hydrogenation of the γ-Ethoxybutanolides 11 and Hydrolysis. 4-Substituted 5-Ethoxy-4,5-dihydro-2(3*H*)-furanones (16). A solution of absolute ethanol containing **11** (0.05 mol in 100 mL) was hydrogenated under the same conditions as above. The residual oil was efficiently distilled under reduced pressure to give pure **16**. Purity of **16** was controlled by gas chromatography. All yields are better than 84%. Anal. Calcd for $C_7H_{12}O_3$ (**16a**): C, 58.31; H, 8.39. Found: C, 58.41; H, 8.30.

Hydrolysis of 16. Hydrolysis of **16a** (3 g, 0.021 mol) under the operating conditions described in the previous paper[1] afforded the crude oil after removal of the solvent. The distillation at 100 °C under reduced pressure (0.05 mm) with the same apparatus as above gave 2 g of a colorless oil: 66% yield; IR ($CHCl_3$) 3400 (OH), 1780 (C=O lactone), 1720 cm^{-1} (C=O aldehyde); NMR ($CDCl_3$) δ 6.45 (complex system, 2 H), 2.50 (m, 3 H), 1.1 (d, 3 H).

Registry No. **1d**·HCl, 78920-01-1; **2a**, 78920-02-2; **2b**, 78920-03-3; **2c**, 78920-04-4; **2d**, 78920-05-5; **2e**, 78920-06-6; **3a**, 78920-07-7; **3f**, 78939-67-0; **4**, 78920-08-8; **7**, 78920-09-9; **8a**, 40834-42-2; **8b**, 1575-49-1; **8c**, 78920-10-2; **8d**, 7755-27-3; **8e**, 78920-11-3; **9**, 78920-12-4; **10**, 78939-69-2; **11a**, 78920-13-5; **11b**, 78920-14-6; **11c**, 78920-15-7; **11d**, 78920-16-8; **11e**, 78920-17-9; **12**, 78920-18-0; **13d**, 78920-19-1; **14a**, 54709-94-3; **14d**, 78920-20-4; **14f**, 78920-21-5; **15b** (R = Ph), 78920-22-6; **15b** (R = Me), 61892-47-5; **16a**, 78920-23-7; **16b**, 78920-24-8; **16c**, 78920-25-9; **16d**, 78920-26-0; **16e**, 78920-27-1; **16f**, 78939-70-5; morpholine, 110-91-8; glyoxylic acid, 298-12-4; propanal, 123-38-6; butanal, 123-72-8; pentanal, 110-62-3; 3-methylbutanal, 590-86-3; benzenepropanal, 104-53-0; benzeneacetaldehyde, 122-78-1; morpholine hydrochloride, 10024-89-2; **11f**, 78920-28-2.

Reactions of Naphtho[1,8-*cd*]-1,2,3-trithiin 1,1,3,3-Tetraoxide (Naphthalene-1,8-disulfonothioic Acid Anhydrosulfide)

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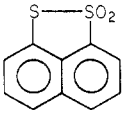
Attempts to oxidize naphtho[1,8-*cd*]-1,2,3-trithiin 1,1,3,3-tetraoxide (**5**) to the corresponding hexaoxide with oxidizing agents such as peracids, ozone, potassium permanganate, ruthenium tetraoxide, etc. were unsuccessful and led only to recovery of **5** unreacted. With the oxidizing agent HO_2^-, however, **5** reacts rapidly; the trithiin ring is cleaved and naphthalene-1-sulfinate-8-sulfonate (**6**) and naphthalene-1,8-disulfinate (**7**) are formed in approximately equal amounts. Opening of the trithiin ring in **5** also occurs readily upon treatment with triphenylphosphine or cyanide ion. With the phosphine an interesting sequence of further reactions follows the opening of the ring and results in the eventual formation of the unusual zwitterionic phosphonium salt **15**. This phosphonium salt undergoes thermal decomposition in boiling decalin to give triphenylphosphine oxide and cyclic thiosulfonate **1**. Alkaline hydrolysis of **5** occurs easily and gives disulfinate **7** plus some sulfite.

The most highly oxidized derivatives of trisulfides known to date are 1,1,3,3-tetraoxides RSO_2SSO_2R.[1] We wished, if possible, to prepare a more highly oxidized derivative, either a 1,1,2,3,3-pentaoxide [$RSO_2S(O)SO_2R$] or a 1,1,2,2,3,3-hexaoxide ($RSO_2SO_2SO_2R$), in order to ascertain its thermal stability and chemistry. Previous work[2] has suggested that oxidation of cyclic thiosulfonates **1** and **2** to the corresponding α-disulfones (1,1,2,2-tetraoxides)



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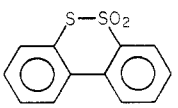

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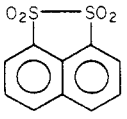

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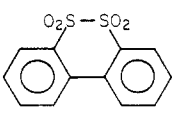

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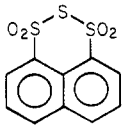
3 and **4** is considerably easier to achieve in good yield than oxidation of an acyclic aryl thiosulfonate to an α-disulfone. We felt therefore that the best chance to prepare a trisulfide hexaoxide would be to synthesize naphtho[1,8-*cd*]-1,2,3-trithiin 1,1,3,3-tetraoxide (naphthalene-1,8-disulfonothioic acid anhydrosulfide, **5**) and then to oxidize **5** with an oxidizing agent that would convert the central sulfur from >S to >SO_2.



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As it turns out, none of the many oxidizing agents tried are effective; most simply lead to recovery of unreacted starting material, while one, HO_2^-, leads to cleavage of the sulfur-containing ring. Although oxidation of **5** to the corresponding 1,2,3-trithiin 1,1,2,2,3,3-hexaoxide has not been achieved, we have found that **5** undergoes some interesting reactions with various reagents that are described and discussed in the present paper. As in the chemistry

(1) Austad, T. *Acta Chem. Scand., Ser. A* **1955**, *A29*, 241.
(2) Chau, M. M.; Kice, J. L. *J. Org. Chem.* **1978**, *43*, 914.

0022-3263/81/1946-4894$01.25/0