α-Methylene-γ-thiobutyrolactone (2-Methylenebutane-4-thiolide)

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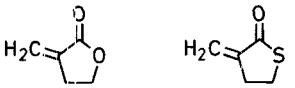
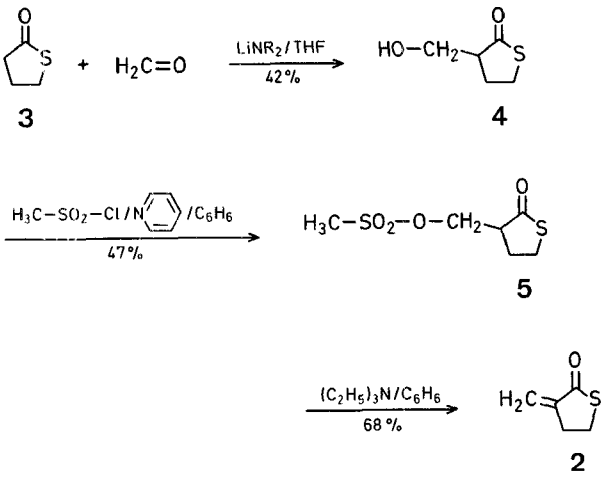
The synthesis of α-methylene-γ-butyrolactones (4-methylene-4-butanolides) has received considerable attention[1] in recent years primarily as a result of known antitumor activity associated with natural products that contain this group[2]. The tumor-inhibiting properties of these compounds have been attributed to the alkylating ability of **1** and its derivatives serving as a Michael substrates in addition reactions with biological macromolecules[2,3]. Tulipalin A (**1**) is a natural product which functions as an antifungal agent in the common tulip, *Tulipa gesneriana*[4]. We would like to report the first synthesis of the α-methylene-γ-thiobutyrolactone (2-methylenebutane-4-thiolide) structural unit (**2**).

Unlike the corresponding oxygen lactones, the α-methylene-γ-thiobutyrolactone system is reactive at three different sites including the electrophilic double bond, the labile thiol ester function, and the sulfhydryl group generated following cleavage of the thiolactone ring. Attesting to this reactivity we have found that an analytically pure sample of **2** undergoes rapid polymerization on warming to about 55°.



1 **2**

Prior to consideration of the potential utility of α-methylene-γ-thiobutyrolactones in chemotherapy, it was necessary to make the parent compound in order to assess its stability and other properties. Several synthetic approaches to **2** were attempted before a successful route was developed. Indeed, based on our present knowledge, it appears that the majority of methods[1] available for the synthesis of **1** or its derivatives will not be effective for the preparation of **2**. For example, approaches used in the synthesis of **1** or derivatives which involve formation of the methylene group prior to or during construction of the lactone ring are clearly not suitable for the preparation of **2**. Thus, we settled on a standard approach for introducing a methylene group α to a carbonyl function involving initial aldol condensation of **3** with formaldehyde to form α-hydroxymethyl-γ-thiobutyrolactone (**4**) followed by conversion to the sulfonate ester **5** and warming with triethylamine in benzene in the critical elimination step that results in the reactive double bond.



3 **4** **5** **2**

Lithium (oxygen) ester enolates prepared using various lithium amide bases have proven effective in aldol condensations with aldehydes and ketones[5]. This method has also been employed in hydroxymethylation of oxygen lactones with formaldehyde for the purpose of synthesizing α-methylene (oxygen) lactones[6]. Recently we found that lithium thiol ester enolates are sufficiently stable to be used in nucleophilic addition reactions with aldehydes or ketones[7]. From our experience lithium diisopropylamide is the preferred reagent for making thiol ester enolates. It may also be used to prepare thiolactone enolates. The lithium enolate of **3** was allowed to react with formaldehyde to give α-hydroxymethyl-γ-thiobutyrolactone (**4**), thus providing the first example of a condensation reaction of formaldehyde with a thiolactone and, more generally, the first example with the thiol ester group. Although hydroxymethylation of lithium (oxygen) lactone enolates[6] was carried out at −20° we

encountered difficulty with this approach. Greater success was experienced when the thiolactone reaction was conducted at the lower (−78°) temperatures employed earlier[5,7]. Vigorous stirring is also essential.

Base-induced elimination of a tosylate[8] or mesylate[7] using pyridine solvent at reflux temperatures has been employed previously to generate α-methylene (oxygen) lactones. This method was not useful for the preparation of the more labile α-methylene-γ-thiobutyrolactone system. Instead it was important to use only one equivalent of a stronger amine base (triethylamine) at a lower temperature (60°) in order to convert **5** to **2**. Such conditions should also prove effective when using the sulfonate elimination method in the preparation of other reactive α-methylene carbonyl systems.

α-Methylene-γ-thiobutyrolactone is stable in the refrigerator for several days. It slowly undergoes polymerization at room temperature to give a colorless solid that is insoluble in methanol, benzene or dichloromethane. Polymerization of an analytically pure sample was complete within 30 min on warming to 55°. When pure **2** was placed between two sodium chloride salt plates, polymerization was complete within 18 h at room temperature. The I.R. spectrum of this material showed a strong absorption at 1675 cm^{-1} but the peaks at 1635 and 940 cm^{-1} corresponding to the methylene double bond in **2** were greatly diminished. A 10% solution of pure **2** in methanol was stable for one week at room temperature, however, polymerization was complete within an hour when **2** was added to methanol containing 1% sodium hydrogen carbonate.

Having established the feasability of synthesizing **2** and with an understanding of the stability and properties of the α-methylene-γ-thiobutyrolactone system, we plan to extend these studies to derivatives including the development of methods for the introduction of the α-methylene-γ-thiobutyrolactone group into natural products of chemotherapeutic interest.

Preparation of α-Hydroxymethyl-γ-thiobutyrolactone (4):
α-Thiobutyrolactone (**3**; 10.2 g, 0.10 mol) in dry tetrahydrofuran (10 ml) was added over 2 min to a stirred solution of lithium diisopropylamide [prepared from diisopropylamine (10.1 g, 0.10 mol) and *n*-butyllithium (62.5 ml of 1.6 *M* solution in hexane, 0.10 mol)] in tetrahydrofuran (150 ml) at −78°. After stirring for 10 min, formaldehyde [formed by heating paraformaldehyde (30 g, 1 mol) to 150° in a stream of nitrogen] was added over a 2.5 h period. During this time the solution was maintained at −78° and agitated by very vigorous mechanical stirring. After 30 min additional stirring, the solution was quenched at −78° by dropwise addition of dilute hydrochloric acid and the solution was allowed to warm to room temperature and then filtered through celite. The filtrate was extracted with ethyl acetate (5 × 100 ml), the combined organic layers were dried (Na_2SO_4), and then concentrated under reduced pressure to give an oil that was chromatographed on silica gel using benzene/ethanol (10:1) as eluent; yield: 5.47 g (42%); b.p. 80° (bath temperature)/0.25 torr.

$C_5H_8O_2S$	calc.	C 45.43	H 6.10	S 24.26
(132.2)	found	45.35	6.15	24.34

I.R. (film): ν_{max} = 3460, 1675 cm^{-1}.

^{1}H-N.M.R. (D_2O): δ = 4.54 (s, HDO), 3.74 (d, 2H, *J* = 4 Hz), 3.49–3.16 (m, 2H), 3.00–1.85 ppm (m, 3H).

Preparation of α-Hydroxymethyl-γ-thiobutyrolactone Methanesulfonate (5):
Pyridine (4.90 g, 61.5 mmol) was added to **4** (5.10 g, 38.6 mmol) in benzene (40 ml). This was followed by methanesulfonyl chloride (8.60 g, 61.5 mmol). The solution was allowed to stand at room temperature for 24 h. It was the extracted with dilute hydrochloric acid (2 × 20 ml), the aqueous fractions were reextracted with benzene and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was chromatographed on silica gel using benzene/ethanol (10:1) as eluent. Crystallization from benzene/hexane gave colorless needles (m.p. 63–65°); yield: 3.22 g (47%). The analytical sample was obtained by a second crystallization: m.p. 65–66°.

$C_6H_{10}O_4S_2$	calc.	C 34.27	H 4.79	S 30.50
(210.3)	found	34.16	4.80	30.68

I.R. (KBr): ν_{max} = 1675, 1340, 1160 cm^{-1}

^{1}H-N.M.R. ($CDCl_3$): δ = 4.40 (d, 2H, *J* = 4 Hz), 3.56–3.21 (m, 2H), 3.02 (s, 3H), 2.88–2.03 ppm (m, 3H).

Preparation of α-Methylene-γ-thiobutyrolactone (2):
Sulfonate ester **5** (1.00 g, 4.76 mmol) and triethylamine (0.510 g, 4.97 mmol) in benzene (30 ml) were warmed to 60° and maintained there for 2 h. The benzene was evaporated at 25° under reduced pressure and the residue chromatographed on silica gel using dichloromethane/pentane (3:1) as eluent. Analytically pure material was obtained by short path distillation under reduced pressure (10^{-2} torr) at room temperature; yield: 0.37 g (68%); n_D^{26} = 1.5617.

C_5H_6OS	calc.	C 52.60	H 5.30	S 28.09
(114.2)	found	52.70	5.41	27.88

I.R. (film): ν_{max} = 1680, 1635, 940 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 5.90 (m, 1H, A of AMX_2, *J* = 0.8, 2.1 Hz), 5.35 (m, 1H, M of AMX_2, *J* = 0.8, 2.1 Hz), 3.56–2.83 (m, 4H).

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