## Alkyl-Substituted Thiolo-, Thiono-, and Dithio- $\gamma$ -butyrolactones: New Classes of Convulsant and Anticonvulsant Agents

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A series of sulfur-containing congeners have been prepared from  $\alpha$ -ethyl- $\alpha$ -methyl- $\gamma$ -butyrolactone,  $\beta$ -ethyl- $\beta$ -methyl- $\gamma$ -butyrolactone, and  $\alpha, \alpha, \beta, \beta$ -tetramethyl- $\gamma$ -butyrolactone as potential neuropharmacologic agents. The lactones were treated with benzyl mercaptide anion to form 4-(benzylthio)butyric acid, which, on treatment with trifluoroacetic acid, cyclized to yield thiololactones. The thiono- and dithiolactones were prepared by treating the corresponding lactones either with Lawesson's reagent or with phosphorus pentasulfide, respectively. As had been observed previously for the lactones, the  $\beta$ -substituted and  $\alpha, \beta$ -substituted congeners were potent convulsants that caused generalized clonic and tonic seizures in mice. The  $\alpha$ -substituted congeners were effective in inhibiting pentylenetetrazole-induced seizures in mice.  $\alpha$ -Ethyl- $\alpha$ -methylthiolo- $\gamma$ -butyrolactone showed an increase in potency over the congeneric  $\alpha$ -ethyl- $\alpha$ -methyl- $\gamma$ -butyrolactone and, additionally, was effective against maximal electroshock seizures. In no cases was a convulsant converted to an anticonvulsant or vice versa by sulfur-for-oxygen substitution.

Alkyl-substituted  $\gamma$ -butyrolactones (GBLs) are known to be neuropharmacologically active agents that exhibit either convulsant or anticonvulsant activities dependent on their substitution pattern.<sup>1-5</sup>  $\alpha$ -Substituted GBLs are effective in inhibiting pentylenetetrazole (PTZ)-induced seizures in experimental animals, whereas  $\beta$ - and  $\alpha$ , $\beta$ substituted GBLs cause convulsive seizures that can be blocked by drugs which are effective against petit mal seizures, such as ethosuximide (ESM), as well as by  $\alpha$ substituted GBLs.

In the course of our structure-activity studies of substituted GBLs we became interested in what effects heteroatom substitution might have on neuropharmacological activity. It is well-known that the unsubstituted sulfurcontaining congener thiolo- $\gamma$ -butyrolactone (3d) (Scheme I) is a potent convulsant,<sup>6,7</sup> whereas  $\gamma$ -butyrolactone (1d) causes only mild sedation and nonconvulsive seizures.<sup>8</sup> That this seemingly minor sulfur-for-oxygen substitution led to such a striking change in the activity of GBL suggested to us that differences in activity might also be observed between the alkyl-substituted GBLs and their sulfur-containing congeners. To explore this possibility, we have prepared a series of sulfur-containing analogues of GBL, replacing with sulfur either the endocyclic oxygen (thiolo-GBLs) (**3a**-c), the exocyclic oxygen (thiono-GBLs) (4a-c), or both oxygens (dithio-GBLs) (5a-c). The compounds have been screened for either convulsant or anticonvulsant activity in mice.

**Chemistry.** All the sulfur-containing congeners were prepared from their corresponding GBLs (1a-c) (Scheme I). The thiono-GBLs (4a-c) and dithio-GBLs (5a-c) were obtained directly from the GBLs on treatment with either 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiaphosphetane, 2,4disulfide (Lawesson's reagent),<sup>9,10</sup> or phosphorus pentasulfide.<sup>11</sup> respectively. Attempts to convert either  $\alpha$ -

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ethyl- $\alpha$ -methyl-GBL ( $\alpha$ -EMGBL, 1a) or  $\alpha, \alpha, \beta, \beta$ -tetramethyl-GBL (TMGBL, 1c) to their thiolo- analogues via the HBr-thiourea method<sup>12</sup> were unsuccessful. However, all three thiolo-GBLs (**3a**-c) could be obtained by a method described by Lumma et al.<sup>13</sup> in which treatment of the GBLs with benzyl mercaptide anion yielded the corresponding 4-(benzylthio)butyric acids (**2a**-c), which, in the presence of trifluoroacetic anhydride, cyclized to thiolo-GBLs (**3a**-c). This method resulted in low yields (13-20%) and was extremely unpleasant to carry out due to the odor of benzyl mercaptan. Thiolo- $\alpha$ -EMGBL (**3a**) was more conveniently prepared by treatment of  $\alpha$ -EMGBL (**1a**) with potassium thioloacetate in dimethyl-

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acetamide.<sup>14</sup> Both  $\beta$ -EMGBL (1b) and TMGBL (1c) failed to yield the desired thiolo-GBLs under these conditions.

Characterization of these congeners is achieved on the basis of <sup>1</sup>H NMR, IR, and UV spectra. Compounds with endocyclic sulfur atoms (thiolo- and dithio-GBLs) can be distinguished from those with endocyclic oxygen due to an upfield shift of around 1 ppm in the resonances of the protons on the  $\gamma$ -carbon of the sulfur-containing compounds. The thiolo-GBLs exhibit strong infrared C==O stretching bands at around 1700 cm<sup>-1</sup>. Those compounds with exocyclic sulfur (thiono- and dithio-GBLs) exhibit strong UV bands: thiono-GBLs at around 250 nm ( $\epsilon$  11000) and dithio-GBLs at around 312 nm ( $\epsilon$  13000). Thiolo-GBLs exhibit UV absorbance at around 235 nm ( $\epsilon$  3700). All elemental analyses are in good agreement with calculated values.

## **Pharmacological Results and Discussion**

All of the prepared compounds were screened for convulsant activity in mice. Solutions of the compounds in 30% polyethylene glycol were administered by ip injection at varying dose levels up to 500 mg/kg. Seizures were monitored by observation for the onset of myoclonic twitches, generalized clonic seizures, and tonic seizures. Those compounds that did not produce convulsant activity were screened for anticonvulsant activity against pentylenetetrazole. Anticonvulsant activity was determined by a drug's ability to either delay the onset of clonic seizures or completely block clonic or tonic seizures when given 30 min prior to ip administration of 100 mg/kg of pentylenetetrazole. Time-response relationships for these compounds have not been determined, and all tests were performed at 30 min, since previous studies with GBLs and observation of the toxicities of thio-GBLs indicate that at 30 min the drug's effects are near maximal. Screening against other convulsants was likewise performed by administration of the convulsant challenge 30 min following anticonvulsant treatment. Since the thiono- and dithio-GBLs were extremely unpleasant to work with due to their foul odors, only small quantities were prepared and only a limited range of dosages were tested. Thiolo- $\alpha$ -EMGBL (3a) was tested against maximal electroshock seizures using the protocol described by Swinyard and co-workers.<sup>15</sup> The neurotoxicity of 3a was evaluated by using the standard rotorod test.<sup>16</sup>

The unsubstituted cogeners, thiono-GBL (4d) and dithio-GBL (5d), were subjected to very preliminary investigation only. Thiono-GBL was found to be a potent convulsant, causing generalized clonic and tonic seizures. Administration of 500 mg/kg of dithio-GBL had little effect on the mice, causing very brief periods of staring and drowsiness but otherwise not affecting normal activity. Treatment of mice with dithio-GBL had no effect on PTZ-induced seizures. Although the neuropharmacology of 4d and 5d was not more fully investigated, it appears that the pharmacology of these unsubstituted congeners differs considerably from that of the substituted compounds, as has already been reported for GBLs<sup>1</sup> and is reported here for thiolo-GBLs.

All of the  $\beta$ - and  $\alpha$ , $\beta$ -substituted congeners were found to be convulsants that caused generalized clonic seizures

Table I.	Dose-Response	Data of	Convulsant	β- and
$\alpha,\beta$ -Subst	ituted Congener	rs <sup>a</sup>		

	dose		frac experio seizu	tion encing ures
compd	mg/kg	mmol/kg	clonic	tonic
1 <b>b</b> <sup>b</sup>	12.5	0.10	0/4	0/4
	18	0.14	3/4	0/4
	30	0.23	3/4	2/4
	50	0.39	4/4	4/4
3b	3.1	0.021	1/3	0/3
	5.0	0.035	3/4	0/4
	6.25	0.043	3/3	1/3
	10	0.069	5/5	5/5
	12.5	0.087	3/3	3/3
	15	0.10	5/5	5/5
3c	25	0.16	5/5	3/5
	50	0.32	5/5	5/5
	100	0.63	6/6	6/6
4b	12.5	0.087	0/3	0/3
	25	0.17	3/3	0/3
	50	0.35	4/4	2/4
	100	0.69	3/3	3/3
<b>4c</b>	100	0.63	5/5	0/5
	250	1.6	3/3	0/3
5b	12.5	0.078	1/2	0/2
	25	0.16	8/8	3/8
	50	0.31	5/5	5/5
	75	0.47	5/5	5/5
	100	0.62	5/5	5/5
5c	25	0.14	5/5	5/5
	50	0.29	5/5	5/5

<sup>a</sup>Female CF1 strain mice treated by ip injection. <sup>b</sup> Data from ref 1.

(Table I). The most potent convulsant of the group was thiolo- $\beta$ -EMGBL (3b), which had approximate CD<sub>50</sub>'s of 4 mg/kg for clonic and 7 mg/kg for tonic seizures. All the convulsant compounds except thiono-TMGBL (4c) produced clonic seizures at dose levels below 25 mg/kg and tonic seizures below 50 mg/kg. With compound 4c, the weakest convulsant tested, all animals experienced clonic seizures at dose levels below 100 mg/kg and no tonic seizures were observed at 250 mg/kg, the highest dose tested.

All the  $\alpha$ -substituted congeners exhibited some form of anticonvulsant activity against PTZ-induced seizures (Table II). Thiono- and dithio- $\alpha$ -EMGBL (4a and 5a) displayed moderate activity. At a dose of 250 mg/kg, 4a offered some, but not complete, protection against both clonic and tonic seizures. Compound 5a slightly delayed the onset of clonic seizures at a dose of 100 mg/kg and offered some protection against tonic seizures at 500 mg/kg. Thiolo- $\alpha$ -EMGBL (3a) was the most potent anticonvulsant tested, delaying the onset of clonic seizures at doses as low as 10 mg/kg and completely protecting against clonic and tonic seizures at 250 mg/kg.

In experiments not shown, similar effects against seizures induced by 50 mg/kg of  $\beta$ -EMGBL (1b) were observed. Compound 5a had only a slight activity at 500 mg/kg, and 3a completely blocked tonic seizures and partially protected against clonic seizures at 250 mg/kg.

Of particular interest from a therapeutic standpoint was the effect of thiolo- $\alpha$ -EMGBL (3a) on maximal electroshock seizures (MES). We found that 3a was able to protect mice against MES with an ED<sub>50</sub> of approximately 230 mg/kg. This compares favorably with the clinically useful anticonvulsant valproic acid, which has a reported ED<sub>50</sub> of 272 mg/kg against MES.<sup>17</sup> In contrast, neither

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Table II. Dose-Response Data of Anticonvulsant a-Substituted Congeners against 100 mg/kg of Pentylenetetrazolea

	dose		mean time to seizure, <sup>b,c</sup> s		
compd	mg/kg	mmol/kg	clonic	tonic	
control <sup>d</sup>			$56 \pm 20 (25/25)$	$324 \pm 202 (21/25)$	
1a	62.5	0.49	$150 \pm 18^{e} (4/4)$	$1015 \pm 65^{e} (4/4)$	
	125	0.98	$365 \pm 192 (4/4)$	$1078 \pm 222^{e} (4/4)$	
	250	2.0	$163 \pm 16^{e} (4/4)$	$844 \pm 362 (4/4)$	
	375	2.9	(0/4)	(0/4)	
	500	3.9	(0/4)	(0/4)	
3a	10	0.069	$110 \pm 25^{e} (3/3)$	$423 \pm 49 (3/3)$	
	25	0.17	$73 \pm 16 (3/3)$	$500 \pm 113 (3/3)$	
	50	0.35	$142 \pm 24^{e} (3/3)$	$1835 \pm 837 (3/3)$	
	75	0.52	$592 \pm 217^{e} (3/3)$	3072 (1/3)	
	100	0.69	$416 \pm 253^{e} (5/6)$	$1708 \pm 468^{e} (2/6)$	
	250	1.7	(0/3)	(0/3)	
	500	3.5	(0/3)	(0/3)	
4a	250	1.7	$155 \pm 33^{e} (3/5)$	$341 \pm 140 \ (3/5)$	
5a	100	0.62	$87 \pm 29 (5/5)$	$728 \pm 223 (5/5)$	
	500	3.1	$218 \pm 24^{e} (3/5)$	1200 (1/5)	

<sup>a</sup>Female CF1 strain mice were pretreated with the anticonvulsant 30 min prior to PTZ challenge. <sup>b</sup>Numbers represent mean time  $\pm$  SD for the animals that experienced seizures. <sup>c</sup>Numbers in parentheses indicate number of animals experiencing seizures/number of animals tested. <sup>d</sup>No pretreatment of animals. No difference was observed when animals were pretreated with carrier. <sup>e</sup>Significantly different from control by Students t test, p < 0.01.

ethosuximide nor  $\alpha$ -EMGBL (1a) is effective against MES. Using the rotorod test for acute toxicity, we found that **3a** has a TD<sub>50</sub> of approximately 350 mg/kg, resulting in a therapeutic index of 1.5, compared to 1.6 for valproic acid.<sup>17</sup> Thus, substitution of a sulfur for the ring oxygen in 1a results in both an increase in anticonvulsant potency and a broader spectrum of anticonvulsant activity.

To address whether the cyclic or the ring-opened compounds were responsible for the observed activities, we investigated the stabilities of solutions of thiololactones 3a and 3b, thionolactones 4a and 4b, and dithiolactones 5a and 5b. Hydrolysis of thiololactones results in 4mercaptobutyric acids with concomitant loss of UV absorbance at 235 nm. Thionolactones undergo hydrolysis to yield 4-hydroxythionobutyric acids. Thiono acids are known<sup>19</sup> to readily tautomerize to thiolo acids, resulting in loss of absorbance at 250 nm. Similarly, hydrolysis of dithiolactones results in loss of absorbance at 312 nm. We found that in phosphate buffer at pH 7.4, none of these compounds underwent significant hydrolysis either at 23 °C over a 4-h period or at 37 °C over a 1-h period. Although without metabolic studies we cannot rule out in vivo hydrolysis of the lactone rings, the above results suggest that in the absence of such metabolic activity the primary chemical species in vivo are the cyclic compounds.

The results we have obtained are consistent with the general observation of Klunk et al.<sup>1-3</sup> that  $\alpha$ -substituted GBLs are anticonvulsant and  $\beta$  and  $\alpha$ , $\beta$ -substituted GBLs are convulsant. Heteroatom substitution does not seem to affect this pattern. The similarity of activity against PTZ-induced clonic seizures of these drugs with the GBLs suggests that the actions of these congeners are mediated by the same mechanisms which mediate the activities of the GBLs. Both the convulsant and anticonvulsant GBLs are believed to exert their effects via a common molecular receptor located adjacent to a  $\gamma$ -aminobutyric acid regulated chloride channel.<sup>3,18</sup> It has been demonstrated that  $\alpha$ -EMGBL (1a) and  $\beta$ -EMGBL (1b) both bind to such a receptor, the putative picrotoxinin receptor in rat brain.<sup>20,21</sup>

Studies are currently under way to investigate the interactions of these sulfur-containing congeners with this receptor.

## **Experimental Section**

The GBLs (1a-c) were prepared as described.<sup>1-3</sup>  $\beta$ -EMGBL (1b) was prepared as an approximately 6:1 mixture of 1b and  $1a^{22}$ and was used without further purification. Dihydro-2(3H)furanthione (4d) and dihydro-2(3H)-thiophenethione (5d) were prepared by literature methods.9 Potassium thiolacetate and benzyl mercaptan were obtained from Aldrich Chemical Company, Milwaukee, WI. <sup>1</sup>H NMR spectra for all compounds except 2a-c were recorded on a Varian Associates XL-300 FT-NMR spectrometer at 300 MHz. <sup>1</sup>H NMR spectra of 2a-c were recorded on a Varian Associates T-60 NMR spectrometer at 60 MHz. Samples were dissolved in CDCl<sub>3</sub>, and chemical shifts are reported as  $\delta$  values in ppm relative to tetramethylsilane as an internal standard. IR spectra were recorded on a Perkin-Elmer 710B spectrophotometer. UV spectra were recorded in 95% EtOH on a Beckman DU-8 spectrophotometer. Melting points were measured in sealed evacuated capillary tubes on a Thomas-Hoover melting point apparatus and are reported uncorrected. Thin-layer chromatography (TLC) was performed on 250-µm-thick silica gel G plates obtained from Analtech, Inc., Newark, DE, using 9:1 hexanes/EtOAc as eluting solvent. Dry-column grade silica gel was obtained from Universal Scientific, Inc., Atlanta, GA. Sublimations and bulb-to-bulb distillations were performed on an Aldrich Kugelrohr apparatus at 0.2 mmHg with a bath temperature of 75 °C. Microanalyses were carried out by Micro-Analysis, Inc., Wilmington, DE.

**Pharmacological Screening.** Female CF1 strain mice (6-8 weeks old, 20-25 g) obtained from Sasco (Omaha, NE) were used for all studies. The drugs were dissolved or suspended in 30% polyethylene glycol and administered by ip injection in a volume of 10  $\mu$ L/g. Seizures were monitored by observation for the onset of myoclonic twitches, generalized clonic seizures, and tonic seizures. Those drugs screened as anticonvulsants were given 30 min prior to ip administration of 100 mg/kg of PTZ. No significant effect was observed for vehicle-treated controls.

**Dihydro-3-ethyl-3-methyl-2(3H)-thiophenone (3a).** Utilizing a method described by Gerecke et al.,<sup>14</sup> a mixture of 8.90 g (69.4 mmol) of 1a and 12.4 g (109 mmol) of potassium thiolacetate in 50 mL of N,N-dimethylacetamide was heated at 150–160 °C with stirring for 4 h. The dark-brown mixture was partitioned between hexane (200 mL) and water (200 mL). The aqueous phase

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was further extracted with two 100-mL portions of hexane, and the combined organic extract was washed with water (100 mL) followed by saturated NaCl (50 mL), then dried over Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed, and the red residue was distilled in vacuo to yield 7.80 g (78%) of **3a** as a colorless liquid: bp 59–61 °C/0.5 mmHg; <sup>1</sup>H NMR 3.24 (t, 2, J = 7 Hz,  $\gamma$ -CH<sub>2</sub>), 2.26–1.97 (m, 2,  $\beta$ -CH<sub>2</sub>), 1.64–1.52 (m, 2, CH<sub>2</sub>CH<sub>3</sub>), 1.12 (s, 3, CH<sub>3</sub>), 0.90 (t, 3, J= 8 Hz, CH<sub>2</sub>CH<sub>3</sub>); IR (neat) 1700 (C==0, thiolester) cm<sup>-1</sup>; UV  $\lambda_{max}$ 234 nm (log  $\epsilon$  3.58). A second distillation yieled an analytical sample. Anal. (C<sub>7</sub>H<sub>12</sub>OS) C, H, S.

Dihydro-4-ethyl-4-methyl-2(3H)-thiophenone (3b). According to the method of Lumma, Dutra, and Voeker,<sup>13</sup> 6.6 mL (7.0 g, 56 mmol) of benzyl mercaptan (BzSH) was added, with cooling and stirring, to a suspension of 1.36 g (57 mmol) of NaH in 10 mL of dimethylformamide (DMF). To the cooled suspension was added 2.45 g (19.1 mmol) of 1b, and the mixture was then stirred at 135 °C for 18 h. After cooling, it was acidified with concentrated HCl and ice and extracted with ether. The ether extract was washed with water, then extracted into 10% K<sub>2</sub>CO<sub>3</sub>. The base extract was cooled in an ice bath, acidified with 20% HCl, and extracted into ether. The ether extract was washed with water followed by saturated NaCl, and dried over Na<sub>2</sub>SO<sub>4</sub>. Removal of the solvent yielded crude 3-ethyl-3-methyl-4-(benzylthio)butyric acid (**2b**) as an oil: <sup>1</sup>H NMR 9.66 (br s, 1, COOH), 7.04 (s, 5, ArH), 3.60 (s, 2 ArCH<sub>2</sub>), 2.49 (s, 2, SCH<sub>2</sub>C), 2.28 (s, 2, CCH<sub>2</sub>COOH), 1.7-1.2 (m, 2, CH<sub>2</sub>CH<sub>3</sub>), 0.98 (s, 3, CH<sub>3</sub>), 0.77 (t, 3, J = 6 Hz,  $CH_2CH_3$ ).

The crude acid was cooled in an ice bath while trifluoroacetic anhydride (5 mL) was added dropwise. The mixture was stirred at room temperature for 30 min, then at reflux for 30 min. The mixture was poured into ice (50 mL) and extracted into ether. The ether extract was washed with 5% K<sub>2</sub>CO<sub>3</sub> until the washings were basic to litmus, then washed with water followed by saturated NaCl, and dried over Na<sub>2</sub>SO<sub>4</sub>. Removal of solvent followed by bulb-to-bulb distillation, chromatography on silica gel using hexanes/CH<sub>2</sub>Cl<sub>2</sub> (2:1) as eluent, and a second distillation yielded 373 mg (14%) of **3b** as a colorless oil: TLC,  $R_f = 0.45$ ; <sup>1</sup>H NMR 3.26 (d, 1, J = 11 Hz,  $\gamma$ -CH<sub>2</sub>), 3.09 (d, 1, J = 11 Hz,  $\gamma$ -CH<sub>2</sub>), 2.45 (d, 1, J = 16 Hz,  $\alpha$ -CH<sub>2</sub>), 2.34 (d, 1, J = 16 Hz,  $\alpha$ -CH<sub>2</sub>), 1.59 (q, 2, J = 7 Hz,  $CH_2$ CH<sub>3</sub>), 1.21 (s, 3, CH<sub>3</sub>), 0.95 (t, 3, J = 7 Hz, CH<sub>2</sub>CH<sub>3</sub>); IR (neat) 1710 (C=O, thiol ester) cm<sup>-1</sup>; UV  $\lambda_{max}$  236 nm (log  $\epsilon$  3.56). Anal. (C<sub>7</sub>H<sub>12</sub>OS) C, H, S.

Dihydro-3,3,4,4-tetramethyl-2(3*H*)-thiophenone (3c). As described above, 1.16 g (8.13 mmol) of 1c was treated with 496 mg (21 mmol) of NaH and BzSH (2.5 g, 20 mmol) in DMF (10 mL) to obtain crude 2,2,3,3-tetramethyl-4-(benzylthio)butyric acid (2c): <sup>1</sup>H NMR 11.1 (br s, 1, COOH), 7.24 (s, 5, ArH), 3.68 (s, 2, ArCH<sub>2</sub>), 2.62 (s, 2, SCH<sub>2</sub>C), 1.16 (s, 6, CH<sub>3</sub>), 1.03 (s, 6, CH<sub>3</sub>).

Treatment of **2c** with trifluoroacetic anhydride (5 mL), as described above, gave **3c**, which was purified by recrystallization from EtOH/H<sub>2</sub>O followed by sublimation to yield 170 mg (13%) of colorless needles: mp 131–137 °C dec; <sup>1</sup>H NMR 3.06 (s, 2,  $\gamma$ -CH<sub>2</sub>), 1.09 (s, 6, CH<sub>3</sub>), 1.02 (s, 6, CH<sub>3</sub>); IR (neat) 1690 (C=O, thiol ester) cm<sup>-1</sup>; UV  $\lambda_{max}$  235 nm (log  $\epsilon$  3.57). Anal. (C<sub>8</sub>H<sub>14</sub>OS) C, H, S.

General Procedure for Preparation of Thiono-GBLs (4a-c) and Dithio-GBLs (5a-c). The appropriate GBL (1a-c) was treated either with Lawesson's reagent<sup>9,10</sup> or with  $P_4S_{10}^{11}$  in xylenes at 130 °C for 18 h. The crude reaction mixtures were filtered through silica gel and eluted with  $CH_2Cl_2$ . After removal of the solvent in vacuo the products were purified as described below.

**Dihydro-3-ethyl-3-methyl-2(3H)-furanthione (4a).** Compound **4a** was prepared from 2.04 g (15.9 mmol) of **1a** and 3.22 g (8.66 mmol) of Lawesson's reagent in xylenes (25 mL). The yellow oil obtained was chromatographed on silica gel using hexanes/benzene (3:1) as eluent. The material at  $R_f = 0.36$  was distilled bulb-to-bulb to yield 596 mg (26%) of **4a** as a pale-yellow oil. A second distillation yielded an analytical sample: <sup>1</sup>H NMR 4.55 (t, 2, J = 7 Hz,  $\gamma$ -CH<sub>2</sub>), 2.29–2.00 (m, 2,  $\beta$ -CH<sub>2</sub>), 1.76–1.60 (m, 2, CH<sub>2</sub>CH<sub>3</sub>), 1.29 (s, 3, CH<sub>3</sub>), 0.95 (t, 3, J = 7 Hz, CH<sub>2</sub>CH<sub>3</sub>); UV  $\lambda_{max}$  250 nm (log  $\epsilon$  4.02). Anal. (C<sub>7</sub>H<sub>12</sub>OS) C, H, S.

**Dihydro-4-ethyl-4-methyl-2(3H)-furanthione (4b).** Compound **4b** was prepared from 2.26 g (17.6 mmol) of 1**b** and 3.58 g (9.61 mmol) of Lawesson's reagent in xylenes (25 mL). The yellow oil obtained was distilled bulb-to-bulb, then chromatographed on silica gel using hexanes/benzene (3:1) as eluent. The material at  $R_f = 0.39$  was twice distilled bulb-to-bulb to yield 556 mg (22%) of 4**b** as a pale-yellow oil: <sup>1</sup>H NMR 4.39 (d, 1, J = 9 Hz,  $\gamma$ -CH<sub>2</sub>), 4.32 (d, 1, J = 9 Hz,  $\gamma$ -CH<sub>2</sub>), 2.89 (d, 1, J = 18 Hz,  $\alpha$ -CH<sub>2</sub>), 2.84 (d, 1, J = 18 Hz,  $\alpha$ -CH<sub>2</sub>), 1.52 (q, 2, J = 7 Hz,  $CH_2$ CH<sub>3</sub>), 1.15 (s, 3, CH<sub>3</sub>), 0.92 (t, 3, J = 7 Hz, CH<sub>2</sub>CH<sub>3</sub>); UV  $\lambda_{max}$  249 nm (log  $\epsilon$  4.05). The product was contaminated with around 15% of 4a (determined by NMR). Anal. (C<sub>7</sub>H<sub>12</sub>OS) C, H, S.

Dihydro-3,3,4,4-tetramethyl-2(3H)-furanthione (4c). Compound 4c was prepared from 3.60 g (25 mmol) of 1c and 5.10 g (14 mmol) of Lawesson's reagent in xylenes (30 mL). The sticky yellow solid obtained was sublimed, then chromatographed on silica gel using hexanes/EtOAc (9:1) as eluent. The material at  $R_f = 0.42$  was recrystallized from EtOH/H<sub>2</sub>O to yield 1.3 g (33%) of 4c as off-white needles. An analytical sample was obtained by sublimation: mp 121–122 °C; <sup>1</sup>H NMR 4.27 (s, 2,  $\gamma$ -CH<sub>2</sub>), 1.16 (s, 6, CH<sub>3</sub>), 1.03 (s, 6, CH<sub>3</sub>); UV  $\lambda_{max}$  248 nm (log  $\epsilon$  4.07). Anal. (C<sub>8</sub>H<sub>14</sub>OS) C, H, S.

**Dihydro-3-ethyl-3-methyl-2(3H)-thiophenethione (5a).** Compound **5a** was prepared from 2.19 g (17.1 mmol) of **1a** and 5.22 g (11.7 mmol) of  $P_4S_{10}$  in xylenes (20 mL). The orange oil obtained was chromatographed on silica gel using hexanes/benzene (3:1) as eluent. The material at  $R_f = 0.56$  was collected to yield 1.43 g (52%) of **5a** as an orange oil. It was twice distilled bulb-to-bulb in order to obtain an analytical sample: <sup>1</sup>H NMR 3.33 (t, 2, J = 7 Hz,  $\gamma$ -CH<sub>2</sub>), 2.47-2.21 (m, 2,  $\beta$ -CH<sub>2</sub>), 1.76-1.60 (m, 2, CH<sub>2</sub>CH<sub>3</sub>), 1.21 (s, 3, CH<sub>3</sub>), 0.93 (t, 3, J = 8 Hz, CH<sub>2</sub>CH<sub>3</sub>); UV  $\lambda_{max}$  312 nm (log  $\epsilon$  4.13),  $\lambda_{max}$  221 nm (log  $\epsilon$  3.44). Anal. (C<sub>7</sub>H<sub>12</sub>S<sub>2</sub>) C, H, S.

**Dihydro-4-ethyl-4-methyl-2(3H)-thiophenethione (5b).** Compound **5b** was prepared from 2.03 g (15.8 mmol) of 1**b** and 4.13 g (9.30 mmol) of  $P_4S_{10}$  in xylenes (20 mL). The yellow oil obtained was twice chromatographed on silica gel using hexanes/benzene (10:1) as eluent. The material at  $R_f = 0.59$  was distilled bulb-to-bulb to yield 580 mg (23%) of **5b** as an orange oil: <sup>1</sup>H NMR 3.49 (d, 1, J = 11 Hz,  $\gamma$ -CH<sub>2</sub>), 3.28 (d, 1, J = 11 Hz,  $\gamma$ -CH<sub>2</sub>), 2.90 (s, 2,  $\alpha$ -CH<sub>2</sub>), 1.59 (q, 2, J = 7 Hz, CH<sub>2</sub>CH<sub>3</sub>), 1.21 (s, 3, CH<sub>3</sub>), 0.96 (t, 3, J = 7 Hz, CH<sub>2</sub>CH<sub>3</sub>); UV  $\lambda_{max}$  312 nm (log  $\epsilon$  4.13),  $\lambda_{max}$  221 nm (sh). Anal. (C<sub>7</sub>H<sub>12</sub>S<sub>2</sub>) C, H, S.

**Dihydro-3,3,4,4-tetramethyl-2(3H)-thiophenethione (5c).** Compound **5c** was prepared from 760 mg (5.1 mmol) of 1c and 700 mg (1.6 mmol) of  $P_4S_{10}$  in xylenes (10 mL). The yellow oil obtained was chromatographed on silica gel using hexanes/ benzene (3:1) as eluent. The material at  $R_f$  0.62 was collected to yield 320 mg (36%) of **5c** as a yellow solid. An analytical sample was prepared by sublimation: mp 140–142 °C; <sup>1</sup>H NMR 3.20 (s, 2,  $\gamma$ -CH<sub>2</sub>), 1.11 (s, 12, CH<sub>3</sub>); UV  $\lambda_{max}$  313 nm (log  $\epsilon$  4.14),  $\lambda_{max}$  221 nm (log  $\epsilon$  3.46). Anal. (C<sub>8</sub>H<sub>14</sub>S<sub>2</sub>) C, H, S.

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