Synthesis and Reactions of 4-Dimethylsulfuranylidene-2,3-dioxotetrahydrofuran Derivatives

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The cyclic sulfonium ylides, 4-dimethylsulfuranylidene-2,3-dioxotetrahydrofuran derivatives (**8**), were synthesized in good yields by reactions of methyl and ethyl dimethylsulfuranylidenepyruvates (**3** and **4**) with carbonyl compounds. The reactions of **8** with *p*-toluenesulfonyl chloride and benzoyl chloride gave 4-methylthio-3-(*p*-toluenesulfonyloxy)- and 4-methylthio-3-benzoyloxy-2-oxo-2,5-dihydrofuran derivatives respectively in high yields. The ylides (**8**) reacted with mercaptans to afford 4-substituted products (**14**—**16**), whereas, on the reactions with thiourea, the demethylation of the dimethylsulfonium group proceeded exclusively.

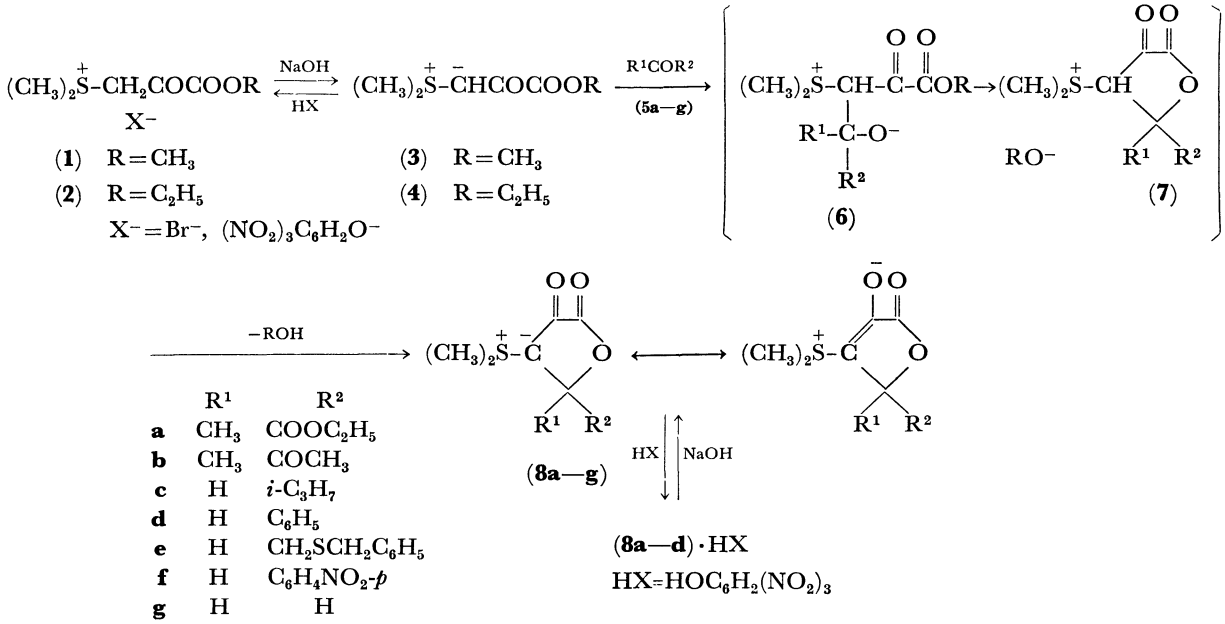
Recently, a number of carbonyl-stabilized sulfonium ylides have been synthesized and their properties studied.[1-3] These ylides are of interest because reactions using them provide useful methods for the syntheses of many organic compounds.[1,2,4,5] Among the synthetic methods of cyclic sulfonium ylides, the conversion of simple carbonyl-stabilized sulfonium ylides into cyclic sulfonium ylides, such as 3-dimethylsulfuranylidene-2,4,5-pyrrolidinetrione and 5-dimethylsulfuranylidene-2,6-diacetyl-2,6-dimethyl-4-oxo-1,3-dioxane, have been reported only by Howard[6] and Payne.[7]

In the course of the synthetic study of sulfonium ylides in our laboratory,[5] the cyclic sulfonium ylides, 4-dimethylsulfuranylidene-2,3-dioxotetrahydrofuran derivatives (**8**), were successfully synthesized by the reactions of methyl and ethyl dimethylsulfuranylidenepyruvates (**3** and **4**), and their reactivity was investigated.

Synthesis of 8. The sulfonium ylides, **3** and **4**, were prepared from the corresponding sulfonium bromides or picrates (**1** and **2**) by a procedure similar to that used for ordinary carbonyl-stabilized sulfonium ylides.[2] The use of stable sulfonium picrates (**1** and **2**, $X=(NO_2)_3C_6H_2O$) was advantageous for this conversion, since the corresponding bromides (**1** and **2**, X=Br)[8] were very hygroscopic and were less stable compounds which decomposed slowly upon exposure to air.

The treatment of **2** ($X=(NO_2)_3C_6H_2O$) with 1 equivalent of 50% aqueous sodium hydroxide and saturated potassium carbonate solution in methylene chloride gave ethyl dimethylsulfuranylidenepyruvate (**4**) as pale yellow hygroscopic crystals. The IR spectrum showed bands at 1720 and 1550 cm^{-1} attributable to the ester and the ylide carbonyl group[9] respectively. The NMR spectrum was consistent with the structure of **4**; a singlet at δ 4.68 (1H) for the methine proton and a singlet at δ 3.00 (6H) for the two methyl groups attached to the sulfonium group. In a similar way, **3** was prepared from the corresponding sulfonium salt (**1**) in a 64% yield. The treatment of **3** and **4** with picric acid in ethanol yielded the corresponding sulfonium picrates quantitatively.

The reactions of **3** and **4** with carbonyl compounds were carried out in expectation of the formation of 4-dimethylsulfuranylidene-2,3-dioxotetrahydrofuran derivatives (**8**) *via* the intermediate betaine (**6**), which would be cyclized by an intramolecular nucleophilic



(**1**) R=CH_3 (**3**) R=CH_3
(**2**) R=C_2H_5 (**4**) R=C_2H_5
X^-=Br^-, $(NO_2)_3C_6H_2O^-$

(**6**) (**7**)

	R^1	R^2
a	CH_3	$COOC_2H_5$
b	CH_3	$COCH_3$
c	H	*i*-C_3H_7
d	H	C_6H_5
e	H	$CH_2SCH_2C_6H_5$
f	H	$C_6H_4NO_2$-*p*
g	H	H

Scheme 1.

attack of the alkoxide anion on the alkoxycarbonyl group.

The reaction of **4** with ethyl pyruvate proceeded at room temperature. However, an attempt to isolate the new sulfonium ylide directly from the reaction mixture failed. The addition of picric acid to the mixture gave yellow crystals (mp 142—143 °C (dec)), whose elemental analysis agreed with the expected picrate of **8a**. The IR spectrum showed the characteristic bands of a five-membered lactone and an ester at 1790 and 1775 cm^{-1}. The picrate in methylene chloride was treated with 50% aqueous sodium hydroxide to give 5-ethoxycarbonyl-4-dimethylsulfuranylidene-5-methyl-2,3-dioxotetrahydrofuran (**8a**) (mp 132—134 °C (dec)), which was then recrystallized from ethanol–ether. The ylide (**8a**) reverted to the picrate quantitatively by means of picric acid in ethanol. The IR spectrum showed an absorption at 1620 cm^{-1} attributable to the ylide carbonyl,[9] and the NMR spectrum (δ, in $CDCl_3$) showed two singlets, at 3.30 (3H) and 3.14 (3H), ascribable to the two methyl groups of the sulfonium group. The nonequivalence of the two methyl groups at the sulfonium group was observed also in DMSO-d_6 or at temperature between 30 and 100 °C. It may be due to the assymentric carbon (C_5).

In a similar manner, the reactions of **4** with carbonyl compounds (**5b—d**) gave the corresponding new sulfonium ylides (**8b—d**), which were isolated as their picrates.

The reaction of **4** with benzylthioacetaldehyde in methanol precipitated the new sulfonium ylide (**8e**) as crystals (mp 147—148 °C (dec)) directly from the reaction mixture. The structural assignment of **8e**

Table 1. Reactions of methyl and ethyl dimethylsulfuranylidenepyruvates(**3** and **4**) with carbonyl compounds(**5a—g**)

Sulfonium ylide	Carbonyl Compound	R^1	R^2	Solvent	Time (day)	Product (**8**)[a]	Yield(%)	Mp(dec)(°C)
4	**5a**	CH_3	$COOC_2H_5$	EtOH	2	**8a**-pic	71	142—143
4	**5a**	CH_3	$COOC_2H_5$	THF	2	**8a**-pic	41	
3	**5b**	CH_3	$COCH_3$	MeOH	0.5	**8b**-pic	66	148—149
4	**5b**	CH_3	$COCH_3$	MeOH	1	**8b**-pic	61	
4	**5b**	CH_3	$COCH_3$	EtOH	2	**8b**-pic	44	
4	**5b**	CH_3	$COCH_3$	THF	2	**8b**-pic	41	
4	**5c**	H	i-C_3H_7	MeOH	1	**8c**-pic	49	128—130
4	**5d**	H	C_6H_5	MeOH	1	**8d**-pic	52	145—146
4	**5e**	H	$CH_2SCH_2C_6H_5$	MeOH	1	**8e**	78	147—148
3	**5f**	H	$C_6H_4NO_2$-p	MeOH	0.5	**8f**	70	170
4	**5f**	H	$C_6H_4NO_2$-p	MeOH	1	**8f**	71	
4	**5f**	H	$C_6H_4NO_2$-p	EtOH	2	**8f**	41	
4	**5f**	H	$C_6H_4NO_2$-p	THF	2	**8f**	0	
4	**5g**[b]	H	H	MeOH	1	**8g**	80	139—140

a) pic: picrate. b) Paraformaldehyde was used.

Table 2. Physical constants of new sulfonium ylides(**8**)

Sulfonium ylide	R^1	R^2	Mp(dec)(°C) (solvent)	$IR^{KBr}_{\nu C=O}$ (cm^{-1})	NMR (δ) $(CH_3)_2S^+$-	NMR (δ) Others	Solvent[b]
8a	CH_3	$COOC_2H_5$	132—134 (EtOH-Et_2O)	1765, 1750, 1625	3.30(3H, s) 3.14(3H, s)	1.30(3H, t), 1.71(3H, s), 4.23(2H, q)	A
8b	CH_3	$COCH_3$	120—122 (MeOH-Et_2O)	1765, 1760, 1715, 1625	3.30(3H, s) 3.11(3H, s)	1.61(3H, s), 2.26(3H, s)	A
8c	H	i-C_3H_7	124—125 (THF)	1775, 1740, 1620	3.25(6H, s)	0.84(3H, d), 1.06(3H, d), 1.7—2.2(1H, m), 4.87(1H, d)	A
8d	H	C_6H_5	162—163 (MeOH-Et_2O)	1750(sh)[a], 1745, 1620	3.07(3H, s) 2.89(3H, s)	5.83(1H, s), 7.35(5H, m)	A
8e	H	$CH_2SCH_2C_6H_5$	147—148 (MeOH-H_2O)	1740, 1620	3.02(6H, s)	2.76(2H, d), 3.79(2H, s), 5.16(1H, t), 7.28(5H, m)	A
8f	H	$C_6H_4NO_2$-p	170 (EtOH-H_2O)	1750, 1620	2.92(6H, s)	6.16(1H, s), 7.67(2H, d), 8.28(2H, d)	B
8g	H	H	139—140 (MeOH)	1750, 1635	2.98(6H, s)	4.83(2H, s)	B

a) sh: shoulder absorption. b) Solvent: A, $CDCl_3$; B, DMSO-d_6.

was made on the basis of its spectral data and elemental analysis. However, the two methyl groups at the sulfonium group of **8e** appeared as a single peak at δ 3.02, which was in striking contrast to that of **8a**. In the case of the reaction with *p*-nitrobenzaldehyde or paraformaldehyde, the ylides (**8f** and **8g**) were also obtained as stable crystals. The results and physical data of **8** are shown in Tables 1 and 2 respectively. Further attempts were made to improve the yields of **8** in the reactions with diacetyl and *p*-nitrobenzaldehyde. As is shown in Table 1, methanol was proved to be the best solvent among the solvents examined, and **3** was more favorable than **4** to these reactions. Although the reaction of **3** or **4** in methanol with 1 equivalent of the carbonyl compound at room temperature produced good results in each case, at an elevated temperature or in the presence of excess carbonyl compound the desired products were not obtained.

The results are different from those for carbonyl-stabilized sulfonium ylides, such as dimethylsulfuranylideneacetophenone and ethyl dimethylsulfuranylideneacetate, which have been reported to be relatively unreactive toward ordinary carbonyl compounds.[2,3] It is reasonable to consider that the reaction of **3** or **4** with carbonyl compounds proceed through the intermediate betaine (**6**), which in turn cyclizes to form **8**, as is shown in Scheme 1. The cyclization, effected by the formation of a stable five-membered ring from **6**, must be the driving force of this reaction.

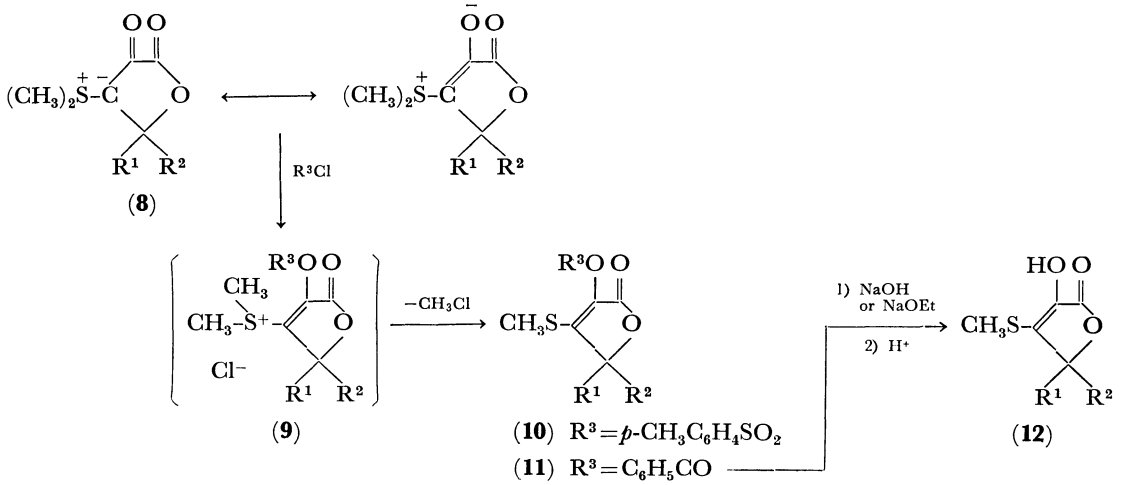
Reactivities of 8. In the presence of a catalytic amount of pyridine, the treatment of **8a** with *p*-toluenesulfonyl chloride in methylene chloride at room temperature afforded 5-ethoxycarbonyl-5-methyl-4-methylthio-2-oxo-3-(*p*-toluenesulfonyloxy)-2,5-dihydrofuran (**10a**) as colorless needles (mp 69—70 °C). The IR spectrum showed absorptions at 1785 (five-membered lactone), 1745 (ester), and 1615 cm^{-1} (double bond). The NMR spectrum exhibited two singlets, at δ 2.45 (3H) and 2.75 (3H), attributable to the methylthio group and the methyl protons of the tolyl group. Similar reactions of **8b** and **8g** afforded 3-*O*-tosylate (**10b** and **10g**) in good yields (see Table 3). The reaction of **8a** with benzoyl chloride in methylene chloride was completed in 30 min under ice-cooling to give 3-benzoyloxy-5-ethoxycarbonyl-5-methyl-4-methylthio-2-oxo-2,5-dihydrofuran (**11a**) as colorless needles (mp 95—96 °C). Similarly, **11b** and **11e—g** were readily obtained from the corresponding sulfonium ylides **8** (see Table 3). Although the evolution of methyl chloride was not detected, it seems likely that the formations of **10** and **11** result from the loss of methyl chloride from the intermediate sulfonium salt (**9**) derived from the betaine structure in **8**.

O-Benzoate (**11a**) was relatively stable under acidic conditions, whereas hydrolysis occurred in ethanolic sodium hydroxide to yield 5-ethoxycarbonyl-3-

Table 3. Reactions of **8** with *p*-toluenesulfonyl chloride and benzoyl chloride

Compound **8**	R^1	R^2	Chloride[a]	Product	Yield (%)	Mp (°C)
8a	CH_3	$COOC_2H_5$	TsCl	**10a**	87	69—70
8b	CH_3	$COCH_3$	TsCl	**10b**	83	79—80
8g	H	H	TsCl	**10g**	88	84—85
8a	CH_3	$COOC_2H_5$	BzCl	**11a**	84	95—96
8b	CH_3	$COCH_3$	BzCl	**11b**	88	Syrup
8e	H	$CH_2SCH_2C_6H_5$	BzCl	**11e**	89	54—55
8f	H	*p*-$NO_2C_6H_4$	BzCl	**11f**	72	153—154
8g	H	H	BzCl	**11g**	76	83—84

a) TsCl: *p*-toluenesulfonyl chloride; BzCl: benzoyl chloride.



Scheme 2.

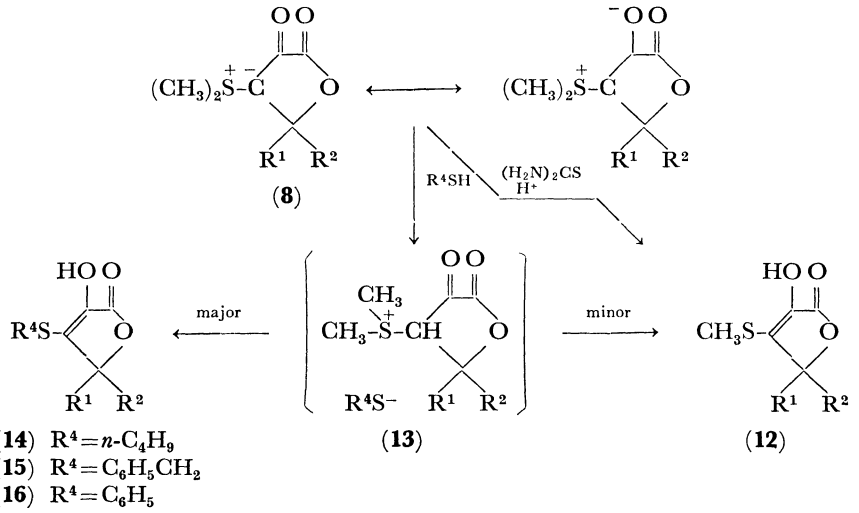
hydroxy-5-methyl-4-methylthio-2-oxo-2,5-dihydrofuran (**12a**) (mp 67—68 °C), which gave a blue color with ferric chloride. Under similar conditions, **11e** was also converted into the 3-hydroxy derivative (**12e**) in a good yield.

Methyl iodide and benzyl bromide, unexpectedly, were unreactive toward **8** under similar conditions. A prolonged reaction at an elevated temperature resulted in the formation of intractable products.

The reactions with nucleophilic reagents, such as mercaptans or thiourea, were also examined. When a mixture of **8e** and benzylmercaptan in 90% aqueous ethanol was refluxed, 4-benzylthio-5-benzylthiomethyl-3-hydroxy-2-oxo-2,5-dihydrofuran (**15e**) was obtained in a 67% yield (mp 89—91 °C). The product combined with ferric chloride to give a blue color. The structural assignment for **15e** was made on the basis of the elemental analysis and its spectral properties. In this manner, various 4-substituted products (**14**—**16**) were obtained from **8** and mercaptans (see Table 4). As is shown in Table 4, the yields increase with a decrease in the bulkiness of the mercaptans and substituents at the C_5-position of **8**. The reactions probably proceed through the nucleophilic displacement of the dimethylsulfonium group by the mercaptide anion of the intermediate sulfonium salt (**13**) formed by protonation. The reaction of **8a** which has two substituents at C_5, however, afforded the 4-substituted product in a low yield. In this case, the nucleophilic attack of the mercaptide anion on the C_4-position of **13** is unfavorable because of the steric hindrance.

On the other hand, the reaction of **8e** with thiourea in the presence of *p*-toluenesulfonic acid in refluxing ethanol yielded **12e** (95%) and *S*-methylisothiouronium *p*-toluenesulfonate. The analogous reactions of picrate of **8a** and **8c** gave demethylated products exclusively in a good yield. However, complicated reactions occurred in the absence of an acid.

In this reaction, it seems not unreasonable to explain that the preferential attack of thiourea on the less reactive methyl group rather than on the C_4-position



(**14**) $R^4 = n\text{-}C_4H_9$
(**15**) $R^4 = C_6H_5CH_2$
(**16**) $R^4 = C_6H_5$

Scheme 3.

Table 4. Reactions of **8** with mercaptans and thiourea

Compound **8**	R^1	R^2	Nucleophilic reagent	Product	Yield (%)	Mp (°C)
8a	CH_3	$COOC_2H_5$	$n\text{-}C_4H_9SH$	**14a**	22	Syrup
8a	CH_3	$COOC_2H_5$	$C_6H_5CH_2SH$	**15a**	26	74—75
8a	CH_3	$COOC_2H_5$	C_6H_5SH	**16a, 12a**[b]	(30)	(Syrup)
8a	CH_3	$COOC_2H_5$	$(H_2N)_2CS$[a]	**12a**	84	67—68
8c	H	$i\text{-}C_3H_7$	$n\text{-}C_4H_9SH$	**14c**	76	59—61
8c	H	$i\text{-}C_3H_7$	$C_6H_5CH_2SH$	**15c**	70	97—98
8c	H	$i\text{-}C_3H_7$	C_6H_5SH	**16c**	56	103—104
8c	H	$i\text{-}C_3H_7$	$(H_2N)_2CS$[a]	**12c**	75	125—126
8e	H	$CH_2SCH_2C_6H_5$	$n\text{-}C_4H_9SH$	**14e**	75	52—54
8e	H	$CH_2SCH_2C_6H_5$	$C_6H_5CH_2SH$	**15e**	67	89—90
8e	H	$CH_2SCH_2C_6H_5$	C_6H_5SH	**16e**	32	Syrup
8e	H	$CH_2SCH_2C_6H_5$	$(H_2N)_2CS$[a]	**12e**	95	85—86
8g	H	H	$n\text{-}C_4H_9SH$	**14g**	81	40—42
8g	H	H	$C_6H_5CH_2SH$	**15g**	83	107—108
8g	H	H	C_6H_5SH	**16g**	85	140—142

a) The reactions were carried out in the presence of acid. b) The mixture of **12a** and **16a** in the ratio of 1 : 2.

is due to a steric hindrance.

Furthermore, although the reactions with active methylene compounds, such as malononitrile and ethyl cyanoacetate, were examined under similar conditions, the desired reaction did not proceed. However, the cyclic sulfonium ylides (**8**) can be used as intermediates for the synthesis of 3-hydroxy-4-mercapto-2-oxo-2,5-dihydrofuran derivatives.[10]

Experimental

All the melting points are uncorrected. The IR spectra were determined with a Shimadzu IR-27G spectrophotometer. The NMR spectra were recorded on a Hitachi R-20A instrument, using TMS as the internal standard. The elemental analyses of all the new compounds except for **1** and **2** are listed in Table 7.

*Dimethyl(methoxalylmethyl)sulfonium Picrate (**1**) and Dimethyl(ethoxalylmethyl)sulfonium Pictrate (**2**).* Dimethyl(ethoxalylmethyl)sulfonium bromide[8] (194 g, 0.753 mol) and picric acid (174 g, 0.76 mol) in water were stirred for 1 hr at room temperature. The precipitate thus formed was collected by filtration and washed with ethyl acetate to give 261 g (81%) of the picrate (**2**, X=$(NO_2)_3C_6H_2O$). Recrystallization from ethyl acetate gave a pure sample as yellow needles; mp 95—97 °C (dec), $\nu_{C=O}$ (KBr) 1740 cm^{-1}.

Found: C, 36.93; H, 3.67; N, 9.88; S, 7.78%. Calcd for $C_{13}H_{15}N_3O_{10}S\cdot H_2O$: C, 36.89; H, 3.62; N, 9.93; S, 7.75%.

In a similar manner, 70.3 g of dimethyl(methoxalylmethyl)-sulfonium picrate (**1**, X=$(NO_2)_3C_6H_2O$) was prepared from 86.5 g of the bromide (**1**, X=Br)[8] and 82 g of picric acid. Recrystallization from acetone-ether gave yellow needles; mp 106—108 °C (dec), $\nu_{C=O}$ (KBr) 1745 cm^{-1}.

Found: C, 35.24; H, 3.69; N, 10.18; S, 7.59%. Calcd for $C_{12}H_{13}N_3O_{10}S\cdot H_2O$: C, 35.21; H, 3.69; N, 10.26; S, 7.83%.

*Methyl and Ethyl Dimethylsulfuranylidenepyruvate (**3** and **4**).*

*a) Preparation of **4** from the Picrate (**2**):* A mixture of the picrate (**2**, X=$(NO_2)_3C_6H_2O$, 11.15 g, 0.0265 mol), 50% aqueous sodium hydroxide (2.15 g, 0.0265 mol), and a saturated potassium carbonate solution (6.5 ml) in methylene chloride (50 ml) was stirred vigorously under ice-cooling for 30 min. After the removal of the inorganic precipitate by filtration, the methylene chloride layer was separated and dried over potassium carbonate. The removal of the solvent under reduced pressure at room temperature gave 3.69 g (80%) of **4** as pale yellow hygroscopic crystals: $\nu_{C=O}$ (KBr) 1720 and 1550 cm^{-1}; NMR (δ in $CDCl_3$) 4.68 (1H, s), 4.25 (2H, q), 3.00 (6H, s) and 1.34 (3H, t). This ylide was treated with picric acid in ethanol to give the picrate (**2**) quantitatively.

*b) Preparation of **4** from the Bromide (**2**):* By the same procedure, the bromide (**2**, X=Br, 2.57 g, 0.01 mol) afforded 1.27 g (72%) of **4**.

*c) Preparation of **3** from the Picrate (**1**):* According to the procedure described above, 3.95 g (64%) of **3** was obtained from 15.7 g of the picrate (**1**, X=$(NO_2)_3C_6H_2O$): pale yellow crystals; $\nu_{C=O}$ (KBr) 1725 and 1565 cm^{-1}; NMR (δ in $CDCl_3$) 4.68 (1H, s), 3.78 (3H, s) and 2.99 (6H, s). This ylide was converted to the picrate (**1**) quantitatively by treatment with picric acid in methanol.

*4-Dimethylsulfuranylidene-2,3-dioxotetrahydrofuran Derivatives (**8**).*

*a) Preparation of **8a—d**:* A solution of **4** (1.76 g, 0.01 mol) and ethyl pyruvate (**5a**, 1.16 g, 0.01 mol) in ethanol was allowed to stand at ambient temperature for 2 days. The addition of picric acid (2.3 g) to the reaction mixture and the removal of the solvent under reduced pressure left a syrup, which was crystallized by the addition of ethyl acetate. Filtration and washing with ethyl acetate gave 3.37 g (71%) of the picrate of 4-dimethylsulfuranylidene-5-ethoxycarbonyl-5-methyl-2,3-dioxotetrahydrofuran (**8a**), which was subsequently recrystallized from ethanol to afford a pure sample as yellow needles; mp 142—143 °C (dec), $\nu_{C=O}$ (KBr) 1790 and 1775 cm^{-1}. The analytical data are shown in Table 7.

To a vigorously stirred suspension of the picrate of **8a** (1.80 g, 3.8 mmol) in methylene chloride (10 ml) was added, in one portion, 50% aqueous sodium hydroxide (0.31 g, 3.8 mmol) and a saturated potassium carbonate solution (3 ml). After 30 min the methylene chloride layer was separated and dried over potassium carbonate. The subsequent removal of the solvent gave 0.71 g (76%) of the sulfonium ylide (**8a**) as pale yellow needles which was crystallized from ethanol-ether (mp 132—134 °C (dec)). The ylide was treated with picric acid in ethanol to give the picrate of **8a** quantitatively.

Similarly, the reactions of **3** and **4** with **5b—d** afforded picrates of **8b—d**, which were converted into **8b—d** in 82, 78, and 72% yields respectively. The results and the spectral data are listed in Tables 1 and 2.

*b) Preparation of **8e—g**:* A solution of **4** (21.0 g, 0.119 mol) and benzylthioacetaldehyde (**5e**, 19.6 g, 0.119 mol) in methanol (100 ml) was allowed to stand at room temperature for 24 hr. The precipitates thus formed were collected by filtration and washed with methanol to give 27.3 g (78%) of 4-dimethylsulfuranylidene-5-benzylthiomethyl-2,3-dioxotetrahydrofuran (**8e**) as light yellow needles; it was subsequently recrystallized from aqueous methanol; mp 147—148 °C (dec).

In this way, **8f** and **8g** were obtained by the reactions of **3** and **4** with *p*-nitrobenzaldehyde (**5f**) and paraformaldehyde (**5g**) respectively. The results and the spectral properties are shown in Tables 1 and 2.

*Reactions of **8** with* p-*Toluenesulfonyl Chloride.* A solution of **8a** (2.31 g, 9.4 mmol), *p*-toluenesulfonyl chloride (1.82 g, 9.5 mmol), and 3 drops of pyridine in methylene chloride (10 ml) was refluxed for 1 hr, and then washed with water and dried over sodium sulfate. The removal of the solvent gave 2.56 g (87%) of 5-ethoxycarbonyl-5-methyl-4-methylthio-2-oxo-3-(*p*-toluenesulfonyloxy)-2,5-dihydrofuran (**10a**) (mp 69—70 °C), which was subsequently recrystallized from benzene-cyclohexane.

By a similar procedure, **10b** and **10g** were obtained from the corresponding **8**. The results and the spectral data are given in Tables 3 and 5.

*Reactions of **8** with Benzoyl Chloride.* To a solution of **8a** (1.37 g, 5.85 mmol) in methylene chloride (7 ml) stirred under ice-cooling was added drop by drop benzoyl chloride (0.84 g, 5.9 mmol). After stirring for 30 min, the reaction mixture was washed with water, dried, and then evaporated to give a solid. Recrystallization from benzene-cyclohexane afforded 1.64 g (84%) of 3-benzoyloxy-5-ethoxycarbonyl-5-methyl-4-methylthio-2-oxo-2,5-dihydrofuran (**11a**) as colorless needles; mp 95—96 °C. Similarly, **8b** and **8e—g** furnished the corresponding benzoates (**11**). The results and the spectral properties are shown in Tables 3 and 5.

The structural assignment of the syrupy product (**11b**) was made on the basis of the IR and NMR spectra with a sample purified by the chromatography of silica gel G (methylene chloride).

*Hydrolysis of **11**.* To a solution of **11a** (1.67 g, 5 mmol) in ethanol (9 ml) stirred under ice-cooling was added drop by drop a solution of sodium hydroxide (0.20 g, 5 mmol)

Table 5. Spectral data of tosylates(**10**) and benzoates(**11**)

Compd	ν_{max}^{Nujol} cm^{-1}	NMR (δ, in $CDCl_3$)
10a	1785, 1746, 1615, 1380, 1175	1.28(3H, t), 1.74(3H, s), 2.45(3H, s), 2.74(3H, s), 4.25(2H, q), 7.37(2H, d), 7.95(2H, d)
10b	1770, 1730, 1600, 1375, 1170	1.14(3H, s), 2.20(3H, s), 2.47(3H, s), 2.67(3H, s) 7.40(2H, d), 7.79(2H, d)
10g	1765, 1600, 1377, 1175	2.46(3H, s), 2.45(3H, s), 4.87(2H, s), 7.39(2H, d), 7.94(2H, d)
11a	1785, 1745, 1630	1.52(3H, t), 1.83(3H, s), 2.56(3H, s), 4.30(2H, q), 7.3—8.2(5H, m)
11b	1780, 1775, 1733,[a] 1627	1.70(3H, s), 2.29(3H, s), 2.56(3H, s), 7.3—8.3(5H, m)
11e	1775, 1750, 1630	2.48(3H, s), 2.69(1H, q), 3.04(1H, q), 3.85(2H, s), 5.06(1H, q), 7.2—8.2(10H, m)
11f	1780, 1750, 1637, 1525, 1355	2.44(3H, s), 6.00(1H, s), 7.2—8.5(9H, m)
11g	1768, 1740, 1630	2.46(3H, s), 4.92(2H, s), 7.2—8.3(5H, m)

a) Measured as a film.

Table 6. Spectral data of 3-hydroxy-2-oxo-2,5-dihydrofuran derivatives

Compd	ν_{max}^{Nujol} cm^{-1}	NMR (δ, in $CDCl_3$)
12a	3240, 1770, 1725, 1665	1.30(3H, t), 1.74(3H, s), 2.67(3H, s), 4.26(2H, q), 6.8—7.3(1H)[b]
12c	3300, 1725, 1665	0.67(3H, d), 1.15(3H, d), 2.10(1H, m), 2.67(3H, s), 4.73(1H, d), 6.5—7.2(1H)[b]
12e	3320, 1735, 1665	2.53(1H, q), 2.63(3H, s), 2.90(1H, q), 3.76(2H, s), 4.85(1H, q), 6.8—7.5(1H)[b], 7.24(5H, s)
14a	3310, 1760, 1663[a]	0.90(3H, m), 1.1—1.9(4H, m), 1.29(3H, t), 1.73(3H, s), 3.20(2H, t), 4.25(2H, q), 6.0—7.0(1H)[b]
14c	3310, 1735, 1663	0.74(3H, d), 0.9(3H, m), 1.15(3H, d), 1.1—1.9(4H, m), 2.1(1H, m), 3.21(2H, t), 4.69(1H, d), 6.4—7.2(1H)[b]
14e	3300, 1738, 1660	0.93(3H, m), 1.2—1.9(4H, m), 2.60(1H, q), 2.98(1H, q), 3.16(2H, t), 3.79(2H, s), 4.90(1H, q), 6.9(1H, broad s)[b], 7.28(5H, s)
14g	3200, 1740, 1057	0.93(3H, m), 1.1—2.0(4H, m), 3.09(2H, t), 4.72(2H, s), 6.8—7.3(1H)[b]
15a	3300, 1760, 1743, 1665	1.21(3H, t), 1.54(3H, s), 4.12(2H, q), 4.36(2H, s), 7.28(5H, s), 7.35(1H, broad s)[b]
15c	3310, 1728, 1660	9.63(3H, d), 1.08(3H, d), 2.06(1H, m), 4.40(2H, s), 4.60(1H, d), 7.0—7.5(1H)[b], 7.24(5H, s)
15e	3300, 1730, 1665	2.39(1H, q), 2.84(1H, q), 3.72(2H, s), 4.30(2H, s), 4.76(1H, q), 6.6—7.5(1H)[b], 7.25(10H, s)
15g	3250, 1720, 1650	4.37(2H, s), 4.55(2H, s), 6.6—7.2(1H)[b], 7.30(5H, s)
16c	3300, 1730, 1668	0.84(3H, d), 1.03(3H, d), 2.10(1H, m), 4.73(1H, d), 6.0—6.6(1H)[b], 7.2—7.6(5H, m)
16e	3270, 1740, 1670[a]	2.52(1H, q), 2.92(1H, q), 3.70(2H, s), 4.94(1H, q), 5.4—6.1(1H)[b], 7.1—7.6(10H, m)
16g	3280, 1750, 1665	4.50(2H, s), 6.0—6.8(1H)[b], 7.2—7.7(5H, m)

a) Measured as a film. b) D_2O-exchangeable peak.

in ethanol (4 ml). After stirring for 30 min at room temperature, the reaction mixture was concentrated to dryness under reduced pressure. The residue was dissolved in water and washed with ether. The aqueous solution was acidified with hydrochloric acid and then extracted with ether. The removal of the solvent left a syrup, which was subsequently crystallized by the addition of cyclohexane. Recrystallization from benzene-cyclohexane afforded 0.95 g (81%) of 5-ethoxycarbonyl-3-hydroxy-5-methyl-4-methylthio-2-oxo-2,5-dihydrofuran (**12a**); colorless needles; mp 67—68 °C.

When sodium ethoxide was employed, **11a** (1.67 g) gave **12a** (0.88 g) in a 76% yield.

Similarly, the treatment of **11e** (1.93 g) with ethanolic sodium hydroxide gave **12e** (1.14 g, 81%); mp 85—86 °C.

Both products were treated with ferric chloride in ethanol to give a blue color.

The IR and NMR spectra are shown in Table 6.

Reactions of **8** *with Mercaptans.* A solution of **8c** (1.01 g, 5 mmol) and *n*-butylmercaptan (0.63 g, 7 mmol) in ethanol (10 ml) was refluxed for 1 hr and evaporated under reduced pressure to give a colorless syrup. The resulting residue was dissolved in warm cyclohexane and allowed to stand overnight at room temperature. Filtration and washing with cyclohexane afforded 0.87 g (76%) of 4-butylthio-3-hydroxy-5-isopropyl-2-oxo-2,5-dihydrofuran (**14c**) as colorless needles; it gave a blue color with ferric chloride.

According to the procedure described above, the reactions of **8** with mercaptans furnished 4-substituted products (**14**—**16**) except for the treatment of **8a** with phenylmercaptan. The results and the spectral data are summarized in Tables 4 and 6 respectively. The structures of the syrupy products (**14e** and **16e**) were confirmed by the IR and NMR spectra of the sample purified by column chromatography on silica gel G (methylene chloride).

The reaction of **8a** (1.00 g, 4.07 mmol) with phenylmercaptan (0.66 g, 6 mmol) in refluxing ethanol (10 ml) for 9 hr gave 0.34 g of a mixture of **12a** and **16a** in the ratio of 1 : 2 (total yield of 30%) as a viscous syrup. Since the separation of the mixture was unsuccessful, the product composition was determined from the peak areas of the protons of the methylthio group (δ 2.66) and the phenylthio group (δ 7.2—7.6) in the NMR spectrum.

Reactions of **8** *with Thiourea.* A mixture of **8e** (2.96 g, 10 mmol), thiourea (1.14 g, 15 mmol), and *p*-toluenesulfonic acid in 90% ethanol (30 ml) was refluxed for 4 hr and then evaporated to dryness. The residue was combined with water and extracted with benzene, and the organic layer was washed with water, dried, and evaporated to give 2.68 g (95%) of 4-benzylthio-5-benzylthiomethyl-3-hydroxy-2-oxo-2,5-dihydrofuran (**12e**) as colorless needles after recrystallization from benzene-cyclohexane. The ethanolic solution of **12e** was combined with ferric chloride to give a blue color. The aqueous phase which was separated from the organic layer was treated with picric acid (2.3 g) to afford *S*-methylisothiuronium picrate (2.52 g, 79%) as yellow needles (mp 223 °C) after recrystallization from ethanol.

By the procedure described above, **12a** and **12c** were obtained from the picrates of **8a** and **8c** in 84 and 65% yields respectively.

The IR and NMR spectra are shown in Table 6.

Table 7. Elemental analyses of new compounds

Compd No	Formula	Calcd (%)				Found (%)			
		C	H	N	S	C	H	N	S
8a-picrate	$C_{16}H_{17}N_3O_{12}S$	40.43	3.60	9.04	6.74	40.70	3.46	8.95	6.76
8b-picrate	$C_{15}H_{15}N_3O_{11}S$	40.46	3.39	9.43	7.20	40.66	3.42	9.50	7.47
8c-picrate	$C_{15}H_{17}N_3O_{10}S$	41.76	3.97	9.74	7.43	41.85	3.99	9.76	7.21
8d-picrate	$C_{18}H_{15}N_3O_{10}S$	46.46	3.25	9.03	6.89	46.41	3.35	9.08	6.91
8e	$C_{14}H_{16}O_3S_2$	56.73	5.44		21.36	56.60	5.52		21.59
8f	$C_{12}H_{11}NO_5S$	51.25	3.94	4.98	11.41	51.31	4.00	4.94	11.63
8g	$C_6H_8O_3S$	44.99	5.03		20.01	45.19	5.17		19.82
10a	$C_{16}H_{18}O_7S_2$	49.74	4.69		16.56	50.01	4.75		16.38
10b	$C_{15}H_{16}O_6S_2$	50.54	4.53		17.98	50.67	4.64		17.79
10g	$C_{12}H_{12}O_5S_2$	47.98	4.02		21.34	48.10	4.09		21.02
11a	$C_{16}H_{16}O_6S$	57.13	4.80		9.53	56.94	4.96		9.27
11e	$C_{20}H_{18}O_4S_2$	62.15	4.69		16.59	61.98	4.80		16.48
11f	$C_{18}H_{13}NO_6S$	58.21	3.52	3.77	8.63	58.16	3.62	3.69	8.72
11g	$C_{12}H_{10}O_4S$	57.58	4.02		12.81	57.60	4.03		12.64
12a	$C_9H_{12}O_5S$	46.54	5.21		13.81	46.26	5.37		13.67
12c	$C_8H_{21}O_3S$	51.06	6.42		17.04	51.01	6.54		17.02
12e	$C_{13}H_{14}O_3S_2$	55.29	4.99		22.70	55.23	5.15		22.76
14c	$C_{11}H_{18}O_3S$	57.36	7.87		13.92	57.63	7.79		13.70
14e	$C_{16}H_{20}O_3S_2$	59.22	6.21		19.76	59.33	6.16		19.61
14g	$C_8H_{12}O_3S$	51.04	6.42		17.03	51.20	6.36		17.20
15a	$C_{15}H_{16}O_5S$	58.43	5.23		10.05	58.52	5.55		10.24
15c	$C_{14}H_{16}O_3S$	63.60	6.10		12.15	63.49	6.27		12.05
15e	$C_{19}H_{18}O_3S_2$	63.66	5.06		17.88	63.93	5.09		17.82
15g	$C_{11}H_{10}O_3S$	59.44	4.53		14.42	59.51	4.67		14.28
16c	$C_{13}H_{14}O_3S$	62.37	5.64		12.81	62.28	5.82		12.90
16g	$C_{10}H_8O_3S$	57.76	3.83		15.39	57.77	4.07		15.27

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