Stereochemical Studies on Hemiorthothiol and Hemiorthothiolate Tetrahedral Intermediates[1,2]

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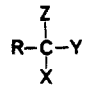
Abstract: This study deals with hemiorthothiol—$RC(OR')_2SH$—tetrahedral intermediates including (a) two acyclic ones of type [**11**], (b) two types of monocyclics [**12**] and [**13**], and (c) four bicyclic systems [**14**], [**15**], [**16**], and [**17**]. The breakdown of [**11**] (R = Ph, R′ = Et) led to thiono esters **34** and **35**; that of [**12**] (R = Me, Ph) resulted in hydroxy thiono esters **36–39**, whereas the cleavage of [**13**] (R = Me, Et) yielded thionolactones **49–53** and hydroxy thiono esters **55–58**. The study of rigid bicyclic intermediates [**14**]–[**17**] helped uncover the role of stereoelectronic effects in the breakdown of hemiorthothiol tetrahedral intermediates. Finally, a family of isolable hemiorthothiolate tetrahedral intermediates—$RC(OR')_2S^{-+}Na$—viz. [**91**$^-$]–[**94**$^-$] (monocyclic) and [**20**$^-$] (bicyclic) is reported.

Tetrahedral intermediates, resulting from nucleophilic attack on carbonyl groups or their analogues [**1**],[3] play a central role in a variety of chemical and biochemical reactions.[4] Since the pioneering work of Bender,[5] tetrahedral intermediates have been

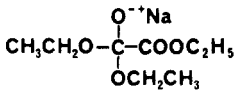


[**1**]

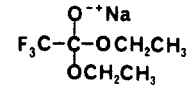
X,Y,Z : O-,N-,S-bearing groups

the subject of numerous kinetic,[6] spectroscopic,[7] and theoretical[8] studies. Transient, unstable three-heteroatom intermediates have been postulated in the lytic reactions of carboxylic esters,[9] lactones,[10] amides,[11] thiolo[12] and thiono[13] esters, imidate esters,[14] ortho esters,[15] amide acetals,[16] thioamides,[17] and amidines.[18] A variety of neutral (T^0)[19] tetrahedral intermediates have been detected spectroscopically, trapped or isolated.[20-25]

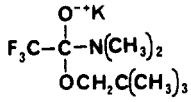
Whereas T^+ cationic intermediates have not been isolated, three anionic (T^-) and one zwitterionic ($T^{\pm}$) three-heteroatom tetrahedral intermediates have been reported. Intermediates [**2**],



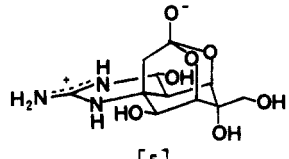
[**2**]



[**3**]



[**4**]

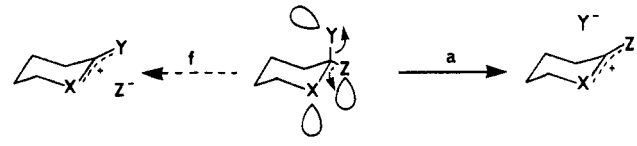


[**5**]

isolated by Adickes,[26] [**3**], postulated by Swarts[27] and characterized by Bender,[7m] and [**4**], observed spectroscopically,[28] lack rigorous structural proof. Tetrodotoxin [**5**][29] is thus the only properly characterized (zwitterionic) tetrahedral species.[30]

In 1969, Eliel and Nader reported that the reactions of Grignard reagents with ortho esters are subject to stereoelectronic control.[31] The generation and breakdown of short-lived intermediates of types $RC(OR')(OH)_2$, $RC(OR')_2OH$, and $RC(OR')(NR_2)OH$ are also subject to stereoelectronic control as evidenced by Deslongchamps'

Scheme I



7B [**6**] 7A

elegant studies on the ozonolysis of acetals,[32] carbonyl exchange reactions,[33] hydrolyses of cyclic ortho esters[34] and imidate salts,[35]

† Dedicated to the memory of Prof. Khatcher M. Kaloustian.

(1) The Chemistry of Tetrahedral Intermediates. 11. Preliminary communication of this work has appeared in (a) *J. Am. Chem. Soc.* **1979**, *101*, 2249–2251 and (b) **1980**, *102*, 7579–7581. Part 10: Bodine, J. J.; Kaloustian, M. K. *Synth. Commun.* **1982**, *12*, 787–793.

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(3) All tetrahedral species in the sequel, regardless of their respective lifetimes, are indicated with square brackets.

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(5) Bender, M. L. *J. Am. Chem. Soc.* **1951**, *73*, 1626.

(6) (a) McClelland, R. A.; Santry, L. J. *Acc. Chem. Res.* **1983**, *16*, 394–399. (b) DeTar, D. F. *J. Am. Chem. Soc.* **1982**, *104*, 7205–7212. (c) Khan, M. Y.; Olagbemiro, T. O. *J. Org. Chem.* **1982**, *47*, 3695–3699. (d) McClelland, R. A.; Alibhai, M. *Can. J. Chem.* **1981**, *59*, 1169–1176. (e) Jencks, W. P. *Acc. Chem. Res.* **1980**, *13*, 161–169.

(7) (a) Chahine, J.-M. El-H.; Dubois, J.-E. *J. Am. Chem. Soc.* **1983**, *105*, 2335–2340. (b) Tee, O. S.; Trani, M.; McClelland, R. A.; Seaman, N. E. *Ibid.* **1982**, *104*, 7219–7224. (c) Capon, B.; Ghosh, A. K.; Grieve, D. M. A. *Acc. Chem. Res.* **1981**, *14*, 306–312. (d) Capon, B.; Grieve, D. M. A. *J. Chem. Soc. Perkin Trans. 2* **1980**, *2*, 300–305. (e) Kovač, F.; Plesničar, B. *J. Chem. Soc., Chem. Commun.* **1978**, 122–124. (f) Cipiciani, A.; Linda, P.; Savelli, G. *Ibid.* **1977**, 857–858. (g) Capon, B.; Gall, J. H.; Grieve, D. M. *Ibid.* **1976**, 1034–1035. (h) Gravitz, N.; Jencks, W. P. *J. Am. Chem. Soc.* **1974**, *96*, 489. (i) Bowie, J. H.; Williams, B. D. *Aust. J. Chem.* **1974**, *27*, 1923. (j) Hine, J.; Ricard, D.; Perz, R. *J. Org. Chem.* **1973**, *38*, 110. (k) Robinson, D. R. *J. Am. Chem. Soc.* **1970**, *92*, 3138. (l) Bladon, P.; Forrest, G. C. *J. Chem. Soc., Chem. Commun.* **1966**, 481. (m) Bender, M. L. *J. Am. Chem. Soc.* **1953**, *75*, 5986.

(8) (a) Wipff, G.; Dearing, A.; Weiner, P. K.; Blaney, J. M.; Kollman, P. A. *J. Am. Chem. Soc.* **1983**, *105*, 997–1005. (b) Lehn, J.-M.; Wipff, G. *Ibid.* **1980**, *102*, 1347–1354. (c) Guthrie, J. P. *Ibid.* **1978**, *100*, 5892. (d) Guthrie, J. P. *Can. J. Chem.* **1976**, *54*, 202. (e) Fastrez, J. *J. Am. Chem. Soc.* **1977**, *99*, 7004. (f) Alagona, G.; Scrocco, E.; Tomasi, J. *Ibid.* **1975**, *97*, 6976–6983. (g) Lehn, J.-M.; Wipff, G. *Ibid.* **1974**, *96*, 4048–4050. (h) Lehn, J.-M.; Wipff, G.; Bürgi, H. B. *Helv. Chim. Acta* **1974**, *57*, 493–496.

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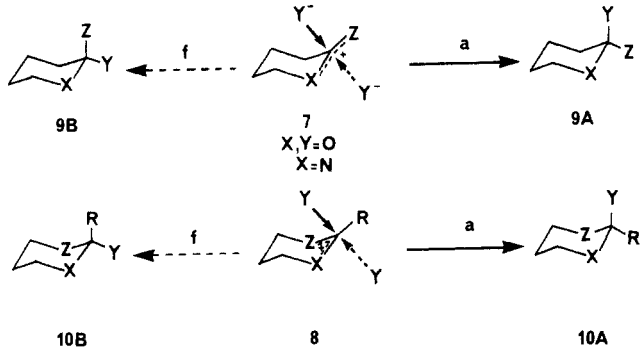
(11) (a) Kluger, R.; Lam, C.-H. *J. Am. Chem. Soc.* **1978**, *100*, 2191. (b) Fox, J. P.; Jencks, W. P. *Ibid.* **1974**, *96*, 1436.

(12) Hupe, D. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 451.

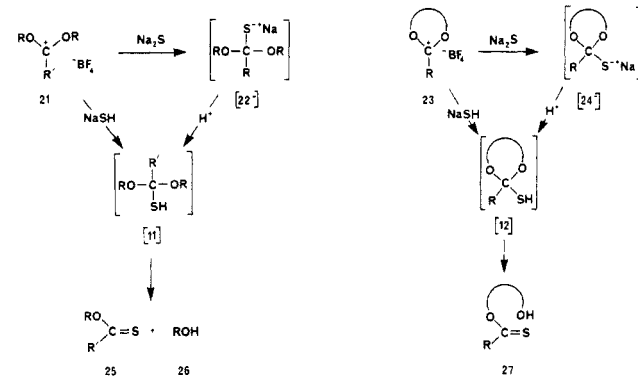
0002-7863/86/1508-6683$01.50/0

Scheme II



and oxidative cleavages of vinyl ortho esters.[36] By using convincing experimental evidence, Deslongchamps advanced a stereoelectronic theory[37] for the breakdown of tetrahedral intermediates. According to this theory, a carbon–heteroatom bond, C–Y, in a tetrahedral intermediate RC(X)(Y)(Z) [**6**] is severed relatively easily if there are two nonbonded electron pairs (one on X, one on Z) antiperiplanar to C–Y; other things being equal, the cleavage of C–Y is appreciably less facile if one or no antiperiplanar electron pair is present. The term "Deslongchamps effect" has been coined to describe this effect.[38] Under kinetic control, these cleavage patterns hold true, *regardless* of the relative thermodynamic stabilities of the cleavage products **7A** and **7B**, and *provided* **7A** and **7B** are both thermodynamically more stable than [**6**] (Scheme I).

Scheme III



The Deslongchamps theory provides a satisfactory qualitative rationalization of cleavage patterns of a variety of tetrahedral intermediates and remains a useful tool for the prediction of the breakdown of such short-lived species. The theory has survived even Perrin and Arrhenius' "critical test".[39] Despite the remarkable success of the theory, there are cases where apparent noncompliance with the theory has been noted.[6d,7d,14b,c,40] It may be argued that in these latter cases, experimental conditions were inadequate for observing the outcome of the *kinetic* breakdown; thus, mixing of kinetic and thermodynamic routes is very likely to have been a source of complications.

Caserio and co-workers[41] have examined the gas-phase ionization of cyclic ortho esters and discovered that, unlike in solution, there is only 10% preference for cleavage of the axial methoxyl groups.

The *generation* of tetrahedral intermediates can also be subject to stereoelectronic control. In a cyclic system such as **7** or **8**, the incoming nucleophile Y^- prefers a pseudoaxial approach to yield **9A** and **10A** rather than **9B** or **10B**. The available experimental

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(16) (a) Brown, R. S.; Ulan, J. G. *J. Am. Chem. Soc.* **1983**, *105*, 2382–2388. (b) McClelland, R. A. *Ibid.* **1981**, *103*, 6908–6911. c) McClelland, R. A. *Ibid.* **1978**, *100*, 1844–1849.

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(19) T^0, T^+, T^-, $T^\pm$ (or T^*) represent neutral, cationic, anionic, and zwitterionic tetrahedral species, respectively.

(20) (a) Meerwein, H.; Hinz, G. *Justus Liebigs Ann. Chem.* **1930**, *484*, 1. (b) Meerwein, H.; Sonke, H. J. *J. Prakt. Chem.* **1933**, *137*, 295.

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(26) (a) Adickes, F. *Chem. Ber.* **1925**, *58*, 1992; **1926**, *59*, 2522. (b) The equilibrium constant for the formation of the methyl hemiortho ester anion analogous to [**3**] has been reported (Guthrie, J. P. *Can. J. Chem.* **1976**, *54*, 202–209).

(27) Swarts, F. *Bull. Soc. Chim. Belges* **1926**, *35*, 412.

(28) Fraenkel, G.; Watson, D. *J. Am. Chem. Soc.* **1975**, *97*, 231–2.

(29) Kishi, Y.; Aratani, M.; Fukuyama, T.; Nakatsubo, F.; Goto, T.; Inoue, S.; Tanino, H.; Sugiura, S.; Kakoi, H. *Ibid.* **1972**, *94*, 9217–9219.

(30) (a) An isolable four-heteroatom T^- intermediate (orthocarbonate ester anion) has been reported, cf. structure **110**, page 1349 in Deslongchamps, P. *Pure Appl. Chem.* **1977**, *49*, 1329. (b) An isolable (−78 °C) two-heteroatom T^- species—$C_6H_5CH(SR)S^-Li^+$—has also been reported. (cf. Geiss, K.-H.; Seebach, D.; Seuring, B. *Chem. Ber.* **1977**, *110*, 1833–1851; we thank Prof. Seebach for drawing our attention to this reference.)

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(36) Deslongchamps, P.; Beaulieu, B.; Chênevert, R.; Dickinson, R. A. *Ibid.* **1980**, *58*, 1051.

(37) (a) Deslongchamps, P. *Tetrahedron* **1975**, *31*, 2463. (b) Deslongchamps, P. *Pure Appl. Chem.* **1975**, *43*, 351. (c) Deslongchamps, P. *Heterocycles* **1977**, *7*, 1271.

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(40) (a) Burdick, B. A.; Benkovic, P. A.; Benkovic, S. J. *Ibid.* **1977**, *99*, 5716; see also ref 71, pp 149–151. (b) Cravey, M. J.; Kohn, H. *Ibid.* **1980**, *102*, 3928.

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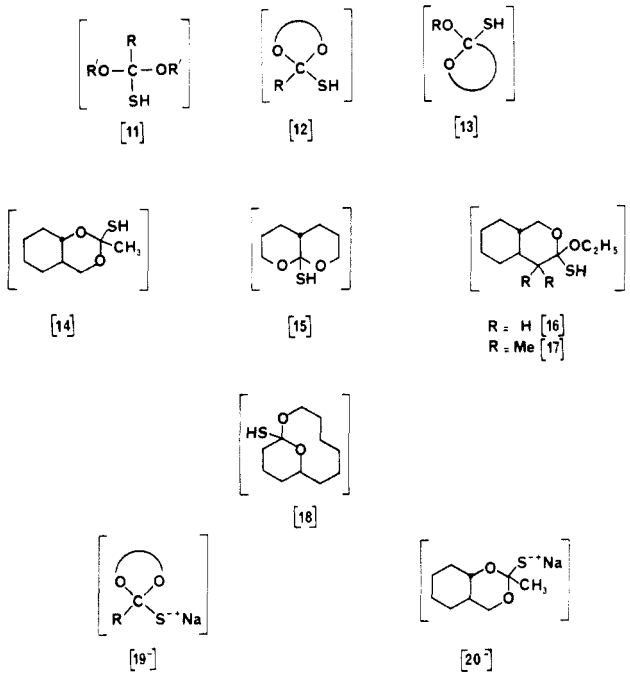
evidence provided by Eliel[31] and Deslongchamps[34] amply corroborates the preceding statement (Scheme II).

The present project was undertaken in order to gain an understanding of three-heteroatom intermediates and to uncover any intrinsic stereoelectronic factor in their generation and breakdown. In order to eliminate any ambiguity about the preferential protonation of the leaving group, hemiorthothiol ester tetrahedral intermediates—$RC(OR')_2SH$ [**11**]—were chosen as our model systems. In these systems $\Delta pK \simeq 0$, i.e., the protonation of the two oxygen leaving groups is equally facile; consequently, proton transfer from S to either O in an intermediate of type [**11**] is equally likely, and, other things being equal, both C–O bonds would be equally reactive. Preferential cleavage of one of the C–O bonds over the other, e.g., in especially designed semirigid or rigid models, then would be only the result of stereoelectronic assistance (Deslongchamps effect).

The present study deals with (a) the generation and breakdown of two acyclic intermediates [**11**], two types of monocyclic intermediates [**12**] and [**13**], and four bicyclic hemiorthothiol ester



intermediates—[**14**], [**15**], [**16**] and [**17**], (b) the attempted generation of [**18**], and (c) the synthesis and chemistry of hemiorthothiol ester anions [**19**$^-$] and [**20**$^-$].

Results

Monocyclic and Acyclic Hemiorthothiol Ester Tetrahedral Intermediates of Type [11] and [12]. Tetrahedral intermediates of type [**11**] and [**12**] were generated (a) by the reaction of a dialkoxycarbocation, **21** or **23**, with hydrosulfide anion under anhydrous conditions or (b) by the reaction of sulfide ion with **21** or **23** (to give [**22**$^-$] or [**24**$^-$], followed by protonation to [**11**] and [**12**]. In all cases, [**11**] and [**12**] immediately led to cleavage products (Scheme III; [**11**] → **25** + **26**; [**12**] → **27**). The experimental conditions for the addition of sulfur nucleophiles to two acyclic (**28** and **29**) and four cyclic dialkoxycarbocations (**30**–**33**) and the yields of the resultant thionobenzoates (**34** and **35**) or monothiono esters of 1,2- and 1,3-diols (**36**–**39**) are summarized in Table I.[42]

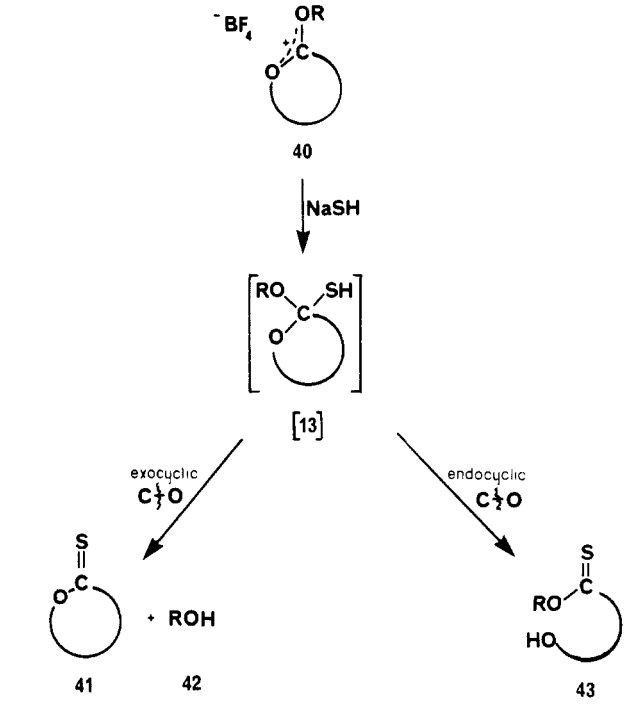
Monocyclic Hemiorthothiol Ester Tetrahedral Intermediates of Type [13]. Transient intermediates of this type, generated from *O*-alkyllactonium fluoborate salts **40** and anhydrous NaSH, led

(42) For recent methods for the synthesis of thiono esters, see: Reid, D. H., Ed.; *Organic Compounds of Sulfur, Selenium, and Tellurium*; The Chemical Society: London, 1970; Vol. 1, pp 220–221; 1973; Vol. 2, pp 250–254; 1975, Vol. 3, pp 284–288; 1977; Vol. 4, pp 177–181; 1979; Vol. 5, pp 174–176; 1981, Vol. 6, pp 189–190.

Table I. Results of the Sulfohydrolysis of Dialkoxycarbonium Salts **28**–**33**

salt	T (°C)	reagent	time (h)	thionoester	isoltd yield (%)
28	−23	1. Na_2S 2. H_2S	1.5	PhCOMe **34**	46
29	−23	1. Na_2S 2. ethereal HBF_4	2	PhCOEt **35**	40
30	0	NaSH	5.5	$HO(CH_2)_2OCMe$ **36**	60
31	−23	1. Na_2S 2. satd aq Na_2S	2	$HO(CH_2)_2OCPh$ **37**	77
32	0	NaSH	8.5	$HO(CH_2)_3OCMe$ **38**	78
33	−23	1. Na_2S 2. H_2O	3	$HO(CH_2)_3OCPh$ **39**	85

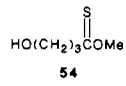
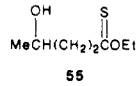
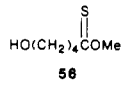
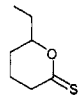
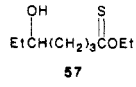
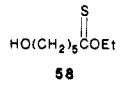
Scheme IV



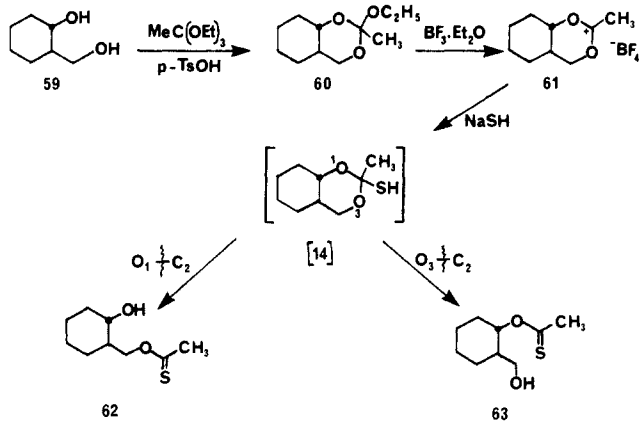
to cleavage products **41** + **42**/**43** (Scheme IV). While TLC of the reaction mixture of all sulfhydrolyses in acetonitrile at 0 °C revealed approximately 1:1 ratios of thionolactones **41** and their corresponding hydroxy thiono esters **43**, varying degrees of rearrangement of hydroxy thiono esters to thionolactones occurred during chromatographic isolation. The results of the sulfhydrolysis of salts **44**–**48** are shown in Table II.

At −78 °C, sulfhydrolysis of lactonium salt **47** (NaSH, Me_2CO, 18-crown-6) resulted in the predominant formation of hydroxy thiono ester **57** (R_f 0.54, $CHCl_3$–CH_3CN, 5:1 v/v) with only a small amount (by TLC analysis) of thionolactone **52** (R_f 0.73, same solvent mixture). Room temperature TLC analysis of a reaction mixture of **47** and NaSH in CH_3CN (obtained at −42

Table II. Results of the Sulfohydrolysis of Lactonium Salts **44–48**

lactonium salt	time (h)	thiono-lactone	isoltd yield (%)		isoltd yield (%)
44	2.5	 **49**	100	 **54**	0
45	1.5	 **50**	78	 **55**	10
46	2	 **51**	54	 **56**	40
47	2.5	 **52**	43	 **57**	49
48	2	 **53**	44	 **58**	17

Scheme V

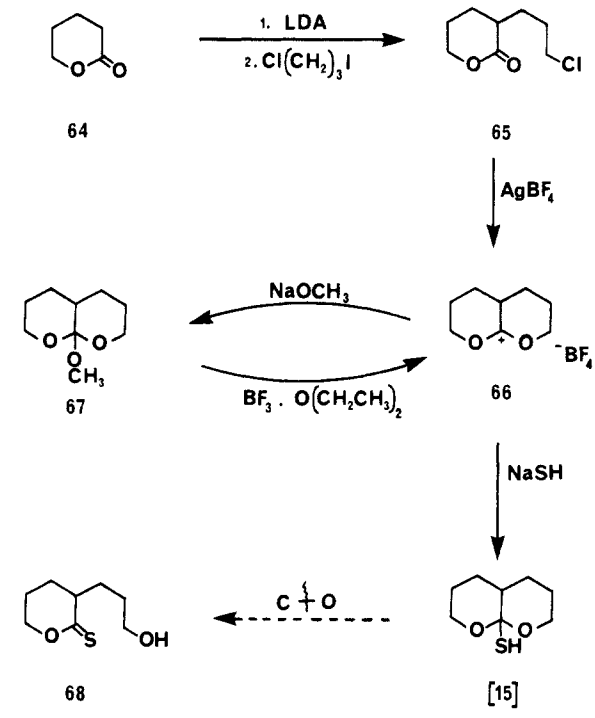


°C) revealed the formation of **57** and **52** in an approximate ratio of 4:1, as judged from the intensity of the brown spots obtained upon spraying the TLC plate with 5% aqueous $PdCl_2$. The **57/52** product ratio for the reaction conducted at 0 °C was found to be 47:53.

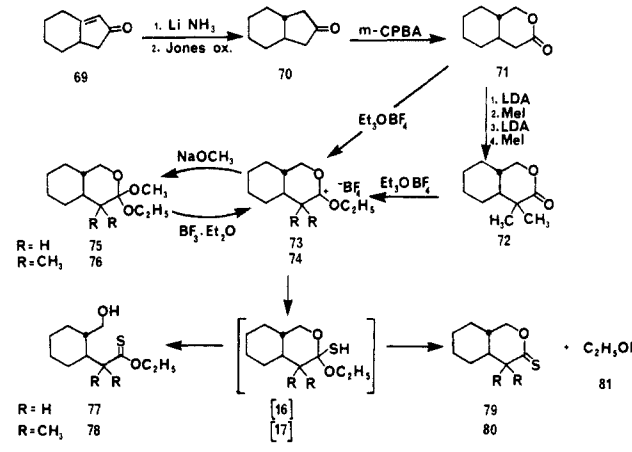
Bicyclic Hemiorthothiol Ester Tetrahedral Intermediate [14]. Known trans diol **59**[43] was made to react with triethyl orthoacetate in the presence of *p*-toluenesulfonic acid[44] to give bicyclic ortho ester **60** in 23.2% yield. Reaction of this ortho ester with boron trifluoride etherate in anhydrous ether[44] at −78 °C gave the desired fluoborate salt **61** as a viscous oil (94.8% yield). Treatment of **61** with anhydrous NaSH in acetonitrile at 0 °C proceeded to give a mixture of the isomeric thionoacetates **62** and **63** in a molar ratio of 1.6:1 (50.5% isolated yield) (Scheme V).

Bicyclic Hemiorthothiol Ester Tetrahedral Intermediate [15]. Treatment of δ-valerolactone (**64**) with lithium diisopropylamide in THF at −78 °C, followed by alkylation with 3-iodochloropropane in HMPT,[45] afforded chlorolactone **65** in 49.3% yield (Scheme VI). Addition of $AgBF_4$ in anhydrous ether at room temperature resulted in the instantaneous precipitation of AgCl with concomitant formation of **66**. To rid **66** of traces of silver ions, it was converted to ortho ester **67** with subsequent demethoxylation with BF_3·Et_2O. Conversion to ortho ester **67** was

Scheme VI



Scheme VII



effected by the addition of sodium methoxide to **66** in methanol–isopropanol at −78 °C.[34b,46] The overall yield for the **65** → **66** → **67** route was 41.6%. Finally, pure **66** was obtained in 98.7% yield as a white crystalline solid by treating **67** with BF_3·Et_2O in anhydrous ether at −78 °C.[47]

Treatment of **66** with anhydrous NaSH in dry CH_3CN at 0 °C gave a relatively nonpolar material (R_f 0.64, $CHCl_3$–CH_3CN, 5:1 v/v) as the only sulfur-containing product (20.2% yield after careful and rapid preparative layer chromatography under argon).

Bicyclic Hemiorthothiol Tetrahedral Intermediates [16] and [17]. Lactonium salts **73** and **74**, used to generate [**16**] and [**17**], respectively, were prepared as outlined in Scheme VII. Reduction[49]

(43) (a) Blomquist, A. T.; Wolinsky, J. *J. Am. Chem. Soc.* **1957**, *79*, 6025. (b) Bailey, W., private communication.

(44) Kovacs, O. K. J.; Schneider, G.; Lang, L. K.; Apjok, J. *Tetrahedron* **1967**, *23*, 4181.

(45) (a) Herman, J. L.; Schlessinger, R. H. *J. Chem. Soc., Chem. Commun.* **1973**, 711. (b) Posner, G. H.; Loomis, G. L. *Ibid.* **1972**, 892.

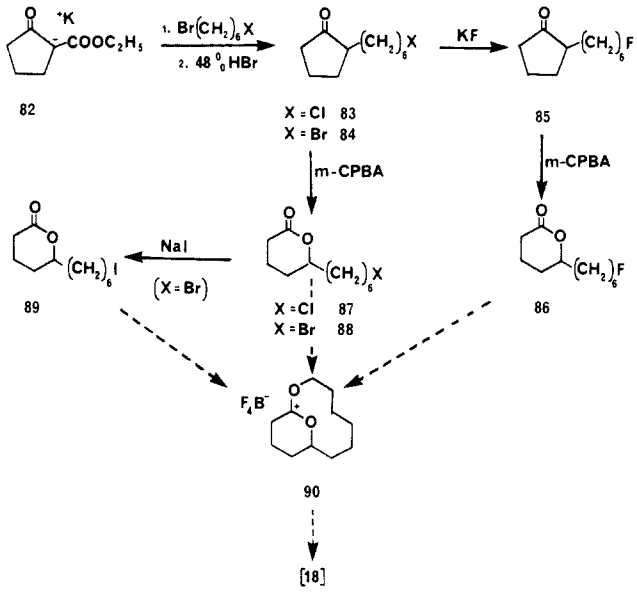
(46) Ortho ester **67** had the trans ring junction (δ 3.19 (3 H, OMe) ppm) with less than 10% of the known cis isomer[34b,37] (δ 3.28 (3 H, OMe) ppm); further, trans ortho ester **67** was found to rearrange thermally to a 1:1 mixture of trans:cis isomers during distillation at 60 °C (0.25 torr) or higher temperatures).

(47) (a) Meerwein, H.; Bodenbenner, K.; Borner, P.; Kunert, F.; Wunderlich, K. *Justus Liebigs Ann. Chem.* **1960**, *632*, 38–55. (b) Meerwein, H. *Angew. Chem.* **1955**, *67*, 374. (c) The proton magnetic resonance spectrum of **66** displayed a low-field triplet at δ 4.99 and a significant quintet[48] at δ 3.20 ($CDCl_3$).

(48) Hart, H.; Tomalia, D. *Tetrahedron Lett.* **1966**, 3383.

(49) Caine, D. In *Organic Reactions*; Wiley: New York, 1976; Vol. 23, Chapter 1, p 33.

Scheme VIII



of enone **69**,[50] with lithium in liquid ammonia afforded a *mixture* of *trans*-hydrindanone (**70**) along with the corresponding alcohol(s) in a ratio of 1:2.5. However, Jones oxidation[51] of the entire mixture gave **70**[49] in 70.8% yield. Further oxidation of **70** with *m*-chloroperbenzoic acid in CH_2Cl_2[34b,52] gave lactone **71**[53] in 90.1% yield. Alkylation of the latter lactone with triethyloxonium fluoborate gave lactonium salt **73** which was derivatized as the ortho ester[34b] **75** (76.8%) and regenerated cleanly from **75** in 83.8% yield by treatment with $BF_3{\cdot}Et_2O$.

Alkylation of **71** through two consecutive runs of LDA in THF followed by CH_3I in HMPT[54] at −42 °C gave dimethyllactone **72** in 88.9% yield. Ortho ester **76** was isolated in 23.3% yield from **72** by alkylation with $Et_3O^+{}^-BF_4$ and treatment with sodium methoxide.[34b] Methoxide abstraction from **76** with $BF_3{\cdot}Et_2O$ gave lactonium salt **74** in 84.3% yield. The sequences **73** → **75** → **73** and **74** → **76** → **74** were essential in order to get **73** and **74** free of $Et_3O^+{}^-BF_4$.

Treatment of lactonium salts **73** and **74**, under conditions identical with those for the sulfhydrolysis of **47** (NaSH, Me_2CO, 18-crown-6, −78 °C) led, by way of intermediates [**16**] and [**17**], exclusively to hydroxy thiono esters **77** (R_f 0.53) and **78** (R_f 0.55) ($CHCl_3$–CH_3CN, 5:1 v/v), respectively (Scheme VII). Attempts to isolate these hydroxy thiono esters were thwarted because of their propensity to undergo rearrangement to the corresponding thionolactones (**79** and **80**) with concomitant generation of EtOH (**81**). However, when a sample of **74** in CD_3CN was placed in an NMR tube and made to react with NaSH, freshly generated hydroxy thiono ester **78** was detected by TLC (R_f 0.55, $CHCl_3$–CH_3CN, 5:1 v/v).

Attempted Generation of Bicyclic Tetrahedral Intermediate [18]. The successful intramolecular alkylation of lactone **65** prompted us to extend the same methodology to the construction of salt **90** from halolactones **86–89**, in the presence of silver ion or other Lewis acids (Scheme VIII). Intramolecular alkylation was attempted on lactones **86–89** under a wide range of experimental conditions, varying the following parameters: halide acceptor, acceptor/lactone ratio, solvent, concentration of lactone, duration, and temperature of reaction. Unfortunately, all attempts at the synthesis of **90** were unsuccessful, and hence the subsequent sulfhydrolysis could not be undertaken.

(50) Islam, A. M.; Raphael, R. A. *J. Chem. Soc.* **1952**, 4086.
(51) Fieser, M.; Fieser, L. F. *Reagents for Organic Synthesis*; Wiley: New York, 1967; Vol. 1, p 142.
(52) Untch, K. G.; Lüthy, C.; Konstantin, P. *J. Am. Chem. Soc.* **1978**, *100*, 6211.
(53) Granger, R.; Boussinesq, J.; Girard, J.-P.; Rossi, J.-C. *Bull. Soc. Chim. Fr.* **1969**, 2801–2806.
(54) Grieco, P. *Synthesis* **1975**, 67.

Scheme IX

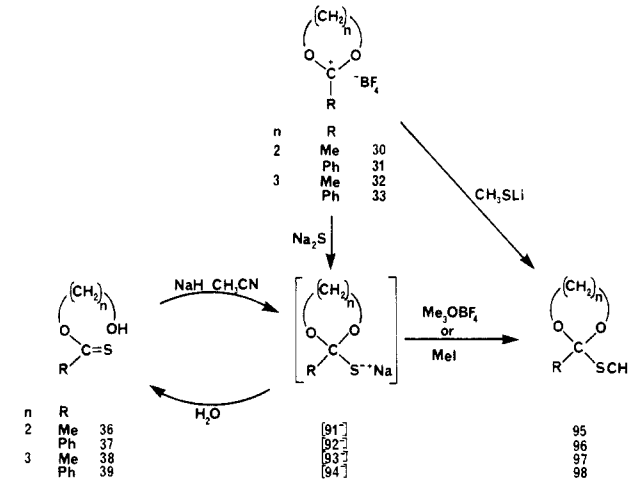
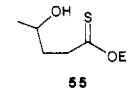
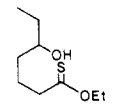
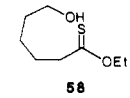
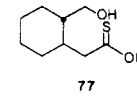
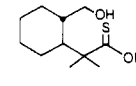


Table III. R_f's of Thionolactones and Their Corresponding Hydroxy Thion Esters ($CHCl_3$–CH_3CN, 5:1 v/v)

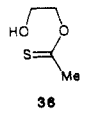
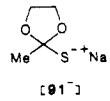
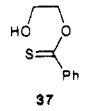
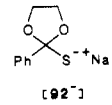
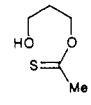
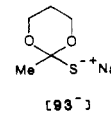
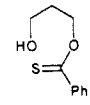
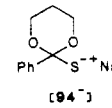
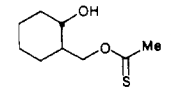
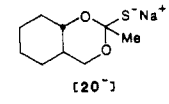
thionolactone	R_f	hydroxy thion ester	R_f
 **50**	0.74	 **55**	0.52
 **52**	0.73	 **57**	0.54
 **53**	0.76	 **58**	0.51
 **79**	0.78	 **77**	0.53
 **80**	0.77	 **78**	0.55

Monocyclic Anionic Hemiorthothiol Ester Tetrahedral Intermediates of Type [19⁻]. Method 1. The addition of Na_2S to each of ions **30–33** gave a crude white solid which, after thorough washing with acetonitrile under nitrogen, could be hydrolyzed to give a thiono ester (**36–39**, respectively, Scheme IX). Treatment of the solid derived from **31** with 1.5 equiv of $Me_3O^+{}^-BF_4$ (CH_2Cl_2, 0 °C, 1 h) led to orthothioester **96** (59.0% yield) which proved to be identical (IR, NMR) with the product obtained from the reaction of **31** with $Li^+{}^-SCH_3$[55] (CH_2Cl_2, 0 °C, 2 h). Parallel observations were made on cations **30**, **32**, and **33** (Scheme IX). These results suggested that the white solid adduct of Na_2S and each of ions **30–33** consisted of hemiorthothiolate ester anions [**91**⁻]–[**94**⁻], respectively, along with $NaBF_4$ and unreacted Na_2S.

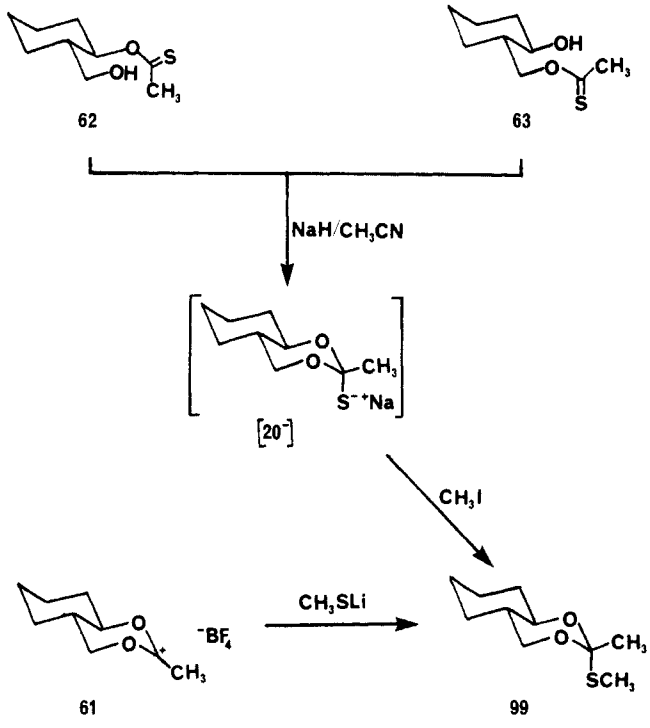
Method 2. Anions [**91**⁻]–[**94**⁻] were also prepared by the reaction of the corresponding hydroxy thiono esters with NaH in CH_3CN (0 °C, 30 min; −4 °C, 24–48 h); the anionic intermediates [**91**⁻]–[**94**⁻] so obtained (in 42, 78, 35 and 67% yield, respectively, Table III) were then cleanly methylated with $Me_3O^+{}^-BF_4$ in CH_2Cl_2 to the corresponding orthothioesters **95–98** (100, 90, 69, and 73% yield, respectively, Table IV). The orthothioesters **95–98** proved to be identical with authentic samples prepared by the addition of $Li^+{}^-SCH_3$ to the corresponding cations **30–33** (yields:

(55) Kelly, T. R.; Dali, H. M.; Tsang, W.-G. *Tetrahedron Lett.* **1977**, 3859–3860. For the preparation of NaSMe, see: Kornblum, N.; Carlson, S. C.; Smith, R. G. *J. Am. Chem. Soc.* **1978**, *100*, 289.

Table IV. Results of Cyclization of Hydroxy Thio Esters (NaH/MeCN)

hydroxy thion ester	anionic intrmdte	isoltd yield (%)
 **36**	 [91⁻]	42
 **37**	 [92⁻]	78
 **38**	 [93⁻]	35
 **39**	 [94⁻]	67
 **62** **63**	 [20⁻]	35

Scheme X



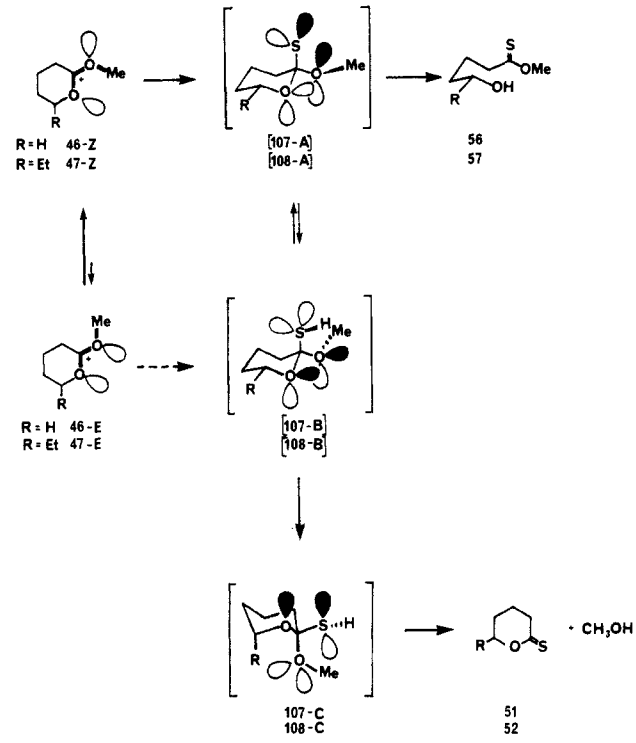
40, 78, 52, and 100%, respectively). Anions [**91**⁻]–[**94**⁻], upon hydrolysis, gave the corresponding hydroxy thiono esters **36**–**39** in quantitative yields (Scheme IX).

Bicyclic Hemiorthothiol Ester Anion [20⁻]. Treatment of a mixture of **62** + **63** (Scheme V) with NaH in dry CH_3CN gave hemiorthothiolate intermediate [**20**⁻] (Scheme X) in 35% yield; upon alkylation with MeI, the latter was transformed to orthothioester **99** in quantitative yield. The product proved to be identical with the one obtained from **61** and CH_3SLi.

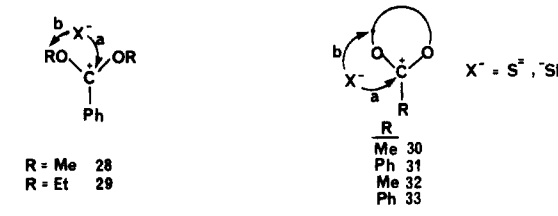
Discussion

Hemiorthothiol Ester Tetrahedral Intermediates of Type [12]. These tetrahedral intermediates, generated by the reaction of **30**–**33** with hydrosulfide ion or through the sulfide ion-addition-

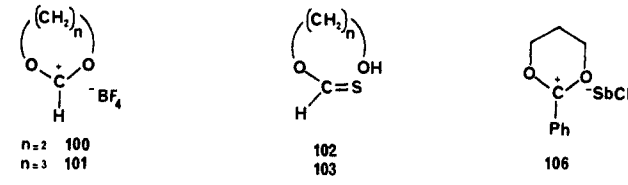
Scheme XI



protonation sequence, cleave rapidly to yield thionobenzoate esters and monothiono esters of 1,2- and 1,3-diols, with no detectable amounts of any mercapto esters (Table I). This means that the nucleophilic attack on the cation is virtually exclusively at C-2 (path **a**).

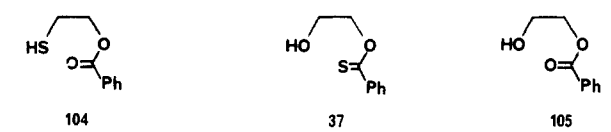


While the sulfhydrolyses of 1,3-dioxolan-2-ylium and 1,3-dioxan-2-ylium tetrafluoborates (**100** and **101**, respectively) to the corresponding ω-hydroxyalkyl thionoformates **102** and **103** were successful (TLC and NMR evidence), the isolation of the hydroxythionoformates was thwarted by their high reactivity.



In the case of acyclic **28** and **29**, the lower yields of thionobenzoates obtained indicate competing dealkylation (path **b**).[56] Attempts to extend the procedure to other acyclic fluoborate salts of the type $RC^+(OEt)_2{}^-BF_4$ (R = H, Me, Et) did not yield the thiono esters, most probably due to dealkylation.

In a comparative study of the cleavage of cation **31** with different nucleophilic sulfur reagents, the reaction with H_2S in acetonitrile (0 °C, 38 h) gave only mercapto ester **104** (8%), thiono ester **37** (19%), and hydroxy ester **105** (27%). These results are



(56) Dimroth, K.; Heinrich, P. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 676.

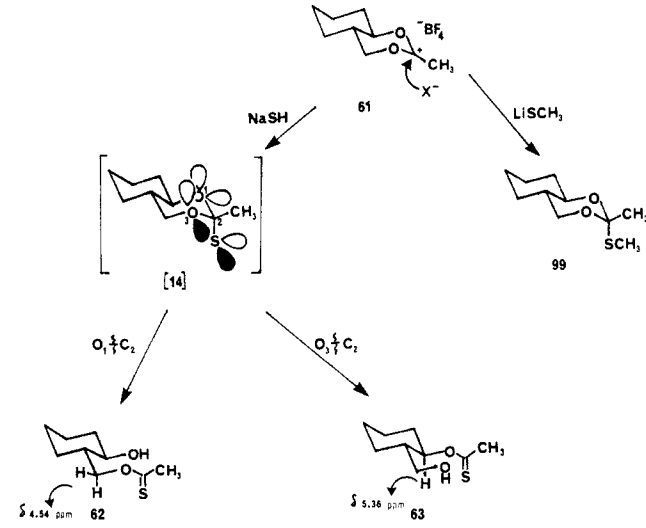
in agreement with the expected effect of the nucleophile on the course of the reactions of ambident cations;[57,58] the kinetic product (path **a**), resulting from the pathway with lower activation energy (ion–ion combination), is usually favored by the use of the more nucleophilic reagent (Na_2S > NaSH > H_2S).[57-59] In one case, reaction of the hexachloroantimonate salt **106** with Na_2S led to the formation of an orange precipitate, presumably Sb_2S_3, and the sulfhydrolysis results could not be determined.

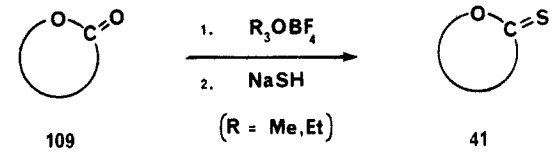
Monocyclic Hemiorthothiol Ester Tetrahedral Intermediates of Type [13]. The breakdown of tetrahedral intermediates of type [**13**], transiently generated from **40** (Scheme IV), may be rationalized on the basis of Scheme XI depicted for model tetrahedral intermediate [**107**]. At 0 °C, **46** exists probably almost exclusively as the *Z* conformer.[60] Addition of hydrosulfide to (*Z*)-**46** results in the formation of intermediate [**107A**] which undergoes preferential cleavage of the endocyclic C–O bond to give hydroxy thiono ester **56**. Rotation about the C–O bond of [**107A**] leads to [**107B**] which lacks proper orbital orientation to permit cleavage of *either* C–O bond; such an unreactive intermediate would undergo further conformational change to give [**107C**]. The latter would then undergo stereoelectronically-assisted ejection of the axial methoxy group to give thionolactone **51**. Hence, if the temperature is lowered (to slow down rates of conformational changes) or if the conversion of [**107B**] to [**107C**] is blocked (by ring substitution), sulfhydrolysis should proceed with exclusive formation of hydroxy thiono esters, i.e., the (*Z*)-**46** → **107A** → **56** (Scheme XI) pathway should be favored. Indeed, at −78 °C, sulfhydrolysis of lactonium salt **47** (NaSH, Me_2CO, 18-crown-6) resulted in the predominant formation of the corresponding hydroxy thiono ester **57** (R_f 0.54, $CHCl_3$–CH_3CN, 5:1 v/v), with only a small amount (<2% by analytical TLC) of thionolactone **52** (R_f 0.73, same solvent system). However, purified **57**, upon rechromatography, also showed the same minute amount of **52**, thereby indicating that the latter component is an artifact formed on the analytical TLC plate. Room temperature TLC analysis of a reaction mixture of **47** and NaSH in CH_3CN, freshly prepared at −42 °C, revealed the formation of **52** and **57** in an approximate ratio of 4:1; that is, at −42 °C, the [**108B**] → [**108C**] → **52** is still partially operative.

The possibility that thionolactones are being formed as secondary products by rearrangement of the hydroxy thiono esters *under the reaction conditions* was eliminated when pure thiono ester **57** was recovered unchanged after stirring with an equivalent amount of NaSH in CH_3CN at 0 °C for 3 h. Possible acid catalysis of the rearrangement by traces of HBF_4 (formed by partial hydrolysis of the lactonium salt) was discounted with the finding that the reactions of lactonium salt **47** with NaSH in the presence of varying amounts (0.1, 0.5, 1.0, and 2.0 equiv) of different bases (diisopropylamine, diisopropylethylamine, isopropylhexylamine, or 1,8-bis(dimethylamino)naphthalene) did not cause a noticeable change in the 1:1 ratio of **52**/**57**. All attempts at trapping the kinetic products by acetylation, by using varying stoichiometries of AcCl–pyridine or Ac_2O–pyridine, failed. Numerous attempts at cyclizing hydroxy thiono esters **55**–**58** (Table III) to the corresponding thionolactones were also unsuccessful, owing to rapid decomposition of the acid- and water-sensitive thionolactones. These attempts at cyclization involved (a) removal of the alcohol as a binary azeotrope with acetonitrile, cyclohexane, methylcyclohexane, or xylene, with or without Rohm and Haas Amberlyst-15 or (b) acid-catalyzed cyclization utilizing Amberlyst-15, *p*-toluenesulfonic acid, oxalic acid, and ethereal HBF_4 in CH_3CN. With the exception of **58**, all other hydroxy thiono esters **54**–**57** (Table II) underwent some degree (15–20%) of cyclization on contact with Amberlyst-15, *p*-toluenesulfonic acid, or ethereal HBF_4, after which rapid decomposition ensued within 10 min. The reluctance of **58** to cyclize to **53** suggests strongly that thionolactone **53**, and probably a major fraction of each of **49**–**52**, is a primary product resulting directly from the breakdown of the corresponding hemiorthothiol ester intermediate.

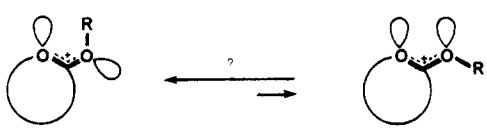
The sulfhydrolytic studies described above provided the basis of a two-step preparative route to thionolactones from lactones (**109** → **41**). Our results are summarized in Table II. The above two-step method is shorter and more convenient than the low-temperature (−78 °C) sulfhydrolysis-acetylation[65] of *N*,*N*-(di-

Scheme XII





(57) Hünig, S. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 548.
(58) Pittman, C. U.; McManus, S. P.; Larsen, J. W. *Chem. Rev.* **1972**, 357.
(59) In dioxolenium rings fused to biased cyclohexane systems, the two **a**-type cleavages with nucleophilic reagents occur selectively (cf. King, J. F.; Albutt, A. D. *Can. J. Chem.* **1969**, *47*, 1445–1459; **1970**, *48*, 1754–1769).
(60) While dialkoxycarbocations,[61] protonated esters,[62] and protonated acids[63] have been the subject of extensive investigations, spectroscopic studies on the conformational preference of O-alkylated salts **40** are lacking. The *Z* form of lactonium salts (**40**-*Z*) would correspond to the syn,anti acyclic analogue *syn,anti*-**21**, known[61a-c] to predominate at −30 to −80 °C; the *E* form (**40**-*E*) resembles conformer *syn,syn*-**21**. According to Olah and co-workers,[64] the PMR and CMR spectra (−78 °C) of protonated lactone **111** point to a single conformer, even though the syn or anti assignment could not be made.

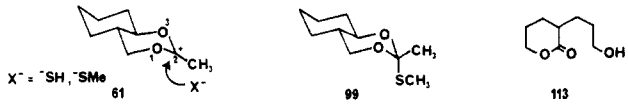


(61) (a) Ramsey, B. G.; Taft, R. W. *J. Am. Chem. Soc.* **1966**, *88*, 3058. (b) Borch, R. F. *Ibid.* **1968**, *90*, 5303. (c) Dusseau, C. H.; Schaafsma, S. E.; Steinberg, H.; deBoer, T. J. *Tetrahedron Lett.* **1969**, 467. (d) Paulsen, H. *Pure Appl. Chem.* **1975**, *41*, 69. (e) Paulsen, H.; Dammeyer, R. *Chem. Ber.* **1976**, *109*, 1837.
(62) Olah, G. A.; O'Brien, D. H.; White, A. M. *J. Am. Chem. Soc.* **1967**, *89*, 5694.
(63) (a) Hogeveen, H.; Bickel, A. F.; Hilbers, C. W.; Mackor, E. L.; MacLean, C. *J. Chem. Soc., Chem. Commun.* **1966**, 898. (b) Brookhart, M.; Levy, G. C.; Winstein, S. *J. Am. Chem. Soc.* **1967**, *89*, 1735. (c) Olah, G. A.; White, A. M. *Ibid.* **1967**, *89*, 3591. (d) Hogeveen, H. *Recl. Trav. Chim. Pays-Bas* **1968**, *87*, 1313.

methylimino)lactonium salts and is also of wider scope than that effected by thionation of lactones with P_4S_{10}[66] or the dimer of *p*-methoxyphenylthionophosphinyl sulfide (**110**).[67] Thionations with these two reagents are generally carried out under drastic thermal conditions (110–114 °C). Under these conditions, the formation of thionolactones is often accompanied by isomerization to thiololactones or further transformation to dithiolactones.[66a,b] While the reaction with Lawesson's reagent (**110**) was only cleanly applied to the synthesis of five-membered thionolactones (δ-thionovalerolactone (**51**) decomposes under the reaction conditions),[67] our method offers a thermally milder (0 °C) route to five-, six-, and seven-membered thionolactones in good to moderate yields. No thiololactones or dithiolactones could be detected in any of our experiments. Finally, our method should be applicable to the thionation of macrocyclic lactones, since the thionolactone does not have to form by recyclization (cf. seven-membered ring case **53** discussed above).

Bicyclic Hemiorthothiol Ester Tetrahedral Intermediate [14]. Short-lived bicyclic intermediate [**14**], as expected on stereoelectronic grounds, underwent cleavage of both O_1–C_2 and C_2–O_3 bonds (vide supra, Scheme V). There appears to be a slight kinetic preference for the formation of **62** over **63** (**62**/**63** = 1.60; $\Delta\Delta G^{\ddagger}$ = 0.25 kcal/mol at 273 K). This ratio of **62**/**63** was estimated by integrating the ^{1}H NMR signals for H_α (apparent doublet at δ 4.54 ppm, J = 6.0 Hz) in **62** and H_α' (broad multiplet at δ 5.36 ppm) in **63**. Isomeric thionoacetates **62** and **63** coeluted on TLC ($CHCl_3$–CH_3CN, 5:1 v/v), and no attempt was made to separate them.

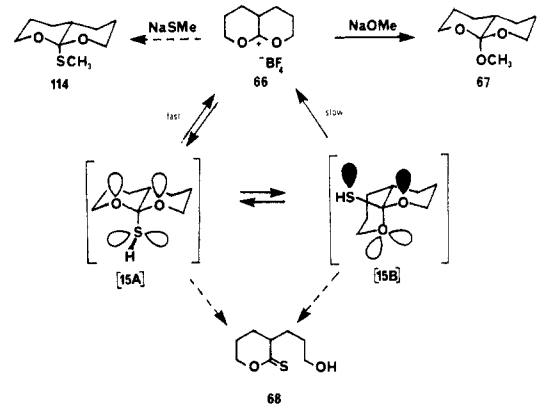
That the approach of the hydrosulfide ion (X^- = ^-SH) to C-2 of **61**, to give [**14**] rather than the C-2 epimeric analogue (Scheme XII), is pseudoaxial was based on the analogous reaction of **61** with $CH_3S^-{}^+Li$ (X^- = $^-SCH_3$). The exclusive product of the latter



reaction was orthothioester **99** in which the smaller[68] thiomethyl group assumes the axial position. Preferred *pseudoaxial* approach in the reaction of $^-OCH_3$ to bicyclic dialkoxycarbocations had been established previously by Deslongchamps and co-workers;[34b] by analogy with both $^-OCH_3$ and $^-SCH_3$, the approach of ^-SH is believed to be dominantly, if not exclusively, pseudoaxial too.

Bicyclic Hemiorthothiol Ester Tetrahedral Intermediate [15]. The proton magnetic resonance spectrum of the relatively nonpolar sulfur-containing material (R_f 0.64, vide supra) exhibited a multiplet at δ 1.2–2.2 ppm integrating for 10 hydrogens and another multiplet at δ 3.5–3.9 ppm integrating for four hydrogens; its solid state (KBr disc) IR spectrum showed striking similarity to that of ortho ester **67** (Scheme VI), suggesting a similar skeletal structure. The mass spectrum exhibited a peak at m/e 140 (M^+ − 34) indicating the presence of a free thiol.[91] Careful chromatographic analysis of the nonpolar material above in ether resulted in two components in an approximate 1:1 ratio; the fast component (R_f 0.48, ether) rapidly equilibrated during isolation (after completing the preparative TLC experiment) to give the original 1:1 mixture; the slow component (R_f 0.36, ether) also equilibrated, albeit over a longer period of time (2 h), to yield an identical 1:1

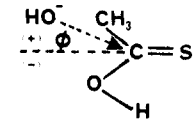
Scheme XIII



mixture. Treatment of the isolated mixture above with moist ethereal HBF_4 gave **113** quantitatively, with evolution of hydrogen sulfide; each component in the mixture, after chromatographic separation and subsequent exposure to moist air, also rapidly yielded hydroxylactone **113**. In the light of these findings, structures [**15A**] and [**15B**] were assigned to the two components in the nonpolar material (R_f 0.64, $CHCl_3$–CH_3CN, 5:1 v/v) (Scheme XIII).

Quite possibly, [**15A**] and [**15B**] interconvert by dissociation and recombination of hydrosulfide ion. The labile nature of the C–S bond in [**15A**] and/or [**15B**] is further substantiated by the absence of the ordinarily weak CS–H stretching band in the infrared spectra and by our failure to synthesize **114** by the addition of CH_3SLi to **66** under a wide variety of conditions, including those for the successful synthesis of **67**. In contrast, addition of NaOMe to **66** did yield **67** (60% yield) (cf. Schemes VI and XIII).

The reluctance of [**15B**] to transform to **68** (Scheme XIII), despite stereoelectronic assistance by two antiperiplanar nonbonded electron pairs, may be explained on kinetic and/or thermodynamic grounds. The kinetic explanation stems from a vector analysis[70] for the C(=S)OR function and the principle of microscopic re-



versibility. Models indicate that the locus of points to be traced by the departing hydroxyl oxygen of [**15B**] should be along the axis of the S–C bond (away from the C) and that such a motion is possible only through high-energy boat-type conformations which must be strained even more as the oxygen group departs. Hence, the barrier for the breakdown of [**15B**] may be unusually high because of the demands of the leaving group. The thermodynamic explanation,[71] on the other hand, remains a plausible alternative. It would require that the interconversion of [**15A**] and [**15B**] take place by C–O cleavage via intermediate **68** and that the equilibrium [**15A**] + [**15B**] ⇄ **68** lie to the left.

Recent MNDO calculations[92] on the trajectory at 2.0 Å for the attack of ^-OH on C=S in (*Z*)-$CH_3C(=S)OH$ yielded an orbital φ of "+" 32° (!), the consequence of a large amount of electron density in the O–C–S quadrant which causes the "hole" or virtual density to appear in the opposite quadrant (the one in the vicinity of the methyl group). The electrostatic (polarization) trajectory φ was found to be toward the interior of the C=S system as this dipole is opposite to that of the carbonyl group. The result is a θ = 87° and ϕ = +72°, leading to a trajectory

(64) Olah, G.; Prakash, G. K.; Rawdah, T. N.; Whittaker, D.; Rees, J. C. *J. Am. Chem. Soc.* **1979**, *101*, 3935.

(65) (a) Nader, R. B.; Kaloustian, M. K. *Tetrahedron Lett.* **1979**, 1477. (b) Kaloustian, M. K.; Aguilar-Laurents de Gutierrez, M. I.; Nader, R. B. *J. Org. Chem.* **1979**, *44*, 666–668. (c) Nader, R. B., Ph.D. Dissertation, Fordham University, 1980.

(66) (a) Renson, M.; Colliene, R. *Bull. Soc. Chim. Belges* **1964**, *73*, 491. (b) Rioult, P.; Vialle, J. *Bull. Soc. Chim. Fr.* **1968**, 4483. (c) Scheeren, J. W.; Ooms, P. H. J.; Nivard, R. J. F. *Synthesis* **1973**, 149.

(67) (a) Scheibye, S.; Kristensen, J.; Lawesson, S.-O. *Tetrahedron* **1979**, *35*, 1339. (b) Shabana, R.; Scheibye, S.; Clausen, K.; Olesen, S. O.; Lawesson, S.-O. *Nouv. J. Chim.* **1980**, *4*, 47–51.

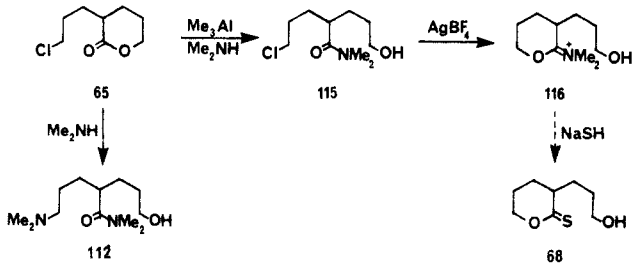
(68) While the quantitative preference of SMe at C-2 of 1,3-dioxane is not known, the axial preference should be substantially smaller than that of methyl for steric reasons;[69] furthermore, the SMe group should indeed be subject to a "mild" axial preference due to the anomeric effect.

(69) Nader, F. W.; Eliel, E. L. *J. Am. Chem. Soc.* **1970**, *92*, 3050. The C-2 methyl group in 1,3-dioxane has a dominant equatorial preference $-\Delta G^\circ$ = 3.97 kcal/mol.

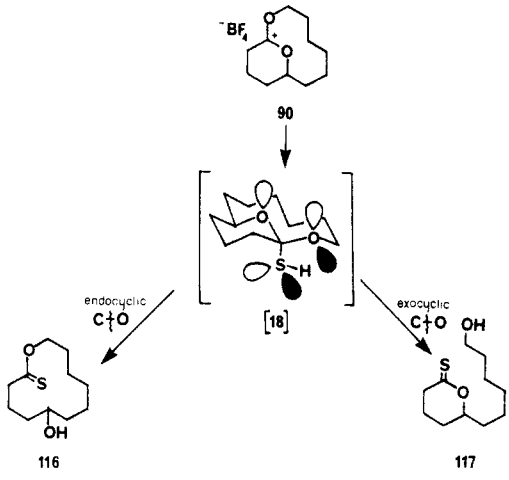
(70) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 738.

(71) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: Oxford, p 95.

Scheme XIV



Scheme XV

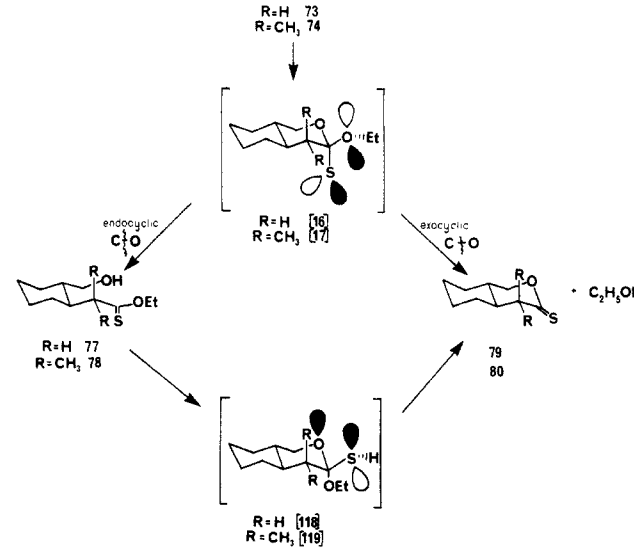


difficult to follow in the ring opening (or reverse) of [**15B**] and of [**15A**]. These steps would have been facile had the ϕ angle been between −10° and −20°. These calculations are in strong support of the kinetic explanation. It must be noted that heating of a mixture of [**15A**] and [**15B**] in xylene (130 °C) under nitrogen, for 30 min, generated only minute amounts of a much more polar $PdCl_2$-positive (sulfur-containing) spot. The latter is most probably **68**, the R_f of which (0.31) is reminiscent of that of the known hydroxylactone **113** (R_f 0.20, $CHCl_3$–CH_3CN, 5:1 v/v). Continued heating of the xylene solution resulted in the complete decomposition of **68**. To help distinguish between the kinetic and thermodynamic explanations, we attempted an independent synthesis of **68**; unfortunately it was unsuccessful; the dimethylaminolysis product **115** (Scheme XIV), successfully obtained (42% yield) by reacting **65** with Me_3Al–Me_2NH,[93,72] failed to undergo $AgBF_4$-induced ring closure to the corresponding (dimethylimino)lactonium fluoborate salt **116**. The sulfhydrolysis of the latter would then have yielded the desired **68**.

Bicyclic Hemiorthothiol Ester Tetrahedral Intermediate [18]. The design of this intermediate was based on the expectation that in reactive conformer [**18**], the "endocyclic" C–O bond would cleave selectively as a result of the Deslongchamps effect;[73] that is, under kinetic control **116** would predominate over **117** (Scheme XV).

As pointed out under Results, efforts to synthesize precursor salt **90** by intramolecular alkylation of halolactones **86–89** proved to be futile.[2] Illuminati and co-workers[74] have investigated quantitatively the lactonization of ω-bromoalkanoate ions in 99% aqueous dimethyl sulfoxide and found that the rates of formation of the four-, five-, and six-membered ring lactones exceeded that

Scheme XVI



of the ten-membered ring by factors of 10^4–10^6. If one notes that the cyclization, en route to **90**, would involve the formation of a ten-membered ring and that the nucleophilicity of the lactone carbonyl oxygen in our systems (**86–89**) is less than that of their alkanoate anions, it is reasonable to assume that formation of a ten-membered lactonium salt **90** would be extremely sluggish; hence, the failure in the formation of **90**. The Ag^+-induced enhancement of the leaving ability of the halide group in **86–89** appears to be ineffective.

Hemiorthothiol Tetrahedral Intermediates [16] and [17]. Since our efforts to generate [**18**] were foiled, owing to the inaccessibility of precursor **90**, we turned our attention to tetrahedral intermediates [**16**] and [**17**] as substitute models for [**18**].

The breakdown of each of these intermediates would constitute a test for stereoelectronic control in an *intramolecular* competition between two leaving groups of very similar leaving abilities (except for orientation of electron pairs). That is to say, if stereoelectronic factors were to play a role, one would expect to observe the preferential cleavage of the *endocyclic* C–O bond over the *exocyclic* C–O bond, despite a counteracting entropy term (Scheme XVI).

Experimentally, the cleavage of [**16**] and [**17**], under kinetic conditions (vide supra, Results), led to the almost exclusive formation[75] (TLC at room temperature) of **77** and **78**, respectively (Scheme XVI). In view of the minute amounts of the kinetic products (**77** and **78**) formed, at −78 °C, and their marked propensity to undergo cyclization (**77** → **79**; **78** → **80**), we could not isolate and characterize them directly. But, when a sample of **73** (Scheme VII) was treated with NaSH in CD_3CN, rapid scanning of the δ 4.0–5.0 ppm range revealed a characteristic quartet ($C(=S)OCH_2CH_3$) at 4.50 ppm, at the same time that an aliquot of the NMR sample showed an intense $PdCl_2$-positive spot on TLC (R_f 0.55). Subsequent TLC analysis as a function of time, showed this spot to disappear gradually in favor of another thiono compound (R_f 0.75). Correlation of the R_f values (Table III) of fully characterized hydroxy thiono esters **55**, **57**, and **58** (R_f's 0.53 ± 0.02) and thionolactones **50**, **52**, and **53** (R_f's 0.76 ± 0.02) from the sulfhydrolysis of **45**, **47**, and **48** further supports the structural assignments of **77** and **78** (R_f's 0.53 and 0.55, respectively) and **79** and **80** (R_f's 0.78 and 0.77, respectively). As the temperature was raised, the spots with R_f's 0.53 and 0.55 gradually grew fainter while those with R_f's 0.78 and 0.77 intensified. (All of the R_f's above were determined on Merck precoated silica gel 60F-254 by eluting with $CHCl_3$–CH_3CN, 5:1 v/v). Further, despite the instability of these thionolactones,[76]

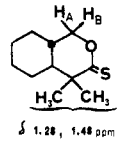
(72) The product of direct aminolysis of **65** proved to be **112** and not **115** (Scheme XIV).

(73) The "endocyclic" C–O bond of [**18**] is antiperiplanar with respect to two electron pairs, one on the "exo" O and one on the sulfur; in contrast, the "exocyclic" C–O is antiperiplanar with respect to the one on S, the other antiperiplanar position is occupied by a localized C–O bond (Scheme XV).

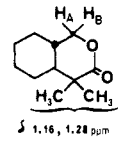
(74) (a) Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95–102. (b) Mandolini, L.; Galli, C. *J. Chem. Soc., Chem. Commun.* **1982**, 251–253. (c) Illuminati, G.; Galli, C.; Mandolini, L.; Tamborra, P. *J. Am. Chem. Soc.* **1977**, *99*, 2591. (d) Illuminati, G.; Galli, C.; Mandolini, L. *Ibid.* **1973**, *95*, 8374.

(75) As explained in footnote 23 of ref 1b, control experiments indicated that minute amounts of thionolactones **79** and **80** in the respective mixtures are, in all likelihood, artifacts of the TLC experiment.

we were able, in one instance, to isolate and characterize **80**. Its



80



72

spectral features were found to be strikingly similar to those of lactone **72**. The methyl singlets in **80** were shifted to δ 1.28 and 1.48 ppm as compared to δ 1.16 and 1.28 for those of **72**. Furthermore, the AB part of the ABX spin system in **80** (δ_A 3.90, δ_B 4.39 ppm, J_{AB} = 12.0 Hz, J_{AX} = 11.5 Hz, J_{BX} = 5.0 Hz) corresponded to the AB pattern in the ^{1}H NMR spectrum of lactone **72** (δ_A 3.80, δ_B 4.22 ppm, J_{AB} = 11.0 Hz, J_{AX} = 11.0 Hz, J_{BX} = 4.5 Hz).

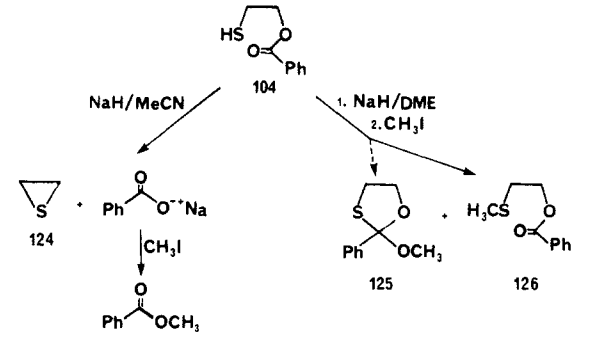
On the basis of the findings above, we assume a minimum rate constant ratio of 100:1 for $k_{[16]\rightarrow[77]}/k_{[16]\rightarrow[79]}$ and $k_{[77]\rightarrow[78]}/k_{[17]\rightarrow[80]}$. If one disregards the entropy term,[77] the difference in free energies of activation, $\Delta\Delta G^{\ddagger}$, in effect the stereoelectronic factor, may be estimated at 2.0 kcal/mol at −78 °C. If one does not disregard the entropy term, the cleavage of the exocyclic C–O bond in each of [**16**] and [**17**] (giving two molecules—thionolactone and alcohol—starting with one) should be favored by part of the total entropy term,[77] depending on the extent of cleavage in the transition states. The stereoelectronic factor, in that case, has to be *in excess* of the 2.0 kcal/mol value estimated above.

In their "alternative explanation" for the lack of lactone formation in the kinetic cleavage of hemiortho esters, Perrin and Arrhenius[39] assume that the entropic contribution to transition states is minimal, whereas the enthalpic contribution is practically maximal. Such a situation leads to an unrealistic energy profile for the two competing pathways.

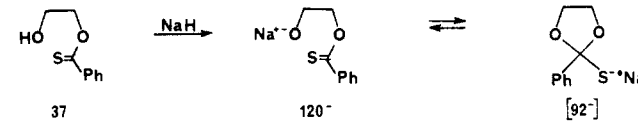
The selective C–O bond cleavages in the case of [**16**] and [**17**] constitute proof for the presence of a Deslongchamps effect in the kinetic breakdown of neutral hemiorthothiol intermediates with two intrinsically identical leaving groups (except for the orientation of nonbonded electron pairs on the leaving oxygenated functions). The cyclizations **77** → **79** and **78** → **80** proceed, at higher temperatures, presumably through intermediates [**118**] and [**119**] (Scheme XVI). Clearly, under thermodynamic conditions, the system **79** + *EtOH* is more stable than **77**; the same is true for **80** + *EtOH* vs. **78**.

Anionic Hemiorthothiol Ester Tetrahedral Intermediates of Type [19⁻]. The transformation of thionobenzoate **37** to anion [**92**⁻] (Scheme IX) was followed by monitoring the disappearance of the $n\rightarrow\pi^*$ (418 nm) band of **37** in hexane as increasing amounts of NaH were added (Figure 2 in ref. 1a); also, the simultaneous gradual fading of the yellow thionobenzoate solution to give an almost *colorless* suspension was observed. White solid [**92**⁻], and similarly-obtained solids [**91**⁻], [**93**⁻], and [**94**⁻], proved to be insoluble in a variety of inert solvents (CH_2Cl_2, $CHCl_3$, hexane, acetone, acetonitrile); hence, their ^{13}C NMR, ^{1}H NMR, UV, and solution-IR spectra could not be recorded. However, swift manipulation of these solids enabled us to record their infrared spectra in KBr, at room temperature. The fingerprint regions of anions [**91**⁻] – [**94**⁻] on the one hand, and those for the corresponding

Scheme XVII



orthothioesters **95**–**98** on the other, showed striking similarities, thereby suggesting a common skeletal structure.[79] Moreover, all spectra of orthothioesters (**95**–**98** and orthothiolate ester anions [**91**⁻] – [**94**⁻] lacked the strong band around 1230 cm^{-1} attributable to the C=S vibration of thiono esters.[80] It was conceivable that deprotonation of **37** with NaH would lead to **120**⁻ in equilibrium with [**92**⁻] and that during subsequent alkylation [**92**⁻] would react faster than **120**⁻. To rule out such a kinetic preference for S- over O-alkylation (e.g., [**92**⁻] over **120**⁻), a mixture of sodium hexoxide

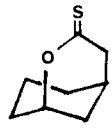


37 **120**⁻ [**92**⁻]

(13 mg, 0.10 mmol) and sodium *n*-hexylmercaptide (19 mg, 0.13 mmol), prepared from the corresponding alcohol and mercaptan with NaH in CH_2Cl_2, was alkylated with a limited amount of $Me_3O^+BF_4^-$ (15.5 mg, 0.10 mmol) in dry CH_2Cl_2 (1.50 mL) at 0 °C for 1.5 h. The residue, after filtration and careful removal of the solvent, displayed a singlet at δ 3.31 (OMe) ppm and another singlet at δ 2.08 (SMe) ppm, in a ratio of 1.6:1, showing that there is no dominant preference for S- over O-alkylation and that for these systems, under the specified experimental conditions, O-alkylation is competitive with S-alkylation. Strikingly, after the methylation of [**92**⁻] (MeI or $Me_3O^+BF_4^-$ in CH_2Cl_2), no O-alkylated product was observed, thereby lending further proof to the assignment of orthothiolate anion structures [**91**⁻]–[**94**⁻] to the isolated solid tetrahedral species. This was confirmed by comparison of TLC, IR, and ^{1}H NMR data of authentic 2-methoxyethyl thionobenzoate (**121**, prepared from 2-methoxyethanol and methyl thionobenzoate in the presence of NaH in dimethoxyethane.) Further, only small amounts (~5%) of **121** were detected (TLC, R_f 0.45, $CHCl_3$; ^{1}H NMR O*Me* at δ 3.44 ppm), when the entire crude and heterogeneous mixture of 2-hydroxyethyl thionobenzoate **37** (87 mg, 0.47 mmol) in cold (0 °C) dry CH_3CN (15.5 mL) and NaH (11.5 mg, 0.47 mmol) was trapped, after 15 min, with 1 equiv of $Me_3O^+BF_4^-$ (70.6 mg, 0.47 mmol). Thus, the assignment of orthothiolate anion structures [**91**⁻]–[**94**⁻] appears to be valid not only for the solids but for their solutions in CH_2Cl_2 or CH_3CN as well.

The thermal stability of anionic intermediates [**91**⁻]–[**94**⁻] is surprising and significant. According to the stereoelectronic theory, these intermediates are subject to both primary and secondary stereoelectronic effects. However, the unusual thermal stability of these systems must be due to (a) the localization of the negative charge on the softer sulfur atom (instead of the oxygen atom of the acyclic $^-O(CH_2)_nOC(=S)R$) and (b) the formation of a strong C–O bond at the expense of a weaker C=S π-bond.

(76) The bicyclic thionolactone shown below (cf. Ayral-Kaloustian, S.; Agosta, W. C. *J. Org. Chem.* **1982**, *47*, 284 and *Synth. Commun.* **1981**, *11*, 1011) is, to the best of our knowledge, the most stable nonaromatic thionolactone reported to date).



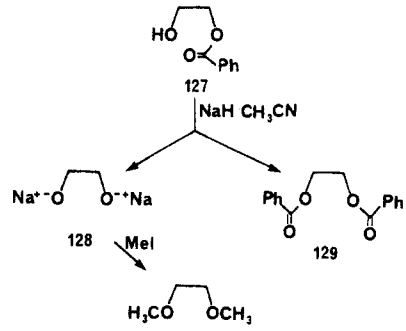
(77) At a standard state of 1 M, $\Delta S°$ for a typical reaction in which one molecule of reactant breaks into two would be +35 *G* and the corresponding $\Delta G°$ would be −10.5 kcal/mol.[78] The true value is of course different, and it may be obtained by taking into account the differential changes in entropies of the specific incipient product molecules in the transition states.

(78) Jencks, W. P. *Adv. Enzymol.* **1975**, *43*, 276.

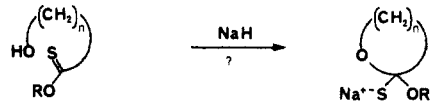
(79) The spectra for **37**, [**92**⁻], and [**96**] were given in Figure 3 of ref 1a; the spectra for the analogous members show similar features.

(80) This assignment of the C=S vibration in thiono esters was based on the comparison of the infrared spectra of methyl and ethyl thionobenzoates with methyl and ethyl benzoate, respectively. In our hands the spectra of methyl thionobenzoate and ethyl thionobenzoate revealed characteristic strong C=S bands at 1235 and 1245 cm^{-1}, respectively; these bands are absent in spectra of methyl and ethyl benzoate.

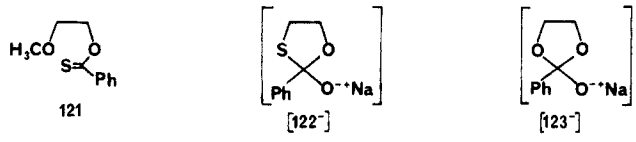
Scheme XVIII



The isolation of these tetrahedral species was facilitated by their fortuitous, insoluble nature of the sodium salts in acetonitrile. The successful formation of anionic intermediates [**91**$^-$]–[**94**$^-$] should be, in principle, extendable to cyclization of the type



With the intention of generating [**122**$^-$], in a manner similar to the above **37** → [**92**$^-$] cyclization (Scheme IX), mercaptobenzoate **104** was made to react with NaH in dry dimethoxyethane, followed by treatment with MeI. Only thioether **126** was



obtained; no 2-methoxy-2-phenyl-1,3-oxathiolane (**125**) could be detected. The reaction of **104** with NaH in acetonitrile, with no subsequent methylation, resulted in the precipitation of a solid which, after filtration and alkylation with MeI to methyl benzoate, was identified as sodium benzoate (Scheme XVII); no attempt was made to detect or isolate any ethylene sulfide that may have been present in the cyclization reaction mixture. This neighboring group displacement giving sodium benzoate (Scheme XVII) finds precedent in the work of Hine[7j] in which sodium trifluoroacetate and ethylene oxide were obtained upon treating 2-hydroxyethyl trifluoroacetate with base.

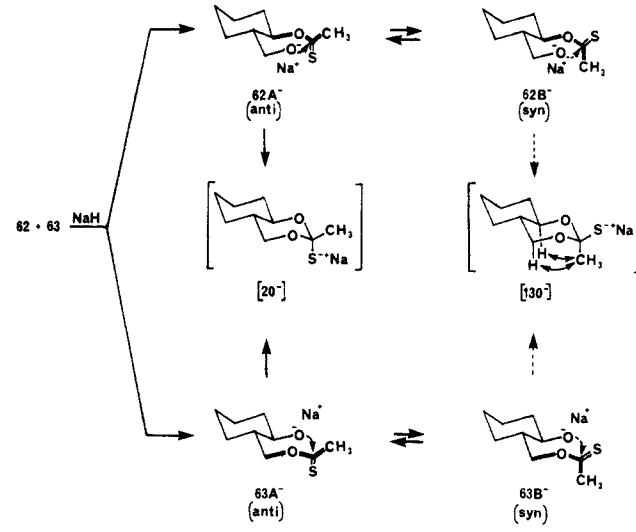
In an attempt to generate [**123**$^-$], 2-hydroxyethyl benzoate (**127**) was treated with NaH in acetonitrile. However, the products consisted of the disodium salt of ethylene glycol (**128**; identified after alkylation with MeI to dimethoxyethane) and 1,2-dibenzoyloxyethane **129** (Scheme XVIII).

Bicyclic Hemiorthothiol Ester Anion [20$^-$]. Orthothioester **99**, obtained by methylation of anionic intermediate [**20**$^-$] (vide supra Scheme X), proved to be identical (^{1}H NMR) with the product obtained from the reaction of **61** and MeS$^-$ $^+$Li (Scheme X). This comparison confirms the axial assignment of the methylthio group in **99**. Consequently, the anionic intermediate must be assigned structure [**20**$^-$] with an axial mercaptide group; this implies that the diastereofacioselective attack of the alkoxide end in **62A**$^-$ and **63A**$^-$ on the thionoacetate groups proceeds to give a single product viz. [**20**$^-$], rather than [**130**$^-$]. Such 6-*endo*-Trig cyclizations are intelligible in terms of different rotational isomers of the thionoacetate groups in **62** and **63** (Scheme XIX). Rotamers **62A**$^-$ and **63A**$^-$ with anti thionoacetate moieties would cyclize to intermediate [**20**$^-$] with an axial mercaptide, whereas cyclization of rotamers **62B**$^-$ and **63B**$^-$ (syn thionoacetates) are expected to lead to the hypothetical intermediate [**130**$^-$]. The cyclization **62B**$^-$ → [**130**$^-$] (or of **63B**$^-$ → [**130**$^-$]) has a higher energy of activation than that of **62A**$^-$ → [**20**$^-$] (or of **63A**$^-$ → [**20**$^-$]) owing to the severe[69] steric compression of the axial methyl group in [**130**$^-$].

Experimental Section

General Methods. Commercially available organic and inorganic chemicals were used as supplied unless otherwise noted. Melting points

Scheme XIX



were determined on a Fisher-Johns apparatus and are uncorrected. Ultraviolet and visible spectra were recorded on a Cary 14 spectrophotometer. Infrared (IR) spectra were recorded on a Perkin-Elmer 710B spectrophotometer. Nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Varian A-60A, XL-100 or a Perkin-Elmer R12B instruments.

Dichloromethane, acetonitrile, benzene, dimethoxyethane, diisopropylamine, and HMPA (0.5 torr) were distilled from CaH_2. Nitromethane was distilled from P_2O_5, THF from $LiAlH_4$, methanol from magnesium methoxide, and isopropyl alcohol from aluminum isopropoxide. Acetone (ACS reagent) was dried by stirring overnight over boric anhydride followed by filtration and fractional distillation.[81] Anhydrous ether was used as supplied by Mallinckrodt and Fisher.

Analytical thin-layer chromatography (TLC) was conducted on precoated plates (silica gel 60F-254, layer thickness 0.25 mm) manufactured by E. Merck. Preparative layer chromatography was carried out on 20 × 20 cm glass plates coated with 2-mm thickness of EM silica gel 60 PF-254. For silica gel columns EM silica gel 30 (70–230 mesh ASTM) was used; when a quartz column was used, this silica gel was mixed with 1% w/w of "Baker Fluorescent Indicator, Activated Zinc Silicate".

All reactions involving air- or moisture-sensitive compounds were performed in flame-dried glassware under nitrogen or argon; such compounds were handled or stored in dry Schlenckware under an inert atmosphere. Elemental analyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, MI; Schwarzkopf Microanalytical Laboratory, Inc., Woodside, NY; Chemalytics, Inc., Tempe, AZ. Satisfactory analyses could not be obtained for certain compounds sensitive to moisture, air, or light.

Key reagents trimethyloxonium tetrafluoroborate,[82] triethyloxonium tetrafluoroborate,[83] anhydrous sodium hydrosulfide,[84] 96% sodium sulfide ("anhydrous sodium sulfide"),[85] lithium methylmercaptide,[55] 2-methyl-1,3-dioxolane,[86] 2-phenyl-1,3-dioxolane,[86] 2-phenyl-1,3-dioxane,[87] trimethyl orthobenzoate,[88] phenyl dimethoxycarbonium tetrafluoborate (**28**),[47a] diethoxycarbonium tetrafluoborate,[47a] ethyl diethoxycarbonium tetrafluoborate,[47a] 1,3-dioxolane-2-ylium tetrafluoborate (**100**),[47a] 2-methyl-1,3-dioxolane-2-ylium tetrafluoborate (**30**),[89] and 2-phenyl 1,3-dioxolane-2-ylium tetrafluoborate (**31**)[89] were prepared following literature procedures. Triethyl orthoformate, triethyl orthoacetate, butyrolactone, δ-valerolactone, δ-valerolactone, and caprolactone were purchased from Aldrich Chemical Company. Phenyl diethoxycarbonium tetrafluoborate (**29**) was prepared according to the procedure described for the methyl analogue.[47a]

Sulfhydrolysis of O-Alkyllactonium Tetrafluoroborate Salts. Thermodynamic Control. General Procedure. Anhydrous sodium hydro-

(81) Burfield, D. R.; Smithers, R. H. *J. Org. Chem.* **1978**, *43*, 3966.
(82) Curphey, T. *Org. Synth.* **1971**, *51*, 142.
(83) Meerwein, H. *Organic Synthesis*; Wiley: New York, 1973; Collect. Vol. V, p 1080.
(84) Eibeck, R. E. *Inorg. Synth.* **1963**, *7*, 128.
(85) Brauer, G., Ed.; *Handbook of Preparative Inorganic Chemistry*; Academic Press: New York, 1963; Vol. 1, p 360.
(86) Hibbert, H.; Timm, J. *J. Am. Chem. Soc.* **1924**, *46*, 1283.
(87) Eliel, E. L.; Knoeber, M. C., Sr. *J. Am. Chem. Soc.* **1968**, *90*, 3444.
(88) McElvain, S. M.; Venerable, J. T. *J. Am. Chem. Soc.* **1950**, *72*, 1661.
(89) Meerwein, H.; Hederich, V.; Morschel, H.; Wunderlich, K. *Justus Liebigs Ann. Chem.* **1960**, *635*, 1–21.

sulfide[84] was added from a Schlenck tube under nitrogen to a cold (0 or −42 °C) solution of O-alkyllactonium tetrafluoroborate in dry CH_3CN. The mixture was stirred in the cold for the specified period of time, diluted with ether, and filtered through Celite. The filtrate was concentrated by careful distillation of the solvent (for **49**, **50**, and **51**) or in vacuo. Chromatographic separation of the residue (dry silica gel column or preparative layer chromatography) afforded the desired thionolactones and hydroxy thiono esters.

Thionobutyrolactone (49). This was prepared from **44** (167 mg, 0.89 mmol) and sodium hydrosulfide (49.8 mg, 0.89 mmol) in dry cold (−42 °C) CH_3CN (1.75 mL) for 2.5 h. Preparative layer chromatography eluting with $CHCl_3$–MeCN (5:1 v/v) gave 91 mg (100%) of thionolactone **49**: NMR ($CDCl_3$) δ 2.28 (2 H, quintet, CH_2), 3.06 (2 H, t, $CH_2C{=}S$), 4.66 (2 H, t, OCH_2); IR (neat) 1380, 1320, 1240, 1175, 920 cm^{-1}. Anal. Calcd for C_4H_6OS: C, 47.03; H, 5.92. Found: C, 46.98; H, 5.81.

γ-Thionovalerolactone (50). This thionolactone was prepared from lactonium salt **45** (500 mg, 2.31 mmol) and sodium hydrosulfide (130 mg, 2.32 mmol) in dry MeCN (3 mL) at 0 °C for 1.5 h. Preparative layer chromatography ($CHCl_3$–MeCN, 5:1 v/v) gave 205 mg (77.6%) of **50**: NMR ($CDCl_3$) δ 1.50 (3 H, d, J = 7.0 Hz, CH_3), 1.75–2.60 (2 H, complex m, CH_2), 3.10 (2 H, m, $CH_2C{=}S$), 5.00 (1 H, m, OCH); IR (neat) 1450, 1345, 1310, 1235, 1150, 1030, 860 cm^{-1}. Anal. Calcd for C_5H_8OS: C, 51.69; H, 6.94. Found: C, 51.98; H, 7.10.

δ-Thionovalerolactone (51). Reaction of lactonium salt **46** (308 mg, 1.52 mmol) and sodium hydrosulfide (101 mg, 1.80 mmol) in dry CH_3CN (3 mL) at 0 °C for 2 h gave, after workup and dry-column chromatography (CH_2Cl_2) 97 mg (54.8%) of the thionolactone: NMR ($CDCl_3$) δ 1.70–2.00 (4 H, m, CH_2), 3.04 (2 H, t, $CH_2C{=}S$), 4.44 (2 H, t, OCH_2); IR (neat) 1280, 1255, 1145, 1080, 890 cm^{-1}. No satisfactory analysis was obtained, owing to the instability of the thionolactone.

5-Ethyl-δ-thionovalerolactone (52). A cold (0 °C) solution of lactonium salt **47** (714 mg, 2.92 mmol) in dry MeCN (5.8 mL) was treated with sodium hydrosulfide (0.164 g, 2.92 mmol) for 2.5 h. Preparative TLC, after the workup, eluting with $CHCl_3$–CH_3CN (5:1 v/v) gave 181 mg (43.0%) of **52**: NMR ($CDCl_3$) δ 1.06 (3 H, t, CH_3), 1.40–2.20 (6 H, m, CH_2), 3.00 (2 H, m, $CH_2C{=}S$)), 4.28 (1 H, m, OCH); IR (neat) 1465, 1370, 1280, 1250, 1160, 1100, 1000, 965 cm^{-1}. Ethyl 5-hydroxythionoheptanoate (**57**) (272 mg, 49%) was also obtained: NMR ($CDCl_3$) δ 0.94 (3 H, t, CH_2CH_3), 1.20–2.20 (10 H, m, CH_2's, OCH_2CH_3, and OH), 2.74 (2 H, t, $CH_2C{=}S$)), 3.52 (1 H, quintet, CHOH), 4.48 (2 H, q, OCH_2CH_3); IR (neat) 3400, 1460, 1375, 1300, 1260, 1200, 1100, 1040 cm^{-1}.

ε-Thionocaprolactone (53). This thionolactone was prepared from lactonium salt **48** (300 mg, 1.30 mmol) and sodium hydrosulfide (73.1 mg, 1.30 mmol) in dry MeCN (2.0 mL) at 0 °C for 2 h. Preparative TLC ($CHCl_3$–MeCN, 5:1 v/v) gave 76 mg (44%) of thionolactone: NMR ($CDCl_3$) δ 1.60–1.90 (6 H, m, CH_2), 3.00–3.30 (2 H, m, $CH_2C{=}S$)), 4.35–4.60 (2 H, m, OCH_2); IR (neat) 1385, 1295, 1240, 1165, 1065, 975 cm^{-1}. Ethyl 6-hydroxythionohexanoate (**58**) (38 mg, 16.5%) was also obtained: NMR ($CDCl_3$) δ 1.36 (3 H, t, CH_3), 1.10–2.10 (7 H, m, CH_2 and OH), 2.71 (2 H, t, $CH_2C{=}S$)), 3.61 (2 H, t, CH_2OH), 4.48 (2 H, q, OCH_2CH_3); IR (neat) 3400, 1440, 1260, and 1040 cm^{-1}. Anal. Calcd for $C_6H_{10}OS$: C, 55.35; H, 7.74. Found: C, 55.64; H, 7.98.

Sulfhydrolysis of 61. A cold (0 °C) solution of fluoroborate salt **61** (0.975 g, 4.03 mmol) in dry MeCN (8.5 mL) under a nitrogen atmosphere was made to react with anhydrous sodium hydrosulfide (0.377 g, 6.37 mmol) added in 50-mg portions. After stirring the mixture at 0 °C for 5 h, it was filtered and concentrated in vacuo to leave a light brown residue. Chromatography through a dry silica gel column in a 3.5-cm (i.d.) quartz column eluting with $CHCl_3$–MeCN (5:1 v/v) and evaporation of the solvent led to 383 mg (50.5%) of product the NMR of which showed a mixture of two thionoacetates **62** and **63** (ca. 1.6:1 by integration of the $MeC(=S)OCH_n$ signals): NMR ($CDCl_3$) δ 1.10–2.30 (20 H, m, ring methylenes and OH), 2.60 (6 H, s, $CH_3C(=S)O$), 3.50 (3 H, m, CH_nOH), 4.54 and 5.36 (3 H, m, $MeC(=S)OCH_n$); IR (neat) 3400, 1460, 1275, 1220, 1030 cm^{-1}. The two isomers eluted as one spot on TLC (R_f 0.47) and had to be used immediately in the subsequent cyclization to give [**20**$^-$].

3,4,4a,5,6,7-Hexahydro-2*H*-pyrano[2,3-*b*]pyran-8a-ylium Tetrafluoroborate (1−) (66). A solution of ortho ester **67** (346 mg, 2.01 mmol) in anhydrous diethyl ether (3.5 mL) was placed in a 10-mL, two-necked, pear-shaped flask equipped with a nitrogen inlet and a rubber septum. After cooling in a dry ice–acetone bath for 10 min, distilled boron trifluoride etherate (0.381 g, 2.68 mmol) was introduced dropwise through the septum. After having stirred at −78 °C for 20 min, the cooling bath was removed, and the white solid was observed to melt and resolidify on stirring. The supernatant ether was drawn off, and the solid was washed with 3 3-mL portions of anhydrous ether and dried in vacuo (0.1 torr) to give 0.452 g (98.7%) of the desired product: NMR ($CDCl_3$–CD_3CN, 6:1 v/v) δ 1.50–2.40 (8 H, m, CH_2), 3.20 (1 H, quintet, CH), 4.99 (4 H, t, OCH_2).

***trans*- and *cis*-Hexahydro-2*H*,8a*H*-pyrano[2,3-*b*]pyran-8a-thiol ([15]).** A solution of **66** (452.5 mg, 1.98 mmol) in cold (0 °C) CH_3CN (4.25 mL) was made to react with anhydrous NaSH (161.3 mg, 2.88 mmol) under nitrogen for 3 h. The reaction mixture was filtered under nitrogen, and the filtrate was concentrated in vacuo. The resulting crude oil was chromatographed without delay on two 20 × 20 cm silica gel plates eluting with degassed $CHCl_3$–CH_3CN (5:1 v/v) in a chromatographic chamber that was thoroughly purged and filled with argon [recovered yield 70 mg (20.2%) of a UV-detected (254 nm) component (R_f 0.64); NMR ($CDCl_3$) δ 1.20–2.20 (10 H, m, ring methylenes), 3.50–3.90 (4 H, m, OCH_2's); IR (neat) 1240, 1210, 1165, 1140, 1080, 1025, 995 cm^{-1}; MS, *m/e* 140 ($M^+ - 34$)]. This material could be further resolved into two components with R_f's 0.48 and 0.36. The former rapidly equilibrated to a 1:1 mixture of both components before any spectra could be recorded; the latter had less than 5% of the fast isomer but, after 2 h, also equilibrated to a 1:1 cis/trans mixture [IR (neat) fast—1445, 1380, 1165, 1100, 915 cm^{-1}; slow—1140, 1080, 975 cm^{-1}].

Sulfhydrolysis of O-Alkyllactonium Tetrafluoroborate Salts (Kinetic Control). General Procedure. Anhydrous NaSH (2 equiv) was added, under nitrogen, to a cold (−78 °C) solution of the lactonium salt (1 equiv) in dry acetone. The mixture was stirred at −78 °C for 5 h, after which the flask was tightly stoppered and stored in dry ice for 16–48 h. TLC analysis was carried out, when desired, by drawing an aliquot from the reaction mixture and immediately quenching it in ether order to precipitate unreacted NaSH and to prevent any rearrangement to the thermodynamic product. The ethereal layer was then subjected to immediate TLC analysis.

Sulfhydrolysis of Lactonium Salt 47. Lactonium salt **47** (130 mg, 0.53 mmol) and 18-crown-6[90] (141 mg, 0.53 mmol) in cold (−78 °C) dry acetone (1.06 mL) were treated with NaSH (59.7 mg, 1.06 mmol) at −78 °C for 5 h, followed by storing in dry ice for 16 h. TLC analysis after rapid quenching of an aliquot in ether indicated exclusive formation of hydroxy thiono ester **57** (R_f 0.54, $CHCl_3$–MeCN, 5:1 v/v). The remainder of the reaction mixture was warmed up to room temperature, filtered, and concentrated in vacuo to a residue, which, on preparative TLC ($CHCl_3$–MeCN, 5:1 v/v) gave 34 mg (33.5%) of thiono ester **57**.

Sulfhydrolysis of Lactonium Salt 73. This reaction was conducted according to the general procedure above with 75 mg (0.27 mmol) of the lactonium salt, 73.3 mg (0.27 mmol) of 18-crown-6,[90] and NaSH (31.1 mg, 0.55 mmol) in dry acetone (0.6 mL) at −78 °C for 5 h and storage in dry ice for 48 h. TLC analysis ($CHCl_3$–MeCN, 5:1 v/v) revealed exclusive formation of hydroxy thiono ester **77** (R_f 0.53) which rapidly rearranges (on attempted chromatographic isolation) to the corresponding unstable thionolactone **79** (R_f 0.78).

Sulfhydrolysis of Lactonium Salt 74. The sulfhydrolyses of **74** and **73** (vide supra) were carried out simultaneously under identical conditions. The reaction for **74** utilized 103 mg (0.34 mmol) of lactonium salt, 96 mg (0.34 mmol) of 18-crown-6,[90] and 38.8 mg (0.69 mmol) of NaSH in dry acetone (0.76 mL). TLC analysis, as in the above case, showed exclusive formation of a hydroxy thiono ester (**78**) (R_f 0.55) which rapidly rearranged to the corresponding, relatively more stable, thionolactone (**80**) (R_f 0.77): NMR ($CDCl_3$) δ 1.28 (3 H, s, CH_3), 1.48 (3 H, s, CH_3), 0.90–2.10 (10 H, m, CH_2), 3.60–4.60 (2 H, AB of ABX, CH_2O; δ_A 3.90, δ_B 4.39, J_{AB} = 12.0 Hz, J_{AX} = 11.5 Hz, J_{BX} = 5.0 Hz); IR (neat) = 1460, 1250, 1180, 970 cm^{-1}.

General Procedure for the Cyclization of Hydroxy Thiono Esters (36–39, 62 + 63) to Tetrahedral Intermediates ([91$^-$]–[94$^-$] and [20$^-$]). Sodium hydride (50% dispersion in oil, washed with pentane) was added under nitrogen, in 1 portion, to a stirred, cold (0 °C) solution of the hydroxy thiono ester in dry CH_3CN. The solution was kept stirring at 0 °C for 1 h (until evolution of gas ceased). The flask was tightly stoppered under nitrogen and placed in the freezer for 48 h during which time a white solid precipitated. The solid was filtered under nitrogen, washed thoroughly with anhydrous ether, and allowed to dry under a stream of nitrogen. These solids were manipulated under nitrogen with total exclusion of moisture.

Sodium 2-Methyl-1,3-dioxolan-2-thiolate ([91$^-$]). 2-Hydroxyethyl thionoacetate (**36**) (112 mg, 0.93 mmol) and NaH (22.4 mg, 0.93 mmol) in dry CH_3CN (20 mL) gave 56 mg (42.2%) of tetrahedral intermediate

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[91⁻] [IR (IBr) 1135, 1100, 1030, 950, 845 cm⁻¹]. The solid shows signs of decomposition overnight even when stored under argon.

Sodium 2-Phenyl-1,3-dioxolan-2-thiolate ([92⁻]). This solid was prepared from hydroxy thiono ester **37** (292 mg, 1.60 mmol) and NaH (38.5 mg, 1.60 mmol) in dry CH_3CN (51 mL): yield 254 mg (77.6%); mp (sealed tube) 115 °C dec; IR (KBr) 1210, 1035, 925 cm⁻¹. Anal. Calcd for $C_9H_9O_2SNa$: C, 52.93; H, 4.44. Found: C, 52.60; H, 4.61.

Sodium 2-Methyl-1,3-dioxane-2-thiolate ([93⁻]). This solid was obtained from hydroxy thiono ester **38** (163 mg, 1.21 mmol) and NaH (29.2 mg, 1.21 mmol) in dry CH_3CN (15 mL): yield 66.4 mg (35%); IR (KBr) 1120, 1060, 890, 800 cm⁻¹. The solid decomposes on storing overnight.

Sodium 2-Phenyl-1,3-dioxane-2-thiolate ([94⁻]). The salt was prepared in 66.8% yield (223 mg) from hydroxy thiono ester **39** (300 mg, 1.53 mmol) and NaH (36.75 mg, 1.53 mmol) in dry CH_3CN (50 mL): mp (sealed tube) 115 °C dec; IR (KBr) 1210, 1060, 1015, 950, 900 cm⁻¹.

Sodium (2*R,4a*S**,8a*R**)-Hexahydro-2-methyl-1,3-benzodioxan-2-thiolate ([20⁻]).** Sodium hydride (33.4 mg, 1.39 mmol) was added in 1 portion, under a nitrogen atmosphere, to a stirring ice-cold solution of a freshly prepared mixture of thionoacetates **62** and **63** (262 mg, 1.39 mmol) in dry CH_3CN (27.5 mL). After stirring for 30 min, the flask was tightly stoppered and placed in the freezing compartment of a refrigerator (−4 °C) overnight. The precipitated white solid was filtered under nitrogen, washed with anhydrous ether, and dried: yield 102.3 mg (35.0%); IR (KBr) 1440, 1200, 1160, 1065, 1000, 940, 805 cm⁻¹.

(2*R,4a*S**,8a*R**)-Hexahydro-2-methyl-2-(methylthio)-1,3-benzodioxan (99).** Methyl iodide (64.9 mg, 0.45 mmol) was added, under a nitrogen atmosphere, to a suspension of the freshly obtained anionic intermediate [**20**⁻] (96.0 mg, 0.45 mmol) in dry CH_3CN (1.9 mL) at 0 °C. The mixture was stirred for 1 h at 0 °C after which it was diluted with dry CH_2Cl_2 (5.0 mL) and filtered under nitrogen. Concentration of the filtrate gave 93.0 mg (100%) of the title compound: NMR ($CDCl_3$) δ 1.10–2.20 (9 H, m, ring methylenes), 1.75 (3 H, s, CH_3), 2.00 (3 H, s, SCH_3), 3.40–4.00 (3 H, m, OCH and OCH_2); IR (neat) 1450, 1380, 1210, 1160, 1140, 1065, 940, 830 cm⁻¹. (An analytical sample was prepared by short-path distillation: oil bath temperature 120–140 °C, pressure 20 torr). Anal. Calcd for $C_{10}H_{18}O_2S$: C, 59.36; H, 8.96. Found: C, 59.55; H, 8.86.

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Supplementary Material Available: Syntheses and spectral data for compounds **32–39**, **44–48**, **60–61**, **65–67**, **70–76**, and **95–98** (20 pages). Ordering information is given on any current masthead page.

Thermal Reactions of Cyclopropenone Ketals. Key Mechanistic Features and Scope of the Cycloaddition Reactions of Delocalized Singlet Vinylcarbenes: Three-Carbon 1,1-/1,3-Dipoles

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Abstract: Full details of the key mechanistic features and the preparative scope of the thermal reactions of cyclopropenone ketals which proceed by the thermal generation and subsequent cycloaddition reactions of π-delocalized singlet vinylcarbenes, three-carbon 1,1-/1,3-dipoles lacking octet stabilization, are described and include $_{\omega}2_a$ participation in cheletropic [$_{\pi}2_s + _{\omega}2_a$] nonlinear cycloadditions with an observable endo effect suitable for a one-step, stereoselective construction of *cis*-cyclopropaneacetic acid esters, formal $_{\pi}2_a$ participation in [$_{\pi}2_s + _{\pi}2_a$] cycloadditions suitable for the preparation of functionalized cyclopentenes in which each of the five carbons of the newly formed five-membered ring may bear functionality capable of additional transformations, and $_{\pi}2_s$ participation in [$_{\pi}4_s + _{\pi}2_s$] cycloadditions with selected dienes in direct [3 + 4] cycloadditions suitable for the preparation of functionalized cycloheptadienes capable of further elaboration to tropones/tropolones. The full scope of the thermal reactions of cyclopropenone ketals is demonstrated with the preparation of the complete range of (methoxycarbonyl)tropones, 2-, 3-, and 4-(methoxycarbonyl)tropone and tropone, utilizing the appropriate choice of starting diene and complementary choice of conditions for promoting the thermal [3 + 4] or [4 + 2] cycloaddition of a cyclopropenone ketal. Additional details of a preliminary study of the scope of the cycloaddition reactions of the apparent π-delocalized singlet vinylcarbenes with carbon–heteroatom double bonds are described.

Extensive efforts have focused on the investigation, development, and subsequent application of 1,3-dipolar cycloaddition processes,[2] and the studies in recent years have been characterized by the variety of ways in which the processes can be implemented in the total synthesis of natural products or utilized for the preparation of heterocycles.[2,3] Despite these efforts, the development or use of simple three-carbon 1,3-dipoles in *thermal* cycloaddition reactions has not been described, and their expectant utility remains unrealized.[2,4] The potential participation of three-carbon 1,3-

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