Thiosulfonium Ions. Methylthiolation of Thioketals

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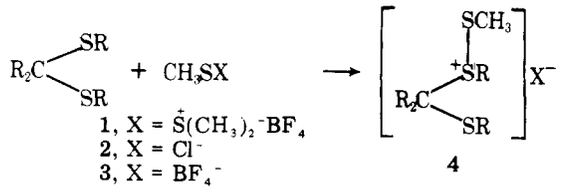
Dimethyl(methylthio)sulfonium fluoroborate (**1**) and methanesulfenyl chloride (**2**) react rapidly with 2,2-bis(methylthio)propane (**5**), 2,2-dimethyl-1,3-dithiolane (**6**), and 2,2-dimethyl-1,3-dithiane (**7**) in nitromethane or dichloromethane to cleave *both* thioketal carbon–sulfur bonds. A product of structure $(CH_3)_2C(SCH_3)X$, X = Cl or $S^+(CH_3)_2$, $^-BF_4$, was obtained from all three acetone thioketals together with methyl disulfide from **5** and polymer from **6** and **7**. These reactions appear to involve thiosulfonium ion intermediates analogous to **1** that rearrange by cleavage and reformation of carbon–sulfur and sulfur–sulfur bonds. The 2-(methylthio)propyl cation $[(CH_3)_2C^+(SCH_3)$, **10**] is evidently a common intermediate that is trapped by the nucleophile $\ddot{X}$ to form the observed product. Reversible dissociation of this product results in its slow decomposition as the intermediate cation **10** reverts to thioketal **5** and other products. The behavior of a representative thioacetal, bis(2-methoxyethylthio)-methane, with **1** was comparable to that of thioketals with **1** and resulted in rupture of the thioacetal function by way of rearrangements involving C–S^+ and S–S^+ cleavage.

Thioacetals and thioketals are useful intermediates in the synthesis and protection of aldehydes and ketones. However, they are less easily hydrolyzed to the parent carbonyl compounds than are the oxygen analogues, acetals and ketals. Proton acid catalysts are unsatisfactory although Lewis acid catalysts such as zinc chloride, titanium tetrachloride, and mercuric salts have been widely used.[1] More recently, hydrolytic cleavage of thioketals has been achieved by activation of the carbon–sulfur bonds through oxidation and alkylation[2] and selenation.[3] In fact, the work described herein began initially with the objective of developing a mild and convenient method of thioketal hydrolysis by way of *alkylthiolation* reactions. It was known from earlier work that carbon–sulfur bonds of sulfides become labile on alkylthiolation at sulfur, and that alkylthiosulfonium ions so formed are highly reactive intermediates that seldom can be isolated.[4–6] We therefore considered the feasibility of thioketal hydrolysis by the reaction sequence summarized in eq 1, where the methylthiolating agent is either dimethyl(methylthio)-sulfonium fluoroborate (**1**) or methanesulfenyl chloride (**2**).

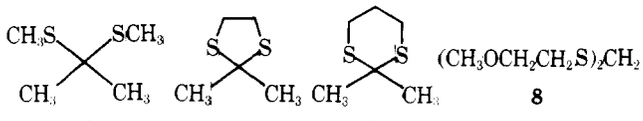


$$\xrightarrow{H_2O} R_2C{=}O + RSSCH_3 + RSH + HX \quad (1)$$

Indeed, we were able to show that treatment of 2,2-dimethyl-1,3-dithiolane with an equivalent of **1** in nitromethane, followed by addition of water, produced acetone, albeit in only 40% yield. Although we have not pursued this reaction further as a practical method of thioketal hydrolysis, we have studied the behavior of several thioketals with **1** and **2** in aprotic solvents. The results are somewhat complex but interesting from a structure-reactivity standpoint and parallel to some extent the alkylselenation reactions of thioketals described by Barton et al.[3] The main point that emerges from this study is that methylthiolation at sulfur of a thioketal at ambient temperature or below leads to rapid cleavage of both carbon–sulfur bonds of the thioketal function.

Results and Discussion

The thioketals employed in this study included acyclic and cyclic derivatives of acetone, **5, 6,** and **7**, as well as the formaldehyde derivative, bis(2-methoxyethylthio)methane (**8**). Their reactions with the sulfenyl salt **1** were carried out in nitromethane as solvent or in mixtures of nitromethane and dichloromethane at 0 °C or below, whereas reactions with methanesulfenyl chloride (**2**) utilized dichloromethane at −35 °C. In all cases, the reactions were followed by NMR, and the products were isolated and analyzed by NMR, GPC, and mass spectrometry where possible.



5 **6** **7** **8**

It was anticipated that reaction would initially involve transfer of a methylthio group of the sulfenyl reagent to sulfur of the thioketal, as shown in eq 1. The results to be described bear this out, but the intermediate thiosulfonium ions **4** are evidently so reactive that they defy isolation or even observation by direct physical methods. Furthermore, the *same* product, **9** or **13**, was formed from each of the three thioketals **5–7**. The identity of this product is the key to understanding the course of these reactions and is described first in connection with the methylthiolation of **5**.

2,2-Bis(methylthio)propane (5) with Dimethyl(methylthio)sulfonium Fluoroborate. The acyclic thioketal **5** reacted rapidly with 1 molar equiv of **1** in nitromethane at 0 ° C to give a product mixture from which two volatile products, methyl sulfide and methyl disulfide, were separated by distillation at reduced pressure. The amount of disulfide formed was quantitative (cf. Table I). In contrast, methyl sulfide was formed in variable and nonreproducible amounts and appears to be a secondary product formed during the evaporative distillation of the reaction mixture. The NMR spectrum of the reaction mixture prior to distillation showed *no* resonance at 2.08 ppm characteristic of methyl sulfide but rather three singlet resonances at δ 1.86, 2.38, and 2.78 with intensities approximating the ratio 6:9:6. The singlet at δ 2.38 was assigned in part to that of methyl disulfide, and the singlet at δ 1.86 was assigned to the geminal methyl groups. Although the singlet resonance at δ 2.78 is almost certainly that of a methylsulfonium group, the chemical shift did not remain constant but shifted progressively to higher fields with time. These observations were at first puzzling, but it became apparent that the major product (besides methyl disulfide) was a sulfonium salt that was unstable, unisolable, and which eliminated methyl sulfide slowly in solution at room temperature, and more rapidly on removal of the solvent by distillation. The product was identified as the methylated thioketal **9** based on NMR evidence, its chemical behavior, and the nature of the reagents from which it is formed (eq 2), as will be described.

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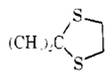
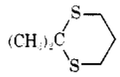
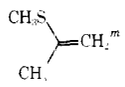
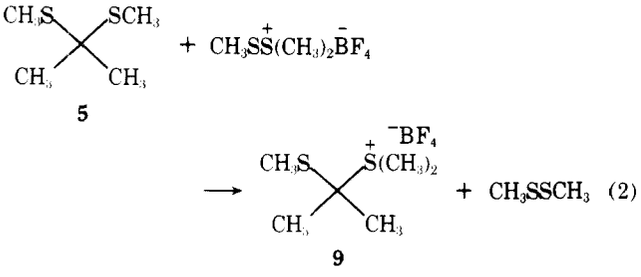
Table I. Summary of Products of Methylthiolation of Thioketals

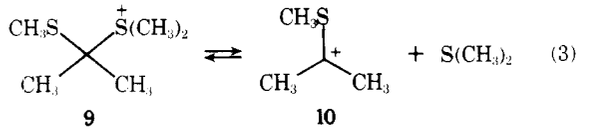
substrate	reagent	initial products[a]		final products,[b,c] % $(CH_3)_2S$[n]	CH_3SS-CH_3[o]	5	11[e,p]	polymer	other	starting substrate
$(CH_3)_2C$-$(SCH_3)_2$ (5)[j]	CH_3SS^+-$(CH_3)_2$[d]	$(CH_3)_2C$-$[S(CH_3)_2^+]$-SCH_3 (9)	CH_3SSC-H_3	56	99[i]		<5			
	CH_3SCl[f]	$(CH_3)_2C$-$(SCH_3)Cl$ (13)	CH_3SSC-H_3	5	100[i]	32	12			
	$(CH_3)_3O^+$			25	<1	36	7		$(CH_3)_3S^+$[d] (30)	36
	CH_3SS^+-$(CH_3)_2$[d]	9	$(C_2H_4S_2)_x$	58	22	<5	<5	64	h	25
	CH_3SCl	13	$(C_2H_4S_2)_x$	<2	23	30	8	65		28
6[k]	CH_3SBF_4		$(C_2H_4S_2)_x$	<1	5	2	<2	20	h	60
	CH_3SS^+-$(CH_3)_2$[d]	9	$(C_3H_6S_2)_x$	69	17	<5	<2	68		18
7[l]										
	HCl[g]	13		<1	<4	30	<2			7

[a] Determined by NMR analysis of the mixture obtained within the first hour of reaction. [b] Obtained after 4–6 days of reaction by distillation of the mixture and GPC–NMR analysis of the distillate. [c] Molar percentage based on the amount of thioketal initially used. [d] Fluoroborate salt in nitromethane. [e] Obtained by hydrolysis of the distillation residue. [f] In dichloromethane. [g] Less than 0.10 molar equiv. [h] A solid of mp 180–182 °C of unknown structure was obtained on hydrolysis of distillation residue. [i] See reaction 5 for stoichiometry. [j] Registry no. 6156-18-9. [k] Registry no. 6008-78-2. [l] Registry no. 6007-22-3. [m] Registry no. 7594-44-7. [n] Registry no. 75-18-3. [o] Registry no. 624-92-0. [p] Registry no. 23550-40-5.



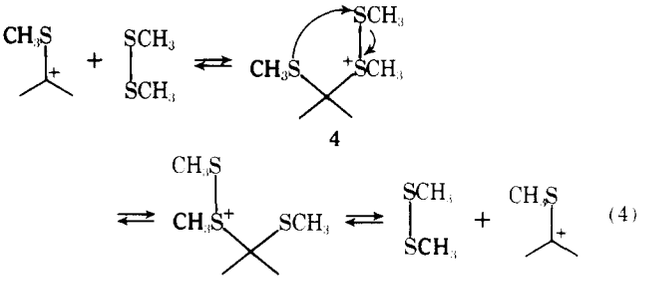
5 9

The NMR spectrum of **9** is of some interest. The singlet resonances at δ 1.86, 2.38, and 2.78 are assigned respectively to protons of methyl groups at carbon, neutral sulfur, and positive sulfur. The δ 2.38 resonance could not be resolved from that of methyl disulfide and, upon addition of methyl sulfide, the δ 2.78 resonance moved to higher fields. The extent of the shift was proportional to the amount of methyl sulfide added yet *no* resonance for methyl sulfide appeared at δ 2.08. There is clearly a rapid exchange reaction occurring between **9** and methyl sulfide that averages the methyl proton resonance of the dimethylsulfonium group of **9** with that of methyl sulfide. The exchange reaction with methyl sulfide is best explained as the result of a reversible dissociation of **9** to methyl sulfide and the 2-(methylthio)propyl cation **10** (eq 3). Because the chemical shifts of the methylthio and gem-dimethyl protons of **9** are relatively unaffected by this exchange, we conclude that the equilibrium of eq 3 strongly favors the sulfonium ion **9** over the carbocation **10.**



9 10 (3)

Less certain, but quite possibly, there is a second rapid exchange reaction involving **9** and methyl *disulfide* that averages the methylthio proton resonances of **9** and the disulfide. Exchange with methyl disulfide is less obvious than with the monosulfide but depends upon the dissociation reaction of eq 3. Presumably, the carbocation **10** produced by dissociation can react with either a monosulfide or a disulfide nucleophile. A reversible reaction with methyl disulfide (eq 4) produces a thiosulfonium ion **4** which bears a nucleophilic methylthio group and an electrophilic methylthio group. Therefore, internal methylthiolation is possible and amounts to a degenerate rearrangement of **4** by methylthio transfer from S^+ to S. If rearrangement is rapid on the NMR time scale, the disulfide and methylthio resonances become indistinguishable. Barring coincidental chemical shifts, this appears to be the case as only one 9-proton resonance at δ 2.38 was observed for the methylthio groups of both **9** and methyl disulfide.

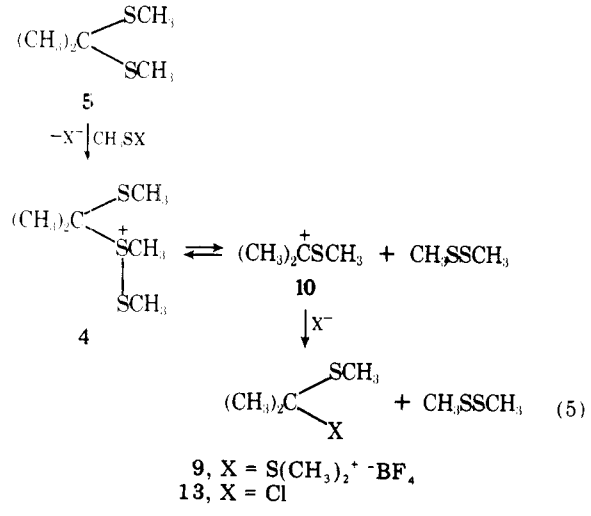


4 (4)

Independent chemical verification of the exchange and rearrangement reactions described by eq 4 was obtained from the reaction of **9** with dimethyl-d_6 disulfide. In this experiment, a solution of **9** in nitromethane was first prepared almost free of methyl disulfide by the methylthiolation of the 1,3-dithiolane derivative **6** (see Experimental Section); to this solution was added 0.25 molar equiv of dimethyl-d_6 disulfide. Subsequently, the disulfide was recovered by preparative GPC and analyzed by mass spectrometry. The analysis showed clearly that molecular ions of *m/e* 94, 97, and 100 corresponding respectively to methyl-d_0, -d_3, and -d_6 disulfide were present in the ratio of 44:44:12. Extensive sulfur–sulfur and carbon–sulfur cleavage must have occurred, and the most reasonable pathway for these events is by the reactions of eq 3 and 4.

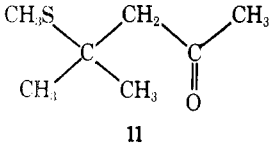
Regarding the way in which **9** is formed from the thioketal

5, it may at first appear that the sulfenyl salt 1 transfers a methyl group rather than a methylthio group to a sulfur atom of 5 (eq 2). This is not the case, however. The products, particularly those from the cyclic thioketals described later, can only be rationalized by a stepwise reaction sequence. With 5, initial *methylthiolation* leads to the thiosulfonium ion 4 which then dissociates to methyl disulfide and the carbocation 10. The ion, 10, is subsequently trapped by methyl sulfide to give 9. The overall sequence is summarized in eq 5. As a general



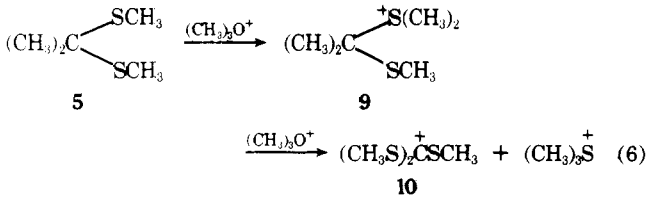
observation in this and previous work,[7-9] thiosulfonium ions such as 4 are appreciably more reactive than the corresponding sulfonium ions such as 9 (X = $S(CH_3)_2^+$) and readily undergo heterolysis of a C–S^+ bond. Evidently, a disulfide is superior to the corresponding sulfide as a leaving group in S_N1-type reactions.

Methylation of 2,2-Bis(methylthio)propane. In principle, the fluoroborate salt 9 could be formed by direct methylation of 5 with trimethyloxonium fluoroborate. However, the reaction turned out to be unexpectedly complex, and 9 was not formed as a stable product. A 1:1 mixture of 5 and the oxonium salt in nitromethane–dichloromethane solution reacted slowly at room temperature and after 6 days showed no further change. The major product was trimethylsulfonium fluoroborate (30%), methyl sulfide (25%), together with 36% of recovered starting material. Hydrolysis of the reaction mixture gave (in addition to the aforementioned products) two minor products 11 and 12 of boiling point 61–62 °C at 6 mm and melting point 180–182 °C dec, respectively. The structure of 12 is unknown, but that of 11 is assigned as 4-methyl-4-(methylthio)-2-pentanone (see Experimental Section).



11

The absence of 9 as a product of this seemingly simple methylation reaction was unexpected and difficult to explain until we realized that 9 readily dissociates to methyl sulfide and 10 in nitromethane. It now appears that 9 is indeed formed in the methylation of 5 but, in the presence of the methyloxonium salt, it dissociates *irreversibly* because the



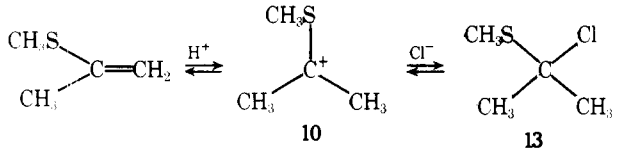
methyl sulfide produced by dissociation of 9 is further methylated to give trimethylsulfonium as the fluoroborate salt (eq 6). The fate of the carbocation 10 formed by this reaction is less easily accounted for because, apart from the minor hydrolysis products 11 and 12 and uncharacterizable resin, no other products were identified that could be ascribed to 10. However, further information on the reactivity of 10 was obtained from attempts to form the ion by proton transfer to 2-(methylthio)propene, as described in a later section.

2,2-Bis(methylthio)propane (5) with Methanesulfenyl Chloride. In most respects, the reaction of 5 with methanesulfenyl chloride (2) parallels that of 5 with the sulfenyl salt 1. Reaction was rapid in dichloromethane at −35 °C, and methyl disulfide was formed quantitatively (Table I). The other major product could not be isolated from solution without decomposition, but its NMR spectrum and its behavior in the dissolved state are consistent with the assigned structure as 2-chloro-2-(methylthio)propane (13). Thus the crude reaction mixture from the addition of equimolar amounts of 2 and 5 in dichloromethane showed (by NMR) the presence only of methyl disulfide (δ 2.40) and 13 (δ 1.91, 6 H; δ 2.37, 3 H). However, the chloride 13 proved to be unstable and slowly reverted to the starting thioketal 5 at room temperature. After 4 days, the only major products identified were methyl disulfide and 5 in a molar ratio of 3:1. Hydrolytic workup of the reaction mixture gave 12% of the ketone 11 (Table I).

Formation of 13 follows from the reaction sequence of eq 5 (X = Cl), but unlike the related product 9 (X = $S(CH_3)_2^+$), the chloride 13 does not exhibit a rapid exchange reaction with methyl disulfide, at least not in dichloromethane solution. Although this indicates that 13 does not rapidly and reversibly dissociate to chloride ion and 10, its slow reversion to starting thioketal can be rationalized as the result of ionic dissociation. In other words, the entire reaction sequence of eq 5 seems to be reversible. Although the rate of the forward process, and hence the net equilibrium, favors formation of disulfide and 13, the small amount of back reaction *and* the instability of methanesulfenyl chloride leak the reaction products back to thioketal 5 and methyl disulfide (a product of decomposition of 2). However, this cannot be the only route back to 5 because the amount of recovered disulfide exceeds that expected of simple reversal of eq 5 (cf. Table I). Also, 13 converts to 5 in the absence of disulfide (see later discussion).

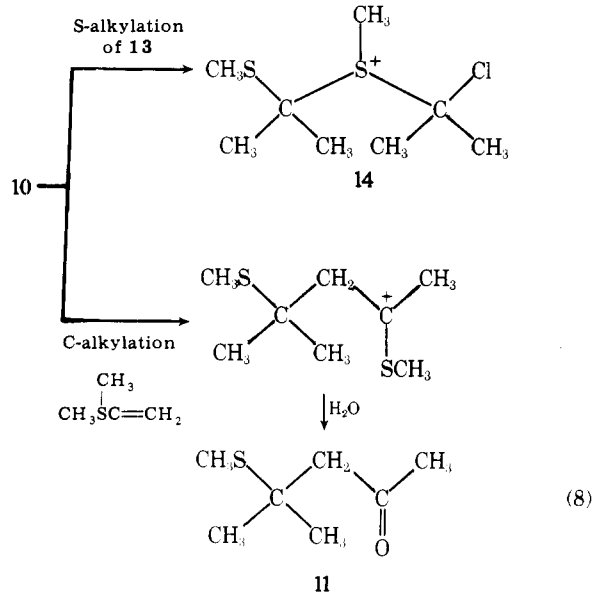
2-Chloro-2-(methylthio)propane from 2-(Methylthio)propene. To verify the formation of 13 in the reaction of 5 with methanesulfenyl chloride, we sought to prepare it by an independent route. Compound 13 is an α-chlorothioether and therefore may be expected to be highly reactive and to eliminate readily. Thus far, its isolation and characterization have not been achieved although two previous attempts at its synthesis have been reported.[10,11] Both routes involve the chlorination of isopropyl methyl sulfide, one with thionyl chloride,[10] the other with molecular chlorine.[11] It appears that both reactions produce 13 which subsequently eliminates HCl to give 2-(methylthio)propene. With chlorine, further addition and elimination occur to give the observed product, 1-chloro-2-(methylthio)propene. We attempted to prepare 13 by the addition of dry hydrogen chloride to 2-(methylthio)-propene, but the only isolable products were 5 (35%) and 11 (5%), together with an appreciable amount of resinous material. However, using a catalytic amount of HCl, the reaction could be followed conveniently by NMR. From the spectrum of the crude reaction mixture it was clear that only three components were initially present, namely thioketal 5, unreacted 2-(methylthio)propene, and the desired α-chloro thioether 13. After 6 days at room temperature, the resonances due to 13 disappeared leaving 5 as the only significant product.

There remains little doubt that **13** is formed in both the hydrochlorination of 2-(methylthio)propene and in the methylthiolation of **5**, but it slowly disproportionates to thioketal **5** and polymer. The process probably involves initial dissociation of **13** to the carbocation **10** which can then alkylate at sulfur of another molecule of **13** (eq 7). The result is a sulfonium ion **14** that can readily dissociate to **5**. The counterion would readily hydrolyze or lead to polymer.[12] The small amount of **11** produced in reactions involving **10** suggests that some C-alkylation also occurs, probably by the addition of **10** to 2-(methylthio)propene (eq 8).



10 **13**

$$5 + [(CH_3)_2\overset{+}{C}Cl] \quad (7)$$



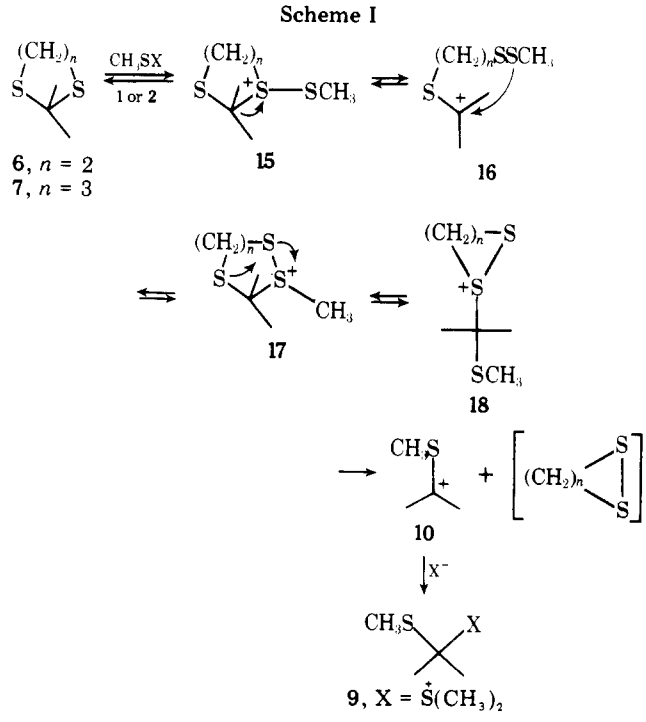
14 **11**

(8)

Methylthiolation of Cyclic Thioketals. The reaction of 2,2-dimethyl-1,3-dithiolane (**6**) with the sulfenyl salt **1** in nitromethane or dichloromethane was rapid at 0 °C and led to the immediate precipitation of a white solid having mp 123–132 °C dec and elemental composition $(C_2H_4S_2)_x$. The corresponding 1,3-dithiane **7** also gave a highly insoluble solid product with mp 68–72 °C dec and composition $(C_3H_6S_2)_x$ on reaction with **1**. The surprising feature of both reactions was that the major product remaining in solution was the same for both the five- and six-ring thioketals and was indistinguishable from **9** obtained from the acyclic thioketal **5**. The NMR spectra of the reaction mixtures from **6** and **7** showed three major singlet resonances at δ 1.89, 2.38, and 2.77 with relative intensities approximately 6:3:6. The conclusion reached from these results is that the sulfenyl reagent **1** effectively cleaves *both* carbon–sulfur bonds in the cyclic thioketals, **6** and **7**. To explain this interesting circumstance it is necessary to recognize that thiosulfonium ions of the type R_2S^+SR are exceptionally prone to S^+–S and C–S^+ cleavage and to rearrangement by way of alkyl migration from positive sulfur to neutral sulfur.[7-9] Carbon–sulfur cleavage and alkyl migration are especially facile when the alkyl group can form a relatively stable carbocation. All of these events can be seen in the methylthiolation reactions of **6** and **7** and are summarized in the reaction sequence of Scheme I, each step of which is based on analogy to previous work. The initial reaction is almost certainly methylthiolation at sulfur to give a thiosulfonium ion **15**. Like its counterpart **4**, this ion undergoes C–S^+ cleavage to form a sulfur-stabilized carbocation **16**. Since the disulfide moiety in **16** is unsymmetrical and still attached to the ion, it can recyclize conveniently to form a new C–S^+ bond as in **17**. The transformation **15** to **17** amounts to a ring-expanding 1,2-rearrangement whereupon carbon migrates from S^+ to S. The rearranged ion **17** has built-in nucleophilic and electrophilic sulfur atoms and may be expected to rearrange further to give **18** by S^+–S cleavage and transfer of an alkylthio group to neutral sulfur. Subsequent C–S^+ cleavage leads to **10** and hence to **9** (X = $S(CH_3)_2^+$). The insoluble material that is formed in these reactions is evidently a polymer of 1,2-dithietane (n = 2) or 1,2-dithiolane (n = 3) that is a product of the dissociation of **18**. To our knowledge 1,2-dithietane is unknown and may be expected to be unstable because of the highly strained disulfide function in which the dihedral angle deviates considerably from the normal value of 90°.[13] If, as we suggest, 1,2-dithietane is formed, it would probably undergo ring-opening polymerization.[14] The solid polymer that was actually obtained from this reaction proved difficult to characterize beyond an elemental analysis because of its extreme insolubility. In the case of the six-ring thioketal, the sequence in Scheme I predicts that the dissociation of **18** would give 1,2-dithiolane, which is a known compound,[15] albeit very sensitive to ring opening of the disulfide link and easily polymerized. Thus, if 1,2-dithiolane is formed, it is doubtful that it could be isolated as such. Again, the solid polymer obtained could not be fully characterized but it is consistent with the formulation $(C_3H_6S_2)_x$.

Methanesulfenyl chloride reacted with **6** in a manner entirely analogous to that described for the sulfenyl salt. The products obtained from an equimolar mixture of **6** and **2** in dichloromethane at −35 °C included the same insoluble solid product described previously (mp 123–32 °C) together with 2-chloro-2-(methylthio)propane (**13**) formed in 68% yield (by NMR integration). Approximately 23% methyl disulfide was also formed, and 30% of the starting thioketal remained unreacted. Formation of **13** can be accounted for by the reaction in Scheme I (X = Cl), and we note again that both cyclic and acyclic thioketals of acetone give the same product on methylthiolation with **2**. As observed in the analogous reaction with **5**, the product **13** was unstable and could not be isolated. After

Scheme I



6, n = 2
7, n = 3

15 **16** **17** **18** **10** **9**, X = $\overset{+}{S}(CH_3)_2$

4 days at room temperature in dichloromethane, **13** formed from **6** was completely converted to other products, mainly to the acyclic thioketal **5** (Table I). Even though the yield of **13** was initially 68% based on the starting sulfenyl chloride, the yield of **5** was only 30%, which means that slightly more than 2 mol of **13** are consumed to give 1 mol of **5**. Also formed was the usual few percent of **11**. The nature of these reactions has been discussed already and they represent alkylation by the carbocation of a sulfur nucleophile (eq 7) and a carbon nucleophile (eq 8).

Methylthiolation of **6** was also achieved with methanesulfenyl fluoroborate (**3**) (prepared from **2** and silver fluoroborate in a mixture of nitromethane and dichloromethane). As before, a white solid (mp 127–132 °C dec) formed immediately on mixing the reagent. The supernatant, by NMR, showed the presence of unreacted starting thioketal, a broad C-methyl resonance at δ 1.85, and numerous smaller unidentifiable peaks. On adding methyl sulfide to this solution the spectrum changed remarkably. The broad resonance became a sharp C-methyl singlet of **9** and the two other resonances of **9** at δ 2.38 and 2.75 were evident. As more methyl sulfide was added, the latter two peaks became coincident at δ 2.45. It seems that the fluoroborate salt of the carbocation **10** is formed in the methylthiolation of **5** with CH_3SBF_4 and is converted to **9** on addition of methyl sulfide.

Methylthiolation of Bis(2-methoxyethylthio)methane (8). The facile cleavage of thioketals with sulfenyl reagents to form sulfur-stabilized carbocation intermediates prompted us to see if similar reactions occur with thioacetals. The choice of the thioacetal **8** formed from formaldehyde and 2-methoxyethanethiol was somewhat peripheral to the objectives of the present investigation but pertains to our work on the generation of *gaseous* sulfur-stabilized carbocations. We observed in a previous study[16] that when the cation $CH_3OCH_2CH_2SCH_2^+$ is formed in the gas phase at low pressures, it rearranges by a 1,6-hydride transfer end-for-end and fragments to formaldehyde and a sulfonium ion (eq 9).

$$\underset{\mathbf{19}}{CH_3OCH_2CH_2SCH_2^+} \rightarrow {}^+CH_2OCH_2CH_2SCH_3 \rightarrow CH_2O + (CH_2)_2SCH_3^+ \quad (9)$$

It was of interest to see if ion **19** in solution would undergo a similar rearrangement. Therefore, we investigated the methylthiolation of **8** with the sulfenyl salt **1** in dichloromethane as a possible route to **19** in condensed phase. The outcome of this reaction was in all respects similar to the related reactions of thioketals. Addition of 1 molar equiv of the salt **1** to a solution of **8** in dichloromethane caused immediate dissolution of the salt and the formation of two volatile products that were identified as symmetrical and unsymmetrical disulfides **20** (55%) and **21** (45%). The NMR spectrum of the crude reaction mixture showed, in addition to the resonances of **20** and **21**, two broad resonances centered at δ 3.0 and 4.6 that we attribute respectively to the *S*-methyl and methylene protons of **22**. The reaction can be explained adequately by the sequence of steps in Scheme II. Thus, a similar pattern of rearrangement of intermediate thiosulfonium ions observed with thioketals is evident with the thioacetal **8**. In particular, alkyl migration by C–S^+ cleavage and alkylthio migration by S–S^+ cleavage clearly must occur. However, if rearrangement by C–S^+ cleavage produces the carbocation **19**, the ion does not rearrange by a 1,6-hydride transfer as does the gaseous ion because no products having the structural feature $CH_3SCH_2CH_2O^-$ were formed.

Thiols behave similarly to thioacetals on methylthiolation. Thus, 2-methoxyethanethiol reacted with **1** in dichloromethane to give a mixture of disulfides, **20** and **21**, according to the steps in equation 10.

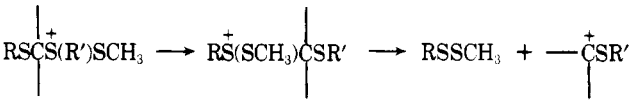
$$RSH \xrightarrow{1} RS\overset{+}{S}(H)CH_3 \rightarrow \underset{\mathbf{21}}{RSSCH_3} + H^+$$

$$RS\overset{+}{S}(H)CH_3 \xrightarrow{RSH} \underset{\mathbf{20}}{RSSR} + CH_3SH + H^+ \quad (10)$$

Summary

The conclusion reached from this study is that thioacetals and thioketals can be activated by methylthiolating (sulfenyl) reagents. Transfer of CH_3S^+ to sulfur of a thioketal greatly increases the reactivity of the C–S^+ bond in the thiosulfonium function

which is the first-formed intermediate. Rapid dissociation to a sulfur-stabilized carbocation R-S-C<$^+$ and disulfide CH_3SSR occurs. The second C–S bond of the thioketal cleaves by related reactions that amount to rearrangement by internal alkylthiolation followed by dissociation.

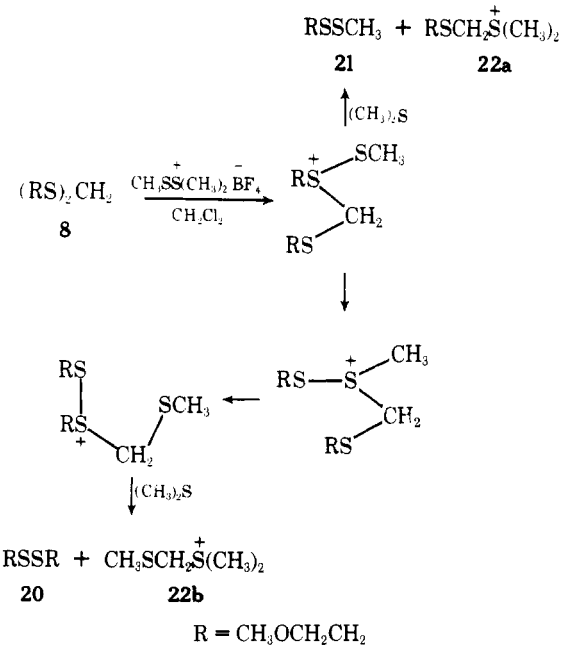


In the absence of water, which would hydrolyze >C^+SR' to the parent ketone, the ion destructs by traditional pathways of elimination and alkylation of nucleophilic sulfur and carbon.

Experimental Section

2,2-Dimethyl-1,3-dithiolane (6) was prepared from acetone (25 mL) and 1,2-ethanedithiol (28.2 g; 0.3 mol) by dropwise addition of 2–3 mL of boron trifluoride dimethyl etherate to the cooled mixture. The organic layer was washed with 50 mL of 5% sodium bicarbonate solution, dried ($MgSO_4$), and distilled to give 34–37 g (85–92%) of **6**: bp 48 °C at 6–7 mm (lit.[17] bp 89 °C at 11 mm); NMR (CCl_4) δ 1.75 (s, 6 H), 3.30 (s, 4 H). **2,2-Dimethyl-1,3-dithiane (7)** was prepared similarly from acetone and 1,3-propanedithiol in 55% yield: bp 59 °C at 3 mm (lit.[18] bp 65 °C at 5 mm); NMR (CCl_4) δ 1.62 (s, 6 H), 1.90 (m, 2 H), 2.74 (t, 4 H). **2,2-Bis(methylthio)propane (5)** was prepared by passing methanethiol gas into a mixture of acetone (29 g; 0.5 mol)

Scheme II



and boron trifluoride dimethyl etherate at −10 °C at such a rate that no thiol escaped. Addition was continued until the reaction mixture had increased in weight by an amount corresponding to the addition of 2 molar equiv of thiol. There was obtained 56 g (82%) of **5**: bp 51–52 °C at 16 mm (lit.[19] bp 45–47 °C at 11 mm); NMR (CCl_4) δ 1.52 (s, 6 H), 2.03 (s, 6 H). A byproduct of 2-methylthiopropene (8 g, 10%) was also obtained, bp 88–89 °C (lit.[20,21] bp 91 °C). **2-(Methylthio)propene** was synthesized independently by the following procedure: Methanethiol gas was led into a mixture of ethyl acetoacetate (65 g; 0.5 mol) and boron trifluoride dimethyl etherate (5 mL) at −10 °C. When the weight of added thiol reached 48 g (1 mol), 200 mL of 2% sodium hydroxide and 200 mL of ethanol were added. The mixture was refluxed for 2 h and then was neutralized with 1 N HCl to give white crystals of 3-(methylthio)-2-butenoic acid (42 g, 70%, mp 112–114 °C). The acid was decarboxylated by heating above its melting point; crude 2-(methylthio)propene obtained was redistilled to give 17 g (61%) of product: bp 88–89 °C (lit.[20-21] bp 91 °C); NMR (CCl_4) δ 1.94 (m, 3 H, CH_3), 2.11 (s, 3 H, CH_3S), 4.52 (m, 1 H, vinyl), 4.92 (m, 1 H, vinyl).

Methylthiolation Using Dimethyl(methylthio)sulfonium Fluoroborate.[6,22] A typical procedure follows: To a stirred solution or suspension of 7.84 g (0.04 mol) of **1** in 10 mL of dry nitromethane (or 30 mL of dichloromethane) at 0 °C or below was added 0.04 mol of thioketal **5, 6,** or **7** in 5 mL of nitromethane (or dichloromethane). In the case of **6** and **7**, reaction was evident by the precipitation of a white solid. The progress of reaction was followed by NMR over a period of several days (see text), and when no further change occurred the mixture was filtered and the solvent and volatile products removed by distillation at reduced pressure keeping the pot temperature below 40 °C. The neutral products were analyzed by NMR and GPC. The residue after distillation was generally a dark semisolid resinous material. Treatment of this residue with 5–10 mL of water led to the recovery of small amounts of product identified as 4-methyl-4-(methylthio)pentan-2-one: bp 61–2 °C at 6 mm (lit.[25] bp 78 °C at 15 mm); NMR ($CDCl_3$) δ 1.38 (s, 6 H), 2.05 (s, 3 H), 2.13 (s, 3 H), and 2.68 (s, 2 H), and an unidentified solid product (mp 180–2 °C; NMR (CD_3NO_2) δ 1.76 (s, 6 H), 2.67 (s, 2 H), 2.81 (s, 1 H), and 3.41 (s, 2 H); IR 2970, 1460, 1395, 1372, 1272, 1250, 1040 cm^{-1}).

The polymeric white product that precipitated from reaction mixtures of **6** or **7** with **1** proved to be insoluble in organic solvents. The solid product from **6** had mp 123–132 °C dec: IR (KBr) 2950, 1400, 1180, 1170, 1090, 1050, 1010, 710, 655, 640 cm^{-1}. Anal. Calcd for $(CH_2S)_x$: C, 26.05; H, 4.37. Found: C, 25.80; H, 4.36. The solid product from **7** had mp 68–72 °C dec (lit.[15] mp. 65–70 °C): IR (KBr) 2955, 1430, 1403, 1321, 1280, 1222, 1160, 1100, 940, 814, 745, 689 cm^{-1}. Anal. Calcd for $(C_3H_6S_2)_x$: C, 33.92; H, 5.69. Found: C, 33.20; H, 5.42.

Methylthiolation of bis(2-methoxyethylthio)methane (8) was accomplished by adding 0.53 g (0.0027 mol) of **1** to 0.53 g (0.0027 mol) of **8** in 5 mL of dichloromethane at 25 °C. The salt dissolved readily. The NMR of the reaction mixture showed the appearance of product $CH_3OCH_2CH_2SSCH_3$ (**21**) δ (CCl_4) 3.53 (t, 2 H), 3.30 (s, 3 H), 2.80 (t, 2 H), 2.38 (s, 3 H) and $(CH_3OCH_2CH_2S)_2$ (**20**) δ (CCl_4) 3.53 (t, 4 H), 3.30 (s, 6 H), 2.80 (t, 4 H). Broad resonances at δ 3.0 and 4.6 also were evident. No resonance appeared near δ 2 that could be ascribed to dimethyl sulfide or methyl alkyl sulfide. The mixture was extracted with 30 mL of ether and 50% aqueous potassium bicarbonate. The ether fraction was dried ($MgSO_4$) and evaporated. Analysis by GPC of the residual oil showed the presence of two components which were separated by preparative GPC and identified as **20** and **21**. Methylthiolation of 2-methoxyethanethiol was performed similarly.

Methylthiolation Using Methanesulfenyl Chloride (2). To a solution of thioketal **5** or **6** (0.04 mol) in 20 mL of dichloromethane was added 3.3 g (0.04 mol) of freshly prepared methanesulfenyl chloride[23] in 10 mL of dichloromethane. The temperature was maintained at −35 °C and the reaction was evidenced by the disappearance of the orange color of the sulfenyl chloride. When the color was discharged the reaction mixture was allowed to reach room temperature. Any further change was followed by NMR. The products were separated insofar as possible by distillation, as described for the related reactions with **1**.

Methanesulfenyl fluoroborate was prepared in solution according to the procedure of Smit et al.[24] Silver fluoroborate (7.8 g; 0.04 mol) was dissolved in 6 mL of nitromethane and cooled to −60 °C. Methanesulfenyl chloride (3.3 g; 0.04 mol) in 20 mL of dichloromethane was added slowly to the solution of the salt. Reaction was exothermic and silver chloride precipitated immediately. After being stirred for 30 min, the chloride was removed by vacuum filtration through a sintered glass filter disk. The filtrate was used immediately in reactions with thioketal **6**.

Methylation of 5 was attempted by the addition of **5** (5.45 g; 0.04 mol) in 10 mL of dichloromethane at −35 °C to a solution of trimethyloxonium fluoroborate (5.9 g; 0.04 mol) in 10 mL of nitromethane. No visual change occurred. On warming to room temperature, the mixture discolored and became progressively darker. After 6 days, the solution was dark brown. The changes occurring were followed by NMR as described in the text.

2-(Methylthio)propene with Hydrogen Chloride. To a mixture of 2-(methylthio)propene (4.4 g; 0.05 mol) in 20 mL of dichloromethane at −50 °C was added less than 5 mmol of dry hydrogen chloride gas. On warming to room temperature, the reaction mixture turned blue and then dark brown. Progress of the reaction was followed by NMR, as described in the text. During reaction, a cold trap was set up to collect any volatile products that could conceivably be formed in the decomposition of the chloride **13**, but none were detected.

Exchange Reaction of 9 with Methyl Disulfide. Methylthiolation of **6** (0.05 mol) with **1** (0.05 mol) in nitromethane solution was achieved by the procedure described above. The solid precipitate was removed by filtration, and to the filtrate was added 0.012 mol of dimethyl-d_6 disulfide. After several days at room temperature when no further change occurred in the reaction mixture, the volatile products, methyl disulfide and **5**, were removed and separated by preparative GPC. The disulfide was analyzed by ion cyclotron mass spectrometry as a 44:44:12 mixture of methyl-d_0, -d_3, and -d_6 disulfide. The NMR spectrum of the thioketal **5** showed singlet resonances at δ 1.52 (C-CH_3) and 2.03 (S-CH_3) in the area ratio of 66:34 which implies that approximately 48% of the methylthio groups are present as SCD_3.

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Registry No.—**1**, 5799-67-7; **2**, 5813-48-9; **8**, 69177-64-6; **9**, 69177-65-7; **13**, 13557-26-1; **20**, 69177-66-8; **21**, 69177-67-9; 1,2-ethanediol, 107-21-1; 1,3-propanedithiol, 10980-8; methanethiol, 74-93-1; 2-methylthiopropene, 7594-44-7; ethyl acetoacetate, 141-97-9; 3-(methylthio)-2-butenoic acid, 69177-68-0; 2-methoxyethanethiol, 10494-75-4; methanesulfenyl fluoroborate, 337-27-96-7; 1,2-dithietane homopolymer, 69177-69-1; 1,2-dithiolane homopolymer, 33087-69-3.

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Notes

Alkyloxycarbonyl Thiosulfate, a New Family of Water-Soluble Acylating Agents: Amidation and Hydrolysis Reactions[1a]

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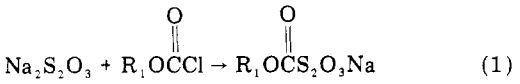
Many times it is necessary or convenient to perform acylation reactions of amines in aqueous media. Accordingly, a water-soluble acylating agent which undergoes hydrolysis slowly would be highly desirable whenever the presence of water is required or cannot be excluded from a reaction medium. Ito[2] prepared the water-soluble, but easily hydrolyzed, sodium benzoyl thiosulfate which reacts with amines and phenols in aqueous media to yield the corresponding benzoyl derivatives.[3] Caldwell, Ledger, and Milligan[4] carried out the reaction of benzyl chloroformate with sodium thiosulfate to yield the water-soluble sodium benzyloxycarbonyl thiosulfate which readily underwent reaction with amines and amino acids in aqueous media, and Lindemann and Wolfram[5] have reported the preparation and reaction of the bifunctional arymethyloxycarbonyl thiosulfate, disodium 1,4-xylylenebis(oxycarbonyl thiosulfate). To date, however, the preparation of alkali or alkaline earth alkyloxycarbonyl thiosulfates has not been reported. Green and Hudson[6] have described the reaction of ethyl chloroformate with sodium thiosulfate, but there is no indication that they isolated or identified the reaction product.

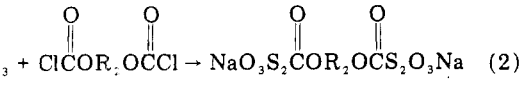
Results

We have now prepared, by the reaction of the appropriate chloroformate and sodium thiosulfate, several monofunctional (1) and difunctional (2)[7] sodium alkyloxycarbonyl thiosulfates.



(1)

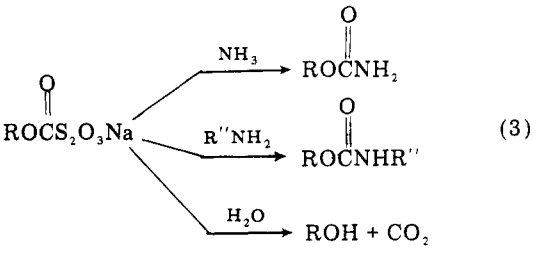
R_1 = n-C_4H_9, n-C_6H_{13}, n-C_8H_{17}



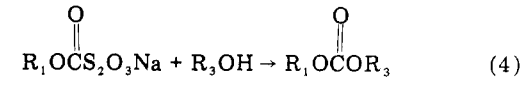
(2)

R_2 = $(CH_2)_4$, $(CH_2)_6$, $(CH_2)_8$

These compounds exhibit some degree of water solubility and react with ammonia and amines, both in the presence and absence of water, to form the corresponding carbamates and with water to liberate the parent alcohol (3). Alkyloxycarbonyl thiosulfates would be expected to react with alcohols to form the corresponding carbonate (4); however, this reaction was not examined in this study. Specifically, sodium n-octyloxycarbonyl thiosulfate (5) reacts with ammonia and 2-aminoethanol to yield O-(n-octyl) carbamate (6) and O-(n-octyl) 2-hydroxyethylcarbamate (7), respectively. The possibility exists, of course, of an initial acylation of the hydroxyl group followed by an O-N-acyl migration reaction.



(3)



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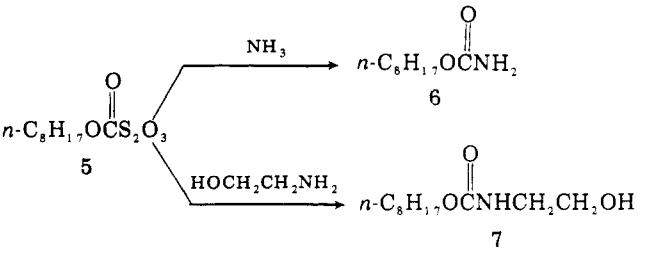

5 + $HOCH_2CH_2NH_2$ → $C_8H_{17}OCOCH_2CH_2NH_2$ → 7

A review of the literature yielded no information concerning the relative rates of acylation of the hydroxyl and amino groups in 2-aminoethanol. Acylation reactions of 2-aminoethanol with acid chlorides[8,9] and 3-aminopropanol with ethyl chloroformate[10] under mild conditions resulted in high yields of amides and carbamate respectively with no report of ester or carbamate formation. In the absence of evidence to the contrary, and considering that water reacts more slowly with the acyloxycarbonyl thiosulfate than does the amino group, we suggest that N-acylation occurs with little or no O-acylation in the reaction of 5 with 2-aminoethanol.

A brief kinetic study of the reaction of the mono- and bifunctional alkyloxycarbonyl thiosulfates with 2-aminoethanol or water at pH 8.0 resulted in the relative rates for amidation and hydrolysis noted in Table I.

These data indicate that, for a given monofunctional alkyloxycarboxyl thiosulfate, the rate of carbamate formation is approximately an order of magnitude greater than the corresponding rate of hydrolysis and suggest that the rate of either reaction increases with decreasing carbon chain length. Similarly, for various bifunctional alkyloxycarbonyl thiosulfates the rate of amidation was found to be between five and ten times greater than the rate of hydrolysis, and again the reaction rate of these compounds is seen to increase with decreasing chain length. It is interesting to note that the monofunctional compounds appear to be somewhat more reactive

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