case discussed above, elimination is not possible and the salt from thiourea attack at carbon is a product. In this case the amounts of the salt formed are very close to those calculated by eq 2, Table III. Normally such a rate–product correlation would be interpreted in terms of an S_N2 mechanism.[5,8] However, this equation should also closely describe the S_N1 mechanism if, as is true in the benzhydryl case, return is important (k_{-1}/k_2 or α = 39 here),[17] since again we are seeing competitive, rate-determining destruction of a species by two nucleophiles (water and thiourea in this case).

In discussing the 2-adamantyl, 1-adamantyl, and 2-(methylthio)ethyl cases above, we concluded that thiourea addition should cause a rate retardation for S_N1 substrates because of a reduction in solvent ionizing power. However, we now see that we must qualify this conclusion for "complex" S_N1 substrates in which return processes are affected by added nucleophiles. In these instances thiourea can also give a rate acceleration (and even a reasonable rate–product correlation) that looks deceptively like that observed for an S_N2 process. As noted above, Queen's other additives gave a rate retardation with benzhydryl solvolysis. Presumably these additives are too weakly nucleophilic to compete for the carbocation intermediate and give a rate acceleration by reducing the amount of return. Apparently thiourea is such a powerful nucleophile that the small changes in solvent ionizing power are overwhelmed for benzhydryl. Alternatively, but less likely, the effects on the four processes concerned (k_{-1}, k_1, k_2, k_N) balance out.

As noted above, Queen used the effects of thiourea on benzhydryl solvolysis to predict the effects of thiourea addition on the "rate of ionization" of *p*-methoxybenzyl chloride. We would concur in this approach if the term "rate of ionization" is understood to include nucleophilic attack by thiourea on the carbocation intermediate to reduce return. Queen uses this assumption to fit the data for *p*-methoxybenzyl to an expression derived for a reaction scheme including nucleophilic attack of thiourea on neutral substrate (or ion pair) as well as free carbocation. We will not review this study here, but we do note that the rate–product correlation in this case, is poor, eq 2 and Table III. This result indicates that a more complex situation does obtain and thus is consistent with Queen's conclusion.

Experimental Section

Chemicals. Reagent grade substrates, obtained commercially (Eastman and Aldrich), were used as received from freshly opened bottles. Ethyl and *endo*-2-norbornyl tosylates were prepared by the standard pyridine method[35] and purified by repeated recrystallization at −70 °C from low boiling petroleum ether. These materials had properties consistent with samples previously prepared in our laboratories.[2,22] All tosylates and brosylates were stored at −10 °C. Solvents were purified in the normal way to remove water,[2,22] distilled, and stored in a desiccator until used or mixed with cosolvents.

Kinetics. Rates were determined by an automated conductimetric procedure previously described.[36] Each kinetic sample contained about 10 mL of solvent ca. 10^{-3} M in substrate and ca. 3×10^{-3} M in 2,6-lutidine. Samples of substrate with and without thiourea were run in solvent from the same batch and rates were determined side-by-side to assure the best comparison. Unless specified in Table II, at least duplicates were determined. Thiourea molarities stated are for 25 °C.

Product Studies. In the case of *tert*-butyl chloride the products with and without thiourea were determined by gas chromatography using a packed OV-101 column and *n*-propanol as internal standard. The *tert*-butyl alcohol and ethyl *tert*-butyl ether peaks overlapped; therefore, their yields were not separately calculated. In 60% aqueous ethanol solution 0.0, 0.5, and 1.0 M in thiourea, the yields of isobutylene are, respectively, 3.1, 4.5, and 7.9%. A plot of logarithm of the *tert*-butyl chloride rates vs. isobutylene yields gave a straight line (r = 0.997). The rate–product correlation equation, eq 2, was also applied (see Discussion section). Isolation studies were attempted to see if the isothiouronium salt from carbon attack occurred. However, only the salt with HCl was found. ^{1}H NMR studies also failed to indicate presence of the *tert*-butyl thiouronium salt.

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Registry No. 1-AdBr, 768-90-1; 2-AdOTs, 25139-43-9; $MeSCH_2CH_2Cl$, 542-81-4; MeOTs, 80-48-8; EtOTs, 80-40-0; 2-OctOMs, 924-80-1; BzBr, 100-39-0; *t*-BuCl, 507-20-0; *endo*-2-NbOTs, 840-90-4; thiourea, 62-56-6.

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Transannular Addition of α-Lithio Sulfoxides to Inactivated Double Bonds. Regio- and Stereochemical Aspects

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Cyclic eight–ten-membered (*E*)-homoallylic sulfoxides undergo regiospecific BuLi-promoted transannular cyclization, yielding saturated bicyclic products. The reaction appears to be a nucleophilic addition of a "carbanion" (an α-lithium sulfoxide) to a nonactivated double bond and occurs readily provided a compatible proton source is available, proton donation being normally performed by the unmetalated sulfoxide itself. The nature of the products and the epimers distributions indicate the reaction is kinetically controlled. The regio- and stereochemical courses are suggested to be largely dependent on the conformational properties of the monocyclic precursors. The differential reactivity of *E* vs. *Z* substrates is also rationalized in conformational terms and in relation to Menger's theory of intramolecular reactivity.[43]

Polar addition to multiple bonds, like its microscopic reverse, elimination, is believed to occur by way of a spectrum of transition states gradually merging into one another and differing in the extent and timing of the bond

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Table I. Carbon-13 NMR shifts of *cis*-2-Thiabicyclo[3.3.0]octanes and Their 2-Oxides[a]

	δ							
compd	C_1	C_3	C_4	C_5	C_6	C_7	C_8	Me
4	51.8	(32.9)	[38.0]	47.8	(31.3)	25.1	[36.3]	
4a	51.5	43.5	46.0	60.3	27.6	25.5	35.4	28.8
								24.6
4b	52.1	[48.5]	46.8	[47.7]	(32.0)	24.5	(35.4)	19.5
4c	52.8	[43.9]	46.2	[47.3]	(31.7)	25.4	(37.1)	20.6
5	71.7	49.2	(30.2)	43.6	(31.8)	25.9	27.8	
5a	75.2	62.2	46.3	59.2	(29.2)	(26.8)	(28.7)	30.5
								25.4
5b	70.6	61.8	35.6	40.8	(31.6)	24.6	(29.1)	13.8
5c	71.8	54.6	37.8	43.9	32.8	26.4	28.2	10.4
6	64.8	53.3	(30.5)	46.0	(31.6)	[26.8]	[23.4]	
6a	(61.2)	64.4	40.3	(59.6)	29.8	[27.3]	[24.9]	30.3
								21.8
6b	65.8	60.5	38.7	46.3	32.0	27.1	23.6	11.2
6c	(62.1)	(61.3)	36.7	44.2	32.5	[27.1]	[23.9]	13.1

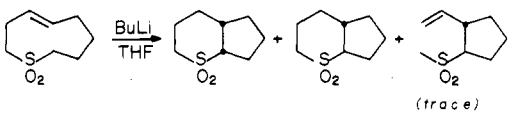
[a] Values in parentheses or in brackets may be interchangeable.

making and breaking processes.[1] At one extreme, the attachment of the electrophile takes the lead and the nucleophile follows suit, either at a later stage of the transition state or in a separate step. Conversely, at the other extreme, the nucleophile takes precedence and the electrophile follows. Additions may take the characteristics of one or the other extreme mechanism depending on the polarization of the double bond; nonpolar and polar double bonds tend to react by the electrophilic and nucleophilic addition mechanism, respectively.

Although this categorization is completely general, evidence is beginning to emerge indicating unactivated, homopolar, multiple bonds may, under certain circumstances, undergo nucleophilic addition.[2] Apparently the requirements to be met are that nucleophile and unsaturated center be within the same molecule and the geometry be such as to place them close together and suitably aligned. Fitting examples are the additions *under basic conditions* of oxygen[3] and nitrogen[4] nucleophiles in alkene–alcohols and –amines, and the additions of phenoxides in alkene–[5] and alkyne–phenols[6] recently studied in detail by Kirby and Evans.

The reaction we now describe belongs to this category, its novelty residing in the nature of the nucleophile, a carbanion. The reaction is a transannular cyclization of mesocyclic homoallylic sulfoxides or sulfones under the action of metalloalkyls, resulting in the formation of saturated bicyclics.[7]

The reaction was discovered accidentally when, in an attempt to α-alkylate a cyclic nine-membered (*E*)-homoallylic sulfone, we found that treatment with butyllithium resulted in almost complete loss of unsaturation. Two major products, identified as the trans and cis epimers of 2-thiabicyclo[4.3.0]nonane 2,2-dioxide,[7] had been formed. A minor unsaturated product was also formed which we later established to be the ring contracted methyl *trans*-2-vinylcyclopentyl sulfone (eq 1).



The nature of the products indicates the organometallic reagent has promoted the formation of a transannular bond between one of the α-carbon (C_9) and one of the olefinic carbons (C_5). No products arising from alternative directions of addition (C_9 to C_4 or C_2 either C_4 or C_5) could be detected. The addition was therefore regiospecific.

The reaction appears not to be restricted to the sulfone functionality or to ring size nine; it is equally feasible with the sulfoxide and with ring sizes eight and ten. However, one condition appears to be indispensable for the reaction to occur, that is, the *E* configuration of the double bond: no products of transannular cyclization were detected with the *Z* isomers, at least under conditions (time and temperature) where the α-thia "carbanions" are not consumed otherwise.

The detailed studies reported herein have been obtained with sulfoxides. Their use has several favorable features with respect to sulfones: (i) Only saturated bicyclic products are obtained, uncontaminated by ring-contracted products; (ii) the rate of cis/trans interconversion of epimeric bicyclic products is normally slow enough to permit the evaluation of the cis/trans kinetic ratio; (iii) the chiral sulfoxide function provides a stereochemical handle which may be useful for drawing mechanistic inferences. The behavior of sulfones will be examined in a future paper.

Results

Formation and Transannular Cyclization of (*RR*,*SS*)- (2) and (*RS*,*SR*)-(*E*)-Thiacyclooctene 1-Oxide (3). We have reported previously that aqueous $NaIO_4$ oxidation of (*E*)-thiaclooct-4-ene produces only one of the two possible diastereomeric sulfoxides; however, some $E \rightarrow Z$ isomerization takes place concomitantly.[8] It has now been found that low temperature *m*-chloroperbenzoic acid (MCPBA) oxidation produces the same diastereomer, without causing any $E \rightarrow Z$ isomerization. Since the sulfide exists, like the corresponding carbocycle,[9]

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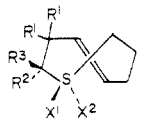
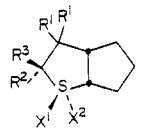
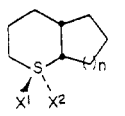
as a pair of nonrapidly interconverting enantiomeric conformers ($\Delta G^{\ddagger}$ for racemization on the order of 30 kcal/mol),[10] the observation that only one sulfoxide stereoisomer is formed means that oxidation occurs with 100% asymmetric induction independent of the nature of the oxidizing agent. This remarkable stereospecificity clearly arises



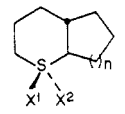
1; 1a: R^1=CH_3
2: X^1=O; 2a: X^1=O, R^1=CH_3
3: X^2=O; 3a: X^2=O, R^1=CH_3



4; 4a: R^1=CH_3; 4b: R^2=CH_3; 4c: R^3=CH_3
5: X^1=O; 5a: X^1=O, R^1=CH_3; 5b: X^1=O, R^2=CH_3
5c: X^1=O, R^3=CH_3
6: X^2=O; 6a: X^2=O, R^1=CH_3; 6b: X^2=O, R=CH_3
6c: X^2=O, R^3=CH_3.



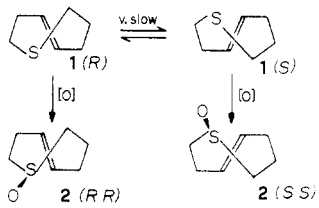
8 : n=2 11 : n=1,
8a: n=2, X^2=O 11a: n=1, X^2=O
8b: n=2, X^1=O 11b: n=1, X^1=O



9 : n=2 12 : n=1
9a: n=2, X^2=O 12a: n=1, X^2=O
9b: n=2, X^1=O 12b: n=1, X^1=O

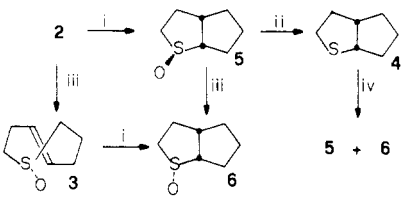
All R's = H and X's = lone pair unless specified otherwise

from the molecular shape; force field calculations indicate the sulfide populates essentially exclusively a twist conformation[11] whose geometry leaves only one face of the sulfide sulfur exposed to external reagents, the other face being screened by the transannular ring portion comprising the double bond carbons. Inspection of the geometry shows the *R* and *S* enantiomers expose respectively the *pro-R* and *pro-S* face of the S atom. Thus oxidation will produce the *RR,SS* diastereoisomer **2**. When this sulfoxide was treated with 0.5 equiv of BuLi in THF at 0 °C a single saturated sulfoxide **5** was formed (Scheme I) which, when reduced with PCl_3, gave *cis*-2-thiabicyclo[3.3.0]octane (**4**) identical with an authentic sample prepared from cyclopentanone by an independent route (see Experimental Section). Oxygen-methylation ($CH_3OSO_2CF_3$) of **5** followed by alkaline hydrolysis[12] gave the inverted sulfoxide **6**. The latter was also obtained by transannular cyclization of **3**, the monocyclic *SR,RS* sulfoxide obtained from **2** by sulfur inversion.[12] On the other hand MCPBA oxidation of **4** gave a 4:1 mixture of sulfoxides **5** and **6** (Scheme I).



The *gem*-Me_2-substituted exo sulfoxide **5a** was obtained by transannular cyclization of **2a**, obtained, as a single diastereomer, by oxidation of sulfide **1a**. The endo sulfoxide **6a** was obtained from **5a** by inversion of the sulfoxide configuration.

Scheme I[a]



[a] (i) [1] BuLi (0.5 equiv), THF, 0 °C, [2] H_2O; (ii) PCl_3, CH_2Cl_2; (ii) [1] $CF_3SO_2OCH_3$, CH_2Cl_2, 0 °C, [2] NaOH (0.02 M); (iv) MCPBA, CH_2Cl_2, −80 °C.

The 2-methyl-substituted sulfoxide **6c** was obtained stereospecifically by CH_3I quenching of the α-lithio derivative of **6**. In this system methylation occurs trans to oxygen, in conformity with Marquet's generalization.[13] In contrast, however, the exo sulfoxide **5** alkylates nonstereospecifically and gives a ~1:1 mixture of **5c** and **5b**. As we had previously pointed out in reporting exceptions to the rule of trans alkylation,[14] the stereochemistry of α-Li sulfoxide alkylation must not be governed solely by the requirements of Li-cation chelation.[13]

The ~1:1 **5c**/**5b** ratio changed to ~6:1 when the mixture was treated with BuLi (0.3 equiv) and let stand for a few minutes at room temperature before quenching. This ratio did not change further when the contact time was prolonged and is therefore the equilibrium ratio.

Transannular Cyclization of (*E*)-Thiacyclodec-4-ene 1-Oxide (7). The title compound was obtained by MCPBA oxidation of (*E*)-thiacyclodec-4-ene which had been in turn obtained by ring expansion of the methylide from 1-methyl-2-vinylthiepanium triflate.[15] The room temperature ^{13}C NMR spectrum consists of nine sharp lines which on lowering the temperature separate in two sets of approximately 2:1 intensity ratio (see Experimental Section), indicative of **7** existing as two interconverting diastereomeric conformers. The barrier to interconversion was evaluated by computer simulated line shape analysis in the 212–217 K interval,[16] using the two pairs of corresponding lines relative to the olefinic carbons. The exchange process is characterized by $\Delta G^{\ddagger}$ = 11.5 kcal/mol. This value is close to that (10.7 kcal/mol) recorded for the interconversion of the 2-methylthiacyclodec-4-ene epimers[17] and just slightly lower than the barrier (12.4 kcal/mol) recorded for (*E*)-cyclodecene derivatives.[18] For cyclic ten-membered *trans*-olefins a barrier of such magnitude is associated with a process of inversion of the chiral plane which involves an inside-out rotation of the double bond.[19]

Upon treatment with BuLi, **7** gave two isomeric saturated products, **8a** and **9a**, in about equal amounts

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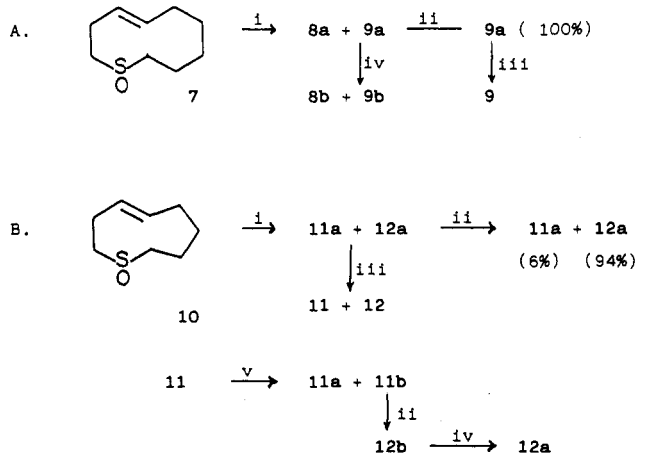
(19) That the sulfur heterocycle has a somewhat lower barrier is consistent with the longer C–S (relative to C–C) bond distance making the ring "hole" larger and easier to pass through.

Table II. Carbon-13 NMR Shifts of 2-Thiabicyclo[4.3.0]nonanes and Their 2-Oxides[a]

compd	δ							
	C_1	C_3	C_4	C_5	C_6	C_7	C_8	C_9
11	42.4	(26.4)	23.4	(28.3)	39.4	(26.7)	21.8	(31.0)
12	[47.0]	(29.8)	(27.9)	(30.9)	[47.8]	(32.1)	20.6	(31.1)
11a	56.5	44.1	(14.6)	(25.1)	39.0	31.3	(21.6)	24.1
11b	64.8	46.7	[16.7]	(25.5)	39.1	(29.1)	[21.1]	(26.1)
12a	67.9	52.7	24.0	(30.0)	42.5	(31.2)	21.1	(28.2)
12b	60.4	46.2	[16.3]	(30.9)	(33.3)	(31.0)	[20.2]	25.0

[a] Values in parentheses or in brackets may be interchangeable.

Scheme II[a]



[a] (i) [1] BuLi (0.5 equiv), −20 °C, 2 h, [2] H_2O; (ii) BuLi (0.5 equiv), room temperature, 2 h; (iii) PCl_3, CH_2Cl_2; (iv) [1] $CF_3SO_3CH_3$, CH_2Cl_2, 0 °C, [2] NaOH (0.02 M); (v) MCPBA, CH_2Cl_2, −80 °C.

(Scheme IIA), which on standing in the presence of BuLi, isomerized to give **9a** as the equilibrium product. The latter was recognized through its ^{13}C NMR spectrum, identical with that reported for *trans*-1-thiadecalin 1α-oxide.[20] Accordingly, PCl_3 reduction of **9a** gave a sulfide, **9**, whose ^{13}C NMR spectrum coincides with that recorded for *trans*-1-thiadecalin.[21] The circumstance that **8a** equilibrates to **9a** by base catalysis, a process which does not affect the configuration of the sulfur center, is consistent with **8a** and **9a** being epimers at the α bridgehead carbon and having the same configuration at sulfur. This was confirmed by subjecting **8a + 9a** to configurational inversion of the sulfoxide function;[12] the inverted sulfoxides, **8b** and **9b**, had ^{13}C NMR spectra identical with those reported for *cis*-[22] and *trans*-1-thiadecalin 1β-oxide,[20] respectively.

Transannular Cyclization of (*E*)-Thiacyclonon-4-ene 1-Oxide (10). The title compound was obtained by MCPBA oxidation of the corresponding sulfide.[15] The room temperature ^{13}C NMR spectrum of **10** shows extensive line broadening due to exchange between unequivalent sites. On lowering the temperature to −30 °C the spectrum displays two sets of signals of the same line width (intensity ratio ~8:1), while a sharp eight-line spectrum could be obtained at 100 °C in toluene-d_8. (See Experimental Section). By computer simulation of line shapes of corresponding signals in the 283–324 K range the activation barrier for the exchange process was calculated to be $\Delta G^{\ddagger} = 16.4$ kcal/mol.[16] A value in this range is consistent with the exchange process arising as a result of equilibration between epimeric conformers by inversion of the chiral plane associated with the trans double bond. Indeed for a process of this type in (*E*)-thiacyclononenes, $\Delta G^{\ddagger}$ values of 16.3 and 17.1 kcal/mol have been previously reported,[17] just slightly lower than for (*E*)-cyclononene itself.[23,19]

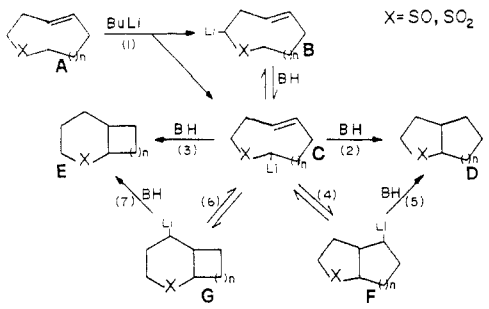
Upon treatment with BuLi at −30 °C in THF, **10** undergoes cyclization forming two saturated products in comparable amounts, **11a** and **12a** which, on standing in base, interconvert and reach equilibrium when **12a**/**11a** ≃ 15 (Scheme IIB). From the rate of equilibration at −30 °C the initial product ratio can be estimated to be **12a**/**11a** ≃ 0.7. Reduction of **11a + 12a** gave a mixture of two sulfides, **11** and **12**. The ^{13}C NMR spectrum (Table II) of the former was identical with that of *cis*-2-thiabicyclo[4.3.0]nonane synthetized by an independent route (see Experimental Section). Since **11a** and **12a** are interconvertible under base catalysis, they must have the same configuration at the sulfur atom and be epimeric at the bridgehead. Therefore **12** is the trans-fused epimer of **11**. Oxidation of sulfide **11** gave two oxides **11a** and **11b** in a ~1:4 ratio, which could be separated by flash chromatography (Scheme IIB). Base-catalyzed epimerization of **11b** gave **12b** which by sulfur inversion, gave **12a**. The assignment of the α-O configuration to **11a** and **12a** rests on the comparison of their ^{13}C NMR spectra with those of **11b** and **12b**, respectively (Table II). Especially significant in this connection are the spectral changes brought about by sulfur inversion in the conformationally rigid trans-fused pair **12a,b**. In the latter the S–O bond is necessarily axial and exerts its powerful shielding effects on the carbons β and γ to oxygen.[20,24]

The transannular cyclization of **10** was subjected to a number of tests where the medium, the base, and its concentration were changed. No major rate effects[25] were observed on changing the solvent from THF to ether or toluene. Equally uninfluential proved to be the presence of a lithium salt (LiBr, 0.1 M) or of nitrobenzene (0.1 M), while a slight acceleration was observed in the presence of diazabicyclooctane (0.1 M). An alkoxide base (*t*-BuOK) was unable to promote the cyclization, while with lithium or potassium bis(trimethylsilylamide) the reaction took place though considerably more slowly ($t_{1/2} \simeq 40$ min at 25 °C). Interestingly, the silylamide base is rather ineffective in promoting the epimerization of the bicyclic products: The epimer ratio, **11a**/**12a** = 1.5, was equal to the extrapolated zero-time ratio from the BuLi experiments and did not change appreciably with time (at least up to ~80% conversion).

As expected, the rate depends on the amount of BuLi used to promote the reaction, but the change of rate with

(20) Rooney, R. P.; Evans, S. A., Jr. *J. Org. Chem.* **1980**, *45*, 180–183.
(21) Vierhapper, F. W.; Willer, R. L. *Ibid.* **1977**, *42*, 4024–4029.
(22) Claus, P. K.; Vierhapper, F. W.; Willer, R. L. *Ibid.* **1979**, *44*, 2863–2870.
(23) Cope, A. C.; Banholzer, K.; Keller, A.; Pawson, B. A.; Wang, J. J.; Winkler, H. J. S. *J. Am. Chem. Soc.* **1965**, *87*, 3644–3649.
(24) (a) Buchanan, G. W.; Durst, T. *Tetrahedron Lett.* **1975**, 1683–1687. (b) Barbarella, G.; Dembech, P.; Garbesi, A.; Fava, A. *Org. Magn. Reson.* **1976**, *8*, 469–476.
(25) Our rate measurements are roughly approximate. Most kinetics runs comprised only two or three points and were based on relatively coarse analytical methods (^1H, ^{13}C NMR and/or GLC).

Scheme III



changing the BuLi to substrate ratio was striking. At −30 °C in THF/hexane (88/12 v/v) and 0.1 M substrate, the first-order rates of transannular addition were (10^4k, s^{-1}) 1.1, 1.7, 1.8, 1.7, 1.6, 1.3, 0.4, and ~0 for BuLi/substrate ratios of 0.15, 0.30, 0.5, 0.6, 0.7, 0.8, 0.9, and 1.1, respectively. That is the rate first increases with increasing the proportion of BuLi, passes though a flat maximum at 0.5, and decreases to become essentially nil for BuLi/substrate ≥1. A similar set of experiments conducted at 5-fold dilution yielded substantially indentical results. Since alkyllithiums irreversibly convert sulfoxides to their α-lithio derivatives, these results indicate that *for the cyclization to occur, the substrate must be incompletely metalated.* Most likely the unmetalated sulfoxide plays the role of an acid catalyst, transferring a proton to the metalated form in a crucial step of the reaction. In this connection a relevant observation is that if complete metalation of **10** is performed with lithium diisopropylamide, rather than BuL, the intramolecular cyclization takes place without difficulty ($t_{1/2} \simeq 90$ min at −30 °C.[26] Apparently under these conditions it is the free aliphatic amine, formed as a result of the metalation of the sulfoxide, that functions as the proton donor.

Discussion

For a discussion of the results it may be useful to outline first a gross reaction scheme, ignoring at this stage the questions of regio- and stereospecificity. The initial step of any possible reaction sequence must be the irreversible metalation (step 1, Scheme III) of the substrate A, forming two α-lithio regioisomers, B and C, probably in comparable proportions.[27] One of them, B, metalated at C_2, appears to be unproductive. Since the substrate is converted essentially quantitatively to products arising from C, the two regioisomers must be in equilibrium (probably mediated by a proton-transfer agent, BH) and their interconversion must be rapid relative to the overall cyclization reaction. From C, transannular addition may occur either to the C_4 or to the C_5 end of the double bond, yielding regioisomeric products D or E, respectively. Neglecting for the moment the problem of which factors determine the direction of addition, the question arising is that of the course through which the monocyclic lithio sulfoxide C evolves toward a bicyclic structure. The change in rate with changing metalation fraction indicates that proton transfer from unmetalated sulfoxide or from another suitable proton source (see the LDA metalation experiment) is crucial. Two reaction courses compatible with this observation may be envisioned: either the transannular addition of the α-sulfinyl "carbanion" at one end of the double bond is concerted with the transfer of a proton at the other end by an "acid", BH (step 2 or 3), or addition and proton transfer occur in separate steps 4 and 5 or 6 and 7) through the intermediacy of a secondary arlkyllithium (F or G). The alternative courses could be distinguished on kinetic grounds;[29] however, the nature of the reactants, in particular their tendency to associate in the medium used, renders such distinction dubious.[26] The observation that in the nine- and ten-membered ring cyclizations the less stable epimer (cis) is formed in a proportion far exceeding its equilibrium population indicates the reaction is kinetically controlled. This would be consistent with a concerted mechanism or with a two step mechanism where the intermediate (F or G) has little chance to escape capture by the proton donor. Further work is required to solve this question.[30]

Regio- and Stereospecificity. The addition is regiospecific; however, the prevailing direction appears to depend on the ring size: In the eight-membered ring addition occurs at C_4, while in both nine- and ten-membered rings it occurs in the alternative direction. Since the reaction is kinetically controlled, addition may not necessarily take the direction of the more stable of the alternative bicyclic systems. This would well be the case of the nine-membered ring where the regioisomer obtained, 2-thiabicyclo[4.3.0]nonane, is estimated to be less stable than 7-thiabicyclo[4.3.0]nonane, which would arise by addition to the other end of the double bond.[31] The factors determining regio- and stereochemistry are likely to be conformational. Consider the eight-membered ring, whose conformational properties are known from force field analysis. If the sulfoxide (more precisely, the α-lithio sulfoxide) adopts the same (twist) conformational type as the sulfide,[11,33] it is easily realized (see structure **2**) that the carbanionic carbon at C_8 faces the C_4 end of the double bond. If, following Baldwin,[34] the angle of approach to one or the other end of the double bond is assumed as the criterion for ring closure, it will be seen that attack at C_4 is favored relative to C_5 since the line of approach of C_8 to C_4 deviates from the tetrahedral angle much less than the line of approach to C_5. Thus the kinetic product will be a *cis*-2-thiabicyclo[3.3.0]octane (which happens to be the thermodynamically favored epimer also).[35]

As to the nine- and ten-membered ring sulfoxides, although there is no question about the regiochemical course

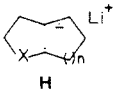
(26) Cerè, V.; Paolucci, C.; Pollicino, S.; Sandri, E.; Fava, A. *J. Chem. Soc., Chem. Commun.* **1986**, 223–224.

(27) Complete metalation of **10** followed by D_2O quenching gave the two regioisomeric α-d_1 derivatives in comparable amounts.[28]

(28) Cerè, V., to be published.

(29) Jenks, W. P. *Acc. Chem. Res.* **1976**, *9*, 425–432; **1980**, *13*, 161–169.

(30) A possible mechanistic variant is that where metalation (step 1 in Scheme III) is followed by electron transfer to give the anion diradical species (H) whose recombination would produce the alkyllithium intermediate F (or G). No free radicals could be detected, however, when the transannular cyclization of **10** was carried out in the ESR tube.



(31) The estimate is based on the following argument: The 2-thia system is made up of one thiane and one cyclopentane unit, while the 7-thia system has one cyclohexane and one thiolane unit. One may use the known heats of formation of the above ring units to approximate the differential heat of formation of the isomeric bicyclics:[32]

$$\Delta H_{7\text{-thia}} - \Delta H_{2\text{-thia}} \simeq (\Delta H_{\text{cyclohexane}} + \Delta H_{\text{thiolane}}) - (\Delta H_{\text{thiane}} - \Delta H_{\text{cyclopentane}}) = -4 \text{ kcal/mol}$$

(32) Benson, S. W.; Cruickshank, F. R.; Golden, D. M.; Haugen, G. R.; O'Neal, H. E.; Rodgers, A. S.; Shaw, R.; Walsh, R. *Chem. Rev.* **1969**, *69*, 279–324.

(33) This condition will be tacitly assumed throughout the discussion which follows.

(34) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734–736.

(35) Allinger, N. L.; Hickey, M. J. *J. Am. Chem. soc.* **1975**, *97*, 5167.

to depend on geometrical factors, any rationalization is unwarranted in the absence of detailed conformational information. On the other hand the stereochemistry of the ring junction may more easily accounted for, at least qualitatively. Inspection of approximate models (Dreiding) shows all reasonable ring conformations fall in one of two categories differing for the orientation of S–C_n relative to the double bond. Consider, for example, the nine-membered ring; the two conformational types are represented by J and K, in which the S–C_9 and the C_4=C_5 bonds are oriented (roughly) parallel or crosswise, respectively.

J K

Formation of the C_9–C_5 transannular bond will produce the cis or trans epimer according to whether type J or K conformers, respectively, are involved.[36] Thus the concurrent formation of cis and trans epimers may be rationalized in terms of addition occurring competitively from either conformational type.

A final facet of stereochemistry concerns the configuration at sulfur. The eight-membered ring sulfoxides were considered earlier (Scheme I), and their case was clear-cut: transannular cyclization of the *RR,SS* and *RS,SR* sulfoxides gave the exo and endo products **5** and **6**, respectively. The cyclization then occurs stereospecifically with configurational retention, as expected for a reaction not directly involving the sulfur stereocenter.

For the larger and more mobile rings, however, the results are puzzling: only bicyclic sulfoxides of the α series were obtained even though, from low temperature ^{13}C NMR evidence, the nine- and ten-membered ring sulfoxides appear to consist of pairs of equilibrating diastereomers separated by ~16 and ~11 kcal/mol barriers, respectively. The cyclization then is stereoconvergent, consistent with its occurring from only one of the two diastereomers, which by inspection is inferred to have the *RR,SS* configuration.

There are two possible explanations for this stereochemical course: (i) The equilibrium distribution of the α-lithio sulfoxides does not reflect that of the sulfoxide precursors but favors the *RR,SS* diastereomer nearly exclusively. (ii) The *RR,SS* α-lithio sulfoxide cyclizes considerably more rapidly than the *RS,SR*; the two diastereomers being in rapid equilibrium, the whole product would arise from the more reactive isomer. No evidence being available, further work is necessary for testing these two possibilities.

The final comment must be made on why the reaction occurs rapidly with (*E*)-but not with (*Z*)-homoallylic substrates. The inertness of the *Z* isomers may not be imputed to an unfavorable energy change. Consider the thiacyclooctenes, the smaller of the ring systems examined, for which the differential strain, *E* – *Z*, will be at a maximum.[37] From published force field calculations[11,35] the enthalpy change for the transformation (*E*)-thiacyclooct-4-ene → *cis*-2-thiabicyclo[3.3.0]octane may be estimated to be ca. –30 kcal/mol. The differential strain (*E* – *Z*) has been computed to be 9.6 kcal/mol,[40] very close to that of the corresponding hydrocarbons, 9.3 kcal/mol. Therefore the cyclization of (*Z*)-thiacyclooct-4-ene and, a fortiori, of the larger (*Z*)-thiacycloalkenes[37] is still a highly favored process thermodynamically.

The problem then is one of kinetics. An attractive hypothesis could be that the torsional distorsion and consequent weakening of the π bond in mesocyclic *trans*-alkenes[41] results in a decrease of the activation barrier for nucleophilic attack. This explanation, however, cannot be fully satisfactory since it would imply proportionality between rate and torsional strain. On this basis the expected rate change would be 8 > 9 > 10, in contrast with observation (8 < 9 > 10). Therefore this factor, though it may contribute to the greater reactivity of the *E* substrates, cannot be the sole cause of it.

The answer probably lies in the conformational properties of the (*E*)- relative to the (*Z*)-cycloalkenes. In general a trans double bond in a medium ring determines conformations, lying in relatively steep energy minima, where the allylic carbons are joined to the saturated chain by bonds which are nearly perpendicular to the (distorted) double bond plane.[42] The results is a kind of trapezoidal loop with the longer sides roughly parallel and at relatively short distance. This geometry implies a very sharp differentiation of the peripheral from the inner side of the ring, in particular with respect to solvation. It follows that intramolecular reactions between the double bond and any functional group facing it transannularly will be highly privileged, the reaction centers being already set in place and without solvent molecules in between. Collapse of the carbanionic carbon on to one of the transannular double bond carbons requires minor geometrical changes and is not hampered by the need of extension desolvation along the line of approach: it will then occur readily and give the addition product whenever a proton donor, however weak, is available. On the other hand the *Z* substrates have no cogent conformational constraint forcing the transannularly located functional groups to stay "poised in a position to react".[43] The carbanionic site will swing from one side to the other of the double bond, but the fraction of time spent within interactive distances will be too minute for the rate to compare with that of the *E* substrates.

These conclusions adhere to the views recently expressed by Menger about intramolecular and enzymatic reactivity.[43]

Experimental Section

General. Proton NMR spectra were recorded at 60, 100, or 300 MHz on Varian EM-360, XL-100, and Bruker CPX 300 instruments, respectively. The XL-100 instrument was used to obtain the proton noise decoupled ^{13}C NMR spectra at 25.15 MHz by the FT technique. Single-frequency off-resonance spectra were obtained by irradiation at δ –4 in the proton spectrum. Proton and ^{13}C shifts are in ppm from $(CH_3)_4Si$ and, unless otherwise specified, refer to $CDCl_3$ solvent. For the dynamic ^{13}C NMR experiments the temperature was measured with a thermocouple

(36) Formation of the alternative transannular bond (C_9–C_4) would result in the opposite stereochemical course, i.e., J → trans, K → cis.

(37) The *E* – *Z* differential strain is known to decrease rapidly with increasing ring size: In the cycloalkenes the values drop from 9.3[32] to 2.9[32] and to ~1[38,39] kcal/mol in the cyclooctene, -nonene, and -decene series.

(38) Ermer, O.; Lifson, S. *J. Am. Chem. Soc.* **1973**, *95*, 4121–4132.

(39) Allinger, N. L.; Sprague, J. T. *J. Am. Chem. Soc.* **1972**, *94*, 5734–5747.

(40) Molecular mechanics calculations (MM2) indicate the differential strain (*E*)- – (*Z*)-thiacyclooct-4-ene amounts to 9.6 kcal/mol (personal communication from A. Bongini, of this university).

(41) The steric strain of *trans*-cycloalkenes reflects itself in large torsional distorsions of the double bond. For the eight-, nine-, and ten-membered (*E*)-cycloalkenes the dihedral angles at the π bond have been computed by Ermer and Lifson to e 138.0°, 150.5°, and 168.5°, respectively.[38] Other force fields give somewhat different values.[39] For (*E*)-thiacyclooct-4-ene the computed dihedral angle was 141.5°,[11] very close to that of the carbocycle.

(42) Still, W. C. *J. Am. Chem. Soc.* **1979**, *101*, 2493–2495.

(43) For a recent discussion on the factors favoring intra- over intermolecular reactions, see: Menger, F M. *Acc. Chem. Res.* **1985**, *18*, 128–134.

inserted in a dummy tube before and after each spectral determination. Spectra simulation were carried out with the DNMR program developed by Binsch.[16] The rate constants thus obtained were fitted to the Eyring equation to obtain the $\Delta G^{\ddagger}$ values.

The ^{13}C NMR spectral assignments were based on the following: (i) off-resonance decoupling experiments; (ii) comparison with the ^{13}C NMR behavior of structurally similar systems;[44] (iii) shielding effects of the sulfoxide function and its conformational dependence.[20,24] The latter are so large and specific that they alone provide adequate information for the unequivocal assignment of both the sulfoxide configuration and the stereochemistry of the ring fusion. Several ambiguities remain, however, mostly concerning the carbons that are δ with respect to the sulfoxide oxygen; but their resolution would not in any way affect the configurational assignments.

Mass spectra were obtained with a Jeol JMS-D100 instrument. GLC analyses were performed on a Varian 3700 instrument. Silica gel 60 M and silica gel coated plates (both Merck) were used for column and thin-layer chromatography, respectively. Solvents were reagent grade. Tetrahydrofuran (THF) was dried over Na/benzophenone at reflux. All reactions involving organolithium reagents were conducted under an argon atmosphere, reactants being injected by syringe. The trivial α and β notations for the bicyclic sulfoxides indicate substituents on the opposite and on the same side, respectively, as the H atom at the bridgehead farther from the heteroatom.

Synthesis of (*E*)-Thiacycloalk-4-enes. The homoallylic sulfide precursors employed in this work were synthetized as previously reported[10,15,45] by the ring-expansion methodology[46] based on the 2,3-sigmatropic rearrangement of sulfonium ylides. For the larger unsubstituted rings this synthetic method affords the *E* isomers exclusively but affords an 85/15 *Z*/*E* mixture for the eight-membered ring system.[15] The pure *E* isomer was in this case obtained by configurational inversion of the *Z* form.[8] When, however, some contamination from the *Z* isomer was inconsequential, the *E* isomer was more expeditiously obtained by extraction with 20% aqueous silver nitrate of the crude *Z*/*E* mixture. Recovery of the highly enriched minor isomer ($E/Z \simeq 4$) was effected by treatment with 28% aqueous NH_3 followed by pentane extraction.

(*E*)-Thiacycloalk-4-ene 1-Oxides. General Procedure. The required sulfide (ordinarily 10 mmol) dissolved in CH_2Cl_2 and cooled at −80 °C was reacted with an equivalent amount of MCPBA under stirring. After the mildly exothermic reaction had subsided, the temperature was raised to −55 °C, stirring being continued for 1 h. The mixture was washed three times with 30 mL of saturated aqueous $NaHCO_3$ and then with H_2O and dried over $CaSO_4$. After solvent removal the oily residue was purified either by column chromatography or by distillation under reduced pressure. No overoxidation to sulfone took place with this procedure, which was then used throughout.

Inversions of sulfoxide configuration were effected according to a slightly modified Johnson's procedure[12] using methyl triflate in CH_2Cl_2 at 0 °C for 30 min and allowed the reaction mixture to stand at room temperature for 12 more hours. After removal of solvent the residue was hydrolyzed by dissolving it in 0.02 M aqueous NaOH and extracted with CH_2Cl_2. Configurational inversions in the neighborhood of 95% were normally obtained.

Reductions of bicyclic sulfoxides were performed with PCl_3 in CH_2Cl_2 according to a published procedure.[47] Yields were normally on the order of 80%.

(*RR*,*SS*)-(*E*)-Thiacyclooct-4-ene 1-oxide (2) was obtained as a single product from racemic (*E*)-thiacyclooct-4-ene. Contrary to our previous report, where $NaIO_4$ had been employed,[8] no *E* → *Z* isomerization took place in the low-temperature MCPBA oxidation: ^1H NMR (300 MHz) δ 5.58 and 5.40 (octets, 1 H each, J = 16.0, 10.8, and 4.0 Hz, olefinic protons), 3.51 (m, 2 H), 3.13, 2.81, 2.65, 2.43, and 2.35 (m's, 1 H each), 2.16 and 1.92 (m's, 3 H overall); ^{13}C NMR δ 135.2 (C_4), 131.1 (C_5), 61.7, 62.1 (C_2, C_8, interchangeable), 32.0, 29.8 27.3. Anal. Calcd for $C_7H_{12}OS$: C, 58.29; H, 8.39; S, 22.23. Found: C, 57.91; H, 8.44; S, 22.19.

(*RS*,*SR*)-(*E*)-Thiacyclooct-4-ene 1-oxide (3) was obtained from **2** by inversion of the sulfoxide configuration: ^1H NMR (300 MHz) δ 5.98 (octet, J = 15.5, 11.0, and 4.0 Hz, 1 H, C_5H), 5.60 (octet, J = 15.5, 10.0, and 3.5 Hz), 3.61, 3.42, and 2.98 (m's, 1 H each), 2.6–1.9 (m, 7 H overall); ^{13}C NMR δ 128.5 (C_4), 137.0 (C_5), 56.9, 48.8 (C_2, C_8, interchangeable), 32.3, 26.4, 22.8.

(*RR*,*SS*)-(*E*)-3,3-Dimethylthiacycloct-4-ene 1-oxide (2a) was obtained from **1a**[45] as a single product. The configuration was assigned on the basis of geometrical consideration, as for the parent sulfoxide (see text): ^1H NMR (60 MHz) δ 5.50 (m, 2 H, olefinic H's), 3.18 (AB q, $\Delta\nu$ = 37.0 Hz, J = 12.0 Hz, SCH_2CMe_2), 1.42 and 1.17 (s's, CH_3's); ^{13}C NMR δ 144.5 (C_4), 126.06 (C_5), 73.7 (C_2), 62.3 (C_8), 38.5 (C_3), 32.0, 28.6 (C_6, C_7, interchangeable), 28.6, 22.4 (CH_3's). Anal. Calcd for $C_9H_{16}OS$: C, 62.74; H, 9.36; S, 18.61. Found: C, 61.08; H, 9.46; S, 18.54.

(*E*)-Thiacyclonon-4-ene 1-oxide (10): bp 126 °C (0.5 mm); 300-MHz ^1H NMR [consists of unresolved m's typical of system undergoing slow exchange] δ 5.45 (2 H, olefinic protons), 3.32 (2 H), 3.1–2.7 (3 H), 2.49, 2.27, 2.08, and 1.50 (1 H each), 1.34 (3 H); ^{13}C NMR the ambient temperature spectrum shows broadening, while at 100 °C (in toluene-d_8) a sharp spectrum obtains: δ 133.2, 129.8 (C_4, C_5, interchangeable), 62.7, 57.3 (C_2, C_9, interchangeable), 32.2, 27.6, 26.3, and 22.3. At −30 °C in $CDCl_3$ the spectrum splits into two sets of sharp lines (intensity ratio, 8:1). The first figure of each pair pertains to the major component: δ 131.4–136.2, 130.5–127.0 (C_4, C_5, interchangeable), 61.9–64.0, 55.6–60.3 (C_2, C_9, interchangeable), 31.8–34.0, 27.4–28.5, 26.1–22.7, 22.7–21.5. Anal. Calcd for $C_8H_{14}OS$: C, 60.72; H, 8.92; S, 20.26. Found: C, 59.94; H, 9.00; S, 20.05.

(*E*)-Thiacyclodec-4-ene 1-oxide (7): bp 128 °C (0.4 mm); ^1H NMR (300 MHz) δ 5.62 and 5.44 (m's, 1 H each, HC=CH), 3.2 (m, 2 H), 2.96, 2.84, 2.67, 2.59, 2.21, and 2.10 (m's, 1 H each), 1.9–1.5 (m, 6 H); ^{13}C NMR δ 134.6, 128.5 (C_4, C_5, interchangeble), 53.2, 53.8 (C_2, C_{10}, interchangeable), 31.6, 26.5, 25.6, 25.4, 21.6. On lowering the temperature the spectrum broadens until at −80 °C it becomes sharp again separating into two sets of nine lines (intensity ratio ~2:1). The major and, in brackets, minor signals are as follows: δ 134.1 [135.3], 129.4 [128.9] (C_4, C_5, interchangeable), 54.5, 53.2 [52.7, 53.4] (C_2, C_9, interchangeable), 30.1, 27.1, 26.3, 24.7, 21.4 [33.7, 25.5, 25.0, 24.1, 23.1]. The correspondence between major and minor signals was established for the olefinic carbons only, which were used for line shape analysis in the 212–217 K range. Anal. Calcd for $C_9H_{16}OS$: C, 62.74; H, 9.36; S, 18.61. Found: C, 63.00; H, 9.40; S, 18.43.

Transannular Cyclization of (*E*)-Thiacycloalk-4-ene 1-Oxides. The homoallylic sulfoxide (2 mmol, freshly distilled or carefully dried in vacuo over P_2O_5 for no less than 48 h) was dissolved in freshly distilled dry THF and placed in a cold bath. BuLi (1 mmol, 1.65 M in hexane) was added and the reaction monitored by GLC. After 30–40 min the reaction was complete, and the solution was quenched with H_2O. The residue after removal of solvent was extracted with CH_2Cl_2, and the dried organic layer was evaporated and dried in vacuo over P_2O_5.

In the experiments where the rate of transannular cyclization was measured as a function of the metalation fraction the substrate was the nine-membered sulfoxide **10** and the solvent was a THF/hexane (88:12) mixture. For measurable rates the reaction was run at −30 °C. Sampling at this temperature was inconvenient, however; thus for each value of the [Bu/Li]/[substrate] ratio three distinct experiments were run where the whole reaction mixture was quenched at times corresponding to conversions from 40% to 70%. In one experiment (metalation fraction of 0.5) the reaction was followed in a wider conversion range (15–85%) to make sure a first-order rate law was obeyed. Although this was the case, there is evidence that in the runs where the [BuLi]/[substrate] ratio is low, the specific rate tends to decrease at the longer reaction times. This is likely to be due to side reactions consuming the organometallic reagent. The quenched reaction mixture was analyzed by GLC and checked also by ^1H (decrease of the olefinic signal) and by ^{13}C NMR. The first-order rates are reproducible to within ±10%.

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***cis*-2-Thiabicyclo[3.3.0]octane 2-*exo*-Oxide (5)**: obtained as a single product by transannular cyclization of **2**; bp 113 °C (0.4 mm); ^{1}H NMR (300 MHz) δ 3.41, 3.13, 2.93, 2.70, 2.52 (m's, 1 H each), 2.2–1.8 (m, 3 H), 1.6–1.0 (m, 4 H); ^{13}C NMR [shifts of bicyclic [3.3.0] compounds are collected in Table I]. Anal. Calcd for $C_7H_{12}OS$: C, 58.29; H, 8.39; S, 22.23. Found: C, 57.81; H, 8.48; S, 21.96.

***cis*-2-Thiabicyclo[3.3.0]octane 2-*endo*-Oxide (6)**: obtained both from **5** by inversion of the sulfoxide configuration and by transannular cyclization of **3**; bp 98 °C (0.4 mm); ^{1}H NMR (300 MHz) δ 3.39, 3.03, 2.79, 2.53 (m's, 1 H each), 2.3–2.0 (m, 3 H), 1.68 and 1.47 (m's, 5 H overall).

***cis*-2-Thiabicyclo[3.3.0]octane (4)**, obtained by reduction of **5**, was identical with the product prepared by the following independent route: the pyrrolidine enamine of cyclopentanone was reacted with ethyl bromoacetate according to a known procedure.[48] Ethyl (2-oxocyclopentyl)acetate[48] was obtained, whose standard $LiAlH_4$ reduction gave the corresponding diol, 2-(2-hydroxyethyl)cyclopentanol, in overall 90% yield: bp 118–121 °C (1 mm). Anal. Calcd for $C_7H_{14}O_2$: C, 64.58, H, 10.84. Found: C, 64.31; H, 11.01.

The diol appears to consist of two isomers. The major (~75%) and, in brackets, the minor isomer display the following ^{13}C NMR shifts: δ 78.7 [74.2] (*C*HOH), 62.2 [61.9] (*C*H_2OH), 46.8 [44.2] (*C*HCH_2), 36.6, 34.0, and 30.9 [34.4, 31.9, and 29.5] (C_2, C_4, and $CHCH_2CH_2OH$, interchangeable), 21.2 [22.0] (C_3). That the corresponding resonances of the major product are downfield relative to the minor one suggests they are *trans*- and *cis*-2-(2-hydroxyethyl)cyclopentanol, respectively. To this isomeric mixture (14.1 g, 0.107 mol) dissolved in 150 mL of dry pyridine at 0 °C was slowly added methanesulfonyl chloride (36 g, 0.315 mol), and esterification was continued for 4 days at 5 °C. The reaction mixture was then poured on ice and aqueous HCl and extracted with CH_2Cl_2. The organic layer was washed successively with dilute HCl and $NaHCO_3$ solutions and dried. Evaporation of the solvent left a crude dimesylate (28.6 g, 90%) which was used as such in the next cyclization step. For this the dimesylate (28.6 g, 0.1 mol) dissolved in EtOH (100 mL) was added dropwise to a solution of $Na_2S·9H_2O$ (36 g, 0.15 mol, in 270 mL of EtOH) and the mixture heated at reflux for 16 h. After solvent evaporation, water was added and the mixture extracted with petroleum ether. The crude after solvent removal was distilled under reduced pressure, yielding two major fractions of which the lower boiling one [bp 45 °C (0.5 mm); 6.0 g, 42%] contained as a single product the title compound: ^{1}H NMR (300 MHz) δ 3.76 (octet, 1 H, J = 8.0, 7.0, and 3.5 Hz, CHS), 2.61 (m, 3 H), 1.96 and 1.75 (m's, 6 H overall), 1.56 and 1.34 (m's, 1 H each). Anal. Calcd for $C_7H_{12}S$: C, 65.57; N, 9.43; S, 25.00. Found: C, 66.11; H, 9.38; S, 25.11. (The higher boiling fraction [bp 140–150 °C (0.5 mm)] was not analyzed. See below, however, under the preparation of the higher homologue **11**).

Low-temperature MCPBA oxidation of **4** gave a 4:1 mixture of sulfoxides **5** and **6**, which could be separated by flash chromatography.

Methylation of 5. *cis*-3-*endo*- (5b) and *cis*-3-*exo*-Methyl-2-thiabicyclo[3.3.0]octane 2-*exo*-Oxide (5c). To a solution of **5** (0.216 g, 1.5 mmol) in THF at −40 °C was added 1.6 equiv of MeLi (1.6 M in Et_2O). Methyl iodide was added (4 equiv) after 15 min and the temperature maintained for 30 min. Low-temperature quenching and workup as usual gave a product which, analyzed by ^{13}C NMR, appeared to consist of a mixture of two α-methyl derivatives **5b** and **5c**, in about equal amounts. This is a kinetic ratio for, if the **5b**/**5c** mixture in THF is treated with BuLi at room temperature and quenched after some time, an equilibrium mixture obtains where **5c**/**5b** = 6, a value which does not change further by prolonging the contact with BuLi. The relative configuration of **5b** and **5c** rests on the ^{13}C shifts of the methyl carbons, trans and cis to the vicinal oxygen (γ-gauche and γ-anti effects) in **5b** and **5c**, respectively.

Methylation of 6. *cis*-3-*exo*-Methyl-2-thiabicyclo-[3.3.0]-octane 2-*endo*-Oxide (6c). Methyl iodide quenching of the α-lithio sulfoxide from **6** (obtained as described above for **5**) gave a single product, **6c**, bp 90 °C (0.3 mm). The configurational assignment rests on the identification of the sulfide **4c**, obtained by reduction of **6c**, identical with that obtained by the reduction of **5c**. Furthermore, configurational inversion of **6c** yielded **5c**, while inversion of the kinetic ~1:1 **5b**/**5c** mixture produced **6b** + **6c**.

***cis*- (11a) and *trans*-2-thiabicyclo[4.3.0]nonane 2-α-oxide (12a)** were obtained as a mixture by BuLi-promoted cyclization of **10** at −30 °C. Their proportion changed during the course of the reaction from an initial **11a**/**12a** ≃ 3:2 (extrapolated to zero time) to a final ≃1:15 ratio when the reaction product was allowed to equilibrate at room temperature before quenching. Reduction of a mixture of **11a**/**12a** ≃ 1:3 gave a mixture of sulfides **11** and **12** whose minor component, **11**, was identical with *cis*-2-thiabicyclo[4.3.0]nonane prepared by the independent route described below.

***cis*-2-Thiabicyclo[4.3.0]nonane (11).** Ethyl acrylate alkylation of the cyclopentanone pyrrolidine enamine followed by LAH reduction yielded (80% overall) 2-(3-hydroxypropyl)cyclopentanol, bp 130–132 °C (1 mm) [lit.[49] bp 119 °C (0.05 mm)]. The ^{13}C spectrum of the diol shows it consists of a 3:1 mixture of isomers. The major and minor (in brackets) isomers have the following ^{13}C NMR shifts: δ 78.4 [73.8] (C_1), 62.0 [62.2] (*C*H_2OH), 47.0 [45.6] (C_5), 34.1 [34.2] (C_2), 30.7, 29.6 [31.2, 28.9] (C_4 and $CH_2CH_2CH_2OH$, interchangeable), 29.6 [25.0] (C_5CH_2), 21.5 [21.5] (C_3). The trans and cis geometry can be assigned to the major and minor isomer, respectively. No separation was attempted of the diols, and their mixture (18.0 g, 0.105 mol) was esterified as such with methanesulfonyl chloride and the mesylates cyclized with Na_2S as above. The crude product (26 g, 82%) was fractionally distilled. The lower boiling fraction (3.5 g, 28.6%), bp 60–61 °C (0.8 mm), consisted of the title compound as the sole component, identical with the sulfide obtained by reduction of sulfoxide **11a**. Anal. Calcd for $C_8H_{14}S$: C, 67.51; H, 9.92; S, 22.54. Found: C, 67.40; H, 9.83; S, 22.44.

The higher boiling fraction [6.0 g, 49%, 160–170 °C (0.8 mm)] showed two GLC peaks (5:2 ratio) both *m*/*e* 250. The ^{13}C NMR spectrum displays two sets of eight signals each (intensity ratio, 1.5:1) two of which are in the olefinic and six in the aliphatic region. Chemical shifts and signal multiplicities (in parentheses) are as follows (the first eight figures refer to the more intense signals): δ 143.5 (s), 123.8 (d), 35.1, 32.5, 31.9, 30.8, 27.9, and 23.5 (all t's), 134.9 (d), 130.4 (d, 43.5 (d), 32.5, 31.9, 29.8, 28.1, 23.5 (all t's). The spectral evidence is compatible with this material being made up of a mixture of acyclic sulfides the organic part of which are the 3-(cyclopent-1-enyl)prop-1-yl and 3-(cyclopent-2-enyl)-prop-1-yl groups, symmetrically and unsymmetrically combined. The sulfides would conceivably arise from intermolecular displacement of the primary mesylate by the primary thiolate *and* β-elimination of the secondary mesylate. That the 3-(cyclopent-1-enyl)prop-1-yl moiety is the more abundant merely reflects the fact that β-elimination altogether occurs somewhat preferentially in the direction of the more substituted olefin. It is remarkable that no appreciable trans bicyclic sulfide **12** (the thermodynamically favored isomer) is formed in the cyclization, although some 25% of the starting dimesylate has the cis geometry required for generating the trans sulfide. Apparently anti β-elimination to 1-alkylcyclopentene derivatives completely overcomes displacement of the secondary sulfonate.[50] On the other hand the relative yield of cyclic and acyclic sulfide demands that the trans dimesylate also undergoes elimination (both syn and anti) in comparable proportion to substitution.

***cis*- (11b) and *trans*-2-Thiabicyclo[4.3.0]nonane 2-β-Oxide (12b).** Oxidation of **11** gave a 1:4 mixture of **11a** and **11b**, from which the major component could be obtained by flash chromatography. Treatment of **11b** in THF with 0.5 equiv of BuLi caused partial epimerization to **12b**. After 2 h at room temperature the ratio **12b**/**11b** was estimated by ^{13}C NMR to be ~2. Epimerization was not pursued further, and the mixture was subjected to inversion of the sulfoxide configuration. The inverted mixture contained the same two products **11a** and **12a** originally obtained

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in the transannular cyclization of **10**.

***cis*- (8a) and *trans*-2-Thiabicyclo[4.4.0]decane 2-α-Oxide (9a).** Treatment of **7** in THF with 0.5 equiv of BuLi at −20 °C produced a mixture of the title compounds whose proportion changed during the course of the reaction from ~1:1 to ~100% of **9a**[20] when the mixture was allowed to equilibrate. Reduction of **9a** gave sulfide **9**,[21] while reduction of a **8a**/**9a** ≃ 1:3 mixture gave the expected mixture of *cis*- and *trans*-1-thiadecalin (**8** and **9**).[21] Inversion of the same **8a**/**9a** ≃ 1:3 mixture gave a sulfoxide product whose major component was the trans β-oxide **9b**,[20] while the minor component was the cis β-oxide **8b**.[22] Consequently **8a**, from which **8b** obtains by sulfur inversion, must be *cis*-2-thiabicyclo[4.4.0]decane 2-α-oxide: ^{13}C NMR δ 56.4 (C_1), 43.8 (C_3), 34.6, 31.9 (C_5, C_7, interchangeable), 25.6, 24.2 (C_8, C_9, interchangeable), 20.7 (C_{10}), 16.6 (C_4), 21.5 (C_7).

Attempted Cyclization of (*Z*)-Thiacycloalk-4-enes. The oxides of (*Z*)-thiacyclooct-4-ene[15] and (*Z*)-7,7-dimethylthiacyclono-4-ene[45] in THF were treated with BuLi (0.5 equiv) at room temperature. Quenching with H_2O after various lenghts of time (up to 2 h) failed to yield any product of transannular cyclization.

Registry No. (±)-**1**, 104808-85-7; (±)-**1a**, 104808-86-8; (±)-**2**, 72074-95-4; (±)-**2a**, 79760-34-2; (±)-**3**, 104872-74-4; (±)-**4**, 104808-82-4; (±)-**4a**, 104808-96-0; (±)-**4b**, 104872-88-0; (±)-**4c**, 104872-89-1; (±)-**5**, 104808-81-3; (±)-**5a**, 79760-35-3; (±)-**5b**, 104808-83-5; (±)-**5c**, 104872-77-7; (±)-**6**, 104872-75-5; (±)-**6a**, 79813-60-8; (±)-**6b**, 104872-90-4; (±)-**6c**, 104872-78-8; (±)-**7**, 104808-80-2; (±)-**8**, 104808-94-8; (±)-**8a**, 104872-83-5; (±)-**8b**, 104872-85-7; (±)-**9**, 87716-82-3; (±)-**9a**, 104872-84-6; (±)-**9b**, 104872-86-8; (±)-**10**, 104808-79-9; **10** (sulfide), 68013-79-6; (±)-**11**, 104808-84-6; (±)-**11a**, 104872-79-9; (±)-**11b**, 104872-81-3; (±)-**12**, 104808-89-1; (±)-**12a**, 104872-80-2; (±)-**12b**, 104872-82-4; $\overline{CH_2}$-$\overline{(CH_2)_2CH{=}C(CH_2)_3S(CH_2)_3CHCH{=}CHCH_2}CH_2$, 104808-93-7; (±)-*trans*-2-(2-hydroxyethyl)cyclopentanol, 104872-76-6; (±)-*cis*-2-(2-hydroxyethyl)cyclopentanol, 62324-21-4; (*E*)-thiacyclodec-4-ene, 68013-80-9; cyclopentanone (pyrrolidine enamine), 7148-07-4; ethyl bromoacetate, 105-36-2; (±)-ethyl (2-oxocyclopentyl)acetate, 104808-87-9; 2-(2-hydroxyethyl)cyclopentanol (dimesylate), 104808-88-0; ethyl acrylate, 140-88-5; (±)-*trans*-2-(3-hydroxypropyl)cyclopentanol, 104808-90-4; (±)-*cis*-2-(3-hydroxypropyl)cyclopentanol, 104808-91-5; bis(3-(cyclopent-1-enyl)prop-1-yl) sulfide, 104808-92-6; (±)-(*Z*)-thiacyclooct-4-ene oxide, 104872-87-9; (±)-(*Z*)-7,7-dimethylthiacyclonon-4-ene oxide, 104808-95-9; bis(3-(cyclopent-2-en-1-yl)prop-1-yl) sulfide, 104808-97-1.

A Stereospecific Tandem Wagner–Meerwein Rearrangement in the Solvolysis of 19-Mesyloxy Steroids

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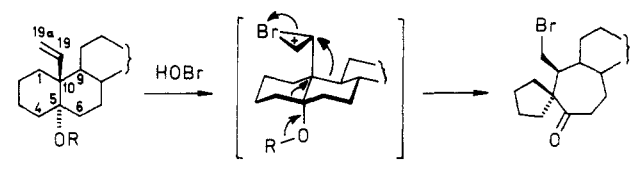
Acetolysis of 5α-cholestane-5,19-diol 19-methanesulfonate (**9**) smoothly leads to a new spirocyclic compound **11** as a result of tandem migrations of two antiparallel skeletal carbon–carbon bonds. This stereospecific, cascade rearrangement is found to be a general reaction of 5α-hydroxy and 5α-alkoxy steroids with an electron-deficient center at C(19) and may be viewed as a double pinacol rearrangement. The driving force for the rearrangement to occur is the eventual conversion of the hydroxyl or alkoxyl into the carbonyl group. The importance of the stereoelectronic control in the Wagner–Meerwein rearrangement is demonstrated. The structure of the spirocyclic compound **11** was determined by single-crystal X-ray analysis.

The course of the Wagner–Meerwein rearrangement[1] can be dramatically influenced by stereoelectronic effects (Figure 1). The importance of overlap between the carbocationic vacant orbital and the σ bond in the transition state was demonstrated by von Schleyer and co-workers.[1b,2]

Scheme I



1, R = H
2, R = CH_3
3, R = H
4, R = CH_3
5

Nickon and Weglein[3] pointed out that for a concerted Wagner–Meerwein rearrangement to occur the leaving and the migrating group should be antiperiplanar in an ideal case (sp^3 alignment factor). Accordingly, if two groups are

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