^{13}C spectra which proved considerably more valuable in the structural analysis of 1-thiadecalins.

Experimental Section

Synthesis and analytical data of the compounds investigated are described in detail elsewhere.[3]

NMR spectra were recorded on a Varian XL-100 pulsed Fourier transform nuclear magnetic resonance spectrometer. ^1H NMR spectra were recorded in the CW mode, in 5-mm o.d. tubes. ^{13}C spectra were measured at 25.16 MHz, in the pulsed mode, in 10-mm o.d. tubes. Solvent in both cases was $CDCl_3$, with 2–5% Me_4Si admixed as internal reference; the deuterium of the solvent provided the internal lock signal. Integration of corresponding signals in the low-temperature spectra was effected by counting squares of the signal areas, and by multiplication of signal height with half-width, after expanding electronically as much as resolution and noise level permitted. The following signals (numbers refer to position of carbon atoms) were integrated and gave the following (parenthesized) percentages (only one conformer of each pair is reported): **11A** 2 (60), 4 (58), 5 (58), 6 (59), 9 (58), 10 (58); **14A** 4 (32), 6 (34), 9 (33); **17A** 5 (14), 9 (17), CH_3 (19). Error limits are estimated to be of the same size as reported in ref 13, that is, ±2% (in favorable cases of $K \approx 1$) to ±10% (in unfavorable cases of $K \approx 20$). The resulting errors for the $\Delta G°$ values in Table II are ±0.06 kcal/mol or better.

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Stereochemistry of α Halogenation of Sulfoxides. 1. A Proton Nuclear Magnetic Resonance Study of the Bromination of *trans*-2-Thiahydrindan 2-Oxide

Anna Garbesi*

Laboratorio CNR, Ozzano Emilia, Bologna, Italy

Antonino Fava*

Istituto di Chimica Organica, Universitá di Bologna, Bologna, Italy

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The stereochemistry of bromination of the title compound with bromine in the presence of pyridine to give the α-bromo sulfoxide has been studied by ^1H NMR and stereospecific deuterium labeling methods. The reaction appears to be completely regio- and stereospecific and involves inversion of configuration at both sulfur and α carbon. This result is discussed on the basis of various possible halogenation mechanisms. However, no clear-cut mechanistic choice appears to be possible.

The stereochemistry of α halogenation of sulfoxides by halogens or halogen sources (X_2) in the presence of base (B:)[1] has been extensively investigated in recent years.

$$RS(O)CHR_1R_2 \xrightarrow[B:]{X_2} RS(O)CXR_1R_2$$

The reaction is normally found to be stereospecific, and occasionally highly so, at both sulfur and α carbon.[7] The results, however, are puzzling, as the actual steric course appears to depend rather unpredictably both on sulfoxide structure (open chain[7] or cyclic,[8-11] type and nature of the substituent at C_α[7,12]) and reaction conditions (halogenating agent, presence or absence of an electrophile such as $AgNO_3$).[7] Thus, if it is reasonable to suppose that a single fundamental mechanism is operating in every case, it has been nevertheless impossible to fit all the results in a coherent framework. Apparently, the factors which ultimately control the stereochemistry are incompletely understood.

It has been suggested that the conformational flexibility of the substrate and/or reactive intermediates formed along the reaction path may play a key role in determining the steric course,[11,12] yet no comprehensive study has been reported on the halogenation of conformationally rigid sulfoxides.[13] In this paper we report on the stereochemistry of bromination of *trans*-2-thiahydrindan 2-oxide (**1a**), a system which, by virtue of the trans ring fusion, cannot undergo appreciable skeletal deformation at the reaction centers.[14] This system is particularly advantageous, since the four α protons are all stereochemically different, either because of their relation to the S–O bond or the ring fusion, and can be readily identified in

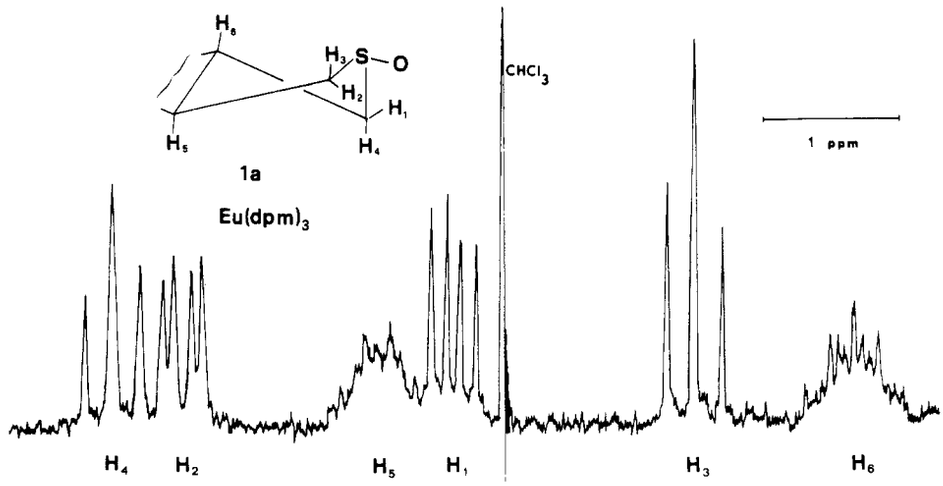


Figure 1. Proton NMR spectrum of *trans*-2-thiahydrindan 2-oxide (**1a**) in $CDCl_3$ in the presence of $Eu(dpm)_3$ 4:3 molar ratio.

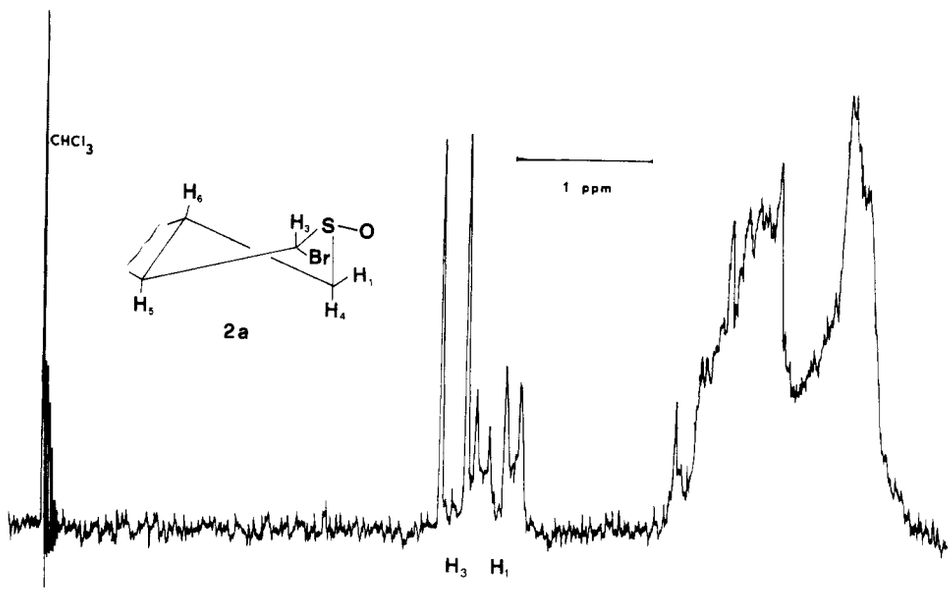
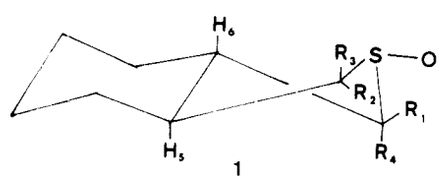


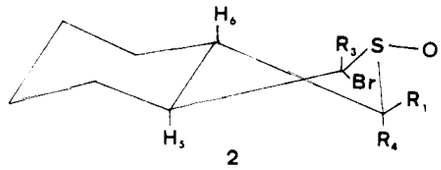
Figure 2. Proton NMR spectrum of *trans*-2-thia-1-bromohydrindan 2-oxide (**2a**) in $CDCl_3$

the NMR. This is true also for the bromosulfoxide product and, consequently, the steric course of halogenation can be conveniently followed by NMR methods.



1

a, $R_1 = R_2 = R_3 = R_4 = H$
b, $R_1 = R_2 = R_4 = H$; $R_3 = D$
c, $R_1 = R_3 = R_4 = H$; $R_2 = D$



2

a, $R_1 = R_3 = R_4 = H$
b, $R_1 = R_3 = H$; $R_4 = D$
c, $R_3 = R_4 = H$; $R_1 = D$

Results

The 100-MHz NMR spectrum of **1a** has been previously discussed.[16] At 60 MHz the two quasi-equatorial protons H_1 and H_2 still appear as separate resonances, δ 3.65 and 2.83, respectively. (In $CDCl_3$ the shifts are concentration dependent; these values refer to a 0.44 M solution.) All other protons appear as two very broad signals centered at δ 1.95 and 1.2, respectively. The addition of shift reagent [$Eu(dpm)_3$] gradually resolves the heterocyclic part of the spectrum, all the protons eventually becoming neatly separated. This is shown in Figure 1, which corresponds to a 4:3 sulfoxide/shift reagent molar ratio.

Bromination of **1a** in acetonitrile in the presence of pyridine (48 h, room temperature) gave, together with unreacted sulfoxide and some sulfone (<10%), a 30% yield of a α-bromosulfoxide. Its presence was clearly evinced in the NMR spectrum of the crude reaction product by the appearance of a low-field doublet[17] [1 H, J = 11 Hz, δ 4.18 (concentration dependent)] whose splitting unequivocally establishes the axial orientation of the methyne proton geminal to bromine (henceforth the equatorial orientation of bromine itself). No other doublet was visible in the NMR of the crude product,

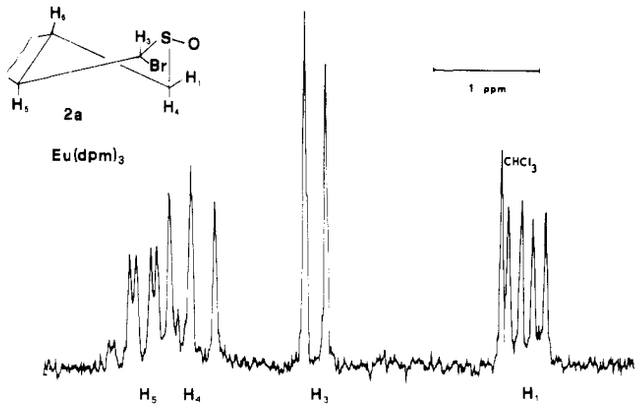


Figure 3. Proton NMR spectrum of *trans*-2-thia-1-bromohydrindan 2-oxide (**2a**) in $CDCl_3$ in the presence of $Eu(dpm)_3$ 1:1 molar ratio.

as well as in the isolated bromosulfoxide fraction. In TLC this appears to be a single product. Therefore, within the limits of the sensitivity of the NMR method, only one α-bromosulfoxide was formed, and the reaction appears to be extremely regio- and stereoselective. The spectra of the isolated bromosulfoxide fraction in the absence and in the presence of shift reagent [$Eu(dpm)_3$, 1:1 molar ratio] are reported in Figures 2 and 3, respectively. It is immediately apparent that the methyne doublet has been shifted downfield much less than the signal of the other axial α proton (H_4), strong evidence[18] that the proton geminal to bromine is trans with respect to oxygen; hence the bromosulfoxide has the structure **2a.** Additional definitive stereochemical proof was provided by the finding (see below) that in the reductive debromination ($Zn/MeOD/D^+$) of the bromosulfoxide product, the deuterium label turned up exclusively at positions R_2 and R_3, bound, that is, to C_1. Henceforth the Br atom must also be bound to C_1, a result that, given the axial setting of the geminal methyne, is compatible only with structure **2a.**

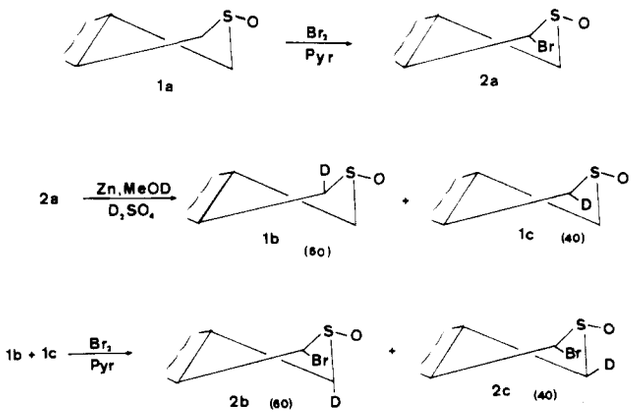
Since the steric course of halogenation is known to often change drastically in the presence of silver nitrate,[7] the bromination of **1a** was also carried out in the presence of $AgNO_3$ (2 equiv). Under these conditions the reaction went to completion in a relatively very short time. Again, however, **2a** was the only bromosulfoxide formed together with some sulfone (20%).[19] Since in the case at hand $AgNO_3$ merely accelerates the reaction without altering its course, all further experiments were carried out in the presence of $AgNO_3$.

The question of the steric course was approached through the use of specifically deuterium labeled derivatives of **1**, as described in the following (Schemes I–III). Bromosulfoxide **2a** was subjected to reductive debromination by Zn in methanol-*O*-*d* in the presence of acid catalyst (D_2SO_4). Previously, on an open-chain substrate, complete inversion of configuration had been found by Montanari and co-workers.[7,20] On this basis, the product expected with our substrate was **1b,** where the D atom is quasi-axial and trans to S–O. Instead (Scheme I) a mixture was obtained of **1b** (60%) and **1c** (40%) corresponding to the reductive debromination occurring with 80% racemization and 20% net inversion.

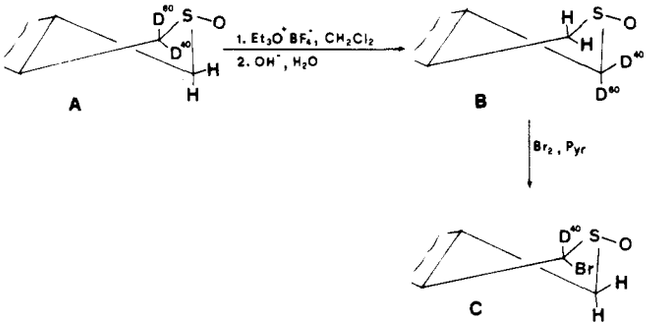
This material, subjected to bromination under the usual conditions, gave a bromosulfoxide containing 100% protium at the R_3 position (geminal to Br), but only about 60 and 40% protium respectively at R_4 and R_1. In other words, the product was made up of a mixture of **2b** and **2c** (Scheme I). This finding demonstrates that bromination of **1a** occurs completely regiospecifically at C_3 and stereospecifically at sulfur with steric course inversion.

In order to ascertain the steric course at the α carbon, one needs to know which of the protons at C_3 was replaced by

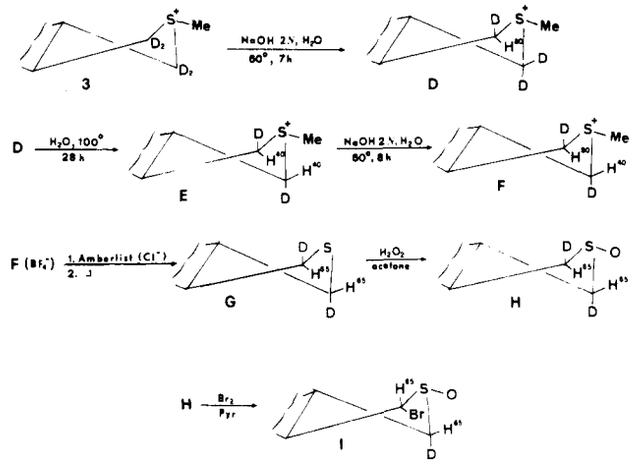
Scheme I



Scheme II



Scheme III



bromine, and this requires differential labeling at R_1 and R_4. A preliminary experiment was carried out starting with the 60:40 mixture of deuteriosulfoxides **1b** and **1c,** obtained as described above, by reductive debromination of **2a** (Scheme II).[21] Treatment of this mixture (**A**) with triethyloxonium fluoborate in CH_2Cl_2, followed by basic hydrolysis, inverted the configuration at sulfur[22] producing **B,** partially deuterated at R_1 and R_4. Bromination of **B** gave a bromosulfoxide **C** with a protium content of 100% at both R_1 and R_4, but only about 40% at R_3, the position geminal to Br. This result, while confirming the inversion steric course at sulfur, is indicative of at least predominant inversion of configuration at the α carbon as well.

It was felt, however, that the differential deuterium labeling at R_1 and R_4 was insufficient to unambigously establish the stereoselectivity of removal and consequently the stereochemistry at C_3. A method was therefore sought to label only one of the positions at C_3. Since the experiment of Scheme II

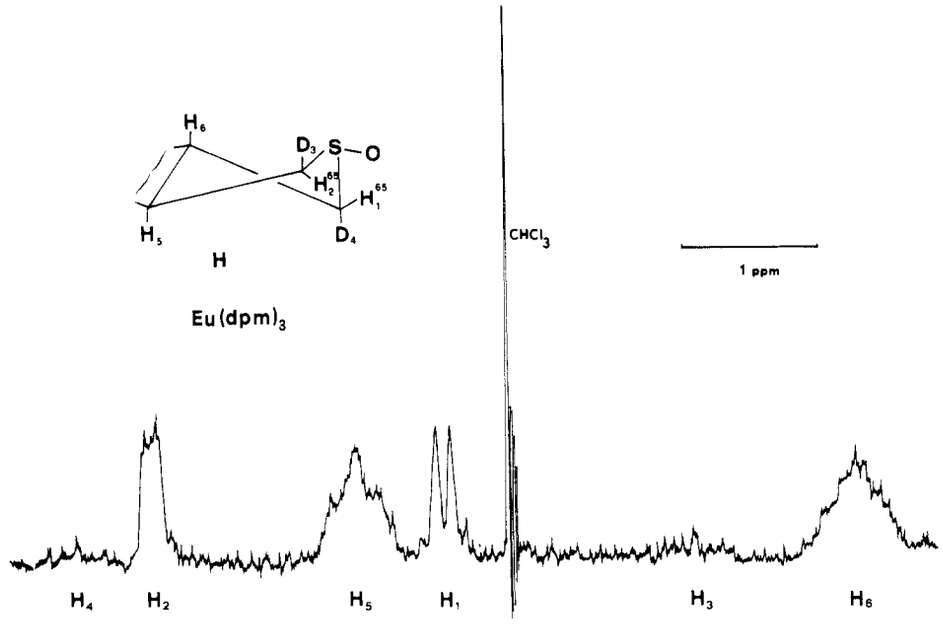


Figure 4. Proton NMR spectrum of specifically deuterated 2-thiahydrindan 2-oxide (**H**, Scheme III) in $CDCl_3$ in the presence of $Eu(dpm)_3$ 1.2:1 molar ratio.

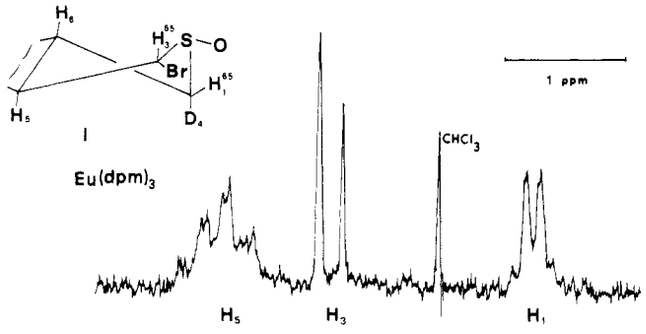


Figure 5. Proton NMR spectrum of the specifically deuterated bromosulfoxide **I** (see Scheme III) in $CDCl_3$ in the presence of $Eu(dpm)_3$ 1:1 molar ratio.

seemed to indicate preferential removal of H_4, it appeared desirable to deuterate precisely this position so that proton removal during bromination would eventually work against the kinetic isotope effect.[23] To this end the sequence of Scheme III was applied.

The S-methyl derivative of thiahydrindan-*1,1,3,3-d*$_4$ (**3**) was prepared as previously described.[24] From previous work this sulfonium salt was known to undergo highly stereoselective base-catalyzed H/D exchange at position R_2.[24] Treatment of **3** with 2N NaOH in H_2O (7 h, 60 °C) resulted in 80% exchange at the R_2 position giving **D.** This was subjected to thermal pyramidal inversion at sulfur, a process which exchanges corresponding positions across the sulfur atom.[24] Indeed the material (**E**) obtained through thermal equilibration of **D** had the H label equally divided between the quasi-equatorial α positions. This material was once more subjected to H/D exchange to obtain **F.** This was ion exchanged to obtain the chloride salt which was subsequently pyrolyzed to eliminate gaseous CH_3Cl, leaving behind the labeled sulfide **G.** This material was oxidized to the sulfoxide **H,** whose NMR spectrum in the presence of shift reagent is reported in Figure 4. As shown, the protium content at the quasi-equatorial positions R_1 and R_2 appears to be approximately 65%, while that at the quasi-axial positions was still practically negligible.

Bromination of **H** gave bromosulfoxide **I** whose NMR spectrum is reported in Figure 5. No protium appears to have been lost in bromination; it has switched place, however, as 65% protium now appears at R_3, the axial position geminal to Br. Recalling that bromination occurs with complete inversion at sulfur, this result demonstrates that the deuterium atom has been removed at R_4 (in spite of the unfavorable isotope effect),[23] implying essentially complete inversion at the α carbon.

In conclusion, α-bromination of **1a** is completely regio- and stereospecific and involves complete inversion of configuration at both sulfur and α carbon.

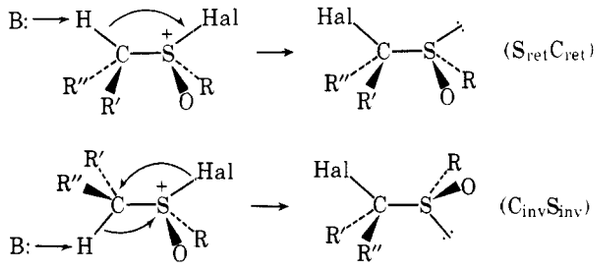
Discussion

All available evidence consistently indicates that the halogenation of sulfoxides with halogen or halogen sources (X_2) in the presence of bases (B:) proceeds through the initial formation of a halooxosulfonium intermediate, whose base-promoted collapse eventually leads to the α-halosulfoxide product.[23]

$$RS(O)CHR_1R_2 \xrightarrow{X_2} RS^{+}(X)(O)CHR_1R_2 \xrightarrow[\text{one step or more}]{B:} RS(O)CXR_1R_2 + BH^{+}X^{-}$$

A sizable deuterium isotope effect, $k_H/k_D \geq 5.5$, has been found for an open-chain substrate,[23] indicating proton abstraction occurs in the rate-determining transition state. In the absence of contrary evidence, this mechanism may be reasonably assumed to have general validity. Kinetic studies cannot provide information about the step in which halogen is attached to the α carbon, since this occurs after the rate-determining step. This is precisely the question that stereochemical studies have sought to answer.

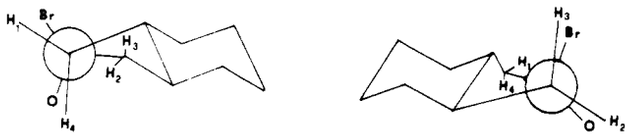
Fundamentally two types of mechanism have been proposed. In one, by Montanari and co-workers,[7] hydrogen abstraction and halogen migration were considered to occur in the same transition state. Such concertedness was assumed specifically in view of the close correlation, which in open-chain substrates was observed between the stereochemical course at sulfur and α carbon, $S_{inv}C_{inv}$ or $S_{ret}C_{ret}$.[7] However, in order to explain the occurrence of various blends of $S_{inv}C_{inv}$



and $S_{ret}C_{ret}$, these authors suggested two processes were competing with each other.

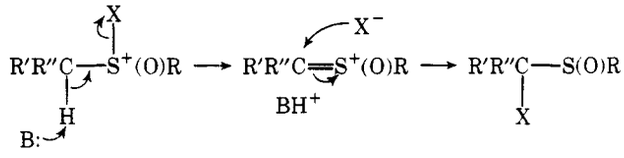
In the first, the halogen would migrate with a *cation* from a syn coplanar conformation, producing retention of configuration at both sulfur and α carbon. In the second, the halogen would migrate as an *anion* from an anti coplanar conformation, involving inversion of configuration at both reaction centers. According to Montanari and his students,[7] the competition between the two paths I and II would be decided by the relative stability of the syn and anti conformers and ultimately by a steric factor: increasing bulk of the groups (R, R_1, and R_2) at the ends of the S–C_α bond destabilizes the syn conformation required for process I, thus shifting the balance toward process II and its attendant $S_{inv}C_{inv}$ steric course.

To visualize how the Montanari mechanism would apply to our substrate it is useful to examine the Newman projections (along the S–C_α bonds) of the key intermediate, the bromooxosulfonium cation.



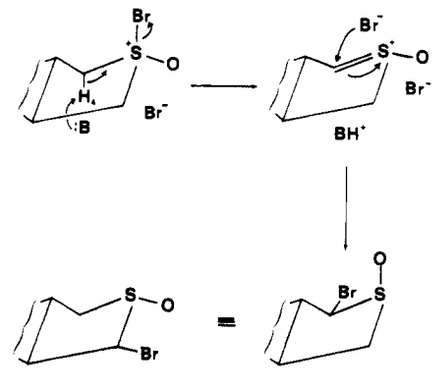
Protons H_2 and H_4 (trans to bromine) appear to deviate considerably from anti coplanarity with the bromine atom; from Dreiding models, the dihedral angles the S–Br bonds make with C–H_4 and C–H_2 are on the order of 140 and 110°, respectively. On the other hand, protons H_1 and H_3 (cis to bromine) deviate less from syn coplanarity, the corresponding dihedral angle being about 20°. Although neither anti or syn coplanarity can be easily achieved in this very rigid system, the geometry is unquestionably more suitable for the occurrence of process I rather than II. Indeed, if the two processes comparably compete in open-chain systems, as proposed by Montanari,[7] process I would be expected to prevail strongly in our system, leading to removal of H_1 and/or H_3 and preferential steric course $S_{ret}C_{ret}$. This expectation is not fulfilled by the experiment, as the proton removed is H_4, one of the protons trans to bromine, and the steric course is $S_{inv}C_{inv}$. Thus Montanari's mechanism, though not rigorously disproved by our results, does not receive support from them.[25]

The second mechanism was proposed by Klein and Stollar[10] and independently by Marquet and co-workers,[9] specifically for explaining the results obtained in the halogenation of six-membered cyclic sulfoxides. It is a two-step process of elimination–addition from the halooxosulfonium ion, in which a rate-determining anti β elimination of HX to form a positively charged "sulfene" is followed by fast halide attack at the α carbon of the sulfene to produce the halosulfoxide.



Applied to our system, this mechanism requires the first step to be the anti elimination of proton H_4 and Br^- (Scheme IV).

Scheme IV



As noted above, the H_4–C–S–Br torsion angle is ~140°; i.e., the C–H_4 and S–Br bonds deviate considerably from the condition of anti coplanarity which is most suitable for trans elimination. This stereoelectronic requirement could be overcome by the elimination occurring via the carbanion mechanism, E1cb, but it may be unnecessary to go as far as that, since concerted anti β eliminations are known to occur without great difficulty even in rigid systems which deviate considerably from anti coplanarity. For example, a case of an essentially exclusive base-catalyzed anti elimination has been reported involving the five-membered ring of a steroidal bromide, 3α-acetoxy-16α-deuterio-17α-bromopregnane-11,20-dione,[26] where the geometrical situation of the groups being eliminated is comparable to that of our bromooxosulfonium intermediate. Moreover, even in norbornyl derivatives, where the anti coplanar arrangement is essentially unaccessible, anti eliminations do occur to some extent.[26] In such cases the E2 transition state may be shifted somewhat toward the E1cb extreme,[27] a requirement which could be accommodated in the elimination from the bromooxosulfonium ion, where substantial carbanion character may be easily achieved.

As far as the second step of the Marquet mechanism is concerned, however, the observed steric course demands that bromide attack on the sulfene occurs exclusively, or very nearly so,[28] on one of the two sides, precisely that where bromide was expelled from the bromooxosulfonium intermediate (equatorial attack). Since, at least in the absence of ionic silver, bromide ions are likely to face both sides of the sulfene, this result is very surprising. It is nevertheless admissible, since the faces of the "sulfene", being diastereotopic, have intrinsically different reactivities. In this connection it may be recalled that in the chlorination of *trans*-4-R-thiane 1-oxide, the observed steric course would require attack on the sulfene to occur preferentially (20:1) on the side opposite to that where chloride was expelled.[9-11]

In conclusion our findings, though not providing additional evidence, may not be incompatible with the Marquet[9] "sulfene" mechanism.

One aspect of the halogenation reaction that this mechanism does not consider explicitly is the role silver ions can play in changing, sometimes very drastically, the steric course (though this was not the case of the present study). We feel this capacity of ionic silver, and perhaps of other electrophiles, may provide the key to a better understanding of the product-forming steps of the halogenation mechanism. We are currently testing the idea that the effect of silver ion may be related to its ability to bind halide ions in solution which might otherwise function as counterion of the halooxosulfonium intermediate. The results of this study will be reported in a forthcoming paper.

Experimental Section

Bromination of *trans*-2-Thiahydrindan 2-Oxide. A solution of bromine (2.01 g, 13 mmol) in anhydrous acetonitrile (15 mL) was added dropwise to a stirred solution of *trans*-2-thiahydrindan 2-oxide[16] (1 g, 6.3 mmol) in a mixture of anhydrous pyridine (3.6 mL) and acetonitrile (20 mL) cooled at −20 °C. The reaction mixture was stirred at room temperature for 48 h. Acetonitrile was removed under reduced pressure; the oily residue was dissolved in chloroform (200 mL) and washed, in order, with aqueous sodium thiosulfate, aqueous sulfuric acid, and saturated aqueous sodium chloride. After drying with anhydrous sodium sulfate, chloroform was evaporated to leave an oil which, analyzed by TLC, resulted in a mixture of bromosulfoxide, starting sulfoxide, and sulfone. The oil was dissolved in ethyl ether (3 mL) and precipitated at −30 °C with light petroleum ether (15 mL) to give 450 mg (30%) of a white crystalline solid. Recrystallized from acetone/ethyl ether at −20 °C, it appeared to be a pure compound (TLC). Unfortunately neither melting point nor elemental analysis could be obtained, since this compound, stable in solution at low temperature, spontaneously and unpredictably undergoes sudden decomposition in the solid. However, mass spectral analysis gave the expected molecular peaks at *m/e* 236 and 238 and a fragmentation pattern consistent with the assigned structure (**2a**). The NMR (60 MHz, 38 mg in 0.5 mL of $CDCl_3$) is shown in Figure 2. The low-field doublet at δ 4.18, due to the methyne proton geminal to bromine, is characterized by an 11-Hz coupling which establishes its quasi-axial setting (trans diaxial vicinal coupling); hence the bromine atom must be quasi-equatorial.

The geometric relation with respect to the S–O function was obtained by lanthanide-induced shift experiments. For instance, the spectrum obtained at the maximum shift reagent to bromosulfoxide molar ratio (1:1) shows (Figure 3) how the methyne proton doublet has moved downfield much less rapidly than the triplet of the axial proton at C_3. Thus the methyne proton is trans and the axial methylene proton at C_3 is cis with respect to S–O.

Bromination in the Presence of Silver Nitrate. A solution of bromine (2 g, 12 mmol) in anhydrous acetonitrile (15 mL) was added dropwise at −20 °C to a stirred solution of sulfoxide (1 g, 6.3 mmol) and silver(I) nitrate (4.2 g, 25 mmol) in a mixture of anhydrous pyridine (3.8 mL) and acetonitrile (30 mL). The reaction mixture was further stirred at −20 °C for 1 h, then at room temperature for 1 h. Filtration of silver bromide and removal of acetonitrile under reduced pressure left a crude oily product which (TLC and NMR) appeared to be made up of bromosulfoxide **2a** (80%) and sulfone (20%). No unreacted sulfoxide could be detected. Workup as described above gave 1.2 g of pure **2a**.

This bromination procedure was applied to the deuterium labeled compounds for which, however, the reaction time was 4 h at −20 °C and 1 h at room temperature.

Reductive Debromination of 2a. Zinc (20 g, 0.3 mol) and a few drops of concentrated deuteriosulfuric acid were added to a stirred solution of bromosulfoxide **2a** (10 g, 0.042 mol) in methanol-*O*-*d* (55 mL). Continuous TLC monitoring of the reaction mixture, stirred at room temperature, showed complete disappearance of the starting sulfoxide after 6 h. Zinc was filtered off and methanol removed under reduced pressure. The residue was dissolved in chloroform (300 mL) and washed with aqueous sodium carbonate and saturated aqueous sodium chloride. After drying with sodium sulfate and removal of chloroform, the residue was purified by column chromatography (silica; chloroform–acetone). The recovered sulfoxide (2 g, 28% yield) was finally distilled at reduced pressure, bp 126 °C (1.5 mm). NMR in the presence of $Eu(dpm)_3$ indicated a 60% protium content at the H_2 position and a 40% protium content at the H_3 position.

Inversion of A to B. The inversion of **A** to obtain **B** was achieved according to the procedure by Johnson and McCants.[22] NMR of the inverted sulfoxide **B** in the presence of $Eu(dpm)_3$ showed protium contents of 51 and 62% at the positions corresponding to H_4 and H_1, respectively.

D/H Exchange of 3 and Pyramidal Inversion. The sulfonium salt **3** (4.5 g, 0.018 mol) was heated at 60 °C for 7 h in 2 N NaOH (70 mL). The recovered salt (4.5 g) was twice crystallized from 95% ethanol, containing a few drops of diluted hydrochloric acid, and ethyl ether.

The NMR of the undeuterated sulfonium salt in D_2O has been previously described.[24] The recovered material, **D**, had 80% protium content at δ 3.40 corresponding to H_2.

A solution of **D** (4 g) in water (50 mL) was refluxed for 28 h. The sulfonium salt **E**, recovered after removal of water under reduced pressure and analyzed by NMR, showed 40% protium contents at δ 3.85 and 3.4 corresponding to H_1 and H_2, respectively.[24]

Four grams of this material was dissolved in 2N NaOH (70 mL) and kept at 60 °C for 8 h. The recovered sulfonium salt (3.5 g) **F** was twice crystallized from 95% ethanol, containing a few drops of diluted hydrochloric acid, and ethyl ether. The protium content (NMR) was found to be 90% at δ 3.4 (H_2) and 40% at δ 3.85 (H_1).[24]

Sulfonium Tetrafluoroborate Anion Exchange and Pyrolysis. The sulfonium tetrafluoroborate **F** (3.5 g) was dissolved in water (50 mL) and the solution eluted through a column of Amberlist 26 (Cl^-). The sulfonium chloride, obtained as a semisolid compound by removal of water under reduced pressure, was decomposed to sulfide and methyl chloride at 160 °C. The resulting crude sulfide was dissolved in chloroform and washed with aqueous sodium thiosulfate and saturated aqueous sodium chloride. After drying with sodium sulfate and removal of chloroform, the residue was distilled under reduced pressure to give 1.6 g (78%) of sulfide **G**, whose NMR spectrum in $CDCl_3$ showed 65% protium content at δ 2.8, corresponding to the pseudoequatorial positions.[2c]

Oxidation of Sulfide G to Sulfoxide H. To a solution of 1.5 g of sulfide **G** in acetone (15 mL) at 0 °C, 1.3 mL of 31% hydrogen peroxide in acetone (10 mL) was added dropwise. The solution was stirred at room temperature for 3 days. Workup gave 1.5 g of pure sulfoxide, whose NMR is reported in Figure 4, containing 65% protium at the positions corresponding to H_1 and H_2.

NMR. All spectra were recorded at 60 MHz (C-60 Jeol). The addition of $Eu(dpm)_3$ shift reagent to chloroform solutions of sulfoxides and bromosulfoxides allowed the complete resolution of the resonances of the heterocyclic ring protons (see, for example, Figures 1 and 3). Assignment of the different resonances to each individual proton was done on the basis of coupling constants and rates of chemical shift changes in the presence of $Eu(dpm)_3$. The percentages of protium at the various positions for the partially deuterated compounds were determined (±10% approximation) using as standard the intensities of the two bridgehead protons (H_5, H_6) for the sulfoxide and of one bridgehead proton (H_5) for the bromosulfoxide.

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Registry No.—**1a,** 51066-12-7; **2a,** 63640-73-3.

References and Notes

(1) Sulfoxides can also be halogenated, in the presence as well as in the absence of base, by a variety of other reagents (SO_2Cl_2,[2] tosyl chloride,[3] NOCl,[4] *t*-BuOCl,[5] *N*-chloro- or *N*-bromosuccinimide[6]) which, however, are likely not to act merely as halogen sources.
(2) (a) K. C. Tin and T. Durst, *Tetrahedron Lett.*, 4643 (1970); (b) G. Tsuchihashi, K. Ogura, S. Iriuchijima, and S. Tomisawa, *Synthesis*, 89 (1971); (c) E. Casadevall and M. M. Bouisset, *Tetrahedron Lett.*, 2975 (1973).
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(4) R. N. Loeppky and D. C. K. Chang, *Tetrahedron Lett.*, 5415 (1968).
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(6) (a) G. Tsuchihashi and K. Ogura, *Bull. Chem. Soc. Jpn.*, **44**, 1726 (1971); (b) S. Iriuchijima and G. Tsuchihashi, *Synthesis*, 588 (1970); (c) F. Jung, K. C. Tin, and T. Durst, *Int. J. Sulfur Chem.*, **8**, 1 (1973).
(7) P. Calzavara, M. Cinquini, S. Colonna, R. Fornasier, and F. Montanari, *J. Am. Chem. Soc.*, **95**, 7431 (1973), and references cited therein.
(8) (a) S. Iriuchijima, M. Ishibashi, and G. Tsuchihashi, *Bull. Chem. Soc. Jpn.*, **46**, 921 (1973); (b) S. Iriuchijima and G. Tsuchihashi, *ibid.*, **46**, 929 (1973).
(9) S. Bory, R. Lett, B. Moreau, and A. Marquet, *C. R. Hebd. Seances Acad. Sci., Ser. C*, **276**, 1323 (1973).
(10) J. Klein and H. Stollar, *J. Am. Chem. Soc.*, **95**, 7437 (1973).
(11) M. Cinquini, S. Colonna, and F. Montanari, *J. Chem. Soc., Perkin Trans. 1*, 1723 (1974).
(12) M. Cinquini, S. Colonna, and F. Montanari, *J. Chem. Soc., Perkin Trans. 1*, 1719 (1974).
(13) Several authors have used conformationally biased 4-substituted thiane 1-oxides for halogenation studies.[8-11] In these systems, however, the biasing substituent at C_4, if it fixes the ground-state conformation, does not at all guarantee against major skeletal deformations that may occur in the transition state at around the reaction centers (S–C_α).
(14) E. Casadevall and co-workers [2c,15] have reported on the chlorination of this sulfoxide. Under the conditions employed by these authors, however (SO_2Cl_2 as chlorinating agent), the reaction appears not to be stereospecific. (See also footnote 1.)
(15) (a) E. Casadevall and M. M. Bouisset, *Tetrahedron Lett.*, 2023 (1975); (b) M. M. Bouisset and E. Casadevall, *ibid.*, 299 (1977).
(16) G. Barbarella, A. Garbesi, and A. Fava, *J. Am. Chem. Soc.*, **97**, 5883 (1975).
(17) Each of the four α-bromosulfoxides which in principle may be formed from **1a** are expected to exhibit a low-field doublet due to the methine proton geminal to Br, and are characterized by either a large (11–12 Hz) or a medium (5–6 Hz) coupling according to whether the geminal halogen is equatorial or axial, respectively.
(18) See, for instance: (a) J. Uebel and R. M. Wing, *J. Am. Chem. Soc.*, **94**, 8910

(1972); (b) R. Lett and A. Marquet, *Tetrahedron*, **30**, 3379 (1974); (c) I. Sataty, *Org. Magn. Reson.*, **6**, 8 (1974).
(19) The formation of sulfone may be minimized by careful exclusion of moisture.
(20) M. Cinquini, S. Colonna, R. Fornasier, and F. Montanari, *J. Chem. Soc., Perkin Trans. 1*, 1886 (1972).
(21) In Schemes II and III partially labeled products are indicated as single products rather than mixtures, as they actually are. Formulas representing such mixtures are indicated by capital letters. The percent deuterium or protium at a given position (as obtained from NMR) is indicated by a figure at the upper right of the symbol. Thus the 60:40 mixture of **1b** and **1c** obtained by reductive debromination of **2a** is indicated by structure **A** in Scheme III.
(22) C. R. Johnson, *J. Am. Chem. Soc.*, **85**, 1020 (1963); C. R. Johnson and D. McCants, *ibid.*, **87**, 5404 (1965).
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(24) G. Barbarella, A. Garbesi, A. Boicelli, and A. Fava, *J. Am. Chem. Soc.*, **95**, 8051 (1973).
(25) Previously, the halogenation of conformationally biased sulfoxides, *trans*-4-R-thiane 1-oxides (R = Ph, *t*-Bu), had also been found to give results incompatible with the concerted mechanism.[8-11]
(26) N. L. Wendler, D. Taub, and N. Kuo, *J. Am. Chem. Soc.*, **82**, 5701 (1960).
(27) C. H. De Puy, C. G. Naylor, and J. A. Beckman, *J. Org. Chem.*, **35**, 2750 (1970).
(28) A small percentage (<5) of the isomeric bromosulfoxide formed by collapse from the opposite side could have escaped detection, however.

Syntheses of and Structural Assignments for Some N-Phosphono-2-iminoimidazolidines (Cyclic Guanidines)[1]

Gary E. Struve,[2] Carlo Gazzola, and George L. Kenyon*[3,4]

Department of Chemistry, University of California, Berkeley, California, 94720, and Department of Pharmaceutical Chemistry, University of California, San Francisco, California 94143

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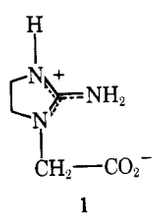
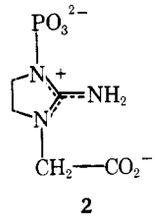
Phosphorylated derivatives of 1-carboxymethyl-2-iminoimidazolidine (1) with phosphorus attached to the primary and secondary nitrogen positions, respectively, were prepared. Dilithium 1-carboxymethyl-3-phosphono-2-iminoimidazolidine (2) was obtained by treatment of 1 with $POCl_3$ in aqueous LiOH solution. Compound 2 was shown to be identical with the product of phosphorylation of 1 by adenosine 5′-triphosphate, catalyzed by creatine kinase. Thus, the previous structural assignment for this compound [G. L. Rowley, A. L. Greenleaf, and G. L. Kenyon, *J. Am. Chem. Soc.*, **93**, 5542 (1971)] is incorrect. 1-Carboxymethyl-2-(diphenoxyphosphinylimino)imidazolidine sodium salt (**13**), the diphenyl ester of the isomeric substance, was obtained by coupling of *N*-(2-aminoethyl)-glycine sodium salt with *S,S*-dimethyl-*N*-(diphenoxyphosphinylimino) dithiocarbonimidate. Structural assignments for both 2 and 13 were made using NMR spectroscopy; especially valuable were measurements of $J_{^{31}P-^{15}N}$ values of appropriate selectively ^{15}N-enriched compounds. Some model 2-iminoimidazolidines, unequivocally phosphorylated on either the primary or secondary nitrogen, were synthesized for use in spectral comparisons. The measured apparent first-order rate constant for the hydrolysis of the P–N bond of 2 at pH 2.96 was found to be consistent with the structural assignment given here.

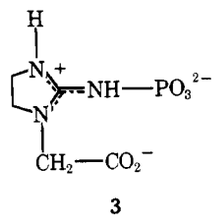
The synthetic creatine analogue 1-carboxymethyl-2-iminoimidazolidine (1)[5] is an excellent substrate for the enzyme creatine kinase, having a maximal velocity of 90% of that of creatine itself.[6] The two possible products of this enzymatic phosphorylation are salts of 1-carboxymethyl-3-phosphono-2-iminoimidazolidine (2) and 1-carboxymethyl-2-(phosphonoimino)imidazolidine (3). After an exhaustive analysis of the products of this enzymatic process, only one of these was detected, and it was tentatively identified as 3.[5] This identification was based upon examination of the proton NMR spectrum of the isolated product and its observed minimal $^{31}P-N-C-^{1}H$ coupling of phosphorus to the protons of one of the ring methylene groups. Such coupling had been anticipated to be relatively pronounced in structure 2, but not in 3.[7] The present work includes the chemical syntheses and structural assignments for 2, the diphenyl ester of 3, and several other *N*-phosphono-2-iminoimidazolidines. As a result of this work, the structural assignment given previously[5] for the product of the creatine kinase catalyzed phosphorylation of 1 has been shown to be incorrect; that is, this product has structure 2, not 3.



1



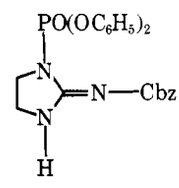
2



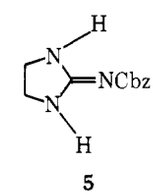
3

Results and Discussion

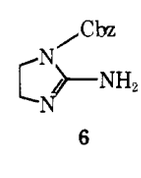
In the course of this work, synthetic routes to both 2 and 3 were sought so that the chemical and biochemical behaviors of each could be examined. One of the compounds synthesized as a potential precursor to 2 was 1-diphenoxyphosphinyl-2-(benzyloxycarbonylimino)imidazolidine (4). The precursor to 4, 2-(benzyloxycarbonylimino)imidazolidine (5), and the isomeric 6 had both been prepared and characterized by Matsumoto and Rapoport.[8] Using proton NMR spectroscopy, the distinction between 5 and 6 is straightforward, since 5 is symmetrically substituted and 6 is not.



4



5



6

Where Cbz = $-CO_2CH_2C_6H_5$

When 5 was treated with diphenyl chlorophosphate and triethylamine in tetrahydrofuran solution, product 4 was generated. Consistent with the structural assignment, the proton NMR spectrum clearly indicated asymmetric substitution, since the two ring methylene groups were now in different magnetic environments. Attempts to carboxymethylate 4 at the N-3 position were unsuccessful,[9] precluding its use as a precursor to 2. The proton NMR spectrum was valuable, however, since 4 *unequivocally* possesses the structure with