graphed on 175 g of silica gel eluted with hexane. The solvent was removed from the appropriate fractions to give a pale yellow liquid which crystallized on standing. Recrystallization from pentane gave a white solid which was dried at room temperature under vacuum: mp 43.2–44.6°; NMR (CCl_4) δ 1.78 (complex m, 9 H), 3.12 (m, 1 H), 4.48 (m, 1 H), 7.36 (complex m, 5 H); ir (CCl_4) 3045, 2922, 2845, 1465, 1436, 1430, 1288, 1180, 1080, 1055, 980, 890, 682, and 648 cm^{-1}; mass spectrum *m/e* (rel intensity, %) 65 (16), 66 (6), 67 (7), 69 (5), 77 (9), 79 (13), 80 (8), 81 (100), 82 (9), 109 (28), 110 (68), 111 (9), 123 (11), 149 (7), 188 (16), 190 (17), 191 (12), 270 (32), 271 (5), 272 (32), and 273 (5).

Competitive Reactions of 4a and 4b with 1-Bromo-2-phenylthiopropane (6). The appropriate isomer (**4a** or **4b**, 0.408 mmol), **6** (0.408 mmol), AIBN (0.0408 mmol), and tributyltin hydride (0.0409 mmol) were treated as previously described for the thermally initiated reactions. The relative reactivity was determined by comparing the amounts of 2-butenes and propene produced by gas chromatography.

Competitive Reactions of 7a and 7b with Bromocyclohexane. Each reaction was run in a sealed vial containing **7a** or **7b** (0.369 mmol), bromocyclohexane (0.369 mmol), AIBN (0.0369 mmol), and tri-*n*-butyltin hydride (0.0369 mmol) in 1.0 ml of toluene at 80° for 2 hr. The reaction mixture was cooled, placed in a flask, and vacuum transferred at room temperature to a trap at −196°. The distillate was subjected to GLC analysis to determine product composition and distribution.

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Conformational Analysis. XXXI. Conformational Equilibria of 1,3-Dioxanes with Polar Substituents at C-5[1]

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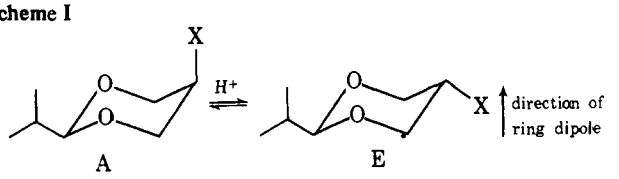
Abstract: The positions of equilibrium, established by acid catalysis, between epimeric 2-isopropyl-5-X-1,3-dioxanes in which X is CH_2OCH_3, $OCOCH_3$, $COCH_3$, $COOCH_3$, COO^-, SCH_3, $S(CH_3)_2^+$, $SOCH_3$, SO_2CH_3, NO_2, NH_3^+, $NH(CH_3)_2^+$, $N(CH_3)_3^+$ are reported and compared with previously published data for X = Me,[2] F, Cl, Br, CN,[3] CH_3O, C_2H_5O,[4] CH_2OH, and OH.[5] In a number of these cases the axial (cis) isomers are favored at equilibrium, even though either steric or dipolar considerations would have led to the opposite prediction. Explanations based on "internal solvation", orbital interaction, and charge attractions are considered; it appears that charge attraction offers the only consistent interpretation for the axial preference of the sulfinyl, sulfonyl, sulfonium, and ammonium and probably also the nitro, CH_2OR, and acetate groups. The mechanism of reaction of methyl mercaptide with diethyl chloromalonate is discussed.

It is one of the basic tenets of conformational analysis[6,7] that axial substituents in six-membered rings are less stable than equatorial ones. We are aware of only one or two exceptions in a monosubstituted cyclohexane: the axial conformation is preferred in cyclohexylmercuric acetate and chloride.[8] Exceptions have long been known, however, in systems where dipolar interactions are dominating; for example, in *trans*-1,2-dibromocyclohexane the diaxial isomer predominates, at least in nonpolar solvents,[9] and in glycosides the axial conformation of the aglycone is preferred because of the operation of the "anomeric effect".[10] We wish to report here several cases of axial predominance of substituents at C-5 in 1,3-dioxanes (cf. Scheme I), even though on both steric and dipolar grounds equatorial preference might have been anticipated.[11,12]

For 2-isopropyl-5-methyl-1,3-dioxane itself (cf. Scheme I, X = Me), the equatorial (trans) isomer is preferred,[2,5] though only by 0.9 kcal/mol (the value is virtually independent of solvent[5]). The difference between this value and the 1.7 kcal/mol preference for the equatorial conformation in methylcyclohexane[13] was explained by the small "effective size" of the unshared pairs on oxygen compared to the syn-axial hydrogen atoms in cyclohexane; however, there is presumably a residual nonbonded repulsion between the carbon and hydrogens of the axial methyl group and the ring oxygen atoms.

Scheme I



When X (Scheme I) is an electronegative group, such as halogen, alkoxy, CH_2OR, or when it is of the type $-Y^{\delta+}-Z^{\delta-}$, one might predict that, because of repulsion of the resultant dipole of the ring (Scheme I) and the dipole of the $\rightarrow X$ or $-Y\rightarrow Z$ substituent, superimposed on the steric factor, the axial isomer would be even more disfavored than for a nonpolar substituent such as methyl. Or, in other words, one might expect that the anomeric effect, which produces an axial preference for electronegative substituents at C-2, would cause an equatorial preference for such substituents at C-5 because of the relative reversal of the ring dipole at C-5 compared to C-2.[14] Previous work[3,5] has, however, suggested that this prediction is false for X = F in any solvent studied and for X = CN, CH_2OH, and OCH_3 in certain of the solvents investigated.[15] We now report on a number of additional substituents which either prefer the axial conformation or for which preference for the equatorial conformation is slight, as shown in Table I. (Positive $\Delta G°$ values indiate axial preference.)

The results show a number of interesting trends, some expected, some surprising. In general, $\Delta G°$ becomes less negative or more positive as the dielectric constant (or, more precisely the E_T (30) value[4]) of the solvent increases. This is as expected, since dipole–dipole interactions (Scheme I) are generally more severe in the axial isomer, and their effect is diminished in more polar solvents in which the axial isomer is thus favored. An exception is seen in the methylsulfinyl ($SOCH_3$) and methylsulfonyl (SO_2CH_3) groups which show small and erratic solvent effects. Either dipole–dipole repulsion is not significant in these compounds or else it is offset by another effect which also responds to solvent dielectric constant (see below).

It was predicted in the introductory section that electronegative groups should show strong preference for the equatorial position, at least in nonpolar solvents. This trend, in ether, is seen for Cl, Br, SCH_3, OCH_3, and possibly CN and COO^- (for which latter only a value in solvent water is available). In contrast, F, CN (in acetonitrile), CH_2OH (in CCl_4; hydrogen bonding to solvent may complicate the situation in other solvents[24]), NO_2, $SOCH_3$, SO_2CH_3, and the positively charged substituents $S(CH_3)_2^+$, $N(CH_3)_3^+$, $NH(CH_3)_2^+$, and NH_3^+ prefer the axial position, and for a

Table I. Conformational Equilibria in 5-Substituted 1,3-Dioxanes (Scheme I)

Substituent, X[a]	Solvent	$\Delta G°$ (temp, °C[b]), kcal/mol	Ref	Substituent, X[a]	Solvent	$\Delta G°$ (temp, °C[b]), kcal/mol	Ref
F	C_6H_{12}[c]	0.21	16	OC_2H_5	C_6H_{12}	−1.23	4
(−0.25)	CCl_4	0.36	3	(−0.9[20])	C_6H_6	−0.82	4
	C_6H_6	0.83 ± 0.04	*e*		CCl_4	−1.09	4
	$CFCl_3$	0.78	17		Ether	−1.05	4
	Ether[d]	0.62 ± 0.04	*e*		$CHCl_3$	−0.51	4
	$CHCl_3$	0.87	3		CH_3CN	−0.19	4
	CH_3CN	1.22 ± 0.04	*e*	CH_2OH	CCl_4[f]	+0.27 ± 0.04 (27)	*e*
	CH_3OH	0.60 ± 0.05	*e*	(−1.65[21])	Ether[f]	−0.03 ± 0.04	5
Cl	CCl_4	−1.40	3		$CHCl_3$[f]	+0.16 ± 0.04	5
(−0.53)	C_6H_6	−0.89	3		DME[f,g]	−0.11 ± 0.04	5
	Ether	−1.20 ± 0.05; −1.26	*e*, 3		CH_3CN[f]	−0.12 ± 0.04	5
	$CHCl_3$	−0.94	3		CH_3OH[f]	−0.03 ± 0.04	5
	CH_3CN	−0.25	3	CH_2OCH_3	Ether	−0.05 ± 0.03 (30)	*e*
Br	CCl_4	−1.71	3	(−1.40[22])			
(−0.48)	C_6H_6	−1.17	3	NO_2	CCl_4	0.38 ± 0.04 (30)	*e*
	Ether	−1.44 ± 0.03; −1.45	*e*, 3	(−1.05)	$CHCl_3$	0.63 ± 0.04	*e*
	$CHCl_3$	−1.35	3		CH_2Cl_2	0.81 ± 0.04 (30)	*e*
	CH_3CN	−0.68	3	SCH_3	C_6H_{12}[c]	−1.82 ± 0.01 (26.5)	*e*
CN	Ether	−0.21 ± 0.04 (30)	*e*, 3	(−1.07)	C_6H_6	−1.55 ± 0.01 (26.5)	*e*
(−0.25)	CH_3CN	+0.55 ± 0.03 (30)	*e*, 3		CCl_4	−1.74 ± 0.02 (26.5)	*e*
$COOCH_3$	Ether	−0.82 ± 0.02 (30)	*e*		Ether	−1.73 ± 0.02 (26.5)	*e*
(−1.31)	CH_3CN	−0.22 ± 0.02 (30)	*e*		DCA[h]	−1.20	*e*
COO^-	H_2O	−1.11 ± 0.13 (107)	*e*		TFA[i]	−0.93	*e*
(−1.96[18])					CH_3CN	−1.13 ± 0.02 (26.5)	*e*
$COCH_3$	*n*-Hexane	−0.51 ± 0.06	19	$SOCH_3$	C_6H_6	0.74 ± 0.07 (54)	*e*
(−1.52[18])	C_6H_{12}[c]	−0.48 ± 0.03	19	(−1.9[20])	CCl_4	ca. 0.6 (54)	*e*
	C_6H_6	−0.42 ± 0.06	19		$CHCl_3$	0.82 ± 0.11 (54)	*e*
	Ether	−0.53 ± 0.05	19		CH_3CN	0.86 ± 0.09 (54)	*e*
	CH_3CN	−0.28 ± 0.06	19	SO_2CH_3	C_6H_{12}[c]	1.16 ± 0.10 (50.0)	*e*
	C_2H_5OH	−0.19 ± 0.06	19	(−2.5[20])	C_6H_6	1.07 ± 0.09 (50.0)	*e*
	CH_3OH	−0.23 ± 0.06	19		$CHCl_3$	1.19 ± 0.10 (50.0)	*e*
$OCOCH_3$	Ether	0.00 ± 0.04	*e*		CH_3CN	~0.9 (50.0)	*e*
(−0.71)				$S(CH_3)_2^+OTs^-$	DCA[h]	>2.0	*e*
OCH_3	C_6H_{12}[c]	−1.03	4	(*j*)	TFA[i]	>2.0	*e*
(−0.55)	C_6H_6	−0.59	4	$N(CH_3)_3^+I^-$	DCA	2.0	*e*
	CCl_4	−0.90	4	(*j*)	HCOOH	1.9	*e*
	Ether	−0.83	4	$NH(CH_3)_2^+$ picrate	TFA[i]–C_6H_5CN	>2.0	*e*
	$CHCl_3$	−0.16	4	(−2.4[20])			
	CH_3CN	+0.01	4	$NH_3^+I^-$	TFA[i]–$CHCl_3$	3.1	*e*
				(−1.7[20])			

[a] Values in parentheses under substituent are $\Delta G°$ values for cyclohexyl–X for comparison. Unless otherwise indicated, these values are from ref 23. [b] 25° if not otherwise indicated. [c] Cyclohexane. [d] Diethyl ether. [e] This work. [f] 0.2 *M*. [g] 1,2-Dimethoxyethane. [h] Dichloroacetic acid. [i] Trifluoroacetic acid. [j] Not reported.

few other substituents, $OCOCH_3$, CH_2OCH_3, and perhaps $COCH_3$ and $COOCH_3$, the situation is borderline with either no preference or only a very slight one for the equatorial conformation.

Except for the cases cited in Table I, there are few known instances of axial preference of polar groups in saturated heterocycles. Urbanski and coworkers[25] have observed axial nitro groups in 5-alkyl-5-nitro-1,3-oxazines, but since the preference for the axial position was not seen in the 5-H-5-nitro compounds, it may be due to the geminal alkyl substituent rather than to the heterocyclic ring system. A preference for axial acetoxyl groups at C-2 and C-4 in pyranose sugars has been reported;[26] these systems are polysubstituted and therefore complex. However, several simple cases of preferred gauche (over anti) conformations in acyclic systems[27] with polar substituents are known. Most closely related to the case of the dioxanes shown in Scheme I are the haloethanols, XCH_2CH_2OH (X = F, Cl, Br),[28] and especially the case of fluoroethyl trichloroacetate,[29] $FCH_2CH_2OCOCCl_3$, in which the preference for the gauche conformation cannot be explained as being due to intramolecular hydrogen bonding. The case of 1,2-difluoroethane, CH_2FCH_2F, has been recently discussed;[30,31] whereas the gauche conformation is clearly preferred in the liquid phase and in polar solvents,[30] the situation in the gas phase[32] is not so clear and probably warrants reinvestigation. Acetylcholine, $CH_3COOCH_2CH_2N(CH_3)_3{}^+X^-$, is known to prefer the gauche conformation even in D_2O solution.[33]

Discussion

Steric effects in the axial position at C-5 are less than corresponding effects for the cyclohexyl system; thus for 5-methyl-1,3-dioxane the difference amounts to 0.8 kcal/mol (1.7 − 0.9). If one looks at the dioxane $\Delta G°$ values (Table I) in ether (ϵ 4.33), carbon tetrachloride (ϵ 2.24), or cyclohexane (ϵ 2.0) and compares them with the corresponding values for cyclohexyl-X (shown in the left column under each substituent), one comes to the qualitative conclusion that a diminished steric effect in the case of the dioxane combined with dipolar repulsion in the axial position may well account for the findings for Cl, Br, CN, $COOCH_3$, $COCH_3$, OCH_3, OC_2H_5, SCH_3, and possibly COO^-. A quantitative assessment is, unfortunately, not possible since no successful calculations of the steric effect in 1,3-dioxanes has yet been made, so that one cannot gauge whether the remaining part of the effect, ascribable to polar causes, is of reasonable magnitude. The polar effect, as one of us has recently pointed out,[34,35] is made up of two terms: one a dipole–dipole interaction term (E_D), which is at a maximum in the vapor phase and tends toward zero in solvents of high dielectric constants (but see below); the other, a solvation term (E_S), which is zero in the vapor phase (ϵ 1) and increases with the dielectric constant of the solvent favoring that conformation which has the higher dipole moment. The total conformational energy difference is thus $\Delta E = \Delta E_{st} + \Delta E_D + \Delta E_S$, where ΔE_{st} is the purely steric (or structural) part of the conformational energy difference.

ΔE_S may not be negligible even in solvents of relatively low dielectric constants, such as ether, and will undoubtedly be substantial in polar solvents such as acetonitrile (ϵ 37.5). The axial (or greatly diminished equatorial) preference for F,[36] Cl, Br, CN, $COOCH_3$, OCH_3, OC_2H_5, and, to a lesser extent, $COCH_3$ in this solvent is thus also accounted for as being due to a diminished ΔE_D term (which favors the equatorial conformation) and enhanced ΔE_S (which favors the axial position).

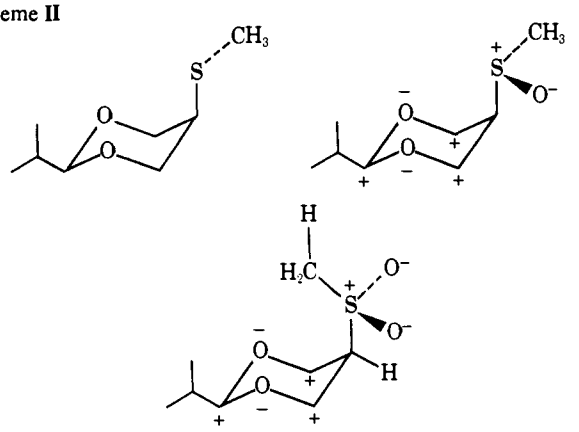
It seems implausible, however, that the axial preference for CH_2OH in solvent carbon tetrachloride (in which neither intermolecular hydrogen bonding to solvent nor intramolecular hydrogen bonding[15] can play a role) or the very faint equatorial preference for CH_2OCH_3 can be explained by a combination of steric and solvation factors. The equatorial preference of 5-CH_3 in 1,3-dioxane is 0.9 kcal/mol; steric factors for CH_2OR should be similar, assuming that the OR group points toward the outside of the ring. Indeed (Table I), the conformational energy for CH_2OH in the cyclohexyl system[21] is virtually the same as that of CH_3. Yet, at C-5 in 1,3-dioxane, the equatorial preference of the CH_2OH group is reduced (compared to that of CH_3) by about 1.1 kcal/mol; the corresponding reduction for CH_2OCH_3 amounts to 0.8 kcal/mol. It is difficult to ascribe these differences entirely to E_S terms in solvents as low in polarity as CCl_4 and ether. Similarly, it is difficult to account for the difference between OCH_3 and $OCOCH_3$ in ether (0.8 kcal/mol favoring axial acetate) on the basis of solvation. The difference between the equatorial preference of the nitro group in cyclohexane and the axial preference in 1,3-dioxane, amounting to over 1.4 kcal/mol in CCl_4, appears to be too large to be accounted for by solvation effects also.

In a preliminary publication[12c] we had speculated that the stabilization of axial nitro might be due to "internal solvation" by the oxygen atoms of the dioxane. In favor of this explanation we pointed out[12c] that the ultraviolet absorption of the axial (cis) nitro compound (A, Scheme I, X = NO_2) is at lower wavelength (278 nm) than that of the equatorial (trans) isomer (E, Scheme I, X = NO_2) (282 nm[37]) in solvent hexane; the bathochromic shift in chromophores involving $n \rightarrow \pi^*$ transitions by *external* solvation is, of course, a well-known phenomenon.[38] We shall return to this point later.

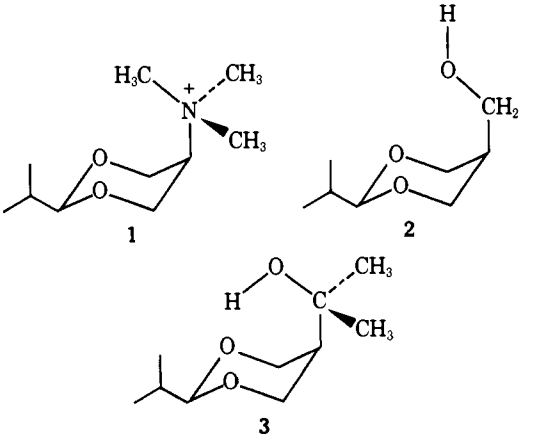
A particular clear-cut case, from the point of view of being able to assess steric factors, is represented by the methyl sulfide, sulfoxide, and sulfone groups (Scheme II). The SCH_3 group favors the equatorial position by 1.82 kcal/mol in cyclohexane. On purely steric grounds, one would expect a slightly larger equatorial preference ($-\Delta G°$) for the corresponding sulfoxide, in which each enantiomer of the axial diastereomer is confined to a single conformation (with a resulting entropy loss—the situation being similar to that of isopropyl—vs. ethylcyclohexane). A much larger $-\Delta G°$ value would be expected for the methyl sulfone in which one of the three terminal ligands on sulfur (methyl or oxygen) must necessarily point into the ring. In fact, however, the methylsulfinyl has an axial preference of 0.74 kcal/mol (in benzene), and the methylsulfonyl group has a corresponding, but even larger, preference of 1.16 kcal/mol (in cyclohexane). Thus, the oxygen ligands on sulfur, far from causing a shift of equilibrium toward the equatorial conformation, in fact, lead to a favoring of the axial isomer by 2.56 and 2.98 kcal/mol, respectively, in the sulfoxide and sulfone.

In the case of the sulfoxide, as in the case of the corresponding nitro compound, the axial chromophore exhibits shorter wavelength transitions than the equatorial one, the absorption maxima being at 202.5 and 222.0 (sh) nm (cyclohexane solvent) for the axial isomer and 208 and 227.5 (sh) nm for the equatorial.[39] The sulfone is transparent in the accessible region of the ultraviolet, but the axial isomer presents an interesting feature in the ^1H NMR spectrum, viz. a remarkably large long-range coupling constant of 1.14 ± 0.02 Hz between the sulfonyl methyl and the hydrogen at C-5 of the dioxane. (The corresponding coupling constant for the equatorial isomer is 0.39 ± 0.02 Hz.) Such a large $^4J_{HH}$ suggests a W-planar[40] arrangement of the coupled protons which, in turn, is possible only if, as shown in Scheme II, the methyl of the sulfonyl group points into

Scheme II



Scheme III



the ring. In the equatorial sulfone, the W-planar arrangement represents only one of three possible rotameric conformations, which may explain why $^4J_{eq} \approx {}^1/_3{}^4J_{ax}$.[41] Since a methyl group is larger than an oxygen atom,[20,22] the fact that it, rather than one of the oxygens, points toward the crowded interior of the dioxane ring in the sulfone depicted in Scheme II can again be explained only on polar grounds.

Two explanations appear possible for the axial preference of nitro, sulfinyl, and sulfonyl groups. One is essentially an electrostatic one: as shown in Scheme II, the positive end of a dipolar axial 5-substituent interacts more favorably with the (negative) ring oxygen atoms than does the (more distant) positive end of the same substituent when it is equatorial. This explanation is able to account for the spectral changes observed as resulting from electrostatic interaction in the ground state which becomes weakened in the (less polar) excited state.[38] An entirely different way of accounting for the axial preference of the above substituents is to postulate p-π overlap of the ring oxygen unshared pairs with the π orbitals of the nitro group and p-d overlap of these pairs with the d orbitals on sulfur. This explanation is also capable of accounting for the observed spectral changes, but now in terms of modifications of the excited state (probably π^* for both NO_2 and SOR and SO_2R). However, it does not readily account for the axial preference in the $^+CH_2$-^-OR case, which can be more readily interpreted on electrostatic grounds.

To gather further evidence on this matter, we examined onium salt equilibria, Scheme I, X = $^+S(CH_3)_2$, $^+NH_3$, $^+NH(CH_3)_2$, $^+N(CH_3)_3$. The results, shown in Table I, show strong axial preferences ($\geq$2 kcal/mol) in all these cases. Whereas p-d orbital overlap can be invoked for $^+S(CH_3)_2$ and the cases of $^+NH_3$ and $^+NMe_2H$ can be explained away by hydrogen bonding, the axial preference of $^+NMe_3$ is unequivocal: it can be accounted for neither by hydrogen bonding (O···H-N^+) nor by p-d overlap, leaving charge interaction as the only remaining plausible explanation.[42,43]

The trimethylammonio compound (**1**, Scheme III) is an analogue of acetylcholine, $CH_3COOCH_2CH_2N^+Me_3$, which is known, from x-ray[44] and NMR[33] studies, to exist predominantly in the gauche form (which corresponds to the axial conformation of the dioxane). The experimental findings in the case of acetylcholine are supported by quantum-mechanical calculations,[45] some of which[45b] suggest that there is sufficient positive charge on the hydrogens of the *N*-methyl groups to provide what is called a hydrogen bond of the type O···H-C-N^+. The crystallographic data bear out this point to the extent that the indicated O···H distance is less than the usual nonbonded distance; however, apart from the difficulty of precisely establishing hydrogen positions from x-ray data, even if the distance is abnormally short, it is not clear whether this is because of an O···H attraction or because other conformational factors press the N-C-H hydrogen close to the acetate oxygen. In our experience, hydrogen bonding in the trimethylammonio compound **1** (Scheme III) is unlikely, since no hydrogen bonding is known[15,46] to occur in **2**, and only very weak hydrogen bonding is found[15] in **3**, even though intrinsically the tendency for formation of an O-H···O hydrogen bond is much greater than for a C-H···O hydrogen bond.[47]

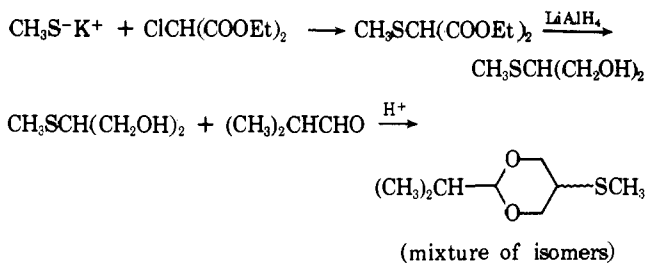
Pending further investigation we believe that electrostatic attraction is the dominant factor favoring the axial conformation in Scheme I when X = $OCOCH_3$, CH_2OH, CH_2OCH_3, NO_2, $SOCH_3$, SO_2CH_3, $^+SMe_2$, and $^+NMe_3$. It is likely to be a contributing factor in other instances where axial X is favored or the preference for equatorial X is weakened (e.g., for X = CN, $COCH_3$, $COOCH_3$).

Synthesis and Assignment of Configuration

The synthesis of the compounds in Scheme I, X = CN,[3] $COCH_3$,[19] and CH_2OH,[15] has been previously described; the assignment of configuration for X = CN[3] and $COOCH_3$ rests on the H-4/H-5 coupling pattern which shows two very small coupling constants (ca. 1.5 Hz) for $J_{4e,5e}$ and $J_{4a,5e}$ when X is axial and one large (ca. 10.5 Hz, $J_{4a,5a}$) and one medium (ca. 5 Hz, $J_{4e,5a}$) coupling constant when X is equatorial. The configuration of the carbinols, X = CH_2OH, is established by that of the esters from which they are obtained by reduction and is corroborated by the ^{13}C NMR spectra, which show higher field signals for C-4,6 and C-5 and lower field ones for CH_2OH in the axial isomer than in the equatorial one, in accordance with expectations based on 5-methyl-1,3-dioxane spectra.[48] The compounds with X = COO^- are correlated with the corresponding acids from which they are obtained. The acetates, X = $OCOCH_3$, were prepared by acylation of the hydroxy compounds[49] of known[3] configuration. The CH_2OCH_3 derivatives were made by methylation of CH_2OH precursors and their configurations corroborated by ^1H NMR spectroscopy. The nitro compounds (Scheme I, X = NO_2) were prepared by condensing commercial $(HOCH_2)_3CNO_2$ with isobutyraldehyde and eliminating the elements of formaldehyde from the resulting 5-hydroxymethyl-2-isopropyl-5-nitro-1,3-dioxanes by means of lithium amide.[50] The major isomer obtained from this procedure was the trans isomer, but on standing the material apparently isomerized, and the cis isomer crystallized. The dipole moment, 4.57 D, served to identify the solid isomer as cis (calculated dipole moment 4.84 D for the cis, 1.85 D for the trans isomer).

The SCH_3 compounds were prepared as shown in Scheme IV, separated by preparative gas chromatography and readily identified as to configuration by the pattern of

Scheme IV



(mixture of isomers)

the H-5 proton, which was a narrow quintet in the compound assigned the axial (cis) configuration and a widely split triplet with superimposed small coupling for the compound assigned the equatorial (trans) configuration. The configurational assignment was corroborated by the H-4,6 signal (narrow, nearly degenerate doublet in the cis isomer, broad multiplet in the trans) and by the position of the H-5 proton: as in other cases of dithianes[51a] and trithianes,[51b] the equatorial proton in the cis isomer resonates at higher field (2.41 ppm) than the axial proton in the trans isomer (2.83 ppm).

The configurations of the sulfoxides and that of the trans sulfone follow from those of the sulfides from which they were prepared by peracid oxidation; the cis sulfone was prepared by isomerization of the trans isomer. The configuration of the sulfones was corroborated by the appearance of a narrow, high-field signal for the equatorial H-5 proton in the axial (cis) isomer contrasted to that of a resolved low-field multiplet for the axial H-5 proton in the trans. The ^{1}H NMR spectra of the sulfoxides were complex and displayed the expected separate signals for the diastereotopic pairs of protons at C-4 and C-6; these protons underwent marked differential downfield shifts upon doping of the solution of the equatorial (trans) isomer with an equimolar amount of Eu(dpm)$_3$. We assume that, in the presence of the shift reagent, the lowest field protons are proximal to the sulfinyl oxygen atom, and the ones moving less are on the side of the *S*-methyl group. This assumption is based on the supposition that the unshared pair on sulfur lies in the symmetry plane of the ring in the sulfoxide–europium complex. The splitting pattern indicates that for both pairs of protons (H-4, H-6), the axial one moves further than the equatorial one. Further corroboration for the configuration of the sulfoxides comes from the experimental dipole moments (in benzene: cis, 3.50 D, trans, 2.46 D).

With reference to Scheme IV, at the time we published our preliminary report,[11b] we hypothesized that the reaction of methyl mercaptide with diethyl chloromalonate was initially a nucleophilic displacement on chlorine with formation of methylsulfenyl chloride, CH_3SCl, and diethyl malonate anion, $^-CH(COOEt)_2$, which would then react to give the product. In support of this hypothesis, we had observed that CH_3SCl, in fact, reacts with the anion of diethyl malonate to give the desired product [albeit in low yield, since $CH_3SCH(COOEt)_2$ is a stronger acid than diethyl malonate and therefore undergoes disproportionation of the anions to produce $CH_3SC^-(COOEt)_2$ which reacts further to give $(CH_3S)_2C(COOEt)_2$]. The mainstay of the hypothesis was the observed formation of CH_3S–SCH_3 in the reaction, believed to result from attack of CH_3SCl on unchanged CH_3S^-. However, it was subsequently brought to our attention[52] that dimethyl disulfide could have been formed by another route: ordinary nucleophilic displacement of chlorine by CH_3S^- (as implied in Scheme IV), followed by displacement on sulfur of the $CH_3SCH(COOEt)_2$ product by CH_3S^- to give CH_3S–SCH_3 and $CH_2(COOEt)_2$. Ample analogy for this two-stage reaction sequence in α-halocarbonyl compounds exists.[53]

In order to settle this matter unequivocally in favor of one reaction course or the other, we studied the reaction of diethyl chloromalonate with methyl mercaptide in the presence of ethyl acetoacetate on one hand and of ethyl α-chloroacetoacetate, $CH_3COCHClCOOEt$, with CH_3S^- in the presence of diethyl malonate, $CH_2(COOEt)_2$ on the other. If disproportionation to CH_3SCl and an α-carbanionic species had occurred, then in either one of the two cases, or possibly both, a cross-over reaction of the type shown in Scheme V should have occurred. In fact, no such cross-over reaction was found: diethyl chloromalonate yielded only diethyl methylthiomalonate and ethyl chloroacetoacetate only ethyl methylthioacetoacetate. Hence, CH_3SCl cannot be an intermediate, and the reaction (Scheme IV) is a direct displacement of Cl by CH_3S^- with the formation of CH_3SSCH_3 being due to a subsequent displacement of CH_3S^- on sulfur in the product.

The methyl sulfonium salts were prepared by methylation of the corresponding methyl sulfides; their configurations follow from the synthesis. The 2-isopropyl-5-amino-1,3-dioxanes were obtained from the corresponding nitro compounds by catalytic hydrogenation. Their configurations were assigned in this fashion though, from the preparative point of view, it was more convenient to reduce the mixed nitro compounds and separate the amines gas chromatographically. Methylation of the NH_2 compounds with formaldehyde and sodium cyanoborohydride[54] gave the corresponding dimethylamino compounds ($-NMe_2$), whereas treatment with an excess of methyl iodide and sodium bicarbonate gave the quaternary ($^+NMe_3$) salts.

Experimental Section

Melting points were obtained in a Mel-Temp and/or Electrothermal melting point apparatus with an open capillary tube.

Microanalyses were performed by Midwest Microlab, Ltd., Indianapolis, Ind. 46226, and Galbraith Laboratories, Inc., Knoxville, Tenn. 37291.

Proton magnetic resonance (^{1}H NMR) spectra were recorded on a Jeol C-60 HL and Varian Models A-60A and XL-100-15 NMR spectrometers. Carbon magnetic resonance (^{13}C NMR) spectra were recorded on a Varian Model XL-100-12 NMR spectrometer. The proton and carbon chemical shifts of samples as 5–20% (W/W) solutions are presented in ppm (δ) downfield from internal tetramethylsilane (Me_4Si), and these values are accurate to ±0.01 ppm unless otherwise indicated. The coupling constants are given in hertz (Hz) and are accurate to ±0.3–0.4 Hz unless otherwise specified.

Infrared spectra were obtained from samples as neat films, Nujol mulls, KBr pellets, and as solutions and were recorded on Perkin-Elmer Models 137, 257, and 457 ir spectrophotometers.

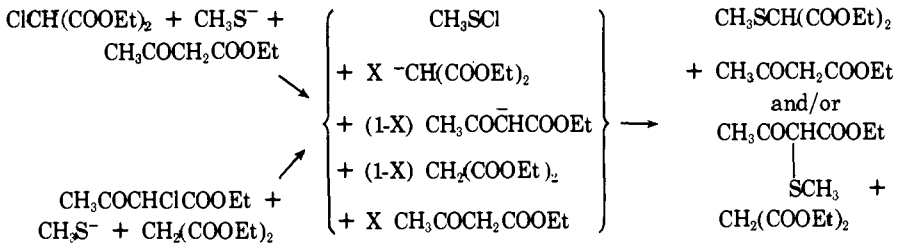
Ultraviolet spectra (320–195 nm) were obtained from samples in dilute solution on a Cary Model 15 spectrophotometer. Most determinations were duplicated with different concentrations as a check on the extinction coefficient in the low-wavelength region (195–230) of the ultraviolet.

Gas–liquid partition chromatography (GLC) analyses were performed on F & M Scientific Corp. Model 810 and Hewlett-Packard Model 5750 research gas chromatographs. Varian Aerograph Series 1520 and 2700 instruments and a Nester-Faust Model 850 Prepkromatic instrument were used for preparative separations.

Dielectric constants were measured on a WTW dipole meter and the dipole moments calculated by the modified Hedestrand method.[55]

The preparation of 5-fluoro-,[3] 5-chloro-,[3] 5-bromo-,[3] 5-cyano-,[3] 5-carbomethoxy,[15] and 5-hydroxymethyl-[15] 2-isopropyl-1,3-dioxanes has been previously described. ^{13}C NMR signals for the 5-hydroxymethyl compounds were: *cis*, C-2, 105.98, C-4,6, 67.32, C-5, 36.71, CH_2OH, 61.35, $(CH_3)_2CH$, 16.77, and 32.72; *trans*, C-2, 105.83, C-4,6, 69.27, C-5, 37.11, CH_2OH, 60.66, $(CH_3)_2CH$, 17.07, and 32.56 ppm.

Scheme V



(hypothetical)

2-Isopropyl-5-methoxymethyl-1,3-dioxanes. A well-stirred mixture of *cis*- and *trans*-5-hydroxymethyl-2-isopropyl-1,3-dioxanes and methyl iodide (20% excess) in dry 1,2-dimethoxyethane (12 ml for a 20-mmol run) was made to react by the cautious addition (over 45 min) of sodium hydride (10% excess) followed, after 30 min, by addition of an amount of CH_3I equal to the first.[56] After 3 h, excess methyl iodide and most of the solvent were distilled and the residue was filtered. The filtrate was gas chromatographed on a 9 ft × ¾ in. biwall column packed with 20% FFAP on Chromosorb W, 45/60 mesh, at 130°, He flow 550 ml/min at 30 psi. The retention time of the cis isomer was 35 min, $n^{25}D$ 1.4311; trans isomer, 48 min, $n^{25}D$ 1.4321. Distinctive ir bands:[57] cis, 1328, trans, 1473 μm. ^1H NMR: CH_2O (cis), δ 3.67 (d, J = 7.2 Hz), (trans) 3.15 (d, J = 6 Hz); CH_3O (cis) 3.4 (s), (trans) 3.29 (s); $(CH_3)_2CH$ and H-5 (cis) 1.4–1.9 (m), (trans) 1.5–2.6 (m); $(CH_3)_2CH$, (cis) 0.90 (d, J = 7.2 Hz), (trans) 0.92 ppm, (d, J = 7.2 Hz). Combined yield 57.4%, composition ca. 1:1.

Anal. Calcd for $C_9H_{18}O_3$: C, 62.04; H, 10.41. Found: (cis isomer) C, 62.27; H, 10.40; (trans isomer) C, 62.15; H, 10.38.

***cis*-5-Acetoxy-2-isopropyl-1,3-dioxane.**[58] A mixture of 2.32 g (15.9 mmol) of *cis*-5-hydroxy-2-isopropyl-1,3-dioxane,[49] 4.1 ml of anhydrous pyridine, and 8.85 g (87.0 mmol) of distilled acetic anhydride was stirred at room temperature for 17 h, then poured, with stirring, into 100 ml of cold 5% aqueous sodium bicarbonate. The solution was extracted with five 100-ml portions of ether which were cleared with five 10-ml portions of water. The ether was dried over $MgSO_4$ and concentrated, and the residue gas chromatographed on a 9 ft × ¾ in. biwall column packed with 20% Carbowax 20M on Chromosorb W (45/60 mesh), at 150°, He flow 460 ml/min at 30 psi, to give 2.45 g (81.5%) of acetate, mp 37–38°.

Anal. Calcd for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found: C, 57.68; H, 8.56.

***trans*-5-Acetoxy-2-isopropyl-1,3-dioxane** was prepared from *trans*-5-hydroxy-2-isopropyl-1,3-dioxane in the same fashion as the cis isomer, yield 90.8%, $n^{25}D$ 1.4329. NMR and ir spectra of both isomers have been recorded.[56]

Anal. Found: C, 57.72; H, 8.31.

2-Isopropyl-5-nitro-1,3-dioxanes. A solution of 110.4 g (0.73 mol) of 2-hydroxymethyl-2-nitro-1,3-propanediol (Aldrich) and 53.9 g (0.75 mol) of isobutyraldehyde in 200 ml of benzene containing 2 g of *p*-toluenesulfonic acid monohydrate in a 500-ml round-bottom flask equipped with a reflux condenser and Dean-Stark trap was heated under reflux for 3 h. The cooled mixture was diluted with 500 ml of ether and washed with four 200-ml portions of 2% aqueous sodium bicarbonate followed by 400 ml of water. The organic layer was dried over anhydrous Na_2SO_4 and concentrated to give 138.3 g (92.6%) of crude 5-hydroxymethyl-2-isopropyl-5-nitro-1,3-dioxanes. The following procedure[50] was carried out in a good fume hood.

In a 3-l. three-necked flask fitted with a mechanical stirrer and dry ice–acetone condenser were placed liquid ammonia (2 l.) and a few crystals of $Fe(NO_3)_3 \cdot 9H_2O$. Stirring was commenced and lithium (3.0 g, 0.43 g-atom) added in small lumps, the color turning from orange-brown first to blue and then to gray (successive portions of Li were added only after the blue color was discharged). When all the Li had reacted, 53.7 g (0.26 mol) of the above nitro alcohol was added in small portions over 30 min. The suspension was stirred for 6 h, 30.0 g of ammonium chloride was added, the condenser disconnected, and the ammonia was allowed to evaporate overnight with stirring. Water was added, stirring continued for 1 h, and the suspension extracted with three 350-ml portions of ether which were cleared, each, with two 100-ml portions of water. The combined ether extracts were dried over $MgSO_4$ and concentrated, and the residue was distilled at 50–55° (0.2 Torr) to give 26.6 g (58.1%) of a mixture of 2-isopropyl-5-nitro-1,3-dioxanes (trans:cis 4:1 by integration of the isopropyl Me signals in ^1H NMR).

When the material was allowed to stand, the cis isomer crystallized, mp 64–65°.

Ir ($CHCl_3$) 3.35 s, 3.49 s, 6.45 s, 6.82 m, 6.87 m, 6.94 m, 7.15 m, 7.36 s, 7.57 m, 7.68 m, 7.69 w, 8.26 bd, 8.69 s, 8.96 s, 9.09 m, 9.32 m, 9.85 m, 10.00 m, 10.62 m, 10.86 m, 11.08 m, 11.83 w μm; ^1H NMR ($CDCl_3$) δ 0.90 (d, 6 H, isopropyl, J_{H,CH_3} = 6.5 Hz), 1.77 (m, 1 H, $CH(CH_3)_2$), 3.93 (m, 1 H), 4.51 (m, 2 H), 4.32 (d, 1 H, H-2, J = 4.5 Hz), 4.78–4.98 (m, 2 H) ppm. λ_{max} (heptane) 278 (ϵ_{max} 33), 213.5 (ϵ_{max} 2454) nm.

Anal. Calcd for $C_7H_{13}NO_4$: C, 48.01; H, 7.43. Found: C, 47.87; H, 7.40. Dipole moment: 4.57 D (benzene).

When the crude material was gas chromatographed immediately on a 20 ft × ¾ in. biwall column packed with 20% QF-1 on Chromosorb W (45/60 mesh) at 130°, the pure trans isomer was eluted as a colorless, mobile oil, $n^{25}D$ 1.4540.

Ir ($CHCl_3$) 8.33 s, 8.74 s, 8.96 s, 9.09 s, 9.15 m, 9.85 w, 10.12 m, 10.28 w, 10.50 m, 10.98 m, 11.76 w μm; ^1H NMR ($CDCl_3$) δ 0.93 (d, 6 H, isopropyl, J_{H,CH_3} = 6.5 Hz), 1.80 (m, 1 H, $CH(CH_3)_2$), 3.74–4.12 (m, 2 H), 4.21 (d, 1 H, H-2, J = 4.5 Hz), 4.57 (m, 3 H) ppm. λ_{max} (heptane) 282 (ϵ_{max} 31), 213.5 (ϵ_{max} 2486) nm.

Anal. Found: C, 48.09; H, 7.77.

Further elution from the preparative column gave the cis isomer described above as colorless needles.

***cis*-5-Amino-2-isopropyl-1,3-dioxane.** Hydrogenation of 5.0 g of the above *cis*-2-isopropyl-5-nitro compound in 20 ml of absolute ethanol over 1.0 g of Pd–C at 32 psi (Parr shaker) took 15 min, but was continued for a further 20 min. The catalyst was filtered, the solution concentrated, and the residue distilled, bp 73–75° (10 Torr), to yield 2.9 g (70%) of a colorless mobile oil, $n^{25}D$ 1.4470.

Ir (neat) 2.95 bd, s, 3.35 s, 3.49 s, 6.05 w, 6.30 m, 6.80 m, 6.90 m, 7.18 m, 7.35 m, 7.68 w, 7.85 w, 8.08 m, 8.40 w, 8.68 s, 9.10 s, 9.34 s, 9.90 s, 10.55 s, 11.50 w, 12.35 m μm; ^1H NMR ($CDCl_3$) δ 0.93 (d, 6 H, isopropyl, J_{H,CH_3} = 6.5 Hz), 1.77 (m, 1 H $CH(CH_3)_2$), 1.84 (s, 2 H, NH_2), 2.65 (m, 1 H, H-5), 3.85, 3.88 (m, 4 H, H-4, H-6), 4.25 (d, 1 H, H-2, J = 4.5 Hz) ppm.

Anal. Calcd for $C_7H_{15}NO_2$: C, 57.90; H, 10.41. Found: C, 57.65; H, 10.55.

The **hydrochloride** of the cis isomer was prepared by anhydrous HCl in anhydrous ether, mp 189.5–190.5° dec.

Anal. Calcd for $C_7H_{16}O_2NCl$: C, 46.28; H, 8.88. Found: C, 46.16; H, 8.89.

The **acetyl derivative,** prepared with acetic anhydride and pyridine, sublimed at 150° (0.05 Torr) and melted at 96–97°.

Ir ($CHCl_3$) 2.72 w, 2.77 w, 2.91 m, 3.32 s, 3.36 s, 3.49 m, 4.11 w, 4.16 m, 6.02 s, 6.62 s, 6.80 m, 7.04 m, 7.16 w, 7.27 m, 7.69 w, 7.88 m, 8.16 s, 8.33 s, 8.65 m, 8.77 w, 9.02 s, 9.17 m, 9.55 m, 9.61 m, 10.83 m, 10.81 s, 11.79 w μm; ^1H NMR (DMSO-d_6) δ 0.89 (d, 6 H, isopropyl, J_{H,CH_3} = 6.5 Hz), 1.71 (m, 1 H, $CH(CH_3)_2$), 1.89 (s, 3 H, acetyl-methyl), 2.51 (m, 1 H, H-5), 3.85, 3.88, 4.25 (d, 1 H, H-2, J = 5.0 Hz), 8.00 (bd, 1 H, HN–) ppm.

Anal. Calcd for $C_9H_{17}NO_3$: C, 57.73; H, 9.15. Found: C, 58.02; H, 9.07.

***trans*-5-Amino-2-isopropyl-1,3-dioxane** was prepared similarly

as the cis isomer but starting with the trans isomer of the nitro precursor: bp 77° (9 Torr), yield 85%, colorless, mobile oil, $n^{25}D$ 1.4521.

Ir (neat) 2.95 s, 3.38 s, 3.40 s, 6.02 w, 6.22 m, 6.85 m, 7.18 m, 7.35 w, 7.70 w, 7.85 w, 8.12 m, 8.38 m, 8.70 s, 8.98 m, 9.15 s, 9.63 s, 9.92 w, 10.05 w, 10.14 m, 10.45 m, 11.05 m, 11.60 w μm; ^{1}H NMR ($CDCl_3$) δ 0.91 (d, 6 H, isopropyl J_{H,CH_3} = 6.5 Hz), 0.97 (s, 2 H, NH_2), 1.75 (m, 1 H, $CH(CH_3)_2$), 3.17 (m, 3 H), 4.08 (m, 2 H), 4.09 (d, 1 H, H-2, J = 5 Hz) ppm.

Anal. Found: C, 58.19; H, 10.69.

The **hydrochloride,** prepared as in the case of the cis isomer, melted at 177–178° dec.

Anal. Found: C, 46.56; H, 8.98.

The **acetyl derivative** melted at 177–178°.

Anal. Found: C, 58.04; H, 9.28.

Ir ($CHCl_3$) 2.72 w, 2.77 w, 2.91 w, 3.32 s, 3.36 s, 3.52 w, 4.11 w, 4.16 m, 4.23 w, 5.97 s, 6.63 s, 6.80 m, 7.04 m, 7.19 m, 7.32 m, 7.71 w, 8.19 s, 8.33 s, 8.73 m, 9.09 m, 9.61 m, 10.56 w, 10.81 m, 11.82 w μm; ^{1}H NMR (DMSO-d_6) δ 0.87 (d, 6 H, isopropyl, J_{H,CH_3} = 6.5 Hz), 1.69 (m, 1 H, $CH(CH_2)_2$), 1.80 (s, 3 H, acetyl-methyl), 2.50 (m, 1 H, H-5), 3.29, 3.93, 4.05, 4.17 (d, 1 H, H-2, J = 4.5 Hz), 7.67 (bd, 1 H, NH-) ppm.

***cis*- and *trans*-5-Amino-2-isopropyl-1,3-dioxane (Alternative Method).** A mixture of *cis*- and *trans*-2-isopropyl-5-nitro-1,3-dioxane (prepared as indicated above), 15.0 g, was dissolved in 150 ml of absolute ethanol and hydrogenated over 3.6 g of 5% Pd/C at 30 psi (Parr shaker) for 1.5 h. The catalyst was filtered, the solution concentrated, and the residue distilled, bp 100–102° (34 Torr), yield 9.0 g (72%) of mixed isomers. Separation was effected on a 12 ft × ⅜ in. 20% Carbowax plus 10% KOH on 60–80 mesh Chromosorb A column at 150°. The cis isomer has the shorter retention time.

***cis*-5-Dimethylamino-2-isopropyl-1,3-dioxane.** To 5.8 g (40 mmol) of *cis*-2-isopropyl-5-amino-1,3-dioxane was added 15 ml of 37% formaldehyde (187 mmol), and the precipitate formed was dissolved in 115 ml of acetonitrile. Then 3.9 g (62 mmol) of sodium cyanoborohydride[54] was added and the mixture stirred for 15 min, neutralized with glacial acetic acid, and stirred for an additional 45 min, more acetic acid being added as necessary to maintain neutrality. The solution was concentrated (rotary evaporator) and the residue poured into 150 ml of 2 N aqueous KOH and extracted with ether (3 × 150 ml). The ether extracts were dried over K_2CO_3 and concentrated to give 5.2 g (75%) of product.

^{1}H NMR ($CDCl_3$) δ 0.93 (d, J = 6.6, $(CH_3)_2CH$-), 1.78 (m, 1 H, Me_2CH-), 2.12 (m, 1 H, C_5-H), 2.47 (s, 6 H, $(CH_3)_2N$-), 3.87 (2 H, $C_{4,6}$-H_a), 4.30 (d, 1 H, J = 5.0, C_2-H); 4.33 (2 H, $C_{4,6}$-H_e) ppm.

Ir (neat) 2.85 m, 2.93 m, 2.96 m, (ν C-H), 6.80 s, 6.83 s, 6.87 m, 7.14 m, 7.63 w, 8.05 w, 8.37 w, 8.66 s, 9.23 s, (ν C-O), 8.93 m, 9.09 w, 9.52 w, 9.78 m, 9.98 m, 10.06 s, 10.58 w, 10.78 m, 11.63 w, 13.85 m μm.

The **picrate** was prepared in the usual way, mp 153–154°.

Anal. Calcd for $C_{15}H_{22}N_4O_9$: C, 44.77; H, 5.51. Found: C, 44.92; H, 5.40.

***trans*-5-Dimethylamino-2-isopropyl-1,3-dioxane** was prepared in similar fashion as the cis isomer starting from the *trans*-2-isopropyl-5-amino precursor, yield 85%.

^{1}H NMR ($CDCl_3$): δ 0.94 (d, J = 6.9 Hz, 6 H, $(CH_3)_2CH$-), 1.82 (m, 1 H, Me_2CH-), 2.25 (s, 6 H, $(CH_3)_2N$-), 2.45 ($J_{H_a\text{-}C\text{-}C\text{-}H_a}$ = 11–12 Hz, $J_{H_a\text{-}C\text{-}C\text{-}H_e}$ = 4–5 Hz, 1 H, C_5-H_a), 3.53 (J_{gem} = 11–12 Hz, $J_{H_a\text{-}C\text{-}C\text{-}H_a}$ = 11–12 Hz, 2 H, $C_{4,6}$-H_a), 4.12 (d, J = 4.8 Hz, 1 H, C_2-H), 4.31 (J_{gem} = 11–12 Hz, $J_{H_a\text{-}C\text{-}C\text{-}H_e}$ = 4–5 Hz, 2 H, $C_{4,6}$-H_e) ppm.

Ir (neat): 3.37 s, 3.50 s, 6.73 s, 6.86 s, 7.14 s, 7.30 w, 7.33 w, 7.87 s, 8.25 w, 8.68 s, 9.09 s, 9.57 s, (C-O), 9.85 w, 10.00 w, 10.22 w, 10.46 m, 10.62 w, 10.81 w, 11.05 w, 11.31 m μm.

The **picrate** melted at 180–181°.

Anal. Found: C, 44.89; H, 5.56.

Trimethyl(5-*cis*-2-isopropyl-1,3-dioxanyl)ammonium Iodide.[59] A mixture of 1.70 g (117 mmol) of *cis*-5-amino-2-isopropyl-1,3-dioxane, 24 ml of CH_3I, and 24 ml of 10% aqueous K_2CO_3 was boiled at reflux for 3 h. The excess CH_3I was then distilled, the residue extracted with two 50-ml portions of ether (discarded), and the product crystallized from the aqueous solution by chilling. The solid was collected and recrystallized from water or ethanol, yield 3.4 g (90%), mp 203–204°.

^{1}H NMR (D_2O-DSS) δ 0.92 (d, J = 6.5 Hz, 6 H, $(CH_3)_2$-CH-), 1.82 (m, 1 H, Me_2CH-), 3.32 (s, 9 H, $(CH_3)_3{}^+N$-), ca. 3.3 (m, 1 H, C_5-H), 4.25 (J_{gem} = 16 Hz, 2 H, $C_{4,6}$-H_a), 4.70 (d, J = 4.0 Hz, 1 H, C_2-H), 4.73 (J_{gem} = 16 Hz, 2 H, $C_{4,6}$-H_e) ppm.

Ir (KBr) 3.38 s, 3.45 m, 3.50 m, (C-H), 6.80 s, 7.09 m, 7.26 m, 7.29 m, 7.35 w, 7.70 m, 8.05 m, 8.40 m, 8.77 s, 9.01 m, 9.32 s, 9.86 w, 10.00 m, 10.45 s, 10.66 m, 10.94 s, 11.11 s, 11.93 w, 12.26 w μm.

Anal. Calcd for $C_{10}H_{22}INO_2$: C, 38.11; H, 7.03. Found: C, 38.40; H, 7.18.

Trimethyl(5-*trans*-2-isopropyl-1,3-dioxanyl)ammonium iodide was similarly prepared from *trans*-5-amino-2-isopropyl-1,3-dioxane, yield 84%, mp 181–182°C.

^{1}H NMR (D_2O-DSS) δ 0.96 (d, J = 6.7 Hz, 6 H, $(CH_3)_2$-CH-), 1.80 (m, 1 H, Me_2CH-), 3.22 (s, 9 H, $(CH_3)_3N^+$-), 3.60–4.75 (6 H, $C_{2,4,6,5}$-H) ppm.

Ir (KBr) 3.36 s, 3.38 m, 3.42 m, 3.50 m, 6.85 s, 7.14 s, 7.25 m, 7.65 m, 8.10 w, 8.70 s, 8.85 s, 9.22 s, 9.62 s, 9.90 w, 10.10 m, 10.36 s, 10.64 s, 11.11 s, 11.70 m μm.

Anal. Found: C, 38.34; H, 7.09.

Diethyl (Methylthio)malonate. (a) Potassium hydroxide (5.6 g, 100 mmol) was dissolved in 30 ml of absolute ethanol, a solution of methanethiol (4.8 g, 5.6 ml, 100 mmol) in 20 ml of ethanol was added, and the mercaptide solution was poured into a cold solution (ice bath) of diethyl chloromalonate (22.3 g, 100 mmol) in ethanol (20 ml). Potassium chloride precipitated immediately. The suspension was stirred at room temperature for 1.5 h, diluted with water (150 ml), and extracted with ether (3 × 100 ml). The ethereal extracts were combined, dried ($MgSO_4$), and concentrated to dryness (rotary evaporator) to afford a yellow oil (19.2 g, 93% crude yield). Distillation afforded a colorless material (17.5 g, 85%): bp 68–70° (0.25 Torr); ir (neat film) 5.73 s and 9.62 s μm; ^{1}H NMR (CCl_4) δ 1.31 (t, J = 7.6 Hz, 6 H, CH_3), 2.23 (s, 3 H, SCH_3), 3.92 (s, 1 H, CH), 4.21 (q, J = 7.6 Hz, 4 H, CH_2) ppm.

Anal. Calcd for $C_8H_{14}O_4S$: C, 46.58; H, 6.84. Found: C, 46.37; H, 6.81.

The reaction of diethyl chloromalonate with excess methanethiol in base gave diethyl malonate and dimethyl disulfide: ^{1}H NMR (CCl_4) δ 2.38 ppm.

(b) *From Methylsulfenyl Chloride and Diethyl Malonate.* The sodium salt of diethyl malonate was prepared by adding diethyl malonate (32.14 g, 200 mmol) in 50 ml of absolute ethanol to a solution containing sodium (4.58 g, 0.200 g-atom) in 80–100 ml of absolute ethanol and refluxing briefly (steam bath). After cooling to 0–5° (ice bath), a solution of 16.5 g (200 mmol) of methylsulfenyl chloride[60] in carbon tetrachloride (90–100 ml) was added. The reaction mixture was stirred at room temperature for 14 h, then diluted with water (25 ml), and extracted with ether (3 × 100 ml). The ethereal solution was dried ($MgSO_4$) and concentrated (rotary evaporator) to give an orange oil (31.0 g).

Distillation under reduced pressure gave the desired product (16 g, 40.2%): bp 65–76° (0.2 Torr); diethyl malonate (ca. 6 g) and diethyl bis(methylthio)malonate (ca. 6 g); ^{1}H NMR diethyl malonate (CCl_4) δ 1.26 (t, J = 7.2 Hz, 6 H, CH_3), 3.22 (s, 2 H, CH), 4.16 ppm (q, J = 7.2 Hz, 4 H, CH_2); diethyl bis(methylthio)malonate (CCl_4) δ 1.30 (t, J = 7.4 Hz, 6 H, CH_3), 2.05 (s, 6 H, SCH_3), 4.23 ppm (q, J = 7.4 Hz, 4 H, CH_2).

Diethyl (Methylthio)malonate-d_1. A suspension of diethyl (methylthio)malonate (22.0 g) in deuterium oxide (10 ml) and anhydrous potassium carbonate (0.5 g) was stirred at room temperature for 48 h. The organic material was extracted with methylene chloride (2 × 50 ml), and the solution dried ($MgSO_4$) and concentrated (rotary evaporator) to give a colorless residue (21.3 g). This material was treated again with potassium carbonate (1.0 g) and deuterium oxide (3 ml) for ca. 3 h. The colorless material was separated, dried ($MgSO_4$), and distilled under reduced pressure to give 20.6 g of a colorless oil: bp 58–60° (0.14 Torr); ^{1}H NMR (CCl_4) δ 1.30 (t, 6 H, J = 6.8 Hz, CH_3), 2.23 (s, 3 H, SCH_3), 4.22 ppm (q, J = 6.8 Hz, 4 H, CH_2).

2-Methylthio-1,3-propanediol. A solution of diethyl (methylthio)malonate (48.1 g, 233 mmol) in 150 ml of anhydrous ether was added (1.5 h) to a suspension of lithium aluminum hydride (18.97 g, 500 mmol) in 300 ml of anhydrous ether under a nitrogen atmosphere. The resulting suspension was refluxed for 22 h and then stirred at room temperature for 20 h.

The suspension was treated with water (18.9 ml), a 15% solution

of NaOH (ca. 20 ml), and more water (ca. 60 ml), and then stirred rapidly for 3 h and filtered; the filtrate was concentrated (rotary evaporator) to give 20.5 g of a yellow oil. Distillation afforded 13.9 g (48.9%) of a colorless material: bp 92–95° (0.11 Torr); ^{1}H NMR (C_6H_6): δ 1.74 (s, 3 H, $-SCH_3$), 2.64 (m, J = 5.8 Hz, 1 H, -CH), 3.13 (t, J = 5.8 Hz, 2 H, OH), 3.69 ppm (t, J = ca. 6 Hz, 4 H, CH_2); ir (neat film) 2.98 s, 9.28 s, 9.76 s μm.

Anal. Calcd for $C_4H_{10}O_2S$: C, 39.35; H, 8.25. Found: C, 40.08; H, 8.39.

2-Methylthio-1,3-propanediol-d_1 was similarly prepared from 18.4 g (89.0 mmol) of diethyl (methylthio)malonate-d_1. Distillation of the product under reduced pressure gave 4.94 g (45.1%) of a slightly yellow material: bp 81.0–83.5° (0.12 Torr); ^{1}H NMR (DMSO-d_6) δ 2.03 (s, 3 H, SCH_3), 3.57 (s, 4 H, CH_2), 4.52 ppm (s, 2 H, O-H); ir (neat film) 2.98 s, 9.62 s, 9.92 s μm.

***cis*- and *trans*-2-Isopropyl-5-methylthio-1,3-dioxane.** A solution of 4.88 g (40.0 mmol) of 2-methylthio-1,3-propanediol, 2.88 g (40.0 mmol) of isobutyraldehyde, and a few crystals of *p*-toluenesulfonic acid in ca. 80 ml of benzene was refluxed until 0.72 ml of water was removed (Dean-Stark trap). The resulting dark orange solution was washed with a 10% solution of KOH (30 ml) and 100 ml of water, dried ($MgSO_4$), and concentrated (rotary evaporator) to afford 7.14 g of a red oil.

Distillation gave 5.02 g (71%) of a colorless material: bp 43.5–47.5° (0.2 Torr). The stereoisomers were separated by GLC employing a 4 ft × ⅜ in. 20% FFAP column (Chromosorb W, 45–60 mesh) at 120°. The trans isomer (shorter retention time) was obtained as the major component (4.06 g) along with 550 mg of the cis isomer. Trans isomer: bp 48.0–49.0° (0.12 Torr); ir (neat film) 8.76 s, 8.99 m, 9.21 s, 9.74 s μm; ^{1}H NMR (CCl_4) δ 0.88 (d, J = 6.8 Hz, 6 H, $(CH_3)_2C-$), 1.71 (m, J = 6.8 Hz, 1 H, CH), 2.10 (s, 3 H, SCH_3), 2.83 (m, 1 H, C_5-H), 3.36 (m, 2 H, $C_{4,6}$-H), 4.02–4.22 ppm, (m, 3 H, $C_{2,4,6}$-H). Cis isomer: mp 32.0–33.0°; ^{1}H NMR (CCl_4) δ 0.89 (d, J = 6.7 Hz, 6 H, $(CH_3)_2C-$), 1.73 (m, J = 6.7 Hz, 1 H, CH), 2.19 (s, 3 H, SCH_3), 2.41 (p, J = 2.4 Hz, 1 H, C_5-H), 4.03 (d, J = 2.4 Hz, 4 H, $C_{4,6}$-H), 4.17 ppm (d, J = 4.6 Hz, 1 H, C_2-H); ir (CCl_4) 7.77 m, 8.08 m, 8.71 m, 8.94 s, 9.34 s, 9.38 s, 9.83 s μm.

Anal. Calcd for $C_8H_{16}O_2S$: C, 54.51; H, 9.15. Found: (trans) C, 54.77; H, 9.06; (cis) C, 54.67; H, 9.00.

***cis*- and *trans*-2-Isopropyl-5-methylthio-1,3-dioxane-5-d_1.** 2-Methylthio-1,3-propanediol-2-d_1 (2.46 g, 20.0 mmol) similarly produced 2.73 g (77.5%) of a mixture of isomeric acetals, bp 40–41° (0.1 Torr) which, by gas chromatography, yielded ca. 2.3 g of the trans and 186 mg of the cis isomer. Trans isomer: bp 52–55° (0.21 Torr): ^{1}H NMR (CCl_4) δ 0.89 (d, J = 6.3 Hz, 6 H, $(CH_3)_2C$), 1.72 (m, J = 6.3 Hz, 1 H, CH), 2.08 (s, 3 H, SCH_3), 3.38 (d, J = 11–12 Hz, 2 H, CH), 4.12 (d, J = 4.7 Hz, 1 H, C_2-H), 4.13 ppm (d, J = 11–12 Hz, 2 H, CH); ir (CCl_4) 8.01 s, 8.72 m, 8.78 s, 8.99 s, 9.14 s, 9.85 s, 11.42 s μm. Cis isomer: mp 31.0–33.5°; ^{1}H NMR (CCl_4) δ 0.89 (d, J = 6.3 Hz, 6 H, $(CH_3)_2C-$), 1.72 (m, J = 6.3 Hz, 1 H, CH), 2.17 (s, 3 H, SCH_3), 4.04 (s, 4 H, $C_{4,6}$-H), 4.18 ppm (d, J = 4.3 Hz, 1 H, C_2-H); ir (CCl_4) 7.83 m, 8.02 m, 8.70 s, 8.98 s, 9.01 s, 9.56 m, 11.56 s μm.

***cis*-2-Isopropyl-5-methylsulfinyl-1,3-dioxane.** A solution of *cis*-2-isopropyl-5-methylthio-1,3-dioxane (360 mg, 2.04 mmol) and *m*-chloroperoxybenzoic acid (400 mg, 2.32 mmol) in ca. 20 ml of chloroform was stirred at 0–5° (ice bath) for 1 h and at room temperature for 14 h. The solution was then washed with saturated aqueous sodium bicarbonate (25 ml) and water (25 ml), dried ($MgSO_4$), and concentrated (rotary evaporator) to afford a colorless solid. Crystallization of this material from *n*-hexane gave 301 mg (77%) of a crystalline solid: mp 88.0–89.0°; ir (CCl_4) 8.72 s, 8.97 m, 9.43 s, 9.82 m, 11.12 m μm; ^{1}H NMR (CCl_4) δ 0.91 (d, J = 6.9 Hz, 6 H, $(CH_3)_2C-$), 1.73 (m, J = 6.9 Hz, 1 H, CH), 2.54 (m, J = 3.8 Hz, 1 H, C_5-H), 2.64 (s, 3 H, CH_3), 3.89–4.18 (m, J = 12 Hz, J = 3.8 Hz, 2 H, $C_{4,6}$-H), 4.22 (d, J = 4.2 Hz, 1 H, C_2-H), 4.23–4.60 ppm (m, J = 12 Hz, 2 H, $C_{4,6}$-H); λ_{max} (cyclohexane) 202.5 nm (ϵ 1490); μ = 3.50 D.

Anal. Calcd for $C_8H_{16}O_3S$: C, 49.97; H, 8.38. Found: C, 50.08; H, 8.38.

***trans*-2-Isopropyl-5-methylsulfinyl-1,3-dioxane.** *trans*-2-Isopropyl-5-methylthio-1,3-dioxane (750 mg, 4.26 mmol) and *m*-chloroperoxybenzoic acid (800 mg, 4.62 mmol) similarly yielded a yellow product, which upon recrystallization from *n*-hexane afforded 665 mg (81%) of colorless needles: mp 91.0–92.0°; ir (CCl_4) 8.73 s, 8.99 s, 9.20 s, 9.39 s, 9.65 m μm; ^{1}H NMR (CCl_4) δ 0.90 (d, 6 H, J = 6.8 Hz, $(CH_3)_2C-$), 1.72 (m, 1 H, J = 6.8 Hz, CH), 2.54 (s, 3 H, CH_3), 2.85 (m, 1 H, C_5-H_a), 4.08 ppm (m, 5 H, $C_{2,4,6}$-H); λ_{max} (cyclohexane) 208 nm (ϵ 3400); μ = 2.46 D.

Anal. Found: C, 49.78; H, 8.39.

***trans*-2-Isopropyl-5-methylsulfonyl-1,3-dioxane.** A solution of *trans*-2-isopropyl-5-methylthio-1,3-dioxane (370 mg, 2.10 mmol) and *m*-chloroperoxybenzoic acid (1.03 g, 5.40 mmol) in 35 ml of chloroform was stirred at room temperature for ca. 8 h. The solution was then washed with saturated aqueous sodium bicarbonate (50 ml) and water (50 ml), dried ($MgSO_4$), and concentrated (rotary evaporator) to give, after recrystallization from *n*-hexane–ethyl acetate, 392 mg (89%) of colorless needles: mp 143.5–144.5°; ir ($CHCl_3$) 7.57 s, 7.59 s, 8.77 s, 9.01 w, 9.18 m μm; ^{1}H NMR ($CDCl_3$) δ 0.89 (d, 6 H, J = 6.6 Hz, $(CH_3)_2C$), 1.81 (m, 1 H, J = 6.6 Hz, CH), 2.86 (s, 3 H, CH_3), 3.21–4.67 ppm (m, 6 H, $C_{2,4,5,6}$-H).

Anal. Calcd for $C_8H_{16}O_4S$: C, 46.13; H, 7.74. Found: C, 46.32; H, 7.72.

***cis*-2-Isopropyl-5-methylsulfonyl-1,3-dioxane.** A solution of pure *trans*-2-isopropyl-5-methylsulfonyl-1,3-dioxane (208 mg, 1.00 mmol) in 8.5 ml of chloroform with a few beads of Amberlyst-15 was equilibrated in a sealed ampule at 55.0° for ca. 5 days. The solution was allowed to cool to room temperature and the reaction stopped by addition of a small quantity of anhydrous potassium carbonate. The solution was decanted and concentrated (rotary evaporator) to afford ca. 200 mg of a crystalline solid. Repeated recrystallization of the ca. 87:13 (cis:trans) mixture from *n*-hexane afforded 120 mg of pure cis isomer: mp 90.0–92.0°; ir ($CHCl_3$) 7.67 s, 8.76 s, 8.89 s, 9.35 m μm; ^{1}H NMR ($CDCl_3$) δ 0.92 (d, J = 6.5 Hz, 6 H, $(CH_3)_2C-$), 1.51–2.07 (m, 1 H, CH), 2.64 (m, 1 H, C_5-H), 3.08 (d, J = 1.13 Hz, 3 H, CH_3), 4.15 (d, m, J_{gem} = 11–13 Hz, 2 H, $C_{4,6}$-H), 4.32 (d, J = 4.8 Hz, 1 H, C_2-H), 4.72 ppm (d, J_{gem} = 11–13 Hz, 2 H, $C_{4,6}$-H).

Anal. Calcd for $C_8H_{16}O_4S$: C, 46.13; H, 7.74. Found: C, 46.37; H, 7.71.

***trans*-2-Isopropyl-5-methylsulfonyl-1,3-dioxane-5-d_1** was prepared from *trans*-2-isopropyl-5-methylthio-1,3-dioxane-5-d_1 (as described above for the protio analogue) and recrystallized from a 80:20 solution of hexane–ethyl acetate: mp 143–144°; ^{1}H NMR ($CDCl_3$) δ 0.90 (d, J = 6.8 Hz, 6 H, $(CH_3)_2C-$), 1.81 (m, J = 6.8 Hz, 1 H, CH), 2.86 (s, 3 H, SCH_3), 3.97 (d, J = 11–12 Hz, 2 H, $C_{4,6}$-H), 4.22 (d, J = 4.8 Hz, 1 H, C_2-H), 4.43 ppm (d, J = 11–12 Hz, 2 H, $C_{4,6}$-H); ir ($CHCl_3$) 7.62 m, 8.73 m, 8.81 m μm.

***cis*-2-Isopropyl-5-methylsulfonyl-1,3-dioxane-5-d_1.** The cis isomer was prepared by a method identical with that described for the trans, or it could be isolated from an equilibrated mixture by the methods previously described: mp 91.0–92.5°; ^{1}H NMR ($CDCl_3$) δ 0.91 (d, J = 6.5 Hz, 6 H, $(CH_3)_2C-$), 1.52–2.09 (m, 1 H, C_5-H), 3.08 (s, 3 H, CH_3), 4.16 (d, J_{ab} = 12 Hz, 2 H, $C_{4,6}$-H), 4.34 (d, J = 4.8 Hz, 1 H, C_2-H), 4.73 ppm (d, J_{ab} = 12 Hz, 2 H, $C_{4,6}$-H).

Ethyl 2-(Methylthio)acetoacetate. A solution of potassium methyl mercaptide (70 mmol, see above) in absolute ethanol was added to a chilled solution (ice bath) of 11.5 g (70 mmol) ethyl 2-chloroacetoacetate in 20 ml of absolute ethanol. After the addition was completed, the suspension was stirred at room temperature for 1.5 h, then diluted with 105 ml water and extracted three times with 70-ml portions of ether which were combined, dried ($MgSO_4$), and concentrated to give 11.3 g (91.6% crude yield) of a yellow oil. Distillation gave the pure product, bp 30° (0.05 Torr); ^{1}H NMR ($CDCl_3$) δ 1.32 and 1.40 (t, J = 6.0 Hz, OCH_2CH_3, enol and keto forms), 2.20 and 2.40 (s, SCH_3 and CH_3CO-), 4.32 and 4.37 (q, J = 6.0 Hz, OCH_2CH_3 enol and keto forms), 4.12 (s, CH_3COCH, keto form), 13.9 ppm (s, HO enol form); ir (neat film) 3.42 w (ν O-H), 5.73 s, 5.85 (ν C=O ester and ketone), 1.595 s and 1.625 s μm (enol form).

Anal. Calcd for $C_7H_{12}O_3S$: C, 47.70; H, 6.86. Found: C, 47.52; H, 6.74.

Reaction of Diethyl (Methylthio)malonate with Potassium Methyl Mercaptide. Potassium methyl mercaptide (20 mmol, in absolute ethanol, see above) was added to a cold solution (ice bath) of 4.12 g (50 mmol) of diethyl (methylthio)malonate in 50 ml absolute ethanol with stirring. After completion of the addition, stirring was continued for 3 h at room temperature, 150 ml of water was then added, and the solution was extracted three times with 60-ml

portions of ether. The combined extracts were dried ($MgSO_4$) and concentrated to give a residue of 2.3 g (71%) of diethyl malonate, identified by GLC and NMR analysis.

Reaction of Potassium Methyl Mercaptide with Diethyl Chloromalonate in the Presence of Ethyl Acetoacetate. A solution of 35 mmol of potassium methyl mercaptide was prepared by reaction of 2.06 g (35 mmol) of KOH in 11 ml of absolute ethanol with 1.68 g (35 mmol) of methanethiol in 11 ml of absolute ethanol. The solution was added with stirring to 15 ml of ice-cold absolute ethanol containing 6.8 g (35 mmol) of ethyl chloromalonate and 4.6 g (35 mmol) of ethyl acetoacetate. The mixture was allowed to warm to room temperature, stirred for 1.5 h, diluted with 53 ml of water, and extracted with three 35-ml portions of ether. The combined ethereal extracts were dried over $MgSO_4$ and concentrated to give a slightly yellow oil (11.0 g). Distillation gave fractions—identified by GLC (on a 10 ft × ⅛ in. 30% SE-30 column on Chromosorb W 60–80 mesh, at 170°) and by ^1H NMR spectroscopy of ethyl acetoacetate (3.2 g, 69.6% recovery), diethyl chloromalonate (2.0 g, 29.4% recovery), diethyl methylthiomalonate (3.3 g, 45.7%), and small amounts of diethyl malonate and diethyl bis(methylthio)-malonate. No ethyl 2-methylthioacetoacetate was detected among the products.

Reaction of Potassium Methyl Mercaptide with Ethyl 2-Chloroacetoacetate in the Presence of Diethyl Malonate. A solution of 50 mmol of potassium ethyl mercaptide in 25 ml of absolute ethanol prepared as described above was added to a well-stirred ice-cold solution of 9.2 g of ethyl 2-chloroacetoacetate (50 mmol) and 8.0 g (50 mmol) of diethyl malonate in 10 ml of absolute ethanol. After completion of the addition, stirring was continued at room temperature for 1.5 h; then 60 ml of water was added and the mixture extracted with three 60-ml portions of ether. The combined ether extracts were dried ($MgSO_4$) and concentrated to afford 12.0 g of a slightly yellow oil. Gas chromatographic analysis (same conditions as in previous experiment) and ^1H NMR spectroscopy showed the product to contain 7.2 g (90% recovery) of diethyl malonate, 6.4 g (72.7% yield) of ethyl 2-methylthioacetoacetate, a small amount of ethyl 2-chloroacetoacetate, and a small quantity of material of longer retention time, possibly ethyl 2,2-bis(methylthio)acetoacetate. Diethyl methylthiomalonate was not present among the products.

Dimethyl(5-*cis*-2-isopropyl-1,3-dioxanyl)sulfonium *p*-Toluenesulfonate. A mixture of 810 mg (4.62 mmol) of *cis*-2-isopropyl-5-methylthio-1,3-dioxane and 1.97 g (10.6 mmol) of methyl *p*-toluenesulfonate was kept at 35° for 3 days. The cake formed was triturated with ether and filtered. The product was recrystallized from absolute ethanol, mp 144–145°, yield 1.35 g (81%).

^1H NMR (D_2O-DSS) δ 0.98 (d, J = 6.6 Hz, 6 H, $(CH_3)_2CH$), 1.82 (m, 1 H, Me_2CH), 2.40 (s, 3 H, CH_3-Ar), 3.00 (s, 6 H, $(CH_3)_2S^+$-), 3.65 (m, 1 H, H_{5e}), 4.45–4.50 (AA′BB′, 4 H, $H_{4,6}$), 4.68 (d, J = 5.0 Hz, 1 H, H_2), 7.49 and 7.83 ppm (AB, J = 9.0 Hz, aromatic H's).

Anal. Calcd for $C_{16}H_{26}O_5S_2$: C, 53.01; H, 7.23. Found: C, 52.99; H, 7.10.

Dimethyl(5-*trans*-2-isopropyl-1,3-dioxanyl)sulfonium *p*-toluenesulfonate was similarly prepared from 1.84 g (10.5 mmol) of *trans*-2-isopropyl-5-methylthio-1,3-dioxane and 4.48 g (24.0 mmol) of methyl *p*-toluenesulfonate, yield 2.0 g (60%), mp 187–188°.

^1H NMR (D_2O-DSS) δ 0.98 (d, J = 6.6 Hz, 6 H, $(CH_3)_2CH$), 1.82 (m, 1 H, Me_2CH), 2.40 (s, 3 H, CH_3-Ar), 2.92 (s, 6 H, $(CH_3)_2S^+$), 3.90–4.60 (6 H, H_2, $H_{4,6}$ and H_5), 7.49 and 7.83 ppm (AB, 4 H, J = 9.0 Hz, aromatic H's).

Anal. Found: C, 53.03; H, 7.25.

Equilibrations and Analysis. In most cases, equilibrations were effected with polystyrenesulfonic acid (Amberlyst-15) as previously described[3] and product analysis was carried out by vapor phase chromatography[3] except in the case of the (involatile) sulfoxides and sulfones where a less accurate analysis was obtained by integration of appropriate peaks in the ^1H NMR spectrum. In the case of the sulfoxides, the analysis was effected in the presence of an equal weight of Eu(dpm)$_3$ to ensure adequate separations of the $(CH_3)_2CH$ peaks used in the analysis; in the case of the sulfones, the CH_3SO_2 peaks were integrated.

The sulfonium and ammonium salts were equilibrated by dissolving them in the acid solvent indicated in Table I and performing the analysis when equilibrium had been reached. In the case of the NH_3^+ compound, the amine was liberated with excess base and the mixture analyzed gas chromatographically. In the case of the SMe_2^+, $NHMe_2^+$ and NMe_3^+ compounds, analysis was effected by integration of the S-CH_3 or N-CH_3 peaks in the ^1H NMR spectrum directly in the equilibrated solution.

The potassium salts of the pure acids[17] were boiled for 2 h with 20% aqueous KOH. The solution was cooled, acidified at 10–15°C with concentrated HCl, and immediately extracted with ether; the ether layer was washed with water, dried, concentrated, and treated with a slight excess (yellow color!) of diazomethane. The resulting solution of the epimeric methyl esters was analyzed gas chromatographically.

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The Structure of Dehydromethionine. An Azasulfonium Salt

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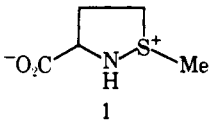
Abstract: The crystal and molecular structure of dehydromethionine has been determined by x-ray crystallographic techniques. The compound crystallizes in the monoclinic space group $P2_1/n$ with $a = 5.658$ (6) Å, $b = 8.844$ (6) Å, $c = 13.605$ (9) Å, $\alpha = 90°$, $\beta = 92.54$ (2)°, $\gamma = 90°$, and $Z = 4$. The atoms other than hydrogen were located using direct methods, and the hydrogen atoms were located by Fourier difference maps. Full-matrix least-squares refinement led to a conventional R factor of 0.044. Key features of the molecular structure are an envelope conformation of the five-membered isothiazolidine ring and trivalent sulfur bonded to pyramidal nitrogen. The geometry about the nitrogen atom suggests the absence of p–d π bonding between the sulfur and nitrogen atoms in the azasulfonium linkage. It is suggested that the geometry and bonding in azasulfonium salts is analogous to that in the isoelectronic sulfonium ylides.

Recently, azasulfonium (aminosulfonium, sulfiminium) salts $RR^1S^+NR^2R^3X^-$ have been the subject of considerable attention. This is due primarily to their use in organic synthesis. They are intermediates in ortho-alkylation and related reactions of aromatic amines.[1] One of their number, the adduct of *N*-chlorosuccinimide and dimethyl sulfide,[2] has been advantageously employed in the oxidation of alcohols.[3] The adducts of *N*-chloro- or *N*-bromosuccinimide and dimethyl sulfide are selective reagents for the conversion of allylic or benzylic alcohols into the corresponding halides.[4] Azasulfonium salts, in which the nitrogen atom is bonded to a hydrogen atom, afford the corresponding conjugate bases, sulfilimines (sulfimides, sulfimines, iminosulfuranes) on treatment with base.[5] The formation of azasulfonium salts by the reaction of sulfilimines with electrophiles has also been studied.[6,7]

The determination of the structures of azasulfonium salts is of interest to facilitate an understanding of their reactions and to reveal the nature of the bonding of the sulfur atom. This latter concern involves two major considerations: (1) the sulfur atom may be trivalent or tetravalent and (2) there may be p(N)–d(S) π bonding. The detailed structure of one azasulfonium salt has already been reported.[8] In the present paper, the determination of the structure by x-ray crystallographic techniques of dehydromethionine, an azasulfonium salt that was reported by Lavine[9] and to which Lavine assigned structure **1** in 1945,[9b] is presented.



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