Tetrahedron. Vol. 27, pp. 341 to 350. Pergamon Press 1971. Printed in Great Britain

3-SUBSTITUTED THIETANE DERIVATIVES
STEREOCHEMICAL CONSIDERATIONS[1,2]

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(*Received in the USA* 17 *September* 1970; *Received in the UK for publication* 23 *September* 1970)

Abstract—Stereochemical assignments could be made for a series of 3-substituted thietane 1-oxides from their NMR spectra. Both isomers appear to reside in conformations with the ring substituent equatorial. The *cis* isomer (equatorial S=O bond) is characterized by a large chemical shift difference for the α-methylene hydrogens. The *trans* isomer is characterized by a significant deshielding of the β-hydrogen (relative to cis isomer, not relative to the parent sulfide). The dominant conformations of 3,3-dimethylthietane 1-oxide and the corresponding 1-tosylimine have the S—X bond equatorial. Stereochemical assignments were made to the α-methylene protons and were confirmed by benzene-induced shift data. As expected for a hydrogen anti to the "lone pair" on sulfur the axial hydrogen of the sulfoxide appeared at higher field, the same was not true for the sulfilimine. Significant stereoselective benzene-induced shifts observed for the N-tosylsulfilimine and N-tosylsulfoximine of 3,3-dimethylthietane indicate that they may constitute a method of configuration assignment for such compounds.

RECENT focus on the stereoselective course of reactions at sulfinyl sulfur and at α-sulfinyl carbon places added importance to methods of configuration assignment. 4-Membered rings provide relatively simple models to study these reactions. Whereas thietane derivatives have received some attention in the investigation of reactions at sulfur[4–6] they have seen little use in the study of reactions at the α-carbon.[7] The investigation of reactions such as α-chlorination[8,9] and base-catalyzed H—D exchange[10–13] necessarily require a reliable method to distinguish the two α-methylene hydrogens.

NMR chemical shift values have been employed to assign stereochemistry to both acyclic[14] and cyclic sulfoxides. Significant among the numerous applications to cyclic systems are the recently reported configuration assignments to the sulfoxides of penicillin[15] and biotin.[16] Whereas other methods (e.g. relative elution rates from chromatography)[17] may be used to distinguish between diastereomeric sulfoxides, only nmr is of general applicability in the absence of the second isomer.

In a preliminary communication we assigned stereochemistry to a series of 3-substituted thietane 1-oxides from the chemical shifts of the α-hydrogens and the chemical shift difference of the α-methylene ring hydrogens.[18] A more detailed examination is presented here.

3-Substituted thietane derivatives. Puckering in thietane ring systems is now well documented.[19–24] Because of the energy barrier to planarity two conformations must be considered for each isomer. (Groups such as t-Bu are reportedly less efficient at "locking" the conformation of a cyclobutane than a cyclohexane ring.)[25] A significant population of the diaxial conformation of *cis* 3-t-butylthietane 1-oxide is unlikely in that this conformation would have severe 1,3-nonbonded interactions. The large chemical shift difference observed for the α-methylene hydrogens (Δ_{ea}) (Table

TABLE 1. α-METHYLENE δ-VALUES (Hz) FOR 3-SUBSTITUTED THIETANE 1-OXIDES[a]

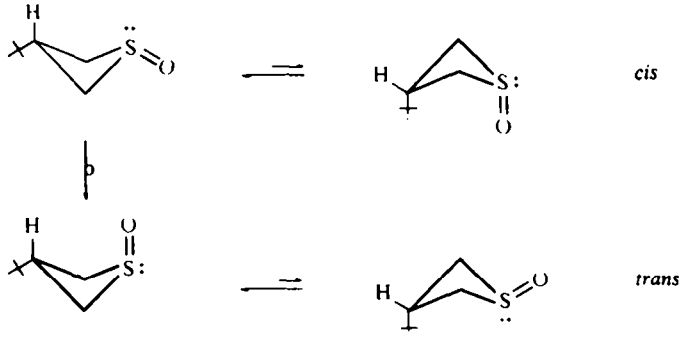
Substituent at C_3	Solvent	*cis*-Sulfoxide	*trans*-Sulfoxide
CH_3--	$CDCl_3$	160–235(m)	195–205[b](m)
t-$C(CH_3)_3$--	CCl_4	155–85; 190–220(m)	175–220[b](m)
C_6H_5--	CCl_4	187–204; 225–240(m)	211 + 217(d)
p-ClC_6H_4--	$CDCl_3$	182–246(m)	212 + 217(d)
Cl--	$CDCl_3$	195–275(m)	218 + 224(d)
CH_3CO_2--	CCl_4	179–213(m) + 236–257(m)	210 + 216(d)

[a] Chemical shift values are reported in Hz downfield from tetramethylsilane as recorded on a Varian A60A Spectrometer at ambient temperature.

[b] Signal for the α-hydrogen was complicated by overlap from the β-hydrogen signal.

1) is in accord with a conformation in which the nonbonded electron pair on sulfur is axial.

Although the energy difference between the two conformers of *trans*-3-t-butylthietane 1-oxide should be smaller than for *cis*, the t-Bu is still expected to have the greater equatorial preference. The large deshielding of the β-hydrogen, is evidence that this is true. The small Δ_{ea} for the methylene hydrogens is also consistent with an axial oxygen. Interconversion of conformers is expected to be fast on the NMR time

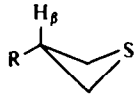
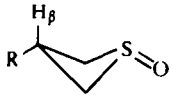
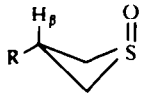
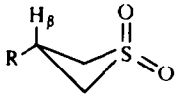


scale and thus the NMR spectrum should reflect a weighted average of the two conformers. In this case they reflect that the two equilibria lie to the left. That this conformational equilibrium is not affected significantly by changes in the substituent at C_3 is implied from the striking similarity in the NMR spectra of the *trans* isomers of a series of 3-substituted thietane 1-oxides.[18]

The nature of the substituent at C_3, the oxidation state at sulfur, or the configuration at sulfur may have an effect on the degree of ring puckering, although by analogy to 1,3-disubstituted cyclobutanes this effect is expected to be small.[26] Even if the difference in puckering between *cis* and *trans* sulfoxides were not significant, a small difference could be sufficient to have a profound effect on coupling of the ring hydrogens.[18] From a dipole moment study of the sulfide, *trans* sulfoxide, and sulfone of 3-chlorothietane, Arbuzov concluded that ring puckering decreases in the order: sulfide (axial) 1,1, sulfoxide, sulfone.[22]

Our equilibration studies reported earlier on the sulfoxides of 3-t-butyl-,

TABLE 2. 3-SUBSTITUTED THIETANES, CHEMICAL SHIFT VARIATION OF THE β-HYDROGEN WITH SUBSTITUTION AT SULFUR

	R = *p*-ClC$_6$H$_4$	R = C$_6$H$_5$	R = t-Bu	R = OAc
	265* (CCl$_4$)	276 (CDCl$_3$)	189* (CCl$_4$)	333 (CCl$_4$)
	193* (CCl$_4$)	214 (CCl$_4$)	116* (CCl$_4$)	291 (CCl$_4$)
	258* (CCl$_4$)	261 (CCl$_4$)	184* (CCl$_4$)	345 (CCl$_4$)
	228* (CDCl$_3$)	227* (CCl$_4$)	147·5* (CCl$_4$)	318 (CDCl$_3$)

* Value was obtained from the spectrum of the α-tetradeuterated thietane, other values represent the center of a multiplet exhibited by the undeuterated compound. The chemical shift values are reported in Hz downfield from tetramethylsilane, recorded on a Varian A60A Spectrometer at room temperature

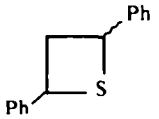
3-*p*-chlorophenyl-, and 3-methylthietane indicate that sulfinyl oxygen exerts an equatorial preference.[17,27] This is most readily attributed to a 1,3-cross ring nonbonded interaction which occurs between the β-hydrogen (axial) and sulfinyl oxygen (likewise axial) in the less favored isomer. When the seemingly anomolous axial preference of sulfinyl oxygen in thiane 1-oxides was first reported, the possibility could not be ruled out that this was a reflection of the greater steric requirement of the nonbonded electron pair (on sulfur) which thus preferred to be equatorial.[28] Recent calculations by Allinger have substantiated an earlier suggestion[28] that the axial preference of sulfinyl oxygen in the thiane 1-oxide case is due to a net attraction between oxygen and the axial hydrogens on C_3 and C_5.[29] In the absence of attractive forces of this type, the equatorial preference for sulfinyl oxygen in 3-substituted thietanes leads to the conclusion that the nonbonded electron pair on sulfur has a comparatively lesser steric requirement.

Crystal structure, dipole moment, and nmr studies have been used to assign configuration to thietane oxides.[18,21,22,24,27] NMR is by far the most versatile and the most readily available. Two phenomena can be used for these assignments: (a) a significant deshielding of the axial β-hydrogen if the S=O bond is axial; and

(b) a large difference in the chemical shifts of the α-methylene hydrogens if the nonbonded electron pair is axial. Such criteria were first employed to assign stereochemistry to 5- and 6-membered ring sulfoxides.[30,31]

There may be a temptation to relate similarities in the structural environment of the β-hydrogen (sulfide with *cis* sulfoxide and sulfone with *trans* sulfoxide) with similarities in the chemical shifts. This type of an analogy has in the case of one thietane system led to an incorrect configuration assignment.[18,32] The puckered thietane ring with an axial hydrogen at C_3 appears to be a reasonable model for examining the "proximity" effects of sulfur in its different oxidation states. Data for four thietane systems are given in Table 2. With one exception (*trans*-3-acetoxythietane 1-oxide) the signal for the β-hydrogen moves to higher field in the order: sulfide, *trans* sulfoxide, sulfone, *cis* sulfoxide. Thus despite the apparent structural similarities, there are no similarities of the chemical shift values of the β-hydrogens of sulfide and *cis* sulfoxide or sulfone and *trans* sulfoxide.

The large deshielding effect of divalent sulfur on the axial β-hydrogen of thietanes (Table 2) is noteworthy. There is also an example of a 2,4-disubstituted thietane system (**1**) in which the relative δ-values of the axial β-hydrogen also decrease in the order: sulfide, sulfone, equatorial sulfoxide (axial sulfoxide was not isolated).[24] In Lautenschlaeger's fused thietane system (**2**) the axial β-hydrogen has the highest δ-value for the axial sulfoxide (possibly a consequence of a more rigid system in which the β-hydrogen and S=O bond are held in a more nearly diaxial conformation), but for the other members of the series the observed order of decreasing chemical shift is: sulfide, sulfone, equatorial sulfoxide.[32,33] (Similar data has been collected



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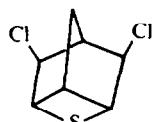

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on an oxathiane S-oxide system,[31c] but the S to β-H distance is different for the 6-membered ring—as evidenced by axial oxygen preference in one case and not the other.[27]) If there is an anisotropic deshielding effect associated with the (axial) S=O bond of the sulfone, it is considerably weaker than that of sulfoxide.

The effect of oxidation state at sulfur on the chemical shift of the α-methylene hydrogens is more difficult to assess from cyclic systems (because of a highly selective shielding—or deshielding—of the two protons in the case of sulfoxide). From acyclic systems the chemical shifts decrease in the order: sulfone, sulfoxide, sulfide,[34] the effect on the α-methylene hydrogens considered to be primarily an inductive effect.

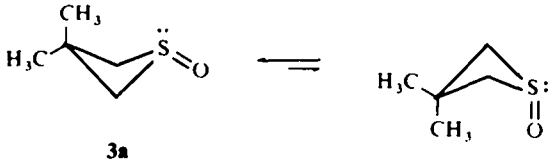
In cyclic sulfoxides a large chemical shift difference (Δ_{ea}) is observed for the α-methylene hydrogens when the nonbonded electron pair on sulfur is axial.[31c,35] To our knowledge for each report where configuration has been assigned to the cyclic sulfoxide and to the α-methylene hydrogens, the proton trans diaxial to the nonbonded electron on sulfur appears at higher field than the equatorial proton.[36] A similar effect has been observed and employed for configuration assignments with nitrogen heterocycles.[37,38] This effect is often attributed to a selective shielding by the electron pair of the trans co-axial α-hydrogen.

It should be pointed out that in assignments published for thiane oxides with an

axial oxygen, the high field α-methylene proton signal is usually assigned to the axial hydrogen.[13,31c,39] The Δ_{ea} for six 3-substituted thietane 1-oxides (Table 1) were significantly larger for the *cis* isomer than for the *trans*. In the *cis* isomers (electron pair axial) the proton signal at higher field presumably corresponds to the axial hydrogen. In the *trans* isomers the signals for the two α-methylene hydrogens are apparently superimposed and appear as a doublet.[40,*]

An axial nonbonded electron pair on heteroatoms is also associated with a more positive value of J_{gem} for the α-methylene protons.[37,38,41] Splitting patterns for the 3-substituted thietanes examined here are too complex to make this criteria as useful as those previously mentioned. A complete analysis of the spectrum of 3-chlorothietane has been reported and illustrates the problem.[23]

3,3-*Dimethylthietane derivatives.* In the conformationally mobile 3,3-dimethylthietane system the α-methylene hydrogen signals are well separated from the methyl signals; the α-hydrogens can be examined free of overlap and free of vicinal coupling. If interconversion of the conformers of 3,3-dimethylthietane 1-oxide (**3**) is rapid on the nmr time scale, the nmr spectrum will most nearly resemble the theoretical spectrum of the more populated conformation. Additional data on the conformational bias of sulfinyl oxygen in the thietane ring system should then be available from the nmr spectrum of **3**. After the completion of our own studies on the system, data similar in part were presented in a communication by Wucherpfennig.[42]

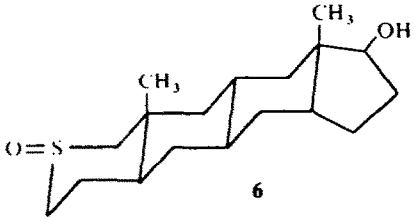


3a **3b**

The spectra of the sulfide (**4**) and sulfone (**5**) consist of two singlets in the ratio 6:4 (Table 3), implying either a rapid interconversion of puckered conformations or, less likely, a planar thietane ring. The spectrum of **3** contains two Me singlets and two methylene multiplets. The large Δ_{ea} (Table 3) for the α-methylene hydrogens is characteristic of an axial nonbonded electron pair on sulfur (conformation **3a**). Further evidence for this conformation is derived from the small difference in chemical shift observed for the two Me substituents. Dodson, *et al.* observed a downfield shift of 21 Hz ($CDCl_3$) for the 19-Me of **7** (in which the Me group is syn-axial to the S=O bond) relative to the 19-Me in **6**.[43] Dodson also observed a considerable difference in the benzene-induced shifts for the 19-CH groups of **6** and **7**. The 19-Me of **6** was shifted 19 Hz to higher field (C_6H_6 *vs* $CDCl_3$), whereas the 19-Me of **7** was shifted only 4 hz in the same direction. If **3b** is the dominant conformation of 3,3-dimethylthietane 1-oxide the axial Me group would be expected to appear at significantly lower field and to exhibit a smaller benzene-induced solvent shift than the equatorial Me. Neither effect is observed. This suggests that the S=O bond is equatorial in the dominant conformation, in agreement with the contention that 1,3-diaxial steric interactions (between oxygen and hydrogen) are responsible for the equatorial

* Thomas *et al.* also report a case in which a change in the configuration at sulfur changes considerably the splitting pattern of the α-methylene hydrogens

preference of oxygen in 3-substituted thietane 1-oxides.[27] Certainly the 1,3-diaxial interaction is greater for conformation **3b** of 3,3-dimethylthietane 1-oxide.



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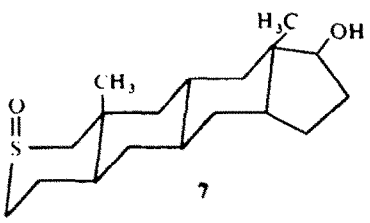

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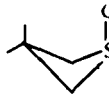
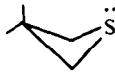
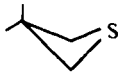
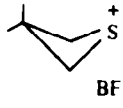
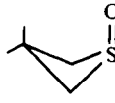
The highfield α-methylene signal of **3** possess fine-splitting which is absent in the lowfield signal and the highfield Me signal has a greater half-width than the lowfield Me. These phenomena are attributed to long range coupling between the axial methylene hydrogen with the axial methyl hydrogens which can assume the planar "W" configuration for coupling over four saturated bonds. Similar assignments involving axial Me groups have been made in other systems.[44] This assignment of the highfield methylene signal to the axial hydrogen is also arrived at on the basis of the apparent selective shielding by an axial nonbonded electron pair on sulfur as discussed earlier. Further confirmation of the assignment is obtained from aromatic solvent induced shifts (Table 3).

Since Dodson reported the aromatic solvent-induced shifts on the 19-CH groups of sulfoxides **6** and **7**, the phenomena has been applied to the assignment of stereochemistry to several cyclic sulfoxides.[45–47] Noteworthy is its application to the penicillin sulfoxides.[15] According to the model proposed by Ledaal,[48] the benzene-solute complex is best described by association of the benzene near the positive end of the polar functional group dipole. In the case of cyclic sulfoxides this would imply association of the benzene on the side of the ring *trans* to sulfinyl oxygen. Those protons in the vicinity of the sulfinyl grouping which are *trans* to oxygen will experience the greater shift to higher field. Accordingly, the α-hydrogen of **3**, given the equatorial assignment, experiences the greater shift (Table 3).

The apparent shielding of an axial hydrogen by an adjacent axial lone pair on nitrogen as a criteria for stereochemical assignments to nitrogen heterocycles[49] has come under question. Criticism has centered on the contribution of the substituent on nitrogen (hydrogen or alkyl) to the selective shielding of the two α-hydrogens and to Δ_{ea}. The rather simple concept of a selective shielding by the axial lone pair on the axial hydrogen has appeal; the equatorial N—R bond is essentially equidistant to the two hydrogens (Fig. 1) and its contribution to selective shielding is generally ignored. Lambert, working with substituted piperidine appears to have separated the two contributions and has concluded that "that the lone pair must give rise to a significant portion of the shielding effect," and, in fact, "it can be the entire cause."[50,51] The effect of the substituent on sulfur has not been considered.

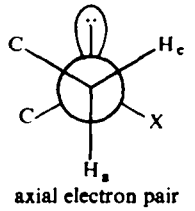
It seemed feasible to qualitatively test the contribution of the S=O bond to the selective shielding of the axial α-hydrogen by replacing the (oxygen) substituent on sulfur. Compound **8** was prepared and its nmr spectrum examined (Table 3). The same factors (1,3-cross ring steric interactions) which make **3a** the favored conformation of 3,3-dimethylthietane 1-oxide are expected to favor the conformation of **8**

TABLE 3. SOLVENT SHIFT DATA FOR 3,3-DIMETHYLTHIETANE DERIVATIVES[a, b]

		$CDCl_3$		C_6H_6		$\Delta[\delta_{CDCl_3} - \delta_{C_6H_6}]$	
		CH_3	α-CH	CH_3	α-CH	CH_3	α-CH
	**4**	76	175	63·5	163·5	12·5	11·5
	**5**	86	228	59	203	27	25
	**3** ax	74	182 (m)	39	158 (m)	35	24
	eq	78	212 (m)	44·5	172 (m)	33·5	40
	**8** ax	80	235 (m)	34·5	220·5 (m)	45·5	14·5
	eq	80·5	211·5 (m)	43·5	161 (m)	37·0	50·5
	**9**	85	226 (m)	---	-	-	---
		94	262 (m)	--	--	---	--
	**10**	90	237 (m)	56	205 (m)	49	32
		87	259 (m)	38	233 (m)	34	26

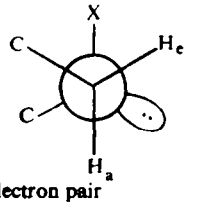
[a] The chemical shift values are reported in Hz downfield from tetramethylsilane as recorded in 5–10% solutions on a Varian A60A Spectrometer.

[b] Multiplets are reported as their arithmatic centers.



axial electron pair

Heteroatom = N,
= S



equation electron pair

X = H or R
X = O or NTs

FIG 1

with the imine group equatorial. The nmr spectrum of **8** is similar to that of **3** having a large Δ_{ea} for the α-methylene hydrogens, indicative of an axial nonbonded electron pair on sulfur. But for **8**, the axial methylene proton signal (fine-splitting from coupling with the axial methyl group) appears at lower field than the equatorial proton. This assignment to the α-methylene hydrogens is confirmed by solvent shift data (Table 3). The benzene-solute complex with **8** should be similar to that with **3** since the S=O and S=N bonds are similarly polarized. The signal assigned to the equatorial α-hydrogen is expected to exhibit the larger shift to highfield in benzene, as is observed (Table 3).

It is noteworthy that **8** is a case where an α-methylene hydrogen *trans*-diaxial to the nonbonded electron pair on trivalent sulfur appears at lower field than the equatorial hydrogen.

The methoxysulfonium salt (**9**) was also prepared and its NMR spectrum examined (Table 3), the pattern was similar to that observed for **3**. The Δ_{ea} values for both the α-methylene and the Me hydrogens are increased slightly over the sulfoxide. Benzene-induced shifts were not obtained for reasons of solubility.

The sulfilimine **8** was oxidized to sulfoximine **10** and its NMR spectrum was examined (Table 3). We are unable to assign a preferred conformation to **10** or, in fact, to rule out the possibility of a planar ring. The α-methylene hydrogens appear as an AB quartet in $CDCl_3$ but show considerable splitting in benzene. The different benzene-induced shifts for the two α-methylene hydrogens and for the two Me groups of **10**, and even more significantly in the case of **8**, are noteworthy. Previous stereochemical assignments to sulfilimines or sulfoximines have necessarily depended on the stereoselectivity (or stereospecificity) of the synthesis from, or conversion to, a compound of known stereochemistry.[52] Aromatic solvent-induced shifts might offer a method to assign stereochemistry directly to sulfilimines and sulfoximines.

It should be pointed out that stereochemical assignments have been reported for the diastereometric α-methylene hydrogens of acyclic systems too, but assignments in the literature do not appear to be mutually consistent.

EXPERIMENTAL

Mg pts are uncorrected. IR spectra were measured on a Perkin–Elmer 621 spectrometer. NMR spectra were obtained on a Varian A-60A spectrometer. Microanalyses were performed by Midwest Microlab, Inc., Indianapolis, Indiana. Syntheses of the 3-substituted thietane derivatives have been reported previously.[17]

3,3-*Dimethylthietane* (**4**). The sulfide **4** was prepared according to the procedure of Searles *et al*;[54,55] NMR ($CDCl_3$) δ 1·27 (s, 6), 2·90 (s, 4).

3,3-*Dimethylthietane* 1-*oxide* (**3**). The sulfide **4** was oxidized with sodium metaperiodate according to the usual procedure and the crude product was purified by chromatography over silica gel to yield a colorless oil; IR (CCl_4) 1010 and 1060 cm^{-1} (SO); NMR ($CDCl_3$) δ 1·23 (s, 3), 1·30 (s, 3), 3·03 (m, 2), 3·53 (m, 2). A *mercuric chloride adduct* was prepared, m.p. 122–124° (lit.[56] m.p. 127°).

3,3-*Dimethylthietane* 1,1-*dioxide* (**5**). Treatment of the sulfide **4** in an acetone soln with excess 30% H_2O_2 at room temp yielded a light yellow oil. Recrystallization from ether-hexane yielded white needles, m.p. 54·5–55·5° (lit.[56] m.p. 54–55°); NMR ($CDCl_3$) δ 1·43 (s, 6), 3·80 (s, 4).

3,3-*Dimethylthietane* 1-p-*toluenesulfonylimine* (**8**). To 820 mg chloramine-T (3·6 mmole) in 16 ml water was added 400 mg (3·4 mmole) of **4** in 5 ml acetone. After stirring for 18 hr at room temp the acetone was evaporated and the aqueous residue was extracted with CH_2Cl_2. The dried ($MgSO_4$) extract was concentrated to a viscous oil which was recrystallized from EtOH to yield 540 mg (56%) of white crystals, m.p.

115–116; IR (CH_2Cl_2) 955, 892, 1015, 1043, 1085, 1138 cm; NMR ($CDCl_3$) δ 1·33 (d, 6), 2·40 (s, 3), 3·53 (m, 2), 3·92 (m, 2), 7·51 (q, 4). (Found: C, 53·31; H, 6·28. Calcd. for $C_{12}H_{17}NO_2S_2$: C, 53·11; H, 6·31%).

3,3-Dimethylthietane 1-oxide 1-p-toluenesulfonylimine (**10**). To 75 mg (0·47 mmole) $KMnO_4$ in 2 ml pyridine was added 120 mg (0·42 mmole) of **8** and the reaction mixture was stirred at room temp for 20 hr. The mixture was evaporated *in vacuo* to dryness and the residue was washed with toluene and chloroform. The washes were filtered and concentrated *in vaco* to a white solid. Recrystallization from acetone-hexane yielded 87 mg (69%) white crystals, m.p. 124–125·5°; IR ($CHCl_3$) 1050, 1090, 1150, 1250, 1310 cm^{-1}; NMR ($CDCl_3$) 1·45 (s, 3), 1·50 (s, 3), 2·38 (s, 3), 3·95 (m, 2), 4·32 (m, 2), 7·50 (q, 4). (Found: C, 50·13; H, 6·04. Calcd. for $C_{12}H_{17}NO_3S_2$: C, 50·15; H, 5·96%).

O-Alkylation of 3,3-dimethylthietane 1-oxide. To 427 mg (4 mmole) sulfoxide and 780 mg (4 mmole) silver tetrafluoroborate in 20 ml $CHCl_2$ added 1·30 g (9 mmole) MeI with stirring. After stirring at room temp for 1 hr the mixture was filtered through celite to remove AgI. The addition of ether to the filtrate precipitated white crystals, m.p. 69–71°. Recrystallization from CH_2Cl_2-ether yielded 100 mg white crystals, m.p. 71–72°. (Found: C, 32·95; H, 6·16. Calcd. for $C_6H_{13}BF_4OS$: C, 32·75; H, 5·95%).

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