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THE ALKENIC UNREACTIVITY OF MONO- AND BI-CYCLIC DERIVATIVES OF 3,6-DIHYDRO-2-(METHYLTHIO)-2*H*-THIOPYRAN *S,S,S',S'*-TETRAOXIDE*†

DOLATRAI M. VYAS AND GEORGE W. HAY
Department of Chemistry, Queen's University, Kingston, Ontario K7L 3N6 (Canada)
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ABSTRACT

The inertness of the alkenic bond towards electrophilic additions in 3-*exo*-cyano-3-(methylthio)-2-thiabicyclo[2.2.1]hept-5-ene *S,S,S',S'*-tetraoxide (**5**), 3,6-dihydro-2-(methylthio)-2*H*-thiopyran-2-carbonitrile *S,S,S',S'*-tetraoxide (**3**), and 2-(acetamidomethyl)-3,6-dihydro-2-(methylthio)-2*H*-thiopyran *S,S,S',S'*-tetraoxide (**4**) is attributed to the "supra-annular effect" and field effects. Conformational analysis of a pentadeuterated derivative of **4** (**10**) is reported. On the basis of the 220-MHz ^{1}H n.m.r.-spectral data of **10**, the compound was concluded to adopt the $^0H_2$ conformation in chloroform solution.

INTRODUCTION

As one facet of the present interest in replacement of the sugar ring-oxygen atom by other heteroatoms, a study of methods whereby sugars having sulfur in the ring may be synthesized via Diels–Alder reactions with methyl cyanodithioformate[1] has been initiated in this laboratory. Earlier papers[1] in this series have described the *cis*-hydroxylation, with osmium tetraoxide, of Diels–Alder adducts obtained by exploitation of the dienophilic properties[2] of methyl cyanodithioformate. Thus, *cis*-hydroxylation of the 1,4-cycloaddition products from the reaction of methyl cyanodithioformate with 1-methoxy-1,3-butadiene and with cyclopentadiene afforded two original types of carbohydrates with sulfur in the ring, namely methyl 3-*O*-methyl-2,6-dithio-α-DL-*arabino*-2-hexulopyranosidononitrile (**1**) and methyl 3-deoxy-3,6-*C*-methylene-2,6-dithio-α-DL-*talo*-hex-2-ulopyranosidononitrile (**2**), respectively.

Direct *trans*-hydroxylation, via epoxidation of the alkenic bond of the Diels–Alder product with peroxy acids, was not feasible because of the susceptibility to oxidation of the (highly nucleophilic) sulfur atoms[3]. The desired transformation to afford 1,3-dideoxy- and 1-amino-3,6-*C*-methylene-2,6-dithio-hex-2-ulopyranosides

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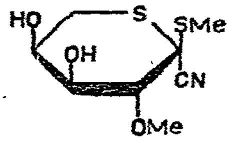
*Dedicated to the memory of Professor J. K. N. Jones, F.R.S.

†Studies on the synthesis of novel carbohydrates having sulfur in the ring, Part IV. For part III, see ref. 1.



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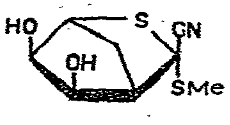

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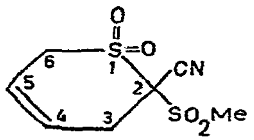
was assumed to be achievable by epoxidation of the fully *S*-oxidized adduct[3b], oxirane ring-opening, and reduction of the sulfonyl groups[4] with lithium aluminum hydride. Surprisingly, it was observed[1,5] that treatment of each of 3,6-dihydro-2-(methylthio)-2*H*-thiopyran-2-carbonitrile, 2-(acetamidomethyl)-3,6-dihydro-2-(methylthio)-2*H*-thiopyran, and 3-*exo*-cyano-3-(methylthio)-2-thiabicyclo[2.2.1]hept-5-ene, with an excess of *m*-chloroperoxybenzoic acid in dichloromethane afforded only the corresponding *S*,*S*,*S'*,*S'*-tetraoxide (**3**, **4**, and **5**), with no trace of epoxidation product. Moreover, **3** was totally inert to Milas' reagent[6], peroxyformic acid, trifluoroperoxyacetic acid, or bromine in carbon tetrachloride. Such inertness of an alkenic bond to addition reactions is striking, especially in the monocyclic systems, as the carbon–carbon double bonds in unsaturated five-[7] and six-membered[3a,8], heterocyclic sulfones undergo facile additions. However, Johnson *et al.*[3b] observed that the alkenic bond in 3,3-dichloro-2-thiabicyclo[2.2.1]hept-5-ene *S*,*S*-dioxide was completely unreactive in electrophilic additions. In addition, Raasch has reported[9] that bromination of 3-hexafluoroisopropylidene-2-thiabicyclo[2.2.1]hept-5-ene *S*,*S*-dioxide was barely perceptible until irradiation was used to induce a free-radical reaction.



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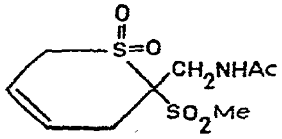

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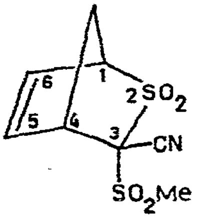

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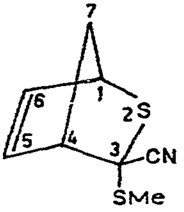
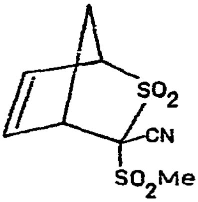
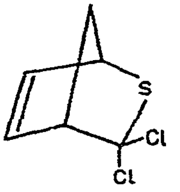
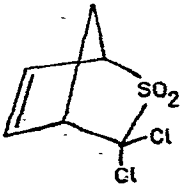
This paper discusses the unreactivity of the *endo*-cyclic double bond in both rigid bicyclic, and conformationally mobile, monocyclic sulfur heterocycles, in terms of electrostatic (field) effects^{10}, inductive effects^{8b,10}, and the "supra-annular effect"^{11}. The preparation and ^{1}H n.m.r.-spectral analysis of 3-*exo*-cyano-3-(methylthio)-2-thiabicyclo[2.2.1]hept-5-ene *S,S,S',S'*-tetraoxide (5) are reported, as well as conformational studies on one deuterated derivative.

RESULTS AND DISCUSSION

Treatment of 3-*exo*-cyano-3-(methylthio)-2-thiabicyclo[2.2.1]hept-5-ene^{2} (6) with an excess of *m*-chloroperoxybenzoic acid in dichloromethane for 48 h at room

TABLE I

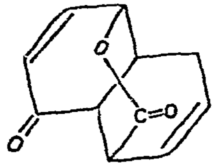
^{1}H N.M.R. CHEMICAL SHIFT (τ) DATA FOR DERIVATIVES OF 2-THIANORBORNENE

Compound	Proton						
		i	4	5	6	7	CH_3
	6 (ref. 2)	5.61m	6.15m	3.50q	3.97q	7.93m	7.64s
	5	5.62m	5.92m	3.28q	3.67q	7.30m	7.00s
	7 (refs. 3b, 9)	5.66m	6.07m	3.82m	3.37q	7.95AB	—
	8 (ref. 3b)	5.74m	6.45m	3.55m	3.55m	7.48	—

temperature afforded only **5**, as a colorless, crystalline compound. The elemental analysis, and i.r. and ^{1}H n.m.r. spectra, were in agreement with the structure. The presence of the alkenic bond was established from the ^{1}H n.m.r. spectrum on the basis of two one-proton signals (at τ 3.28 and 3.67), which were attributed to the resonance of vinyl protons.

Complete n.m.r.-spectral analysis (see Table I) was achieved by considering the chemical-shift data of other relevant 2-thianorbornene derivatives [**7** and **8** (see ref. 3b)] and by double-resonance experiments. Thus, considering the chemical shifts of the H-1 and H-4 protons reported for **6** (ref. 2), **7**, and **8**, the signals at τ 5.62 and 5.92 in the ^{1}H n.m.r. spectrum of **5** were similarly assigned to H-1 and H-4, respectively. This trend in the H-1 and H-4 chemical shifts in all four compounds is consistent with that observed in the studies by Fraser *et al.*[12], and by Boerma *et al.*[13], on other bicyclic, sulfur heterocyles. Finally, assignments of the signals at τ 3.28 and 3.67 to the H-5 and H-6 vinyl protons, respectively, were made on the results of selective irradiation of the H-1 and H-4 signal frequencies.

Attempts to epoxidize the ring double-bond in **5** with *m*-chloroperoxybenzoic acid under more vigorous conditions (boiling benzene) did not afford any epoxide. Under similar conditions, Johnson *et al.*[3b] obtained an epoxide of 3,3-dichloro-2-thiabicyclo[2.2.1]hept-5-ene *S,S*-dioxide (**8**) in 28% yield. The double bond of other *S,S*-dioxide derivatives of 2-thianorbornenes also displayed reactivity to electrophiles[9]. The total unreactivity of the alkenic bond of **5** towards electrophilic addition, under the conditions cited, may be attributed to deactivation by the positively-charged sulfonyl-sulfur atoms[10b] of both the endo- and ring-sulfonyl groups. The *endo*-(methylsulfonyl)-sulfur atom is suitably situated with respect to the double bond so as to impart a "supra-annular effect"[11], with concomitant deactivation of the alkenic bond arising from partial overlapping of the electron-deficient, π-orbital of the S=O group and the π-orbital of the double bond. Woodward and co-workers[14] attributed to the same effect the unreactivity towards bromination of the non-conjugated double bond in the rigid lactone, **9**.



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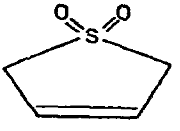
The original application of the "supra-annular effect" to explain the unreactivity of the alkenic bond in some 4-substituted cyclohexenes[11a] was subsequently disproved by ^{1}H n.m.r. studies of conformation[11b]. The inertness to electrophilic attack of the alkenic bond in **3** and **4** as compared to that in "sulfolene[7]" (**11**) or 3,6-dihydro-2*H*-thiopyran *S,S*-dioxide[8] (**12**) could be attributed, in part, to the influence of the exocyclic, sulfonyl group. The adjacent polar bonds[15] in **3** and **4** would impose a special stereochemical requirement that could be a significant factor in controlling the conformational equilibrium in solution. For solutions of cyclohexene, the preponderance of the half-chair conformation is well established[16], but for unsaturated sulfur heterocyclic compounds it is much less certain what is the favored conformation. It has been suggested[17] that 3,6-dihydro-2*H*-thiopyran exists primarily in a boat conformation, and that conformation has been established by X-ray crystallographic measurements on a number of other unsaturated, six-membered sulfur heterocycles[18]. Nevertheless, it was essential to determine the favored conformation of each of **3** and **4** in solution before any explanation of the cause of unreactivity of the ring double-bond could be proposed. This conformational study was accomplished by ^{1}H n.m.r. spectroscopy.



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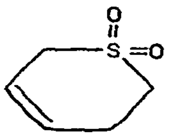

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The 60-MHz ^{1}H n.m.r.-spectral data for **3** and **4** have been reported[5], but coupling constants were unavailable because of the incomplete resolution in those spectra. This information was obtained from the well-resolved 220-MHz ^{1}H n.m.r. spectrum (without the methyl singlet of the acetamido group) of the pentadeuterio derivative[5] (**10**) (see Fig. 1). The vinylic (H-4, H-5), and allylic (H-3, H-3′) proton signals, centered at τ 5.74 and 3.04, respectively, were analysed as an ABCD spin system with the LAOCN-4A program[19]. The calculated chemical-shifts and coupling constants of the ring protons are documented in Table II.

For conformational studies, the Karplus equation[20] could not be employed because of the unsaturation of the compounds. Therefore the empirical Garbisch[21] equation, which is applicable to unsaturated systems, was employed to obtain an estimate of the angle between the ring C–H bonds and the plane of the ring double-bond in **10** from the vicinal coupling-constants $J_{3,4}$ (3.6 Hz) and $J_{3',4}$ (4.6 Hz). These values indicate torsion angles of approximately 60 and 45°, respectively, between the plane of the double bond and H-3 and H-3′. This analysis implies that, in chloroform, compound **10** exists preponderantly in a slightly distorted, half-chair conformation. Drieding models of cyclohexene suggested that the torsion angles between the quasi-equatorial (qe) and quasi-axial (qa) C–H bonds and the plane of the ring double bond were close to 45 and 75°, respectively, in the stable half-chair conformer[22]. The corresponding bonds have been reported to subtend angles of 30 and 90° in some unsaturated carbohydrates[23]. Thus, the spectral analysis of **10** leads to the conclusion that, in chloroform solution, **3** and **4** favor the half-chair confor-

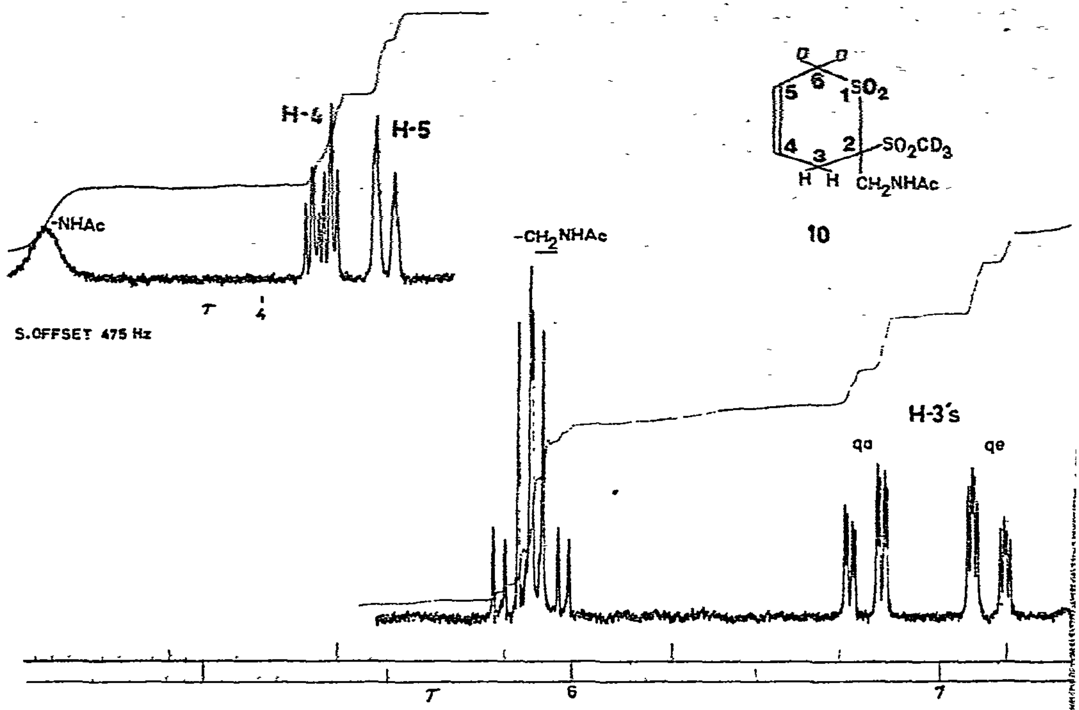
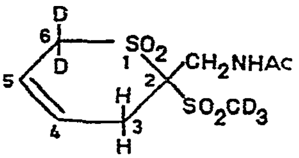


Fig. 1. Partial 220-MHz ^1H n.m.r. spectrum of compound **10**.

TABLE II



CALCULATED* 220 MHz H^1 N.M.R. CHEMICAL-SHIFT (τ) AND COUPLING-CONSTANT (Hz) DATA FOR RING PROTONS OF COMPOUND **10**

Proton	*Chemical shift*	*Coupling constants*† *(Hz)*
H-3	2.88	$J_{3,3'}$ −19.3 $J_{3,4}$ 3.6 (60°) $J_{3,5}$ −2.3
H-3'	3.20	$J_{3',4}$ 4.6 (45°) $J_{3',5}$ −1.6
H-4	5.82	$J_{4,5}$ 10.7
H-5	5.66	

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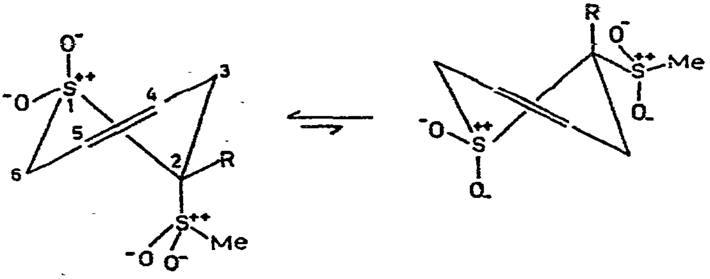
*LAOCN-4A (ref. 19). †The values in parentheses denote the torsion angles corresponding to the coupling constant, as obtained by employing the Garbich equation:

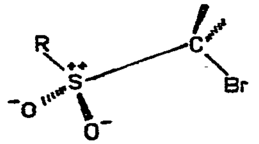
$$J_{vicinal} = 6.6 \cos^2\theta + 2.6 \sin^2\theta (0° \leqslant \theta \leqslant 90°)$$

mation and that the conformational equilibria in solution may be represented as shown (3, R = CN; 4, R = CH_2NHAc).



$^{0}H_2$ $^{2}H_0$

On the basis of the following considerations, the preponderant conformer of 3 in solution was concluded to be $^{0}H_2$: (a) the $^{0}H_2$ conformation would locate the equatorial cyano group in a stabilizing configuration, as the linear C≡N bond would lie on, or close to, the bisector of the ring O–S–O angle. Such an arrangement of adjacent polar bonds has been observed[24] in the crystalline α-bromosulfone **13**. Moreover, in 1,1,2-trihalocyclohexanes[25], the equatorial conformer (**14**) is favored over its axial counterpart. (b) The axially disposed, sulfonyl group would also be in a stabilizing disposition; (c) in contrast, an equatorial sulfonyl group would bring about electrostatic repulsion between the negative, sulfonyl-oxygen atoms, a situation parallel to the well-known "rabbit ear-effect" postulated by Eliel[26]. (d) On the basis of a recent study[27] of the conformational equilibria of 1,3-dioxanes having polar substituents at C-5, it is evident that 3 in the $^{0}H_2$ conformation would experience still further stabilization from an electrostatic attraction between the positively charged, axial sulfur-atom and the somewhat anionic C-6 atom. With these 3,6-dihydro-2*H*-thiopyran derivatives, unlike the case of the 4-substituted cyclohexenes, the evidence argues for the involvement of the "supra-annular effect", together with the aforementioned factors, producing a strong preference in solutions of 3 and 4 for the $^{0}H_2$ conformation, in which there occurs a dramatic deactivation of the ring double-bond towards electrophilic attack.



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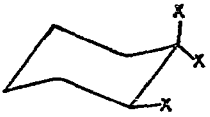

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Whereas studies on pent-2-enofuranoses[28] and hex-2-enopyranoses[29] indicated normal reactivity of the double bond to the standard hydroxylating reagents, some examples of unreactivity of unsaturated carbohydrates toward addition of pseudohalogens have been observed[30]. This lack of reactivity has been attributed to inductive electron-withdrawal by the anomeric centre[31]. However, all electron-withdrawing groups in **3** and **4** are separated from the ring double-bond by at least two σ-bonds. Comparison of the alkenic reactivities of **11** (ref. 7) and **12** (ref. 8) with those of **3** and **4** demonstrates that the inertness is not attributable in any significant measure to an inductive withdrawal of π-electrons. Thus, in the case of the mono- and bi-cyclic systems just described, the deactivation of the ring double-bond results primarily from non-inductive, non-conjugative effects that are maximized in the favored conformation. With compound **5**, the electrostatic (field) effects of the sulfonyl group, in the sense discussed by Kwart *et al.*[10b] in their study of the unreactivity of the double bonds in substituted cyclohexenes and norbornenes, cannot be completely excluded.

EXPERIMENTAL*

*3-*exo*-Cyano-3-(methylthio)-2-thiabicyclo[2.2.1]hept-5-ene* S,S,S',S'*-tetraoxide* (**5**). — *m*-Chloroperoxybenzoic acid (21.0 g, 0.11 mol) in 80 ml of anhydrous dichloromethane was added to 3.0 g (160 mmol) of **6** in 25 ml of anhydrous dichloromethane at ice-bath temperature. The mixture was kept for 48 h at room temperature, whereupon it was washed sequentially with saturated aqueous sodium hydrogensulfite, saturated aqueous sodium hydrogencarbonate, and water. Evaporation of the solvent afforded 4.0 g (97.5%) of white solid which, on recrystallization from 95% ethanol, gave colorless platelets; m.p. 132–133°; ν_{max} (KBr) 3030 (C=CH), 2222 (C≡N), 1333 and 1136 cm^{-1} (SO_2); n.m.r. data in acetone-d_6 (see Table I).

Anal. Calc. for $C_8H_9NO_4S_2$: C, 38.90; H, 3.64. Found: C, 39.30; H, 3.66.

ACKNOWLEDGMENTS

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*For general experimental procedures see reference 1.

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