205. 1-Substituted 1,3-Dihydroisothianaphthen-2,2-dioxides: Preparation and Use as *ortho*-Quinodimethane Precursors in Intramolecular Cycloadditions

Preliminary Communication

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Dedicated to Professor *André Dreiding* on his 60th birthday

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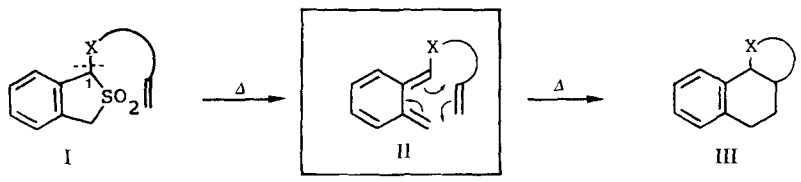
Summary

1,3-Dihydroisothianaphthen-2,2-dioxide (**1**) was readily converted to the 1-substituted sulfones **3** by deprotonation and subsequent electrophilic attack (*Scheme 3* and *Table*). The appropriate 1-alkenyl- and 1-alkenoyl-sulfones **3** on heating at 213° to 240° underwent SO_2-extrusion to give, *via* the non-isolated (*E*)-quinodimethanes II *(Scheme 1)*, polycyclic products such as **4**, **6** and **7** in good yields (*Schemes 4* and *5*). On the other hand, thermolysis of the 1-alkenoyl-1-thioether sulfones **9** furnished mainly the isochromenes **10** *(Scheme 6)*.

The utility of the reaction II → III *(Scheme 1)* for the general, flexible and stereoselective synthesis of polycyclic systems has been amply demonstrated by work from this and other laboratories[1]). Although the transient dienes II are conveniently

Scheme 1



generated and converted to III by heating suitable 1-substituted benzocyclobutenes [1] it seemed worthwhile to explore further routes which could lead to II[2]). Thus, in view of the postulated formation of the unstable *o*-xylylene on heating 1,3-dihydroisothianaphthen-2,2-dioxide [4], we decided to study the thermolysis of the

[1]) Review: [1].

[2]) See for example the preparation and thermolysis of 4-alkenyl-3-isochromanones [1] [2].

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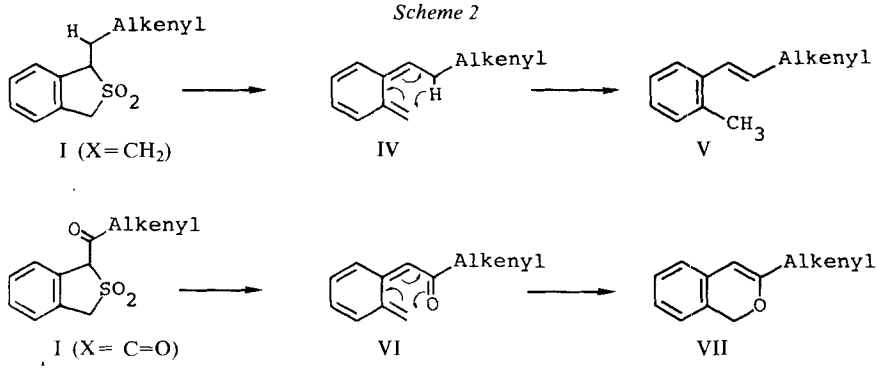
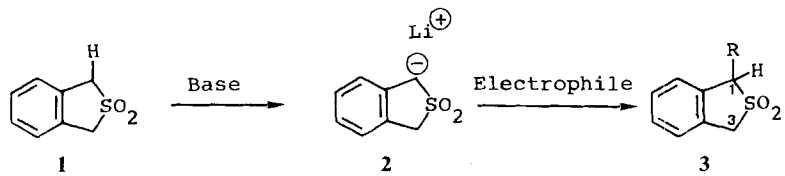
1-substituted sulfones I. This raised the question as to whether the sulfones I would eliminate SO_2 to give the desired (*E*)-diene II or rather the (*Z*)-isomers IV and VI which would be expected to undergo 1,5-H-shift IV → V or cyclization VI → VII, respectively *(Scheme 2)* [1]. Despite this initial uncertainty the apparent accessibility

Scheme 2



of I from the readily available sulfone **1** [4b] by formation of the C(1), X-bond justified this approach. By analogy to the recently studied alkylation of 3-isochromanones [1] [2] and of benzocyclobutyl phenyl sulfone [3] it was anticipated that deprotonation of the sulfone **1** and subsequent electrophilic substitution of the anion **2** would afford the monosubstituted sulfones **3** *(Scheme 3)*. In fact, as indi-

Scheme 3



cated in the *Table*, treatment of **1** with various bases in THF under an argon atmosphere at −78° for 30 min (*entries* A and B) or, more conveniently, with BuLi at −20° for 15 min (*entry* C), followed by rapid addition of 1,1 mol-equiv. of methyl iodide, stirring of the mixture at −20° for 30 min, aqueous work-up and crystallization of the crude product furnished the monomethylated sulfone **3a**[3]) in high yield.

Analogous alkylation of **1** with several, less reactive, alkenyl bromides and tosylates *(Table)* gave mainly the monosubstituted sulfones **3** in satisfactory yields after separation from minor amounts of 1,3-dialkylated products and unchanged **1**. Acylation of **1** required two mol of **2** per mol of acylating agent, and a work-up

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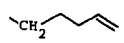
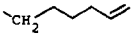
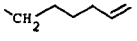
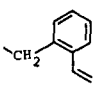
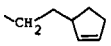
[3]) IR., ^{1}H-NMR. and MS. are in full agreement with the assigned structure. IR. spectra: film unless otherwise specified, ν_{max} in cm^{-1}. – UV. spectra: MeOH, λ_{max} in nm, log ε in parentheses. – ^{1}H-NMR. spectra in $CDCl_3$ at 100 MHz, internal standard tetramethylsilane ($\delta = 0$ ppm), abbreviations: *s* = singlet, *d* = doublet, *J* = spin-spin coupling constant (Hz).

with acid, owing to the acidic nature of the acylsulfone products; the latter were formed in higher yields when esters were used instead of acid chlorides (see for example the preparation of **3f**, *Table, entries* I and J). Similarly, sulfenylation of the anion **2** with 0.5 mol-equiv. of the appropriate disulfide furnished the thioethers **3g**[3]) and **3h**[3]) in good yields. Furthermore, electrophilic attack of **2** by 1 mol-equiv. of 5-hexenyl-carboxaldehyde proceeded smoothly at $-78°$ to $-20°$ to give, after aqueous work-up, a stereoisomeric mixture of 1-(1-hydroxy-5-hexenyl)-1,3-dihydroisothianaphthen-2,2-dioxides[3]) in 79% yield. Having a practical route to various olefinic sulfones in hand we turned our attention to the anticipated thermolyses I → II → III.

Table. *Deprotonation and Substitution of 1,3-Dihydroisothianaphthen-2,2-dioxide by the Electrophiles R–X:* **1** → **2** → **3**

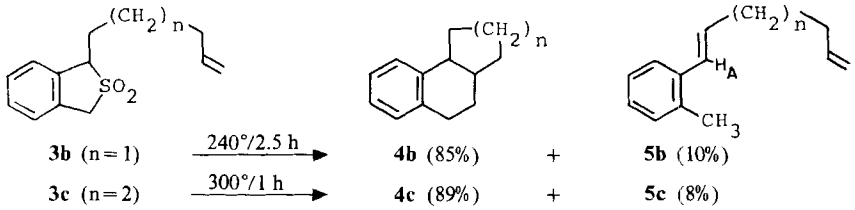
Entry	Reaction Conditions[a])		X	R	Product[3])	% Yield[b])	M.p. (°C)	^{1}H-NMR.[3]) δ(H–C(1))
	1 → **2**	**2** → **3**						
A	LiTMP/ – 78°	– 78° to + 25°	I	CH_3	**3a**	85	96–99	4.30
B	LDA/ – 78°	– 78°/1 h	I	CH_3	**3a**	92	96–99	4.30
C	BuLi/ – 20°	– 20°/0.5 h	I	CH_3	**3a**	91	96–99	4.30
D	BuLi/ – 20° 1 eq. HMPT	– 10°/2 h	Br		**3b**	76	oil	4.22
E	LiTMP/ – 78° 1 eq. HMPT	– 78° to 0°	Br		**3c**	61 (79)	oil	4.22
F	BuLi/ – 78°	– 78° to – 10°	Br		**3c**	52 (86)	oil	4.22
G	BuLi/ – 40°	– 78° to – 20°	Br		**3d**	53	149–150	4.43
H	BuLi/0°	0°/3 h	OTs		**3e**	45 (65)	oil	4.26
I	BuLi/ – 20°	0.5 eq. RX – 78°/5 min	Cl		**3f**	30	oil	5.30
J	BuLi/ – 20°	0.5 eq. RX + 25°/18 h	OEt		**3f**	95	oil	5.30
K	BuLi/ – 20°	0.5 eq. RX – 20°/3 h	SPh	SPh	**3g**	81	77–78	5.42
L	BuLi/ – 20°	0.5 eq. RX – 20°/3 h	SMe	SMe	**3h**	86	65–66	5.14

[a]) The commercially unavailable electrophiles[3]) were prepared by the following standard procedures: *Entry* G: see [5]; *entry* H: tosylation (1.1 mol-equiv. of TsCl/Py/25°/3 h) of the known alcohol [6]; *entry* I: treatment of the 2-cyclopentene-1-acetic acid *(Aldrich)* with an excess of $(COCl)_2$/CH_2Cl_2/25°/18 h; *entry* J: treatment of the above acid chloride with an excess of EtOH/Py/25°/18 h. The reactions were carried out as described above for *entry* C unless otherwise specified; LiTMP = lithium 2,2,6,6-tetramethylpiperidide, LDA = lithium diisopropylamide, HMPT = hexamethylphosphoric triamide. The reaction mixtures obtained in the *entries* I, J, K and L were quenched with aq. 2N HCl.

[b]) The products **3** were obtained by crystallization, distillation and/or chromatography on SiO_2; yields in parentheses are based on recovered **1**, yields cited in the *entries* I, J, K and L are based on the corresponding electrophile.

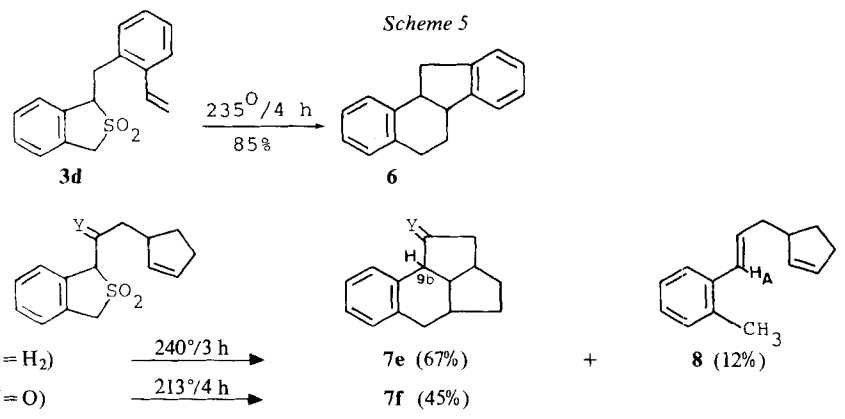
On heating the pentenyl-sulfone **3b** in diethylphthalate[4]) at 240° the extrusion of SO_2 was completed within 2.5 h to give after chromatography the desired adducts **4b**[3])[5]) in 85% yield *(Scheme 4)*. The minor formation of the styrene **5b**[3])[6]) (10% yield) indeed reflects the intermediacy of some (*Z*)-quinodimethane IV. Similar yields of **4c**[3])[5])[7]) and **5c**[3])[6]) were obtained on the analogous pyrolysis[4]) of the homologous hexenyl-sulfone **3c**.

Scheme 4



Tetracyclic systems may be readily formed when the bridge or the olefinic bond of I are part of a ring as illustrated by the efficient conversions[4]) **3d**→**6**[3])[5]) and **3e**→**7e**[3])[5]) *(Scheme 5)*; the latter reaction again furnished the styrene **8**[3])[6]) in low yield (12%). Thermolysis of the ketone **3f** in refluxing 1,2,4-trichlorobenzene gave the crystalline polyfused cyclopentanone **7f**[3])[8]) as a single stereoisomer; the corresponding isochromene VII was isolated from the reaction mixture in 41% yield.

Scheme 5



[4]) 10% solutions of the appropriate alkenyl sulfones in diethylphthalate were heated under an argon atmosphere.

[5]) The ^{13}C-NMR. spectrum agrees with the assigned structure and indicates the presence of two stereoisomers.

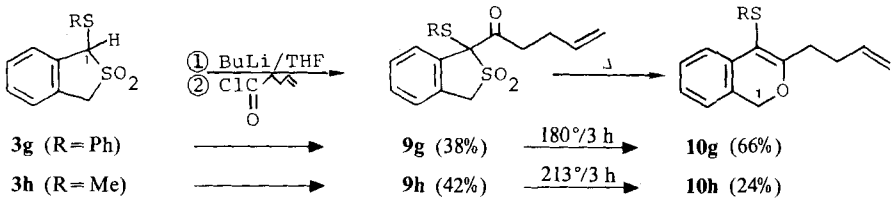
[6]) The styrenes **5** and **8** show in the ^{1}H-NMR. spectrum the *o*-CH_3 signal between $\delta = 2.34$ and 2.38, and the H_A-doublet ($J = 16$) between $\delta = 6.62$ and 6.66. Their UV. spectra: 209 (4.32 to 4.35), 250 (4.10 to 4.14) are typical for *o*-substituted styrenes [7].

[7]) Comparison of the ^{13}C-NMR. spectrum of the thermolysis product **4c** with those of independently prepared samples of *cis*- and *trans*-**4c** [8] showed the *trans*-isomer to predominate.

[8]) M.p. 104–107° (MeOH); IR. (CCl_4): 1745; the ^{13}C-NMR. spectrum confirms the stereoisomeric purity of **7f** which on the basis of the H–C(9b) signal in its ^{1}H-NMR. spectrum at $\delta = 3.61$ ($d \times d$, $J = 10$ and 1) was assigned the all-*cis*-configuration.

On the other hand, the ketothioethers **9**[3]), prepared from **3g** and **3h**[9]) on heating in refluxing *o*-dichlorobenzene or 1,2,4-trichlorobenzene, respectively, furnished exclusively the isochromenes **10**[3])[10]) *(Scheme 6)*, apparently *via* quinodimethane intermediates containing a *cis*-orientated carbonyl group (in analogy to the presumed cyclization VI → VII) *(Scheme 2)*[11]).

Scheme 6



Further work is in progress concerning the functionalization **1** → **3**, in particular involving aryl-substituted dihydroisothianaphthendioxides, and to apply this sequence to the synthesis of natural products. We were pleased to hear very recently that 3-desoxyestrone has been synthesized independently *via* an analogous approach from **1**[12]).

Financial support of this work by the *Swiss National Science Foundation, Sandoz Ltd.*, Basel, and *Givaudan SA*, Vernier, is gratefully acknowledged. We are indebted to Professor *K.P.C. Vollhardt* for providing spectra of the stereoisomeric octahydrophenanthrenes **4c** and to Dr. *B. Willhalm*, Firmenich SA, Genève, for kindly measuring the mass spectra.

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[9]) **3g** and **3h** were treated successively with BuLi (1.05 mol-equiv.) and allylacetyl chloride (1.3 mol-equiv.) in THF at −78°; the mixture was allowed to warm up to +25° and subjected to aqueous work-up.

[10]) **10g**. – UV.: 209 (4.42), 226 (4.25), 248 (4.13), 280 (3.99). – IR.: no C=O, 1590, 1475, 908, 755. – ^{1}H-NMR.: 2 H–C(1) at $\delta = 5.2$ (*s*). – **10h**. – UV.: 208 (4.21), 226 (4.06), 289 (3.93). – IR. (CCl_4): no C=O, 1598, 1480, 900. – ^{1}H-NMR.: 2 H–C(1) at $\delta = 5.0$ (*s*).

[11]) See also the thermolysis of 1-acylbenzocyclobutenes [9].

[12]) Reported by *K.C. Nicolaou* at the 6th International Symposium 'Synthesis in Organic Chemistry', Cambridge, 24–26 July 1979.