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o-Quinodimethanes from 3,6-Dihydrobenzo[b]-1,2-oxathiin-2-oxides

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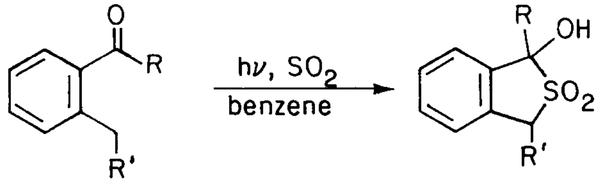
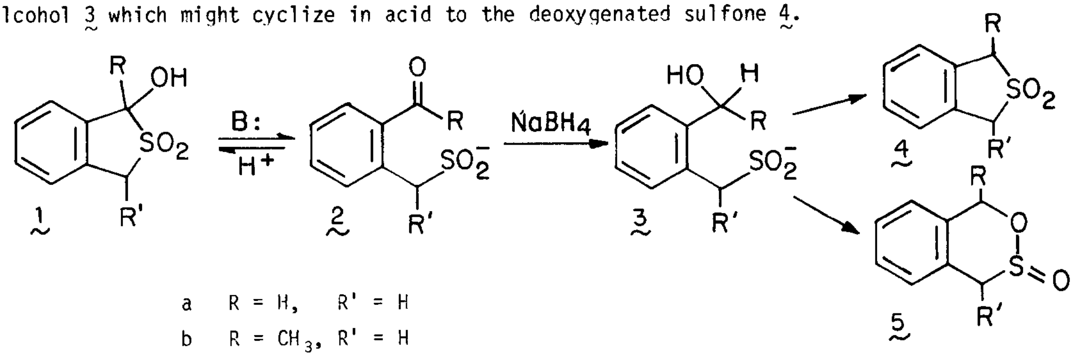
Summary: A two step synthesis of 3,6-dihydrobenzo[b]-1,2-oxathiin-2-oxide 5a from o-tolualdehyde via the photochemically produced 1-hydroxy-1,3-dihydrobenzo[b]thiophene-2,2-dioxide is described. Analogous syntheses of 3 and 6 substituted derivatives of the benzosultines 5 have also been carried out. The feasibility of using these benzosultines as o-quinodimethane precursors has been tested by thermalizing the phenyl sultine 5c in refluxing cyclohexane in the presence of dimethyl fumarate, dimethyl maleate and methyl crotonate to form cycloadducts, stereospecifically and in good yield. The stereochemistry of addition of maleate appears to be exclusively "exo" in conflict with earlier studies on Diels-Alder reactions of α-aryl-o-quinodimethanes.

In our search for synthetically useful o-quinodimethane precursors we recently discovered a photochemical synthesis of the 1-hydroxy-1,3-dihydrobenzo[b]thiophene-2,2-dioxides 1 (1).



	R	R'
1a	H	H
1b	CH_3	H
1c	H	ϕ

While investigating the general chemistry of 1 we attempted a sodium borohydride reduction. Under basic conditions 1 is known to open to the sulfinate anion 2 which can be recyclized to the sulfone with dilute acid (1). It was reasoned that treatment with $NaBH_4$ would lead to the alcohol 3 which might cyclize in acid to the deoxygenated sulfone 4.



a R = H, R' = H
b R = CH_3, R' = H
c R = H, R' = ϕ

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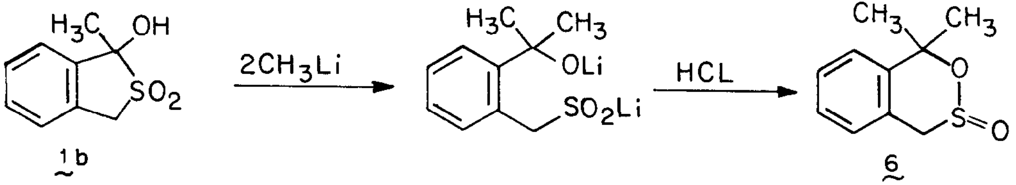
However, strong acidification of the reduction product 3 gave almost exclusively 5. In typical experiments 70 mg of $NaBH_4$ were added to 100 mg of 1a, b or c in 5 ml of methanol at 0°C with stirring. After ½ hour the mixture was warmed briefly to 50°C (3 min.) and then evaporated to dryness. Concentrated hydrochloric acid (5 ml) was added and the mixture stirred for 5 min. at 50°C. Dilution with water and extraction with CH_2Cl_2 gave the sultines 5a, b and c in crude yields of 70, 55 and 79% respectively. 5b ($R=CH_3$, R'=H) was a 50:50 mixture of diasteriomers with the methyl group cis and trans to the sulfinyl oxygen. Although 5c (R=H, R'=ϕ) could also exist as two isomers, only a single isomer was isolated (2,3).

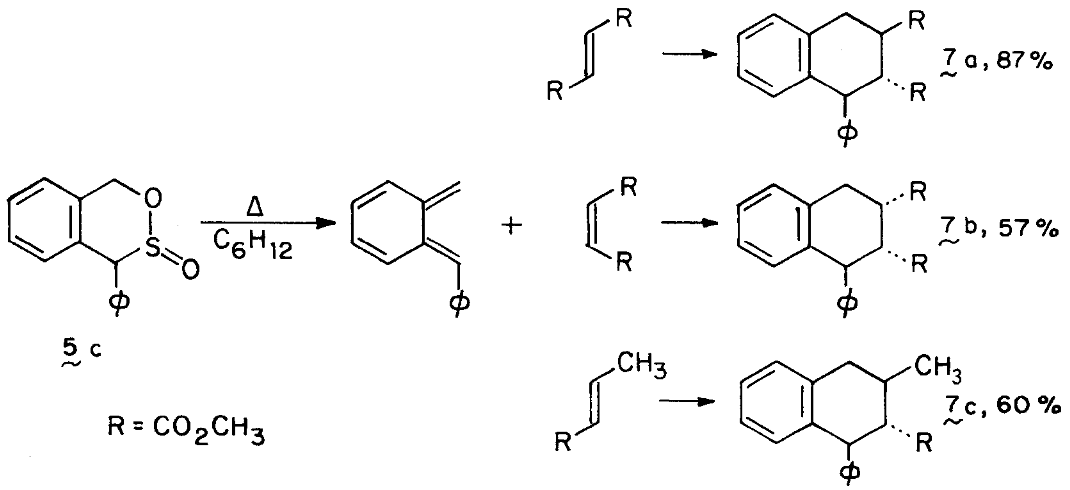
Only very small amounts of the sulfones 4 could be observed in the nuclear magnetic resonance (nmr) spectra of the crude reaction products. Presumably the benzylic cation derived from 3 traps the ambident sulfinate anion via oxygen in contrast to the acid catalyzed closure of 2 to 1 which closes to give only the sulfone (4).

We have also reacted 1b with methyl lithium followed by acid treatment to yield the dimethyl sultine 6 in 80% yield (5).



Disappointingly, the analogous reaction of 1a with phenylmagnesium bromide in ether followed by evaporation and acidification gave only a complex mixture of products.

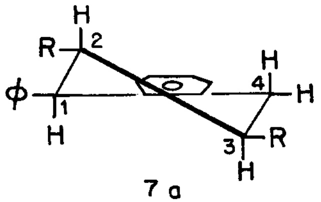
Based on earlier work (5) benzo[b] sultines such as 5 yield o-quinodimethanes at relatively low temperatures. Thus, 5c was thermolyzed (80°C, refluxing cyclohexane) in the presence of dimethyl fumarate, dimethyl maleate and methyl crotonate to form the adducts 7a, b and c (6), respectively.



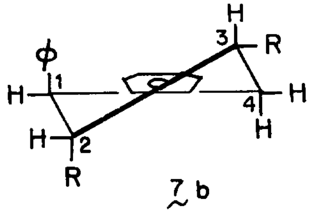
The configurations of the adducts 7 were assigned on the basis of 300 MHz nmr spectra ($CDCl_3$); the key chemical shifts and coupling constants are given in the Table.

TABLE: Chemical shifts and coupling constants for 7a, b and c

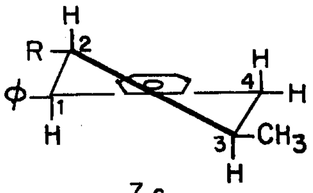
	H_1	H_2	H_3	H_{4e}	H_{4a}	H_8	$J_{1,2}$	$J_{2,3}$	$J_{3,4a}$	$J_{3,4e}$	$J_{4e,4a}$
7a	4.25d		3.1 -	3.3 m		6.78d	11.1	-	-	-	-
7b	4.83d	3.48d	2.97m	3.19dd	3.34dd	7.0	3.0	3.6	11.0	6.2	17.5
7c	4.36d	2.62t	2.27m	2.97dd	2.72dd	6.75d	10.5	10.5	12.0	5.0	16.0



7a



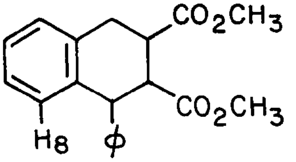
7b



7c

R = CO_2CH_3

While the structures and predominant conformations of 7a and 7c are in no doubt, the spectrum of 7b would appear, at first glance, to be also consistent with the all cis configuration 8.



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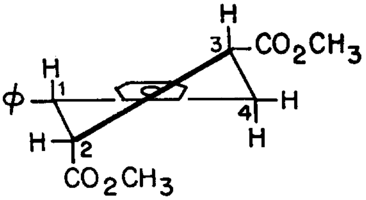
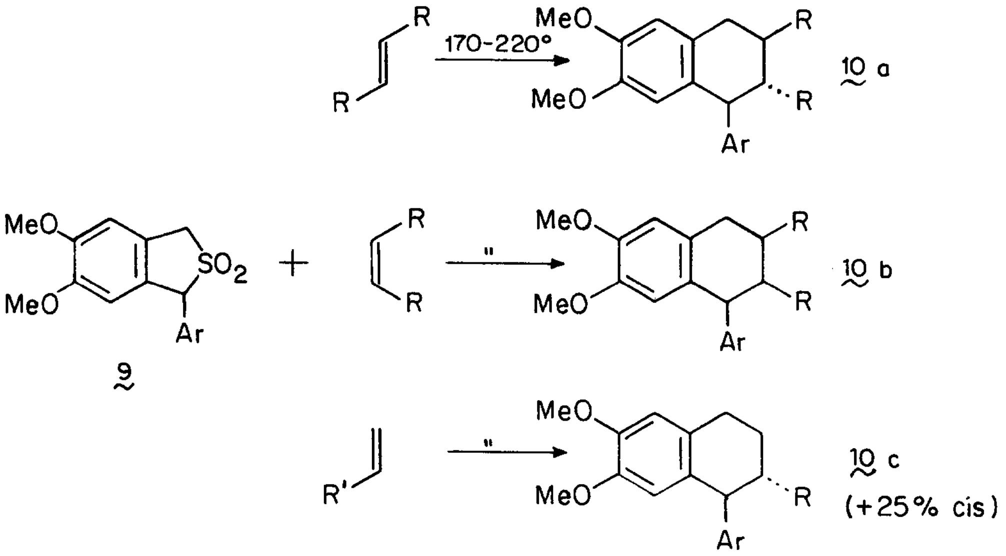


8

Both structures 7b and 8 would have a small (gauche) coupling constant $J_{1,2}$. However, we have noticed a very strong shielding effect on H_8 whenever the phenyl group is equatorial as in 7a and 7b (δ = 6.7-6.8). This shielding effect is not observed in 7b (8) allowing us to eliminate the possibility of structure 8. We also note that other α-arylbenzocyclohexenes can exist in conformations having the aryl group axial, such as, for example, in epipicropodophyllic acid (7). A final confirmation of the structure of 7b by other spectroscopic techniques is in progress.

The current results on the cycloaddition reactions of α-phenyl-o-quinodimethane differ considerably from the results and predictions of Mann and coworkers (8) who studied the pyrolysis (170°-210°)/cycloaddition reactions of the sulfone 9 with fumarate, maleate and acrylate. Especially notable is the configuration of 10b assigned as the all cis configuration and the formation of substantial portion of the cis isomer of 10c. It was claimed that at a slightly lower temperature the yield of cis 10c was increased and that the trans 10c was actually the thermodynamically preferred product resulting from a retro Diels-Alder reaction of the cis adduct. Since our reactions are carried out at 80°C, no such equilibrium is possible and the phenyl is trans to the carboxymethyl group in all adducts. A reinvestigation of the earlier work on 9 or on the corresponding sulfine would appear warrented.



R = CO_2Me
Ar = 3,4-dimethoxyphenyl

A significant advantage of the sultines 5 vs the corresponding sulfones is that thermolysis occurs at convenient temperatures, 80° vs 170°-220°. The ready availability of the benzfused sultines makes them attractive potential intermediates in the synthesis of a number of natural products (9). We are investigating such possibilities.

Acknowledgements

We would like to acknowledge the financial assistance of the Natural Sciences and Engineering Research Council of Canada.

References and Notes

1. J.L. Charlton and T. Durst, Tetrahedron Letters (1984) in press.
2. The nmr spectrum of 5a was identical with that produced by an alternate route (5). 5b: Isomer 1, ^1H NMR ($CDCl_3$) δ 1.82 (d, 3H, J = 6.6 Hz), 3.51 (d, 1H, J = 15.2), 4.57 (d, 1H, J = 15.2), 5.40 (q, 1H, J= 6.6), 7.30 and 7.43 (m, 4H); IR (CH_2Cl_2) 1110, 1140 cm^{-1}. Isomer 2, ^1H NMR ($CDCl_3$) δ 1.85 (d, 3H, J = 6.6 Hz), 3.82 (d, 1H, J = 14.2), 4.01 (d, 1H, J = 14.2 5.07 (q, 1H, J = 6.6), 7.3-7.5 (m, 4H); IR (CH_2Cl_2) 1110, 1140 cm^{-1}. 5c: ^1H NMR ($CDCl_3$) δ 4.71 (s), 5.06 (d, 1H, J = 14.4), 5.43 (d, 1H, J = 14.4), 7.06 (d, 1H, J = 6.0) 7.2-7.5 (m, 9H); IR (CH_2Cl_2) 1130 cm^{-1}.
3. All new compounds described herein gave acceptable elemental analyses.
4. Typically sulfinate anions alkylate preferentially on oxygen when exposed to very reactive, hard alkylating agents. J.S. Meek and J.S. Fowler, J. Org. Chem., 33, 3422 (1968).
5. F. Jung, M. Molin, R. Van den Elzen and T. Durst, J. Am. Chem. Soc., 96, 935 (1974).
6. NMR investigation of the crude products of these reactions indicated less than 10% of alternate isomers. 7b and 7c were accompanied by 25% and 15% respectively of the 1-phenyl-1,3-dihydrobenzo[b]thiophene-2,2-dioxide (5).
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W. Oppolzer, Synthesis 1978, 793.

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