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# On the Synthesis of 2*H*-Benzo[*b*]thiete 1,1-Dioxide

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The synthesis of 2*H*-benzo[*b*]thiete 1,1-dioxide, first described by Dittmer and Davis, has been improved. An intermediate, *trans*-2,5-dibromo-7-thiabicyclo[4.2.0]-1(6)-octene 7,7-dioxide, has been obtained in crystalline form, and from it the title compound has been prepared in 15 % yield with silver oxide in boiling xylene. A new by-product in the cycloaddition of sulfene to 1-(*N*-pyrrolidino)-cyclohexene has been identified as 2-methanesulfonyl 1-(*N*-pyrrolidino)-7-thiabicyclo[4.2.0]octane 7,7-dioxide using $^1$H NMR, $^{13}$C NMR, and mass spectroscopy.

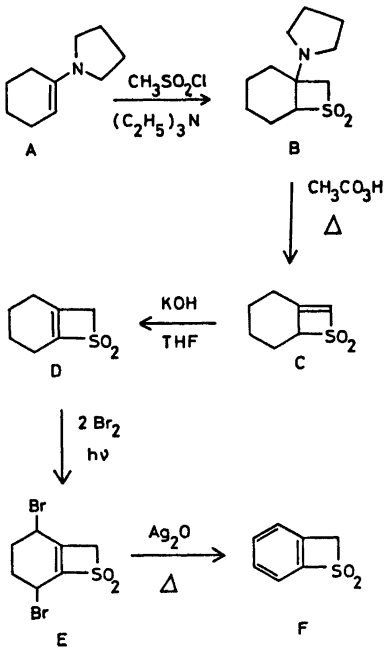


*Fig. 1.* Synthetic route to 2*H*-benzo[*b*]thiete 1,1-dioxide.

In a recent electrochemical study of some cyclic sulfones,[1] the four-membered ring compound 2*H*-benzo[*b*]thiete 1,1-dioxide was included. It was first synthesized by Dittmer and Davis [2] as shown in Fig. 1. The present paper describes a reinvestigation of the synthesis. The original route has been followed, but some modifications have made it possible to increase the yields in some of the steps and at the same time make them technically easier. Thus, the entire preparation can be performed without chromatographic separation.

A different synthetic route, the key step of which is a Diels-Alder reaction between 3-bromothiete 1,1-dioxide and butadiene, has recently been described by Nelsen and Dittmer.[3] The overall yield, starting from thietane, is 10 – 20 %.

In our work, the starting material, enamine A (for brevity, the designations A, B *etc.* in Fig. 1 will be used) was prepared from cyclohexanone and pyrrolidine.[4] The cycloaddition of A to sulfene, generated *in situ*, was carried out according to Dittmer and Davis.[5] In addition to B, a minor amount of another, less soluble product was obtained, which was characterized as 2-methanesulfonyl 1-(*N*-pyrrolidino)-7-thiabicyclo[4.2.0]octane 7,7-dioxide. A possible route to this by-product, G, is shown in Fig. 2.

Borowitz has reported [6] that the four-membered ring adduct of sulfene to 1-*N*-morpholinocyclohexene can be thermally rearranged to a 2:1 mixture of 6-methanesulfonyl and 2-methanesulfonyl 1-*N*-morpholinocyclohexene. Although the temperature required for this, 128 – 137 °C, is much higher than the one

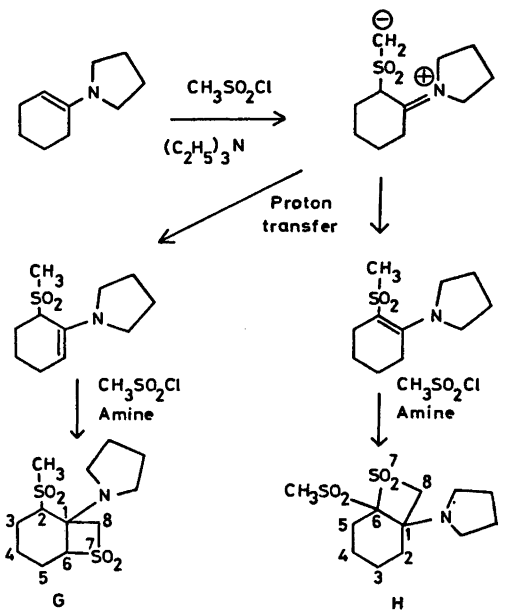


*Fig. 2.* Isomeric 2+1 adducts of sulfene to 1-(*N*-pyrrolidino)-cyclohexene.

in the present synthesis, the finding suggests that methanesulfonyl enamines can be formed as minor products even at low temperature, perhaps *via* proton transfer to or within a zwitterionic intermediate. Addition of a second molecule of sulfene to the 6-methanesulfonyl isomer would yield the by-product observed in this work. The 2-methanesulfonyl isomer is expected to be less reactive both for steric and electronic reasons, and structure G rather than H (see Fig. 2) is therefore preferred.

An unambigous distinction between G and H was provided by $^{13}C$ NMR spectroscopy. The spectrum of the by-product was kindly recorded and interpreted by Prof. Dr. W. v. Philipsborn at the Organisch-Chemisches Institut der Universität Zürich, using a Varian XL-100 instrument. The chemical shift and multiplicity data are given in the Experimental part. In the off-resonance decoupled spectrum, there is one singlet for carbon atom 1 but none for carbon atom 6. There are three resonances at rather high frequency, which must be assigned to three carbon atoms α to the sulfonyl groups; atoms 2, 6, and 8. None of these is a quaternary atom. On the other hand, the low-frequency part of the spectrum exhibits three but not four $CH_2$ resonances for the six-membered ring. The above constitutes three independent pieces of evidence against structure H.

In the Cope elimination step, B→C, it was found to be advantageous to omit the neutralization with sodium carbonate [5] after the oxidation with peracetic acid. In runs with neutralization, a brown, tarry material was formed, rendering the work-up difficult. C, an α,β-unsaturated sulfone, is a good Michael acceptor, and conditions favouring nucleophilic attack should be avoided.

The rearrangement of the *exo* sulfone C to the *endo* isomer D was performed with powdered potassium hydroxide in tetrahydrofuran as described by Dittmer and Davis.[3] In trials with solid lithium hydroxide in tetrahydrofuran and 1,8-bis(*N*,*N*-dimethylamino)naphthalene [7] in benzene, no trace of rearrangement was seen.

The dibromination of D was first made with *N*-bromosuccinimide and a catalytic amount of benzoyl peroxide but, as also found by Dittmer and Davis,[3] the reaction required at least two days at 60 °C. If, instead, the allylic bromination is carried out photochemically using elemental bromine, the time required for reaction was 7 h at room temperature.

The crude dibrominated product is an almost colourless oil. It was fortuitously discovered that half of it can be obtained in crystalline form from a benzene-ether solution. The solid contains benzene of crystallization, which is lost upon drying. Thin-layer chromatography of the noncrystalline part of the oil showed it to contain at least two components, since two spots of roughly equal size were obtained. The slower moving one of these matched the single spot given by the crystalline material. It is tempting to assume that the oil is a mixture of *cis* and *trans* isomers, but, as has been kindly pointed out by Dr. H.-D. Becker at this Department, it could contain structurally different isomers if allylic rearrangement takes place during the bromination.

The crystalline material was first thought to be the *cis* isomer for the following reasons. Allylic bromination of a cyclohexene system should take place (pseudo)axially to allow maximum resonance stabilization of the intermediate radical. As illustrated in Fig. 3, the intermediate monobrominated compound would

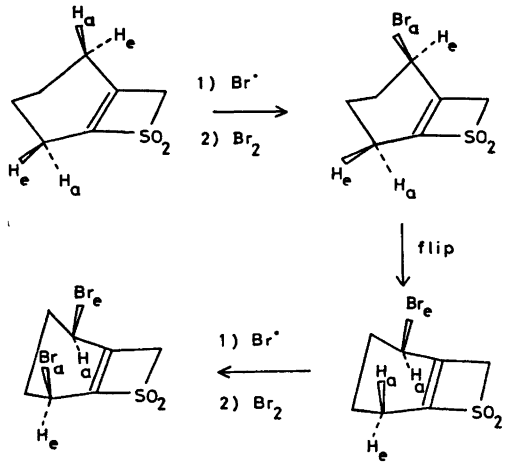


*Fig. 3.* Formation of *cis* isomer of compound E.

then flip to bring the bromine atom into a (pseudo) equatorial position. If the second bromine atom were also introduced (pseudo)-axially, the *cis* compound would result. Another argument for the *cis* assignment is that in the subsequent elimination with silver oxide, a higher yield of the final product F is obtained from the crystalline material than from the isomer mixture. In accordance with well-known rules for eliminations of this kind, a trans-diaxial arrangement of a bromine and a hydrogen atom should favour the reaction, and this arrangement is present in the *cis* isomer.

In collaboration with the Department of Inorganic Chemistry at the Chalmers University of Technology and University of Göteborg, a single-crystal X-ray investigation of the solid isomer was undertaken.[8] The configuration was, in fact, shown to be *trans*. It must therefore be concluded that the arguments presented above have no predictive power. The difference between a pseudoaxial and a pseudoequatorial substituent apparently is not large enough in this system to decide the steric course of the photobromination.

The 60 MHz $^1$H NMR spectrum of the isomer mixture was found to be quite similar to that of the pure, crystalline isomer, and since an attempted preparative layer chromatographic separation failed, further attempts at characterizing the minor component (*cis*?) of the oil were abandoned.

The final conversion E→F gave only a 3 % yield when carried out as originally described.[2] After much experimentation, it was found that silver oxide in refluxing xylene brings about the desired transformation in a yield of 15 % starting with the pure crystalline isomer of E.

The oil containing two isomers of E also yields the product F upon treatment with silver oxide, but the purification in this case is much more difficult since the reaction mixture does not crystallize, and the yield is lower, around 5 %.

A reagent which caused complete reaction of E within a few minutes at room temperature was prepared by dissolving silver phosphate in polyphosphoric acid. However, no trace of F was obtained. Apparently, silver oxide furnishes the best balance between nucleophilic/basic and eletrophilic/acidic conditions among the reagents yet tried.

## EXPERIMENTAL

*1-(N-pyrrolidino)-cyclohexene* (A). This compound was prepared in 97.5 % yield on a 3 mol scale using the standard method.[4]

*1-(N-Pyrrolidino)-7-thiabicyclo[4.2.0]octane 7,7-dioxide* (B) and its *2-methanesulfonyl derivative* (G). Of the above enamine, 442 g (2.93 mol) and 510 ml (3.7 mol) of triethylamine, purified by distillation from phthalic anhydride,[9] were dissolved in 1.5 l of absolute ether. Methanesulfonyl chloride, 375 g (3.27 mol) was added dropwise with stirring and cooling in a Dry Ice-acetone bath to keep the temperature between −10 °C and 0 °C. The reaction mixture was left for 8 h at room temperature and filtered. The triethylamine hydrochloride was washed with ether and the combined filtrate and washings evaporated *in vacuo* below 40 °C. The remainder was dissolved in 500 g of ice and 400 ml of conc. hydrochloric acid. The solution was washed with ether which removed some cyclohexanone resulting from hydrolysis of unreacted enamine, and an excess of aqueous ammonia was added. Cooling to 5 °C gave a semi-crystalline mass. The supernatant water solution was decanted and the crystals were washed with ice-cold water and dissolved in 1 l of ether and 500 ml of benzene. An insoluble rest was filtered off and investigated separately; see below. The clear filtrate was washed with water and evaporated below 40 °C to yield 570 g of product B (85 % yield). Upon being stored at 5 °C, the material slowly crystallized.

The ether-insoluble by-product was recrystallized from a mixture of equal volumes of chloroform and ethanol to yield 18.2 g of colourless crystals, m.p. 195−197 °C with

decomposition; 60 MHz $^1$H NMR ($CDCl_3$) $\delta$ 1.3–2.6 (multiplet, 10 H), 2.8–3.1 (multiplet, 4 H), 3.0 (singlet, 3 H), 3.6–3.9 (multiplet, 1 H), 4.4–4.8 (multiplet, 1 H), 4.5 (singlet, 2 H). The 25.2 MHz $^{13}$C NMR spectrum ($CDCl_3$), recorded using proton noise decoupling, as well as off-resonance decoupling with irradiation at the TMS signal to determine multiplicities, had the following peaks: ($\delta$-value in ppm rel. to TMS, rel. signal height, multiplicity using s for singlet, d for doublet, t for triplet, and q for quartet), 75.6, 94, d, C(2) or C(6); 72.0, 70, t, C(8); 69.0, 74, d, C(6) or C(2); 50.5, 64, s, C(1); 50.0, 168, t+t, 2 $NCH_2$; 40.3, 56, q, $CH_3$; 23.8, 178, t+t+t; 21.4, 56, t; 20.5, 56, t. The resonance at 23.8 ppm could be resolved into a *two*-carbon (t+t) and a *one*-carbon (t) signal using $Pr(fod)_3$ as paramagnetic shift reagent. Thus the 12 carbon atoms are definitely accounted for. The two-carbon (t+t) signal (23.8 ppm) is assigned to the $\beta$ carbons of the pyrrolidine ring whereas the residual resonances at 23.8, 21.4, and 20.5 ppm originate from the three $CH_2$ groups in the six-membered ring.

The mass spectrum, determined on an LKB 9000 instrument using 70 eV electrons for ionization, had the following peaks: *m/e* 307 (parent ion, 16.1 %), 228 ($P-CH_3SO_2$, 32.3 %), 201 (18.2 %), 200 (11.9 %), 164 ($P-CH_3SO_2-SO_2$, 100 %), 150 ($P-CH_3SO_2-CH_2SO_2$, 51.6 %), 149 (37.1 %), 136 (35.5 %), 122 (38.7 %), 110 (19.4 %), 96 (22.6 %), 79 (17.7 %), 77 (21.0 %).

*7-Thiabicyclo[4.2.0]-1(8)-octene 7,7-dioxide* (C). The oxidation of compound B to the corresponding amine oxide was performed according to Ref. 5. Peracetic acid had been prepared the previous day by mixing 2 volumes of glacial acetic acid, 1 volume of 50 % hydrogen peroxide, and 0.03 volume of conc. sulfuric acid. Just before use, enough sodium acetate was added to neutralize the sulfuric acid present.

Contrary to the directions in Ref. 5, the reaction mixture was evaporated *in vacuo* at 60 °C without prior treatment with sodium carbonate. The remaining oil was dissolved in the minimum amount of water and extracted three times with dichloromethane. The combined organic phases were washed with 10 % hydrochloric acid followed by saturated sodium chloride solution and dried over anhydrous magnesium sulfate. Evaporation and trituration with ether caused the *exo* sulfone C to crystallize. The yield in this step varied between 75 and 90 % (Ref. 5; 57 %), 1 mol batches being run.

*7-Thiabicyclo[4.2.0]-1(6)-octene 7,7-dioxide* (D). The rearrangement to *endo* sulfone D was performed with potassium hydroxide in tetrahydrofuran according to Ref. 2. It was found impossible to reproduce the 90 % yield reported. In this work, 70 % was obtained.

*2,5-Dibromo-7-thiabicyclo[4.2.0]-1(6)-octene 7,7-dioxide* (E). Instead of using *N*-bromosuccinimide,[2] a photochemical bromination was performed. A solution of 15.8 g (0.1 mol) of *endo* sulfone D and 32.0 g (0.2 mol) of bromine in 500 ml of ethanol-free chloroform was irradiated in a Rayonet photochemical reactor, using 350 nm lamps. A quartz vessel equipped with an internal cooling tube and a nitrogen bubbler was used, although glass most probably works equally well. The reaction required 7 h and could be easily followed by the evolution of hydrogen bromide. At the end of this period, the bromine colour had completely disappeared. Evaporation of the solution *in vacuo* gave 34.0 g of an almost colourless oil (theoretical yield, based on dibromination). This was dissolved in the minimum quantity of a boiling ether–benzene mixture, 2:1 by volume. Cooling to 5 °C gave large, transparent crystals which were collected and washed. The yield was 17.6 g (42 %), 60 MHz $^1$NMR ($CDCl_3$) $\delta$ 2.0–2.8 (multiplet, 4 H), 4.45–4.65 (multiplet, 2 H), 4.8–5.0 (multiplet, 2 H), 7.35 (singlet, 6 H). The crystals have been shown by X-ray diffraction [8] to be the *trans* isomer of E, and also to contain benzene of crystallization in a molar ratio 1:1 (compare the NMR data). Upon exposure to the atmosphere for a few days or more rapidly *in vacuo*, this benzene disappeared with efflorescence, resulting in a 20 % weight loss. The melting point of the dry material was 107–108 °C. Upon TLC analysis of the mother liquor (silica gel/dichloromethane), two components having $R_F$ values 0.27 and 0.38 were found. The crystalline material gave one spot, $R_F$ 0.27.

*2H-Benzo[b]thiete 1,1-dioxide* (F). Of the dried, solid isomer E, 7.9 g (25 mmol) was refluxed for 10 h under stirring with 20 g (86 mmol) of silver oxide and 50 ml of xylene. Filtration and evaporation *in vacuo* gave 2.0 g of a yellow oil. Addition of a few ml of ether, cooling and scratching gave crystals which were collected and recrystallized from 50 ml of ether. Colourless needles were obtained, 0.75 g, m.p. 127–127.5 °C, lit.[2] 126–128 °C. An impurity, revealed in the $^1$H NMR spectrum, was left behind by sublimation *in vacuo* (80 °C, 27 Pa). The recovery was 0.6 g (15 %), m.p. 127–127.5 °C, 60 MHz $^1$H NMR ($CDCl_3$), $\delta$ 5.1 (singlet, 2 H), 7.55 (singlet, 4 H) in agreement with the literature data.[2]

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