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Base-Induced Rearrangements of Mesityl Thienyl Sulfones[1]

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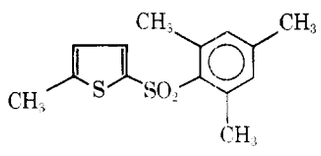
Two mesityl thienyl sulfones (5-mesitylsulfonyl-2-methylthiophene and 2-mesitylsulfonylthiophene) undergo the Truce–Smiles rearrangement. However, the thienyl unit (in contrast to the previously studied naphthyl and substituted phenyl groups) migrates with a change in orientation regardless of the base/solvent system used. The chemistry of 2-mesitylsulfonylthiophene is complicated by the acidity of the open α position, with 2 equiv of base being required for rearrangement. (The monometalated species, on the other hand, slowly decomposes to give mesitylenesulfinic acid as the only isolable product.) A modified Michael addition–β-elimination mechanism has been proposed to explain these results.

Aryl sulfones containing an ortho methyl group rearrange to *o*-benzylbenzenesulfinic acids when treated with *n*-butyllithium in ether[2] or potassium *tert*-butoxide in Me_2SO.[3] The three isomeric mesityl tolyl sulfones all give sulfinic acids with retained tolyl orientation regardless of which of these two base/solvent systems is used. In contrast to this, mesityl α-naphthyl sulfone can be caused to rearrange via two different pathways. In *n*-butyllithium/ether, rearrangement proceeds via direct displacement and retained naphthyl orientation. However, in potassium *tert*-butoxide/Me_2SO an addition–β-elimination sequence occurs, resulting in 2-(2′-naphthylmethyl)-4,6-dimethylbenzenesulfinic acid.[4]

Results and Discussion

It has now been found that treatment of 5-mesitylsulfonyl-2-methylthiophene (**1**) with either *n*-butyllithium/ether or potassium *tert*-butoxide/Me_2SO yields sulfinic acid **2** via an addition–elimination sequence.



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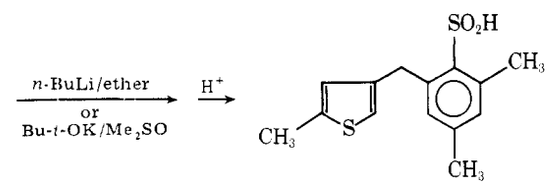
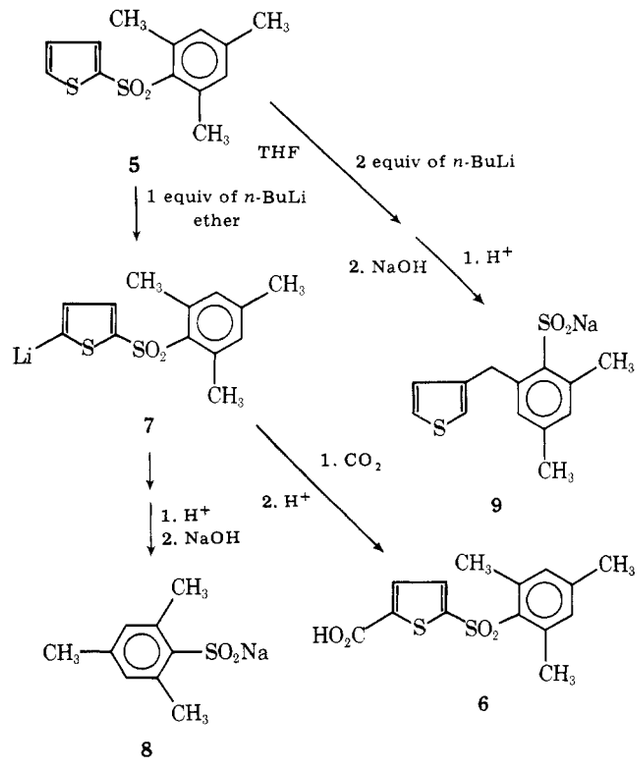


2

That the same sulfinic acid is produced in both base/solvent systems was shown by the identity of IR and NMR spectra as well as the melting point and mixture melting point of their 2-hydroxy-3,5-dichlorobenzyl sulfone derivative. The structure proposed for **2** is supported by the following series of reactions. Sulfinic acid **2** was treated with Raney nickel to reduce the thiophene ring to a saturated hydrocarbon unit, and to remove the sulfinate moiety. The two possible hydrocarbon products, 1-(3,5-dimethylphenyl)hexane (**3**) and 1-(3,5-dimethylphenyl)-2-methylpentane (**4**), were alternatively synthesized from 3,5-dimethylbenzyl bromide by treatment with the appropriate organometallic compounds. The Raney nickel reduction product had physical and spectral properties which matched those of hydrocarbon **4**. The spectral properties of **3** did not correlate, thus confirming **2** as the correct structure for the sulfinic acid product.

2-Mesitylsulfonylthiophene (**5**) has been found to rearrange

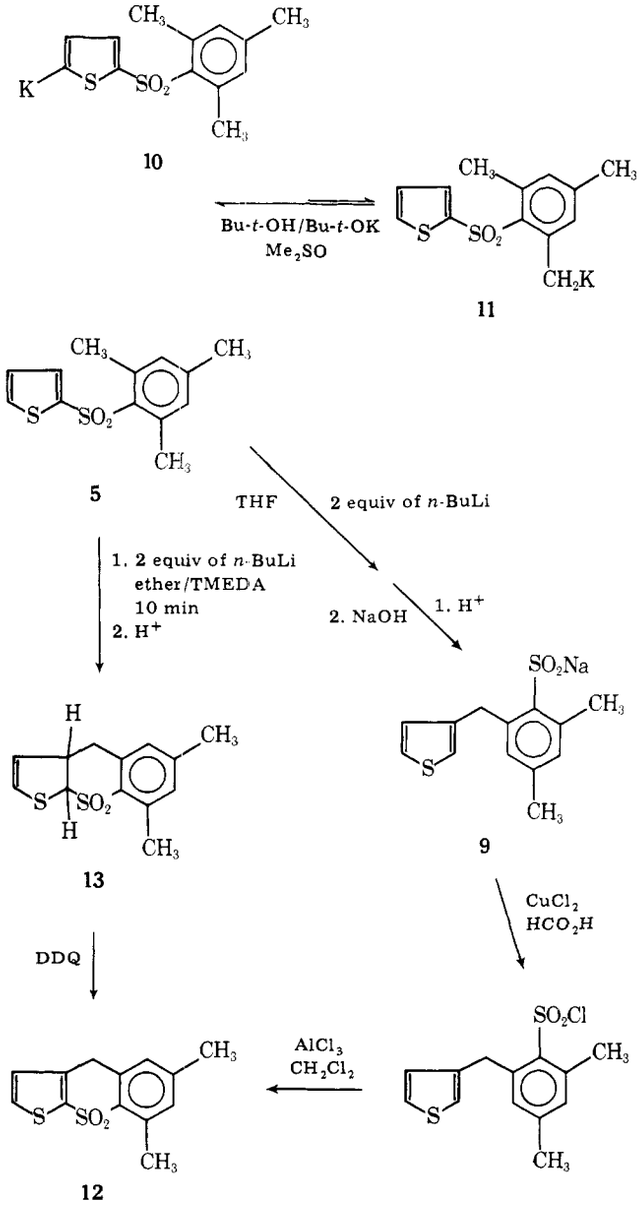


giving similar results. The chemistry of this compound, however, is more complex due to the acidity of the open α-position of the thiophene ring. A metalation study in which **5** was converted to 5-carboxy-2-mesitylsulfonylthiophene (**6**) demonstrated that this is the most acidic proton in the molecule. The lithium derivative **7** is unstable and slowly decomposes at room temperature, giving (after workup) sodium mesitylenesulfinate (**8**) as the only isolable product.

The mechanism of this cleavage reaction has not been determined, although it is possible that **7** unravels to give ethynyl sulfide (which is unstable[5]) in addition to **8**. Analogous ring-opening reactions of metalated thiophenes have previously been reported.[6]

With at least 2 equiv of *n*-butyllithium in THF, **5** rearranges to give sodium sulfinate **9**. The second equivalent of base apparently metalates on a mesityl *o*-methyl, and the dimetalated species then rearranges. Intermediate amounts of *n*-butyllithium in ether (between 1 and 2 equiv) give a mixture of **8** and **9**.

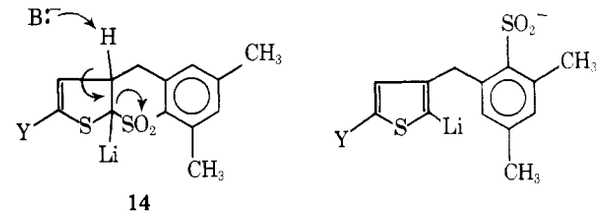
Sulfone **5** also gives sulfinic acid **9** (contaminated with a small amount of **8**) on treatment with potassium *tert*-butoxide/Me_2SO (1 or 2 equiv). In this case, rearrangement with 1 equiv of base can be explained by *tert*-butyl alcohol and potassium *tert*-butoxide aiding in a proton transfer between **10** and **11**.



The structure of sulfinic acid **9** was substantiated by the following series of reactions. The sodium sulfinate (**9**) from the *n*-butyllithium-induced rearrangement was converted to the sulfonyl chloride by reaction with cupric chloride in formic acid solution. Cyclization in a Friedel–Crafts reaction gave 4*H*-thieno[2,3-*b*][1]-6,8-dimethylbenzothiopyran 9,9-dioxide (**12**). This compound was found to be identical by IR, NMR, melting point, and mixture melting point to an authentic sample synthesized by aromatizing Michael adduct **13** with DDQ.

The reason for the occurrence of an addition–β-elimination sequence with the naphthyl mesityl sulfones in potassium *tert*-butoxide/Me_2SO is thought to be the availability of a proton source[4] (*tert*-butyl alcohol). The alcohol apparently protonates the intermediate cyclized carbanion, giving the full Michael adduct. The adduct then can undergo a β-elimination to give a sulfinic acid product with changed naphthyl orientation.

The mesitylsulfonyl-substituted thiophenes (**1** and **5**) are the first example of a system which will undergo rearrangement in aprotic media with a change in aryl orientation. One possible mechanism that would explain these results would involve a β-elimination from the cyclized intermediate **14**, rather than from the full Michael adduct. Because the reaction would be autocatalytic (**14** functioning as a proton source),



14

Y = Li, CH_3

only a small percentage of the product would have to be produced via this modified mechanism. The vast majority could come from a full Michael adduct. A somewhat related ring-opening β-elimination from a dimetalated heterocyclic has been suggested to explain the products arising from 2,3-dilithiobenzo[*b*]selenophene.[7]

Experimental Section

All reactions involving *n*-butyllithium and potassium *tert*-butoxide were performed in a nitrogen atmosphere. The NMR spectra were recorded on a Varian A-60A instrument with Me_4Si used as a standard. The IR spectra were recorded on a Beckman IR-33. All melting and boiling points are uncorrected. The microanalyses were performed by Dr. C. S. Yeh and C. M. Lam of this department.

5-Mesitylsulfonyl-2-methylthiophene (1). 2-Methylthiophene was sulfonated by means of dioxane–sulfotrioxide according to the procedure of Truce and Amos[8] yielding sodium 5-methyl-2-thiophenesulfonate which was converted to the sulfonyl chloride by treatment with phosphorus pentachloride.

The sulfone was then formed by treating a well-stirred solution of 51 g (0.26 mol) of 2-methyl-5-thiophenesulfonyl chloride and 36 g (0.30 mol) of mesitylene dissolved in 200 mL of anhydrous methylene chloride with 34.5 g (0.26 mol) of aluminum chloride at −15 °C. When the addition was completed, the reaction was stirred 25 min longer at −15 °C, and hydrolyzed by pouring onto a mixture of crushed ice and 50% HCl. The layers were separated and the water layer was extracted with methylene chloride. The organic extracts were combined, dried over anhydrous $CaCl_2$, filtered, and evaporated yielding a dark solid which was recrystallized from 95% ethanol, decolorized with charcoal, and filtered, giving 36.8 g (50%) of sulfone **1**. A second recrystallization yielded pure sulfone melting at 93–94.5 °C: NMR ($CDCl_3$) δ 2.25 (s, 3), 2.44 (s, 3), 2.65 (s, 6), 6.67 (d, 1, J = 3.5 Hz), 6.92 (s, 2), 7.42 ppm (d, 1, J = 3.5 Hz).

Anal. Calcd for $C_{14}H_{16}S_2O_2$: C, 60.0; H, 5.7; S, 22.8. Found: C, 60.1; H, 5.89; S, 22.6.

2-Hydroxy-3,5-dichlorobenzyl Chloride. This preparation was adapted from the method of Buehler et al.[9] 2,4-Dichlorophenol (20 g, 0.123 mol) was dissolved in a mixture of 300 mL of concentrated

HCl and 100 mL of ethanol. The solution was warmed to 50 °C, and over a period of 30 min 20 mL of a 40% formaldehyde solution was added. HCl gas was then bubbled through the solution for 24 h. The mixture was then cooled, and the oil which had precipitated was taken up in benzene. This solution was washed with water, dried ($MgSO_4$), and stripped of solvent in vacuo. The product was purified by recrystallization from petroleum ether (90–100 °C): yield 14.0 g (54%); mp 82.5–84 °C (lit.[9] mp 81–84 °C).

General Procedure for the Preparation of 2-Hydroxy-3,5-dichlorobenzyl Sulfone Derivatives. This method was adapted from the work of Beachem et al.[10] A small amount (about 0.5 g) of the sodium salt of the sulfinic acid was dissolved in 5 to 10 mL of absolute methanol. An equimolar amount of 2-hydroxy-3,5-dichlorobenzyl chloride was dissolved in a minimal amount of absolute methanol, and the two solutions were combined. The mixture was allowed to react at room temperature in a covered flask for up to 1 day. Crystals of the sulfone often started to precipitate almost immediately and were collected by filtration when the reaction seemed complete. Generally, one recrystallization from ethanol was sufficient to obtain the derivative analytically pure.

Rearrangement of 5-Mesitylsulfonyl-2-methylthiophene. (A) *n*-Butyllithium in Ether. To 3.0 g (0.011 mol) of 5-mesitylsulfonyl-2-methylthiophene in 120 mL of anhydrous ether[11] was added dropwise a solution of 14 mL (0.018 mol) of *n*-butyllithium diluted with 30 mL of ether. The reaction mixture was stirred for 24 h at reflux in a nitrogen atmosphere, after which it was poured into ice water. The layers were separated, and the aqueous layer was extracted with ether. The aqueous layer was then cooled in an ice bath and acidified with concentrated HCl. The resulting acidic mixture was extracted with ether, and the ether extract was treated with 0.5 N aqueous NaOH. The basic solution was cooled and acidified with concentrated HCl and extracted with ether. The resulting ethereal solution was dried and evaporated, giving 2.1 g (70%) of a light-yellow oil identified as sulfinic acid **2**. One gram of this oil was dissolved in a minimum amount of methanol and neutralized to a phenolphthalein end point with 1 N methanolic KOH. To this was added 0.6 g of 2-hydroxy-3,5-dichlorobenzyl chloride in a minimum amount of methanol. The solution was allowed to stand for 12 h during which the 2-hydroxy-3,5-dichlorobenzyl derivative crystallized. Filtration followed by recrystallization from ethanol gave a 56% yield of the yellow solid: mp 188–191 °C; IR (nujol mull) 3400, 1310, and 1150 cm^{-1}.

Anal. Calcd for $C_{21}H_{23}Cl_2S_2O_3$: C, 55.5; H, 4.4; Cl, 15.4; S, 14.09; mol wt 454. Found: C, 55.50; H, 4.70; Cl, 15.64; S, 14.00; mol wt 446.2.

(B) Potassium *tert*-Butoxide in Dimethyl Sulfoxide. To 1.5 g (0.014 mol) of potassium *tert*-butoxide in 20 mL of Me_2SO was added dropwise a solution of 2.80 g (0.01 mol) of 5-mesitylsulfonyl-2-methylthiophene in 60 mL of Me_2SO. The reaction mixture was stirred in a nitrogen atmosphere at room temperature for 6 h, after which it was poured into ice water and worked up the same as the *n*-butyllithium reaction, giving a quantitative yield of a yellow tar which solidified on standing. Recrystallization from acetone–water gave mp 100–103 °C: NMR (Me_2SO-d_6) δ 2.22 (s, 3), 2.37 (s, 3), 2.63 (s, 3), 4.20 (s, 2), 6.65 (d, 1, J = 1 Hz), 6.67 (d, 1, J = 1 Hz), 6.92 (s, 2), 9.84 ppm (s, 1).

The 2-hydroxy-3,5-dichlorobenzyl derivative was prepared as above: mp 189–191 °C, mixture melting point with derivative from the *n*-butyllithium rearrangement 188–190.5 °C. The infrared spectra of these two products were identical.

Raney Nickel Reduction of the Sulfinic Acid from 5-Mesitylsulfonyl-2-methylthiophene. W-7 Raney nickel was prepared from 42 g of nickel–aluminum alloy (W. R. Grace) by the procedure of Billica and Adkins.[12] This was mixed with 5.04 g (0.018 mol) of sulfinic acid in 150 mL of absolute ethanol. The mixture was stirred at reflux for 24 h in a nitrogen atmosphere, after which it was filtered, and the nickel was washed with hot ethanol. The filtrate was evaporated, giving 3.38 g of a colorless oil. Distillation gave 1.5 g (44%) of a colorless oil boiling at 94–95 °C (3 mm): NMR ($CDCl_3$) δ 0.71–2.1 (m, 11), 2.20–2.9 (m with large s at 2.20, 8), 6.72 ppm (s, 3).

Anal. Calcd for $C_{14}H_{22}$: C, 88.4; H, 11.6; mol wt 190.3. Found: C, 88.26; H, 11.69; mol wt 196.

3,5-Dimethylbenzyl Bromide. A mixture of 30 g (0.25 mol) of mesitylene and 44.5 g (0.25 mol) of *N*-bromosuccinimide was stirred in 1500 mL of CCl_4 at reflux while being irradiated with a sunlamp. The reaction immediately turned pale green, and after 5 min the color had faded. After 2.25 h, the reaction mixture was allowed to cool to room temperature and filtered, and the precipitate was washed with CCl_4, giving 23.50 g (95%) of succinimide. Evaporation of the solvent followed by vacuum distillation gave 25.03 g (50.5%) of a colorless oil: bp 75–77 °C (1.5 mm). The NMR indicated this to be pure 3,5-dimethylbenzyl bromide. A second fraction was collected, bp 77–90 °C (1.5 mm), but an NMR spectrum indicated this is to be only 96% pure (5.50 g, 11%): NMR (neat) δ 2.10 (s, 6), 4.18 (s, 2), 6.75 and 6.83 ppm (two broad singlets, ca. 1: 2, 3).

1-(3,5-Dimethylphenyl)hexane (3). To a mixture of 0.9 g (0.13 g-atom) of Li wire cut into small pieces in 25 mL of anhydrous ether in a niyrogen atmosphere was added 7.85 g (0.052 mol) of *n*-amyl bromide dropwise with vigorous stirring. Stirring was continued for 24 h, after which the reaction mixture was filtered through a glass wool plug into a dropping funnel and slowly added to a solution of 3.98 g (0.02 mol) of 3,5-dimethylbenzyl bromide in 50 mL of ether in a nitrogen atmosphere. The reaction mixture was stirred for 5 min, after which 6 N HCl was slowly added. The layers were separated; the organic layer was washed with water and a saturated salt solution, dried, and evaporated, giving 5.52 g of a colorless oil which was vacuum distilled. Collection of the fraction boiling at 91–148 °C (1.5 mm) followed by VPC purification gave pure 1-(3,5-dimethylphenyl)-hexane (**3**), NMR ($CDCl_3$) δ 0.7–1.9 (m, 11), 2.28 (s, 6), 2.51 (t, 2, J = 7 Hz), 6.82 ppm (s, 3). NMR of the fractions boiling at 84–148 °C (1.5 mm) indicated a total of 0.39 g (10.3%) of the hydrocarbon was produced. During the distillation, 1.89 g (47.5%) of 3,5-dimethylbenzyl bromide was recovered, indicating probable incomplete formation of amyllithium

1-(3,5-Dimethylphenyl)-2-methylpentane (4). To a mixture of 4.8 g (0.2 g-atom) of Mg turnings in 200 mL of ether in a nitrogen atmosphere was slowly added 31.7 g (0.21 mol) of 2-bromopentane. The reaction mixture was stirred at reflux for 5.5 h, after which it was filtered through a glass wool plug in a dropping funnel and added dropwise to a solution of 14.2 g (0.07 mol) of 3,5-dimethylbenzyl bromide in 200 mL of ether. The reaction mixture was stirred at room temperature in a nitrogen atmosphere for 17 h, after which it was poured into 400 mL of 6 N HCl and worked up the same as the *n*-amyllithium reaction, giving 13.61 g of a slightly yellow oil. Distillation gave 2.32 g (17.2%) of a clear oil boiling at 80–90 °C (2 mm) which had IR and NMR spectra identical to the Raney nickel reduction product. A second fraction boiling at 90–125 °C (2 mm), 0.33 g, contained 90% 1-(3,5-dimethylphenyl)-2-methylpentane plus ca. 5% of a product which appears to be 1,2-bis(3,5-dimethylphenyl)ethane. When the pot was cooled, the residue solidified, giving another 3.17 g of impure symmetrical product (41% total): NMR ($CDCl_3$) δ 2.20 (s, 4), 2.75 (s, 12), 6.77 ppm (s, 6).

2-Thiophenesulfonyl Chloride. This preparation was adapted from the method of Steinkopf and Hopner.[13] Thiophene (100 g, 1.18 mol) was added dropwise to a stirred solution prepared from 230 mL (405 g, 3.14 mol) of chlorosulfonic acid and 70 mL of chloroform. The temperature was maintained at 0 °C during the 4.5-h period of addition and then allowed to warm to room temperature before quenching on a large volume of ice. The organic layer was separated, and the aqueous layer was washed three times with chloroform. The washings and the organic layer were combined, dried ($MgSO_4$), and stripped of solvent in vacuo. Vacuum distillation gave 102.2 g (47%) of the pure sulfonyl chloride: bp 82–84 °C (2 mm) [lit.[14] bp 131–132 °C (20 mm)].

2-Mesitylsulfonylthiophene. Anhydrous aluminum chloride (68 g, 0.51 mol) was added in small portions over a 30-min period to a well-stirred mixture of 2-thiophenesulfonyl chloride (91.5 g, 0.5 mol), mesitylene (72.0 g, 0.6 mol), and dichloromethane (200 mL). The temperature was maintained at −15 °C during the period of addition and for an additional 30 min before quenching on an ice/concentrated HCl mixture. The organic layer was separated, and the aqueous fraction was washed with dichloromethane. The washing and organic layer were combined, washed (aqueous $NaHCO_3$), dried ($MgSO_4$), and stripped of solvent in vacuo. The resultant dark-green solid was decolorized (Darco) and recrystallized from ethanol: yield 66.5 g (50%). A second recrystallization from ethanol was required to give pure sulfone (**5**): mp 114–115.5 °C (lit.[15] mp 115–115.5 °C); NMR ($CDCl_3$) δ 2.3 (s, 3), 2.7 (s, 6), 6.95–7.6 ppm (m, 5).

Cleavage of 2-Mesitylsulfonylthiophene. 2-Mesitylsulfonylthiophene (2.0 g, 7.5 mmol) was dissolved in 75 mL of anhydrous ether and stirred under nitrogen in an oven-dried three-necked flask. Over a period of 5 min, 4 mL of 1.9 N *n*-butyllithium was added via syringe while maintaining the reaction temperature at 0 °C. On completion of addition, the mixture was stirred at 0 °C for 5 h and then allowed to slowly warm to room temperature. After a total of 24 h, the reaction was quenched by pouring into 100 mL of water. The layers were separated, and the aqueous layer was washed once with ether. 2-Mesitylsulfonylthiophene (0.4 g, 20%) was recovered from the combined ether layer and washing. The aqueous fraction was heated on a steam bath with Darco, filtered, and chilled to 0 °C. The solution was then acidified with cold dilute HCl and extracted three times with ether. The combined extracts were dried ($MgSO_4$) and stripped of

solvent in vacuo. The crude sulfinic acid was dissolved in 10 mL of methanol and converted to its sodium salt by the addition of 1.0 N NaOH in methanol to a phenolphthalein end point. Removal of the solvent in vacuo gave a dark oil This was taken up in 25 mL of dry benzene and the benzene removed in vacuo. Two more treatments with dry benzene gave 0.5 g of a white powder identified as sodium mesitylenesulfinate (**8**) (24% yield): NMR (D_2O) δ 2.35 (s, 3), 2.7 (s, 6), 4.8 (s, HOD), 7.0 ppm (s, 2).

The 2-hydroxy-3,5-dichlorobenzyl sulfone derivative was prepared by reacting the sodium sulfinate with an equimolar portion of 2-hydroxy-3,5-dichlorobenzyl chloride. After 1 day, the crystalline product was isolated by filtration and recrystallized from an ethanol/water mixture: mp 171–172 °C (lit.[15] mp 170.5–171 °C); NMR ($CDCl_3$) δ 2.3 (s, 3), 2.55 (s, 6), 4.4 (s, 2), 6.1 (s, 1), 6.9–7.3 ppm (m, 4).

5-Carboxy-2-mesitylsulfonylthiophene (6). 2-Mesitylsulfonylthiophene (5.32 g, 20 mmol) was dissolved in 100 mL of anhydrous ether and stirred under nitrogen in an oven-dried three-necked flask. Over a period of 30 min, 10 mL of 2.2 N *n*-butyllithium was added via syringe while maintaining the reaction temperature at −5 °C. On completion of addition the mixture was stirred an additional 5 min and then poured onto dry ice. The dry ice was allowed to evaporate and then 100 mL of water was added. The layers were separated, and the ethereal fraction was washed once with a saturated aqueous $NaHCO_3$ solution. The washing was combined with the aqueous layer, and the solution was acidified with concentrated HCl. The crude product **6** was filtered, washed with water, and recrystallized from aqueous ethanol: yield 2.5 g (41%); mp 205–207 °C; IR (KBr) 1740 (C=O), 1310 and 1140 cm^{-1} (SO_2); NMR ($CDCl_3$) δ 2.3 (s, 3), 2.6 (s, 6), 6.95 (s, 2), 7.5 (s, 2), 8.85 ppm (s, 1, COOH).

Anal. Calcd for $C_{14}H_{14}O_4S_2$: C, 54.17; H, 4.55; S, 20.66. Found: C, 54.07; H, 4.62; S, 20.70.

Rearrangement of 2-Mesitylsulfonylthiophene. (A) *n*-Butyllithium in Tetrahydrofuran. 2-Mesitylsulfonylthiophene (2.0 g, 7.5 mmol) was dissolved in 40 mL of dry THF (distilled from LAH) and stirred under nitrogen in an oven-dried three-necked flask. Over a period of 4 min, 13 mL of 1.0 N *n*-butyllithium was added via syringe while maintaining the temperature at −72 °C. On completion of addition, the mixture was stirred at −72 °C for an additional 15 min. The dry ice-acetone bath was then removed, and the reaction was allowed to warm to room temperature. After a total of 4 h, the reaction was quenched by pouring into 100 mL of water. The layers were separated, and the aqueous layer was washed with ether. Combination of the ether layer and washing, followed by drying ($MgSO_4$), and removal of the solvent in vacuo yielded only traces of neutral material. Workup of the aqueous layer as previously described for the isolation of sodium mesitylenesulfinate gave 1.9 g (88%) of sodium 2,4-dimethyl-6-(3′-thenyl)benzenesulfinate (**9**): NMR (D_2O) δ 1.95 (s, 3), 2.6 (s, 3), 4.1 (s, 2), 4.6 (s, HOD), 6.5–7.1 ppm (m, 5).

The 2-hydroxy-3,5-dichlorobenzyl sulfone derivative was prepared by reacting the sodium sulfinate with an equimolar portion of 2-hydroxy-3,5-dichlorobenzyl chloride. After 1 day, the crystalline product was isolated by filtration and recrystallized from ethanol: mp 142–144 °C (with decomposition); IR (KBr) 3450 (OH), 1305, and 1130 cm^{-1} (SO_2); NMR ($CDCl_3$) δ 2.3 (s, 3), 2.55 (s, 3), 4.0 (s, 2), 4.35 (s, 2), 6.3 (br s, 1), 6.8–7.3 ppm (m, 7).

Anal. Calcd for $C_{20}H_{18}Cl_2S_2O_3$: C, 54.43; H, 4.11; Cl, 16.06. Found: C, 54.50; H, 4.06; Cl, 16.00.

(B) *n*-Butyllithium in Diethyl Ether. 2-Mesitylsulfonylthiophene (2.0 g, 7.5 mmol) was dissolved in 75 mL of dry diethyl ether and stirred under nitrogen in an oven-dried three-necked flask. *n*-Butyllithium (1.25 to 3 equiv) was then added via syringe while maintaining the reaction temperature at 0 °C. The reaction and workup were carried out as previously described for the isolation of sodium mesitylenesulfinate. The NMR spectra of the crude base-soluble acidic fractions showed them to contain mixtures of sodium mesitylenesulfinate and sodium 2,4-dimethyl-6-(3′-thenyl)benzenesulfinate (**9**). With 3 equiv of base, the ratio of cleavage product to rearrangement product was approximately 1 to 10. As the amount of base approached 1 equiv, sodium mesitylenesulfinate became the major product.

(C) Potassium *tert*-Butoxide in Dimethyl Sulfoxide. Potassium *tert*-butoxide (1 or 2 equiv) was suspended in 30 mL of dry Me_2SO (distilled from calcium hydride) and stirred under nitrogen in an oven-dried three-necked flask. A stopple was momentarily removed, and 2-mesitylsulfonylthiophene (4.0 g, 15 mmol) was quickly added in 1 portion. The reaction flask was cooled to maintain the temperature near 20 °C during the first few minutes of reaction. After 6 h of reaction at room temperature, the mixture was quenched by pouring into 200 mL of water. The solution was chilled in an ice bath, acidified with cold dilute HCl, and then extracted three times with ether. The ether fractions were combined and extracted two times with dilute aqueous NaOH. The aqueous extracts were worked up as previously described for the isolation of sodium mesitylenesulfinate. In both cases, mixtures of sodium mesitylenesulfinate and sodium 2,4-dimethyl-6-(3′-thenyl)benzenesulfinate (**9**) were obtained in an overall yield of approximately 60%. About 90% of these mixtures was rearrangement product (as determined from the NMR spectra). The 2-hydroxy-3,5-dichlorobenzyl sulfone derivative of the rearranged sodium sulfinate, once purified, had physical and spectral properties identical to the sulfone prepared in section A.

4*H*-Thieno[2,3-*b*][1]-6,8-dimethylbenzothiopyran 9,9-Dioxide (12). The rearranged sodium sulfinate **9** from the *n*-butyllithium/THF reaction was converted to the corresponding sulfonyl chloride by the method of Pfeil and Velten.[16] Sodium 2,4-dimethyl-6-(3′-thenyl)benzenesulfinate (1.85 g, 6.5 mmol) was dissolved in 20 mL of 88% formic acid. In a separate container, 12 g of cupic chloride dihydrate was dissolved in 12 mL of water and 12 mL of 88% formic acid. The two solutions were combined and stirred for 5 min before pouring onto an ice/concentrated HCl mixture. The pasty solid which precipitated was washed with cold concentrated HCl until the washings were clear. The solid was then taken up in dichloromethane, washed once with concentrated HCl, twice with water, dried ($MgSO_4$), and stripped of solvent in vacuo. The resulting crude sulfonyl chloride (1.6 g, 83%) was not further purified but was dissolved in 40 mL of dichloromethane and treated with 2.5 g of anhydrous aluminum chloride over a 15-min period. The reaction was maintained at 0 °C during the addition and was stirred an additional 45 min at room temperature before quenching in water. The organic layer was separated, and the aqueous layer was washed with dichloromethane. The washing and organic fraction were combined, washed with water, dried ($MgSO_4$), and stripped of solvent in vacuo. The resulting paste was cooled, and, on the addition of 5 mL of carbon tetrachloride, crystallized, giving 0.7 g (41% from **9**) of sulfone **12.** Two recrystallizations from carbon tetrachloride gave pure **12:** mp 160–162 °C; IR (KBr) 1280 and 1140 cm^{-1} (SO_2); NMR ($CDCl_3$) δ 2.3 (s, 3), 2.8 (s, 3), 4.1 (s, 2), 7.0 (s, 2), 6.95 and 7.55 ppm (d, 1 J = 5 Hz).

Anal. Calcd for $C_{13}H_{12}O_2S_2$: C, 59.06; H, 4.58; S, 24.26. Found: C, 59.20; H, 4.69; S, 24.29.

3a*H*,9a*H*,4*H*-Thieno[2,3-*b*][1]-6,8-dimethylbenzothipyran 9,9-Dioxide (13). 2-Mesitylsulfonylthiophene (4.0 g, 15 mmol) was dissolved in 40 mL of dry diethyl ether and 40 mL of tetramethylethylenediamine (distilled from calcium hydride) and stirred under nitrogen in an oven-dried three-necked flask. Over a period of 10 min, 13.5 mL of 2.2 N *n*-butyllithium was added via syringe while maintaining the reaction temperature at 0 °C. The solution was stirred an additional 10 min at 0 °C and then quenced by pouring onto an ice/concentrated HCl mixture. Ether was removed from the acidic heterogeneous solution in vacuo. The crude sulfone was filtered, washed with an aqueous $NaHCO_3$ solution, and suction dried. Recrystallization from ethanol gave 1.3 g (33%) of the product (**13**): mp 138–141 °C; IR (KBr) 1295 and 1135 cm^{-1} (SO_2); NMR ($CDCl_3$) δ 2.3 (s, 3), 2.65 (s, 3), 2.9 and 3.5 (d of d, 1 proton each, J = 6, 14 Hz), 3.9–4.4 (m, 1), 5.1 (d, 1 J = 11 Hz), 5.3 and 5.85 (d of d, 1 proton each, J = 2, 6 Hz). 6.9 ppm (s, 2). Two additional recrystallizations from ethanol gave an analytically pure sample, mp 140.5–142 °C.

Anal. Calcd for $C_{13}H_{14}O_2S_2$: C, 58.62; H, 5.30; S, 24.07. Found: C, 58.35; H, 5.56; S, 23.97.

Alternate Synthesis of 12 from 13. Sulfone **13** (1.3 g, 4.9 mmol), 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (2.5 g, 11.0 mmol), and picric acid (0.2 g) were dissolved in 30 mL of dry benzene. The stirred solution was refluxed for 6 h under nitrogen, during which time a precipitate formed. This was filtered and the filtrate was washed with a saturated $NaHCO_3$ solution until no more color was extracted. The organic phase was then washed successively with 10% aqueous NaOH, water, dilute aqueous HCl, and finally with water again. The benzene solution was then dried ($MgSO_4$), and stripped of solvent in vacuo to yield 1.2 g of a yellow oil. This was placed on an alumina column and eluted with a 1 to 1 mixture of chloroform and benzene. The first fractions contained 0.7 g (54%) of sulfone **12.** Two recrystallizations from carbon tetrachloride gave pure material, mp 161–162 °C. The IR and NMR spectra were identical to those from the sample prepared from sodium sulfinate **9.** A mixture melting point was undepressed.

Registry No.—**1,** 21991-09-3; **2,** 63988-85-2; **2** 2-hydroxy-3,5-dichlorobenzyl sulfone derivative, 63988-86-3; **3,** 63988-87-4; **4,** 63988-88-5; **5,** 21991-08-2; **6,** 63988-89-6; **8,** 50827-54-8; **8** 2-hydroxy-3,5-dichlorobenzyl sulfone derivative, 63988-90-9; **9,** 63988-91-0; **9** 2-hydroxy-3,5-dichlorobenzyl sulfone derivative, 63988-92-1;

12, 63988-93-2; 13, 63988-94-3; sodium 5-methyl-2-thiophenesulfonate, 63988-95-4; 2-methyl-5-thiophenesulfonyl, 55854-45-0; mesitylene, 108-67-8; 2-hydroxy-3,5-dichlorobenzyl chloride, 6333-33-1; 2,4-dichlorophenol, 120-83-2; formaldehyde, 50-00-0; 3,5-dimethylbenzyl bromide, 27129-86-8; amyl bromide, 110-53-2; 2-bromopentane, 107-81-3; 2-thiophenesulfonyl chloride, 16629-19-9; thiophene, 110-02-1; chlorosulfonic acid, 7790-94-5.

Notes and References

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Proaporphine–Aporphine Dimers and a Bisaporphine Derived from the Tumor-Inhibitory Alkaloid Thalicarpine[1a]

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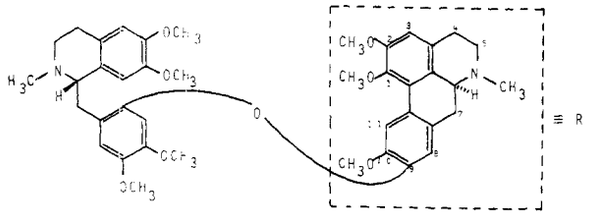
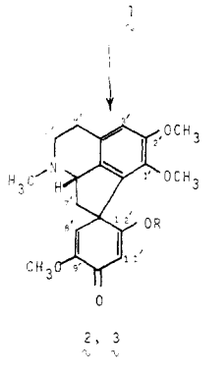
Oxidation of the tumor inhibitory alkaloid thalicarpine (1), a benzylisoquinoline–aporphine dimer, with VOF_3 in TFA gave a mixture of diastereoisomeric dienones **2** and **3**, a new type of proaporphine–aporphine alkaloid. The major isomer **2** was converted to the epimeric dienols **6a** and **6b** which, upon treatment with BF_3–Et_2O in CH_2Cl_2, gave another new type of alkaloid, bisaporphine **8**. Preliminary testing results indicate that bisaporphine **8** is active in vitro against cells derived from the human carcinoma of the nasopharynx (KB).

The alkaloid thalicarpine,[2] which has the aporphine–benzylisoquinoline structure **1**,[3] exhibits a significant inhibitory activity against the Walker 256 intramuscular carcinosarcoma in rats over a wide dosage range.[4]

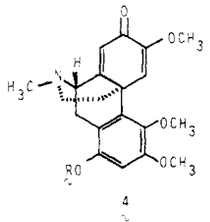
In order to gain some insight into the structure–tumor inhibitory activity relationship in this alkaloid series, we have undertaken studies directed toward structural modifications of thalicarpine. We report herewith the conversion of thalicarpine (**1**) to a new type of alkaloid, proaporphine–aporphine dimers **2** and **3**, and thence to another new type of alkaloid, bisaporphine **8**. Both **2** and **8** serve as models for types of alkaloids which have not been isolated from natural sources to date.





2, **3**

Recently, a number of nonphenol oxidative coupling reactions which yield spirodienone intermediates and products have been reported.[5-10] Thus, morphinandienones (e.g., **4**) have been recognized as the primary products of chemical[5,6] as well as electrooxidative coupling of nonphenolic tetrahydrobenzylisoquinoline precursors. On the other hand, chemical[6] and electrochemical[9] oxidative coupling of tetramethoxylated bibenzyls gave dihydrophenanthrone derivatives via five-membered ring spirodienone intermediates, similar to the proerythrinadienone-type systems (e.g., **5**). Oxidation



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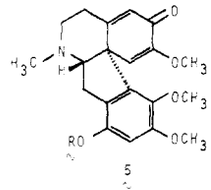

5

of nonphenolic phenethyltetrahydroisoquinolines using vanadium oxytrifluoride (VOF_3) in trifluoroacetic acid (TFA) to homoaporphines via homoproerythrinadienone intermediates[10] was also reported.

Thalicarpine (**1**), a nonphenolic alkaloid, was thus subjected to chemical as well as anodic oxidative coupling reactions to elaborate the benzyltetrahydroisoquinoline part of the molecule. The oxidation of thalicarpine (**1**) was best performed by treating 0.4 mmol of the alkaloid in CH_2Cl_2, TFA,[11] and FSO_3H with 2.5 molar equiv of VOF_3 in TFA and ethyl acetate at −10 °C for 10 min. The product was a mixture of dienones **2** and **3**, diastereomers at the spiro ring junction. The two isomers were separated by preparative thin layer chroma-

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