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February 28, 1992
Quarterly Technical Progress Report No. 6 (draft copy)
Report period: Oct 28, 1991 - Jan 26, 1992

CONTRACT TITLE AND NUMBER:
Task I: Synthesis of 6-Methyl-9-n-propyldibenzothiophene-4-ol (DE-AC22-90PC 90035), ammended to 6-Methyl-9-(1-methylethyl)-dibenzothiophene-4-ol.

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CONTRACT PERIOD: July 25, 1990- July 24, 1992

CONTRACT OBJECTIVE: Synthesis and purification of the amended title compound.

Technical Summary: The material presented below is taken from Status Reports 15, 16 and 17 and covers the progress made toward the synthesis of the modified target molecules 9-isopropyl-4-methoxy-6-methyldibenzothiophene (**13**) and 9-isopropyl-6-methyldibenzothiophene-4-ol (**14**).

The dehydrogenation of tetrahydrodibenzothiophene **12** has been carried out using selenium, palladium-on-carbon, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and 2,3,5,6-tetrachloro-1,4-benzoquinone (Chloranil) under a variety of reaction conditions. While all of these conditions produced the desired, fully aromatic dibenzothiophene **13**, the selenium and palladium-on-carbon reactions also produced significant amounts of the side-product **15**. This latter compound arises from loss of the isopropyl substituent during the reaction. The DDQ reactions at 25 °C and 80 °C in benzene effected the dehydrogenation of **12** to **13** *without* loss of the isopropyl group as determined by GC-MS. However, the reactions were slow at these temperatures: 67% conversion (168 h at 25 °C) and 67% conversion (48 h at 80 °C). The reactions involving Chloranil behaved similarly but were exceedingly slow: only 8% conversion after 72 h at 80 °C. Moreover, increasing the number of equivalents of Chloranil from 1.4 to 4.1 equivalents did not result in improved conversion. In order to achieve complete reaction of **12**, exploratory small-scale reactions with DDQ in refluxing anhydrous p-dioxane (bp 101 °C) were carried out using varying ratios of DDQ to **12**. It was found that a four-fold excess of DDQ was required to convert all of **12** to **13**.

Following the small-scale exploratory runs, an intermediate scale synthesis was carried out with the following objectives:

(1) to evaluate the feasibility of scaling up the synthesis route shown in the attached scheme

(2) to determine an accurate overall yield for the sequence.

(3) to produce 40-50 g of the pure final product dibenzothiophene-4-ol (**14**)

This intermediate-scale synthesis was carried out starting with the bromination of 355 g of commercial (-)-menthone. The purity of the resulting crude 2-bromomenthone product was about 75% by weight and reflected a conversion of *ca.* 76% as determined by GC. We feel that these results are satisfactory for this step considering the scale and complexity of the run. An attempt, on a 5-g scale, to purify the crude 2-bromomenthone by Kugelrohr distillation led to a colorless distillate but one that exhibited new GC peaks. These peaks are believed to result from loss of hydrogen bromide. This finding confirmed our suspicion that 2-bromomenthone is thermally unstable and thus the bulk of the product from the bromination step was used in the next step without purification.

Ketosulfide **11** was thus prepared using 265 g of 2-methoxybenzenethiol and an equivalent amount of the crude monobromide. The recovery from the reaction was high (90% w/w). An attempt to purify the keto sulfide on a 5-g scale by Kugelrohr distillation led to the formation of five new impurities (by GC). Therefore, the bulk of the keto sulfide was purified only by steam-distillation before use.

Since the earlier small-scale exploratory synthesis showed that the PPA cyclization was the lowest yield step in the overall scheme, we attempted to improve this step by running the reaction on a small-scale in refluxing toluene. GC analysis, however, showed

a much slower reaction, no improved conversion and the formation of three new impurity peaks. The bulk of **11** was thus converted to **12** at 100-110 ^{o}C in the absence of solvent in about 41% yield.

The dehydrogenation of **12** to **13** was carried out in refluxing 1,4-dioxane. Following reaction and extractive workup, crude **13** was passed twice through fresh pads of acidic and basic alumina and the filtrate was then rotorvaped and pumped. The dark-brown viscous oil that resulted was treated with picric acid in boiling ethanol and the orange picrate that precipitated was collected, partially dried and then recrystallized from boiling ethanol. The recrystallized picrate was collected, dried, and decomposed over basic alumina with petroleum ether and then toluene. This afforded a total of 35 g (9% overall yield from menthone) of **13** as glistening white crystals, mp 108-110 ^{o}C. Gas chromatographic analysis of this material showed it to be better than 99% pure.

Reprocessing of the mother liquor from the picrate of crude **13** yielded an additional 10.5 g of **13**. This raised the total yield of purified **13** to 45.5 g representing an overall yield (from menthone) of pure material of 12 %.

Furthermore, the demethylation reaction (last step in the attached scheme) has been carried out on a batch of 10.5 g of **13**. The reaction proceeded smoothly with no side products observed. However, despite the use of an excess of boron tribromide (4.6 equivalents of bromine atoms), there remained about 10% unreacted

13 accompanying the phenol product **14**. Separation of **13** from **14** has been carried out by selectively retaining **14** on basic alumina. The resulting pure phenol (>99%) has been shipped to DOE/PETC via UPS (February 19, 1992) as follows:

SJF-IX-11-B	0.108 g in screw-cap vial
SJF-IX-11-B-1	0.105 g in sealed ampoule
SJF-IX-11-B-5	0.113 g in sealed ampoule
SJF-IX-11-B-6	2.472 g in sealed ampoule

Phenol **14** is a white crystalline solid melting without decomposition at 155-156 ^{o}C. It is completely soluble in ether, chloroform, dichloromethane, and acetone. It is insoluble in water and only slightly soluble in low-boiling petroleum ether. It is stable to neutral and basic alumina and to air during handling. However, since 6-methyl-9-(1-methylethyl)dibenzothiophene-4-ol is a phenol, there is the possibility that it could be susceptible to air oxidation if exposed to air for a long period of time.

The preliminary results from Molecular Mechanics (MM2) calculations for dibenzothiophenes **13** and **14** are enclosed. These calculations were carried out on a modified MacIntosh IIfx computer using the Tektronix CAChe™ Molecular Modeling System.[1] The purpose of these calculations was to estimate the total strain energy for dibenzothiophenes **13** and **14** and some of the bond lengths and angles. We wish to stress that these calculation results are preliminary and should be used only as a rough guide. We will report on more accurate calculations when they become available.

Moreover, we have recently gained access to MOPAC, a public domain, semi-empirical molecular calculations package. We plan to use MOPAC to get more accurate estimates.

EXPERIMENTAL

Dehydrogenation with palladium on carbon.[2] Crude **12** (4.6 g), Pd/C (1.0 g) and 10.0 g of 1-naphthoic acid were heated at 300 °C for 4 h. After cooling to room temperature, the black, solid residue was dissolved in ether and filtered through dicalite. The ether filtrate was washed with saturated sodium bicarbonate, brine, dried, filtered, rotorvaped and pumped affording 6.0 g of a black, syrupy liquid, which was passed through neutral alumina with ether and then steam-distilled. Workup of the residue from the steam distillation afforded 2.6 g of a dark-brown, viscous liquid consisting of **13** (35%), **15** (13%) and several impurities (52%). Other Pd/C reactions were carried out similarly.

Dehydrogenation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) at 80 °C.[3,4] 9-Isopropyl-4-methoxy-6-methyl-6,7,8,9-tetrahydro-dibenzothiophene (0.25 g, 0.364 mmol), DDQ (0.22 g, 0.950 mmol) and dry benzene were charged into a dry, 15-mL, round-bottom flask fitted with a stirr bar, a reflux condenser and a drying tube. The resulting black solution was stirred and heated at reflux. Aliquots were removed at regular time intervals and then diluted with benzene. Each such solution was

then filtered through basic alumina (Aldrich), magnesium sulfate, Dicalite, concentrated and then analyzed by gas chromatography.

A similar experiment was carried out at 25 °C for a total of seven days. During this period aliquots were removed, treated as described in the preceding paragraph and analyzed by gas chromatography.

Dehydrogenation with 2,3,5,6-tetrachloro-1,4-benzoquinone (Chloranil). 9-Isopropyl-4-metoxy-6-methyl-6,7,8,9-tetrahydrodibenzothiophene (0.25 g, 0.364 mmol), Chloranil (1.4 equiv) and dry benzene were charged into a dry, 15-mL, round-bottom flask fitted with a stirbar, a reflux condenser and a drying tube. The resulting black solution was stirred and heated at reflux. Aliquots were removed at regular time intervals and then diluted with benzene. Each such solution was then filtered through basic alumina (Aldrich), magnesium sulfate, Dicalite, concentrated, and then analyzed by gas chromatography. The final aliquot taken after 72 h of reflux showed (by GC) that only 8% of **12** was converted to **13** and that there was no evidence for the formation of side-product **15**.

A similar run was carried out at 80 °C using 4.1 equivalents of Chloranil. Again, GC analysis showed that only 8% of **12** was converted to **13** and that there was no evidence for formation of **15**.

2-Bromomenthone. Lithium diisopropyl amide (LDA) was generated in anhydrous tetrahydrofuran (THF) at -78 °C and under an

argon atmosphere using 3.22 mol of n-butyllithium and 2.99 mol of diisopropyl amine. Cold THF solutions of chlorotrimethylsilane (18.0 mol) and commercial (-)-menthone (2.3 mol) were then added at -78 °C followed by the rapid addition of a cold solution (-15 °C) of bromine (2.77 mol) in dichloromethane. After stirring for a short time at -78 °C, a cold saturated sodium bicarbonate solution was added until gas evolution ceased and the pH turned neutral-to-slightly basic. The resulting mixture was diluted with water and extracted with n-hexanes. The organic extracts were combined, washed with sat'd sodium bicarbonate, water, dried (MgSO4), filtered, rotorvaped at room temperature and pumped affording the crude product as a dark-brown liquid that consisted of about 75% w/w 2-bromomenthone (by GC). An attempt to purify 5 grams of this material by Kugelrohr distillation failed to separate the bromo-menthones from unreacted menthones and afforded a colorless distillate containing new peaks at t_R = 6.05 min and 6.27 min [130 °C (3 min) to 290 °C (7 min) at 20 °C/min], which are believed to arise from loss of hydrogen bromide.

6-Isopropyl-2-[(2'-methoxyphenyl)thio]-3-methyl-cyclohexanone. Sodium hydroxide (74 g), ethyl alcohol (500 mL), water (438 mL), and 2-methoxybenzenethiol (265g) were stirred under nitrogen at room temperature for 15 minutes. Crude 2-bromomenthone (1.0 equiv) in ethyl alcohol (550 mL) was then added rapidly. The resulting mixture was heated under nitrogen to reflux over 0.7 h and at reflux for 1h. After cooling to room temperature, the mixture was treated with water (3.0 L) and extracted with ether

(4 x 500 mL). The combined ether extracts were washed with brine, dried (MgSO4), filtered, rotorvaped and pumped affording the crude product as a dark-brown liquid representing a 90% w/w material recovery.

9-Isopropyl-4-methoxy-6-methyl-6,7,8,9-tetrahydrodibenzo-thiophene (**12**). Crude **11** (1.6 mol) and polyphosphoric acid (PPA, 1.9 kg) were heated with mechanical stirring under nitrogen to 100 ^{o}C over 0.5 h and at 100-110 ^{o}C for 1.5 h. The chocolate-brown, syrupy reaction mixture was poured onto 5 L of ice, stirred for 1h to decompose all the unreacted PPA, saturated with sodium chloride and extracted with ether. The combined organic extracts were washed with water, brine, and subjected to steam-distillation. Extractive workup of the residue from the steam distillation afforded the tetrahydro product in an estimated 41% yield as the major constituent of a dark-brown viscous oil possessing a moderate mercaptan odor.

9-Isopropyl-4-methoxy-6-methyldibenzothiophene (**13**). Tetrahydrodibenzothiophene **12** (0.38 mol), obtained as described in the preceding paragraph, was heated at reflux in dry p-dioxane in the presence of 720 g of 2,3-dichloro-5,6-dicyanobenzoquinone under a nitrogen atmosphere for 1.8 h. The resulting black reaction suspension was allowed to cool to room temperature under nitrogen and was then diluted with 4 L of water and 2 L of petroleum ether. The aqueous layer was made basic (pH $\geq$ 10) with sodium hydroxide and was then extracted with 6 x 500 mL of petroleum ether. The

combined dark-brown organic extracts were washed with water, brine, dried ($MgSO_4$) and filtered twice through fresh 200 g-pads each of acidic and basic alumina. The resulting brown filtrate was rotorvaped and pumped and the residual viscous oil was dissolved in hot ethanol and treated with a saturated solution of picric acid in boiling ethanol. The precipitated orange picrate was collected, dried partially and recrystallized from fresh ethanol. The recrystallized picrate, mp 158-159 ^{o}C, was then collected, dried and decomposed over basic alumina using petroleum ether and then toluene. This afforded a total of 35 grams of **13** as glistening white crystals of >99% purity (by GC).

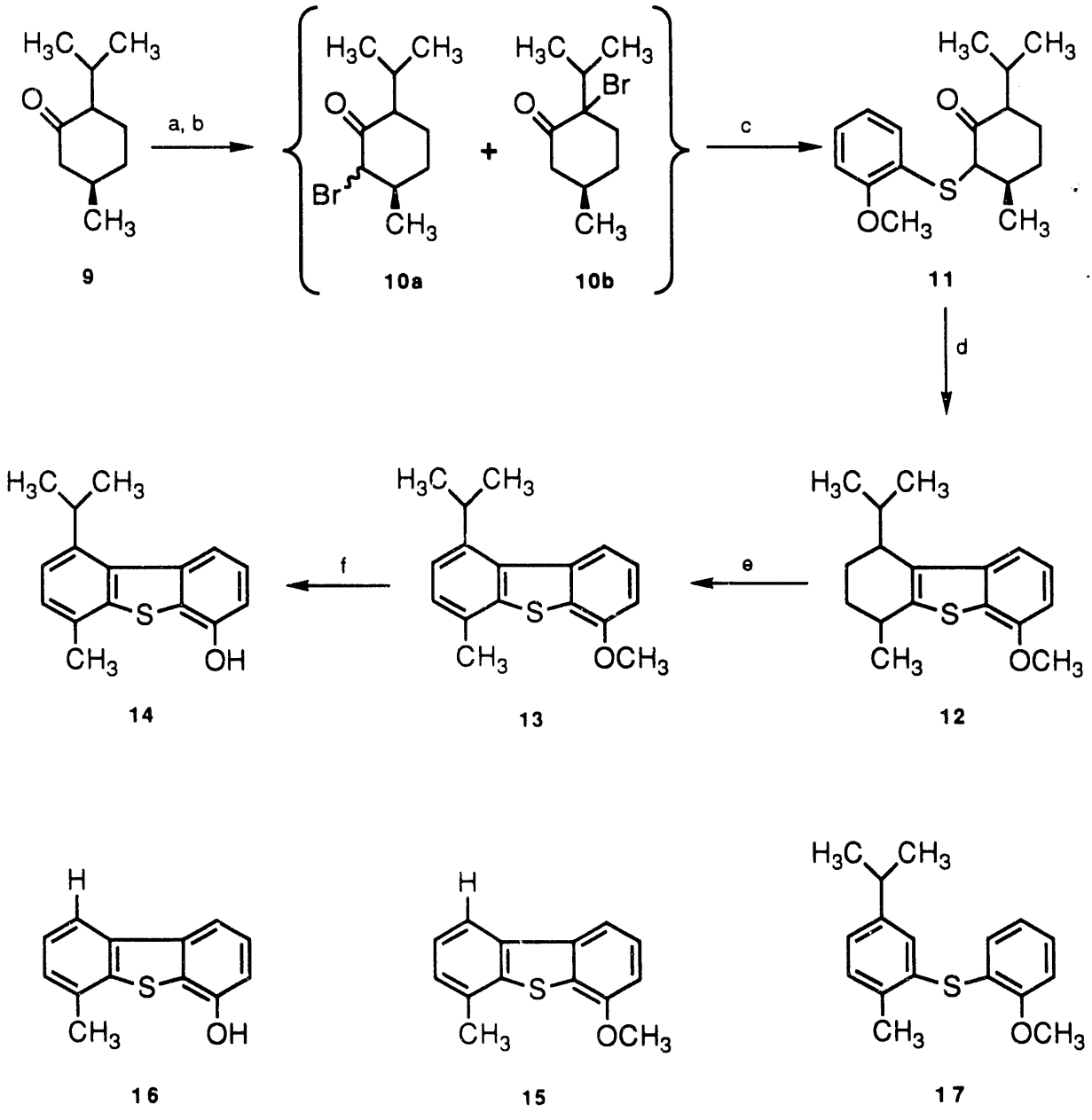
6-Methyl-9-(1-methylethyl)dibenzothiophene-4-ol.[5] Methoxy-dibenzothiophene **13** (10.45 g) and boron tribromide (5.6 mL) were combined in dichloromethane at -78 ^{o}C under a nitrogen atmosphere. The Dry Ice-acetone bath was then replaced with an ice bath and the reaction mixture allowed to warm to 0 ^{o}C Stirring at 0 ^{o}C under nitrogen was continued for 1 h. The reaction mixture was then poured onto 500 mL of ice and the aqueous layer was extracted with 5 x 100 mL of dichloromethane. The combined dichloromethane extracts were washed with water, brine, dried (MgSO4), filtered, rotorvaped and pumped to give 8.92 g of a white crystalline solid, mp 155-156 ^{o}C, consisting (by GC analysis) of phenol **14** (90%) and methoxy precursor **13** (10%). Elution through basic alumina first with low-boiling petroleum ether and then with ether effected the separation of **14** from **13**. Samples of purified **14** were shipped to DOE/PETC for initial evalutions (see Technical Summary).

REFERENCES AND NOTES

1. CAChe™ = Computer-Aided Chemistry.
2. (a) Fu, P.P.; Harvey, R.G. *Chem. Rev.* **1978**,*78*, 317-361. (b) Rylander, P.N. *Organic Syntheses with Noble Metal Catalysts*; Academic Press: New York, NY 1973; pp 1-59.
3. FINDLAY, J.W.A.; TURNER, A.B. *ORG. SYNTH.* **1973**, *COLL. VOL. V*, 428-431.
4. WALKER, D.; HIEBERT, J.D. *CHEM. REV.* **1967**, *67*, 153-195.
5. Vickery, E.H.; Pahler, L.F.; Eisenbraun, E.J. *J. Org. Chem.* **1979**, *44*, 4444-4446.

Current and Future Effort. As agreed during our phone conversation of February 26t, we plan to convert the supply of **13** (except for 5 g) to phenol **14** The latter will be purified and both samples will be sent to PETC.

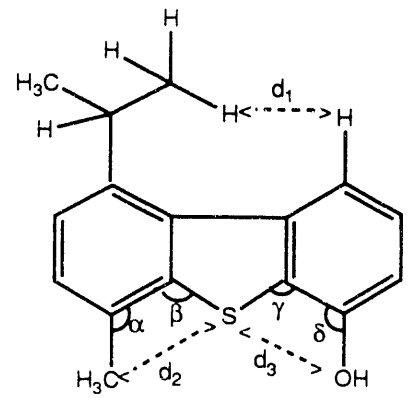
Scheme



[a] LDA, TMSCl, THF, -78 °C. [b] Br_2, CH_2Cl_2, -78 °C. [c] 2-Methoxybenzenethiol, NaOH, EtOH-H_2O, Δ. [d] PPA, Δ. [e] DDQ, 101 °C. [f] BBr_3, CH_2Cl_2, 0 °C.

Augmented MM2 Calculation Results

(On The Tektronix CAChe™ Molecular Modeling System)

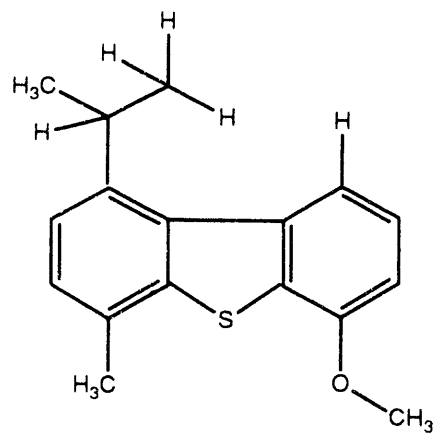


Total Strain Energy = -7.18 Kcal/mol

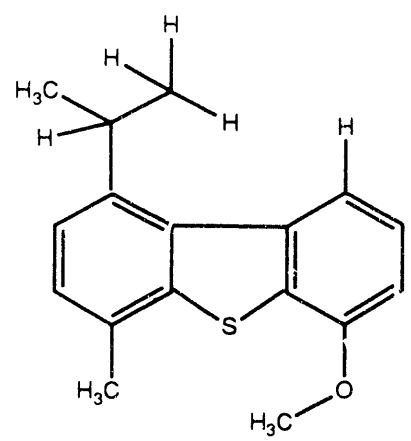
d_1 = 2.418 Å, d_2 = 2.962 Å, d_3 = 3.040 Å

α = 122.98°, β = 123.89°

γ = 124.23°, δ = 122.71°



Total Strain Energy = -3.23 Kcal/mol



Total Strain Energy = +0.27 Kcal/mol

DISCLAIMER

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