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Report period: July 28-Oct 28, 1991

CONTRACT TITLE AND NUMBER:
Task I: Synthesis of 6-Methyl-9-n-propyldibenzothiophene-4-ol
DE-AC22-90PC 90035

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

CONTRACT OBJECTIVE: Synthesis and purification of the title compound.

Technical Summary: The material presented here has been described to some extent in Status Reports 12, 13, and 14 and covers the progress toward the synthesis of the modified target molecules 9-isopropyl-4-methoxy-6-methyldibenzothiophene **(13)** and 9-isopropyl-6-methyldibenzothiophene-4-ol **(14)**. It is divided into three parts:

(a) Dehydrogenation experiments on tetrahydrodibenzothiophene **12**.
(b) methoxyl methyl cleavage of **13** to **14** using boron tribromide.
(c) isolation and purification of methoxydibenzothiophene **13**.

*Part A: Dehydrogenation experiments on 9-isopropyl-4-methoxy-6-methyl-6,7,8,9-tetrahydrodibenzothiophene **(12)**.* The dehydrogenation of the tetrahydrodibenzothiophene **12** was initially carried out on a small scale using selenium metal powder since this reagent has been the most commonly described in the literature for such dehydrogenations.[1] The following reaction conditions were used:

(a) selenium powder, neat, 300 °C, 2.0 h.
(b) selenium powder, 2-methylnaphthalene, 245 °C, 2.0 h.
(c) selenium powder, 2-methylnaphthalene, 245 °C, 22.0 h.

Workup of these reactions involved boiling the crude reaction product in ethanol, filtering through Dicalite, evaporating the solvent, steam-distilling to remove 2-methylnaphthalene and any low boiling side product, extracting the residue into ether followed by washing, drying and concentrating the combined ether extracts. 2-Methylnaphthalene was used as a solvent of a sufficiently high boiling point to produce an observable reaction rate, but one that is still removable by distillation with steam. All three reactions involving selenium produced 4-methoxy-6-methyldibenzothiophene (**15**) as a major component of a multi-component crude product. This side-product arises by loss of the isopropyl group during aromatization, presumably owing to the temperature and the free radical nature of the process. Moreover, reaction condition (a) also produced three isomeric products (relative ratios = 3.3/8.0/1.0) suggesting isopropyl migration to other sites on the aromatic nucleus during the reaction. Reaction conditions (a) and (c) resulted in complete conversion, but condition (b) gave only about 6-15% conversion to the desired compound **13**. These results pointed out that selenium is not suitable as a dehydrogenation agent for the preparation of **13**.

A search for a suitable dehydrogenation reagent and reaction conditions prompted the use of palladium on carbon under a variety of reaction conditions.[2] These were:

(d) Pd/C, neat, 300 °C, 1.3 h.

(e) Pd/C, 1-naphthoic acid, 300 °C, 4.0 h.

(f) Pd/C, 2-methylnaphthalene, 245 °C, 26 h.

(g) Pd/C, 2-methylnaphthalene, maleic acid, 245 °C,1.0 h.

In these reactions,1-naphthoic acid was used as solvent to achieve a reaction temperature around 300 °C and because it could easily be removed by sodium bicarbonate extraction. Maleic acid was used as a possible hydrogen-acceptor and not as solvent. Workup of the Pd/C reactions involved steps similar to those used for the selenium reactions, except that there was an additional sodium bicarbonate extraction step to remove the naphthoic or maleic acids.

The reaction involving palladium on carbon in 2-methylnaphthalene was slow at 245 °C (only about 44% conversion to **13+15** after 26 h of reflux!) but gave rise to only one product isomer. The reaction involving maleic acid gave essentially unreacted starting material. This latter reaction was carried out for only 1h since intense gas evolution was observed during that period. This, however, was an artifact since the gas generated was undoubtedly steam arising from the conversion of maleic acid to maleic anhydride under the reaction conditions. Reaction conditions (d) and (e) both yielded a product mixture in which the desired **13** is a major constituent (*ca.*, 40-60%). But again, all four Pd/C reactions produced 4-methoxy-6-methyldibenzothiophene (**15**) as a significant side-product.

Since the dehydrogenation reactions involving selenium or palladium on carbon produced significant amounts of 4-methoxy-6-methyldibenzothiophene (**15**) as a side-product, the reaction temperature needed to be lowered well below 245 °C. However, Pd/C was already slow reacting even at 245 °C and thus other dehydrogenation procedures were considered.

Thus, the1,4-benzoquinones[3], 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) or Chloranil, as the dehydrogenation agents at 80 °C or 101 °C were explored. The lower reaction temperature (80 °C or 101 °C as compared with 245 °C or 300 °C) might prevent the side reaction (partial loss of isopropyl group) from occurring. Initially, we were hesitant to use these oxidizing agents owing to the reported side-reactions (such as side-chain oxidations and/or Diels-Alder cycloadditions) that sometimes accompany their use.

Trial aromatizations of the tetrahydro precursor **12** using DDQ (1.3 equiv) in benzene at 25 °C and at reflux temperature (80 °C) were carefully monitored by removing aliquots at regular time intervals. These samples were diluted with benzene and then eluted through basic alumina, magnesium sulfate and Dicalite. Gas chromatographic analyses of these aliquots revealed that the reaction was slow: about 28% complete after 24 h at 25 °C and *ca.* 55% complete after 24 h at 80 °C. The desired methoxy dibenzothiophene was the predominant product of the reaction and the loss of isopropyl group did not take place as far as could be determined.

Part B: Methoxyl methyl cleavage reaction. The reaction of a 64/36 mixture of **13**+**15** with boron tribromide was carried out in order to find out if this reaction takes place cleanly, and if boron tribromide itself can be used instead of the more expensive boron tribomide-dimethyl sulfide complex that we originally planned to use. The reaction was adapted from the literature procedure for catechol ethers[4] and proceeded smoothly in dry dichloromethane at 0 °C to give the expected mixture of **14** and **16** (67/33) in about 88% yield. The ^{1}H NMR spectrum (also included with this report) of the product mixture of **14** and **16** clearly lacked the methoxy methyl signals and contained a broad singlet at $\delta = 5.4$ attributed to the phenolic OH resonances. The spectrum also showed that the conversion in this reaction was quantitative and that **13** and **15** are stable to the reaction conditions since no side-products (such as ring bromination products) were observed either by GC or by NMR.

*Part C: Isolation and Purification of methoxy dibenzothiophene **13**.* Since the aromatization reactions using selenium or palladium on carbon all produced mixtures of the desired methoxy dibenzothiophene **13** and the side-product **15**, an isolation approach was developed to isolate the two from the crude product and then to separate **13** from **15**. Thus picric acid in ethanol was used to form the picrates of the mixture of **13** and **15**. The solid picrates were collected, washed with ethanol and decomposed on basic alumina with hexanes affording a 62/38 mixture of **13/15** as determined from the ^{1}H NMR spectrum (included with this report). Other isolation and purification techniques were also tried but were either unsuccessful or only partially successful. They include Kugelrohr distillation under reduced pressure, sublimation, silica gel flash chromatography, elution through neutral and basic alumina contained in a soxhlet extractor and fractional crystallization with ethyl acetate or methanol-ether mixtures.

The purity of the desired 4-methoxy-6-methyl-9-isopropyl-dibenzothiophene (**13**) was then improved from a ratio of 62/38 to a ratio of 98/2 of **13/15** (but to ≥ 90% overall chemical purity) by elution twice through acidic and basic alumina with hexane-toluene following extraction from the crude product with picric acid. The GC trace and the proton NMR spectrum of this small sample (the purest that we have had thus far) are enclosed. The two major contaminants are probably a molecule isomeric with **13** (2%) and 4-methoxy-6-methyl-dibenzothiophene (**15**, 2%). Note that the impurities are present below the level detectable by NMR and consequently the proton spectrum shows this material to be quite clean. We believe that the purity can be improved further by fine tuning the chromatographic procedure and/or by recrystallization when enough of the material becomes available.

Current and Future Effort. We plan to improve the aromatization reaction by increasing the reaction temperature from 80 °C to 101 °C (and slightly higher if necessary), by increasing the number of equivalents of oxidizing agent used. The ≥90% purity that we have achieved is promising and we plan to carry on until a chemical purity of ≥ 98% is attained. We are also planning a large-scale run that we hope will produce about 50 g of final product.

Experimental Section

Dehydrogenation using selenium. Crude **12** (15.4 g) and 16.0 g of powdered selenium metal were heated with stirring under an argon atmosphere in a well-ventilated hood at 300 °C for 2 h. Ethyl alcohol was then added and the heterogeneous mixture was heated at reflux under argon for 1h. It was filtered while hot and the filter cake was washed repeatedly with hot ethanol. The resulting black filtrate was boiled with activated charcoal, filtered again and the new filtrate rotorvaped and pumped affording 10.3 g of the crude product as a black amorphous paste consisting of three isomeric **13**'s (36%), **15** (29%) and several impurities (34%). The other selenium reactions were carried out similarly except that 2-methylnaphthalene (bp 243 °C) was used as solvent and was removed by steam-distillation.

Dehydrogenation with palladium on carbon. 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 and brine solutions, dried ($MgS0_4$), 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 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 reflux..[3] 9-Isopropyl-4-metoxy-6-methyl-6,7,8,9-tetrahydrodibenzothiophene (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 24 h. During this period aliquots were removed, treated as described in the preceding paragraph and analyzed by gas chromatography.

Reaction of aromatic ether 13 with boron tribromide.[4] A 64/36 mixture of **13/15** (1.1 g, 4.4 mmol) was dissolved in 6 mL of dry dichloromethane under a nitrogen atmosphere. The resulting solution was cooled in a Dry Ice-acetone bath. when the internal temperature reached -65 °C, 0.6 mL (6.3 mmol) of boron tribromide (Aldrich) was added. The dry ice-acetone bath was replaced with an ice bath and the dark-brown solution was stirred under nitrogen at 0 °C for 0.5 h. Ice-water was then added to the cold solution, and after vigourous bubbling subsided, the reaction mixture was diluted with water. Extraction with 4 x 100 mL of dichloromethane, workup of the combined dichloromethane extracts, rotorvaping and pumping afforded 0.93 g (88%) of a white fluffy solid that was shown by GC and ^{1}H NMR ($CDCl_3$) spectroscopy to consist of a 61/39 mixture of phenols **14** and **16**.

Isolation of 13 & 15. A hot solution of 10.12 g of picric acid in ethanol was added to a hot ethanol solution of a crude material (7.84 g) containing **13** & **15** (48/52; 47% of the material) and several impurities. The resulting dark-brown solution was allowed to cool and stand at room temperature for several hours. The precipitated muddy-orange crystals were filtered, washed once with ethanol and dried partially by pumping. This material was then placed on top of a column of basic alumina and eluted with refluxing n-hexanes for 0.5 h. Evaporation and pumping of the yellow hexane solution afforded 1.34 g of a colorless, odorless, viscous oil that crystallized completely upon standing at room temperature. GC and proton nuclear magnetic spectroscopy showed this material to consist of a 61:39 mixture of **13/15** and to be 97% chemically pure.

*Separation of **13** from **15**.* A 61/39 mixture (1.96 g) of **13/15** was passed twice through acidic and basic alumina using hexanes-toluene. Rotorvaping and pumping of the filtrate afforded 90 mg of a white crystalline solid, mp 93-96 °C that consisted (by GC) of **13** (90%), **15** (2%) and six small impurities (8%). The ratio of **13/15** is thus 98/2 . The GC trace and proton NMR spectrum of this material are included with this report.

References and Notes

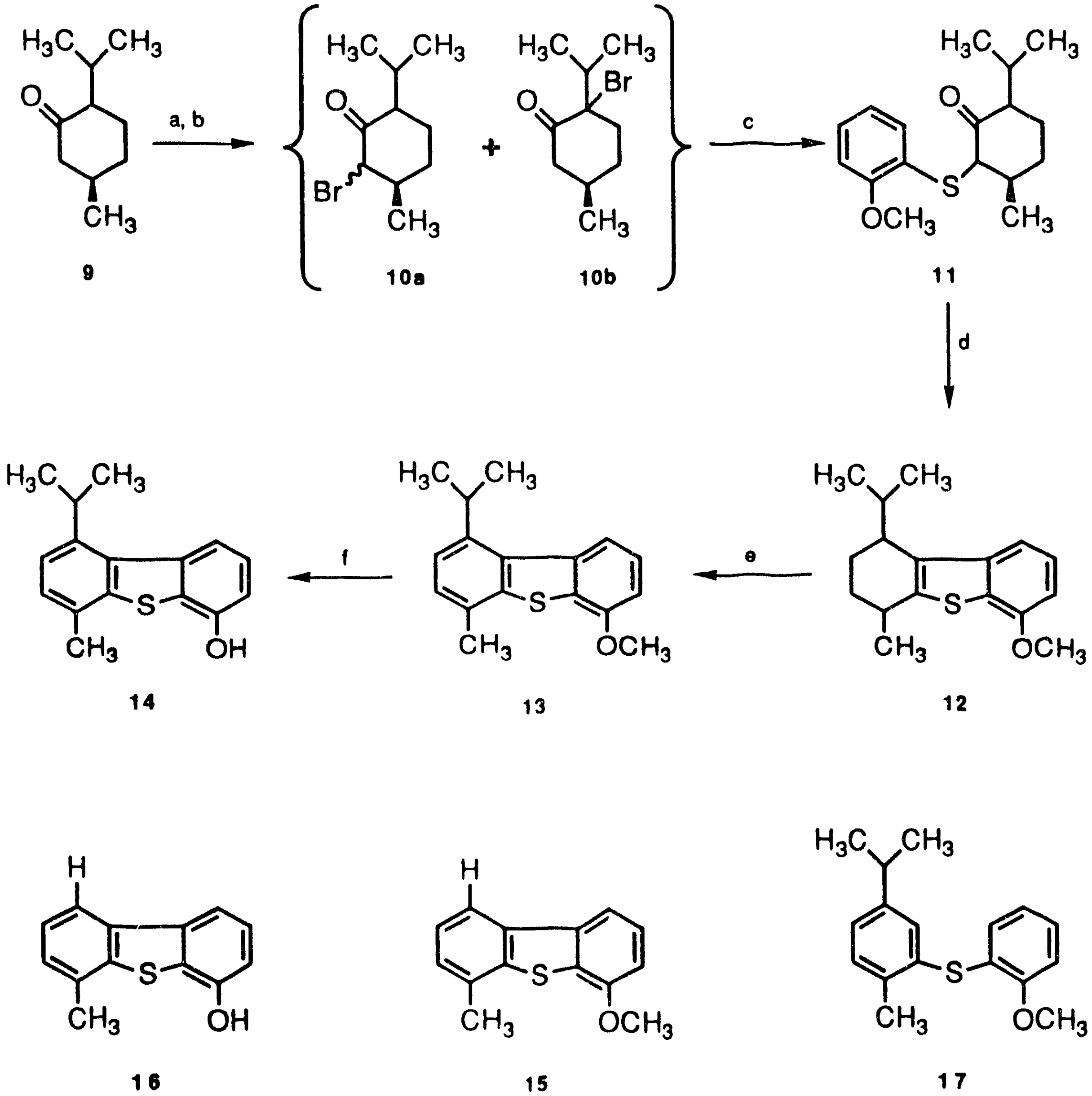
1. Tedjamulia, M.L.; Tominaga, Y.; Castle, R.N.; Lee, M.L. *J. Heterocycl. Chem.* **1983**, *20*, 1485-1495.

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.

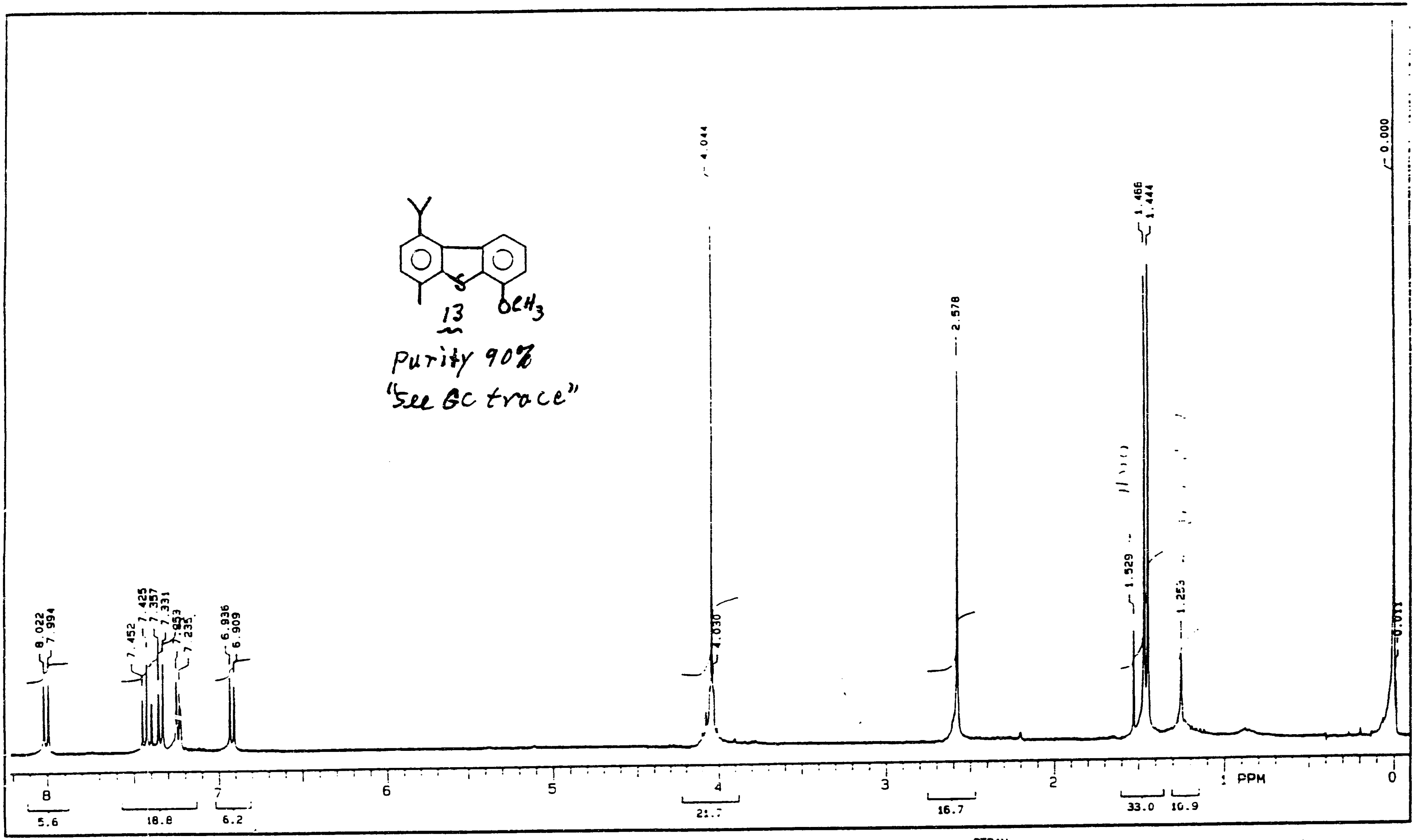
3. (a) Findlay, J.W.A.; Turner, A.B. *Org. Synth.* **1973**, *Coll. Vol. V*, 428-431. (b) Walker, D.; Hiebert, J.D. *Chem. Rev.* **1967**, *67*, 153-195.

4. Vickery, E.H.; Pahler, L.F.; Eisenbraun, E.J. *J. Org. Chem.* **1979**, *44* , 4444-4446.

Scheme



^{a} LDA, TMSCl, THF, -78 °C. ^{b} Br_2, CH_2Cl_2, -78 °C. ^{c} 2-Methoxybenzenethiol, NaOH, EtOH-H_2O at Reflux. ^{d} PPA, heat. ^{e} Se or Pd/C, 300 °C or DDQ, 80 °C. ^{f} BBr_3, CH_2Cl_2, 0 °C.



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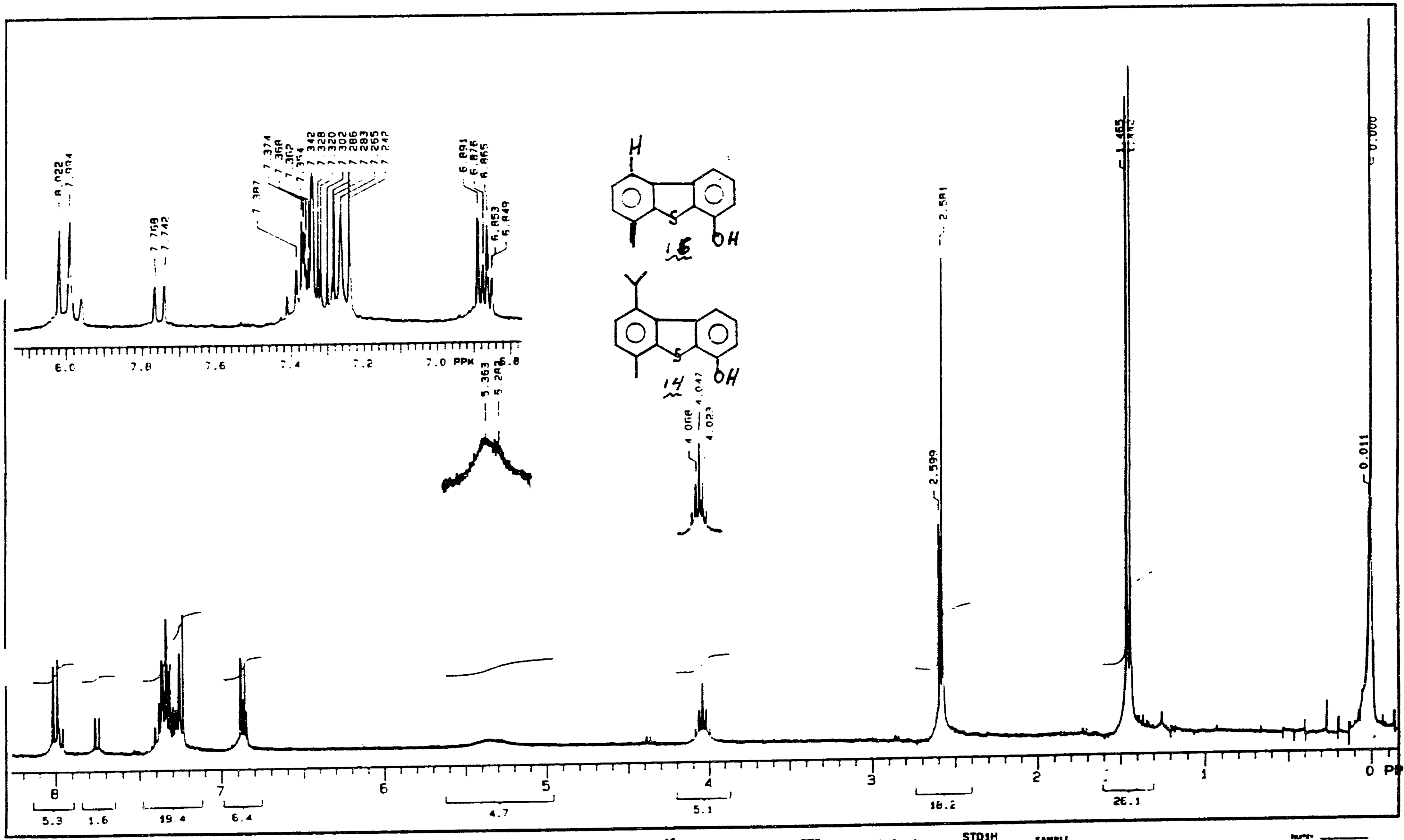

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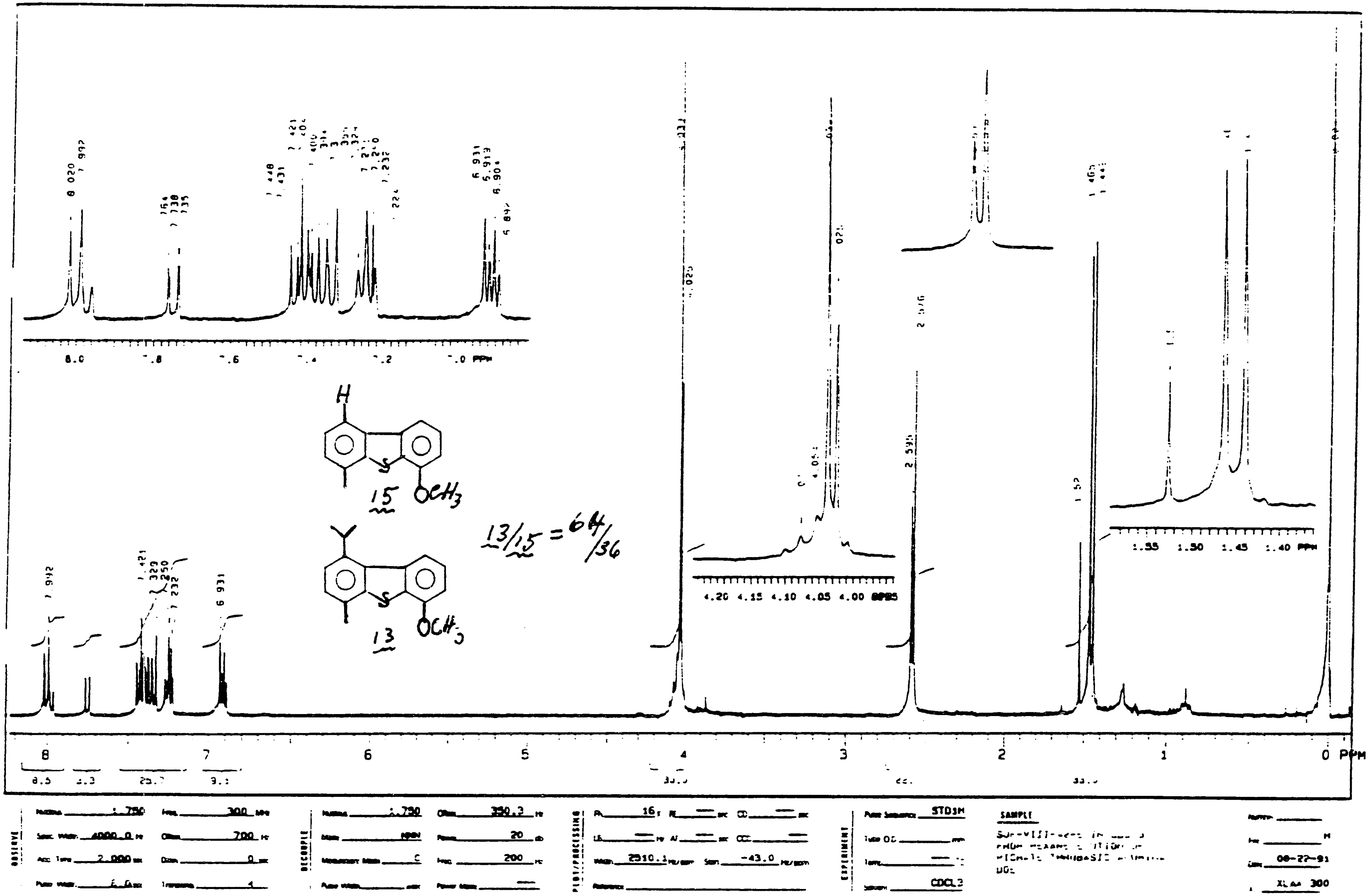
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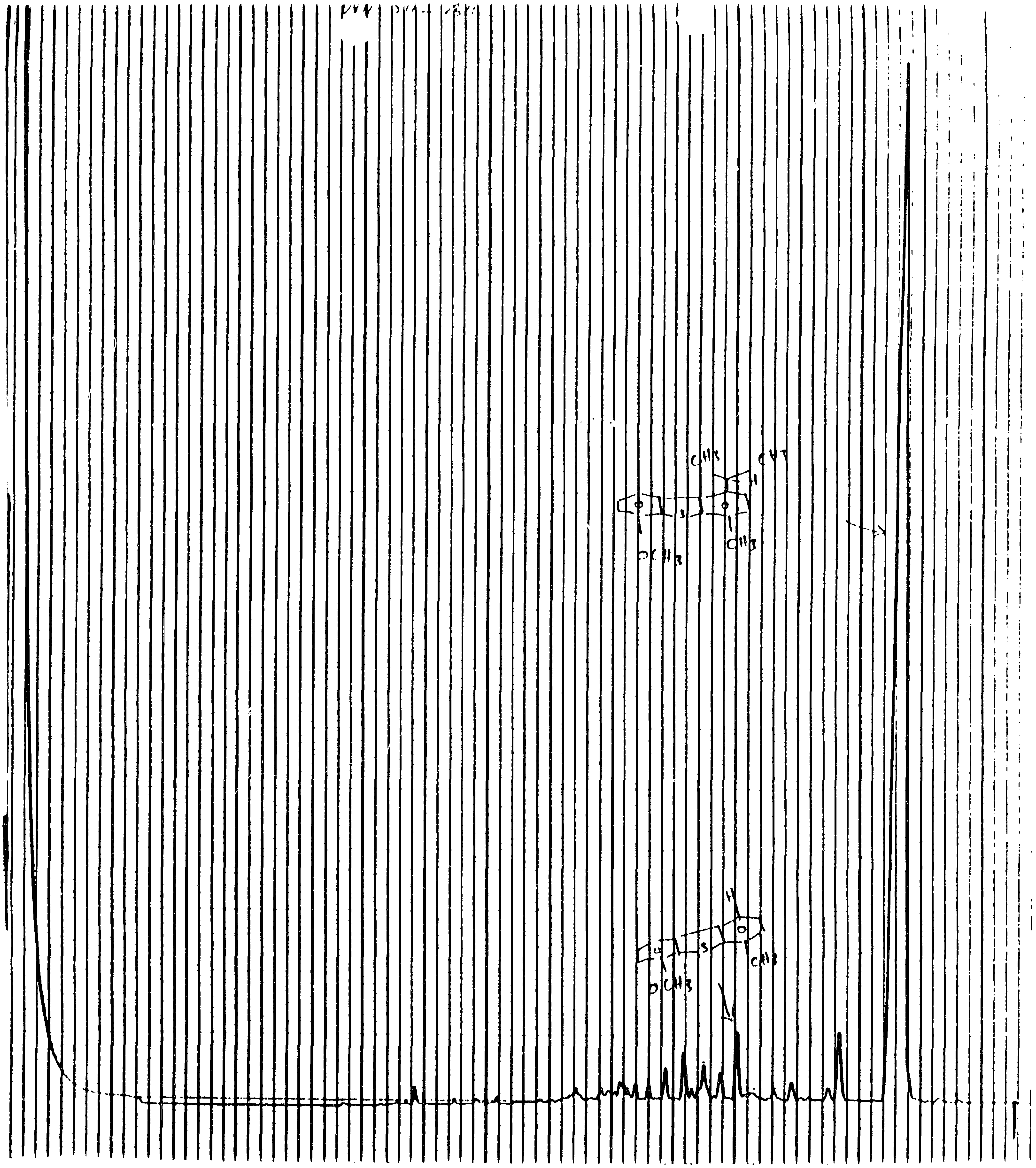
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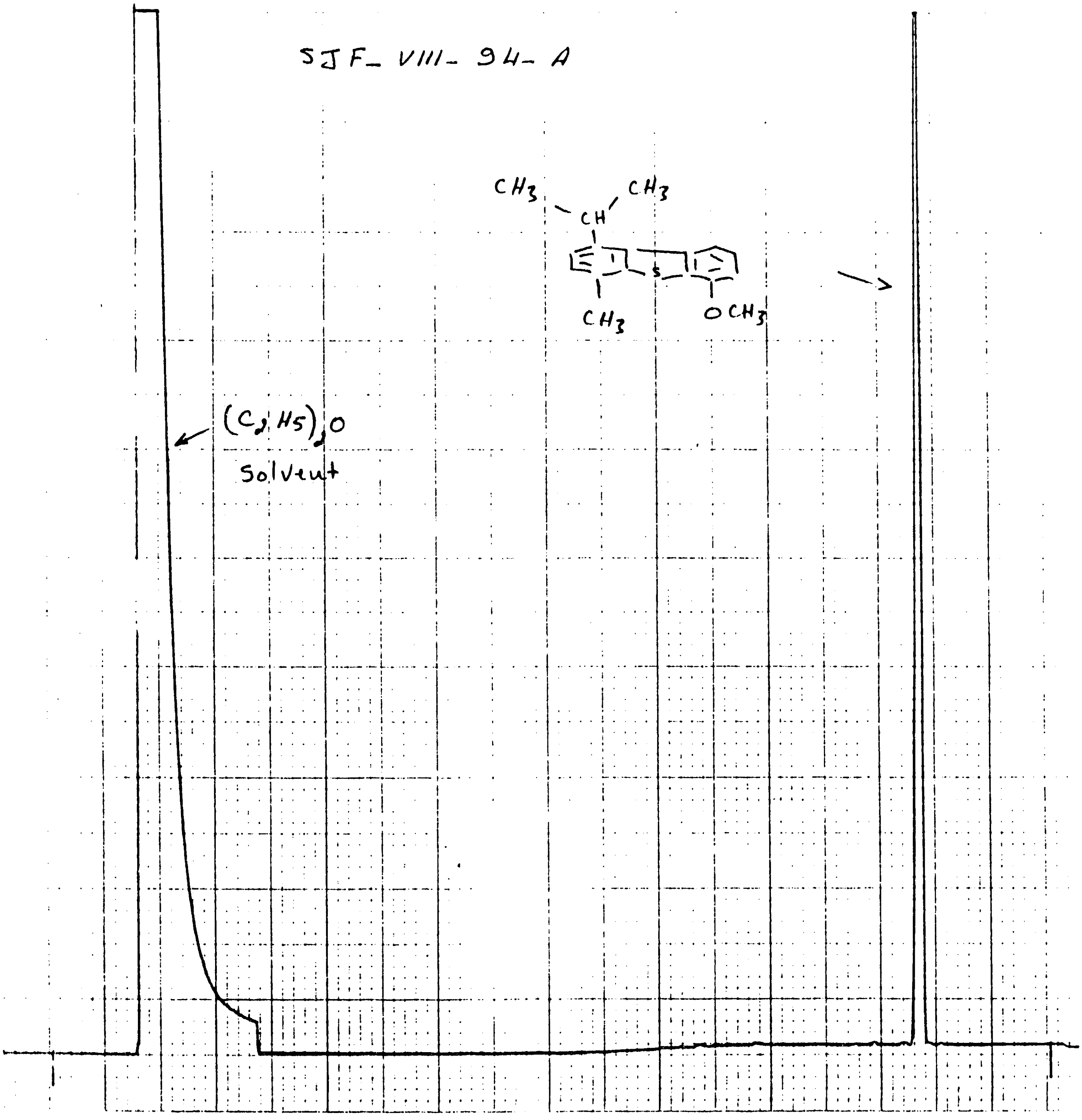

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