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AUTHORITY

USMRDC ltr, 28 Aug 1995

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Rept. D'lmt'd per memo. dtd 28 Aug 95, signed by Col. Gary R. Gilbert, MCMR-RMI-S (70-1y), DCSI Infa Mgmt, Ft. Detrick, MD.

DEPARTMENT OF THE ARMY
U.S. ARMY MEDICAL RESEARCH AND MATERIEL COMMAND
FORT DETRICK, MARYLAND 21702-5012

REPLY TO ATTENTION OF:
MCMR-RMI-S (70-1y)

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28 Aug 95

MEMORANDUM FOR Administrator, Defense Technical Information Center, ATTN: DTIC-HDS/William Bush, Cameron Station, Building 5, Alexandria, VA 22304-6145

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1. The U.S. Army Medical Research and Materiel Command has reexamined the need for the limited distribution statements on technical reports for Contract Number DAMD17-89-C-9057. Request the limited distribution statement for AD Numbers ADB149151, ADB170222, ADB165289, and ADB170839 be changed to "Approved for public release; distribution unlimited." Copies of these reports should be released to the National Technical Information Service.

2. Point of contact for this request is Ms. Judy Pawlus, DSN 343-7322.

for Paulie Rinehart
GARY R. GILBERT
COL, MS
Deputy Chief of Staff
for Information Management

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PREPARATION OF

CHEMICAL COMPOUNDS FOR THE

U.S. ARMY DRUG DEVELOPMENT PROGRAM

ANNUAL REPORT

By

P. Blumbergs
L.V. Dunkerton
B.S. Ross
D.A. Greening
D.J. Dagli
S.W. Warner
A.B. Ash
C.L. Stevens

September 14, 1990

Supported by

U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, Frederick, Maryland 21702-5012

Contract No. DAMD17-89-C-9057

ASH STEVENS INC.
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16. SUPPLEMENTARY NOTATION

17. COSATI CODES			18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)
FIELD	GROUP	SUB-GROUP	
06	01		8-Nitroquinoline, dialkyltetrasulfide, bisquternary pyridinealdoxime, synthesis, [illegible]
06	03		RA 1, 5.

19. ABSTRACT (Continue on reverse if necessary and identify by block number)

The purpose of this contract is to provide chemical compounds for the U.S. Army Medical R & D Command. In the 12 months, 7 assignments were completed. Compounds submitted included a substituted 8-nitroquinoline, five dialkyltetrasulfides and a bisquaternary dioxime.

20. DISTRIBUTION/AVAILABILITY OF ABSTRACT	21. ABSTRACT SECURITY CLASSIFICATION
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Mary Frances Bostian	301-663-7325	SGRD-RMI-S

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FOREWORD

The work described herein was performed under Contract No. DAMD17-89-C-9057 for the Division of Medicinal Chemistry, Walter Reed Army Institute of Research, Walter Reed Army Medical Center. The report covers the period 15 March 1989 to 14 March 1990. Dr. P. Blumbergs served as Principal Investigator, Dr. L.V. Dunkerton as Principal Assistant, Dr. C.L. Stevens as Technical Advisor and Dr. A.B. Ash as Program Manager, phone (313) 872-6400.

The purpose of the contract is to maintain and operate a synthesis laboratory to provide chemical compounds needed in the Drug Development Programs of the U.S. Army Medical Research and Development Command.

Citations of commercial organizations and trade names in this report do not constitute an official Department of The Army endorsement or approval of the products or services of these organizations.

Acknowledgement

The timely advice and assistance of Mr. H.A. Musallam and Dr. Robert R. Engle, the Contracting Officer's Representative (COR), is greatfully acknowledged.

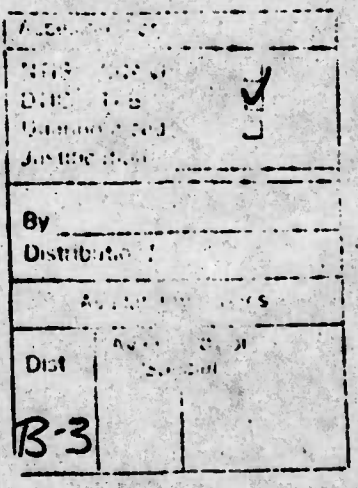

TABLE I

BOTTLE NUMBERS AND WALTER REED NUMBERS

ANNUAL PROGRESS REPORT ENDING MARCH 14, 1990

CONTRACT NO. DAMD17-89-C-9057
(Submitter 0824)

Summary No.	ASI Code No.	Bottle No.	Walter Reed No.	Weight, g	Synthesis Page No. (This Report)
1	DAG-05-126	BL58161 BL58189	248226	15 400(a)	18
2	LVD-01-439	BM01872	41871	9	20
3	BSR-03-154	BM01836	41853	10	21
4	LVD-01-433	BM01854	48634	15	22
5	LVD-01-393	BM01845	48580	15	23
6	LVD-01-437	BM01863	167053	15	24
7	SW-04-44	BM03376	249943	1230	26

(a) Shipped to Franklin Research Center, Morristown, PA.

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PREPARATION OF

CHEMICAL COMPOUNDS FOR THE

U.S. ARMY DRUG DEVELOPMENT PROGRAM

1. SUMMARY OF COMPOUNDS PREPARED AND SUBMITTED

Compounds prepared and submitted from March 15, 1989 through March 14, 1990 are listed below and form the subject matter of this report. These will be discussed in Section 2. Work in progress and assigned compounds will be presented in Section 3, experimental details in Section 4 and references cited in Section 5.

The following assignment were completed in the past twelve months.

1) 5-Hydroxy-6-methoxy-3-methyl-8-nitroquinoline (WR 248226)

a A 400 g sample of the title compound was shipped to Franklin Research Center and a 15 g sample was sent to WRAIR on April 20, 1989, Code No. DAG-05-126, Bottle Nos. BL58189 and BL58161.

2) Dimethyltetrasulfide (WR 41871)

A 9 g sample of the title compound was shipped to WRAIR on October 30, 1989, Code No. LVD-01-439, Bottle No. BM01872.

3) Diethyltetrasulfide (WR 41853)

A 10 g sample of the title compound was shipped to WRAIR on October 30, 1989, Code No. BSR-03-154, Bottle No. BM01836.

4) Dipropyltetrasulfide (WR 48634)

A 15 g sample of the title compound was shipped to WRAIR on October 30, 1989, Code No. LVD-01-433, Bottle No. BM01854.

5) Bis-1-methylethyl)tetrasulfide (WR 48580)

A 15 g sample of the title compound was shipped to WRAIR on October 30, 1989, Code No. LVD-01-393, Bottle No. BM01845.

6) Bis(2-propenyl)tetrasulfide (WR 167053)

A 15 g sample of the title compound was shipped to WRAIR on October 30, 1989, Code No. LVD-01-437, Bottle No. BM01863.

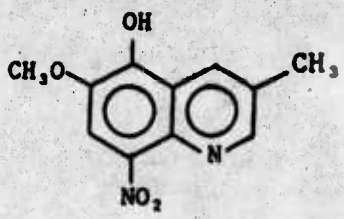
7) 1,1'-Methylenebis[4-(hydroxyiminomethyl)pyridinium] Dichloride (WR 249943)

A 1.23 kg lot of the title compound was shipped to WRAIR on February 9, 1990, Code No. SW-04-44, Bottle No. BM03376.

2. DISCUSSION OF WORK COMPLETED

The seven assignments completed in the past year ending March 14, 1990 are discussed below.

2.1 5-Hydroxy-6-methoxy-3-methyl-8-nitroquinoline (WR 248226)



The title intermediate was prepared previously in these laboratories under another contract (1). The same synthesis sequence shown in Chart No. 1 was used for the current resynthesis. Dinitroveratrole (1) was converted to 4,5-dimethoxy-2-nitroaniline (2) which was condensed with methacrolein in a Skraup cyclization to give 5,6-dimethoxy-3-methyl-8-nitroquinoline (3). The Skraup reaction was modified slightly in that arsenic acid was not used in this step in order to minimize waste disposal problems. Quinoline 3 was obtained in 30% yield as opposed to 45% in the previous preparation. Hydrolysis of 3 gave the title compound.

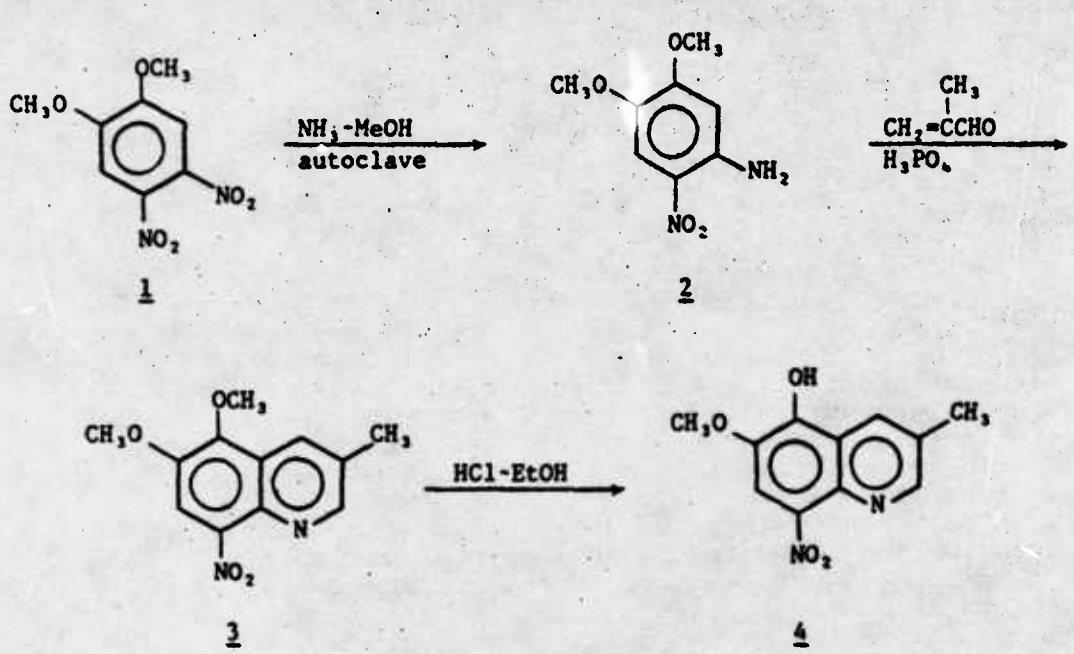
2.2 Dimethyltetrasulfide (WR 41871)

$CH_3SSSSCH_3$

The synthesis sequence to the title compound is shown in Chart No. 2 (R = CH_3) and represents a literature method (2) in which potassium polysulfide, prepared from elemental sulfur, powdered potassium hydroxide and a trace of water is treated with an alkyl halide. In the current work, the procedure was modified slightly in that potassium hydroxide pellets (85%) were used instead of powdered potassium hydroxide. The water in the potassium hydroxide pellets (ca. 15%) was sufficient to catalyze the reaction. The crude product mixture was subjected to rapid vacuum distillation (0.06 mmHg) through a 15 cm Vigreux column in an effort to minimize disproportionation of the tetrasulfide. The fraction containing the most tetrasulfide was redistilled from a radical inhibitor, 3-tert-butyl-4-hydroxy-5-methylphenyl sulfide. The best tetrasulfide-containing fraction was then subjected to vacuum Kugelrohr distillation (0.1 mmHg) to remove trisulfide impurities as the distillate. The pot residue was 93% pure tetrasulfide as analyzed by nuclear magnetic resonance

CHART NO. 1

5-HYDROXY-6-METHOXY-3-METHYL-8-NITROQUINOLINE (WR 248226)



(NMR), and 78% based on analysis by high pressure liquid chromatography (HPLC). The major impurities were trisulfide (4% based on NMR, 7% based on HPLC) and pentasulfide (3% based on NMR, 14% based on HPLC). In view of the many unsuccessful attempts to purify other lots of tetrasulfide which led only to disproportionation, further purification of this lot was not attempted. Elemental analysis was acceptable in carbon, low in sulfur, and high in hydrogen. The hydrogen error is suspect, but the others are consistent with the purity as established by NMR and HPLC. This compound has a persistent stench; appropriate precautions should be taken during handling.

2.3 Diethyltetrasulfide (WR 41853)

$$CH_3CH_2SSSSCH_2CH_3$$

The title compound was prepared using the same modified procedure as that used for dimethyltetrasulfide as shown in Chart No. 2. The crude product was subjected to sequential Kugelrohr, Vigreux, and Kugelrohr distillations without using any radical inhibitors. The nearly pure title compound (100% based on NMR, 95% based on HPLC) had elemental analysis acceptable in carbon and hydrogen, and slightly low in sulfur.

2.4 Dipropyltetrasulfide (WR 48634)

$$CH_3CH_2CH_2SSSSCH_2CH_2CH_3$$

The title compound was prepared using the same modified procedure as that used for dimethyltetrasulfide as shown in Chart No. 2. The crude product was subjected to three successive vacuum distillations, the last two from radical inhibitor. Elemental analysis of the nearly pure title compound (93% based on NMR, 95% based on HPLC) gave results consistent with a mixture containing 93% of the tetrasulfide and 7% of the trisulfide.

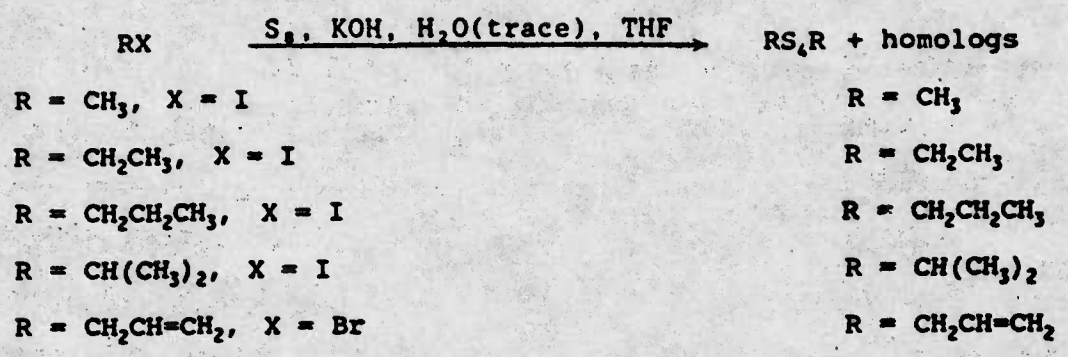
2.5 Bis(1-methylethyl)tetrasulfide (WR 48580)

$$(CH_3)_2CHSSSSCH(CH_3)_2$$

The title compound was prepared using the same modified procedure as that used before for dimethyltetrasulfide as shown in Chart No. 2. One vacuum distillation of the crude product without using a radical inhibitor was sufficient to obtain the title compound nearly pure (100% based on NMR, 87% based on HPLC area, and 90% with 10% trisulfide based on elemental analysis).

CHART NO. 2

DIALKYLTETRASULFIDES

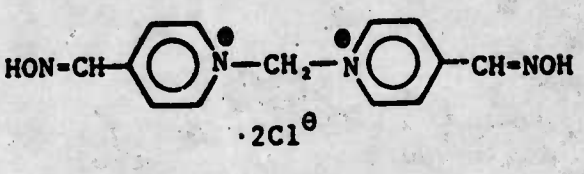


2.6 Bis(2-propenyl)tetrasulfide (WR 167053)

$$CH_2=CHCH_2SSSSCH_2CH=CH_2$$

The title compound was prepared using the same modified procedure as that used before for dimethyltetrasulfide as shown in Chart No. 2. In the first attempt using allyl iodide as the starting material, the crude product polymerized during solvent removal. It was reasoned that more careful temperature control along with using the lower boiling allyl bromide in place of allyl iodide would solve this problem. The next attempt starting with allyl bromide was successful. The crude product was distilled using a Kugelrohr, then the distillate was redistilled through a 15 cm Vigreux column from a radical inhibitor. The best fraction collected was 80% pure title compound, containing 10% each of trisulfide and pentasulfide based on NMR, HPLC, and elemental analysis results.

2.7 1,1'-Methylenebis[4-(hydroxyiminomethyl)pyridinium] dichloride (WR 249943)

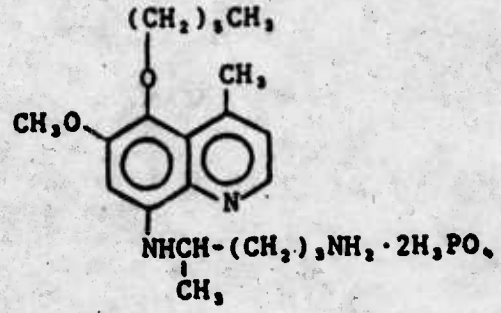


Samples of the title compound were prepared and submitted under previous contracts (3,4). The same procedure was used for the current large scale preparation.

Thus, 4-pyridinealdoxime was treated with methylene bromide in dioxane at reflux for 6 hours. Filtration gave a first crop of crude MMB-4 dibromide. The filtrate was refluxed for an additional 20 h to give a second crop of product, and for 20 more hours to give a third crop. The combined material was recrystallized twice to give pure MMB-4 dibromide. Next, a solution of the dibromide in warm aqueous ethanol was passed over a Dowex 2 ($Cl^{\ominus}$) ion exchange resin. The eluate was diluted with ethanol and the precipitated product was collected and recrystallized from aqueous ethanol to give pure title bisquaternary dichloride.

3. WORK IN PROGRESS AND ASSIGNED COMPOUNDS

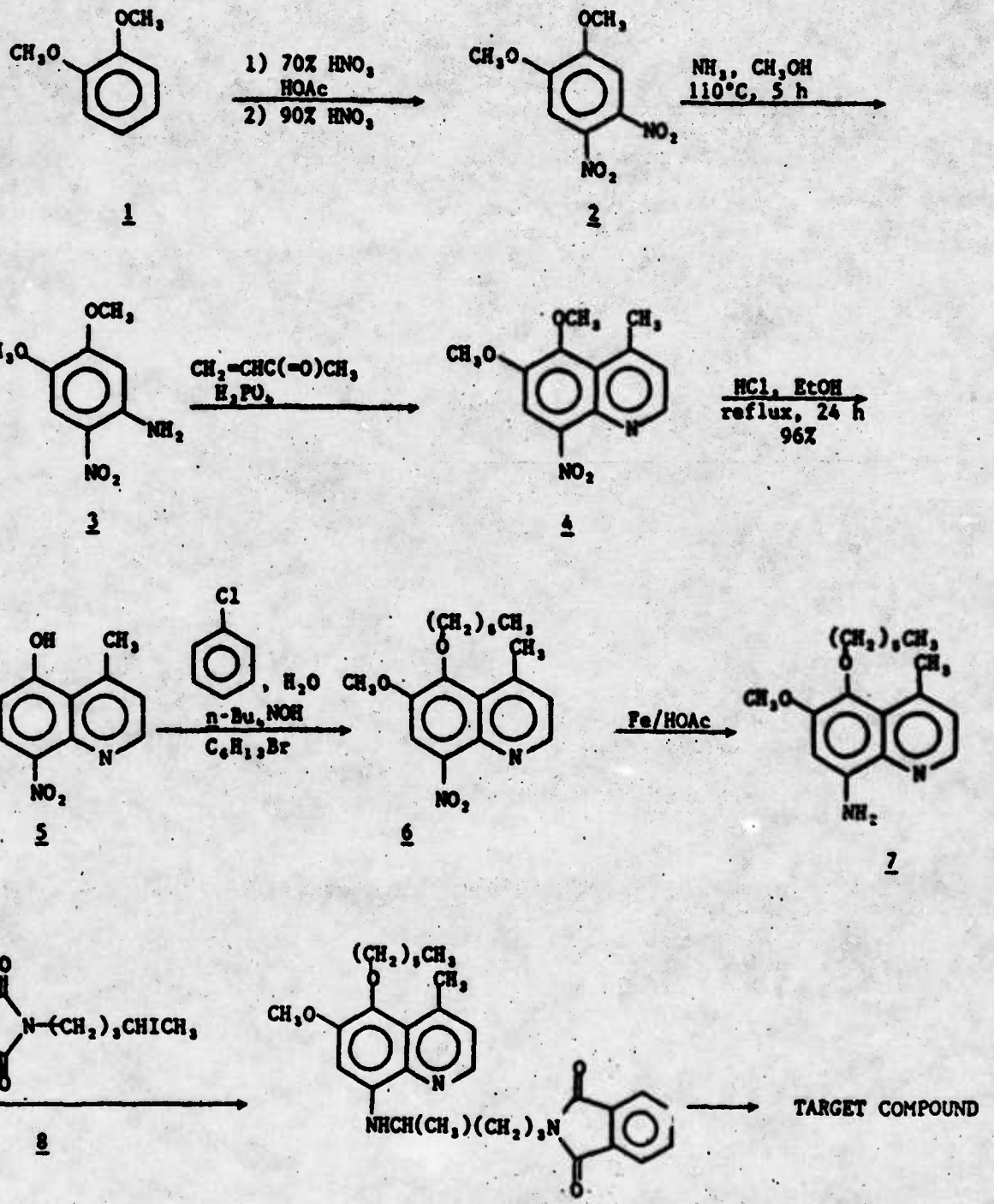
3.1 8-[(4-Amino-1-methylbutyl)amino]-5-(1-hexyloxy)-6-methoxy-4-methylquinoline diphosphate (WR 242511)



The synthesis sequence to the title compound is shown in Chart No. 3. Previously prepared 8-aminoquinoline 7 was coupled with 4-iodopentylphthalimide (8) to give the phthalimido protected quinoline intermediate 9. The crude product 9 was purified by chromatography over silica gel to give 800 g of purified material in the form of an oil which solidified in the refrigerator. The solid was triturated with petroleum ether to yield 650 g of pure compound 9 with acceptable elemental analysis. A small sample of this material was treated with hydrazine to give the title target compound free base. Attempts to convert this material to a diphosphate salt were not successful. The diphosphate salt is strongly acidic and dissociates in solution such that during recrystallization some of the phosphoric acid is lost and the recrystallized product is only a 1.6 or 1.7 phosphate. In view of this, other salts were investigated. The dihydrochloride salt was a gum which could not be obtained in a crystalline form. Citric, DL-tartic, succinic and maleic acid salts were all crystalline. A sample of the DL-tartrate salt was submitted to WRAIR for evaluation. If this material proves to be acceptable, the remainder of intermediate 9 will be converted to the target compound DL-tartrate salt.

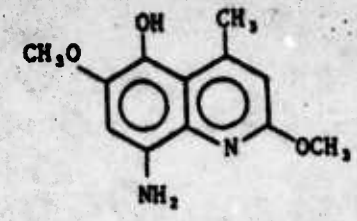
CHART NO. 3

8-[(4-AMINO-1-METHYLBUTYL)AMINO]-5-(1-HEXYLOXY)-6-METHOXY-4-METHYLQUINOLINE DIPHOSPHATE (WR 242511)



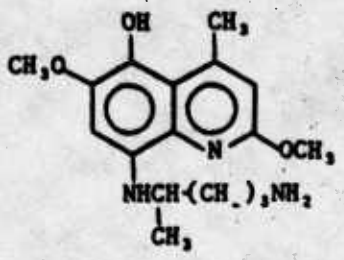
1 2 3 4 5 6 7 8 9

3.2 8-Amino-5-hydroxy-2,6-dimethoxy-4-methylquinoline



The synthesis sequence has been carried to the precursor 5-O-benzyl protected title compound hydrochloride salt. A small sample of this material was hydrogenated over palladium black catalyst to give the presumed 5-hydroxyquinoline target structure. The product appears to be quite unstable, especially in solution. The yield of purified product was less than 35%. A repeat hydrogenation on a larger scale gave incomplete reaction and more forcing conditions (excess acid and 50°C) led to the formation of several side products. The study of this hydrogenalysis step continues.

3.3 8-[(4-Amino-1-methylbutyl)amino]-5-hydroxy-2,6-dimethoxy-4-methylquinoline



The synthesis route to the title compound is shown in Chart No. 4. We note that intermediate 8 is also a precursor to the target compound described in section 3.2 above. A repeat of the synthesis sequence is in progress in order to prepare additional quantities of compound 8 which can be used for both target structures. Work to-date has proceeded to N-oxide 5.

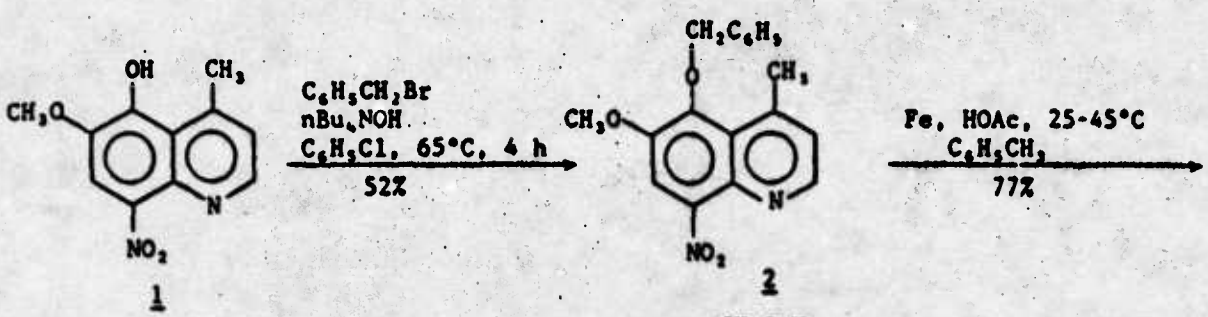
3.4 Thiotaurine

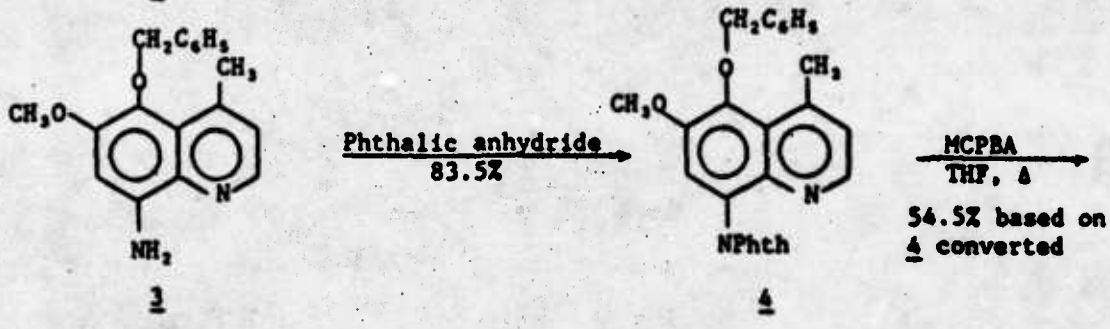
$$H_2NCH_2CH_2SO_2SH$$

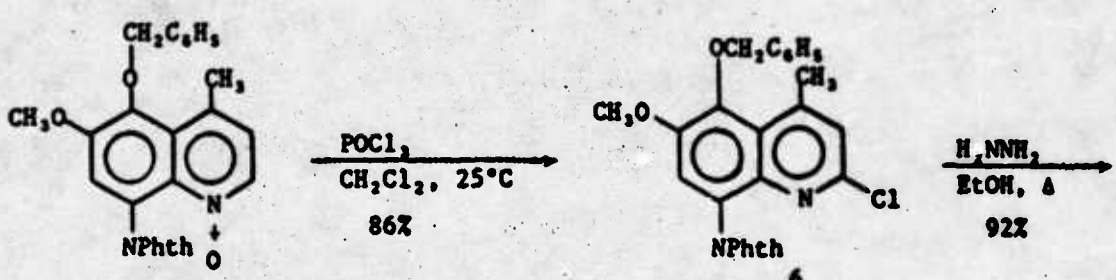
The request is for 100 to 200 g of this structure. Synthesis of the compound has been reported in the literature (5) and work is in progress on step one of the three-step sequence.

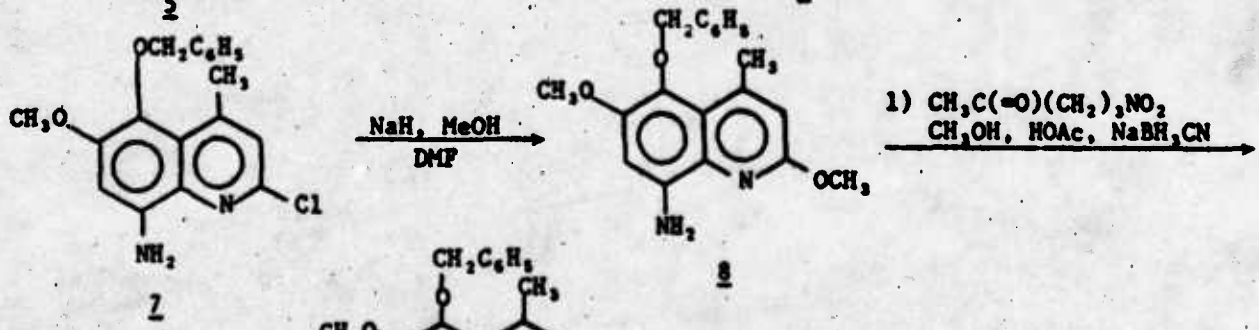
CHART NO. 4

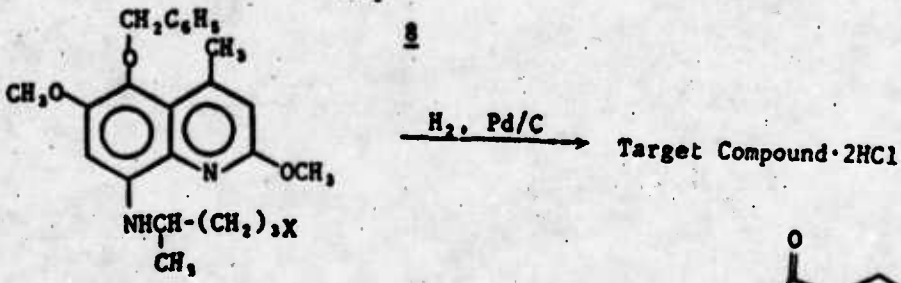
8-[(4-AMINO-1-METHYLBUTYL)AMINO]-5-HYDROXY-2,6-DIMETHOXY-4-METHYLQUINOLINE







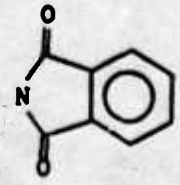




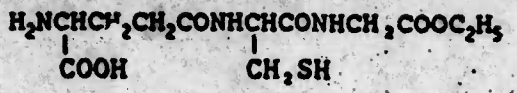
1) Zn, THF-H_2O, NH_4Cl
2) HCl

<u>9</u> X = NO_2

<u>10</u> X = $NH_2 \cdot 2HCl \cdot H_2O$

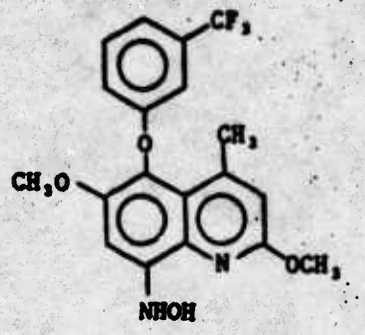


3.5 Glutathione monoethyl ester



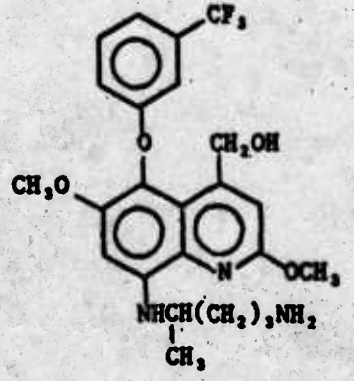
Starting materials for this assignment have been ordered and received. Laboratory work will be initiated shortly.

3.6 8-Hydroxyamino-2,6-dimethoxy-4-methyl-5-(3-trifluoromethylphenoxy)quinoline



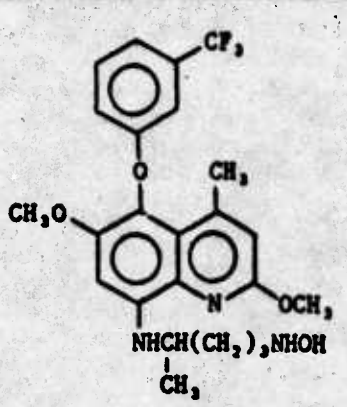
No work was done on this target compound.

3.7 8-[(4-Amino-1-methylbutyl)amino]-4-hydroxymethyl-2,6-dimethoxy-5-(3-trifluoromethylphenoxy)quinoline



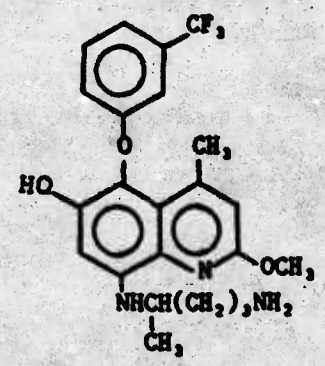
No work was done on this target compound.

3.8 8-[(4-Hydroxyamino-1-methylbutyl)amino]-2,6-dimethoxy-4-methyl-5-(3-trifluoromethylphenoxy)quinoline



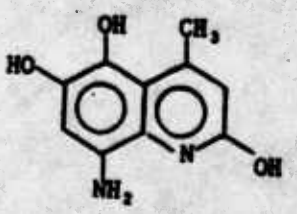
No work was done on this target compound.

3.9 8-[(4-Amino-1-methylbutyl)amino]-6-hydroxy-2-methoxy-4-methyl-5-(3-trifluoromethylphenoxy)quinoline



No work was done on this target structure.

3.10 8-Amino-2,5,6-trihydroxy-4-methylquinoline



No work was done on this target structure.

4. EXPERIMENTAL

All melting and boiling points are uncorrected. Infrared spectra were recorded using a Perkin-Elmer 1310 Spectrometer. Elemental analyses were performed by Midwest Microlab, Ltd., Indianapolis, Indiana. Vapor phase chromatography was performed using an F and M Model 810 with a flame ionization detector. High pressure chromatography was performed using a Beckman Model 110B solvent delivery module with a Milton Roy 3100 variable wavelength detector and a Hewlet Packard HP3394A integrator. NMR spectra were determined on a Varian Model T60 or a Nicolet QE 300 Spectrometer.

4.1 5-Hydroxy-6-methoxy-3-methyl-8-nitroquinoline (WR 248226)

The synthesis sequence to the title compound is shown in Chart No. 1. 4,5-Dimethoxy-2-nitroaniline 2 was prepared according to the previously described procedure (6).

5,6-Dimethoxy-3-methyl-8-nitroquinoline (3) - A mixture of 4,5-dimethoxy-2-nitroaniline (2, 295 g, 1.49 mol) and 85% phosphoric acid (1.33 L) was heated to 90°C (steam bath). Methacrolein (208.7 g, 2.98 mol) was added dropwise over 45 min during which time the internal temperature was maintained at 95-98°C (exothermic reaction). After the addition was completed, the mixture was stirred for 1.5 h at 93-95°C (internal temperature), cooled to 70°C, and poured onto ice (5.5 kg). The aqueous mixture was basified to pH 8-9 by gradual addition of ammonium hydroxide (2 L). The precipitated solid was collected by filtration, washed with water (5 x 300 mL), and air-dried to give 350 g (95%) of crude product. This solid was heated with dichloromethane (1.5 L) at reflux until nearly all of it dissolved. The near solution was dried (K_2CO_3, 200 g) and filtered through celite. The celite pad was washed with dichloromethane (4 x 300 mL). The combined filtrate was concentrated (steam jet) to a volume of ca. 1.2 L and applied onto a column of silica gel (1.0 kg, 86 x 7 cm). The column was eluted with dichloromethane (18 L) and the product-containing fractions were combined and concentrated to an orange-red solid. The solid was triturated with 1:1 ether/petroleum ether (1 L) and the mixture was filtered. The solid was washed with petroleum ether (3 x 200 mL) and air-dried to give 120 g (32%) of partially purified product, a yellow-orange solid, mp 120-121°C.

In this manner, additional aniline 2 (1233 g) was processed to yield 550 g of partially purified product. The combined product (670 g) was dissolved in boiling isopropanol (9.44 L). The solution was treated with Norit A (20.1 g, 3%) and filtered through celite. The filtrate was concentrated to a volume of 2.7 L, then cooled in an ice bath for 3 h. The solid was collected by filtration, washed with cold isopropanol (3 x 300 mL), and air-dried to give 641 g (33%) of nearly pure 3, mp

mp 119.5-121°C. This material was dissolved in boiling methanol (5.5 L). The solution was filtered and the filtrate was cooled (ice bath) for 3 h. The solid was collected by filtration, washed successively with cold methanol (2 x 400 mL), cold isopropanol (2 x 400 mL), and petroleum ether (3 x 500 mL), and dried at 80°C/1 mmHg for 6 h to give 582 g (30%) of pure 3, a yellow crystalline solid, mp 121-122.5°C, lit. mp 120-122°C (1).

Anal. Calcd for $C_{12}H_{12}N_2O_4$ (248.24): C, 58.06; H, 4.87; N, 11.28. Found: C, 58.28; H, 4.71; N, 11.39.

Thin Layer Chromatography Brinkmann Polygram Sil G/UV_{254}

Eluent	R_f	Comment
Dichloromethane	0.30	homogeneous
Toluene/ethanol (5:1)	0.74	homogeneous

Materials

Methacrolein (85%)	Aldrich, Lot No. LV0203DT
4,5-Dimethoxy-2-nitroaniline	ASI Lot No. DAG-05-111-I, -111-II, -112-I, -112-II, and -112-III
Phosphoric acid, 85%	J. T. Baker, Lot No. A13806
Ammonium hydroxide (28-30%)	Ashland, Lot No. 051238E
Silica gel grade 62-H, 60-200 mesh	Davison, Lot No. 7004-53
Sea sand	Fisher Scientific, Lot No. 865733
Potassium carbonate, 99%, anhydrous	Aldrich, Lot No. ML0824ML
Celite 545	Johns Manville, no Lot No.
Petroleum ether (bp 35-60°C)	J.T. Baker, Lot No. A42837
Ethyl ether, purified	Fisher Scientific Lot No. 885835-60
Dichloromethane, ACS reagent	Ashland, Lot No. 0701768E
Norit A, acid washed	Pfanstiehl Laboratories, Lot No. 16838
Isopropanol, 99%	Chemcentral, Lot No. 022289RK
Methanol, 99%	Chemcentral, Lot No. 012088JO

5-Hydroxy-6-methoxy-3-methyl-8-nitroquinoline (4) - A mixture of compound 3 (573 g, 2.31 mol), ethanol (5.40 L), and concentrated hydrochloric acid (575 mL) was heated at reflux for 17 h, then cooled in an ice bath for 2 h. The solid was collected by filtration, washed successively with water (4 x 750 mL), isopropanol (4 x 500 mL), and petroleum ether (4 x 500 mL), and dried at 80°C/1 mmHg for 5 h to give 474 g (88%) of pure 4, a brown crystalline solid, mp 251-253°C (dec), lit. mp 251-253°C (1).

Anal. Calcd for $C_{11}H_{10}N_2O_4$ (234.21): C, 56.41; H, 4.30; N, 11.96. Found: C, 56.52; H, 4.19; N, 11.83.

Thin Layer Chromatography Brinkmann Polygram Sil G/UV_{254}

Eluent	R_f	Comment
Acetonitrile/triethylamine (1:1)	0.38	homogeneous
Isopropanol/water/ammonium hydroxide (7:2:1)	0.81	homogeneous

Materials

5,6-Dimethoxy-3-methyl-8-nitroquinoline (3)	ASI, Lot No. DAG-05-124
Reagent ethanol, 3A	Aaper Alcohol, Lot No. 88J11-R, Serial No. R8824
Hydrochloric acid, ACS reagent	Ashland, Lot No. 120047E
Petroleum ether (bp 35-60°C)	J. T. Baker, Lot No. A42837
Isopropanol, 99%	Chemcentral, Lot No. 022289RK

4.2 Dimethyltetrasulfide (WR 41871)

The synthesis sequence to the title compound is shown in Chart No. 2 (R = CH_3).

To an oven-dried 5-L 3-necked flask equipped with a dropping funnel and overhead stirrer was added potassium hydroxide (85%, 346 g), anhydrous tetrahydrofuran (3.5 L) and powdered sulfur (112 g, 0.44 mol). The mixture was stirred vigorously for 10 min. A solution of methyl iodide (500 g, excess) in tetrahydrofuran (500 mL) was added dropwise over 2 h. The mixture was stirred at room temperature for an additional 19 h. The resulting yellow mixture was filtered and the residue was washed with tetrahydrofuran (ca. 100 mL). The combined filtrate and washings were evaporated (aspirator/steam bath) to a dark red oil. The oil was dissolved in ether (500 mL) and the yellow precipitate was removed by filtration. The filtrate was diluted with ether to a volume of 1 L and washed with 0.02 N HCl (3 x 150 mL) and water (150 mL). The solution was dried ($MgSO_4$) and concentrated (aspirator/steam bath then 1 mmHg/25°C/1 h) to give 63 g of crude product mixture as a red oil. The oil was distilled (0.1 mm Hg/sand bath from 65-100°C) through a 15 cm Vigreux column over 2 h. Two fractions were collected, the first (20 g, bp 40-45°C) over the first h, and the second (15 g, bp 55-65°C) over the second h. The second fraction, based on NMR, contained 25% trisulfide, 61% tetrasulfide, and 14% pentasulfide. It was combined with a 16 g fraction of similar composition from an earlier preparation and distilled (0.06 mm Hg/ sand bath from 75-110°C) through a 15 cm Vigreux column from 3-tert-butyl-4-hydroxy-5-methylphenyl sulfide (1.1 g). Four fractions were

collected. The first fraction (14 g, bp 25-40°C), collected over the first hour, was then redistilled using the Kugelrohr apparatus (0.1 mmHg/40-50°C pot temperature) and 3.9 g of distillate was collected. The pot residue, a light yellow oil, was nearly pure title compound (93% based on NMR and 78% based on HPLC); NMR ($CDCl_3$) δ 2.63 (s).

Anal. Calcd for $C_2H_6S_4$ (156.31); C, 15.37; H, 2.58; S, 82.05. Found; C, 15.21; H, 3.56; S, 81.50.

HPLC (Beckman ultrasphere C_8 5μ, 4.6 mm x 25 cm; 1.2mL/min)

Eluent	R_t	Comment
Methanol/water (3:1)	6.04 min	78% area, 213 nm, S_4
	4.56 min	7% area, 213 nm, S_3
	8.65 min	14% area, 213 nm, S_5

Materials

Potassium hydroxide pellets, 85%	Aldrich, Lot No. 08825KV
Sulfur, sublimed, 100 mesh	Aldrich, Lot No. 04516TV
Tetrahydrofuran, 99.5%	Aldrich, Lot No. 06623CT
3-tert-Butyl-4-hydroxy-5-methylphenylsulfide	Aldrich, Lot No. 00528EM
Methyl iodide	Aldrich, Lot No. 05711PT
Ether, anhydrous	J. T. Baker, Lot. No. 32601
Magnesium sulfate, anhydrous	Curtin Matheson (Chempure) Lot No. M172KBAJ
Hydrochloric acid	Mallinckrodt, Lot No.3560KCRHB

4.3 Diethyltetrasulfide (WR 41853)

The synthesis sequence to the title compound is shown in Chart No. 2 (R = CH_2CH_3).

To an oven-dried 3-L 3-necked flask equipped with a dropping funnel and overhead stirrer was added potassium hydroxide (ground powder, 85%, 75 g), anhydrous tetrahydrofuran (2 L) and powdered sulfur (75 g, 0.3 mol). The mixture was stirred vigorously for 10 min, then ethyl iodide (184 mL, 2.3 mol) was added dropwise over 2 h. The mixture was stirred at room temperature for an additional 1.5 h. The resulting yellow mixture was filtered and the residue was washed with tetrahydrofuran (2 x 250 mL). The combined filtrate and washings were evaporated (aspirator/steam bath) to a dark red oil. The oil was dissolved in ether (600 mL), and the yellow precipitate was removed by filtration. The filtrate was washed with 0.02 N HCl (500 mL), dried ($MgSO_4$), and evaporated (aspirator/steam bath) to give the crude product mixture as a yellow oil. The oil was distilled in the Kugelrohr (0.1 mm Hg/50-80°C) to give 57.4 g of distillate which was redistilled through a jacketed 6-inch

helices-filled column (0.1 mm Hg/oil bath). Four fractions were collected. The last three fractions (32 g, bp 52-77°C/0.1 mmHg), by NMR, were a mixture of trisulfide and tetrasulfide. They were combined and distilled in the Kugelrohr (0.1 mm Hg/ca. 55°C). After collecting ca. 20 g of distillate, the pot residue, 10.5 g, was analyzed by NMR and found to be nearly pure product; NMR ($CDCl_3$) δ 2.97 (q, 4H), 1.41 (t, 6H).

Anal. Calcd for $C_4H_{10}S_4$ (186.38); C, 25.78; H, 5.41; S, 68.82. Found: C, 26.54; H, 5.60; S, 68.50.

HPLC (Beckman ultrashpere C8 5μ, 4.6 mm x 25 cm; 1.2 mL/min)

Eluent	R_t	Comments
Methanol/water (3:1)	9.07 min	95% area, 213 nm, S_4
	13.26 min	3% area, 213 nm, and four other peaks all less than 1% each

Materials

Ethyl iodide	Aldrich, Lot No. 02206HV
Potassium hydroxide pellets, 85%	Aldrich, Lot No. 08825KV
Sulfur, sublimed, 100 mesh	Aldrich, Lot No. 04516TV
Tetrahydrofuran, 99.5%	Aldrich, Lot No. 06623CT
Ether, anhydrous	J. T. Baker, Lot. No. 32601
Magnesium sulfate, anhydrous	Curtin Matheson (Chempure), Lot No. M172KBAJ
Hydrochloric acid	Mallinckrodt, Lot No.3560KCRHB

4.4 Dipropyltetrasulfide (WR 48634)

The synthesis sequence to the title compound is shown in Chart No. 2 (R = $CH_2CH_2CH_3$).

To an oven-dried 5-L 3-necked flask equipped with a dropping funnel and overhead stirrer was added potassium hydroxide (85%, 378 g), anhydrous tetrahydrofuran (3.5 L) and powdered sulfur (97 g, 0.38 mol). The mixture was stirred vigorously for 10 min. A solution of n-propyl iodide (500 g, excess) in tetrahydrofuran (500 mL) was added dropwise over 2 h. The mixture was stirred at room temperature for an additional 19 h. The resulting yellow mixture was filtered and the residue was washed with tetrahydrofuran (ca. 100 mL). The combined filtrate and washings were evaporated (aspirator/steam bath) to a dark red oil. The oil was dissolved in ether (500 mL). The yellow residue was removed by filtration, and the filtrate was diluted with additional ether to 500 mL. The ether solution was washed with 0.02 N HCl (3 x 150 mL), water (500 mL), dried ($MgSO_4$) and concentrated (aspirator/steam bath then 1 mmHg/25°C/1 h) to give the crude product mixture as a red oil. The procedure was repeated to give additional crude product. The combined crude

product was distilled (0.2 mmHg/sand bath 75-120°C) through a 15 cm Vigreux column. Four fractions, 117, 18, 90, and 14 g were collected. The second and third fractions were combined (108 g, bp 65-75°C/0.2 mmHg) and redistilled (0.04 mm Hg/sand bath 70-100°C) through a 15 cm Vigreux column from 3.5 g (5 mole %) of 3-tert-butyl-4-hydroxy-5-methylphenyl sulfide. Three fractions, 8, 34, and 61 g were collected. The third fraction (61 g) was redistilled (0.04 mmHg/ sand bath 80-110°C) through a 15 cm Vigreux column from 2.0 g of the same radical inhibitor. Four fractions, 7, 6, 41, and 3 g were collected. The third fraction, a yellow oil, (41 g, bp 68-71°C/0.04 mm Hg) was nearly pure product (93% based on NMR and elemental analysis and 95% based on HPLC); NMR ($CDCl_3$) δ 2.91 (t, J = 7.2 Hz, 4H), 1.78 (dt, J = 7.2, 7.2 Hz, 4H), 1.01 (t, J = 7.2 Hz, 4H).

Anal. Calcd for $C_6H_{14}S_4$ (214.43); C, 33.61; H, 6.58; S, 59.81. Found: C, 34.10; H, 6.75; S, 59.10.

HPLC (Beckman ultrasphere C8 5μ, 4.6 mm x 25 cm; 1.2 mL/min)

Eluent	R_t	Comments
Methanol/water (3:1)	16.20 min	95% area, 213 nm, S_4
	11.73 min	5% area, 213 nm, S_3

Materials

n-Propyl iodide	Aldrich, Lot Nos. 05612MV, and 16215EW
Potassium hydroxide pellets, 85%	Aldrich, Lot No. 08825KV
Sulfur, sublimed, 100 mesh	Aldrich, Lot No. 04516TV
Tetrahydrofuran, 99.5%	Aldrich, Lot No. 06623CT
3-tert-Butyl-4-hydroxy-5-methylphenylsulfide	Aldrich, Lot No. 00528EM
Ether, anhydrous	J. T. Baker, Lot. No. 32601
Magnesium sulfate, anhydrous	Curtin Matheson (Chempure), Lot No. M172KBAJ
Hydrochloric acid	Mallinckrodt, Lot No.3560KCRHB

4.5 Bis(1-methylethyl)tetrasulfide (WR 48580)

The synthesis sequence to the title compound is shown in Chart No. 2 [R = $CH(CH_3)_2$].

To an oven-dried 5-L 3-necked flask equipped with a dropping funnel and overhead stirrer was added potassium hydroxide (85%, 378 g), anhydrous tetrahydrofuran (3.5 L) and powdered sulfur (97 g, 0.38 mol). The mixture was stirred vigorously for 10 min. A solution of i-propyl iodide (500 g, excess) in tetrahydrofuran (500 mL) was added dropwise over 2 h.

The mixture was stirred at room temperature for an additional 19 h. The resulting yellow mixture was filtered and the residue wash washed with tetrahydrofuran (ca. 100 mL). The combined filtrate and washings were evaporated (aspirator/ steam bath) to a dark red oil. The oil was dissolved in ether (500 mL) and the yellow residue was removed by filtration. The filtrate was diluted with additional ether to 500 mL and washed with 0.02 N HCl (3 x 150 mL) and water (150 mL). The ether was dried ($MgSO_4$) and evaporated (aspirator/ steam bath then 1 mmHg/25°C/ 1 h) to give 125 g of the crude product mixture as a red oil. The mixture was distilled (0.4 mmHg/sand bath 65-85°C) through a 15 cm Vigreux column. Three fractions, 11, 34, and 2 g were collected. The second fraction, a yellow oil, (34 g, bp 62-67°C/0.4 mmHg) was nearly pure title compound (100% based on NMR, 87% based on HPLC, and 90% with 10% trisulfide based on elemental analysis); NMR ($CDCl_3$) δ 3.33 (septet, J = 6.6 Hz, 2H), 1.41, d, J = 6.6 Hz, 6H).

Anal. Calcd for $C_6H_{14}S_4$ (214.43): C, 33.61; H, 6.58; S, 59.81. Found: C, 34.50; H, 6.74; S, 59.36.

HPLC (Beckman ultrasphere C8 5μ, 4.6 mm x 25 cm; 1.2 mL/min)

Eluent	R_t	Comments
Methanol/water (3:1)	19.26 min	87% area, 213 nm, S_4
	30.09 min	9% area, 213 nm, and two additional peaks ca. 1% each

Materials

i-Propyl iodide	Aldrich, Lot No. 00825AW
Potassium hydroxide pellets, 85%	Aldrich, Lot No. 08825KV
Sulfur, sublimed, 100 mesh	Aldrich, Lot No. 04516TV
Tetrahydrofuran, 99.5%	Aldrich, Lot No. 06623CT
Ether, anhydrous	J. T. Baker, Lot. No. 32601
Magnesium sulfate, anhydrous	Curtin Matheson (Chempure), Lot No. M172KBAJ
Hydrochloric acid	Mallinckrodt, Lot No.3560KCRHB

4.6 Bis(2-propenyl)tetrasulfide (WR 167053)

The synthesis sequence to the title compound is shown in Chart No. 2 (R = $CH_2CH{=}CH_2$).

To an oven-dried 5-L 3-necked flask equipped with a dropping funnel and overhead stirrer was added potassium hydroxide (85%, 300 g), anhydrous tetrahydrofuran (3.5 L) and powdered sulfur (76 g, 0.4 mol). The mixture was stirred vigorously for 30 min. A solution of allyl bromide (500 g, excess) in tetrahydrofuran (500 mL) was added dropwise over 2 h. The mixture was stirred at room temperature for an additional 24 h. The resulting yellow mixture was filtered and the residue

was washed with tetrahydrofuran (ca. 100 mL). The combined filtrate and washings were evaporated (aspirator/steam bath) to a dark red oil. The oil was dissolved in ether (500 mL) and the yellow residue was removed by filtration. The filtrate was diluted with additional ether to 1 L. The ether solution was washed with 0.02 N HCl (3 x 100 mL), water (4 x 100 mL) and dried ($MgSO_4$). The solvent was evaporated (aspirator/steam bath then 1 mmHg/25°C/20 h) to give 93 g of the crude product mixture as a red oil. The crude product was distilled in the Kugelrohr apparatus (0.25 mm Hg/65-110°C) to give 71 g of orange oil which by NMR consisted of 2% monosulfide, 8% disulfide, 38% trisulfide, 41% tetrasulfide, and 11% pentasulfide. The oil was redistilled (0.1 mmHg/sand bath 70-120°C) through a 15 cm Vigreux column from 2.2 g of 3-tert-butyl-4-hydroxy-5-methylphenyl sulfide. Four fractions were collected, 28, 5, 25, and 6 g. The third fraction (25 g, bp 68-80°C/0.1 mm Hg) was purified further by Kugelrohr distillation (0.25 mm Hg/40-60°C). After collecting 8.5 g of distillate, the pot residue (a yellow oil, 15.8 g) was 80% pure title compound, containing 10% each of tri and pentasulfides based on NMR, HPLC and elemental analysis; NMR ($CDCl_3$) δ 5.96-5.82 (ddt, J = 17.0, 7.5, 1.2 Hz, 2H), 5.29-5.22 (dd, J = 17.0, 1.2 Hz, 2H), 5.24-5.18 (dd, J = 9.6, 1.2 Hz, 2H); 3.58 (d, J = 7.5 Hz, 4H).

Anal. Calcd for $C_6H_{14}S_4$ (214.43): C, 34.25; H, 4.79; S, 60 96. Found C, 34.46; H, 4.73; S, 60.88.

HPLC (Beckman ultrasphere C8 5μ, 4.6 mm x 25 cm; 1.2 mL/min)

Eluent	R_t	Comments
Methanol/water (3:1)	11.84 min	80% area, 213 nm, S_4
	6.81 min	10% area, 213 nm, S_3
	18.00 min	10% area, 213 nm, S_5

Materials

Allyl bromide	Aldrich, Lot No. 00828PV
Potassium hydroxide pellets, 85%	Aldrich, Lot No. 08825KV
Sulfur, sublimed, 100 mesh	Aldrich, Lot No. 04516TV
Tetrahydrofuran, 99.5%	Aldrich, Lot No. 06623CT
3-tert-Butyl-4-hydroxy-5-methylphenylsulfide	Aldrich, Lot No. 00528EM
Ether, anhydrous	J. T. Baker, Lot. No. 32601
Magnesium sulfate, anhydrous	Curtin Matheson (Chempure), Lot No. M172KBAJ
Hydrochloric acid	Mallinckrodt, Lot No.3560KCRHB

4.7 1,1'-Methylenebis[4-(hydroxyiminomethyl)pyridinium] Dichloride (WR 249943)

The title compound was prepared in the same manner as described previously (3,4). Dioxane was used as the reaction solvent in the first step.

1,1'-Methylenebis[4-(hydroxyiminomethyl)pyridinium] Dibromide: - A mixture of 4-pyridinealdoxime (1.50 kg, 12.28 mol) and dibromomethane (6.45 kg, 37.1 mol) in dioxane (12 L) was heated at reflux under a nitrogen atmosphere for 6 h. A second identical scale run was carried out simultaneously.

The precipitated solid from both runs was collected by filtration in one Buchner funnel, washed with dioxane (4 L) and air-dried to give 866 g of crude product. The filtrate and wash were returned to the two flasks and heated at reflux for 20 h. The precipitated solid was collected again by filtration, washed with dioxane (1 x 2 L, 1 x 1 L), and air-dried to give a 1655 g second crop. The filtrate and wash were returned once more to the flasks and heated at reflux for 20 h. The solid was isolated by filtration, washed with dioxane (1 x 2 L, 1 x 1 L) and air-dried to give a 1124 g third crop. The combined yield of crude product was 3.65 kg (71%).

By this procedure, a total of 9.92 kg of 4-pyridinealdoxime was converted to 13.87 kg of crude product.

The crude product (6.32 kg) was dissolved in warm (60-65°C) ethanol/deionized water (19 L:25 L). The solution was stirred with Norit (632 g) for 30 min and filtered through a pad of celite. The celite pad was washed with 50% aqueous ethanol (1.5 L). The combined filtrate was diluted with ethanol (88 L) and cooled with stirring to 10°C. The mixture was filtered and the solid was washed with ethanol (6.4 L) and air-dried overnight. The solid was dried further at 100°C/1 mmHg for 18 h to give 4.59 kg of once recrystallized product.

A total of 13.86 kg of crude product was processed in this manner to give 9.71 kg of once recrystallized product.

The once-recrystallized material (4.59 kg) was dissolved in a warm (60-65°C) mixture of ethanol and water (13.8 L:18.36 L). The solution was treated with Norit (210 g) and filtered through a pad of celite. The celite pad was washed with 50% aqueous ethanol (3 L). The combined filtrate and wash was diluted with ethanol (64.2 L) and cooled to 10°C. The solid was collected by filtration, washed successively with ethanol (4 x 5 L) and petroleum ether (4 x 5 L) and air-dried overnight. The solid was dried further at 100°C/1 mmHg for 18 h to give 3.81 kg of pure product, mp 229-230°C (dec), lit. mp 244-245°C (dec) (3), mp 237-238°C (dec) (4).

Anal. Calcd for $C_{13}H_{14}Br_2N_4O_2$ (418.09): C, 37.35; H, 3.38; Br, 38.22; N, 13.40. Found: C, 37.37; H, 3.23; Br, 37.98; N, 13.45.

The remainder of the once-recrystallized product (5.12 kg) was treated in identical manner to give 3.96 kg of pure product, mp 229-230°C (dec).

Anal. Found: C, 37.54; H, 3.27; Br, 37.96; N, 13.39.

The yield of pure product, based on 4-pyridinealdoxime, was 46%.

Materials

4-Pyridinealdoxime	Aldrich, Lot No. 03905ET
Dibromomethane	Moore-Tec, No Lot No.
Dioxane Mallinckrodt,	Lot Nos. KAPM and KDPA
Ethanol, reagent	Aaper, Lot Nos. R9529, 89D19-R, 89K06
Norit 211	Kodak, Lot No. 807198C
Celite 545	Johns Manville, Lot No. G5P34633
Water, deionized	Ash Stevens Inc.

1,1'-Methylenebis[4-(hydroxyiminomethyl)pyridinium] Dichloride (WR 249943): - Commercial Dowex 2-X8 (11 kg, chloride form) was packed in a column and washed with 5% aq sodium hydroxide (271 L) until the eluate showed a negative test for chloride ion. The resin was washed with water (63 L) until the eluent was neutral, then with 1.5 N hydrochloric acid (97 L). The resin was washed again with water (124 L) until the eluate was neutral. This gave 13.5 kg of damp, washed resin.

A total of 39 kg of commercial resin was processed in this manner to give 47 kg of damp, washed resin.

A column (100 x 8 cm) was packed with the washed Dowex 2X8 resin (2.2 kg) in warm (50-55°C) 80% aqueous ethanol. A solution of the bisquaternary dibromide (190 g) in warm ethanol/water (570 mL:760 mL, 50-53°C) was applied to the column. The column was allowed to drain and when the solution level reached the top of the resin bed, additional dibromide (190 g) in warm aqueous ethanol was applied to the column. The column was eluted with warm (50-53°C) 80% aqueous ethanol. The first fraction (800 mL) contained no product and it was discarded. The following four fractions (1 L each) were collected, treated with Norit (7 g each), and filtered through a celite pad. The combined stirred filtrate was diluted with ethanol (8 L) and cooled in an ice-acetone bath for 90 min. The solid was collected by filtration, washed successively with cold ethanol (1 L) and ether (2 L), and

dried at 25°C/1 mmHg for 18 h to give 223 g of product, mp 240-241°C (dec).

In this manner, a total of 7.70 kg of the bisquaternary dibromide was processed to give 4.59 kg of product dichloride.

The bisquaternary dichloride (735 g) was dissolved in 50% aqueous ethanol (3.5 L, preheated to 50-53°C). The solution was treated with Norit (73 g) and filtered through a pad of analytical grade celite. A second batch of the dichloride (735 g) was treated in the same manner and filtered through the same celite pad. The celite pad was washed with 50% aqueous ethanol (300 mL). The combined filtrate and wash was stirred and diluted portionwise with ethanol (13.9 L, 13.9 L and 3.5 L). The stirred mixture was cooled in an acetone-ice bath for 2 h and filtered. The solid was washed successively with cold ethanol (2 x 2 L) and ether (3 x 2 L) and air-dried for 2 h. The solid was dried further at 25°C/1 mmHg for 18 h and at 90°C/1 mmHg for 18 h to give 1.25 kg of pure product, mp 239-240°C (dec), Lot No. SW-04-44, lit. mp 250-252°C (dec) (3), mp 245-246°C (dec) (4).

Additional product, 3.1 kg, was recrystallized in two batches of 1.55 kg each to give pure product, 1.41 kg, mp 239-240°C (dec) as Lot No. SW-04-61 and 1.36 kg, mp 238-239°C (dec) as Lot No. SW-04-63. The combined product yield was 4.02 kg (66% based on the dibromide).

Anal. Calcd for $C_{13}H_{14}Cl_2N_4O_2$ (329.19): C, 47.43; H, 4.29; Cl, 21.54; N, 17.02. Found, Lot No. SW-04-44: C, 47.39; H, 4.29; Cl, 21.44; N, 17.23. Found, Lot No. SW-04-61: C, 47.44; H, 4.19; Cl, 21.44; N, 17.03. Found, Lot No. SW-04-63: C, 47.36; H, 4.24; Cl, 21.38; N, 17.04.

Materials

Dowex 2X8, chloride form, 50-100 mesh	Dow, Lot No. MM860722-FA
Sodium hydroxide, reagent	Fisher, Lot Nos. 862372 and 861065
Hydrochloric acid	Ashland, Lot No. 061749F
Ethanol, reagent	Aaper, Lot Nos. 89-K06-R and 90-A124-R
Ether, reagent	Fisher, Lot Nos. 881166-60, 895184-36 and 894961-36
Norit 211	Kodak, Lot No. 807198C
Celite 545	Johns Manville Lot Nos. G5P34633 and 3P-291-34
Celite, analytical	Fisher, Lot No. 312035

5. REFERENCES CITED

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