UNCLASSIFIED

AD NUMBER: AD0441232

LIMITATION CHANGES

TO:

Approved for public release; distribution is unlimited.

FROM:

Distribution authorized to US Government Agencies only; Administrative/Operational Use; 1 May 1964. Other requests shall be referred to Air Force Systems Command, Air Force Avionics Laboratory, Wright-Patterson AFB, OH 45433.

AUTHORITY

USAF ltr dtd 1 Apr 1969

THIS PAGE IS UNCLASSIFIED

L

AL TDR 64-130
Part I

SYNTHESIS OF PANCHROMATIC PHOTOSENSITIZING DYES
Part I. Synthesis

TECHNICAL DOCUMENTARY REPORT NO. AL TDR 64-130, Part I

May 1964

AF Avionics Laboratory
Research and Technology Division
Air Force Systems Command
Wright-Patterson Air Force Base, Ohio

Project No. 6272, Task No. 627204

(Prepared under Contract No. AF 33(657)-11430 by Monsanto Research Corporation, Boston Laboratory, Everett, Massachusetts; John S. Driscoll, Richard H. Nealey, Ann E. Bekebrede, W. R. Smith, and John C. MacDonald, authors)

DDC
RECEIVED
JUN 22 1964
DDC-IRA D

NOTICES

DDC release to OTS not authorized.

U.S. Government agencies may obtain copies from DDC. Other qualified DDC users may request through the Air Force Avionics Laboratory.

FOREWORD

This report was prepared by Monsanto Research Corporation, Boston Laboratory, Everett, Massachusetts under USAF Contract No. AF 33(657)-11430. The contract was initiated under Project No. 6272, Task No. 627204. The work was administered under the direction of the Air Force Avionics Laboratory, Research and Technology Division; Mr. James R. Pecqueux was project engineer.

This report covers work conducted from 1 April 1963 to 31 March 1964.

Dr. John S. Driscoll was Project Leader for Monsanto Research Corporation. The contributions of Mr. W. J. Arigo and Mr. C. Koritsas to the laboratory work are gratefully acknowledged.

ABSTRACT

Seventeen analytically pure cyanine and porphin photosensitizing dyes have been prepared. The synthesis of 1-substituted thionine compounds is also described. Structural proofs, intermediate products, experimental procedures, and spectra are discussed.

This report has been reviewed and is approved.

James R. Pecqueux
Project Engineer
Photographic Branch
Reconnaissance Division
AF Avionics Laboratory

TABLE OF CONTENTS

Page

TABLE OF CONTENTS
(Continued)

Page

TABLE OF CONTENTS
(Continued)

Page

TABLE OF CONTENTS
(Continued)

TABLE OF CONTENTS
(Continued)

TABLE OF CONTENTS
(Continued)

LIST OF FIGURES

LIST OF FIGURES
(Continued)

LIST OF FIGURES
(Continued)

LIST OF FIGURES

LIST OF FIGURES

(Continued)

LIST OF FIGURES

(Continued)

LIST OF TABLES

I. INTRODUCTORY SUMMARY

A. CONTRACT OBJECTIVE

The overall objective of this work was the preparation by reproducible methods of pure dyes for use as photosensitizing agents in the nonconventional photographic systems currently under investigation by the Air Force.

The new photographic systems, though possessing unique processability and sensitivity, are nevertheless deficient in their response to the red region of the visible spectrum. Rather than have the needed sensitizers developed as part of each process research program, the Air Force has established a program to provide a single source of sensitizers for all processes under development.

In order to achieve these objectives, structural proofs were necessary for the final products and were desirable for intermediate compounds. High purity products were also required. Whenever possible, chromatographically, as well as analytically pure samples were prepared.

B. RESULTS

1. Dyes Prepared

Seventeen analytically pure dyes were delivered during the contract period. These compounds were representative of two general classes of dyes, the cyanines and the porphins.

a. Cyanine-Type Dyes

In some instances, references to the cyanine dyes requested were located in the patent literature. As a rule, however, little useful data were obtainable from these references. In other instances, only dyes that were similar to the requested cyanines were located. In several cases, a rigorous structural proof of the dye reaction product led to the assignment of a structure other than that proposed in the patent work.

These syntheses have required as few as one and as many as twelve reaction steps, not including purifications.

b. Porphin Dyes

The synthesis of tetraphenylporphin and its chelates is well described in the chemical literature. The preparation of chromatographically pure porphins, however, is quite difficult. This is partially due to recently improved techniques for the detection of trace impurities. For example, an analytically pure sample of copper (II) tetraphenylporphin, which had been isolated in a single column chromatographic band, was shown to contain two trace

---

Manuscript released by authors 31 March 1964 for publication as an RTD Technical Documentary Report.

impurities by thin-layer chromatography. This necessitated further purification.

The tetrathienylporphin chelates are not characterized in the literature.

The synthesis of a porphin chelate requires a minimum of three reaction steps, one Soxhlet extraction, and four column chromatographic purification steps to produce chromatographically and analytically pure material. The overall yield is one per cent.

c. Thionine Dyes

While no thionine dyes have yet been delivered, a considerable amount of work has been directed towards their synthesis. Several key intermediates have been prepared and characterized. Synthetic work in this area can be classed as relatively difficult.

2. Dye Purity

The achievement of the desired degree of purity was found to be time consuming. In many instances, the synthesis and purification procedures required equal amounts of time.

Thin-layer chromatography, spectroscopic analysis, and elemental analyses were used to determine the purity of the submitted sensitizing dyes.

3. Literature Survey

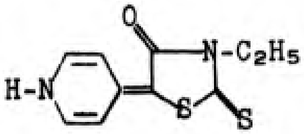
An abstracted literature survey has been carried out in the area of photosensitizing dyes. The survey is critical, not comprehensive. A 1961-1963 thionine dye survey is included. This work is contained in a separate volume as Part II of the final report on AF 33(657)-11430.

C. PLAN OF THE REPORT

The report treats each sensitizing dye in a separate section, with the discussion of the intermediate products, experimental procedures, references and spectra grouped together.

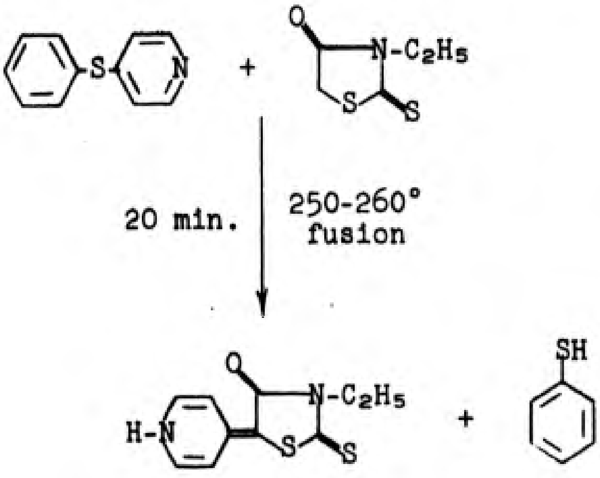
II. SYNTHETIC PROCEDURES

A. 3-ETHYL-5-[4(1H)-PYRIDYLIDENE]RHODANINE (CODE NAME F23M1)



1. Synthesis

a. Discussion of the Literature Method



F23M1

(1) Reaction Products

The synthesis of F23M1 has been described by Jones (ref. 1) and Kodak (ref. 2).

When the reaction was carried out according to the patent procedure (ref. 1), a red crystalline material was obtained in addition to the described orange solid. The two differently colored materials had slightly different decomposition points. A mixed decomposition point is not a conclusive proof of identity. The two compounds had identical infrared spectra and the same relative thin layer chromatographic R_f values in both acetone and methanol. The color of the red material could be changed to orange by grinding. Recrystallization of the red material gave a mixture of red and orange compounds. The different colors are concluded to be due to different crystalline forms of the desired compound.

Crude yields of 40.0 and 30.2% were obtained from two runs.

(2) Proof of Structure

The infrared spectrum of F23M1 is shown in section IIA4 of this report. The carbonyl frequency is weak and at a low frequency compared with unconjugated rhodanine derivatives. The low frequency shift is best explained by the conjugation of the pyridylidene nitrogen with the rhodanine carbonyl group.

The elemental analysis agrees with the calculated values (see Experimental, IIA2).

(3) Purity

The samples submitted to the Air Force are considered to be of high purity for the following reasons:

1. Thin layer chromatography (acetone or methanol elution and iodine development) showed only one spot.
2. The elemental analysis was performed on material taken from the Air Force sample.

(4) Air Force Sample

Four 2.75-gram samples of F23M1 (total 11.0 g), bottled under nitrogen, were submitted on 17 June 1963.

b. Unsuccessful Attempt to Improve the Literature Method

Because the Kodak method gave low yields, several exploratory runs were made to try to improve this synthesis. In a preliminary experiment, purified 3-ethylrhodanine and 4-phenylthiopyridine were reacted in test tubes over an open flame in the solvents listed in Table 1. A dark red color indicates dye formation.

Table 1

REACTION SOLVENTS FOR F23M1 SYNTHESIS

Solvent	Color
none (fusion)	dark red melt
pyridine	no change
pyridine + $(Bu)_3N$	darkening
$(Bu)_3N$	light red solution
$(Bu)_3N$ + diglyme	dark red solution
$(Bu)_3N$ + triglyme	dark red solution
$(Bu)_3N$ + triphenylphosphate	light red solution
triphenylphosphate	dark red solution

Bu = *n*-butyl

No product could be isolated from the triphenylphosphate reaction after benzene extraction to remove the phosphorus-containing solvent.

A trial run on a 10^{-2} molar scale was carried out in diglyme (diethyleneglycol dimethyl ether). Diglyme (bp 162°C) rather than triglyme (bp 216°C) was used for ease of solvent removal. After a 19-hour reflux period, only a small amount of brown solid could be isolated from the dark red solution. Further attempts to improve the literature method were discontinued.

2. Experimental

a. Starting Materials

3-Ethylrhodanine (Eastman 3760, 100 g, \$10.55) was recrystallized from methanol to give yellow needles, mp 38-39°C [lit. (ref. 3) mp 36-38°C].

4-Phenylthiopyridine (Eastman P7805, 25 g, \$8.75) was distilled through an 8-inch Vigreux column, bp 153-155°C/7 mm [lit. (ref. 4) bp 160°C/60 mm].

b. 3-Ethyl-5-[4(1H)-pyridylidene]rhodanine (F23M1)

3-Ethylrhodanine (44.0 g, 0.28 mole) and 4-phenylthiopyridine (54.0 g, 0.29 mole) were mechanically stirred in a round-bottomed flask immersed in an oil bath maintained at 250-260°C. After a 23-minute reaction period, the dark red reaction mixture was cooled to 0°C, and the dark red crystals resulting were filtered. The solid was washed successively with 50 ml of ether, 50 ml of acetone, and 50 ml of ether, and was then dried at 15 mm Hg to yield 26.7 g (40.0%) of dark red crystals (mp darken 270°C, 283-285°C dec.). Recrystallization from hot pyridine with a small amount of methanol added to the pyridine filtrates gave an initial layer of red-purple crystals on the bottom of the flask. The orange needles obtained on prolonged refrigeration were decanted from the red crystals. Further recrystallization of the red material (mp 267-268°C dec.) gave orange solid.

The crude product was recrystallized twice from pyridine-methanol and the resulting F23M1 dried at 80°C/15 mm for 4 hr to give 6.5 g (9.7%) of orange needles [mp darken 265°, 271-272°C dec. (dependent on heating rate); lit. mp 270-271°C dec. (ref. 1); $\lambda_{max}^{CH_3OH}$ 454 mμ (∈ 66,500) and 286 mμ (∈ 6730)]. Each recrystallization reduced the yield by 50%.

Analysis (for $C_{10}H_{10}N_2OS_2$):

	C	H	N	S
Calc'd.	50.39	4.23	11.76	26.91
Found	50.32	4.43	11.52	27.04

c. Unsuccessful Synthesis Using Diglyme as Solvent

Diglyme (the dimethylether of diethyleneglycol) (25 ml) was distilled from 50% sodium hydride in mineral oil directly into a 100-ml round-bottomed reaction vessel. To this solvent was added 2.0 g (1.07×10^{-2} mole) of 4-phenylthiopyridine, 1.72 g (1.07×10^{-2} mole) of 3-ethylrhodanine, and 1.16 g (1.5×10^{-2} mole) of triethylamine, and the mixture was heated to reflux. The solution color changed from light yellow to dark red during the first hour of the 19-hour reflux period. The solution was cooled to room temperature, and the diglyme solvent was removed under reduced pressure to yield a red oil. All attempts to make this oil crystallize failed. Addition of 150 ml of ether produced 100 mg of brown solid (mp 154-?°C). This synthesis was abandoned.

3. References

1. J. E. Jones, U. S. Patent, 2,977,229, March 28, 1961. C.A., 55, 14136d (1961).

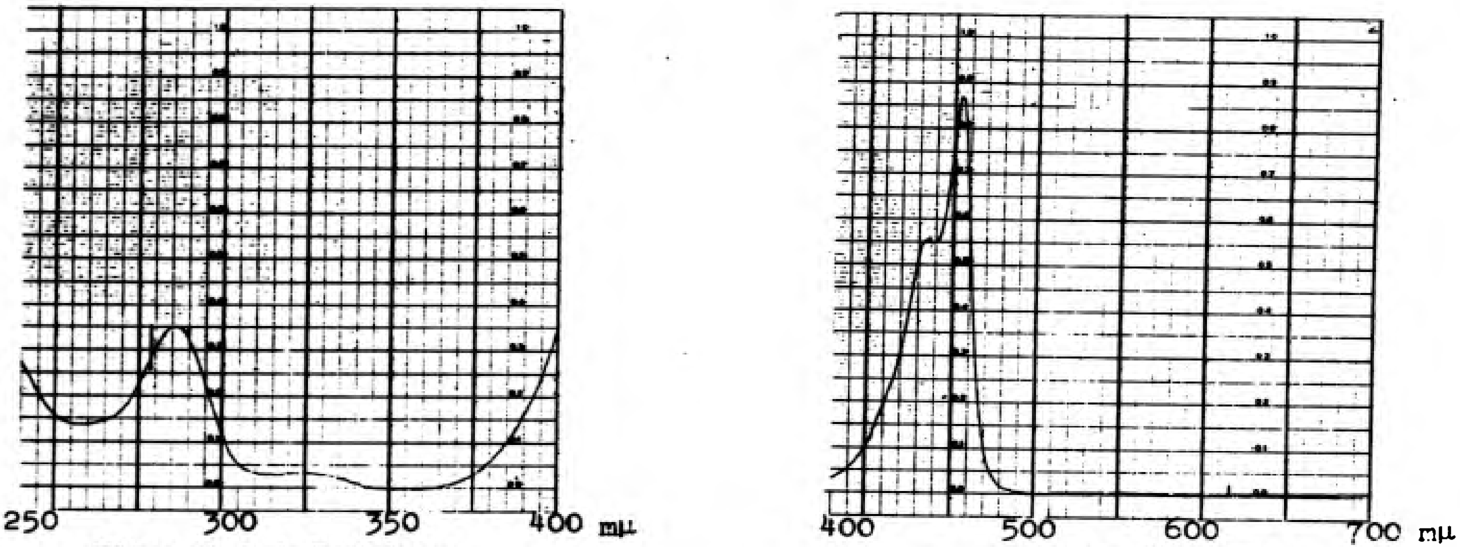
2. Kodak Soc. anon., Belg. Patent 588,862, April 15, 1960. C.A., 55, 12511 (1961).

3. No literature reference to the mp other than that of the supplier could be found.
   <u>Eastman Organic Chemicals</u>, List 43, Compound 3760, p. 118, Dec. 3, 1962.

4. E. Hayashi, <u>et al</u>., <u>Yakugaku Zasshi</u>, <u>80</u>, 1145 (1960). <u>C.A.</u>, <u>55</u>, 546d (1961).

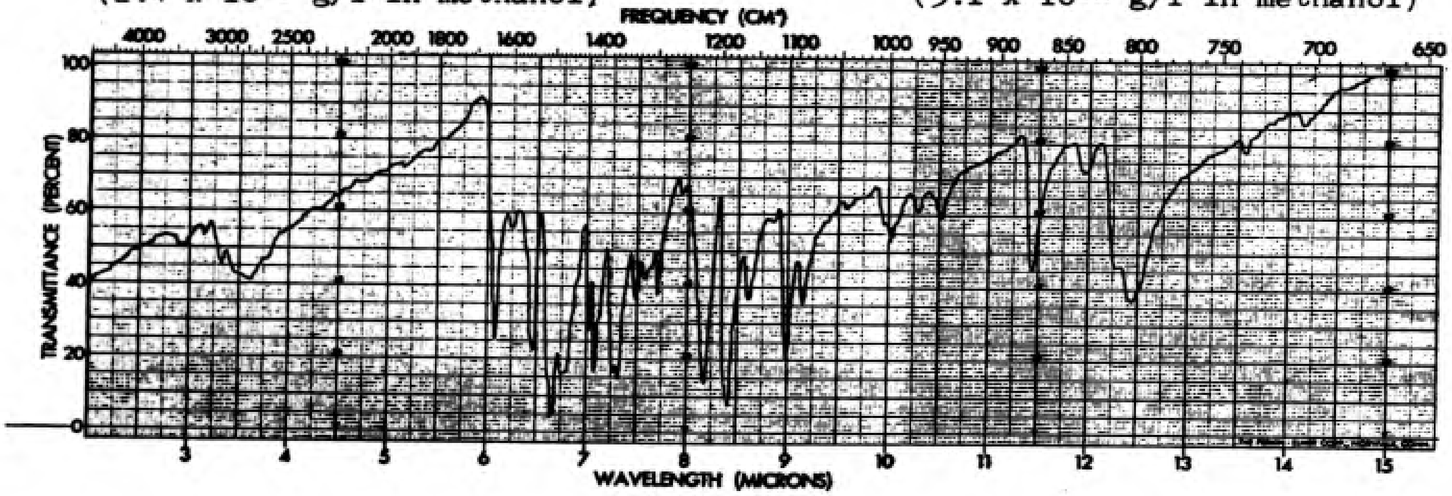
4. Spectra

Spectral data are given in Figure 1.



Ultraviolet Spectrum
(2.4 x 10⁻³ g/1 in methanol)

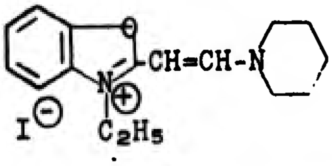
Visible Spectrum
(3.1 x 10⁻³ g/1 in methanol)



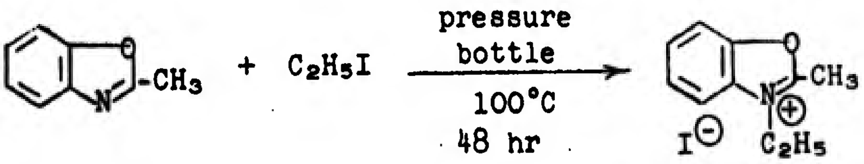
Infrared Spectrum (KBr Pellet)

Figure 1. Spectral Data on 3-Ethyl-5-[4(1H)-pyridylidene]rhodanine (F23M1)

B. 2-[2-(1-PIPERIDYL)VINYL]BENZOXAZOLE ETHIODIDE (CODE NAME F29M2)



1. Synthesis of 2-Methylbenzoxazole ethiodide (B-1)



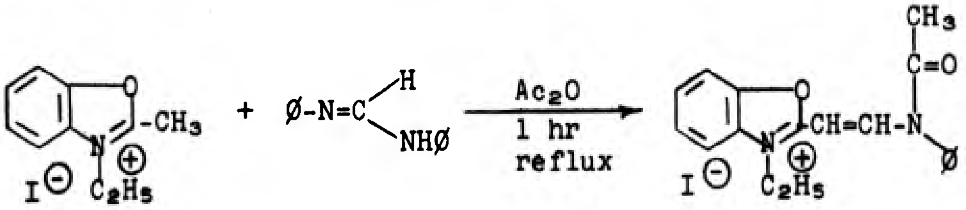
(B-1)

Attempts to synthesize B-1 by refluxing an equimolar mixture of reactants gave very poor yields of the desired compound.

When the reaction was carried out in a sealed glass pressure bottle at 100°C (ref. 1), satisfactory yields of B-1 were obtained. It was found that the reaction mixture attacked the rubber gasket of the pressure bottle, as well as gaskets of Koroseal, a synthetic rubber. Gaskets made of Viton-A have proved very satisfactory. B-1 is attacked by atmospheric moisture and should be recrystallized from absolute ethanol and kept under a nitrogen atmosphere.

The infrared spectrum of B-1 (Figure 2) shows C=N and phenyl C=C bands at 1636, 1602, 1481and 1461 cm^{-1}. Lack of a significant C-O stretch around 1200-1300 cm^{-1} is probably not significant since this sometimes occurs in cyclic ethers such as furans. The infrared spectrum is consistent with the structure.

2. Synthesis of 2-[2-(β-Acetanilido)vinyl]benzoxazole ethiodide (B-2)

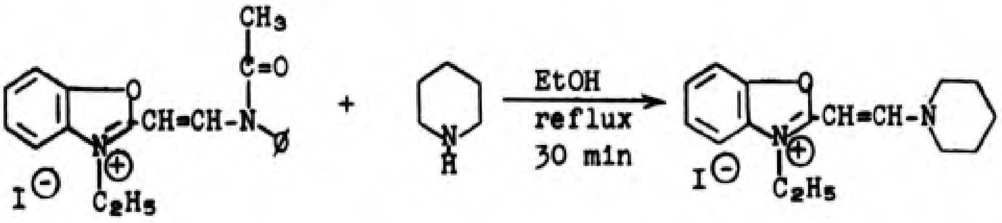


(B-1) (B-2)

The red reaction solution must be filtered, scratched, and cooled before the orange product will precipitate. The infrared spectrum (Figure 3) shows a strong amide carbonyl at 1722 cm^{-1} with C=C and C=N at 1624, 1615, 1602, 1588, 1563, 1489, and 1430 cm^{-1}. The C-O absorption appears at 1221 cm^{-1} with monosubstituted phenyl at 761, 710 and 704 cm^{-1}. The infrared spectrum is consistent with the structure.

Three runs gave yields of 53, 54 and 56 per cent.

3. Synthesis of 2-[2-(1-Piperidyl)vinyl]benzoxazole ethiodide (F29M2)



(B-2) (F29M2)

a. Discussion

This is a straightforward reaction, which presents no difficulties. Three runs gave crude F29M2 in yields of 78, 82, and 89 per cent.

b. Proof of Structure

(1.) Infrared Spectrum

The strong C=O absorption present in the starting material, (B-2), is completely absent as expected (Figure 4). Bands at 1632 and 1591 cm^{-1} indicate C=C and C=N absorptions, while the strong absorptions at 1450 cm^{-1} are characteristic of aliphatic CH_2 groups.

The doublet at 1241 and 1261 cm^{-1} indicates aliphatic C-N and the C-O ether linkage. Ortho benzene substitution (oxazole ring) is seen at 770, 754, and 738 cm^{-1}. The infrared spectrum is consistent with the assigned structure.

Slight frequency and major intensity changes were noted with samples of similar decomposition points that had been recrystallized a different number of times (1 to 3 times). This may be due to different cis-trans isomer ratios, crystal form (polymorphism) or, less likely, impurities in the samples recrystallized only once.

(2.) Elemental Analysis

The elemental analysis agrees with the assigned structure (see Experimental, IIB4).

c. Purity

The sample sent for analysis was taken directly from the sample submitted to the Air Force.

Thin-layer chromatography on Silica Gel-G showed one spot with acetone or monoglyme (dimethyl ether of ethylene glycol) development and iodine treatment. Methanol elution gave uninterpretable results.

d. Air Force Sample

Four 5.3-gram samples of F29M2 (total 21.2 g), bottled under nitrogen, were submitted on 3 July 1963.

4. Experimental

a. Starting Materials

2-Methylbenzoxazole (Eastman No. 982, 100 g - $14.65) was used as received without further purification.

Ethyl iodide, reagent grade (MC and B No. EX685, 1 lb - $11.65) was distilled before use.

N,N'-Diphenylformamidine (K and K, 100 g - \$7.50) was recrystallized from absolute ethanol (1 g /5 ml) [mp 137-139°C; lit. (ref. 3) mp 137°C].

Piperidine (MC and B No. PX1235, 100 g - \$4.60) was used without further purification.

b. 2-Methylbenzoxazole ethiodide (B-1) (ref. 1)

2-Methylbenzoxazole (27.5 g, 0.21 mole) and ethyl iodide (20.0 ml, 38.6 g, 0.25 mole) were placed in a 150-ml pressure bottle (A. H. Thomas Co. No. 2282) equipped with a Viton-A sealing gasket. After being heated on a steam bath for 48 hr, the solidified reaction mixture was washed with six 25-ml portions of anhydrous ethyl ether and filtered. The crude quaternary ethiodide was dried at 60°C/15 mm for 2 hr giving 32.9 g (54%) of buff crystals, [mp soften 193°C, 197-199°C dec.; lit. (ref. 1) mp 195-197°C dec.]. This product was used without further purification.

c. 2-(β-Acetanilidovinyl)benzoxazole ethiodide (B-2) (ref. 2)

2-Methylbenzoxazole ethiodide (27.9 g, 9.3×10^{-2} mole), N,N'-diphenylformamidine (17.8 g, 9.1×10^{-2} mole), and 125 ml of acetic anhydride were refluxed for one hour (calcium sulfate drying tube) during which time the solution color changed from light yellow to dark red. No solid separated on cooling to 0°C. Upon filtration, cooling, and rubbing the filter flask with a spatula, the desired orange solid separated. It was filtered, washed with 2 50-ml portions of cold acetone, and dried at 60°C/15 mm for 4 hr. The crude orange solid, 22.8 g (56%), [mp 217°C dec.; lit. (ref. 4,5) mp 217°C dec.] was used without further purification.

d. 2-[2-(1-Piperidyl)vinyl]benzoxazole ethiodide (F29M2)

2-(β-Acetanilidovinyl)benzoxazole ethiodide (27.6 g, 6.4×10^{-2} mole) and piperidine (16.1 g, 0.19 mole) were added to 210 ml of absolute ethanol in a 500 ml round-bottomed flask. The amber solution was refluxed for one hour (calcium sulfate drying tube) and then chilled with scratching in an ice bath. The pale yellow solid that precipitated was filtered and dried at 50°C/15 mm for 2 hours. The crude, dry F29M2, 20.1 g (82%), mp 234-240°C was recrystallized three times from absolute ethanol (1 g/10 ml) to give light yellow crystals, which were dried at 100°C/0.5 mm for 12 hr [mp 241-242.5° dec.; no literature reference to this compound could be found; λ_{max}^{EtOH} 347 mμ (ε 61,000); no visible absorption]. Each recrystallization reduced the yield by 7%.

Analysis (for $C_{16}H_{21}IN_2O$)

	C	H	N	I
Calc'd.	50.01	5.51	7.29	33.03
Found	50.06	5.53	7.02	33.30

5. References

1. F. M. Hamer, J. Chem. Soc., 1927, 2796.
2. F. L. White and G. H. Keyes, U. S. Patent 2,166,736, July 18, 1939. C.A., 33, 8515 (1939).
3. J. B. Shoesmith and J. Haldane, J. Chem. Soc., 123, 2704 (1923).
4. E. B. Knott, Brit. Patent 585,708, Feb. 20, 1947. C.A., 45, 6517f (1951).
5. E. B. Knott, U. S. Patent 2,487,882, Nov. 15, 1949. C.A., 44, 6318h (1950).

6. Spectra

Spectral data are given in Figures 2, 3, and 4.

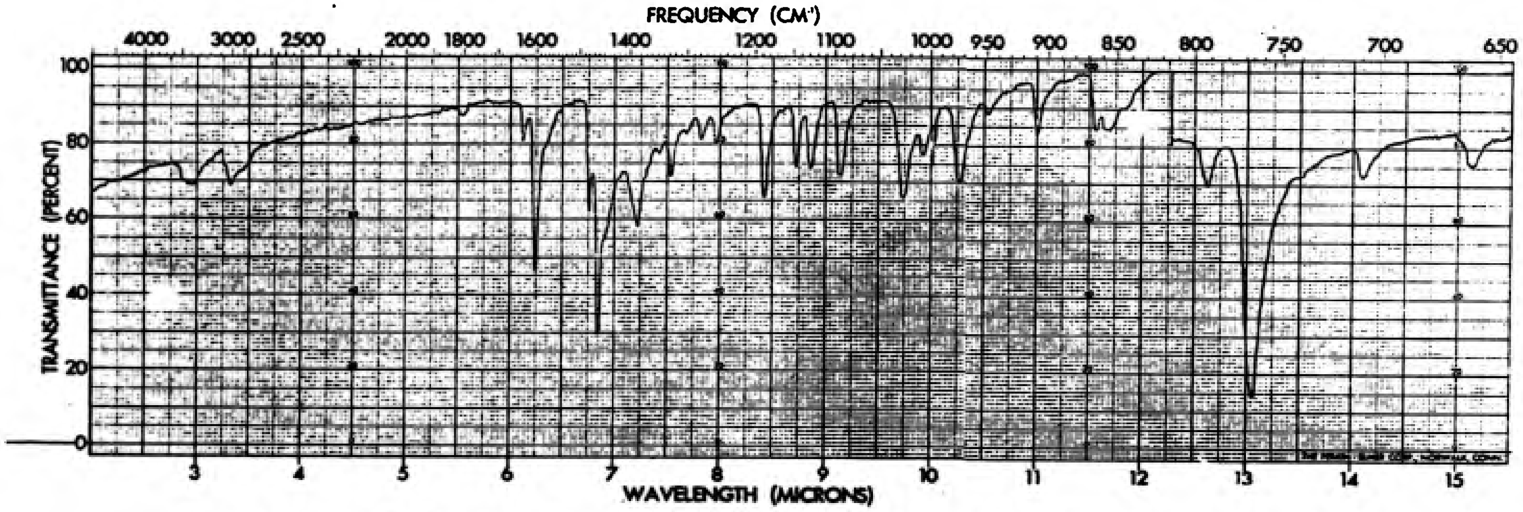


Figure 2. Infrared Spectrum (KBr pellet) of 2-Methylbenzoxazole ethiodide (B-1)

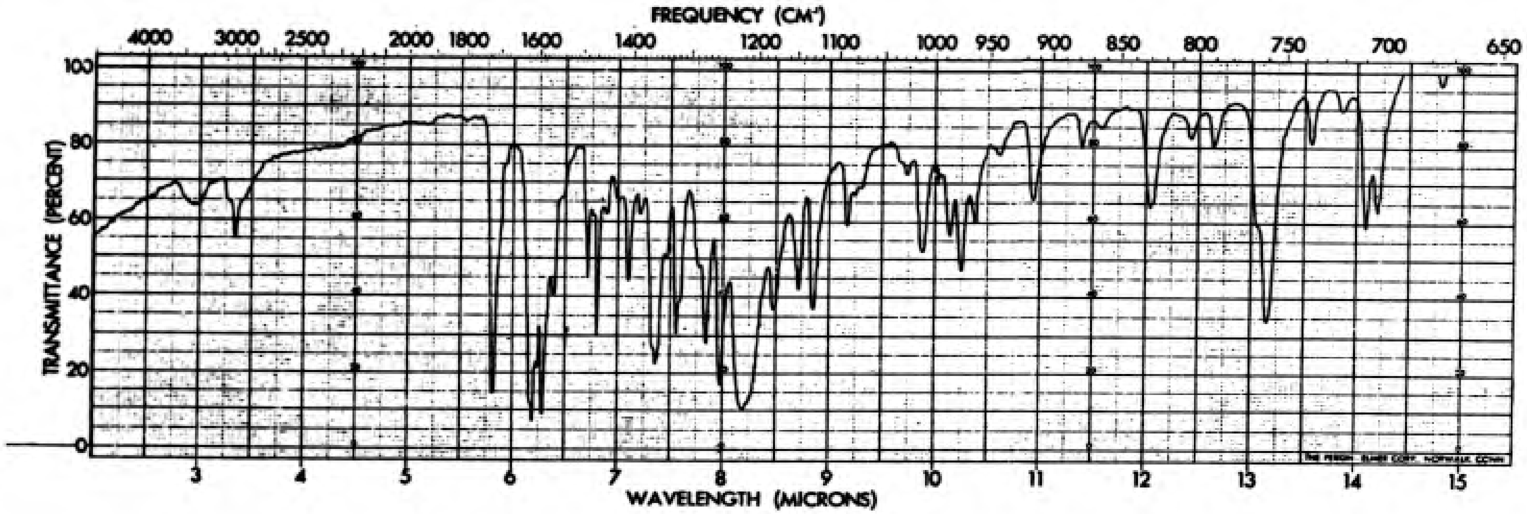
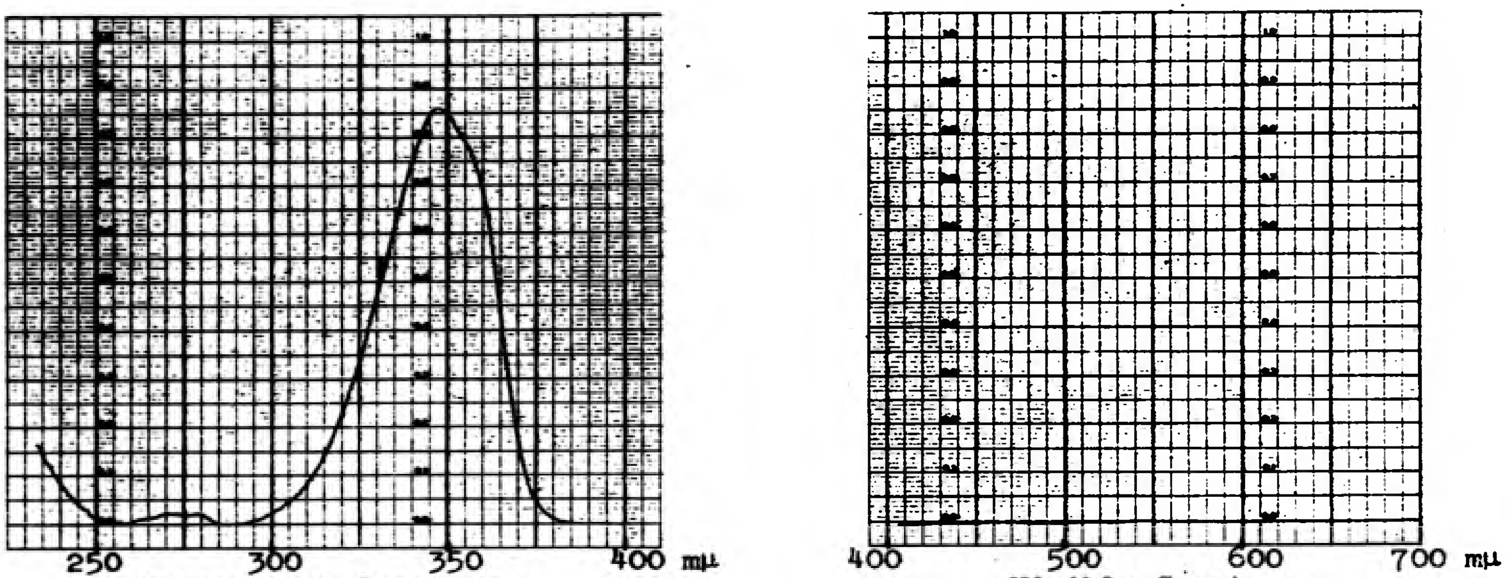


Figure 3. Infrared Spectrum (KBr pellet) of 2-(β-Acetanilidovinyl) benzoxazole ethiodide (B-2)

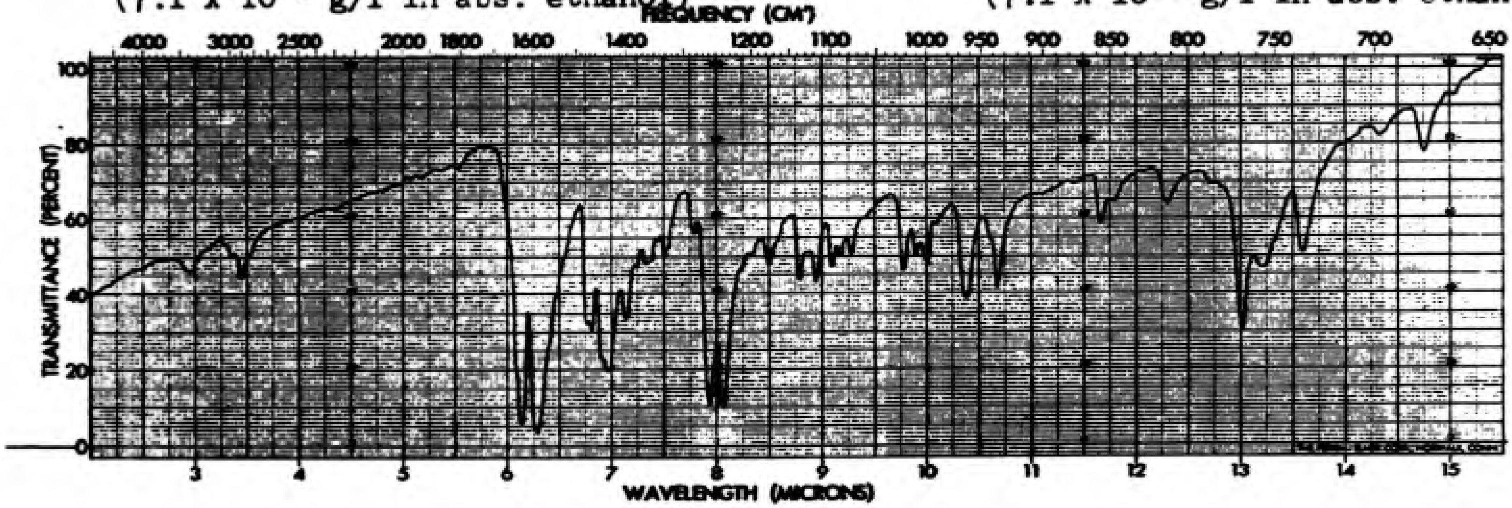


Ultraviolet Spectrum

(7.1 x 10^{-3} g/l in abs. ethanol)

Visible Spectrum

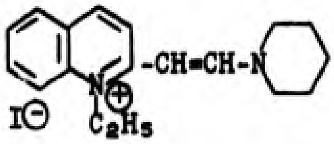
(7.1 x 10^{-3} g/l in abs. ethanol)



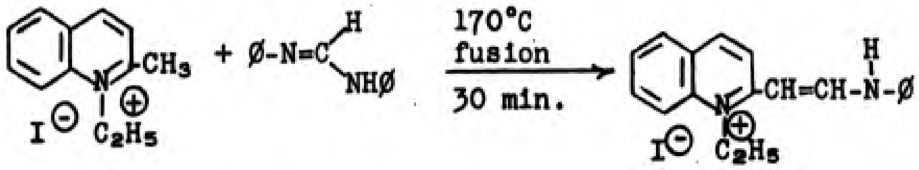
Infrared Spectrum (KBr Pellet)

Figure 4. Spectral Data on 2-[2-(1-Piperidyl)vinyl]benzoxazole ethiodide (F29M2)

C. 2-[2-(1-PIPERIDYL)VINYL]QUINOLINE ETHIODIDE (CODE NAME F31M3)



1. Synthesis of 2-(β-Anilinovinyl)quinoline ethiodide (C-1)

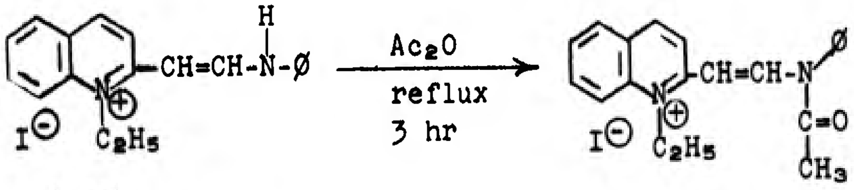


(C-1)

It is important to obtain good stirring of the reactants during the fusion. This reaction is more difficult than the usual reaction of this type. The aniline produced in the reaction is removed with an acetone wash. On a 0.02-molar scale, crude yields of 92, 98, and 102% were obtained, while on a 0.2-molar scale, 98 and 100% yields were found. The 102% figure was probably due to a weighing error or a small amount of aniline that was not removed.

The infrared spectrum of C-1 (Figure 5) showed that neither starting material was present. The N-H stretch at 3150 cm^{-1} is very weak, while the absorption at 1638 cm^{-1} is due to C=C. The five strong bands between 1612 and 1500 cm^{-1} are due to the quinoline ring system while the absorption near 1300 cm^{-1} is attributed to C-N. Mono-phenyl substitution is seen as a singlet at 689 and a triplet at 763, 754, and 747 cm^{-1}, while the four free hydrogens of the quinoline ring, characteristic of ortho-substitution, absorb at 763-747 cm^{-1}. The two other quinoline hydrogens absorb at 882 cm^{-1}. The spectrum is consistent with the structure assigned.

2. Synthesis of 2-(β-Acetanilidovinyl)quinoline ethiodide (C-2)



(C-1)

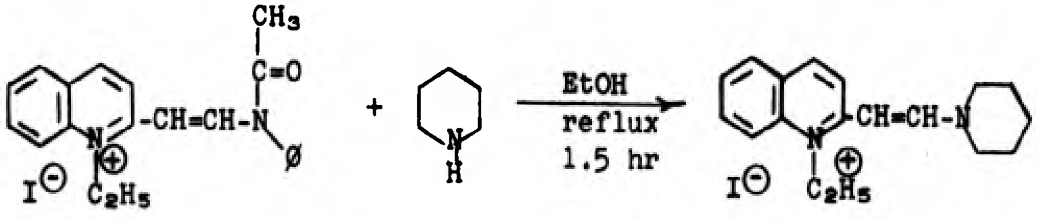
(C-2)

When the reaction mixture was refluxed for ten minutes as suggested in the patent reference (ref. 4), the brown product was mostly recovered starting material. When the reaction time was increased to three hours, yields of 55, 60, and 63 per cent of the desired green needles were obtained in three separate experiments. A satisfactory recrystallization solvent was not found for C-2 , nor was this compound located in the literature.

The infrared spectrum of C-2 (Figure 6) is different from that of the starting material C-1 except in the 1250 - 1150 cm^{-1} region. The amide C=O band at 1690 cm^{-1} is weak in relation to the rest of the spectrum as are the aromatic bands between 900 and 700 cm^{-1}. The conclusion is that the desired acetylation has probably taken place, but certain absorption intensities are not as one would predict.

That the acetylation did take place can be inferred from the reaction of C-2 with piperidine to give the final product, F31M3. An attempt to synthesize F31M3 from the unacetylated derivative C-1 and piperidine was unsuccessful.

3. Synthesis of 2-[2-(1-Piperidyl)vinyl]quinoline ethiodide (F31M3)



(C-2)

(F31M3)

a. Discussion

This reaction proceeds smoothly and no difficulties were encountered. Two runs gave quantitative crude yields.

b. Proof of Structure

(1.) Infrared Spectrum

The carbonyl absorption present in the starting material C-2 is, as expected, not present in F31M3 (Figure 7). The strong band at 1604 cm^{-1} is due to C=N while the absorptions at 1570 and 1504 cm^{-1} are aromatic. This compound does not look like the previous quinoline intermediates, which have 5-8 bands in the 1650-1450 cm^{-1} region. The absorption at 1290 cm^{-1} is probably aliphatic C-N while the benzene substitution (quinoline ring) absorptions occur at 834, 776, 750, and 700 cm^{-1}. The spectrum is indicative of the assigned structure but is not conclusive. Elemental analysis is needed to confirm the structure.

The same variations in intensities mentioned in connection with the infrared spectrum of F29M2 (see Infrared Spectrum, IIB3b) were observed with F31M3. The explanation is probably the same.

(2.) Elemental Analysis

The elemental analysis agrees with the values calculated for F31M3 (see Experimental, IIC4). The structure of the compound is that assigned.

c. Purity

The sample sent for elemental analysis was taken directly from the sample submitted to the Air Force.

Thin-layer chromatography on Silica Gel-G showed one spot with acetone or monoglyme (dimethyl ether of ethylene glycol) development and iodine treatment. Methanol development, as with F29M2, gave uninterpretable results.

d. Air Force Sample

Four 10.0-gram samples of F31M3 (total 40.0g), bottled under nitrogen, were submitted on 3 July 1963.

4. Experimental

a. Starting Materials

1-Ethylquinaldinium iodide (Eastman No. 1318, 100 g - \$8.25) [mp 236°C; lit. (ref. 1) mp 233-234°C] was used without further purification.

N,N'-Diphenylformamidine (K and K, 100 g - \$7.50) was recrystallized from absolute ethanol (1 g/5 ml) [mp 137-139°C; lit. (ref. 2) mp 137°C].

Piperidine (MC and B No. PX1235, 100 g - \$4.60) was used without further purification.

b. 2-(β-Anilinovinyl)quinoline ethiodide (C-1) (ref. 3)

1-Ethylquinaldinium iodide (60.0 g, 0.20 mole) and N,N'-diphenylformamidine (39.5 g, 0.21 mole) were ground in a mortar until homogeneous and placed in a 3-necked, round-bottomed flask equipped with a mechanical stirrer and calcium sulfate drying tube. The mixture was placed in an oil bath at 145°C. The temperature of the bath was raised to 173°C over a 15-min. period and maintained there for an additional 15 min. The oil bath was removed and the brown-black reaction product was allowed to cool to room temperature. The solid was transferred to a beaker, ground thoroughly with 100 ml of cold (0°C) acetone, and filtered. After drying for 2.5 hr at 80°C/15 mm, 79.0 g (98%) of crude brown C-1 was obtained (mp soften 235°C, 240-245°C dec.). Two recrystallizations from methanol (charcoal) raised the mp to 274-275° dec. [lit. (ref. 3) 282-285° dec.]. The crude material was found to be satisfactory for the next reaction.

c. 2-(β-Acetanilidovinyl)quinoline ethiodide (C-2) (ref. 4, modified)

2-(β-Anilinovinyl)quinoline ethiodide (80.5 g, 0.20 mole) was added to 200 ml of acetic anhydride in a 1-liter round-bottomed flask and the solution refluxed (calcium sulfate drying tube) for 3.0 hours. After a thorough chilling at 0°C, the product was filtered, washed with two 100-ml portions of acetone, and dried at 60°C/15 mm for 0.5 hr, yielding 56.3 g (63%) of crude, dark green needles of C-2, [mp 209-210°C dec.; no lit. mp could be found]. This material was used without purification for the next reaction.

d. 2-[2-(1-Piperidyl)vinyl]quinoline ethiodide (F31M3) (ref. 4)

2-(β-Acetanilidovinyl)quinoline ethiodide (54.3 g, 0.12 mole) and piperidine (31.0 g, 0.36 mole) were added to 950 ml of absolute ethanol in a 2-liter flask, and the solution was refluxed (calcium sulfate drying tube) for 1.5 hr. The green solution was cooled to 0°C, and the precipitate was filtered and dried at 50°C/15 mm for 2.0 hours. The green plates [mp 243°C soften, 244-245°C dec., 48.8 g (100%)], were recrystallized three times from methanol (1 g/12 ml). The first two recrystallizations were with activated charcoal (1 g charcoal/5 g). Each recrystallization resulted in a 20% yield decrease. The resulting F31M3 was dried at 100°C/0.5 mm for 6 hr [bright yellow needles, mp 249-250°C dec.; lit. (ref. 4) mp 253-255°C dec.; λ_{max}^{EtOH} 409 mμ (∈42,000) and 315 mμ (∈14,600)].

Analysis (for $C_{18}H_{23}N_2I$)

	C	H	N	I
Calc'd.	54.83	5.88	7.15	32.19
Found	54.31	6.03	6.84	31.98

5. References

1. "Dictionary of Organic Compounds", I. Heilbron and H. M. Bunbury, Eds., Vol. 4, Oxford, N. Y., 1953, 293.
2. J. B. Shoesmith and J. Haldane, J. Chem. Soc., **123**, 2704 (1923).
3. L. G. S. Brooker, et al., J. Am. Chem. Soc., **63**, 3192 (1941).
4. F. L. White and G. H. Keyes, U. S. Patent 2,166,736, July 18, 1939. C.A., **33**, 8515 (1939).

6. Spectra

Spectral data are given in Figures 5, 6, and 7.

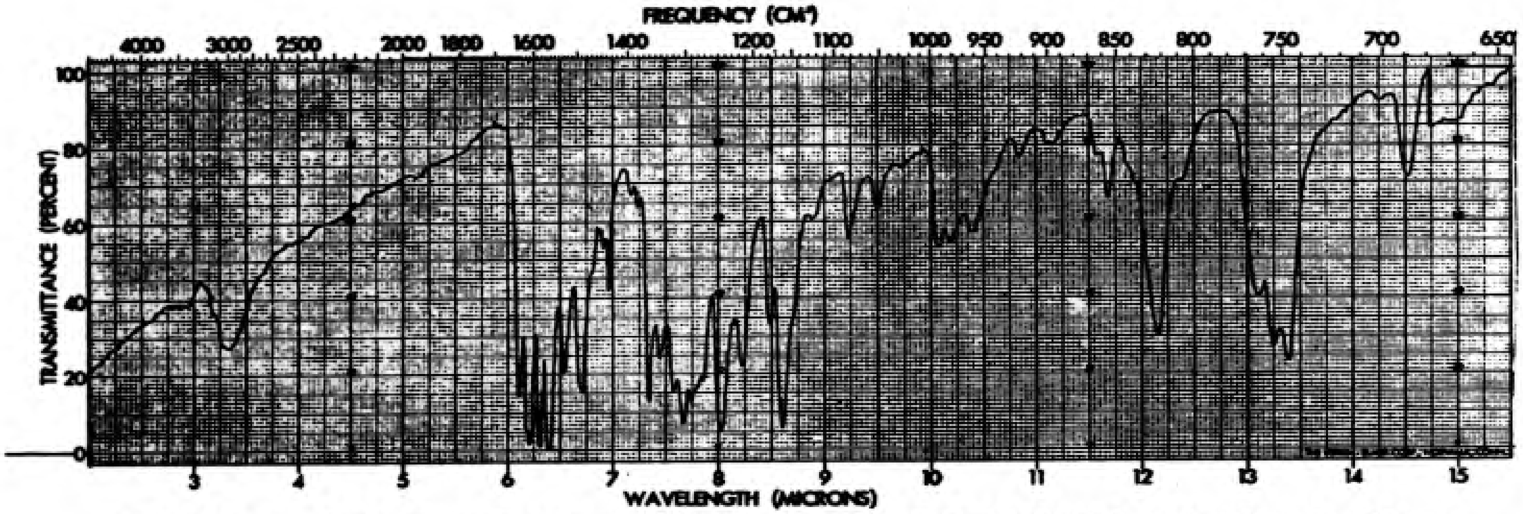


Figure 5. Infrared Spectrum (KBr pellet) of 2-(β-Anilinovinyl)quinoline ethiodide (C-1)

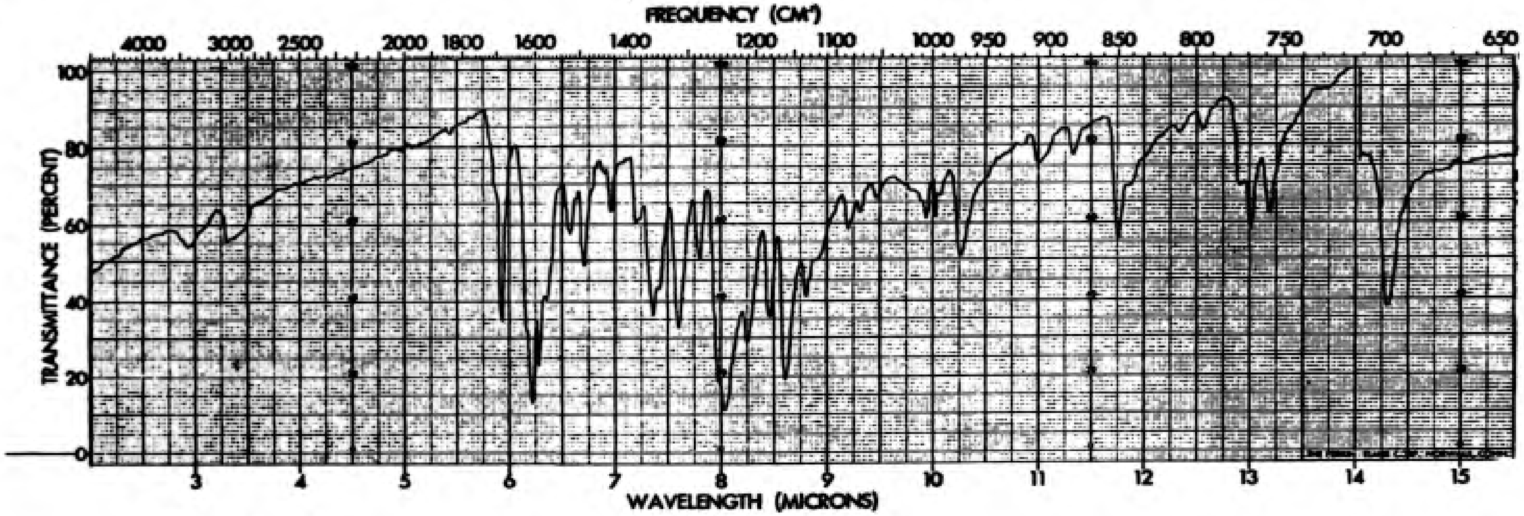
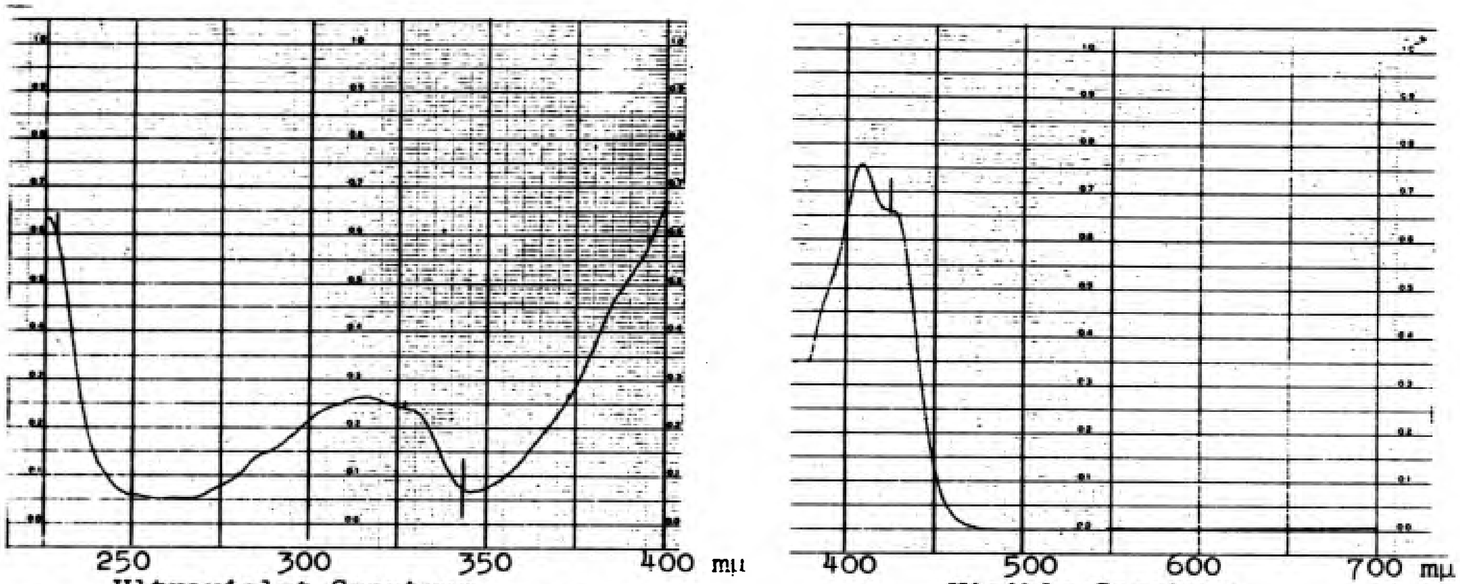
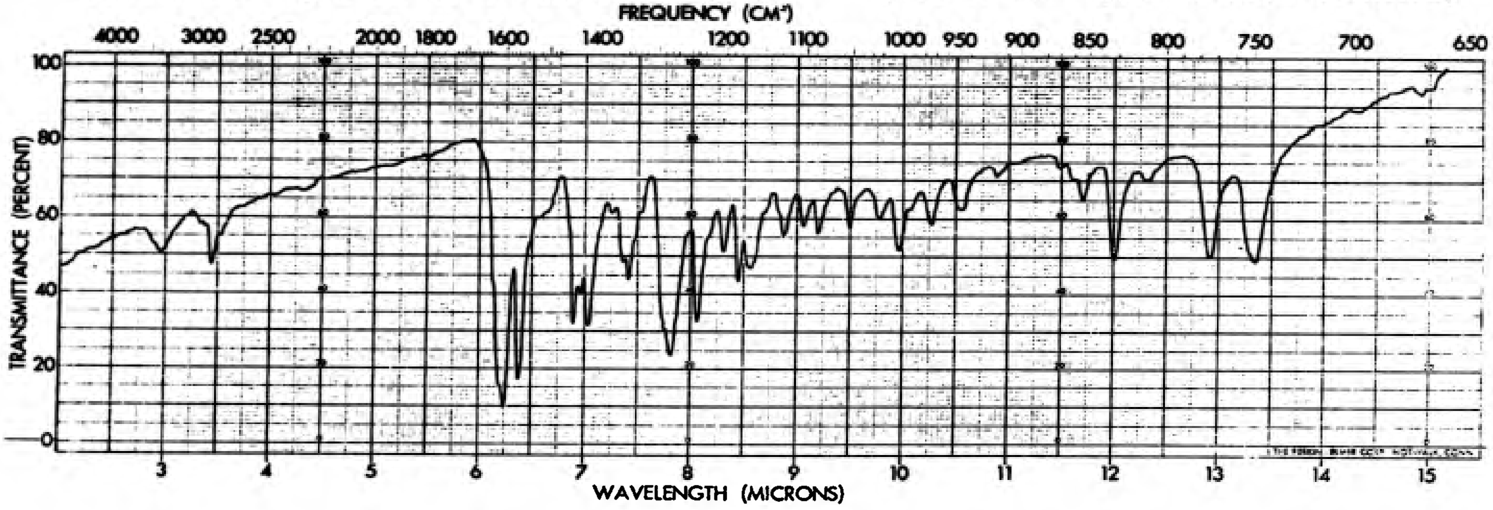


Figure 6. Infrared Spectrum (KBr pellet) of 2-(β-Acetanilidovinyl) quinoline ethiodide (C-2)



Ultraviolet Spectrum
(7.1 x 10^{-3} g/1 in abs. ethanol)

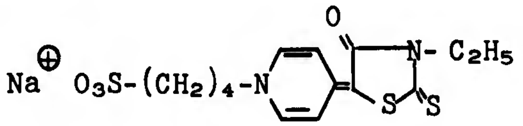
Visible Spectrum
(7.1 x 10^{-3} g/1 in abs. ethanol)



Infrared Spectrum (KBr Pellet)

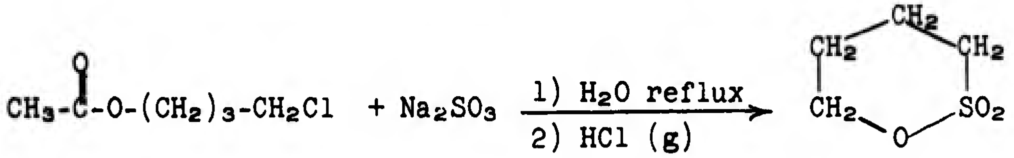
Figure 7. Spectral Data on 2-[2-(1-Piperidyl)vinyl]quinoline ethiodide (F31M3)

D. 3-ETHYL-5-[1-(4-SULFOBUTYL)-4(1H) PYRIDILIDENE]RHODANINE SODIUM SALT (CODE NAME F24M4) AND ITS ACETIC ACID COMPLEX (CODE NAME F24M4·HOAc)



(F24M4)

1. Synthesis of 4-Hydroxy-1-butane-sulfonic acid sultone (D-1)

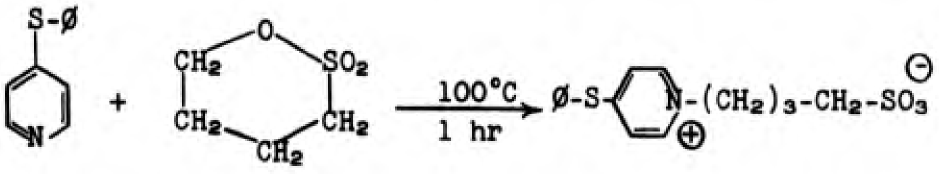


(D-1)

In a synthesis of D-1 , in which the first, seemingly unnecessary, distillation (ref. 3) was omitted, a viscous, undistillable semi-solid was produced. Two distillations with an intermediate drying step were found to be necessary.

The literature method yielded D-1 as a colorless liquid that vapor phase chromatography showed to contain a single component. The infrared spectrum (Figure 8) showed aliphatic CH_2 at 2940 cm^{-1} and strong SO_2 absorptions as a singlet at 1348 cm^{-1} and a triplet at 1186, 1166, and 1149 cm^{-1}. There was no trace of OH or SO_3H bands. The infrared spectrum is consistent with the structure.

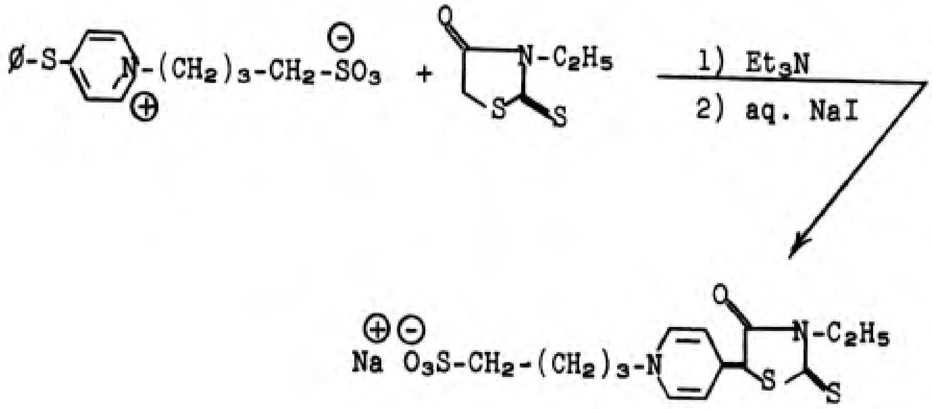
2. Synthesis of Anhydro-4-phenylthio-1-(4-sulfobutyl)pyridinium hydroxide (D-2)



(D-1) (D-2)

Jones (ref. 4) states that 4-phenylthiopyridine is reacted with 1,4-butanesulfone to give D-2 . The correct name of D-1 is not "-sulfone", which contains two oxygen atoms, but rather "-sultone", which contains three. The correct name was used in an earlier patent (ref. 5). There was no difficulty with this preparation. The infrared spectrum and melting point of D-2 were inadvertently not obtained. Three runs gave yields of 81, 86, and 95 per cent.

3. Synthesis of 3-Ethyl-5-[1-(4-sulfobutyl)-4-(1H)pyridylidene] rhodanine sodium salt (F24M4) and its acetic acid complex F24M4·HOAc



(F24M4)

a. Discussion

This reaction presented no difficulties, providing yields of 67 and 72 per cent. Purification by recrystallization from glacial acetic acid gave very poor yields of the acetic acid complex, (F24M4·HOAc).

b. Proof of Structure

(1) Acetic acid complex (F24M4·HOAc)

The infrared spectrum shows a weak band at 1710 cm^{-1} due to the acetic acid carboxyl absorption. The strong band at 1665 cm^{-1} is most likely due to the rhodanine carbonyl group, with frequency lowering due to conjugation as in F23M1. The 1610 cm^{-1} band cannot be assigned. Absorptions at 1180 and 1044 cm^{-1} are due to $-SO_3^{\ominus}$ anion, but an expected band for this group near 650 cm^{-1} is missing.

The complex has a correct elemental analysis.

The acetic acid was quantitatively removed by heating at 216°C/0.5 mm but was not removed at 100°C or 162°C/0.5 mm to give F24M4.

(2) F24M4

The infrared spectrum of F24M4 showed the absence of the acetic acid 1710 cm^{-1} band. The visible and ultraviolet spectra of F24M4 were similar to those of an analogous structure, F23M1 (see II.A). A correct elemental analysis was obtained for F24M4.

c. Purity

The analytical samples were taken from the samples of F24M4 and F24M4·HOAc submitted to the Air Force.

Thin layer chromatography of either compound showed only one spot on Silica Gel-G after methanol or acetone elution and iodine development.

d. Air Force Sample

Two 5.23-gram samples of F24M4 and two 6.21-gram samples of F24M4·HOAc, (total 22.88 grams) under nitrogen were submitted on 8 August 1963.

4. Experimental

a. Starting Materials

4-Chlorobutylacetate (Eastman No. 8503, 100 g - $8.25) was used without further purification.

4-Phenylthiopyridine (Eastman No. 3760, 25 g - $8.75) was distilled through an 8-inch Vigreux column [bp 153-155°C/7 mm; lit. (ref. 1) bp 160°C/60 mm].

3-Ethylrhodanine (Eastman 3760, 100 g - $10.55) was recrystallized twice from methanol before use [mp 38-39°C; lit. (ref. 2) mp 36-38°C].

Inorganic reagents. These were J. T. Baker reagent-grade and were used without further purification.

b. 4-Hydroxy-1-butanesulfonic acid sultone (D-1) (ref. 3)

A mixture of 114.7 g (0.76 mole) of 4-chlorobutyl acetate, 290 g (1.16 moles) of sodium sulfite heptahydrate, and 475 ml of water was refluxed with stirring for 18 hours, and then most of the water was removed under vacuum. The heavy paste remaining was allowed to stand for 4 days with 500 ml of methanol. Then, through a 0.5-inch delivery tube, an excess of hydrogen chloride gas was bubbled into the continuously stirred and refluxed solution for 6 hr. The mixture was refluxed an additional 14 hr, cooled, and filtered. The filtrate was concentrated to 125 ml under reduced pressure, and the residue was distilled at 1.4 mm pressure (130-135°C) to give 76.3 g of wet sultone. After dissolving the sultone in ether and drying over sodium sulfate, redistillation gave 68.3 g (67%) of product [bp 95°C/0.5 mm; lit. (ref. 3) bp 112-113°C/1.5 mm].

c. Anhydro-4-phenylthio-1-(4-sulfobutyl)pyridinium hydroxide (D-2) (ref. 4)

A mixture of 5.61 g (0.03 mole) of 4-phenylthiopyridine and 4.08 g (0.03 mole) of 4-hydroxy-1-butanesulfonic acid sultone were heated on a steam bath for 20 minutes and then placed in an oil bath at 115°C. The oily mixture solidified to a white solid in about two minutes. The reaction mixture was heated in the oil bath for 0.5 hour. The mixture was cooled, then broken up in hot acetone and filtered. The residue was ground under acetone, and the product collected on a filter and washed with acetone. After drying at 80°C/15 mm for 4 hr. the yield of product was 8.4 g (86%).

d. 3-Ethyl-5-[1-(4-sulfobutyl)-4(1H)-pyridylidene]rhodanine sodium salt acetic acid complex (F24M4·HOAc) (ref. 4)

A mixture of 64.6 g (0.20 mole) of anhydro-4-phenylthio-1-(4-sulfobutyl)pyridinium hydroxide, 35.0 g (0.22 mole) of 3-ethylrhodanine, and 20 g (0.20 mole) of triethylamine in 150 ml of pyridine were refluxed 45 minutes. The solution was cooled and stirred with 200 ml of ether. A reddish oil not dissolved by the ether solidified on stirring to an orange solid. The solid was filtered off and placed in a 250-ml beaker. To the solid was added a solution of 40 g of sodium iodide in 100 ml of water. The mixture was stirred thoroughly and cooled in ice water, and the solid was removed by filtration. The solid was dried in a vacuum oven at 80°C/15 mm for 4 hrs to yield 55.0 g (67%) of crude product (mp >310°C).

Two recrystallizations of 80 g from glacial acetic acid gave 26.2 g of pure complex [mp 310°C; lit. (ref. 4) mp >300°C; λ_{max}^{EtOH} 464 mμ (ε 71,000), 289 mμ (ε 6,660)]. Each recrystallization decreased the yield by 50%.

Analysis for $C_{14}H_{17}N_2O_4S_3Na\cdot C_2H_4O_2$

	C	H	N	S
Calcd.	42.09	4.64	6.14	21.07
Found	41.85	4.92	6.53	20.73

e. 3-Ethyl-5-[1-(4-sulfobutyl)-4(1H) pyridylidene]rhodanine sodium salt (F24M4)

The acetic acid complex, F24M4·HOAc, was heated at 216°C/0.5mm for 48 hr to give F24M4 as orange crystals [mp>310°C; lit. (ref. 4) mp>300°C; λ_{max}^{EtOH} 464mμ (ε 85,300), λ^{EtOH} 233mμ (ε8,420), 288mμ (ε 7,570)].

Analysis for $C_{14}H_{17}N_2O_4S_3Na$

	C	H	N	S
Calcd.	42.41	4.32	7.07	24.26
Found	42.00	4.49	6.71	24.26

5. References

1. E. Hayashi, et al., Yakugaku Zasshi, 80, 1145 (1960). C.A., 55, 546d (1961).

2. No literature reference to the mp other than that of the supplier could be found. Eastman Organic Chemicals, List 43, Compound 3760, p. 118, Dec. 3, 1962.

3. W. E. Truce and F. D. Hoerger, J. Am. Chem. Soc., 76, 5358 (1954).

4. J. E. Jones, U. S. Patent 2,977,229, March 28, 1961. C.A., 55, 14136i (1961).

5. Kodak, Soc. anon., Belg. Patent 588,862, April 15, 1960. C.A., 55, 12511 (1961).

6. Spectra

Spectral data are given in Figures 8-10.

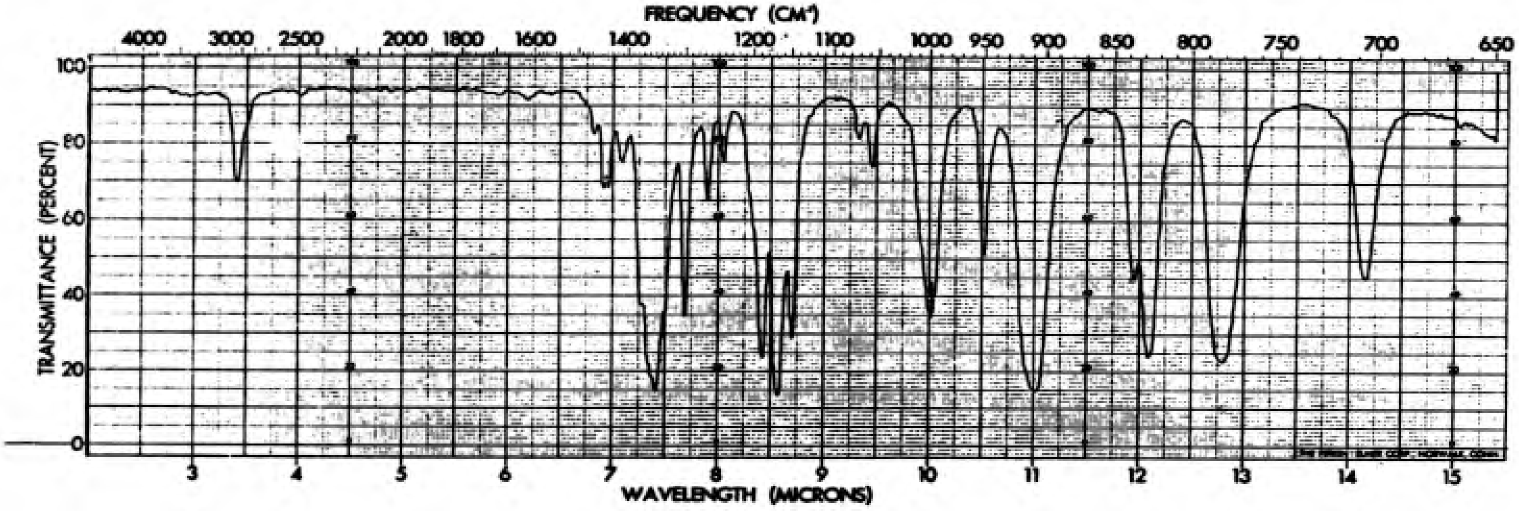
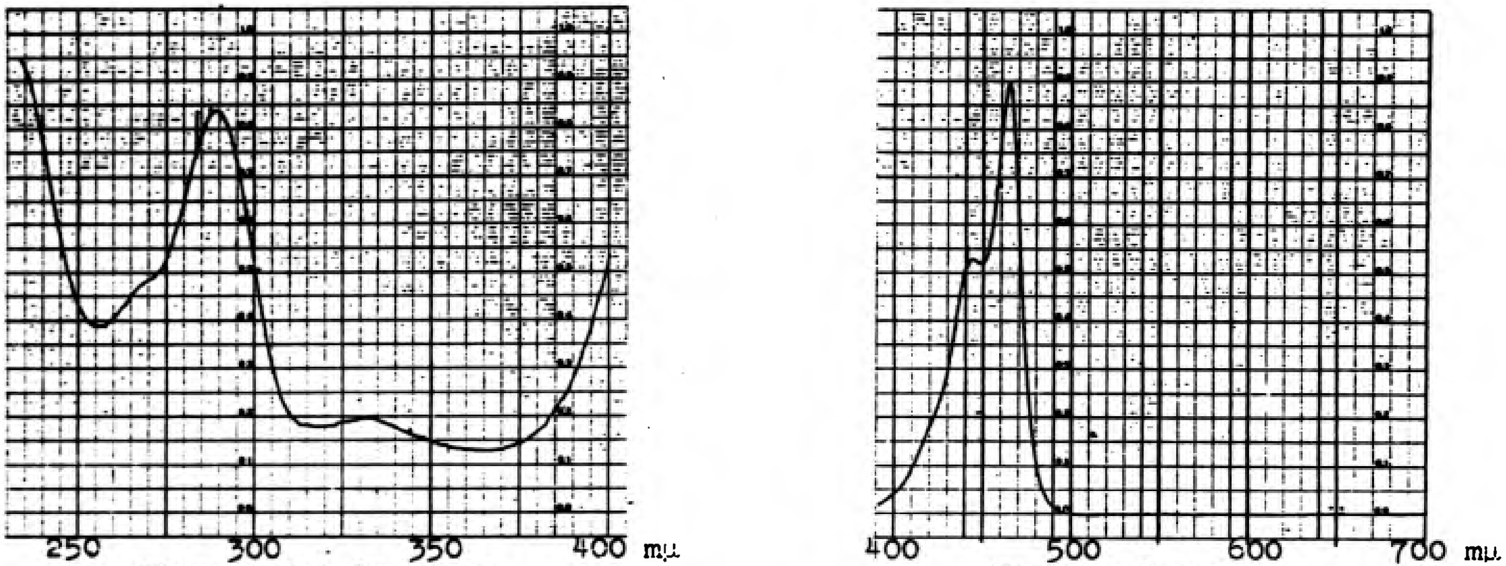
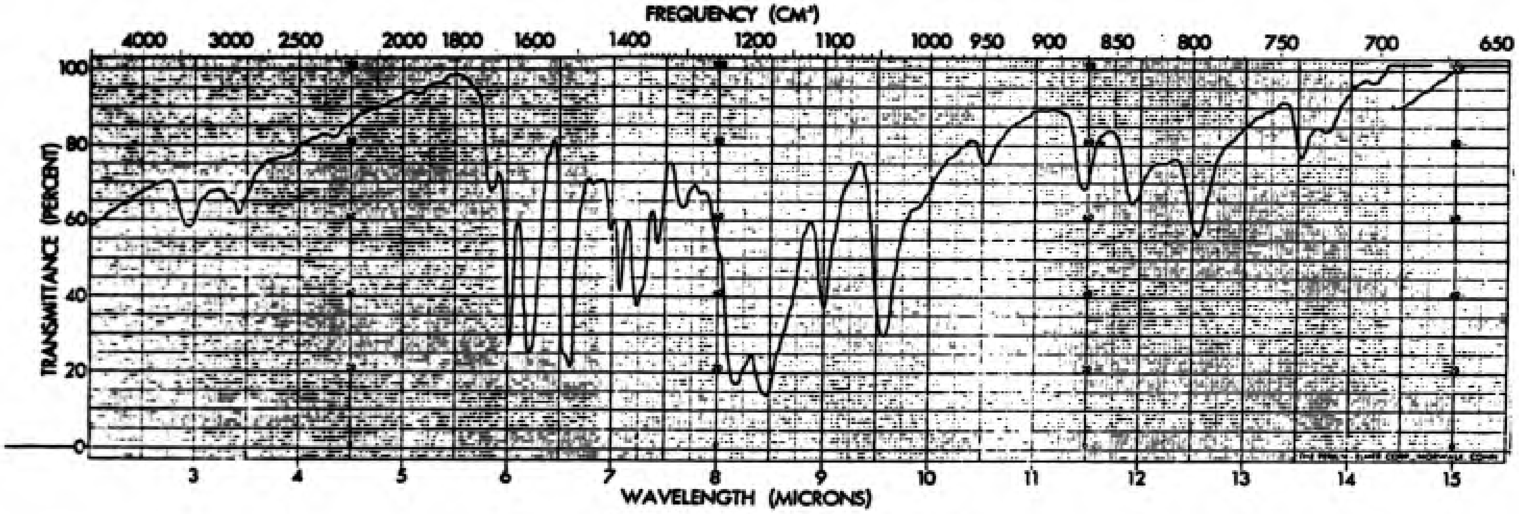


Figure 8. Infrared Spectrum (thin film) of 4-Hydroxy-1-butanesulfonic acid sultone (D-1)



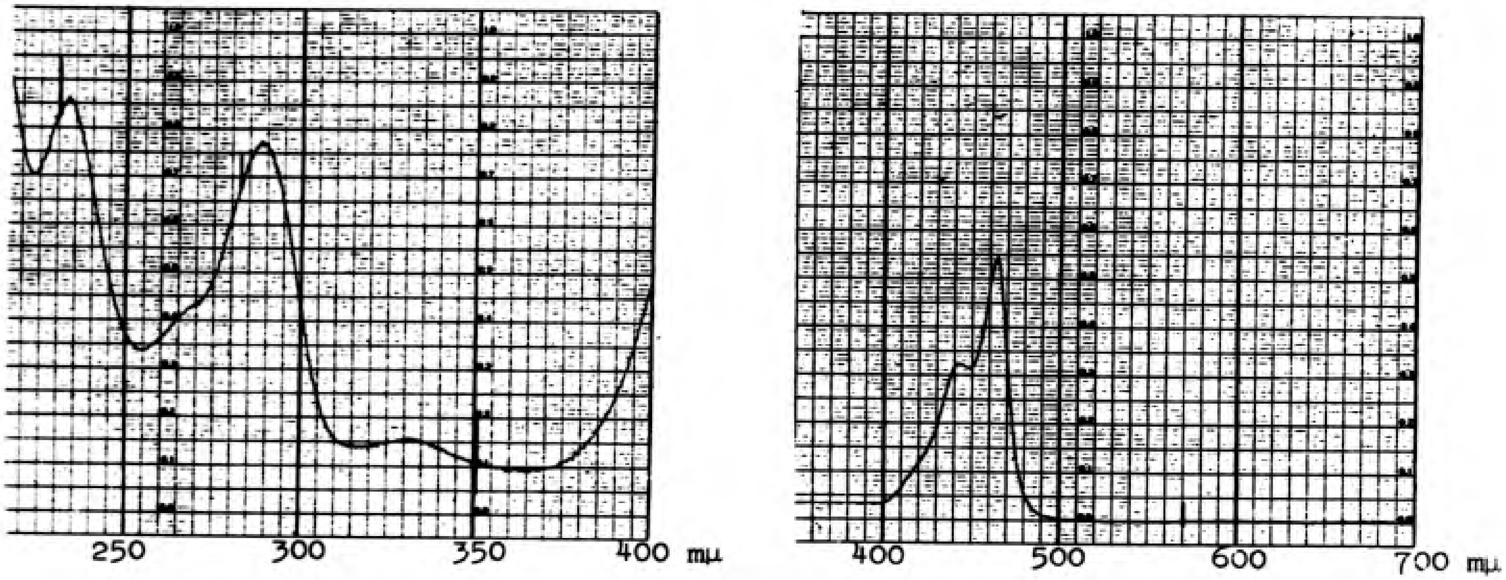
Ultraviolet Spectrum

Visible Spectrum



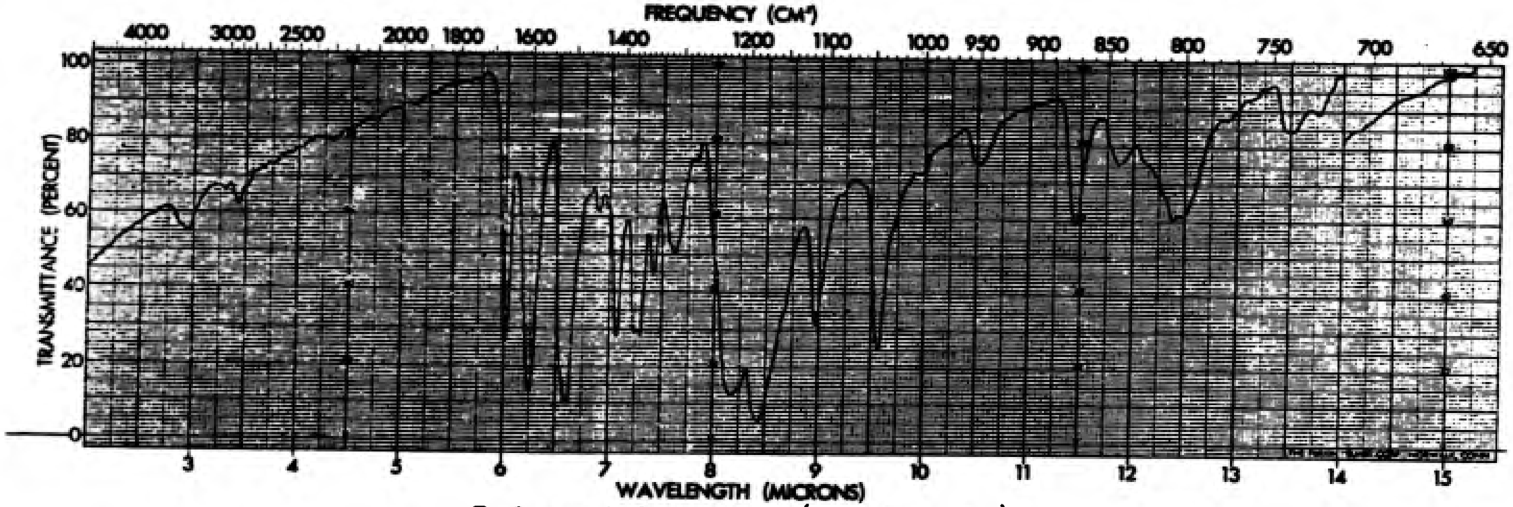
Infrared Spectrum (KBr Pellet)

Figure 9. Spectral Data on 3-Ethyl-5-[1-(4-sulfobutyl)-4-(1H)-pyridylidene] rhodanine sodium salt-acetic acid complex (F24M4·HOAc)



Ultraviolet Spectrum

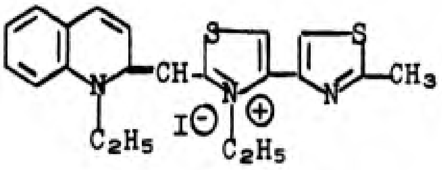
Visible Spectrum



Infrared Spectrum (KBr Pellet)

Figure 10. Spectral Data on 3-Ethyl-5-[1-(4-sulfobutyl)-4-(1H)-pyridylidene] rhodanine sodium salt (F24M4)

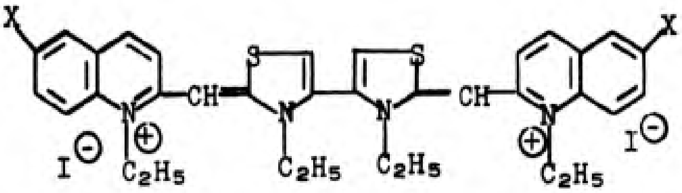
E. (1-ETHYLQUINOLINE-2)(3-ETHYL-2'-METHYL-4,4'-BITHIAZOLE-2)MONOMETHINE CYANINE IODIDE (F47M5)



(F47M5)

1. Discussion

F47M5 was the compound obtained from the attempted synthesis of [2,2'-(3,3'-diethyl) (4,4'-bithiazolyl)] [2,2'-(1,1'-diethylquinolyl)]monomethine cyanine di-iodide, (E-1, X=H) the originally requested dye. Although we were not able to find (E-1, X=H)



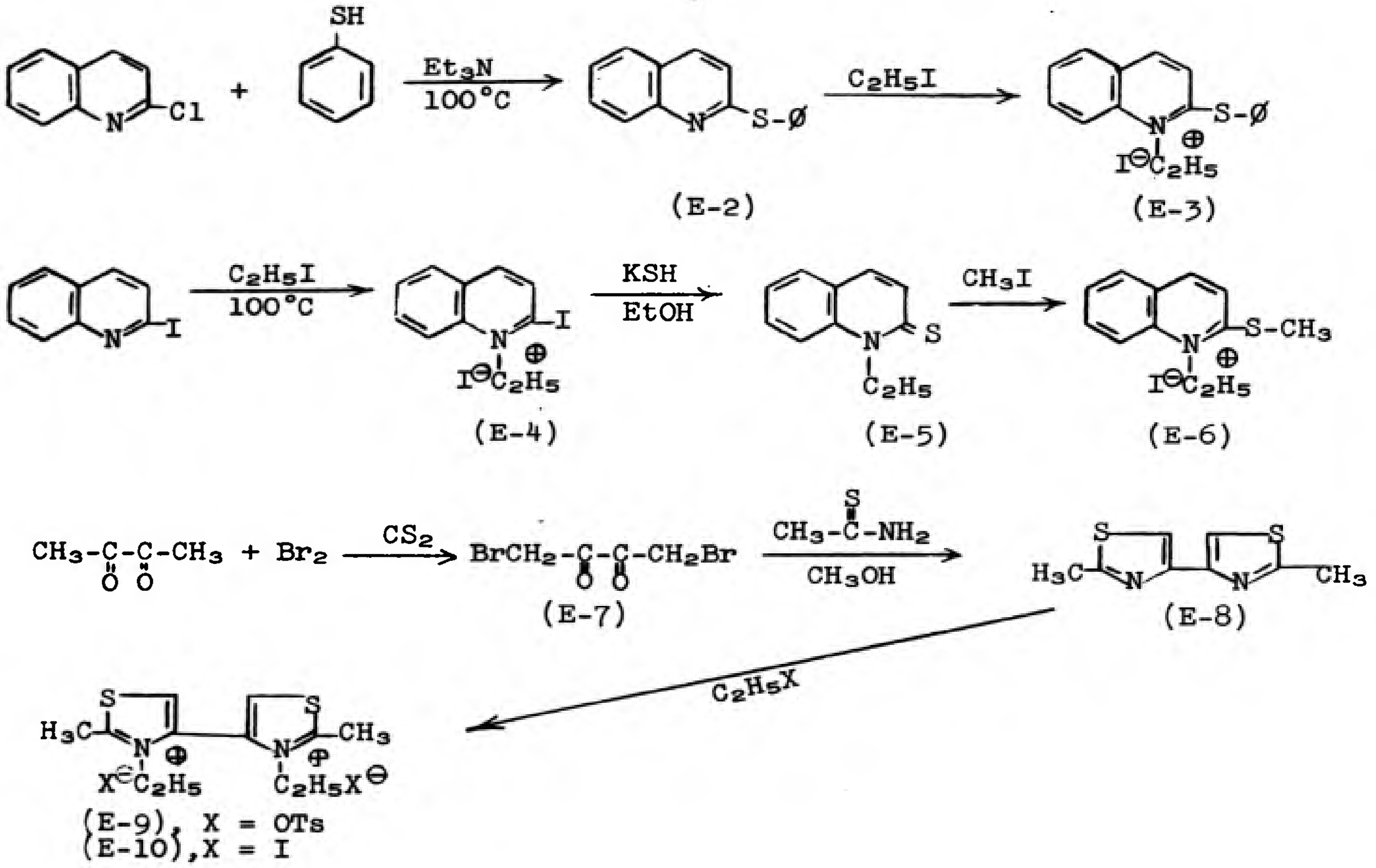
(E-1)

in the literature, we did locate (E-1 X=CH_3) (ref. 3). Upon following the general procedure of reference 3, F47M5, not (E-1, X=H) was obtained. By coincidence, F47M5 and (E-1, X=H) have almost identical calculated carbon and hydrogen percentage values. The structure F47M5 cannot easily be distinquished from (E-1, X=H) on the basis of infrared spectroscopy, and the product is not soluble enough in the common n.m.r. solvents to obtain a good spectrum. The product was assigned the F47M5 structure on the basis of the N,S, and I analyses.

2. Synthesis Procedure (Figure 11)

a. Synthesis of 2-Phenylthioquinoline (E-2)

No difficulty was experienced with this reaction. The VPC analysis (6 ft. 10% SE30, 70-350°C temperature program) of the purified product showed it to be 99.0% pure with no trace of thiophenol or 2-chloroquinoline present. The infrared spectrum (Figure 12) shows



E-3 + E-9 $\longrightarrow$ no isolable product
E-6 + E-9 $\longrightarrow$ no isolable product
E-6 + E-10 $\xrightarrow{Et_3N}$ F47M5

Figure 11. Synthesis of F47M5

eight C=C and C=N bands characteristic of the quinoline ring system between 1615 and 1419 cm^{-1}. Mono-substituted phenyl bands occur as a doublet at 704 and 690 cm^{-1} with a singlet at 747 cm^{-1}. The infrared spectrum is consistent with the structure.

b. Synthesis of 1-Ethyl-2-phenylthioquinolinium iodide (E-3)

No difficulty was encountered in this synthesis. The infrared spectrum (Figure 13) shows characteristic quinoline absorptions at 1613, 1600, 1568 and 1509 cm^{-1} with a strong ring vibration at 1139 cm^{-1}. The three bands near 690 and the four near 760 cm^{-1} indicate monosubstituted phenyl. The three bands near 820 cm^{-1} correspond to the two hydrogen atoms on the quinoline heterocyclic ring, while the ortho-substituted phenyl absorptions of the quinoline system occur around 760 cm^{-1}. The infrared spectrum is consistent with the structure assigned.

c. Synthesis of 1,4-Dibromobutanedione-2,3 (E-7)

Although no difficulty was encountered during the synthesis of (E-7), the reaction is potentially dangerous because of the nature of the bromine and carbon disulfide starting materials. The reaction was run four times on a large scale (1.9 molar in Br_2) with an average yield of 58 per cent. This was the maximum convenient scale.

Biacetyl, the starting material, shows a single infrared carbonyl absorption at 1712 cm^{-1} characteristic of s-trans diketones. The infrared spectrum of the brominated reaction product (Figure 14) shows a carbonyl absorption at a higher frequency (1739 cm^{-1}), which is a good indication that bromination has taken place. A shoulder near 1712 cm^{-1} may indicate only partial bromination. To check this, a sample of (E-7) was run through the VPC; it gave only one peak of any significance. The VPC sample peak was trapped for infrared analysis and it, too, showed the shoulder at 1712 cm. This, along with the correct melting point, indicates the shoulder does not belong to an impurity and implies complete bromination. A doublet at 2980 and 2950 cm^{-1} is indicative of CH_2 stretching. The infrared spectrum is consistent with the assigned structure.

d. Synthesis of 2,2'-Dimethyl-4,4'-bithiazole (E-8)

When the reaction product is quenched with water (see Experimental II.E.3) the resulting solution is acidic. If this cloudy solution is not further acidified with dilute hydrochloric acid until it becomes clear, low yields result.

The synthesis of E-8 was carried out five times with an average yield of 80 per cent. One recrystallization from methanol was necessary, and this lowered the yield to 50 per cent.

Because of the symmetry of E-8 , the infrared spectrum (Figure 15) is of little value in assigning structure. The compound does not show the carbonyl or $-NH_2$ frequencies of the starting materials.

e. Synthesis of 2,2'-Dimethyl-3,3'-diethyl-4,4'-bithiazolium di-p-toluensesulfonate (E-9)

This synthesis required an extensive investigation of variables in order to obtain satisfactory yields of E-9 (see Experimental II.E.3).

A comparison of the infrared spectrum of E-9 with the starting material, E-8, shows an increase in the aliphatic C-H stretching below 3000 cm^{-1}. E-9 shows a phenyl band at 1600 cm^{-1} and para-substituted phenyl at 820 cm^{-1}. The bands near 1030 cm^{-1} and strong absorption at 1200 cm^{-1} are attributed to $SO_3^{\ominus}$. The band at 670 cm^{-1} is due to $SO_3^{\ominus}$ or the bithiazole ring shifted to lower frequency (compared with E-8) by the additional charged substituents. The spectrum is consistent with the structure.

f. Synthesis of 2,2'-Dimethyl-3,3'-diethyl-4,4'-bithiazolium di-iodide (E-10)

Yields of E-10 were increased by 15% when the reaction time was extended from one day to four days. Yields of 45,47,59,59,61, and 63% were obtained. The ethyl iodide was filtered to remove any mercury inhibitor before use.

The infrared spectrum of E-10 shows C-H stretching at 3086 cm^{-1}. The band at 1577 cm^{-1} can be assigned to $N^{\oplus}$ while that at 1499 cm^{-1} might be a conjugated double bond. The strong bands at 1269,1181, 1059, and 962 cm^{-1} occur in the region where E-8 also absorbs. The band at 665 cm^{-1} could be a C-S-C frequency. The spectrum is not inconsistent with the assigned structure.

g. Synthesis of 1-Ethyl-2-iodoquinolinium Iodide (E-4)

A considerable amount of difficulty was encountered with this relatively simple reaction. Under reflux conditions, (72°C), small yields of E-4 were obtained. At 100°C in a pressure bottle, the yields were improved but the production of a black contaminant (mp 154-165°C) increased. The formation of this impurity was traced to small particles of mercury used as an inhibitor in the ethyl iodide. Filtration of the ethyl iodide before use solved this problem.

The five infrared bands between 1613 and 1484 cm^{-1} are characteristic of quinoline C=C and C=N absorptions. Some evidence for $-CH_2$ and $-CH_3$ is noted in absorptions at 1427 and 1381 cm^{-1}. The band at 770 cm^{-1} is assigned to the four adjacent ring hydrogens while the absorption at 825 cm^{-1} is due to the two adjacent hydrogens of the nitrogen-containing ring. The infrared spectrum is consistent with the structure.

h. Synthesis of 1-Ethyl-1,2-dihydroquinoline-2-thione (E-5)

Vigorous mechanical stirring of the reaction mixture was necessary to achieve high yields; magnetic stirring was not good enough. The product, E-5, sometimes crystallized immediately, but more often required a 24-hour refrigeration period.

The infrared spectrum of E-5 shows an aromatic C-H absorption at 3030 cm^{-1}, with aliphatic C-H bands at 2959 and 2915 cm^{-1}. No definite assignment of the C=S vibration can be made since eight major bands occur in the region of C=S absorption: 1570-1395, 1420-1210, and 1140-940 cm^{-1}. The spectrum of E-5 has bands in each of these regions. The doublet at 767 and 751, and the singlet at 825 cm^{-1} are assigned as in E-4. The spectrum is consistent with the structure.

Yields of 50, 62, 71, and 86% were obtained from four reactions.

i. Synthesis of 1-Ethyl-2-methylthioquinolinium iodide (E-6)

This reaction is very exothermic and special caution should be exercised if E-5 is to be used on a scale > 5 grams.

The infrared spectrum of E-6 shows seven bands between 1600 and 1400 cm^{-1} characteristic of the quinoline ring system. The C-S frequency, which is usually between 600 and 700 cm^{-1}, is too weak and variable to be of any use in interpretation. Bands at 808 and 772 cm^{-1} are assigned as in E-4 and E-5. The spectrum is consistent with the structure.

Four reactions gave yields of 87, 93, 94, and 95%.

j. Synthesis of (1-Ethylquinoline-2) (3-ethyl-2'-methyl-4,4'-bithiazole-2) monomethine cyanine iodide (F47M5)

(1) Discussion

An unusual amount of difficulty was encountered in this last step in the synthesis of F47M5.

It was first decided to prepare F47M5 from 1-ethyl-2-phenylthioquinolinium iodide, E-3, rather than the 2-methylthio compound, E-6 (the patent procedure), for the following reasons:

- A phenylthio compound had been successfully used for a similar type of reaction during the synthesis of F24M4 (II.D).

- The starting materials for E-3 were considerably less expensive than those for E-6.

- The simple route to E-6 gave a mixture of products (ref. 5,6) that could not be tolerated.

- The unequivocal synthesis of E-6 required three steps, while that of E-3 required two.

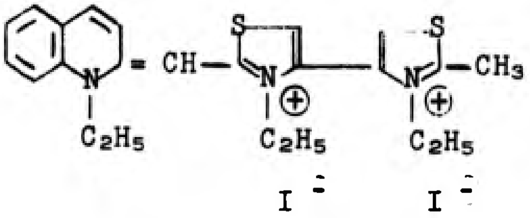
The phenylthio compound, E-3, was prepared successfully, but it failed to undergo the final reaction to give F47M5.

When the patent procedure was duplicated exactly (with E-6 and the bithiazolium ditosylate, E-9, in methanol), no insolable product was obtained. However, when the bithiazolium iodide, E-10 was used with E-6, and the solvent was changed from methanol to isopropanol, good yields of F47M5 were obtained. A fairly large excess of triethylamine was also found to be desirable. Owing to triethylammonium iodide contamination (indicated by TLC), crude yields of F47M5 slightly greater than 100% were obtained. However, only one dye species was present.

The failure to obtain (E-1, X=H) was probably due to one of two factors:

- 2,2'-Dimethyl-4,4'-bithiazole (E-8) may form only a mono-ethyl iodide adduct under the conditions specified in the patent (ref. 3).

- The ethiodide of F47M5 (E-11) may be dealkylated under the reaction conditions to give F47M5, which then has a nonactivated methyl group.



(E-11)

(2) Proof of Structure

(a) Infrared Spectrum

The spectrum of F47M5 shows bands at 1623 and 1567 cm^{-1} that are probably C=C vibrations. The strong band at 1527 cm^{-1} may be the overlapping of two or more bands and might be assigned to C=N. The bands at 797, 765 and 740 cm^{-1} are similar to absorptions in the starting materials. The infrared spectrum could fit the structure, but the evidence is not conclusive. An elemental analysis is necessary.

(b) Nuclear Magnetic Resonance Spectrum

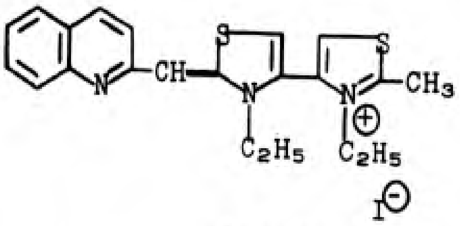
F47M5 was not soluble enough in n.m.r. solvents to permit a spectral interpretation.

(c) Elemental Analysis

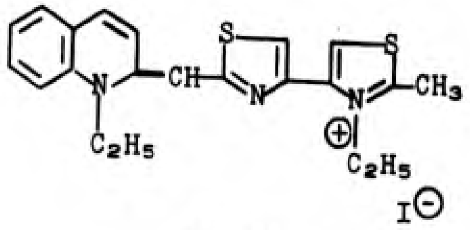
The elemental analysis agrees with the values calculated for F47M5 (see Experimental II.E.3).

(d) Possible Structures

Among the $C_{21}H_{22}IN_3S_2$ structures possible, F47M5 was considered a more likely possibility than either E-12 or E-13 below. The conjugated system present in F47M5, but absent in the other two structures, accounts for the deep color and high visible extiction coefficient of the product.



(E-12)



(E-13)

(3) Purity

The sample sent for analysis was taken from the material submitted to the Air Force. This material was recrystallized twice from pyridine.

Thin layer chromatography on neutral alumina produced one spot with either methanol or acetone elution and iodine development.

(4) Air Force Sample

Four 3.07-gram samples (total 12.28 grams) were submitted to the Air Force on 20 November 1963.

3. Experimental

a. Starting Materials

2,3-Butanedione (Eastman 1591, 500 g - $9.05) was used without further purification.

Thioacetamide (Eastman 1719, 100 g - \$8.25) [mp 111-113°C; lit. (ref. 1) mp 110-111°C] was used without further purification.

2-Chloroquinoline (Eastman 2801, 100 g - \$30.45) was used without further purification.

Thiophenol (Eastman 247, 500 g - \$8.80) was used without further purification.

Ethyl and methyl iodide were filtered before use.

2-Iodoquinoline (Eastman, 25 g - \$22.50) (mp 44-45°C; no lit. mp available) was used without further purification.

b. 2-Phenylthioquinoline (E-2) (ref. 2)

To a mixture of 2-chloroquinoline (50.0 g., 0.31 mole) and thiophenol (65.0 g, 0.59 mole) was slowly added triethylamine (32.8 g, 0.32 mole) in 5 g portions over 1/2 hour. An exotherm occurred, and a yellow solid formed. The reaction mixture was then heated on a steam bath for 45 hours and then cooled in an ice bath. The solid reaction mass was treated with 100 ml of water, made alkaline with potassium carbonate, and extracted three times with Et_2O (150 ml). The ether extracts were dried over potassium carbonate, the ether was removed under reduced pressure, and the residual oil was distilled. The slightly yellow oil [bp 165-168°C/0.8 mm] weighed 56.8 g (77%) [lit. (ref. 2) bp 190°C/ 1 mm].

c. 1-Ethyl-2-phenylthioquinolinium iodide (E-3) (ref. 2)

2-Phenylthioquinoline (23.7 g, 0.10 mole) and ethyl iodide (31.2 g, 0.20 mole) were placed in a 100-ml flask equipped with a Friedrichs condenser and drying tube of calcium sulfate. The reaction mixture was heated on the steam bath for two days. The solid that had formed was pulverized under acetone and filtered. The dried yellow crystals weighed 26.7 g (68.7%) (mp 172.5-174°C). One recrystallization from absolute ethanol gave 21.2 g [mp 181-183°C; lit. (ref. 2) mp 180-181°C].

d. 1,4-Dibromobutanedione-2,3 (E-7) (ref. 3)

A refluxing solution of butanedione-2,3 (8.6 g, 0.1 mole) in carbon disulfide (35 ml) was treated dropwise with stirring with a solution of bromine (10.6 ml, 31.0 g, 0.194 mole) in 20 ml of carbon disulfide. The addition was completed in 2.25 hrs. The heating was continued an additional 3 hr and the reaction mixture was left overnight without heating. Cooling in an ice bath yielded a yellow solid. It was filtered, washed with hexane and air-dried to yield 11.5 g (49%) of light yellow crystals of 1,4-dibromobutanedione-2,3 [mp 117°C; lit. (ref. 4) mp 117°C].

e. 2,2'-Dimethyl-4,4'-bithiazole (E-8) (ref. 3)

1,4-Dibromobutane-2,3-dione (48.6 g, 0.20 mole) and 30.2 g (0.40 mole) of thioacetamide were dissolved in one liter of methanol. In a 2-liter, 3-necked flask equipped with mechanical stirrer, Teflon paddle, reflux condenser, and calcium sulfate drying tube, the reaction mixture was stirred and refluxed for one hour and poured into two liters of distilled water. The cloudy solution (some solid was present) was acidified with dilute hydrochloric acid, and the solution was filtered. The clear filtrate was neutralized to pH ~7 with 10% aqueous potassium hydroxide and the precipitated solid was filtered. The crude product, dried in a vacuum oven at 70°C/15 mm for 4 hours, weighed 37.0 g (95%) (mp 169-173°C). Two recrystallizations from methanol, the second recrystallization using one g of decolorizing charcoal, gave 25.6 g (65.0%) of white needles [mp 173-175°C; lit. (ref. 3) mp 165°C, (ref. 4) 175°C].

f. 2,2'-Dimethyl-3,3'-diethyl-4,4'-bithiazolium di-p-toluene sulfonate (E-9)

A number of reactions were run to determine the conditions necessary for quaternization. The best conditions are detailed below; a table of the reactions performed in this synthesis is included. 2,2'-Dimethyl-4,4'-bithiazole (1.96 g, 0.01 mole) and ethyl p-toluenesulfonate (4.00 g, 0.02 mole) were placed in a 50-ml round-bottomed flask equipped with a calcium sulfate drying tube. The flask was placed in an oil bath whose temperature was maintained at 105-115°C for 90 hr.

The reaction mixture was cooled in an ice bath, and the dark viscous oil was ground under acetone (15 ml). The oil slowly crystallized to a brown solid. The suspension was filtered and the solid was washed with benzene (5 ml) and then 15 ml of acetone and air dried. The weight of crude product obtained was 3.15 g (80%), (mp 195-198°C). The crude product could be recrystallized from abs. ethanol-acetone to give 2.27 g of light tan solid [mp 199-200°C (no lit. mp available)].

The reactions tabulated below were performed in the same manner except for reaction conditions.

2,2'-Dimethyl-4,4'-bithiazole		Ethyl-p-toluene-sulfonate				
grams	moles	grams	moles	Time, hr	Temp, °C	Yield, %
3.92	0.02	8.00	0.02	24	100	- *
1.96	0.01	8.00	0.02	18	110	-
1.96	0.01	4.00	0.02	96	110	80
19.6	0.10	40.0	0.20	92	110	-
19.6	0.10	40.0	0.20	40	110	17
1.96	0.01	4.00	0.02	96	110	58
19.6	0.10	40.0	0.20	96	110	62
19.6	0.10	40.0	0.20	120	110	70
19.6	0.10	40.0	0.20	120	110	95

*Denotes only starting material obtained

The crude diethyl tosylate products from the above reactions were combined and the whole amount (110 g) was dissolved in abs. ethanol (175 ml), treated with charcoal (2 g), and filtered while hot. The clear yellow filtrate was cooled overnight to yield 80.3 g of white solid (mp 200-201.5°C).

g. 2,2'-Dimethyl-3,3'-diethyl-4,4'-bithiazolium diiodide (E-10)

2,2'-Dimethyl-4,4'-bithiazole (11.76 g, 0.06 mole) and filtered ethyl iodide (50.0 ml, 96.5 g, 0.62 mole) were placed in a 150 ml pressure bottle (the rubber gasket was protected by a finger cot) and this solution was heated on a steam bath for 4 days. After cooling to room temperature, the light yellow crystals were filtered and washed with 100 ml of dry ether. The product was air dried to give 18.0 g (59%) of pale yellow crystals [mp 177-178°C (no lit. mp available)]. Attempted recrystallization from ethanol caused decomposition. The crude product was found to be satisfactory for the final reaction.

h. 1-Ethyl-2-iodoquinolinium iodide (E-4)

(1) Method A (Reflux Conditions)

2-Iodoquinoline (4.90 g, 0.02 mole) and ethyl iodide (3.44 g, 0.022 mole) were placed in a 50-ml round-bottomed flask equipped with a reflux condenser and calcium sulfate drying tube. The reaction mixture was refluxed on a steam bath for 16 hr. On cooling, a dark solid formed. To the mixture was added absolute ether (20 ml) and the suspension was filtered. The brownish-yellow solid in the funnel was washed with an additional 20 ml of ether and dried at 80°C/15 mm for 2 hr to give crude product [2.2 g (27% conversion, 89% yield); mp 200-204°C; lit. (ref. 7) 201-201.5°C].

The ether was removed from the filtrate to give unreacted 2-iodoquinoline, 3.4 g. The above reaction was repeated and gave 2.8 g (35% conversion, 71% yield) of crude product that had a mp 193-196°C, and 2.5 g of unreacted 2-iodoquinoline.

The crude ethiodide from the two runs were combined and recrystallized from methanol to give 1.9 g of pure 1-ethyl-2-iodoquinolinium iodide, mp 199-201°C.

(2) Method B (Pressure Bottle)

2-Iodoquinoline (10.00 g, 0.040 mole) and ethyl iodide (60.0 g, 0.385 mole) were placed in a pressure bottle and heated on a steam bath for 7 days. The bottle was cooled to room temperature, 50 ml of absolute ether was added, and the suspension was filtered. The weight of crude product was 11.75 g (73%) (mp 197-199°C dec.).

i. 1-Ethyl-1,2-dihydroquinoline-2-thione (E-5) (ref. 5)

Potassium hydroxide (4.70 g, 0.083 mole) was dissolved in absolute ethanol (25 ml) in a 100-ml, 3-necked flask equipped with mechanical stirrer, Teflon blade, condenser, and drying tube. Hydrogen sulfide gas was passed into the solution for 1/2 hr. A white solid, potassium hydrosulfide, precipitated. After the solution was saturated with hydrogen sulfide gas, the gas inlet tube was removed and 1-ethyl-2-iodoquinolinium iodide (12.27 g, 0.031 mole) was added carefully in 3-g portions to the stirred suspension. Reaction took place immediately with evolution of heat. After the addition was complete, the reaction mixture was refluxed for 75 minutes and then cooled in an ice bath. The reaction mixture was poured into 300 ml of cold distilled water. Cooling and scratching gave a yellow solid that was filtered. The wet solid was recrystallized from 12 ml of absolute ethanol to give 5.08 g (86%) of yellow solid, [mp 54.5-56°C after drying at 20°C/15 mm for 2 hr, lit. mp (ref. 5) 59-60°C].

j. 1-Ethyl-2-methylthioquinolinium iodide (E-6) (ref. 5)

1-Ethyl-1,2-dihydroquinoline-2-thione (2.78 g, 0.015 mole) was magnetically stirred in a 50-ml round-bottomed flask equipped with a reflux condenser. Through the condenser, methyl iodide (1.77 ml, 4.0 g, 0.028 mole), was delivered slowly by pipette. A vigorous reaction set in immediately with the formation of a yellow solid. After the initial reaction had subsided, the mixture was heated on the steam bath for 1 hr. The suspension was cooled and filtered to give 4.65 g (94%) of product (mp 180-183°C). Recrystallization from absolute ethanol (30 ml/g) gave yellow needles, which were dried at 80°C/15 mm for 4 hours to give 3.70 g [mp 186-187°C (dec.); lit. mp (ref. 5) 185°C (dec.)].

k. (1-Ethylquinoline-2) (3-ethyl-2'-methyl-4,4'-bithazole-2) monomethine cyanine iodide (F47M5)

1-Ethyl-2-methylthioquinolinium iodide (0.331 g, 0.001 mole) and 2,2'-dimethyl-3,3'-diethyl-4,4'-bithiazolium di-iodide (0.298 g, 0.5 mmole) were dissolved in isopropanol (5 ml) and triethylamine (0.25 ml, 0.18 g, 1.8 mmole) added. The reaction mixture was refluxed for 16 hr on a steam bath. Methanethiol was evolved. Upon cooling the dark red solution in an ice bath, a dark red solid precipitated and was filtered. Small white needles were interspersed throughout the dark red powder. The product was dried at 80°C/15 mm for 2 hr to give 0.479 g (102%), (mp 228-230°C). After two recrystallizations from pyridine (2 ml/g), the melting point was 238-239°C (no literature mp available).

λ_{max}^{EtOH} 470 mμ (ϵ 41,300), 349 mμ (ϵ 9,100), 303 mμ (ϵ 8,200).

Analysis for $C_{21}H_{22}IN_3S_2$

	C	H	N	S	I	Ash	Mol. Wt.
Calcd.	49.7	4.35	8.28	12.62	25.1	0.0	507
Found	50.4 50.3	4.3 4.3	8.1 -	12.6 12.5	25.4 -	0.0 0.0	336*

---

*Thermoelectric method in methylene bromide.

1. Unsuccessful Preparations of F47M5.

(1) Reaction of 1-Ethyl-2-phenylthioquinolinium iodide with 2,2'-Dimethyl-3,3'-diethyl-4,4'-bithiazolium-di-p-toluenesulfonate

1-Ethyl-2-phenylthioquinolinium iodide (1.6 g, 0.004 mole), 2,2'-dimethyl-3,3'-diethyl-4,4'-bithiazolium-di-p-toluenesulfonate (0.8 g, 0.0013 mole) were added to methanol (16 ml) containing triethylamine (1 ml, 0.73 g, 0.007 mole) in a round-bottomed flask equipped with a reflux condenser and calcium sulfate drying tube. The mixture was refluxed 30 minutes, cooled in an ice bath, and filtered. A small amount of reddish solid was obtained. It was washed with methanol (2 ml) and dried at 80°C/15 mm for 4 hr to give 0.30 g (mp 251-258°C). An attempt to recrystallize this from pyridine gave no product.

The above reaction was twice repeated using a 1-hr reflux period. First, a 2-molar excess of triethylamine per mole of di-p-tosylate and second, a 5-molar excess of amine was used. No product was obtained from these reactions.

The reaction described initially was repeated, but refluxing was continued for 72 hours. No solid could be obtained on prolonged cooling. The mixture was poured into 200 ml of distilled water and extracted with three 50-ml portions of benzene. The benzene extracts were combined and the solvent was removed to give a brown tar that could not be recrystallized. Removal of water from the aqueous layer gave only tar.

The formation of a deep red color indicated that reaction took place but isolation of the product was not practical.

(2) Reaction of 1-Ethyl-2-methylthioquinolinium iodide with 2,2'-Dimethyl-3,3'-diethyl-4,4'-bithiazolium di-p-toluenesulfonate.

1-Ethyl-2-methylthioquinolinium iodide (0.64 g, 0.0019 mole) and 2,2'-dimethyl-3,3'-diethyl-4,4'-bithiazolium di-p-toluenesulfonate (0.60 g, 0.001 mole) were added to methanol (8 ml) containing triethylamine (0.5 ml, 0.36 g, 0.004 mole) in a 100-ml round-bottomed flask, and the mixture was heated gently on a steam bath until methanethiol was no longer evolved (10 minutes). The mixture was left standing overnight and then cooled in an ice bath. Prolonged cooling and scratching did not produce a solid as reported in the patent literature (ref. 3) for a closely analogous compound.

4. References

1. D. Rosenthal and T. I. Taylor, J. Am. Chem.Soc., 79, 2684 (1957).
2. L. G. S. Brooker, et al., J. Am. Chem. Soc., 73, 5326 (1951).
3. L. C. Hensley, U. S. Patent 2,579,432, Dec. 18, 1951. C.A., 46, 2942 (1952).
4. E. D. Sych, Ukrain. Khim. Zhur., 24, 79 (1958). C.A., 52, 18377 (1958).
5. D. J. Fry and J. D. Kendall, J. Chem. Soc., 1716 (1951).
6. B. Beilenson and F. M. Hamer, J. Chem. Soc., 143 (1939).
7. H. L. Braellow and C. A. Vander Werf, J. Org. Chem., 16, 1143 (1951).

5. Spectra

Spectral data are given in Figures 12-21.

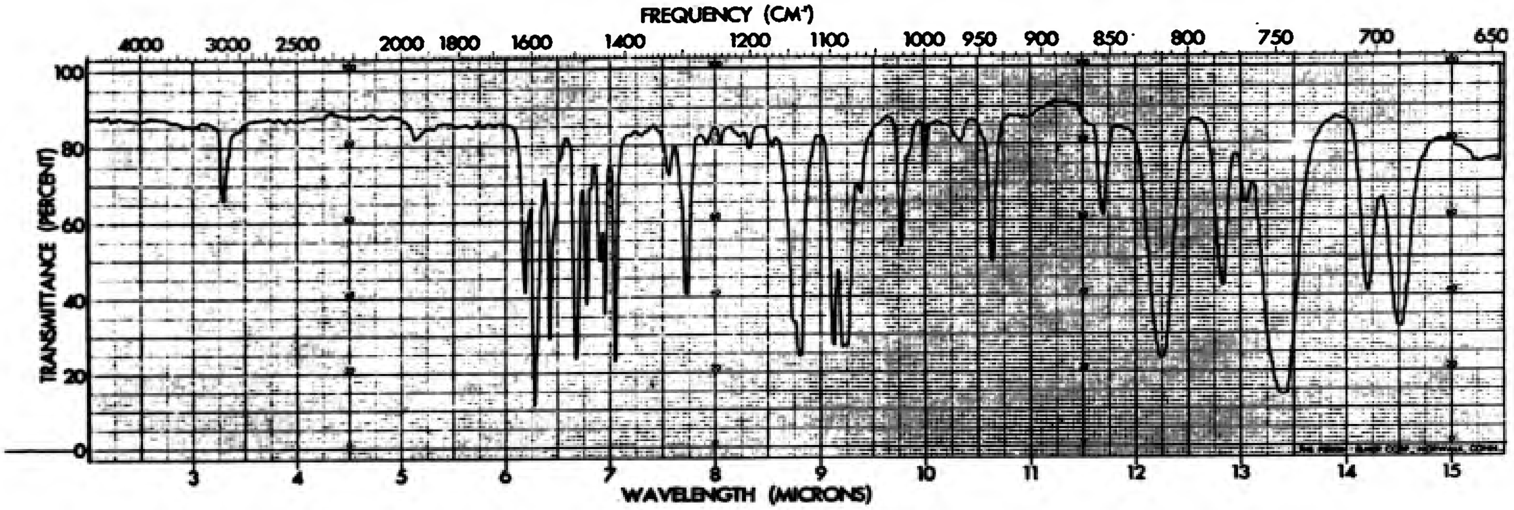


Figure 12. Infrared Spectrum (film) of 2-Phenylthioquinoline (E-2)

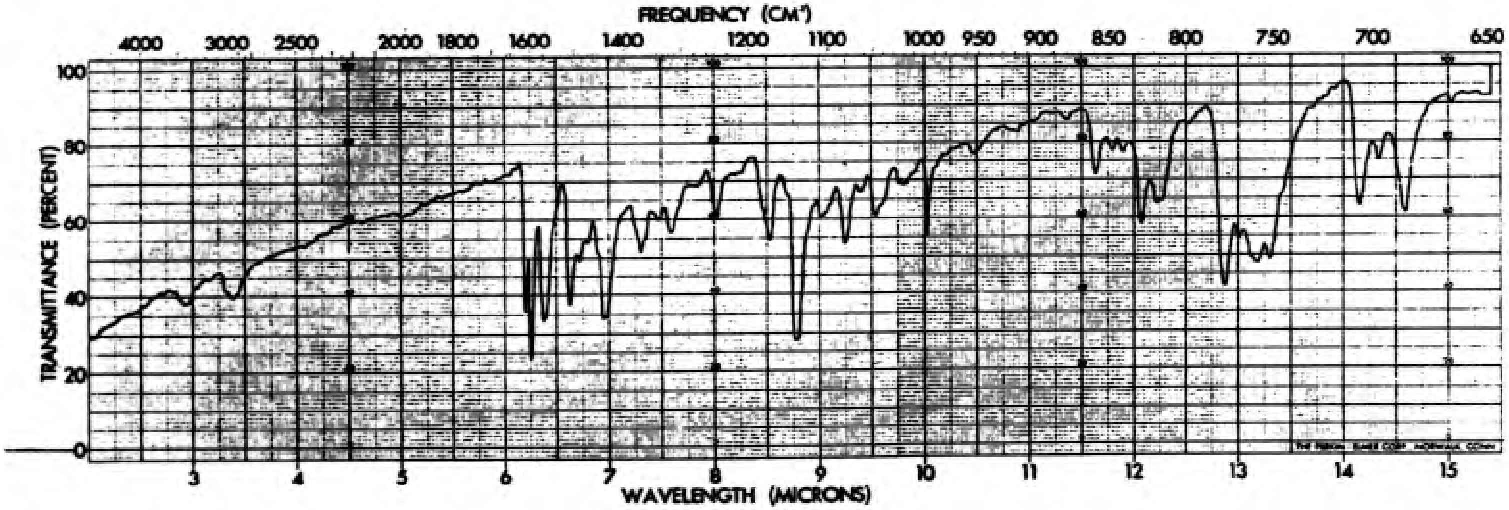


Figure 13. Infrared Spectrum (KBr pellet) of 1-Ethyl-2-phenylthioquinolinium iodide (E-3)

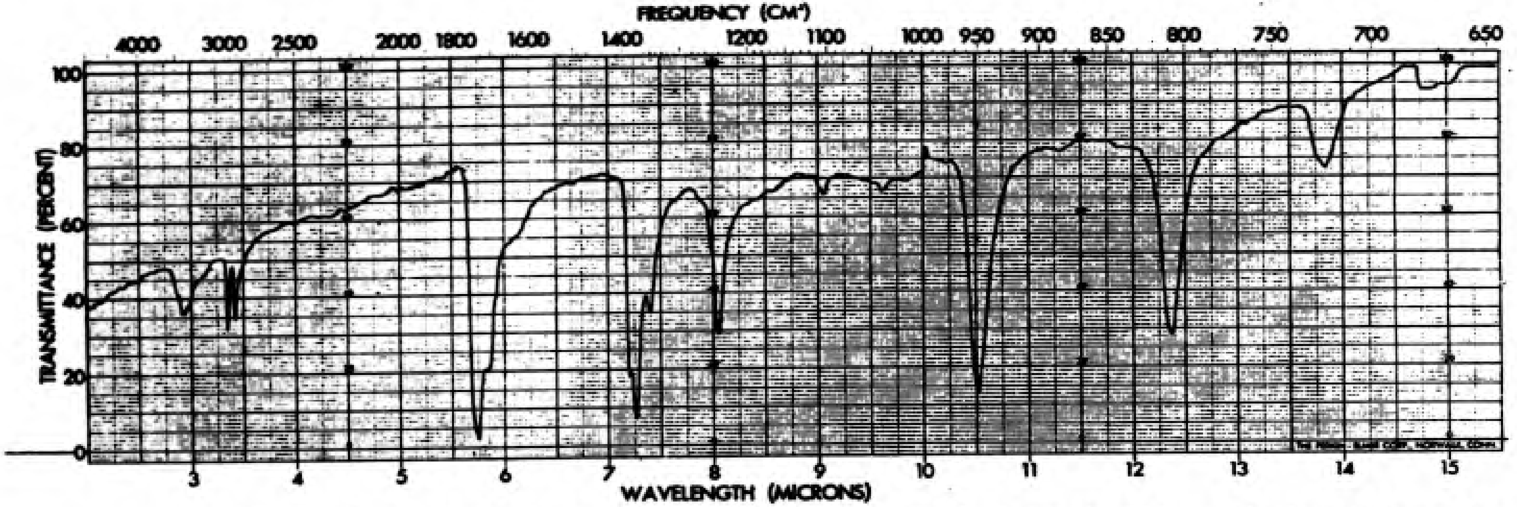


Figure 14. Infrared Spectrum (KBr pellet) of 1,4-Dibromobutanedione-2,3 (E-7)

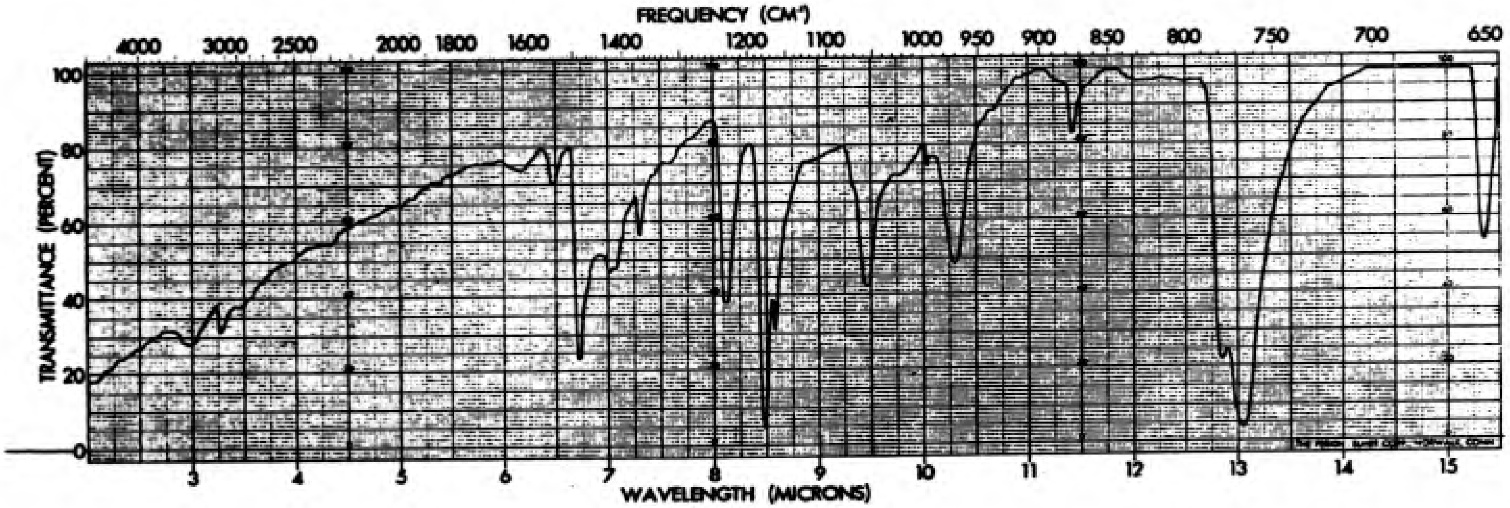


Figure 15. Infrared Spectrum (KBr pellet) of 2,2'-Dimethyl-4,4'-bithiazole (E-8)

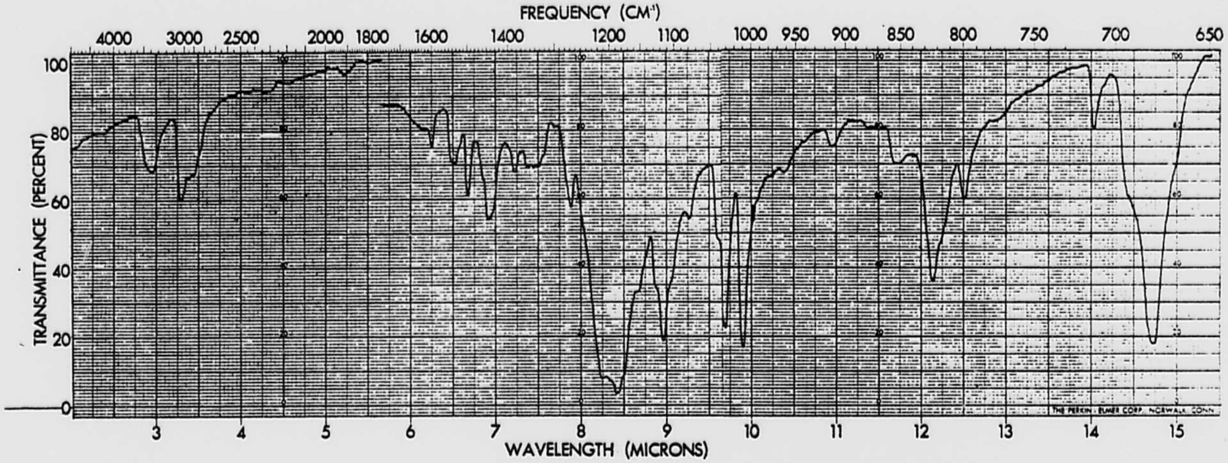


Figure 16. Infrared Spectrum (KBr Pellet) of 2,2'-Dimethyl-3,3'-diethyl-4,4'-bithiazolium di-p-toluenesulfonate (E-9)

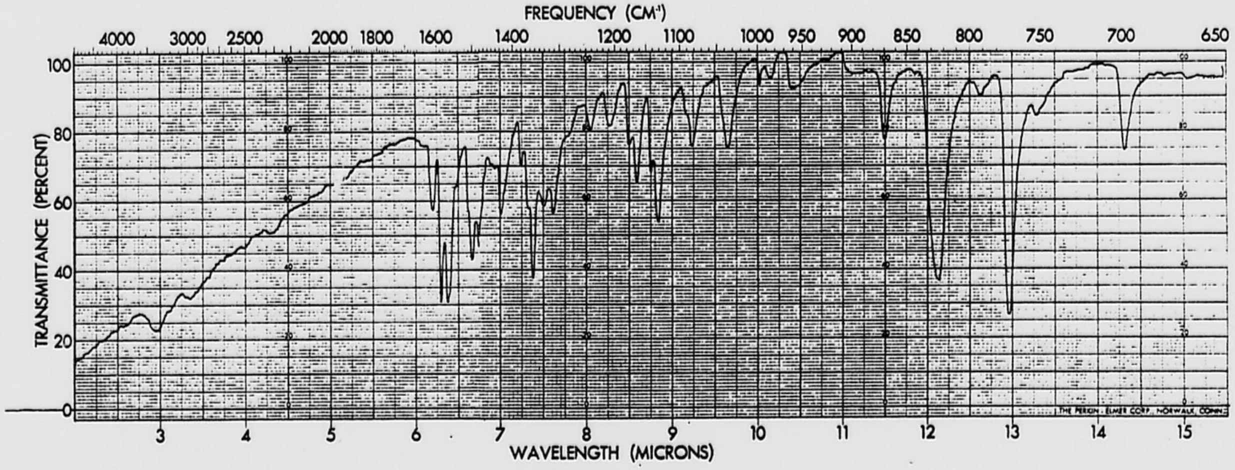


Figure 17. Infrared Spectrum (KBr Pellet) of 1-Ethyl-2-iodoquinolinium iodide (E 4).

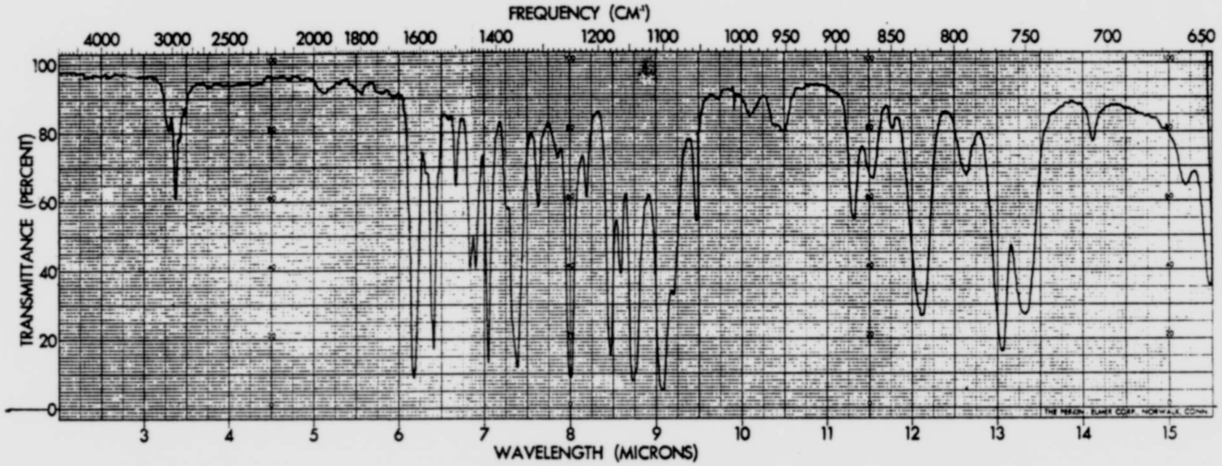


Figure 18. Infrared Spectrum (Melt, Film) of 1-Ethyl-1,2-dihydroquinoline-2-thione (E-5)

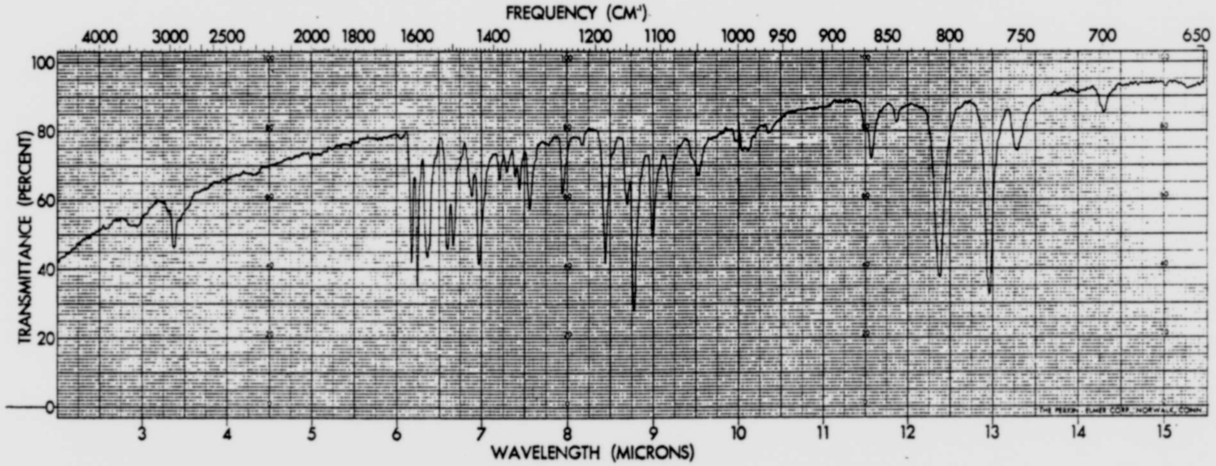


Figure 19. Infrared Spectrum (KBr Pellet) of 1-Ethyl-2-methylthioquinolinium iodide (E-6)

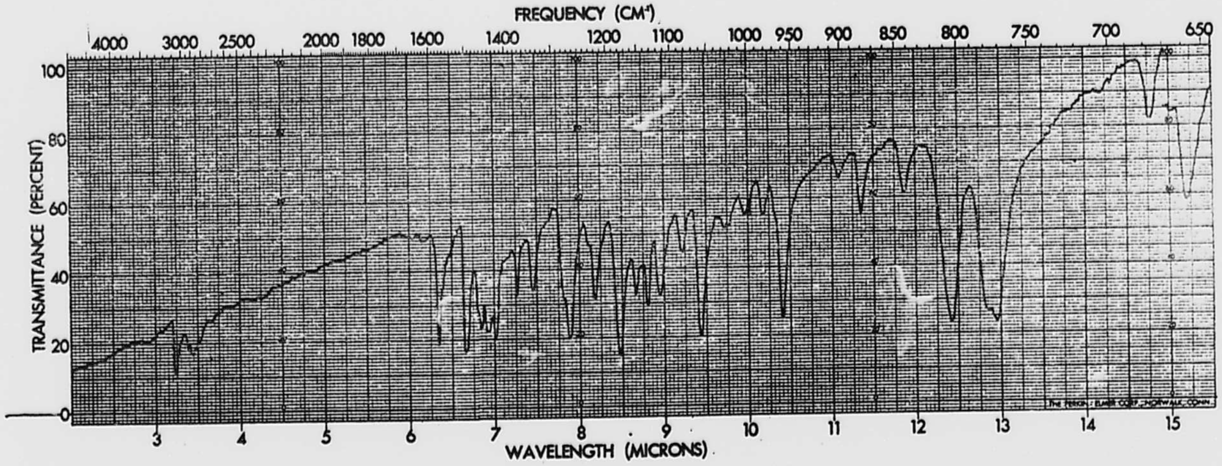
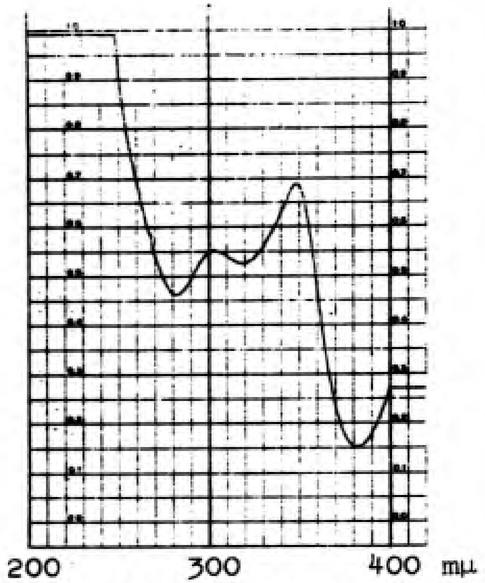
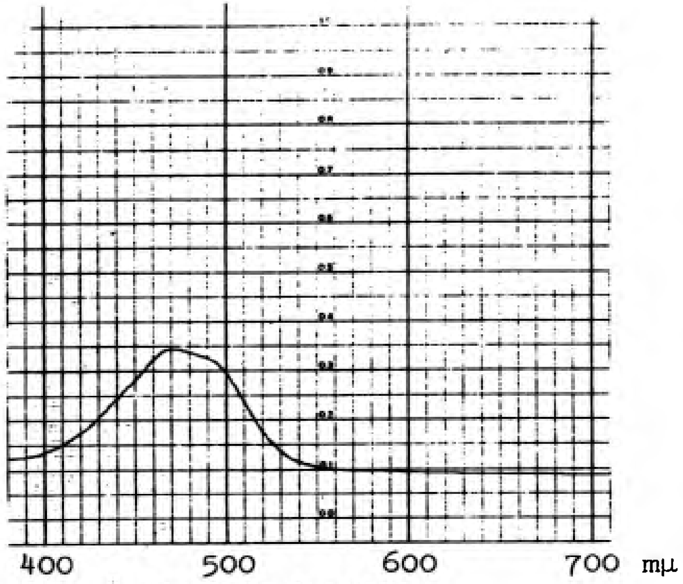


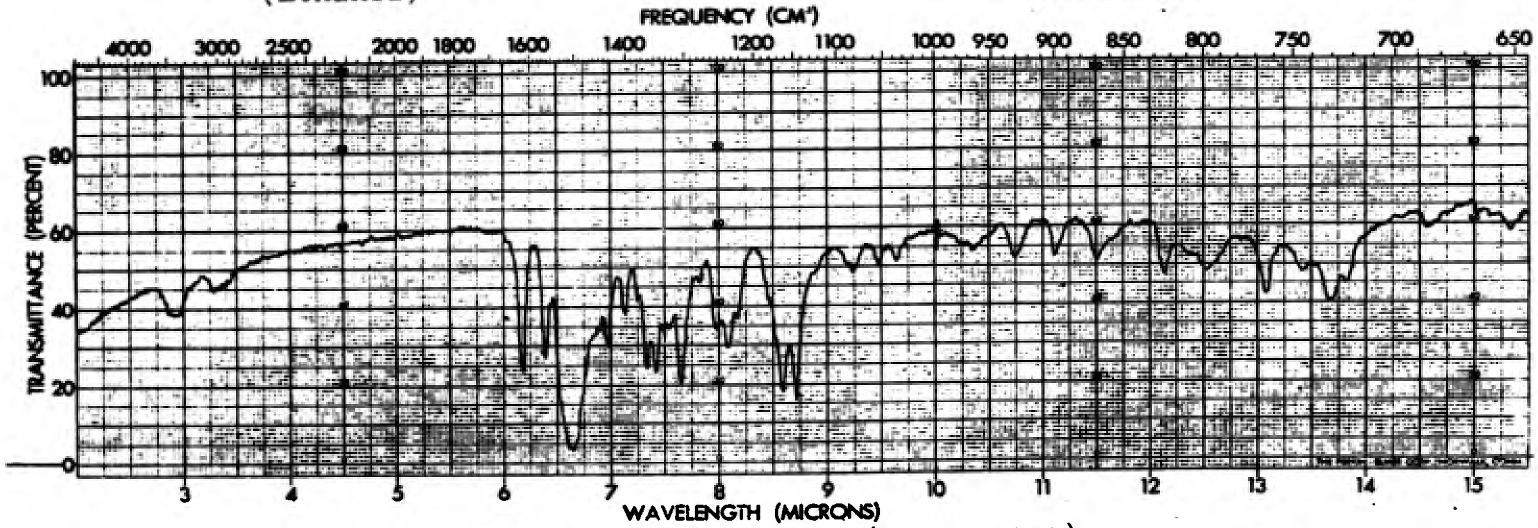
Figure 20 Infrared Spectrum (KBr Pellet) of 2,2'-Dimethyl-3,3'-diethyl-4,4'-bithiazolium diiodide (E-10)



Ultraviolet Spectrum
(Ethanol)



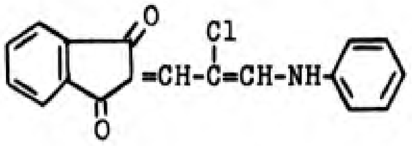
Visible Spectrum
(Ethanol)



Infrared Spectrum (KBr Pellet)

Figure 21. Spectral Data on (1-Ethylquinoline-2)(3-ethyl-2'-methyl-4,4'-bithiazole-2) monomethine cyanine iodide (F47M5)

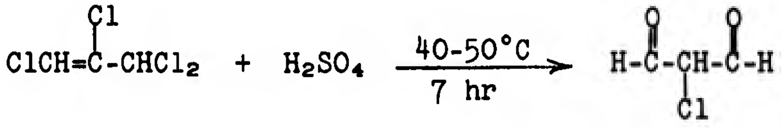
F. 2-(3-ANILINO-2-CHLOROPROPENYLIDENE)INDANEDIONE (F26M6)



(F26M6)

1. Synthesis of Chloromalondialdehyde dianil hydrochloride ethanolate (F-4)

Two routes to F-4 were investigated. The first procedure involved the conversion of 1,2,3,3-tetrachloropropene-1 (F-2) to chloromalondialdehyde (F-1) with sulfuric acid (ref. 1).



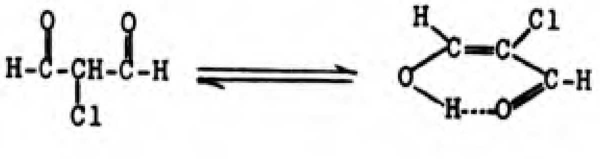
$$\mathrm{ClCH{=}\overset{Cl}{C}{-}CHCl_2} + \mathrm{H_2SO_4} \xrightarrow[7\ \mathrm{hr}]{40\text{-}50°\mathrm{C}} \mathrm{H{-}\overset{O}{C}{-}\underset{Cl}{CH}{-}\overset{O}{C}{-}H}$$

(F-2) (F-1)

The dianil of F-1 is required for reaction with indanedione to give (F26M6).

The synthesis of F-1 and the preparation of its dianil (ref. 1) was chosen over the direct production of the dianil from mucochloric acid (ref. 2) because of the supposed commercial availability of 1,2,3,3-tetrachloropropene-1 and a more modern literature reference.

The synthesis of F-1 by the method of (ref. 1) produced a small yield of brown F-1. The infrared spectrum (Figure 22) of this compound is consistent with that expected of a hydrogen-bonded, conjugated enol (F-1a),

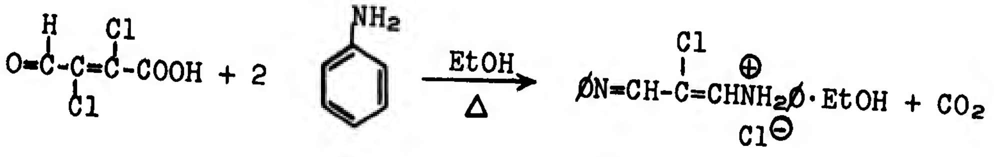


(F-1) (F-1a)

with bonded O-H absorptions between 3200 and 2500 cm^{-1}. The carbonyl frequency is lowered to 1575 cm^{-1} by conjugated chelation. The strong bands near 1178 cm^{-1} are due to C-O and O-H deformations.

Although F-1 was prepared successfully from F-2, the method was abandoned because F-2 was not available commercially and because of the poor yields encountered in the reaction.

The required dianil (F-4) was prepared successfully by the reaction of mucochloric acid (F-3) with aniline.



(F-3)

(F-4)

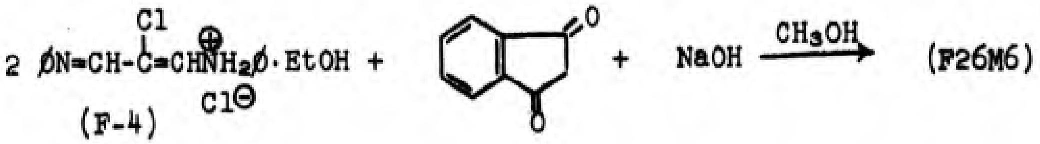
This synthesis presented no outstanding problems, but since the reaction is exothermic with carbon dioxide evolution, some care must be exercised during the addition of aniline. It was also noted that low yields were obtained if the filtrates from the first crop of F-4 were not acidified to provide more product.

The infrared spectrum of F-4 shows it to be that of an alcoholate with O-H stretching at 3400 cm^{-1}. The $\underset{\text{N-H}}{\oplus}$ is assigned the broad absorption at 2900 cm^{-1}, even though it is at somewhat higher frequency than normal for a secondary amine salt. The bands at 1618 and 1575 cm^{-1} may be C=N and C=C conjugated with a phenyl group. The absorption at 1486 cm^{-1} is assigned to phenyl, while monosubstituted phenyl is clearly shown at 690 and 760 cm^{-1}. The broad band at 800 cm^{-1} is assigned to the $-NH_2$ rocking frequency. The spectrum is consistent with the assigned structure.

A Beilstein flame test confirmed the presence of halogen in F-4.

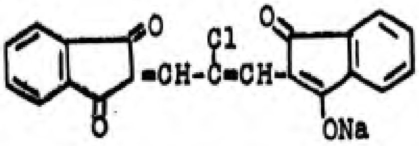
This reaction was carried out five times with average crude and pure yields of 87 and 70%, respectively.

2. Synthesis of 2-(3-Anilino-2-chloropropenylidene)indanedione (F26M6)



a. Discussion

The product of the patent reference (ref. 3) is claimed to be a photographic sensitizer. The patent structural assignment is somewhat tentative: "The dyestuff obtained is probably that of Example 5." (ref. 3).



(Example 5)

The product we obtained after numerous exact duplications of the patent conditions did not have the di-substituted structure of Example 5, but rather the monosubstituted structure of F26M6. From the molar ratios of reactants used in the patent, one would expect to obtain a mono- rather than a di-substituted compound, and this was confirmed by the infrared spectral and elemental analyses of our reaction product.

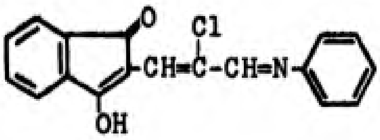
We believe that the patent authors were misled into thinking their product was a sodium salt by the following observation. F26M6 leaves a residue upon combustion. This was observed on every occasion we attempted combustion. When the infrared spectral interpretation ruled out Example 5 as the structure, it was then suspected that the product was F26M6 contaminated with sodium chloride from the reaction. Extractions intended to remove an inorganic salt from F26M6 and vice versa still gave an ash-producing material. Much of the purification difficulty arose from the insolubility of F26M6 in most organic solvents. Recrystallization from acetonitrile finally gave an analytically pure product that we also found to give a combustion residue. However, under the combustion conditions utilized for elemental analysis, the analysis, correct for the monosubstituted product F26M6, showed 0.0% residue.

Early in this work, we utilized the molar ratios of reactants that we felt would have the best chance for the production of "Example 5", i.e., 2:1:2:: indanedione:F-4:sodium hydroxide. A blue color, characteristic of the anion of indanedione resulted, but no characterizable product was obtained.

b. Proof of Structure

(1) Infrared Spectrum

The fairly strong band at 3185 cm^{-1} is most probably N-H stretching. The N-H deformation may be combined with the phenyl band at 1506 cm^{-1} where the absorption is too strong and broad for phenyl group alone. Two carbonyl absorptions are found at 1700 and 1658 cm^{-1} with C-O stretching at 1300 cm^{-1}. These frequencies are characteristic of cyclic anhydride type structures. The carbonyl absorptions are at lower frequencies than those in the starting material, indanedione, which is evidence for greater conjugation in F26M6. The absorption at 1595 cm^{-1} is probably phenyl and conjugated double bonds. The four adjacent hydrogen atoms on the indanedione ring are responsible for the 770 cm^{-1} absorption, while monosubstituted phenyl absorptions, present in the structure of F26M6, but not in "Example 5", are seen at 685 and 735 cm^{-1}. No C=N absorption is present in the product, which favors the assigned structure over that of F-5, a tautomeric form of F26M6.



(F-5)

(2) Elemental Analysis

The elemental analysis agrees with the values calculated for F26M6 (see Experimental II.F.3) but not for "Example 5", which contains sodium and does not contain nitrogen. The structure of the reaction product is that assigned to F26M6.

c. Purity

The sample submitted for elemental analysis had been twice recrystallized and was taken directly from the sample submitted to the Air Force.

Thin-layer chromatography on alumina showed only one spot after methanol or acetone elution and iodine development.

d. Air Force Sample

Four 3.83-gram samples (total 15.32 grams) were submitted to the Air Force on 27 September 1963.

3. Experimental

a. Starting Materials

Mucochloric acid (Eastman, 500 g - $11.05; [mp 125-126°C; lit. (ref. 4) mp 127°C] was used without further purification.

Indanedione (Eastman, 100 g - $27.30) was recrystallized from pet. ether (90-120°C) using a Soxhlet apparatus [mp 131.5-133°C; lit. (ref.5) mp 132-133°C].

Aniline (Eastman, 1 kg - $2.35) was distilled under nitrogen at reduced pressure through a 10-in. Vigreux column equipped with a straight head [bp 66°C/8.5 mm].

Inorganic Reagents were J. T. Baker and Son reagent grade and were used without further purification.

1,2,3,3-Tetrachloropropene-1 (K and K, 10 g - $3.00) was used without further purification.

b. Chloromalondialdehyde (F-1) (ref. 1)

1,2,3,3-Tetrachloropropene (35.4 g, 0.20 mole) was added to 120 ml of concentrated sulfuric acid (d = 1.84 g/ml) and the mixture was stirred at 40-50°C for seven hours. The mixture was poured onto 160 ml of ice water and left standing in a refrigerator for three days. The mixture was filtered to give 9.90 g of dark brown solid. The mother liquor was continuously extracted with ether (150 ml) for eight hours. Removal of ether layer and evaporation of ether gave an additional 1.1 g of brown solid.

An attempt to recrystallize the product from benzene with a little acetone gave a wet brown solid. It was redissolved in benzene and water was removed by distillation with benzene using a Dean-Stark trap. After all the water was removed, the resultant benzene solution of dialdehyde was cooled to give 2.1 g of a light brown solid [mp 151-152°C; lit. (ref. 1) mp 145-146°C]. Evaporation of the mother liquor gave only a brown tar.

c. Chloromalondialdehyde dianil hydrochloride ethanolate (F-4) (ref. 2)

Mucochloric acid (16.9 g, 0.10 mole) was dissolved in absolute ethanol (80 ml) in a 3-necked, round-bottomed flask equipped with a mechanical stirrer, reflux condenser, and calcium sulfate drying tube. A solution of aniline (18.7 g, 0.20 mole) in absolute ethanol (80 ml) was added slowly over a 30 min. period. CO_2 was rapidly evolved and the mixture became warm enough to reflux. When CO_2 evolution, checked by a bubble trap, had slowed, the reaction mixture was heated on a steam bath. When CO_2 evolution had ceased (ca. 0.5 hr), the solution was cooled in an ice bath, and a yellow solid precipitated. This was removed by suction filtration and to the filtrate was added a mixture of distilled water (100 ml) and conc. hydrochloric acid (10 ml). More yellow solid precipitated. This was filtered, combined with the original solid, and washed with cold water (450 ml).

The crude product was recrystallized from absolute ethanol (7 ml/g) and dried at 90°C/15 mm for 3 hr to give 25.22 g (75%) of yellow powder [mp 229-230°C dec.; lit. (ref. 2) mp 228°C dec.]).

d. 2-(3-Anilino-2-chloropropenylidene)indanedione (F26M6) (ref. 3)

Indanedione (2.5 g, 0.017 mole), chloromalondialdehyde dianil hydrochloride ethanolate (12.00 g, 0.035 mole), and sodium hydroxide (0.68 g, 0.017 mole) were dissolved in methanol (250 ml). The mixture was left standing with occasional shaking for three days. At that time a large amount of red solid had formed. It was filtered, washed with two 100-ml portions of absolute ether, and dried at 80°C/15 mm for 2 hr to give 5.13 g (100%) (mp 205-209°C dec.). Attempts to recrystallize this solid from the usual solvents failed. It was recrystallized from acetonitrile (100 ml/g) using a Soxhlet apparatus. The acetonitrile had to be changed after about 8 hr or else the reddish product had a dark coating. Two recrystallizations in this manner afforded a pure product [mp 207°C dec.; no lit.mp; $\lambda_{max}^{CH_3OH}$ 497 mμ (ϵ 45,500) and 246 mμ (ϵ29,400)].

Analysis for $C_{18}H_{12}ClNO_2$

	C	H	N	Cl
Calc'd.	69.79	3.91	4.52	11.45
Found	69.7	3.9	4.3	11.6

e. Unsuccessful Attempts to Prepare 1-Oxy-3-oxyhydrindyl-2-β-chloromethine indanedione sodium salt (Example 5)

Indanedione (2.92 g, 0.02 mole), chloromalondialdehyde dianil hydrochloride ethanolate (3.39 g, 0.01 mole), and sodium hydroxide (0.88 g, 0.022 mole) were dissolved in methanol (250 ml) and left standing 3 days. A very dark brown solid, 2.82 g, was obtained on filtration. This solid gave the deep blue color characteristic of the anion of indanedione when dissolved in methanol. Thin layer chromatographic analysis showed the presence of only a very little colored material of any type.

The reaction outlined above was repeated except the mixture was refluxed on a steam bath overnight. When the mixture was cooled, no solid was formed. Thin layer chromatography again confirmed the presence of the indanedione anion and the absence of any dye.

4. References

1. J. W. Conforth, et al., *J. Chem. Soc.*, *1949*, 1549.

2. W. Dieckmann and L. Platz, *Ber.*, *37*, 4638 (1904).

3. J. Jennen and O. H. Vandenbroele, U. S. Patent 2,644,754, July 7, 1953. *C.A.*, *48*, 67 (1954).

4. "Dictionary of Organic Compounds", I. Heilbron and H. M. Bunbury, Eds., Vol. 4, Oxford, N. Y., 1953.

5. S. J. Huang, et al., *J. Am. Chem. Soc*., *84*, 2819 (1962).

5. Spectra

Spectral data are given in Figures 22-24.

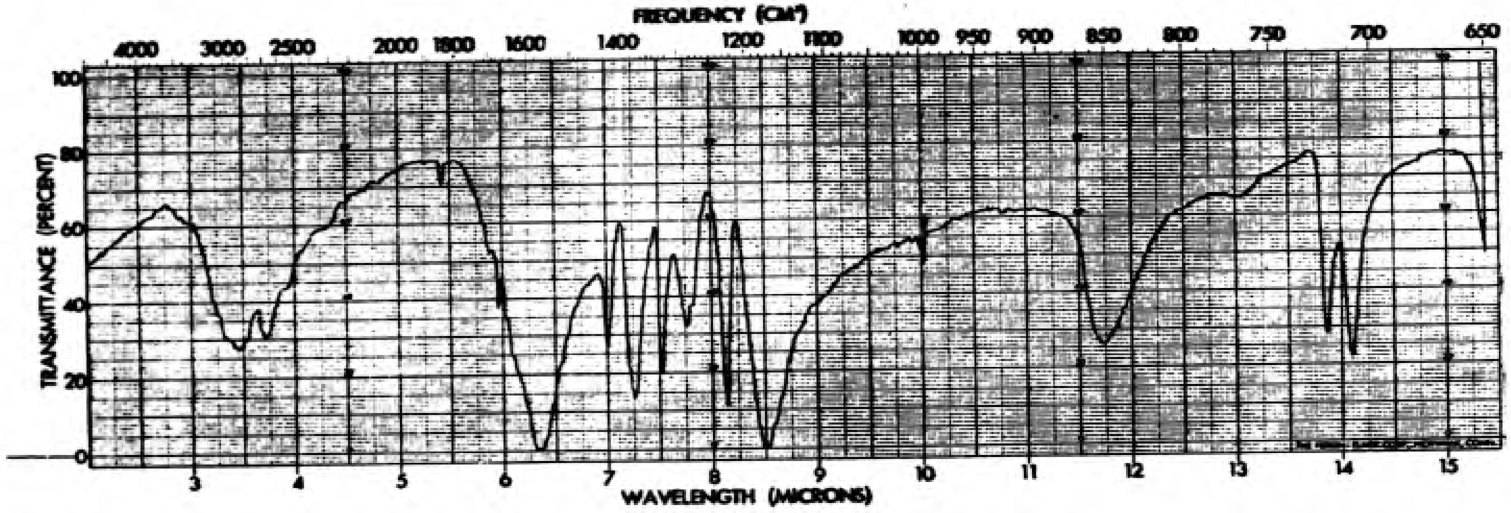


Figure 22 . Infrared Spectrum (KBr pellet) of Chloromalondialdehyde (F-1)

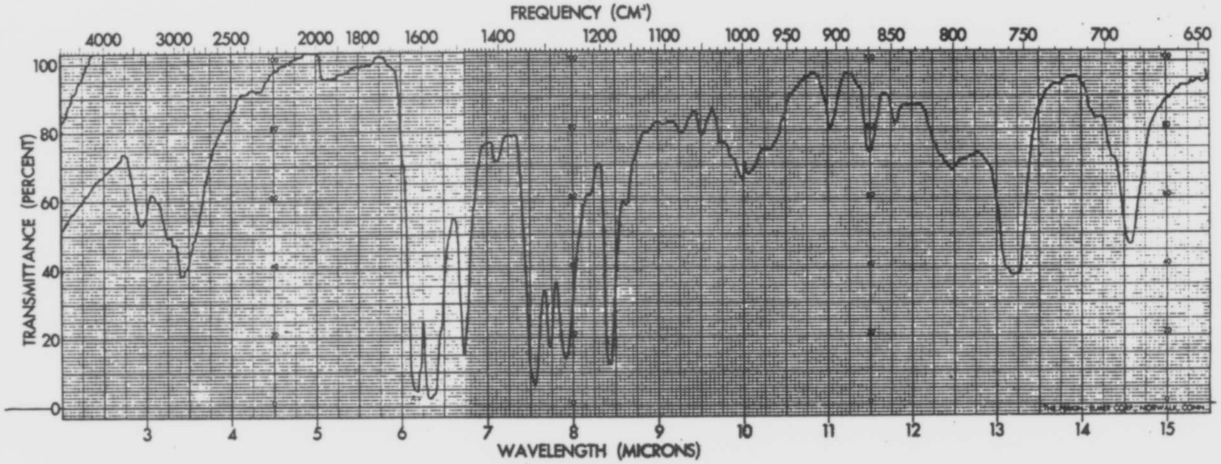
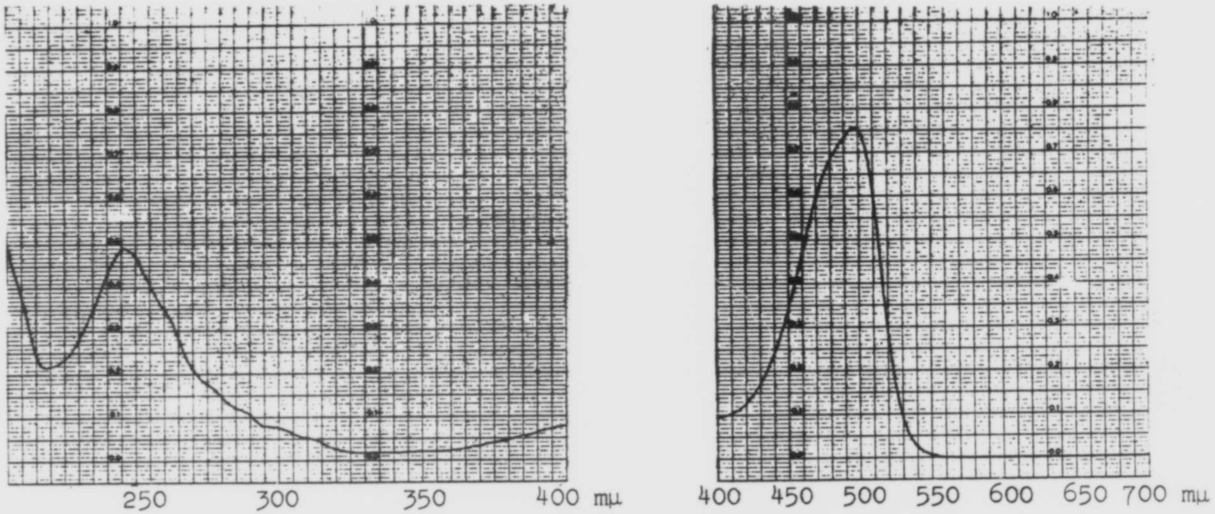
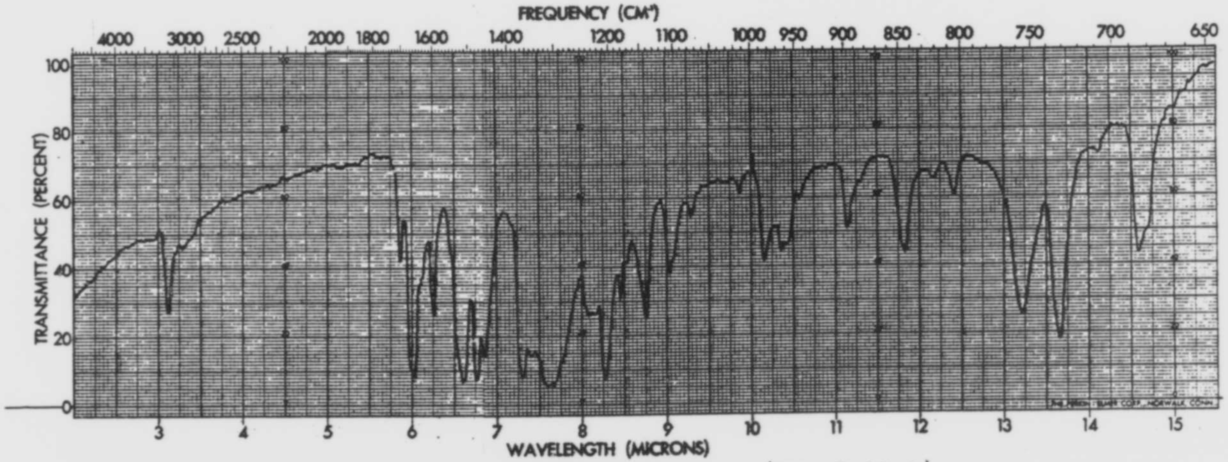


Figure 23. Infrared Spectrum (KBr Pellet) of Chloromalondialdehyde dianil-hydrochloride ethanolate (F-4)



Ultraviolet Spectrum

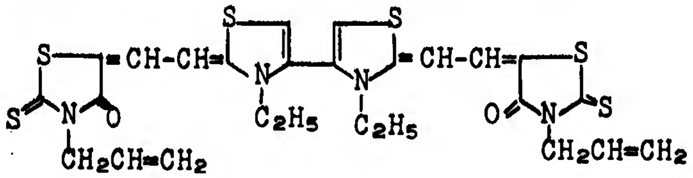
Visible Spectrum



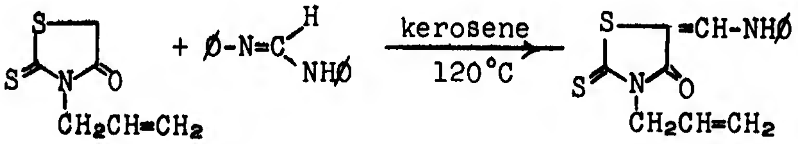
Infrared Spectrum (KBr Pellet)

Figure 24. Spectral Data on 2-(3-Anilino-2-chloropropenylidene)indanedione (F26M6)

G. [2,2'-(3,3'-DIETHYL)(4,4'-BITHIAZOLYL)][5,5'-(3,3'-DIALLYLRHODANINE)]DIMETHINE CYANINE (F48M7)



1. Synthesis of 5-Anilinomethylene-3-allylrhodanine (G-1)



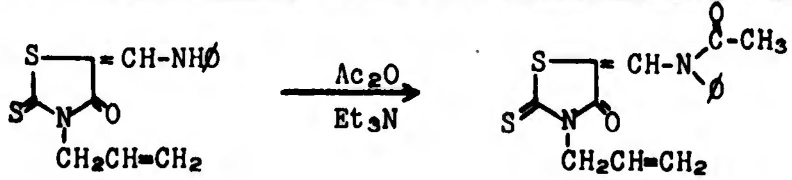
(G-1)

The procedure used was similar to that used to prepare the 3-ethyl derivative (ref. 4).

The major problem in this synthesis was complete removal of the kerosene. It was difficult to wash this completely away from G-1 without losing product. Prolonged drying at reduced pressure and 80°C will remove it, but the high-boiling liquid contaminates the drying oven. Yields of 33, 56, and 80% were obtained. N-Allylrhodanine is easily detected in small quantities, as the compound has a strong garlic odor.

The infrared spectrum of G-1 (Figure 25) shows the N-H stretch as a single band at 3225 cm^{-1}, which is correct for a secondary amine. Phenyl bands are seen at 1587 and 1497 cm^{-1} as well as at 680 and 750 cm^{-1} (mono-substitution). The strong carbonyl absorption at 1733 cm^{-1}, present in the starting material N-allylrhodanine is gone and probably lowered to 1626 cm^{-1} by amine conjugation. Bands at 1689 and 1661 cm^{-1} may be associated with double bond vibrations. The infrared spectrum is consistent with the assigned structure.

2. Synthesis of 5-Acetanilidomethylene-3-allylrhodanine (G-2)



(G-1) (G-2)

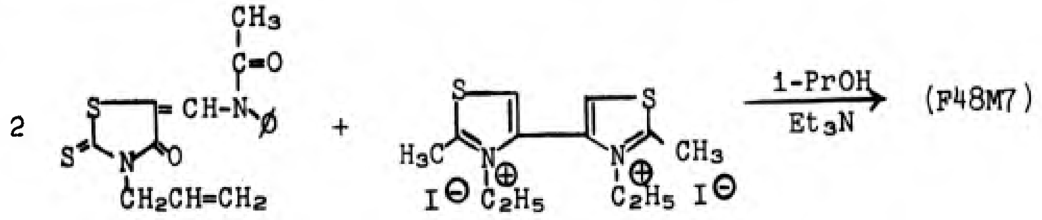
No problems were encountered during this synthesis. The procedure used was similar to that for the acetylation of the 3-ethyl derivative (ref. 4).

The infrared spectrum of G-2 no longer shows the N-H absorption of G-1 at 3225 cm^{-1}. The carbonyl group of the acetylated product is present at 1706 cm^{-1}. Bands at 1608 and 1592 cm^{-1} may include the conjugated rhodanine carbonyl absorption frequency as well as double bonds and phenyl vibrations. The infrared spectrum is consistent with the structure assigned.

3. Synthesis of 2,2'-Dimethyl-3,3'-diethyl-4,4'-bithiazolium diiodide (E-10)

The synthesis and properties of E-10 are described in Section II.E of this report.

4. Synthesis of [2,2'-(3,3'-Diethyl)(4,4'-bithiazolyl)][5,5'-(3,3'-diallylrhodanine)]dimethine cyanine (F48M7)



(G-2) (E-10)

a. Discussion

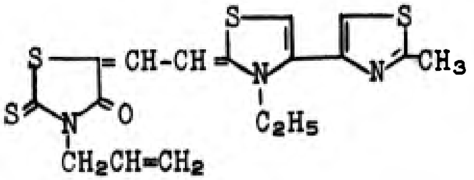
This final reaction proceeds without difficulty if a large excess of triethylamine is used. This is not apparent from the patent reference (ref. 3). When impure F48M7 was first obtained, it deceptively appeared to be pure, melting sharply over a 1°C range near 160°C. This compound has no literature melting point value. The criterion of purity is the absence of the 1706 cm^{-1} infrared absorption band characteristic of unreacted G-2. F48M7 was recrystallized with difficulty because of its insolubility. Recrystallization from isopropanol gave pure material, but over 100 ml of isopropanol per gram of F48M7 were required. However, it was found that analytically-pure material could be obtained by continuously extracting F48M7 with isopropanol in a Soxhlet apparatus.

Yields of 73 and 75% of pure material were obtained.

b. Proof of Structure

(1) Discussion

Because of the previously encountered difficulty in the disubstitution of E-10 (see Section II.E), G-3 had to be considered with F48M7 as a possible structure for the product of the reaction



(G-3)

(2) Infrared Spectrum

Aliphatic and olefinic C-H absorptions are seen in the 3000 cm^{-1} region. The 1706 cm^{-1} amide carbonyl band of G-2 is gone and conjugated carbonyl is present at 1653 cm^{-1}. The mono-phenyl substitution bands of G-2 are also gone. Absorptions at 1595 and 1520 cm^{-1} may be due to conjugated double bonds. The infrared spectrum is consistent with the assigned structure. It does not, however, distinguish between structures F48M7 and G-3.

(3) Nuclear Magnetic Resonance (nmr) Spectrum

Since the dye was soluble in deuterochloroform only to the extent of 3.8 wt-%, a spectrum with a low signal-to-noise ratio was obtained.

NMR SPECTRAL DATA

Chemical Shifts (ppm from tetra-methylsilane)	Assignments (most probable)
7.60 singlet	ring CH (unsat.) or =CH-CH=
7.45 singlet	ring CH (unsat.) or =CH-CH=
7.30 singlet	ring CH (unsat.) or =CH-CH=
6.52 broad	$CH_2-\{CH\}=CH_2$
5.42 broad	$CH=\{CH_2\}$
5.18 broad	$N-\{CH_2\}-C$
4.80 broad	$-\{CH_2\}-CH_3$
2.79 singlet	ring CH_3
1.37 triplet (J_{HH} = 7.2 cps)	$CH_2\{CH_3\}$

An absorption that might be due to a thiazole-methyl group was noted at 2.79 ppm. While this result suggests structure G-3, a conclusive assignment cannot be made on the basis of spectral data.

(4) Elemental Analysis

The calculated elemental values for F48M7 and G-3 are quite similar for all elements. The largest differences are in the nitrogen and oxygen values (1.25 and 1.3%, respectively). When the product dye was analyzed for all elements present (including a direct oxygen analysis), the following results were obtained:

	Analysis, %		
Element	Calcd. F48M7	Calcd. G-3	Found
C	50.45	50.2	50.06
H	4.23	4.2	4.48
N	9.05	10.3	9.26
O	5.17	3.9	5.23
S	31.09	31.4	31.18

The values found are in very close agreement with F48M7. The structure of the product dye is tentatively assigned as F48M7 on the basis of the elemental analytical data.

c. Purity

The sample submitted for elemental analysis was recrystallized twice and was taken directly from the sample submitted to the Air Force.

Thin layer chromatography on Silica Gel-G showed one spot with methanol, acetone, or chloroform elution and iodine development. Iodine reacts with F48M7.

d. Air Force Sample

Four 6.0-gram samples (total 24.0 grams) in nitrogen-filled bottles were submitted to the Air Force on 23 August 1963.

5. Experimental

a. Starting Materials

N-Allylrhodanine (K and K, 10 g - $5.50) was obtained as waxy solid. Its infrared spectrum was consistent with its structure. The compound was used without further purification.

N,N'-Diphenylformamidine (K and K, 100 g - $7.50) was recrystallized from absolute ethanol (1 g/5 ml) [mp 137-139°C; lit. (ref. 1) mp 137°C].

Kerosene (Esso) highest purity without additives was obtained as a gallon sample from the Esso Refinery, Everett, Mass.

Ethyl iodide (MC and B, 1 lb - $11.65) was filtered to remove the mercury inhibitor before use.

Miscellaneous Acetic anhydride, triethylamine and isopropanol were reagent grade and were used without further purification.

2,2'-Dimethyl-3,3'-diethyl-4,4'-bithiazolium di-iodide (E-10) is described in Section II.E of this report.

b. 5-Anilinomethylene-3-allylrhodanine (G-1)

N-Allylrhodanine (27.5 g, 0.159 mole) and N,N'-diphenylformamidine (31.2 g, 0.159 mole) were mechanically stirred in 800 ml of kerosene at 120°C for 1 hr. The light red solution was cooled to room temperature and then chilled to 0°C. The resulting yellow-orange solid was filtered, thoroughly ground with 150 ml of methanol, refiltered, and dried at 80°C/15 mm for 12 hr to remove any residual kerosene. The yellow needles [24.7 g (56%), mp 160°C, lit. (ref. 2), mp 161-162°C] were used without further purification. When less pure products were obtained, one recrystallization from glacial acetic acid (5 ml/g) raised the mp to the literature value with a 30% material loss.

c. 5-Acetanilidomethylene-3-allylrhodanine (G-2)

5-Anilinomethylene-3-allylrhodanine (38.3 g, 0.14 mole), triethylamine (21.0 g, 0.21 mole), and acetic anhydride (400 ml) were refluxed for 1 hr (calcium sulfate drying tube). The dark solution was chilled to 0°C with scratching. The resulting yellow precipitate was filtered, washed with two 100-ml portions of absolute ethanol, and dried at 65°C/15 mm for 2 hr to give 34.0 g (76%) of yellow crystals [mp 168-169.5°C (no lit. mp available)]. This compound was used without further purification.

d. [2,2'-(3,3'-Diethyl)(4,4'-bithiazolyl)][5,5'-(3,3'-diallylrhodanine)]dimethine cyanine (F48M7)

To a mixture of 35.49 g (0.112 mole) of 5-acetanilidomethylene-3-allylrhodanine and 28.75 g (0.056 mole) of 2,2'-dimethyl-3,3'-diethyl-4,4'-bithiazolium diiodide in 1 liter of isopropanol was added 34.00 g (0.336 mole) of triethylamine. The solution was refluxed for 3 hr, cooled to 0°C, and filtered. The resulting purple solid was digested with 500 ml of isopropanol at room temperature for 30 min, chilled to 0°C, filtered, and dried at 65°C/15mm for 2.5 hr to give 37.9 g of purple solid (mp 194-205°C) that contained some starting material as an impurity as indicated by a 1706 cm^{-1} infrared carbonyl absorption. Soxhlet extraction with isopropanol (100 ml/g) gave 26.9 g of purple needles (mp 218-220°C). A repeat Soxhlet extraction gave the analytical sample, 25.27 g (73%) [mp 219-220.5°C; no lit. mp available; $\lambda_{max}^{CH_3CN}$ 534mμ (ε 150,300) and 296mμ (ε 12,300); lit. (ref. 3), λ_{max} 545 mμ.

Analysis for $C_{26}H_{26}N_4O_2S_6$

	C	H	N	S	O
Calc'd	50.45	4.32	9.05	31.09	5.17
Found	50.06	4.48	9.26	31.18	5.23

6. References

1. "Dictionary of Organic Compounds", I. Heilbron and H. M. Bunbury, Eds., Vol. 4, Oxford, N. Y., 1953, 293.
2. H. Fischer, Ger. Patent 834,104, Mar. 17, 1952. C.A., 50, 402h (1956).
3. L. C. Hensley, U. S. Patent 2,586,164, Feb. 19, 1952.
4. L. G. S. Brooker, et al., J. Am. Chem. Soc., 73, 5349 (1951).

7. Spectra

Spectral data are given in Figures 25-27.

The literature λ_{max} visible absorption value (no solvent given) could not be duplicated in ethanol, acetonitrile, cyclohexane, or ethyl ether. Our visible-UV instrument was shown to be perfect by a Cary factory representative.

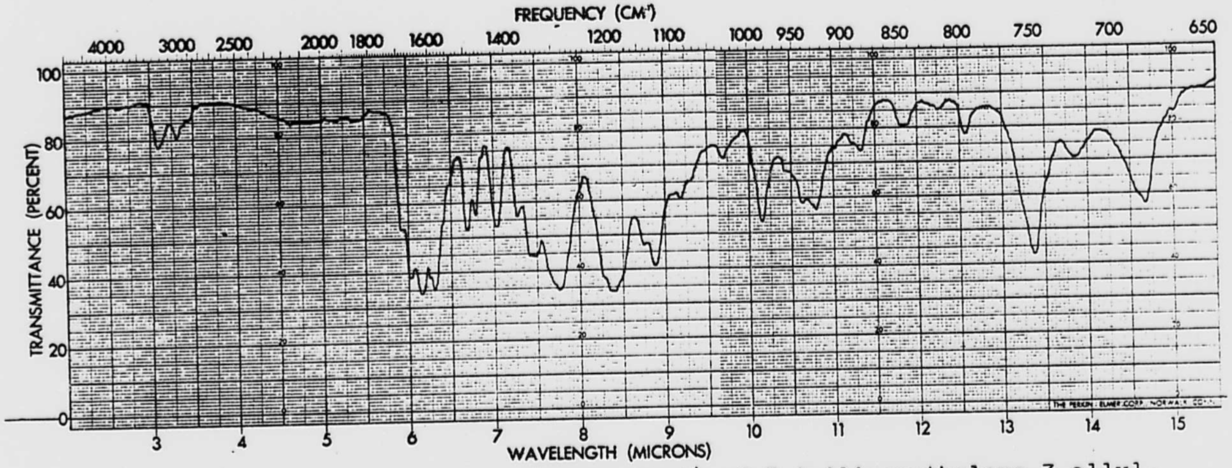


Figure 25. Infrared Spectrum (KBr pellet) of 5-Anilinomethylene-3-allylrhodanine (G-1)

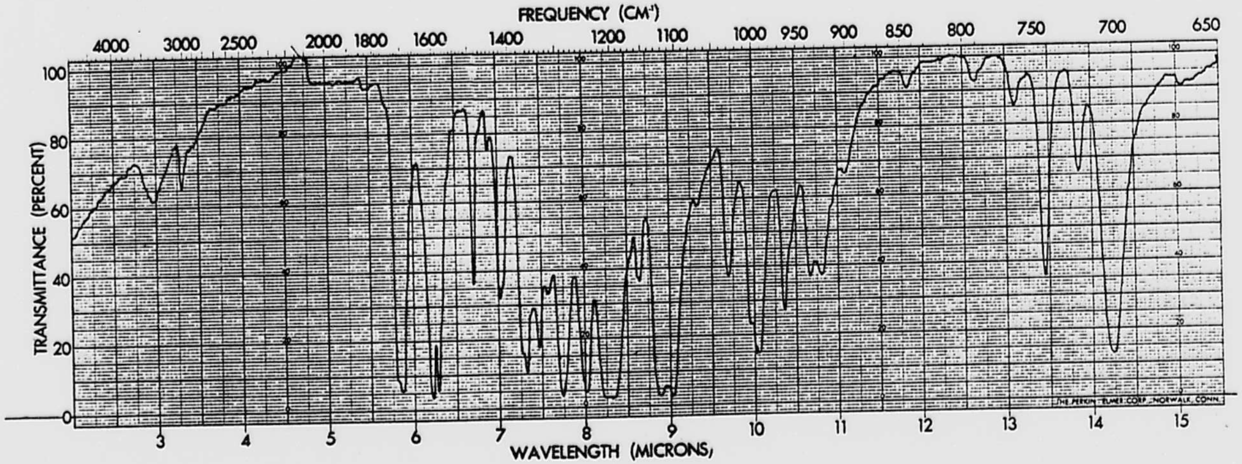
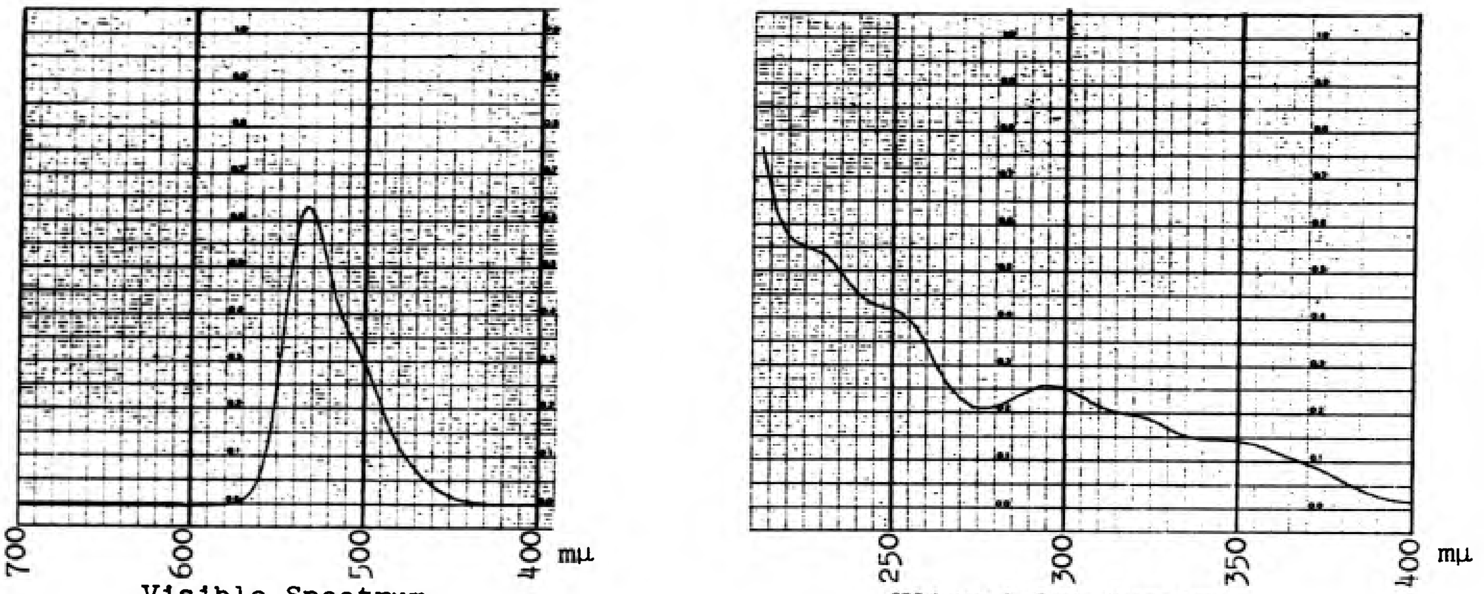
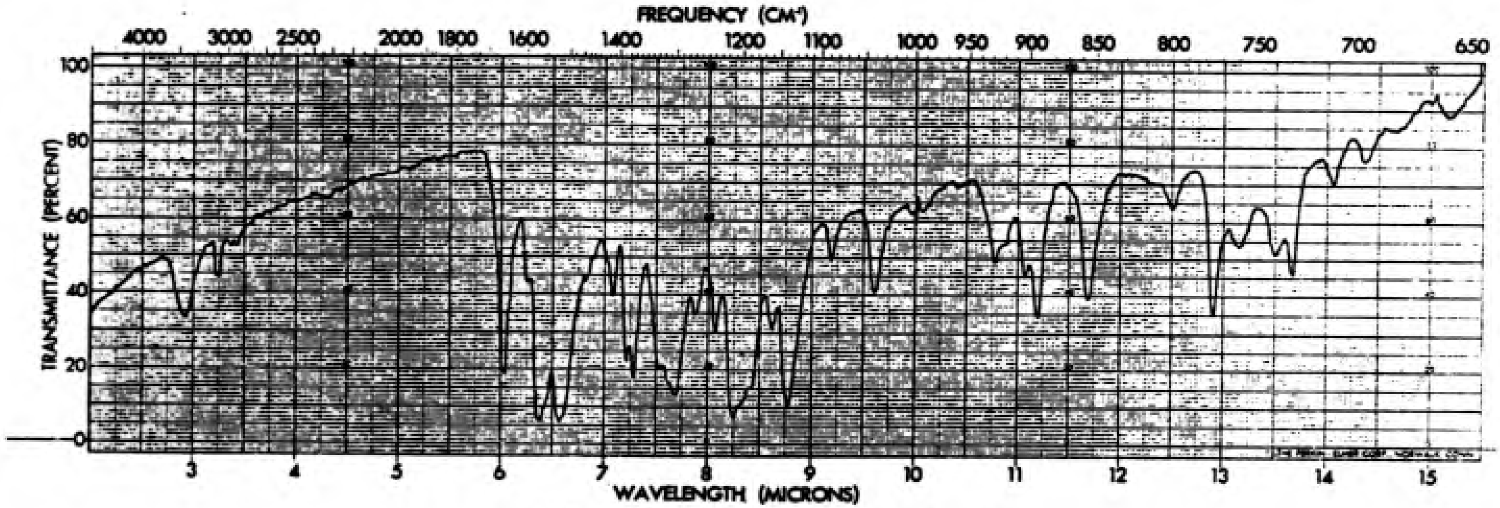


Figure 26. Infrared Spectrum (KBr Pellet) of 5-Acetanilidomethylene-3-allylrhodanine (G-2)



Visible Spectrum

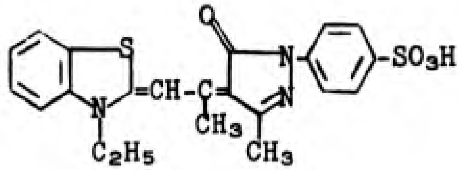
Ultraviolet Spectrum



Infrared Spectrum (KBr Pellet)

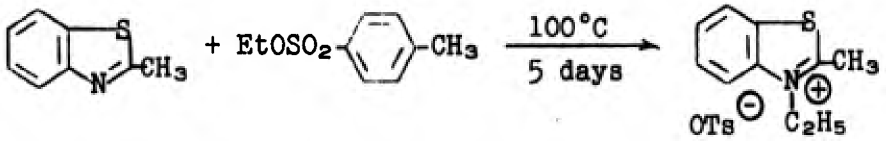
Figure 27. Spectral Data on [2,2'-(3,3'-Diethyl)(4,4'-bithiazolyl)][5,5'-(3,3'-diallylrhodanine)]dimethine cyanine (F48M7)

H. 4-[(3-ETHYL-2(3)-BENZOTHIAZOLIDENE)ISOPROPYLIDENE]-3-METHYL-1-(p-SULFOPHENYL)-5-PYRAZOLONE (F18M9)



(F18M9)

1. Synthesis of 2-Methyl-3-ethylbenzothiazolium-p-toluenesulfonate (H-1)

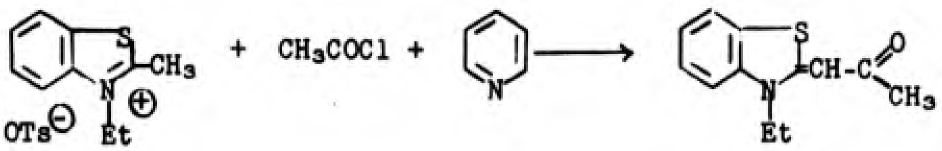


(H-1)

Crude H-1 always resulted as a dark purple or red-brown solid, even when freshly distilled starting materials were used. Although the compound is supposedly recrystallizable from methanol-acetone (ref. 2), the use of this solvent for the purification of H-1 resulted in losses of up to 80%. Yields of 62, 72, and 85% were realized from this reaction.

The infrared spectrum of H-1 shows the expected $SO_3^{\ominus}$ vibrations at 1216 and 1190 cm^{-1}, 1031 and 1010 cm^{-1}, and at 677 cm^{-1}. Para- and ortho-substituted phenyl absorptions are seen at 817 and 784 cm^{-1}, respectively. The spectrum is consistent with the structure. When H-1 was run through a vapor phase chromatographic (VPC) instrument (temperature programed), it was thermally decomposed to give two products that had the retention times and infrared spectra of the starting materials.

2. Synthesis of 2-Acetylmethylene-3-ethylbenzothiazoline (H-2)



(H-1) (H-2)

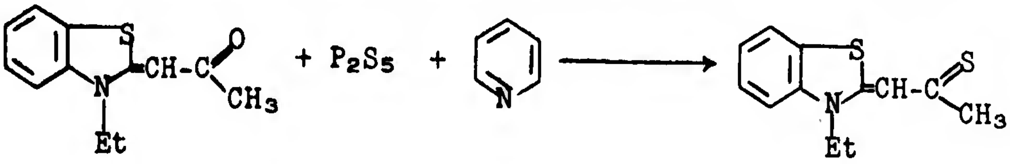
The purification of crude H-2 is better carried out with hexane than pentane.

VPC of a H-2 sample showed it to have a single component.

The infrared spectrum of H-2 shows a strong band at 1610 cm^{-1} in KBr or at 1623 cm^{-1} in carbon tetrachloride solution. This could be the carbonyl absorption, but it is at a lower frequency than that usually associated with a conjugated carbonyl group [1685-1665 cm^{-1} (ref. 7)]. This absorption could also be a C=N absorption or combination of C=N plus phenyl vibrations. The strong band at 1185 cm^{-1} is supporting evidence for a carbonyl group. The very strong absorptions at 1493 and 1460 cm^{-1} are present in many benzothiazole compounds. The spectrum is not inconsistent with the structure.

H-2 was obtained in yields of 63, 63, 65, and 67%.

3. Synthesis of 2-Thioacetylmethylene-3-ethylbenzothiazoline (H-3)



(H-2)

(H-3)

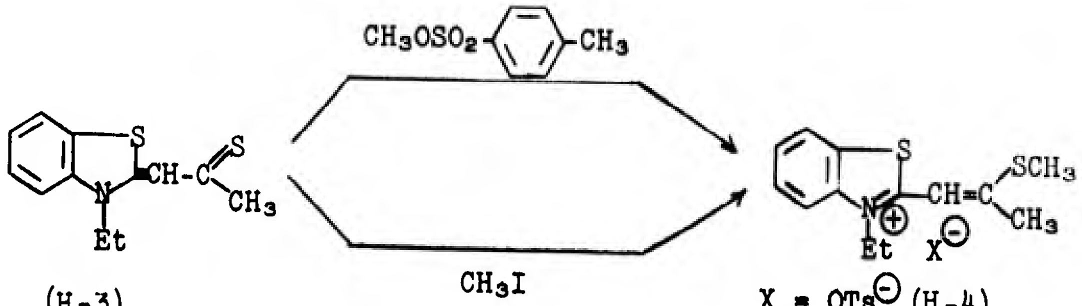
Some difficulty was experienced with gum formation upon pouring the reaction product into detergent solution during the work-up of H-3. It was found that slow addition of the product to a well-stirred aqueous detergent solution improved the results. Heptane was found to be superior to hexane for the extractive purification of crude H-3.

H-3 decomposed on attempted VPC analysis.

The infrared absorption band at 1610 cm^{-1}, tentatively assigned to carbonyl in H-2, has disappeared in H-3, lending support to the carbonyl assignment. The band at 1502 cm^{-1} is a benzothiazole absorption. The thiocarbonyl absorption is quite variable but may be present in the 1292 and 1274 cm^{-1} bands. No concrete justification for the structure proposed can be made on the basis of the spectrum.

H-3 yields of 41, 44, 47, and 49% were obtained.

4. 3-Ethyl-2-(2-methylmercaptopropenyl)benzothiazolium-p-toluenesulfonate (H-4) and Iodide (H-5)



(H-3)

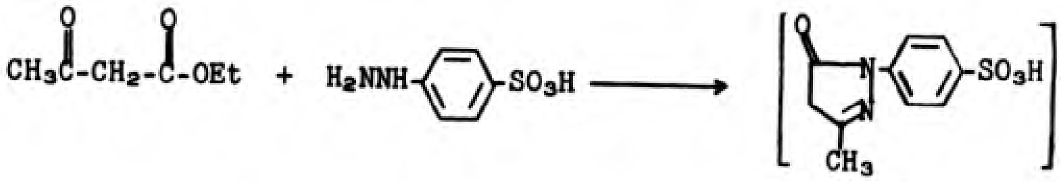
X = OTs⊖ (H-4)
X = I⊖ (H-5)

H-4 was synthesized and isolated with the expectation of using it as an intermediate in the final reaction step to prepare F18M9. It was later found to be more practical not to isolate H-4 before completing the final reaction. No literature melting point is available for H-4 but one is reported for the corresponding iodide (H-5). The reaction of H-3 with methyl iodide was very rapid to give H-5 [mp 236°C dec; lit. (ref. 3) mp 234-236°C dec].

The infrared spectrum of H-4 shows <u>ortho</u>- and <u>para</u>-substituted phenyl at 755 and 815 cm^{-1}, respectively. The absorptions at 1292 and 1274 cm^{-1}, tentatively assigned to thiocarbonyl in H-3, are no longer present, supporting the H-3 structural assignment. The band at 1621 cm^{-1} may be C=N or C=N combined with C=C. The broad absorption at 2700-1700 cm^{-1} suggests free acid present. A check of the methyl-p-toluene sulfonate used showed no acid contaminant. The spectrum is not inconsistent with the structure.

The iodide, H-5, also shows the absence of the H-3 thiocarbonyl band, and although there is not much similarity between the spectra of H-4 and H-5, the spectrum of H-5 is not inconsistent with the structure assigned. H-5 gave a positive Beilstein (halogen) test.

5. Synthesis of 1-p-Sulfophenyl-3-methyl-5-pyrazolone (H-6)



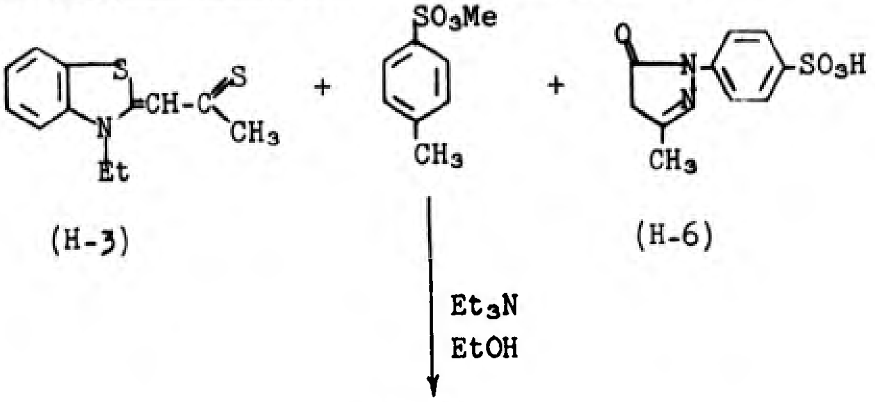
(H-6)

The preparation of H-6 was carried out according to two different procedures (ref. 5,6). Both gave the same product.

Two different procedures were used because the product obtained with the first method had the proper melting characteristics but an unusual infrared spectrum. Purification of H-6 introduced another puzzle into this particular synthesis. H-6 was nicely recrystallized from hot water, but the resulting compound, H-6a, had a different infrared spectrum than H-6. A comparison of the spectrum of H-6a with that of H-6 shows that a H-6 component has been removed or altered with the removal of absorptions at 3100, 1410, 1180, and 800 cm^{-1}. These absorptions are characteristic of a bonded O-H group. Neither H-6 nor H-6a contains a recognizable carbonyl absorption. The nearest possible band, at 1610 cm^{-1}, is too low to be a normal pyrazolone carbonyl and is probably a phenyl band. The absorption at 1550 cm^{-1} could be either an N-H deformation or a C=N band. $SO_3^{\ominus}$ is seen at 1130 and 650 cm^{-1} with para-substituted phenyl at 835 cm^{-1}. No starting material is present in either sample. The infrared spectrum is inconsistent with the structure, but because H-6 does form a condensation product with H-4, we assume that H-6 is the compound used by the patent authors (ref. 4) to prepare F18M9.

The procedures of (ref. 5) and (ref. 6) gave 77 and 85% yields of H-6, respectively.

6. Synthesis of 4-[(3-Ethyl-2(3)-benzothiazolidene)isopropylidene]-3-methyl-1-(p-sulfophenyl)-5-pyrazolone (F18M9)



(H-3)

(H-6)

(F18M9)

a. Discussion

The isolation of the methylated thioketone H-4 or H-5, was not necessary for the preparation of F18M9, although the final product was prepared in both ways. F18M9 was also prepared from crude thioketone, H-3, the method stated in the patent reference (ref. 4). This product was much more impure than that prepared from purified H-3, so the time consuming, but necessary purification of the thioketone starting material was therefore carried out.

Some trouble was encountered during the filtration of F18M9 because the solid, on occasion, would go through the filter paper. Cold solutions appeared to filter best. It was found that the presence of excess triethylamine hydrochloride in the solution greatly facilitated the filtration.

Anhydrous F18M9 was found to react rapidly with atmospheric moisture to form a dihydrate. This was confirmed through elemental analysis and infrared spectral data. The water was easily removed by drying at 100°C/0.1 mm for four hours.

Recrystallizations of F18M9 by the patent method produced a product with variable decomposition points in the 325-335°C temperature range. This does not appear to be a function of the rate of heating.

b. Proof of Structure

(1) Infrared Spectrum

The water absorption band in the dihydrate of F18M9 is found at 3450 cm^{-1}. The broad absorption between 3000 and 2500 cm^{-1} may be the bonded O-H of the sulfonic acid group. The five strong bands between 1250 and 1000 cm^{-1} might also be assigned to SO_3^-, as similar bands are found in p-toluenesulfonic acid. The 1645 cm^{-1} absorption could be due to a conjugated carbonyl group. It is not possible to definitely assign the bands from 1600-1400 cm^{-1}, but these may be due to C=C and C=N absorptions. Each aromatic ring is capable of causing four absorptions in this region. The bands at 840 and 760 cm^{-1} could be due to *para* and *ortho* phenyl substitution. The infrared spectrum is not inconsistent with the structure proposed.

(2) Elemental Analysis

The elemental analyses agree with the values calculated for F18M9 and F18M9$\cdot 2H_2O$ (see Experimental II.H.7). The structure of F18M9 is that assigned.

c. Purity

The samples submitted for elemental analysis were reprecipitated twice from the triethylamine salt and were taken directly from the sample submitted to the Air Force.

F18M9 was insoluble in all common thin-layer chromatographic solvents.

d. Air Force Sample

Four 4.8-gram samples (total 19.2 grams) in nitrogen-filled bottles were submitted to the Air Force on 30 October 1963.

7. Experimental

a. Starting Materials

2-Methylbenzothiazole (MC and B, 100 g - $4.00) was distilled before use [bp 69°C/1.2 mm; lit. (ref. 1a) bp 150°C/15 mm].

Ethyl-p-toluenesulfonate (MC and B, 1 kg - $6.90) was distilled before use [bp 125°C/1.5 mm; lit. (ref. 1b) bp 173°C/15 mm].

Acetyl chloride (MC and B, 500 g - $9.80) was distilled before use [bp 51°C; lit. (ref. 1c) bp 51-52°C].

Methyl-p-toluenesulfonate (MC and B, 500 g -$13.50) was used without further purification.

Ethylacetoacetate (MC and B, 1 kg - $10.10) was used without further purification.

p-Hydrazinobenzenesulfonic acid (Eastman, 500 g - $17.35) was used without further purification.

Phosphorus pentasulfide (J. T. Baker, 1 lb. - $3.15) was used without further purification.

Pyridine and triethylamine were reagent grade and were used without purification.

Hydrogen chloride in methanol

About 70 g of HCl gas can be dissolved in 500 ml of cold methanol over a 3-hr period of slow addition.

b. 2-Methyl-3-ethylbenzothiazolium-p-toluenesulfonate (H-1)(ref. 2)

2-Methylbenzothiazole (53.7 g, 0.36 mole) and ethyl-p-toluenesulfonate (72.0 g, 0.36 mole) were heated in a pressure bottle with a Teflon gasket on a steam bath for 137 hr. The resulting red-brown solid was extracted with two 100-ml portions of acetone to give 106.3 g (85%) of gray-white crystals [mp 160-163.5°C; lit. (ref. 2) mp 163.5-164.5°C].

c. 2-Acetylmethylene-3-ethylbenzothiazoline (H-2) (ref. 3)

2-Methyl-3-ethylbenzothiazolium-p-toluenesulfonate (68.7 g, 0.197 mole) was added to 155 ml (152 g, 1.97 mole) of pyridine and the mechanically stirred solution was cooled to 0°C. Acetyl chloride (23.2 g, 0.296 mole) was added dropwise to the cold solution over a 10-15 min. period. After the addition was complete, the dark brown solution was stirred for 30 min. at 0°C, warmed to room temperature, and heated on a steam bath for 1 hr. About 75% of the pyridine was then removed at 100°C/15 mm, and the dark brown oil was added to 500 ml of water with stirring. The resulting solid was filtered, and dried at 70°C/15 mm to give 31.8 g of purple crystals (mp 96-103°C). This material was continuously extracted in a Soxhlet apparatus with 400 ml of hexane for 15 hr. The hexane was cooled in an ice bath and the yellow needles were filtered to yield 27.1 g (63%) [mp 111-114°C; lit. (ref. 3) mp 111-113°C]. TLC showed this compound to be pure.

d. 2-Thioacetylmethylene-3-ethylbenzothiazoline (H-3) (ref. 3)

To a mechanically stirred solution of 57.0 g (0.26 mole) of 2-acetylmethylene-3-ethylbenzothiazoline in 140 ml of dry pyridine was slowly added 29.4 g (0.13 mole) of phosphorus pentasulfide in small portions. The solution was refluxed for 15 min., cooled to room temperature, and slowly poured into a stirred solution of 1.0 g of detergent (Alconox) in 3 liters of water (HOOD). The black suspension was stirred for 1 hr., filtered, thoroughly washed with three 1-liter portions of water, and dried at 80°C/15 mm to give 57.3 g of black solid (mp 128-130°C). The black solid was extracted with three 1-liter portions of heptane (24 hr per extraction) in a Soxhlet apparatus. A large amount of black residue was left behind. The heptane solution was chilled in an ice bath and the resulting solid was filtered and dried to give 3 crops of brown needles (18.9 g, 4.9 g, 1.0 g), total 24.8 g (41%) [mp 137-145°C; lit. (ref. 3) mp 142-144° dec.]. It was difficult to determine whether decomposition occurred on melting.

e. 3-Ethyl-2-(2-methylmercaptopropenyl)-benzothiazolium-p-toluenesulfonate (H-4) (ref. 3)

3-Ethyl-2-thioacetylmethylenebenzothiazoline (0.88 g, 3.7 mmole) and methyl-p-toluenesulfonate (1.42 g, 7.6 mmole) were heated in a pressure bottle on a steam bath for 89 hr. The resulting solid was filtered from the dark red liquid and washed with two 25-ml portions of ether and two 25-ml portions of acetone to give 0.64 g (43%) of pink crystals, (mp soften 95°C, 212-225°C, no lit. mp available).

f. 1-p-Sulfophenyl-3-methyl-5-pyrazolone (H-6)(H-6a)(ref. 6)

Phenylhydrazine-p-sulfonic acid (20.0 g, 0.106 mole) was added to a stirred solution of 6.4 g (0.159 mole) of NaOH in 150 ml of water. The solution was transferred to a 250-ml, 3-necked, round-bottomed flask equipped with a mechanical stirrer, reflux condenser and a thermometer. Ethylacetoacetate (13.8 g, 0.106 mole) was quickly added to give a miscible solution that underwent a 2°C temperature rise on mixing. The solution was stirred at 30°C for 15 min. and then for 2 hr at 90°C. After cooling to room temperature and acidifying the solution with 24 ml of conc. HCl (stirring), a thick tan precipitate resulted. This was filtered, washed with 50 ml of water, and dried at 75°C/15 mm for 2 hr to give 23.0 g (85%) of tan solid (H-6), [mp 315-316° dec. (no lit. mp available)]. Recrystallization of 1.0 g of H-6 from 20 ml of water with activated charcoal gave 0.8 g of white needles, H-6a (mp 327-327.5°C dec).

g. 4-[(3-Ethyl-2(3)-benzothiazolidene)isopropylidene]-3-methyl-1-(p-sulfophenyl)-5-pyrazolone (F18M9)(ref. 4)

2-Thioacetylmethylene-3-ethylbenzothiazoline (21.7 g, 0.092 mole) and 17.2 g (0.092 mole) of methyl-p-toluenesulfonate were heated on a steam bath for 24 hr. The resulting hard, dark maroon solid was broken up as finely as possible, and 250 ml of absolute ethanol was added. To this suspension was added 23.4 g (0.092 mole) of 1-p-sulfophenyl-3-methyl-5-pyrazolone and 22.3 g (0.22 mole) of triethylamine. This solution was heated at reflux for 2.5 hr. Methyl mercaptan evolution had stopped (bubble trap indicator) after 2.25 hr. The dark solution was transferred to a 1-liter erlenmeyer flask and cooled in an ice bath with magnetic stirring. A solution of HCl in methanol (100 ml of a 0.14 g/ml solution, 0.38 mole) was dropped in over a 10-min. period. The resulting brick red solid was filtered, washed with five 50-ml portions of methanol, and dried at 60°C/15 mm to give 30.6 g (73%), [mp 325-326° dec; lit. (ref. 4) mp > 315°C]. A second crop, 2.1 g (mp 304-305° dec.) was isolated from the filtrates. The sample was stirred with N,N-dimethylformamide (DMF) (10 ml/g) at room temperature for 30 min and filtered. As much DMF as possible was removed from the resulting orange-red solid. The product was washed with six 50-ml portions of ether. The solid was suspended in methanol (50 ml/g), dissolved by the addition of triethylamine (2 ml/g) and reprecipitated by the addition of a 0.16 g hydrogen chloride per ml methanol solution (6 ml soln/g F18M9). After two such reprecipitations, the melting point of the copper colored crystals was raised to 333-334°C dec. [$\lambda_{max}^{0.1N\ NaOH}$ 470 mμ (ε17,100), 267 mμ (ε26,000)].

Anal. Calcd. for $C_{22}H_{21}N_3O_4S_2$: C, 58.00; H, 4.62; N, 9.22; S, 14.05. Calcd. for $C_{22}H_{21}N_3O_4S_2 \cdot 2H_2O$: C, 53.75; H, 5.10; N, 8.05; S, 13.05. Found (after drying at 100°C/0.1 mm): C, 58.9; H, 5.2; N, 8.9; S, 13.7. Found (after exposure of the above sample to the atmosphere): C, 53.3, 53.5; H, 5.3, 5.4. Found (after re-drying sample): C, 58.2; H, 4.9; N, 9.0; S, 14.0; wt. loss on drying, 7.5% (calcd. % H_2O, 7.3).

8. References

1. "Dictionary of Organic Compounds", I. Heilbron and H. M. Bunbury, Eds, Oxford, N. Y., 1953.
   - a. Vol. 3, 316.
   - b. Vol. 4, 518.
   - c. Vol. 1, 22.
2. L. G. S. Brooker and F. L. White, J. Am. Chem. Soc., 57, 547 (1935).
3. L. G. S. Brooker, et al., J. Am. Chem. Soc., 73, 5326 (1951).
4. L. G. S. Brooker and F. L. White, U. S. Patent 2,493,747, Jan. 10, 1950, C.A., 44, 7685c (1950).
5. H. E. Fierz-David and L. Blangey, "Grundlegende Operationen der Farbenchemie," Wien, 1952, 124.
6. G. Reeves, J. Chem. Soc., 1925, 911.
7. L. J. Bellamy, "The Infra-red Spectra of Complex Molecules", Wiley, N. Y., 1956.

9. Spectra

Spectral data are given in Figures 28-37.

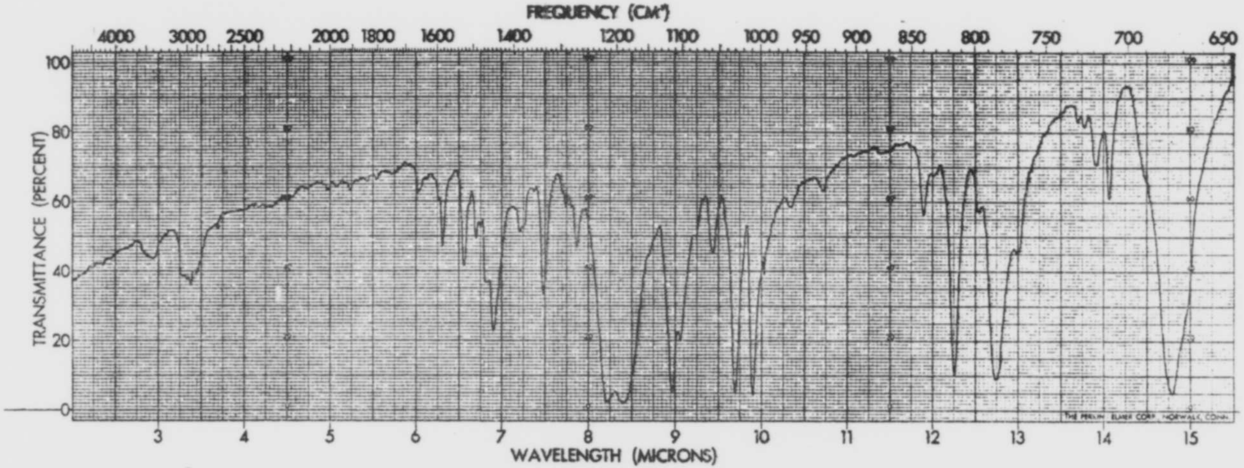


Figure 28. Infrared Spectrum (KBr Pellet) of 2-Methyl-3-ethylbenzothiazolium-p-toluenesulfonate (H-1)

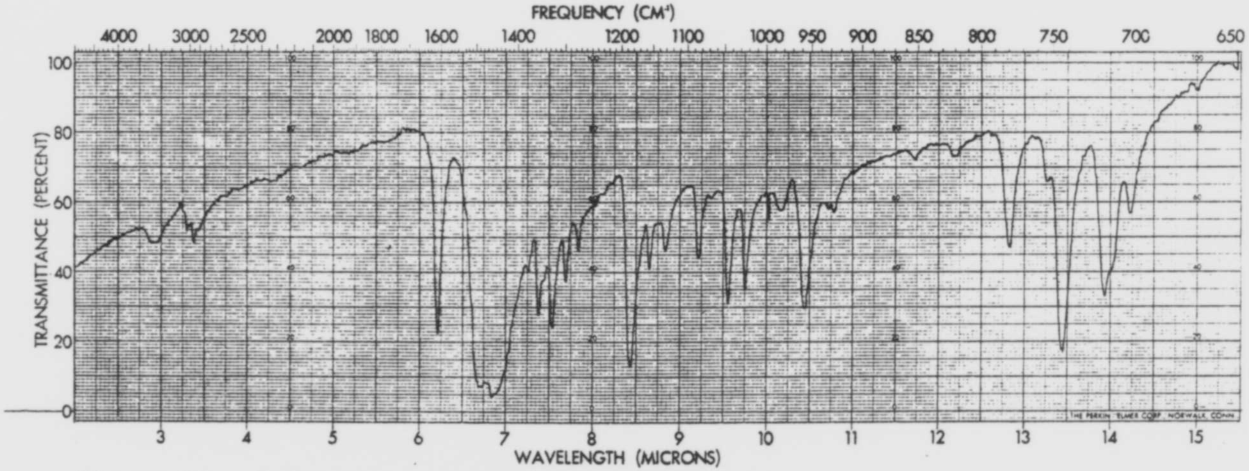


Figure 29. Infrared Spectrum (KBr Pellet) of 2-Acetylmethylene-3-ethylbenzothiazoline (H-2)

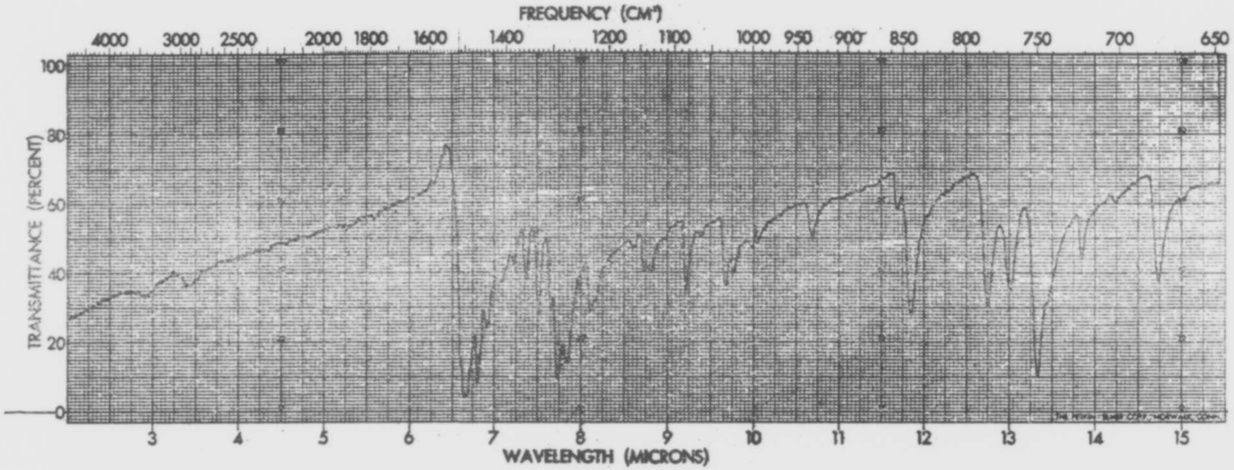


Figure 30. Infrared Spectrum (KBr Pellet) of 2-Thioacetylmethylene-3-ethylbenzothiazoline (H-3)

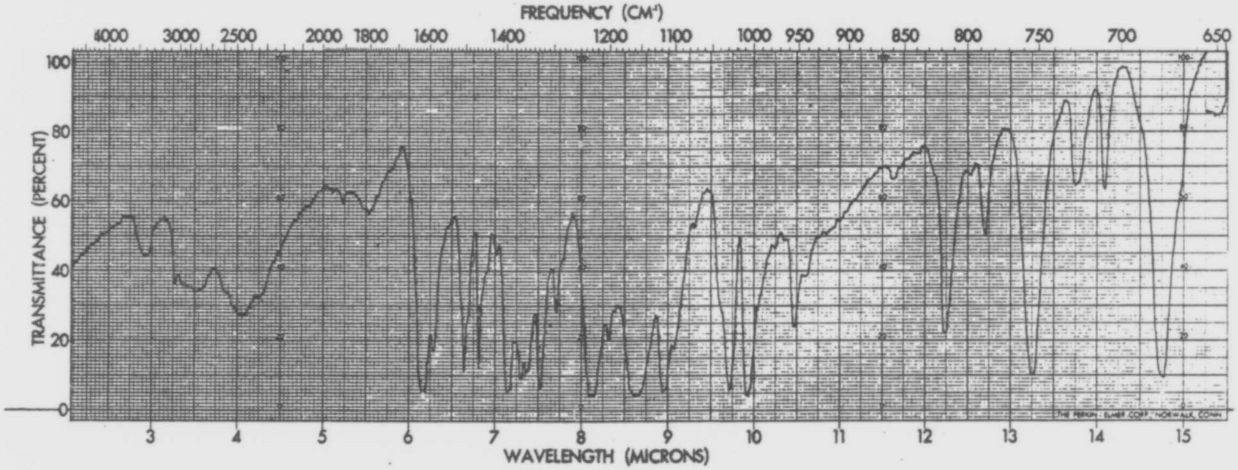


Figure 31. Infrared Spectrum (KBr Pellet) of 3-Ethyl-2-(2-methylmercaptopropenyl)benzothiazolium-p-toluenesulfonate (H-4)

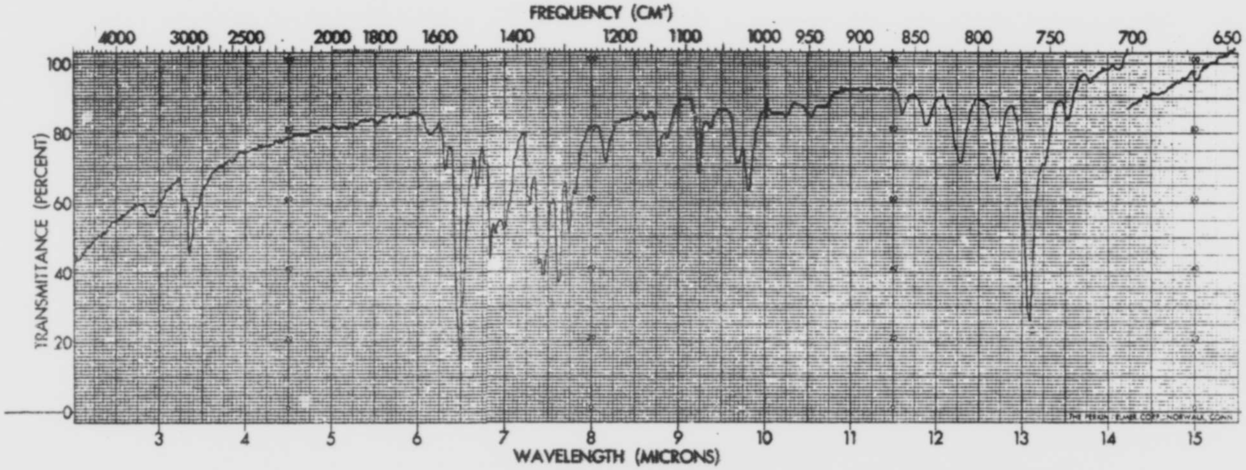


Figure 32. Infrared Spectrum (KBr Pellet) of 3-Ethyl-2-(2-methylmercaptopropenyl)benzothiazolium iodide (H-5)

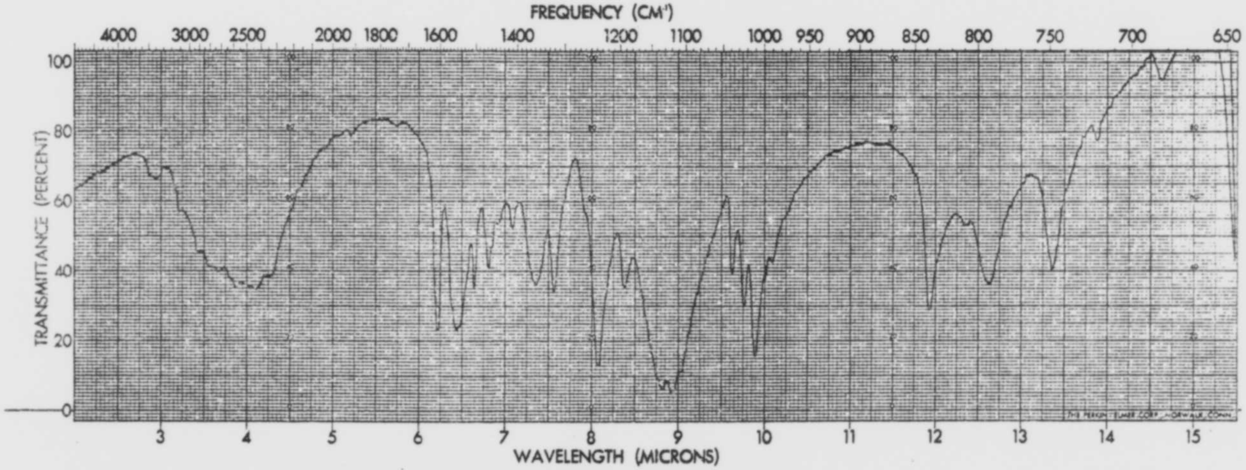


Figure 33. Infrared Spectrum (KBr Pellet) of 1-p-Sulfophenyl -3-methyl-5-pyrazolone (H-6)

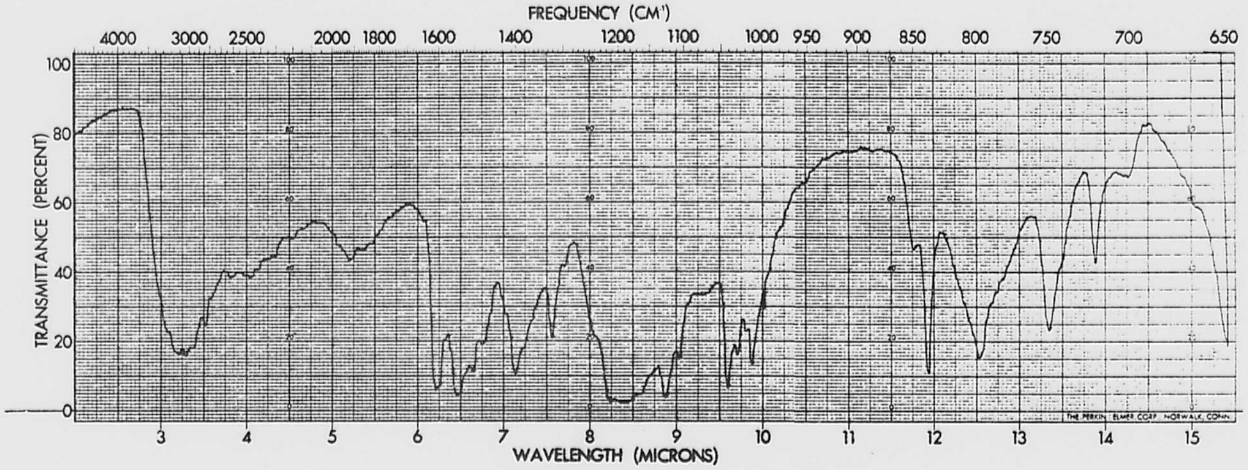


Figure 34. Infrared Spectrum (KBr Pellet) of 1-p-Sulfophenyl-3-methyl-5-pyrazolone recrystallized from water (H-6a)

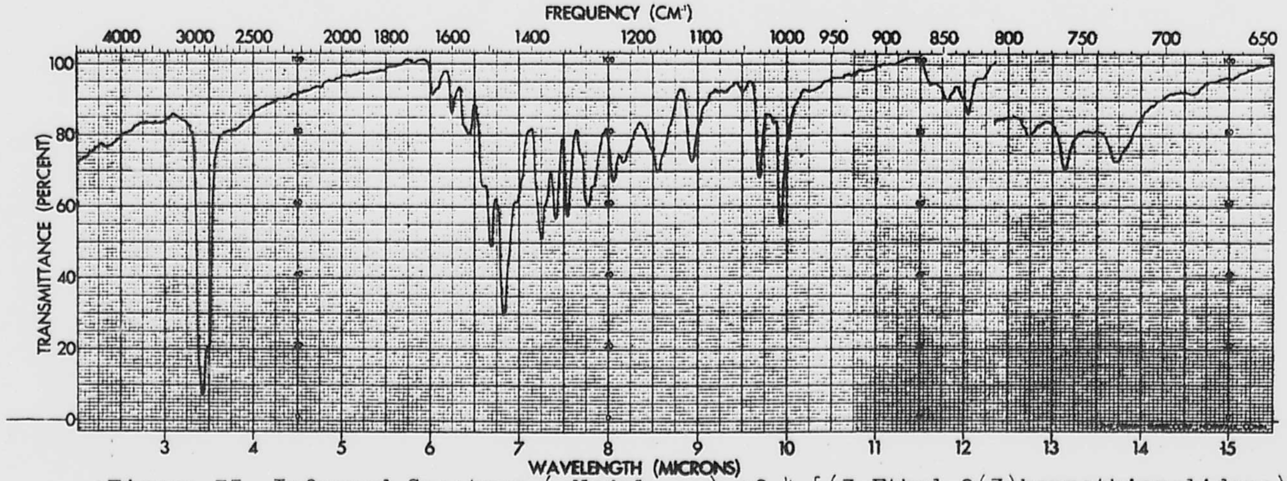


Figure 35. Infrared Spectrum (Nujol) of 4-[(3-Ethyl-2(3)benzothiazolidene) isopropylidene]-3-methyl-1-(p-sulfophenyl)-5-pyrazolone (F18M9)

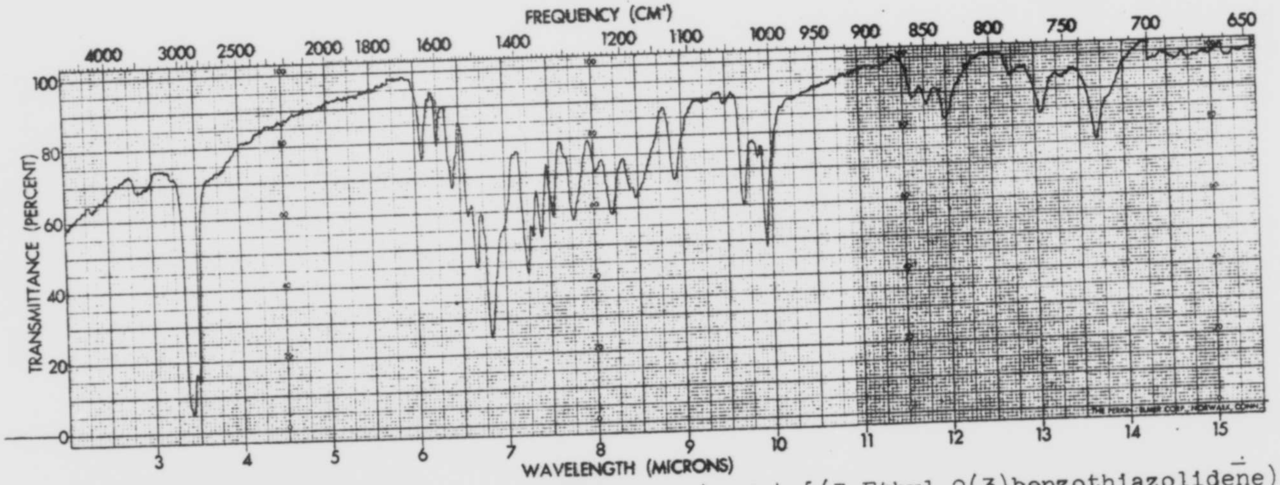
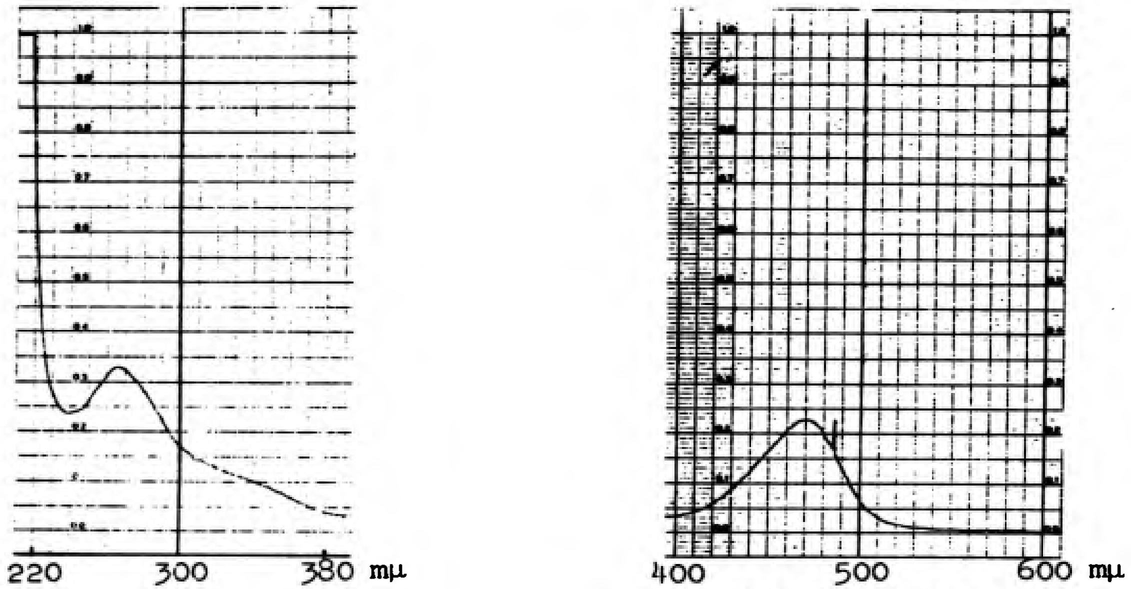


Figure 36. Infrared Spectrum (Nujol) of 4-[(3-Ethyl-2(3)benzothiazolidene) isopropylidene]-3-methyl-1-(p-sulfophenyl)-5-pyrazolone dihydrate ($F18M9 \cdot 2H_2O$)

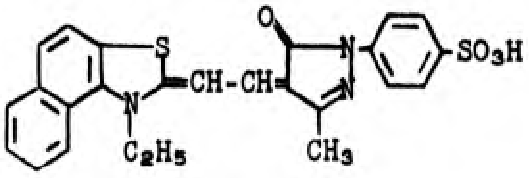


Ultraviolet Spectrum
(0.1N NaOH)

Visible Spectrum
(0.1N NaOH)

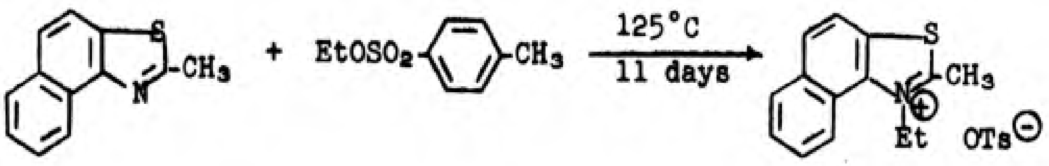
Figure 37. Spectral Data on 4-[(3-Ethyl-2(3)benzothiazolidene)isopropylidene]-3-methyl-1-(p-sulfophenyl)-5-pyrazolone (F18M9)

I. 4-[(1-ETHYL-2(1)-β-NAPHTHOTHIAZOLYLIDENE)ETHYLIDENE]-3-METHYL-1-p-SULFONYL-5-PYRAZOLONE (F19M10)



(F19M10)

1. Synthesis of 2-Methyl-3-ethyl-β-naphthothiazolium-p-toluenesulfonate (I-1)

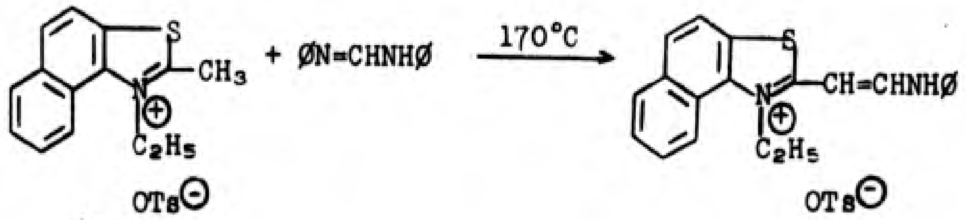


(I-1)

The synthesis of I-1 is straightforward but time-consuming.

The infrared absorption spectrum of an impure sample of I-1 shows an unknown absorption at 3400 cm^{-1}. Aromatic character is seen at 1530 cm^{-1} while the bands at 1430 and 1230 cm^{-1} result from $SO_3^{\ominus}$ absorptions. The spectrum is not inconsistent with the structure.

2. Synthesis of 2-(2-Anilinovinyl)-3-ethyl-β-naphthothiazolium-p-toluenesulfonate (I-2)



(I-1)

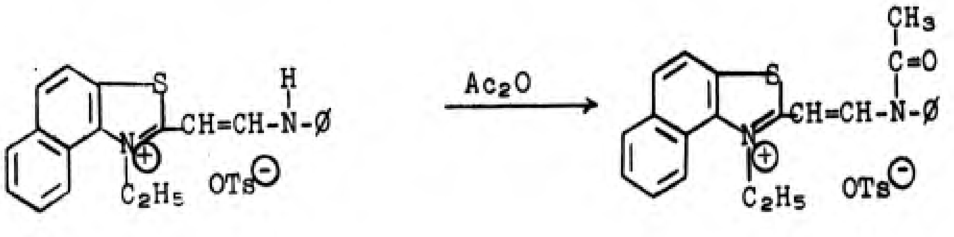
(I-2)

The procedure for the preparation of I-2 was similar to that used for the preparation of the corresponding quinoline compound, C-1 (see II.C).

The heating period was found to influence the yields of I-2. Heating at 170°C for one hour gave average yields of 61% while two hours gave an average yield of 35%. A reaction run at 170°C for four hours gave a red tar from which no product could be isolated.

The infrared spectrum of I-2 shows two weak absorptions at 3270 and 3170 cm^{-1} attributed to NH and CH stretching, respectively. The wide band at 2940 cm^{-1} results from various CH frequencies, while the strong band at 1650 cm^{-1} corresponds to C=C stretching. The bands at 754 and 709 cm^{-1} are characteristic of mono-substituted benzene compounds. The spectrum is consistent with the assigned structure.

3. Synthesis of 2-(2-Acetanilidovinyl)-3-ethyl-β-naphthothiazolium-p-toluenesulfonate (I-3)

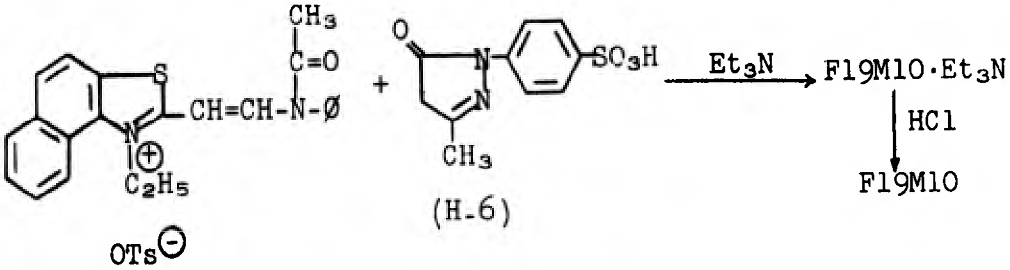


(I-2) (I-3)

No isolable product was obtained from an attempt to prepare I-3 directly from I-1 in a refluxing acetic anhydride/N,N'-diphenylformamidine solution. However, when I-2 was isolated before acetylation, I-3 resulted in yields of 76 and 88%.

A comparison between the infrared spectra of I-3 and I-2 shows that acetylation occurred. The I-3 absorptions at 1726 and 1715 cm^{-1} are attributed to the amide carbonyl grouping. This doublet suggests hydrogen bonding or cis-trans isomerism in the molecule. The absorption at 1654 cm^{-1} is a C=C stretching frequency. Bands indicative of mono-substituted benzene occur at 774 and 699 cm^{-1}. The spectrum of I-3 is consistent with the structure assigned.

4. Synthesis of 4-[(1-Ethyl-2(1)-β-naphthothiazolylidene)ethylidene]-3-methyl-1-p-sulfonyl-5-pyrazolone (F19M10)



(I-3)

(H-6)

a. Discussion

The triethylamine salt of F19M10 is the product that is first isolated from the above reaction. It existed in green and brown crystalline forms. Upon grinding, the green form became brown.

The aqueous methanol solvent recommended in the patent procedure (ref. 5,6) for solution of the salt before acidification proved unsatisfactory. The salt dissolved easily but only a cloudy solution resulted on acidification with a solution of hydrogen chlorine in methanol. The triethylamine salt of F19M10 was not very soluble in absolute methanol, but a good yield of F19M10 was obtained when methanol was used as the acidification solvent. Yields of 66, 71, and 86% were obtained. Each reprecipitation purification reduced the yield by 5%.

b. Proof of Structure

(1) Infrared Spectrum

The spectrum shows an absorption at 1675 cm^{-1}, the region assigned to α,β-unsaturated ketones. The bands at 835 and 817 cm^{-1} are assigned to two ortho aromatic hydrogen atoms. The amide carbonyl stretching frequencies observed in I-3 at 1726 and 1715 cm^{-1} are not present in F19M10.

The spectrum is consistent with the assigned structure.

(2) Elemental Analysis

The elemental analysis agrees with the values calculated for F19M10 (see Experimental II.I.5). The structure of the compound is that assigned.

c. Purity

The sample submitted for elemental analysis was reprecipitated three times and was taken directly from the sample submitted to the Air Force.

F19M10 was not soluble in thin-layer chromatographic solvents.

d. Air Force Sample

Four 6.5-gram samples (total 26.0 grams) in nitrogen-filled bottles were submitted to the Air Force on 27 November 1963.

5. Experimental

a. Starting Materials

2-Methyl-β-naphthothiazole (Gallard-Schlesinger, 1 kg - $320.00), mp 94-95°C, lit. (ref. 1) mp 95-96°C, was used without further purification.

Ethyl p-toluenesulfonate (MC and B, 1 kg - $6.90) was distilled before use [bp 125°C/1.5 mm, lit. (ref. 2) bp 173°C/15 mm].

N,N'-Diphenylformamidine (K and K, 100 g - $7.50) was recrystallized from abs. ethanol (1 g/5 ml) [mp 137-139°C; lit. (ref. 4) mp 137°C].

1-p-Sulfophenyl-3-methyl-5-pyrazolone (H-6) (See Section II.H).

b. 2-Methyl-3-ethyl-β-naphthothiazolium p-toluenesulfonate (I-1) (ref. 3)

2-Methyl-β-naphthothiazole (25.0 g, 0.125 mole) was heated with 25.0 g (0.125 mole)of ethyl p-toluenesulfonate at 125°C for 11 days. Crystallization was induced by scratching the oil during the seventh day. The crude brown solid was ground with 50 ml of ether and filtered, and then the solid was extracted with 250 ml of refluxing ether for 1 hr. This mixture was filtered while hot. The tan solid was washed with 100 ml of acetone and dried at 30°C/15 mm to give 28.8 g (58%) of tan solid [mp soften 120°C, 127-145°C; lit. (ref. 3) mp soften 140, 151-154°C]. While the melting point of the product could be raised to soften 135°C, 147-151°C, by further ether and acetone extractions, the crude material proved satisfactory for the next reaction step.

c. 2-(2-Anilinovinyl)-3-ethyl-β-naphthothiazolium p-toluenesulfonate (I-2)

A mixture of 50.0 g (0.125 mole) of 2-methyl-3-ethyl-β-naphthothiazolium p-toluenesulfonate and 20.8 g (0.106 mole) of N,N'-diphenylformamidine was thoroughly ground and heated at 170°C for 1 hr with an oil bath. After cooling, the resulting dark solid was ground with two 500-ml portions of acetone; it was then filtered and dried at 65°C/15 mm to yield 36.7 g (69%) of green solid [mp 249.5-250.5°C (no lit. mp available)].

d. 2-(2-Acetanilidovinyl)-3-ethyl-β-naphthothiazolium p-toluenesulfonate (I-3)

A solution of 36.7 g (0.073 mole) of 2-(2-anilinovinyl)-3-ethyl-β-naphthothiazolium p-toluenesulfonate in 225 ml of acetic anhydride was refluxed for 3 hr and allowed to stand at room temperature for 2 days. The brown precipitate was filtered and washed first with 200 ml of ether and then with two 100-ml portions of acetone. After drying, 25.0 g of brown crystals [mp 216-220°C (dec?) (no lit. mp available)] were obtained. Evaporation of the acetic anhydride filtrate gave a brown solid that was washed with three 100-ml portions of acetone to yield an additional 5.35 g of product (mp 215-219°C) identified by its infrared spectrum. The two crops were combined to give 30.35 g (76%) of product.

e. 4-[1-Ethyl-2(1)-β-naphthothiazolylidene)ethylidene]-3-methyl-1-p-sulfonyl-5-pyrazolone (F19M10)

Triethylamine (6.4 g, 64 mmoles) was added to a stirred suspension of 8.1 g (32 mmoles) of 1-p-sulfophenyl-3-methyl-5-pyrazolone and 17.5 g (32 mmoles) of 2-(2-acetanilidovinyl)-3-ethyl-β-naphthothiazolium p-toluenesulfonate in 180 ml of absolute ethanol. The mechanically stirred mixture was refluxed on a steam bath for 1 hr. The solution was chilled in an ice bath, and the resulting brown precipitate was filtered, ground with three 150-ml portions of acetone, and extracted with 100 ml of boiling acetone. The product was filtered and dried at 80°C/15 mm to give 14.65 g of the brown triethylamine salt of F19M10 (mp 286-286.5°C dec). The salt was dissolved in 1450 ml of methanol by refluxing for 1 hr; the solution was filtered and acidified at room temperature with 30 ml of a HCl in methanol solution (0.12 g HCl/ml, 0.1 mole HCl) to yield 11.1 g (71%) of a yellow-orange solid (mp 327.5°C dec). The product was purified by addition of triethylamine (0.29 g/g product) to the product in methanol (175 ml/g product). The red-purple solution was refluxed for 1 hr and filtered, and the stirred, hot solution was acidified with excess HCl in methanol. After three such re-precipitations, the yellow-orange product had a mp 327°C dec [lit. (ref. 5,6) mp >315°C]. $\lambda_{max}^{0.01N\ NaOH}$ 470 mμ (є54,700), 264 mμ (є24,800).

Analysis for $C_{25}H_{21}N_3O_4S_2$

	C	H	N	S
Calcd.	61.2	4.37	8.55	13.04
Found	61.1	4.5	8.2	13.1

6. References

1. F. M. Hamer, J. Chem. Soc., 1929, 2598.

2. "Dictionary of Organic Compounds", I. Heilbron and H. M. Bunbury, Eds, Vol. 4, Oxford, N. Y., 1953, 518.

3. L. G. S. Brooker and F. L. White, J. Am. Chem. Soc., 57, 457 (1935).

4. J. B. Shoesmith and J. Haldane, J. Chem. Soc., 123, 2704 (1923).

5. L. G. S. Brooker and F. L. White, U. S. Patent 2,526,632, Oct. 24, 1950, C.A., 47, 432h (1953).

6. L. G. S. Brooker and F. L. White, U. S. Patent 2,493,747, Jan. 10, 1950, C.A., 44, 7684f (1950).

7. Spectra

Spectral data are given in Figures 38-41.

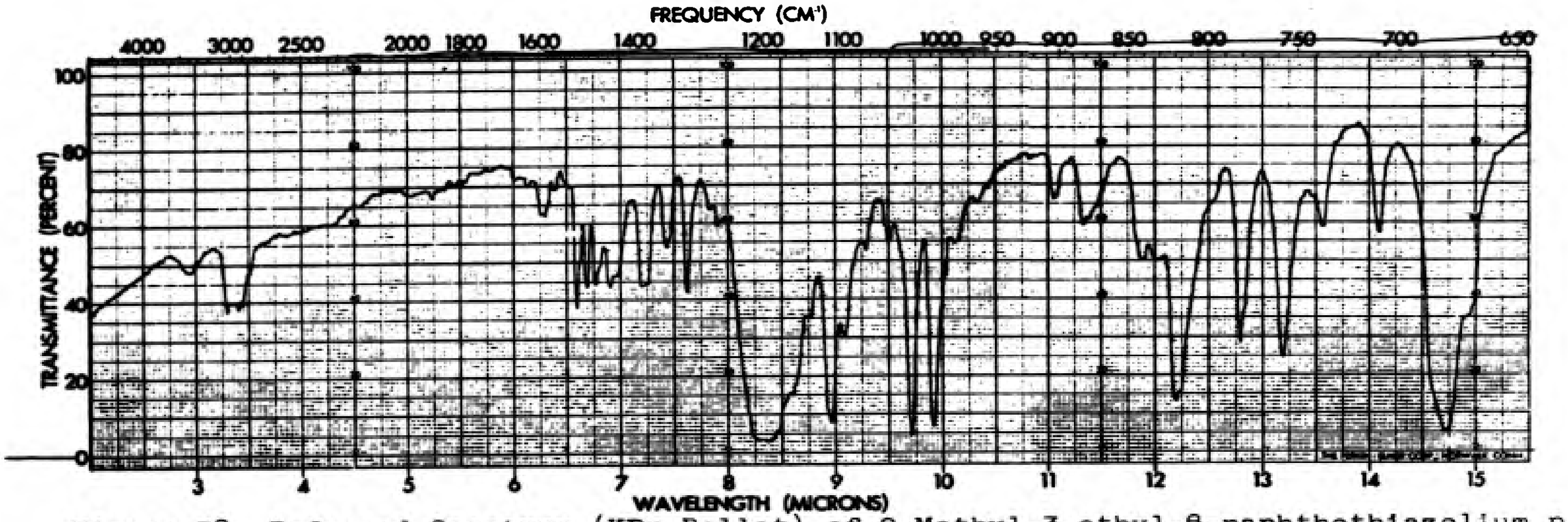


Figure 38. Infrared Spectrum (KBr Pellet) of 2-Methyl-3-ethyl-β-naphthothiazolium p-toluenesulfonate (I-1)

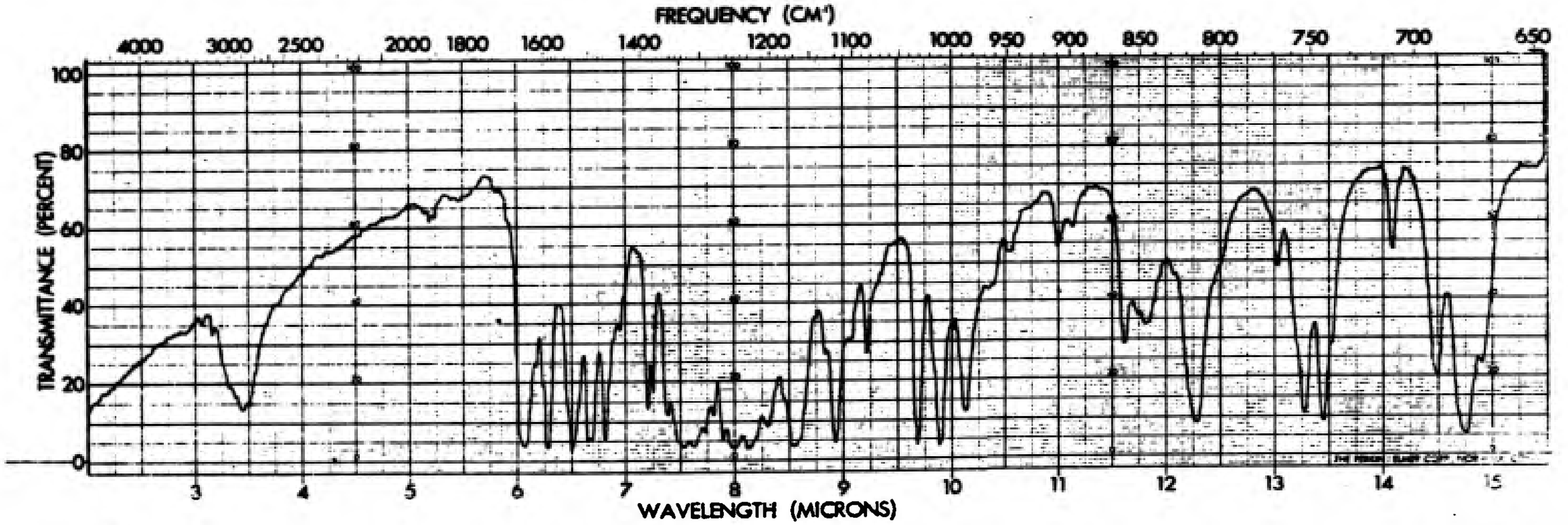


Figure 39. Infrared Spectrum (KBr Pellet) of 2-(2-Anilinovinyl)-3-ethyl-β-naphthothiazolium p-toluenesulfonate (I-2)

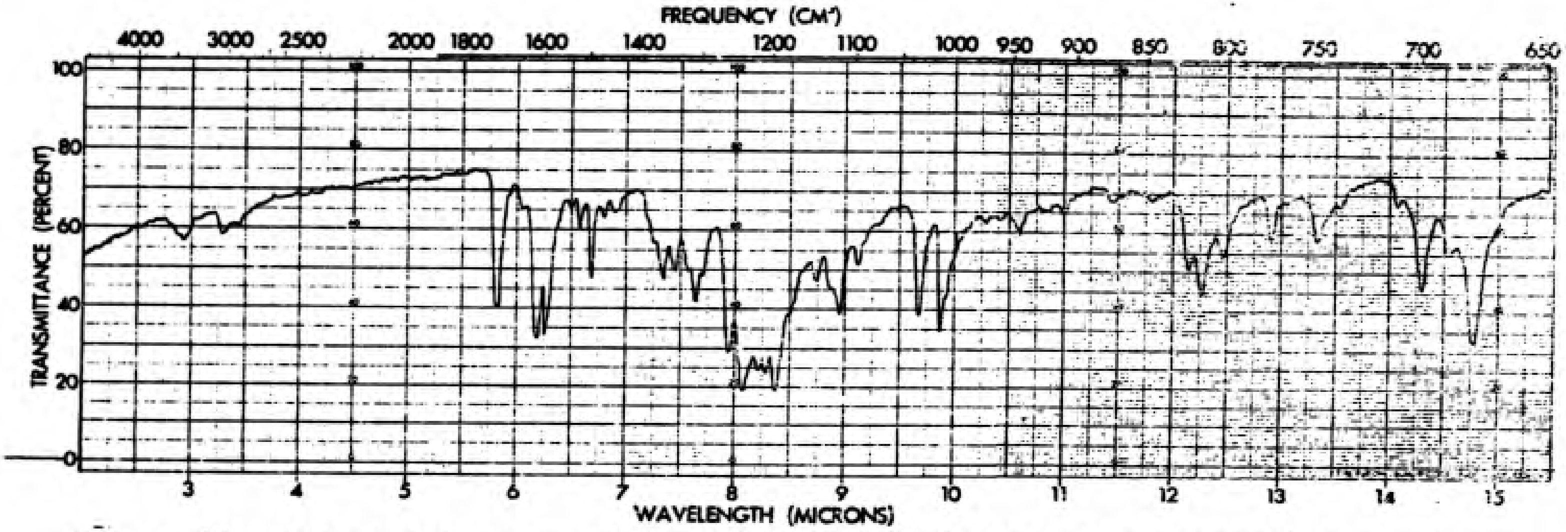
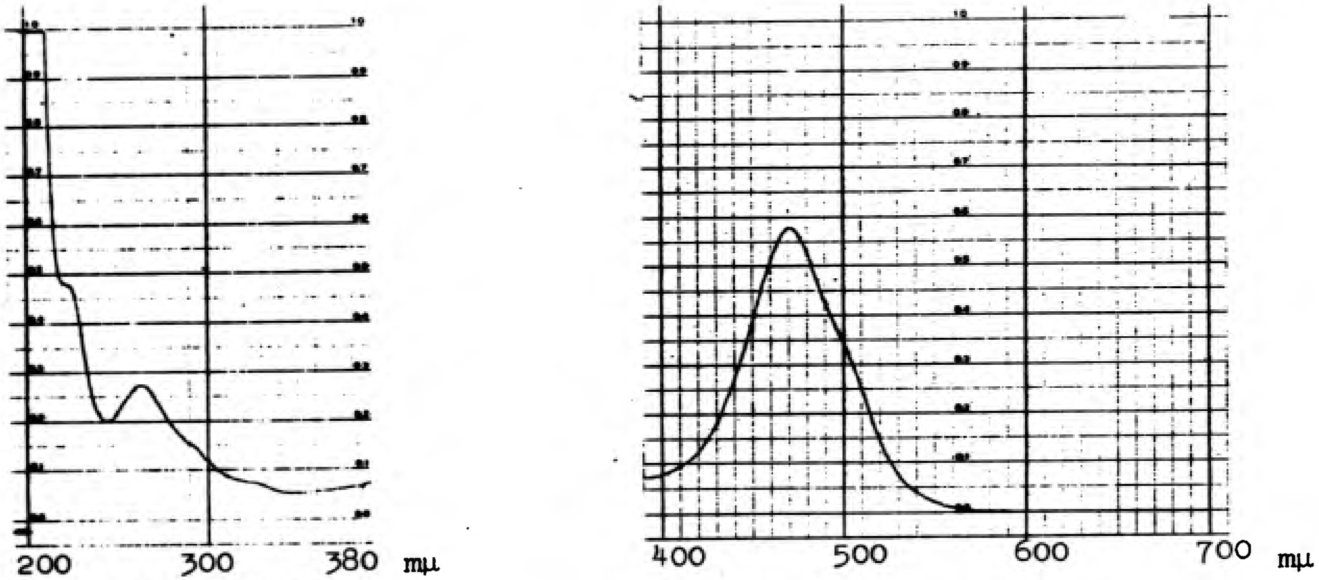
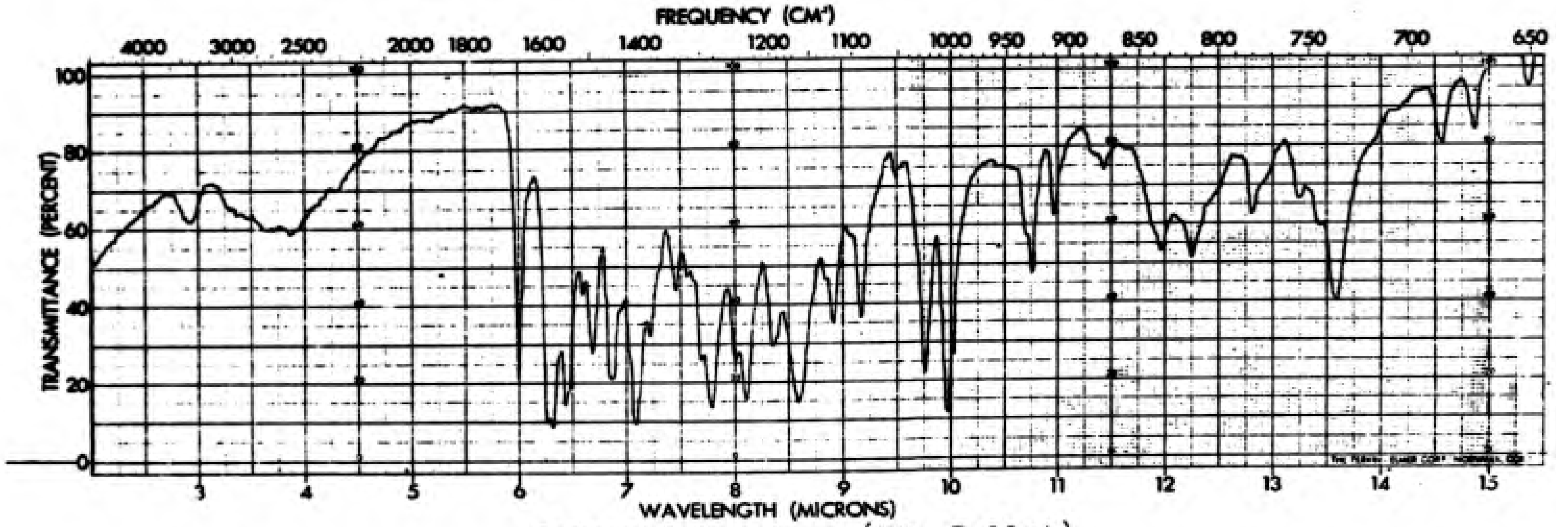


Figure 40. Infrared Spectrum (KBr Pellet) of 2-(2-Acetanilidovinyl)-3-ethyl-β-naphthothiazolium p-toluenesulfonate (I-3)



Ultraviolet Spectrum (0.01N NaOH)

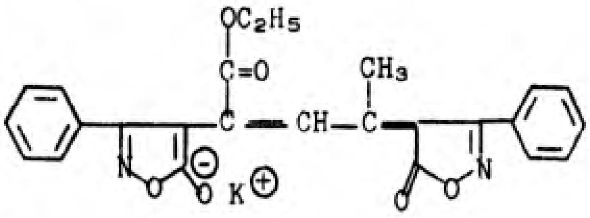
Visible Spectrum (0.01N NaOH)



Infrared Spectrum (KBr Pellet)

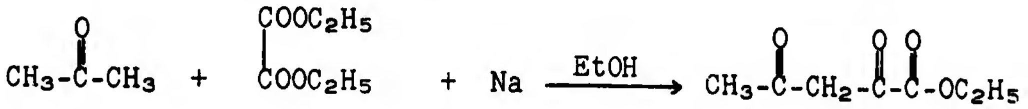
Figure 41. Spectral Data on 4-[(1-Ethyl-2(1)-β-naphthothiazolylidene)ethylidene]-3-methyl-1-p-sulfonyl-5-pyrazolone (F19M10)

J. 5-HYDROXY-3-PHENYLISOXAZOLYL-α-CARBETHOXY-α'-METHYLTRIMETHINE-3-PHENYLISOXAZOLONE-5 (K SALT) (F27M17)



(F27M17)

1. Synthesis of Ethylacetylpyruvate (J-1)



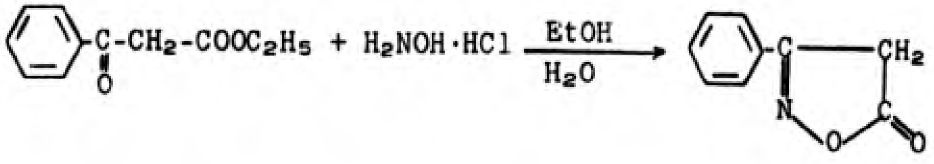
$$\mathrm{CH_3{-}\overset{O}{\overset{\|}{C}}{-}CH_3} \;+\; \begin{array}{l}\mathrm{COOC_2H_5}\\ \;|\\ \mathrm{COOC_2H_5}\end{array} \;+\; \mathrm{Na} \xrightarrow{\mathrm{EtOH}} \mathrm{CH_3{-}\overset{O}{\overset{\|}{C}}{-}CH_2{-}\overset{O}{\overset{\|}{C}}{-}\overset{O}{\overset{\|}{C}}{-}OC_2H_5}$$

(J-1)

No problems were encountered during this synthesis. Vapor phase chromatographic (VPC) analysis of J-1 showed several components, the main one comprising 72% of the sample. The sharp distillation temperature (see Experimental, II.J.4.), however, is indicative of a pure compound. It is believed that J-1 either decomposes on the VPC column or is a mixture of keto-enol tautomers.

Although there is no hydroxyl evidence for an enol form in the infrared spectrum of J-1, an enol tautomer is indicated by the absorptions at 1648 and 1610 cm^{-1} assigned to C=C stretching frequencies. The band at 2990 cm^{-1} is a methyl CH absorption, while the bands at 1750 and 1740 cm^{-1} are attributed to the ester and keto carbonyl groups, respectively. The strong band at 1268 cm^{-1} is a CO absorption. The spectrum is consistent with the assigned structure.

2. Synthesis of 3-Phenylisoxazol-5-one (J-2)

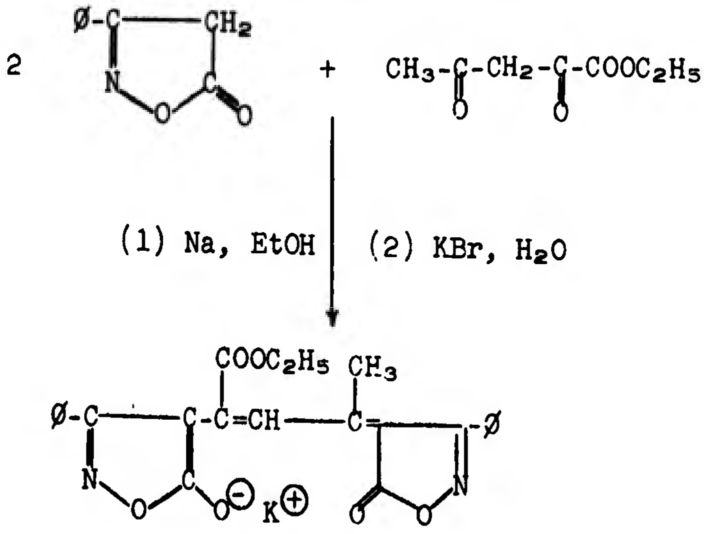


(J-2)

This uncomplicated synthesis yields pure J-2. Recrystallization of J-2 reduced the yield by 15-20% but did not alter the melting point.

The infrared spectrum of J-2 shows a strong absorption at 1808 cm^{-1} that is assigned to the ring carbonyl group. The 1608 cm^{-1} band is probably the C=N absorption, but assignment is complicated by the presence of the phenyl group. The band at 1163 cm^{-1} is assigned to a C-O stretching mode, while the absorptions at 764 and 695 cm^{-1} are indicative of mono-substituted benzene. The spectrum is consistent with the structure and the spectrum given in the literature (ref. 3).

3. Synthesis of 5-Hydroxy-3-phenylisoxazolyl-α-carbethoxy-α'-methyltrimethine-3-phenylisoxazolone-5 (K salt) (F27M17)



(F27M17)

a. Discussion

The preparation of F27M17 by the patent procedure (ref. 4) resulted in a mixture of compounds that were never successfully separated. Continuous extraction of the crude product with anhydrous ether removed several impurities. A satisfactory recrystallization solvent could not be found among the 25 tried.

A number of substrates and eluents were investigated in an unsuccessful attempt to purify F27M17 by column chromatography. Chromatography over silica gel with acetone produced the best sample, a mixture of two or three compounds as indicated by thin-layer chromatography. The infrared spectrum (Nujol mull) indicated the presence of a non-carboxylic hydroxyl group. This implied that the hydroxyl analog of the potassium salt was a major impurity. This supposition was also indicated by the elemental analysis of the product which had values between those calculated for the salt and hydroxy compound.

From the vague statements in the patent procedure (ref. 4), it is not possible to determine whether pure F27M17 was ever prepared. On the basis of our work on F26M6 (see II. F) and F27M17, it is our opinion that the work in reference 4 is questionable.

b. Proof of Structure

(1) Infrared Spectrum

The infrared spectrum of the F27M17 shows bands at 1735 and 1640 cm^{-1}, which are due to the α, β-unsaturated ester grouping and C=C absorption, respectively. The absorption at 1680 cm^{-1} is attributed to the ring carbonyl, which is now shifted to lower frequency by steric effects. The most indicative infrared bands are the doublets at 772, 764, and 704, 698 cm^{-1}. These bands are assigned to two mono-substituted benzene groups in different chemical environments. The absorption at 3440 cm^{-1}, present in both the KBr and Nujol spectra, was indicative of hydroxyl. This absorption was not removed by drying the sample at 100°C/0.1 mm. The spectrum is not inconsistent with the assigned structure, but it indicates a mixture of products.

c. Purity

The sample sent for analysis was taken from the sample submitted to the Air Force.

Thin-layer chromatography on silica gel with methanol elution showed the sample to be a mixture of two or three components.

d. Air Force Sample

One 5.5-gram and one 0.5-gram sample (total 6.0 grams) were submitted to the Air Force on 13 March 1964.

4. Experimental

a. Starting Materials

Acetone (Howe and French) was 100% pure by VPC analysis.

Diethyl oxylate (MC and B, 500 g - $2.55) was 100% pure by VPC analysis.

Ethyl benzoylacetate (MC and B, 500 g - $14.55) was 89% pure by VPC analysis and was used as received.

Hydroxylamine hydrochloride (Baker, 1 lb. - $11.46) was used without further purification.

b. Ethyl acetylpyruvate (J-1) (ref. 1)

Small pieces of sodium (23.0 g, 1.0 mole) were added to 400 ml of absolute ethanol over a 2-hr period (mechanical stirring). The mixture was allowed to remain at room temperature overnight to insure complete reaction of the sodium. The yellow solution was cooled to -5°C with a salt-ice bath, and a solution of 58.0 g (1.0 mole) of acetone in 146.0 g (1.0 mole) of diethyl oxalate was added dropwise with rapid stirring over a 2-hr period. The temperature was kept between 0-4°C by regulating the rate of addition. Ethanol (100 ml) was added to the thick yellow precipitate. The suspension was stirred at room temperature for 5 hr and allowed to stand overnight. The suspension was cooled to 0°C with stirring and 16.7% aq. sulfuric acid (310 g solution, 0.53 mole H_2SO_4, 1.06 equiv. H_2SO_4) was carefully added until pH 1-2 was reached. The resulting precipitate was filtered and washed with two 50-ml portions of absolute ethanol. The filtrate and washings were combined and extracted with two 250-ml portions of benzene. The benzene extracts were washed with 250 ml of water, separated, and dried over anhydrous sodium sulfate. After filtration, the drying agent was washed with 50 ml of benzene. The benzene extracts (550 ml) were evaporated to dryness *in vacuo* to yield a brown oil that distilled at 80°C/6 mm [lit. (ref. 1) bp 82°/6.5 mm] to yield 79.55 g (50%) of clear liquid product, which was a white solid at 0°C.

c. 3-Phenylisoxazol-5-one (J-2)(ref. 2)

Ethyl benzoylacetate (153.6 g, 0.8 mole) was added to a mechanically stirred solution of 56.0 g (0.8 mole) of hydroxylamine hydrochloride in 600 ml of water. The suspension was warmed on a steam bath and ethanol (400 ml) added until a tan solution resulted. The solution was refluxed with stirring for 1 hr (a precipitate resulted after 20 min.). The suspension was cooled in an ice bath and filtered. The resulting product was washed with 400 ml of cold water and then with 400 ml of cold ethanol to yield 78.4 g (61%) of white needles, mp 150.5-153°C [lit. (ref. 3) mp 151-152°C]. Recrystallization from ethanol (15 ml/g) did not change the melting point.

d. 5-Hydroxy-3-phenylisoxazolyl-α-carbethoxy-α'-methyl trimethine-3-phenylisoxazolone-5 (K salt) (F27M17)

Sodium (1.15 g, 0.05 mole) was added to 250 ml of absolute ethanol and the mixture stirred until all the sodium had reacted. Ethyl acetoacetate (7.90 g, 0.05 mole) was added and the yellow Na salt precipitated. After stirring for 15 min., 16.10 g (0.1 mole) of 3-phenylisoxazol-5-one was added and the red solution was stirred for 15 min. at room temperature. The solution, which became intensely purple on heating, was refluxed on a steam bath for 2 hr. The mixture was added to a stirred solution of 370 g of potassium bromide in 1500 ml of water. A purple tar precipitated. The liquid was decanted, and the tarry product was dried at 70°C/15 mm to yield 12.3 g of purple crystals with a golden sheen, mp 124°C-? (mp depended on rate of heating). Continuous extraction of the product with hot ether for 20 hr gave 0.24 g of purple crystals, mp 224°C-? dec., which were insoluble in cold ether. Evaporation of the ether extracts gave 1.29 g of brown solid (mp 105-145°C dec). These fractions were discarded. A purple solid, 9.5 g (39%) (mp 206°C dec) remained unextracted in the Soxhlet thimble.

The ether-extracted product from several reactions was chromatographed in the following general manner:

F27M17 (13.0 g) was chromatographed over 450 g of Baker silica gel in a 1.5 in. x 36 in. column with acetone as the eluent.

CHROMATOGRAPHY RESULTS

Cut	ml, eluent	color of eluent
1	330	clear
2	30	light to dark purple
3	820	dark purple
4	20	purple and yellow
5	300	dark yellow-brown
6	100	light yellow

Evaporation of Cut 3 *in vacuo* gave 10.18 g of purple crystals (golden reflex), mp 128-130°? C dec. Evaporation of Cut 5 gave 0.08 g of a brown solid, mp 65-112°C with a complex infrared spectrum.

When the material from Cut 3 was rechromatographed under the same conditions, the cuts were the same, including the brown fractions. Evaporation of the dark purple cut gave purple crystals (mp soften 127°C, 137-140°C dec). During drying at 100°C/0.1 mm for 16 hr, a brown oil sublimed out of the sample to give purple crystals (mp very heating rate dependent, fast heating mp 165°C dec., slow heating (1°C/min) mp $>$ 325°C). When a sample of F27M17 was inserted into the melting point both at 238°C, it immediately decomposed, while at the same time a sample that had been heated slowly from 30° to 238°C was unaffected.

Anal.

Calc.	$C_{25}H_{19}KN_2O_6$	Calc. $C_{25}H_{20}N_2O_6$	Found
C	62.24	67.6	66.2, 66.1
H	3.94	4.51	4.4, 4.3
N	5.81	6.31	6.0, 6.1
O	19.93	21.60	- -
K	8.12	0.00	3.4, 2.8*

---

* Calc. from per cent ash as K_2CO_3.

e. Unsuccessful Chromatographic Procedures

	Substrate	Eluent	Remarks
1.	Woelm acidic alumina	Ether-acetone	Poor separation
2.	MCB neutral alumina	Acetone-methanol	F27 changed
3.	Baker silica gel	Ether-acetone	Slow separation
4.	Woelm neutral alumina	Acetone-methanol	Poor separation, poor yield
5.	MCB F-1 alumina	Methanol	Poor yield, poor separation

f. Attempted Recrystallizations (Unsuccessful)

(1) First Attempt

F27M17 (0.1 g) in a microsoxhlet extractor from a solution of 14.5 ml ether and 0.5 ml acetone gave no isolable product.

(2) Second Attempt

Twenty-six common solvents were tested as fractional crystallization media. None were applicable.

5. References

1. D. Liebermann, et al., Bull soc. chim. France, 1958, 687. C.A., 52, 20147e (1958).

2. A. Hantzch, Ber., 24, 495 (1891).

3. C. L. Angyal and R. J. W. LeFevre, J. Chem. Soc., 1953, 2181.

4. J. J. Jennen and O. H. Vandenbroele, U. S. Patent 2,644,754, July 7, 1953. C.A., 48, 67 (1954).

6. Spectra

Spectral data are given in Figures 42-44.

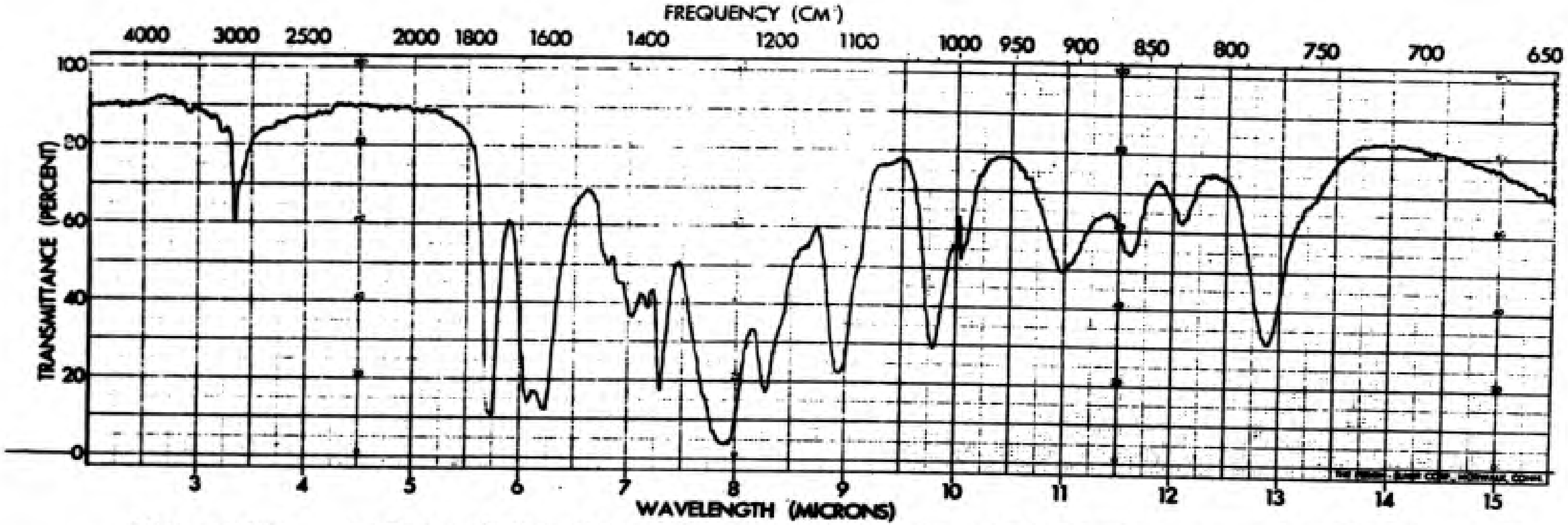


Figure 42 . Infrared Spectrum (Thin Film) of Ethyl Acetylpyruvate (J-1)

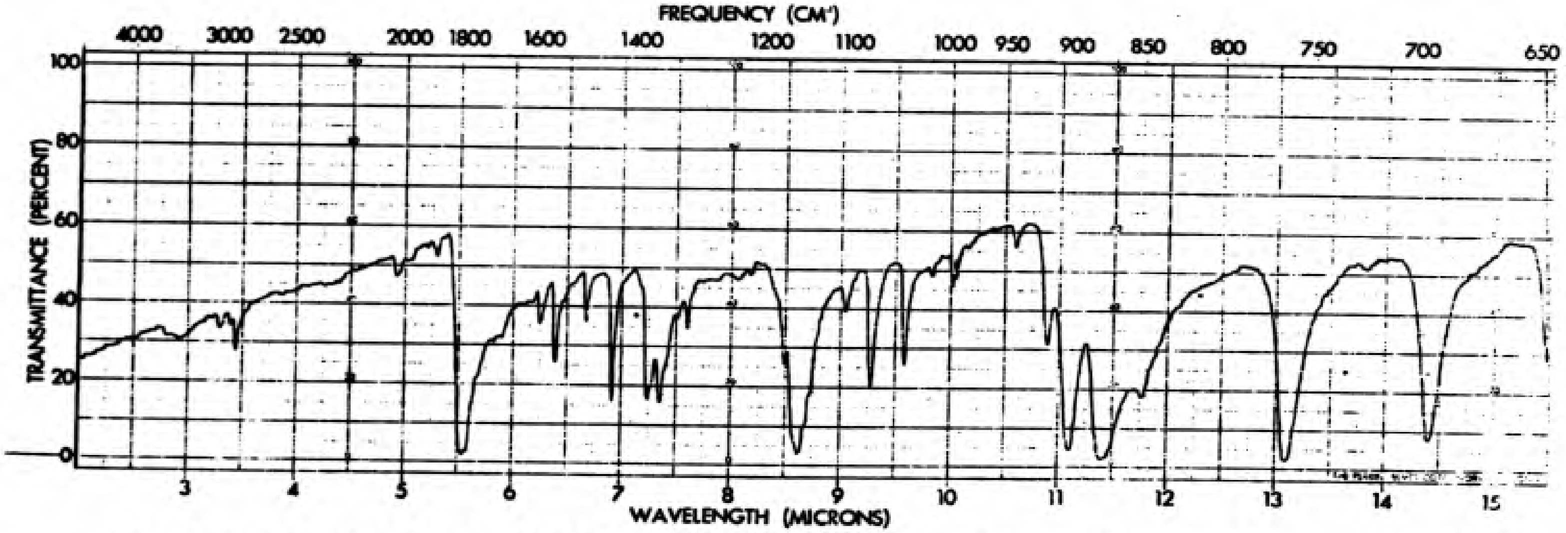
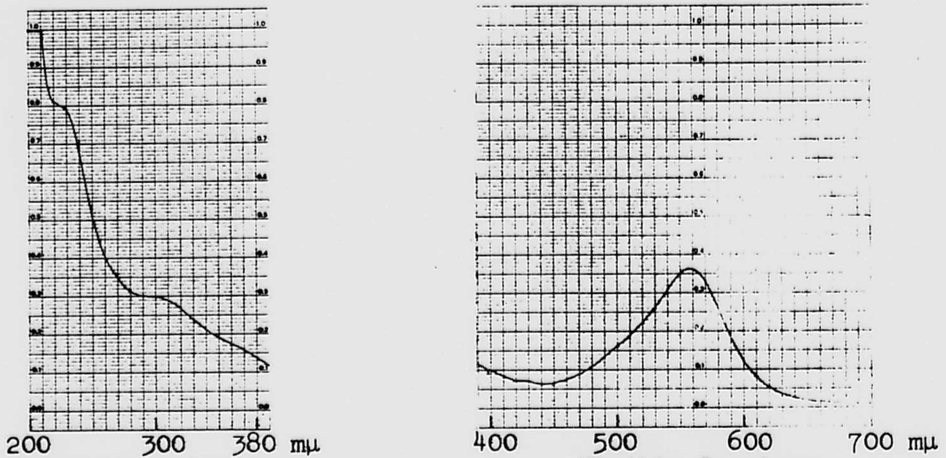
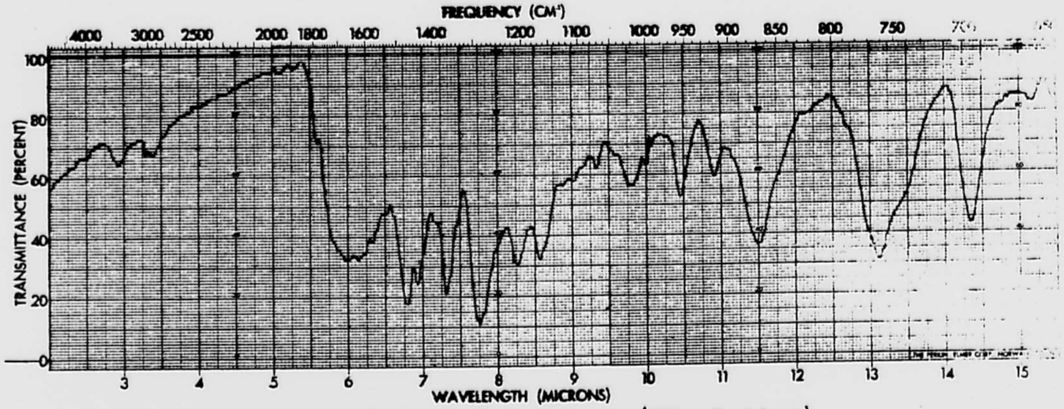


Figure 43. Infrared Spectrum (KBr Pellet) of 3-Phenylisoxazol-5-one (J-2)



Ultraviolet Spectrum
(Ethanol)

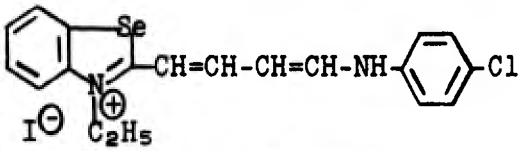
Visible Spectrum
(Ethanol)



Infrared Spectrum (KBr Pellet)

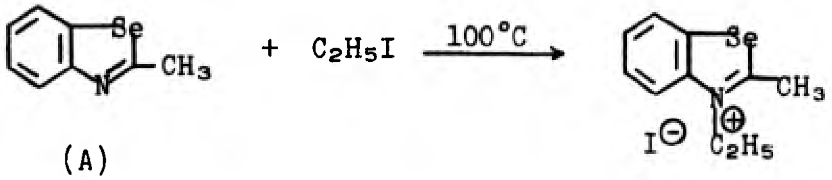
Figure 44. Spectral Data on 5-Hydroxy-3-phenylisoxazolyl-α-carbethoxy-α'-methyltrimethine-3-phenylisoxazolone-5-(K salt) (F27M17)

K. 2-(4-p-CHLOROANILINO-1,3-BUTADIENYL)-3-ETHYLBENZOSELENAZOLIUM IODIDE (F30M14)



(F30M14)

1. Synthesis of 2-Methyl-3-ethylbenzoselenazolium iodide (K-1)



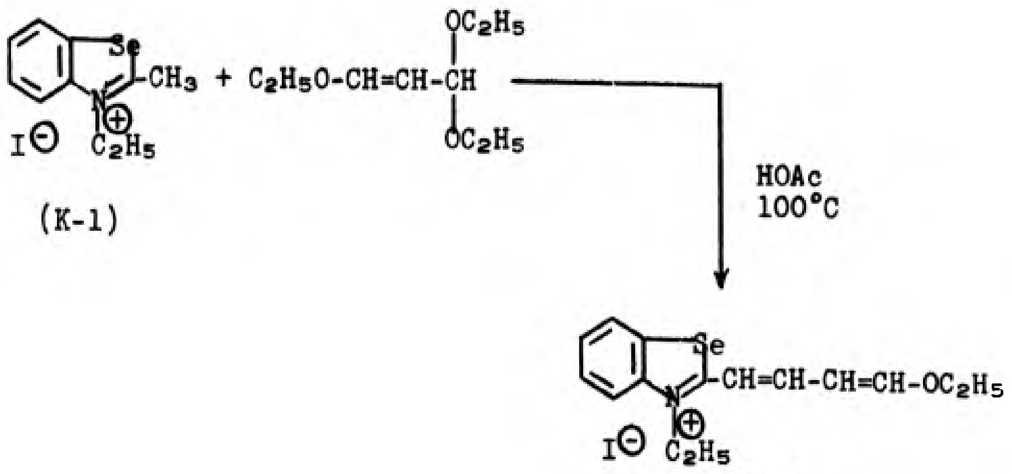
(A) (K-1)

Because of the high cost of the starting material, benzoselenazole, (A), a number of small-scale reactions were carried out to optimize the yield of K-1.

No difficulty was encountered with this reaction once the proper reaction time was determined. Yields averaged 80-90%.

The infrared spectrum of K-1 is similar to that of A, with two major exceptions. The 768 cm^{-1} ortho-substituted benzene (heterocyclic) band in A has been shifted to 778 cm^{-1} in K-1 by the ethiodide formation. The new absorptions due to the ethyl group are readily seen 3040, 2980, 2930, and 2900 cm^{-1}. The spectrum is consistent with the assigned structure.

2. Synthesis of 2-(4-Ethoxy-1,3-butadienyl)-3-ethyl-benzoselenazolium Iodide (K-2)



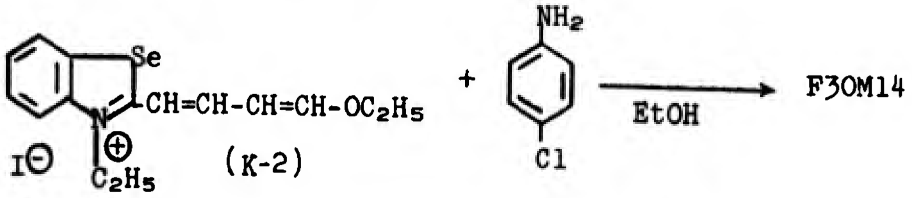
(K-1)

(K-2)

The reaction time used in the preparation of K-2 was varied between 3 and 15 minutes with satisfactory results. Mechanical stirring was important.

The infrared spectrum of K-2 shows a strong band at 1613 cm^{-1} attributed to conjugated C=C stretching. The absorption at 1268 cm^{-1} is an ether band while the ortho-substituted benzene absorption is now at 758 cm^{-1}. The remainder of the spectrum is similar to that of K-1 with the exception of changes in the CH stretching region. The spectrum is consistent with the assigned structure.

3. Synthesis of 2-(4-p-Chloroanilino-1,3-butadienyl)-3-ethylbenzoselenazolium iodide (F30M14)



(K-2)

a. Discussion

Our original synthesis of F30M14 was a 100°C fusion reaction. It was based on a method previously used to prepare similar compounds (ref. 4,5). While the desired product was obtained by this procedure, it was impure and the yield was excessively reduced on purification. The use of ethanol as a reaction solvent was found to give better yields and a much purer product.

b. Proof of Structure

(1) Infrared Spectrum

The spectrum of F30M14 is qualitatively similar to that of K-2. The introduction of the p-chloroanilino group is confirmed by an increase in aromatic C=C vibrations (1600-1500 cm^{-1}) and the appearance of a p-substituted benzene band at 827 cm^{-1}. The band at 1640 cm^{-1} is attributed to the conjugated double bonds of the side chain while the absorptions at 771 and 747 cm^{-1} are due to ortho-substituted benzene and C-Cl stretching, respectively. The NH stretching band is seen at 3170 cm^{-1}. The spectrum is consistent with the assigned structure.

(2) Elemental Analysis

The elemental analysis agrees with the values calculated for F30M14 (see II.K.4). The structure of F30M14 is that assigned.

c. Purity

The sample sent for analysis was taken directly from the sample submitted to the Air Force.

Thin layer chromatography on Woelm alumina (neutral) gave one spot on elution with either acetone or methanol.

d. Air Force Sample

Two samples of F30M14 (5.0 and 1.5 grams; total 6.5 grams) were delivered to the Air Force on 2 April 1964.

4. Experimental

a. Starting Materials

2-Methylbenzoselenazole (Gallard-Schlesinger, 25 g - \$27.50) was obtained as a low melting solid. Analysis by vapor phase chromatography showed it to be 97.6% pure. The infrared spectrum was consistent with the structure.

1,3,3-Triethoxy-1-propene (Aldrich, 100 g - \$30.00) was obtained as a liquid. The infrared spectrum was consistent with the structure but indicated impurities. Vapor phase chromatographic analysis was unsuccessful due to decomposition on the column. The compound was used without further purification since distillation was reported to cause decomposition (ref. 1).

p-Chloroaniline (Eastman, 500 g - \$15.35) was found to be 100% pure by vapor phase chromatography.

Ethyl iodide (MC and B, 1 lb - \$11.65) was filtered before use to remove the mercury inhibitor.

Miscellaneous, Acetic acid and acetone were reagent grade and were used without further purification.

b. 2-Methyl-3-ethylbenzoselenazolium iodide (K-1) (ref. 2)

2-Methylbenzoselenazolium(7.92 g, 0.040 mole) and ethyl iodide (6.80 g, 0.044 mole) were placed in a pressure bottle and the bottle was sealed with a rubber finger cot. The bottle was heated on a steam bath for 46 hr and then cooled in an ice bath. The resulting yellowish solid was pulverized under 150 ml of absolute ether and filtered. The product was washed with an additional 100 ml of ether and air dried to yield 12.34 g of product. This was recrystallized with charcoal(0.1 g/g product) from absolute ethanol (40 ml/g) to give 10.54 g (75%) of colorless needles [mp 211-213°C; lit. (ref. 2), mp 212°C].

c. 2-(4-Ethoxy-1,3-butadienyl)-3-ethylbenzoselenazolium iodide (K-2) (ref. 3)

2-Methyl-3-ethylbenzoselenazolium iodide (21.12 g, 0.06 mole) and 1,3,3-triethoxy-1-propene (20.88 g, 0.12 mole) were mixed with 30 ml of glacial acetic acid in a 250-ml, round-bottomed flask equipped with a condenser and mechanical stirrer with a Teflon blade. The stirred reaction mixture was heated on a steam bath for 5 min. and then cooled in an ice bath. The resulting greenish-black solid was filtered, washed with ether (2 x 100 ml) and acetone (2 x 5 ml), and air dried to yield 18.5 g of product. Recrystallization from methanol (12 ml/g) gave 12.21 g (47.5%) of green crystals [mp 162-167°C (dec.); lit. (ref. 3) mp 176-177°C (dec.)].

d. 2-(4-p-Chloroanilino-1,3-butadienyl)-3-ethylbenzoselenazolium iodide (F30M14)

p-Chloroaniline (4.21 g, 0.033 mole) was dissolved in 125 ml of absolute ethanol in a 500-ml, round-bottomed flask equipped with a condenser, magnetic stirrer, and heating mantle. The stirred solution was brought to reflux and 2-(4-ethoxy-1,3-butadienyl)-3-ethylbenzoselenazolium iodide (7.20 g, 0.017 mole) was added through the condenser in 2-g portions over a period of 5 minutes. Upon addition of the first portion, the reaction mixture immediately turned deep purple. The sides of the condenser were washed with an additional 25 ml of absolute ethanol and the mixture was refluxed for 1 hour and allowed to cool slowly. After being chilled in an ice bath, the reaction mixture was filtered and the bluish product was dried at 70°C/15 mm for 2 hr to yield 8.67 g (99%) of blue-black powder [mp 230-233°C, no lit. mp available]. The powder was recrystallized from 95% ethanol (125 ml/g) in a Soxhlet apparatus. The ethanol solution was allowed to cool slowly to room temperature and was then chilled in an ice bath and filtered. The product was dried at 80°C/15 mm for 2 hr to give 4.87 g of purple crystals [mp 230-231°C]. This product was recrystallized a second time from 95% ethanol (100 ml/g) in the same manner and dried to yield 3.81 g. of purple crystals (mp 231-232°C).

Analysis for $C_{19}H_{18}ClIN_2Se$

	C	H	N	Se
Calc'd	44.25	3.52	5.43	15.31
Found	43.07	3.25	5.39	15.12
	43.74	3.60		
	43.57	3.57		

5. References

1. W. T. Simpson, *J. Am. Chem. Soc.*, *71*, 754 (1949).
2. L. M. Clark, *J. Chem.Soc.*, *1928*, 2313.
3. Kodak Ltd., Brit. Patent 556,266, Sept. 28, 1943.
4. F. M. Hamer, *J. Chem. Soc.*, *1949*, 32.
5. F. L. White, U. S. Patent 2,369,509, Feb. 13, 1945. *C.A.*, *39*, 3744 (1945).

6. Spectra

Spectral data are given in Figures 45-47.

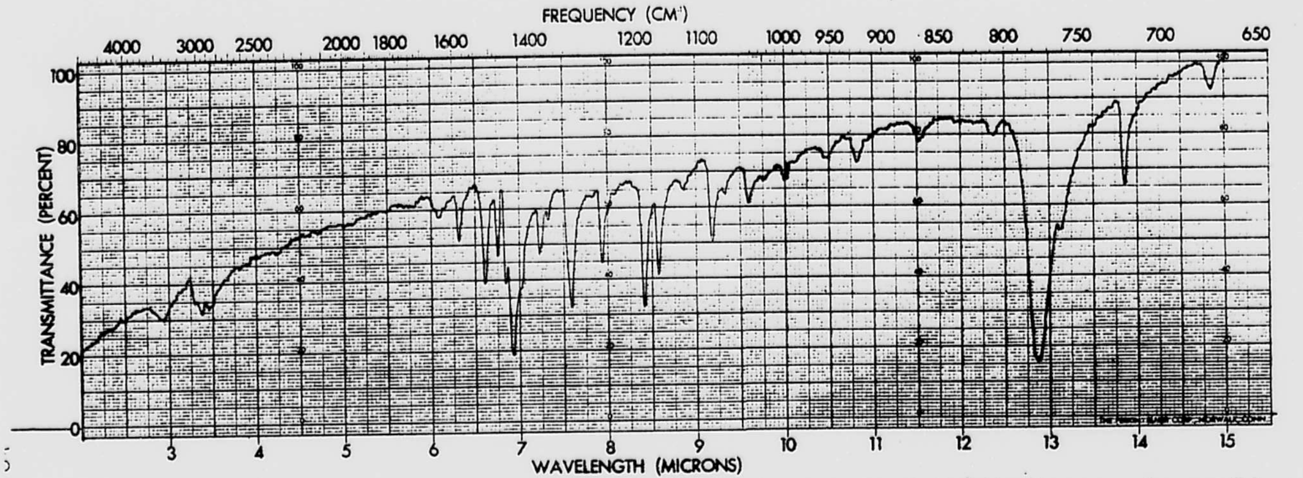


Figure 45. Infrared Spectrum (KBr Pellet) of 2-Methyl-3-ethylbenzoselenazolium iodide (K-1)

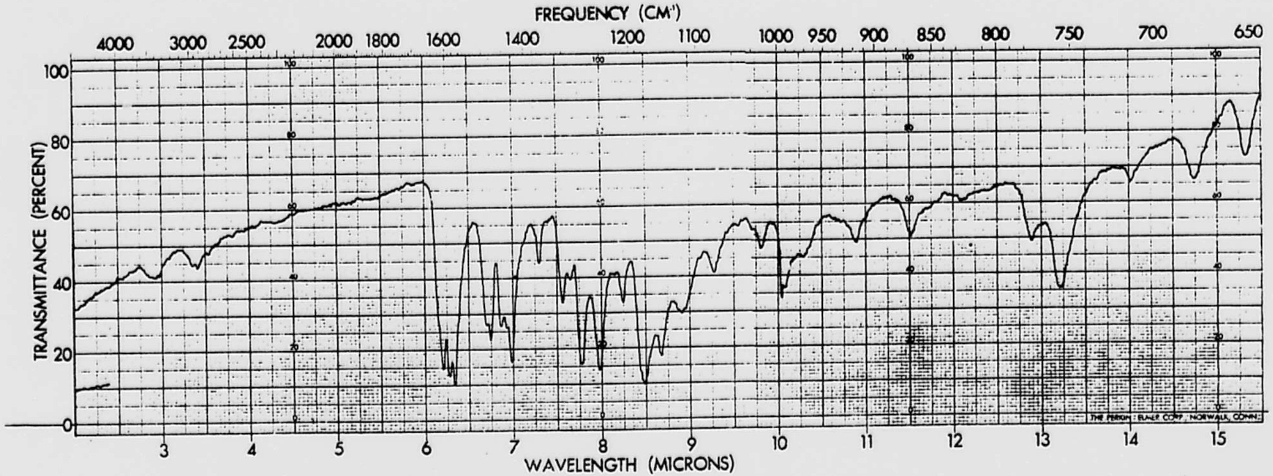
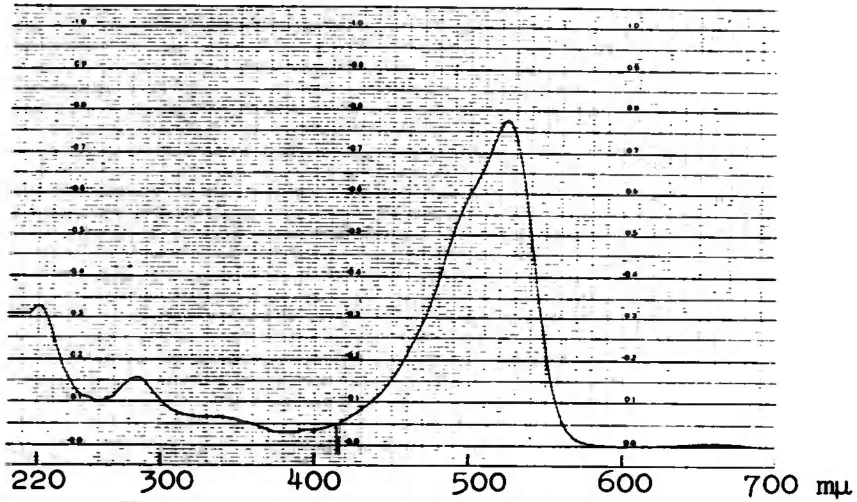
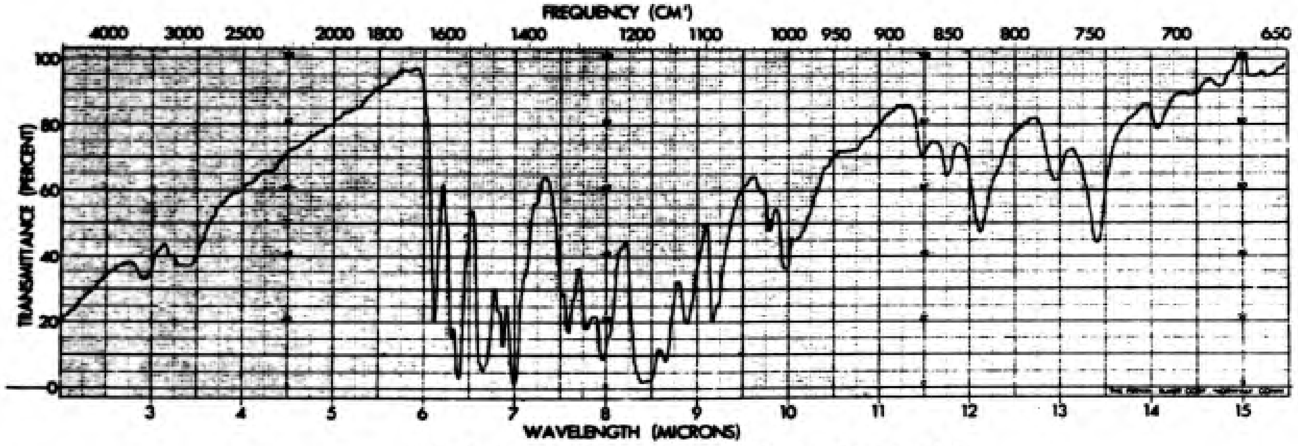


Figure 46. Infrared Spectrum (KBr Pellet) of 2-(4-Ethoxy-1,3-butadienyl)-3-ethylbenzoselenazolium iodide (K-2)



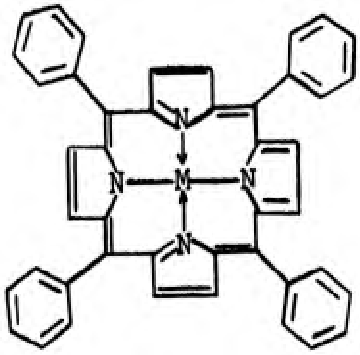
Ultraviolet and Visible Spectrum
(Methanol)



Infrared Spectrum (KBr Pellet)

Figure 47. Spectral Data on 2-(4-p-Chloroanilino-1,3-butadienyl)-3-ethylbenzoselenazolium iodide (F30M14)

L. TETRAPHENYLPORPHIN CHELATES (L)



(L)

1. Discussion

a. Porphin Synthesis Procedures

The reaction between aromatic or heterocyclic aldehydes and pyrrole to produce meso-substituted porphins has undergone some improvements since its discovery. The original preparation of tetraphenylporphin (TPP) (ref. 1) used pyridine as solvent and led to yields of 10%. Since no rigorous purification of product was made, the purity of product is questionable.

Ball, Dorough and Calvin (ref. 2) found that addition of zinc acetate to the reaction mixture led to high yields of zinc TPP from which the free base could be obtained by hydrolysis with dilute hydrochloric acid. It was further claimed that the TPP produced in this manner was free of chlorin, a dihydroporphin that was an impurity in the product if zinc acetate was not employed. Sharp (ref. 4) found that the absence of the pyridine solvent in the zinc acetate procedure led to higher yields of ZnTPP.

Two Carius tube sizes were employed in our work (Figures 48 and 49). The small tube was used in exploratory work.

Our early Carius tube reactions were carried out in both evacuated and nitrogen-filled tubes. The latter procedure appeared to be more satisfactory.

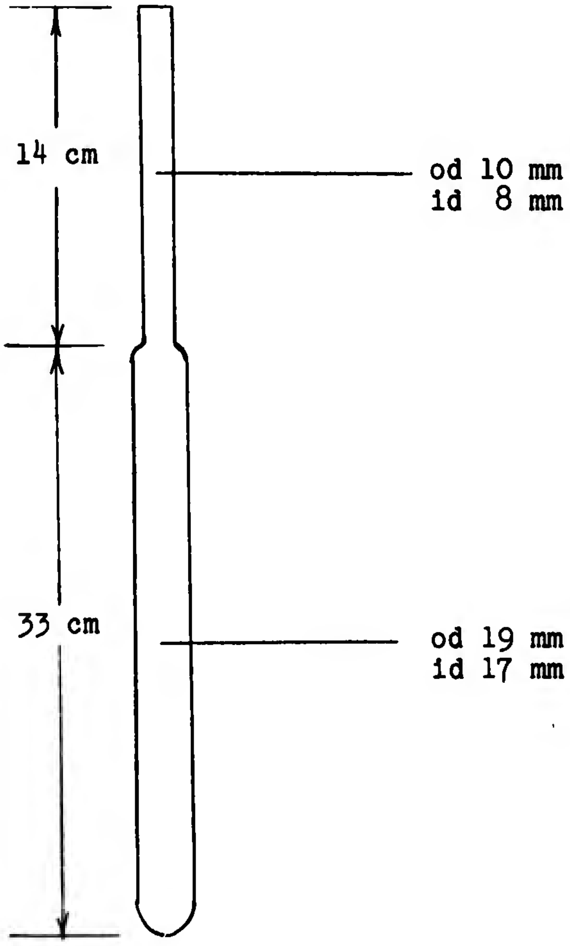


Figure 48. Carius Tube Used for Small-Scale Porphin Synthesis.

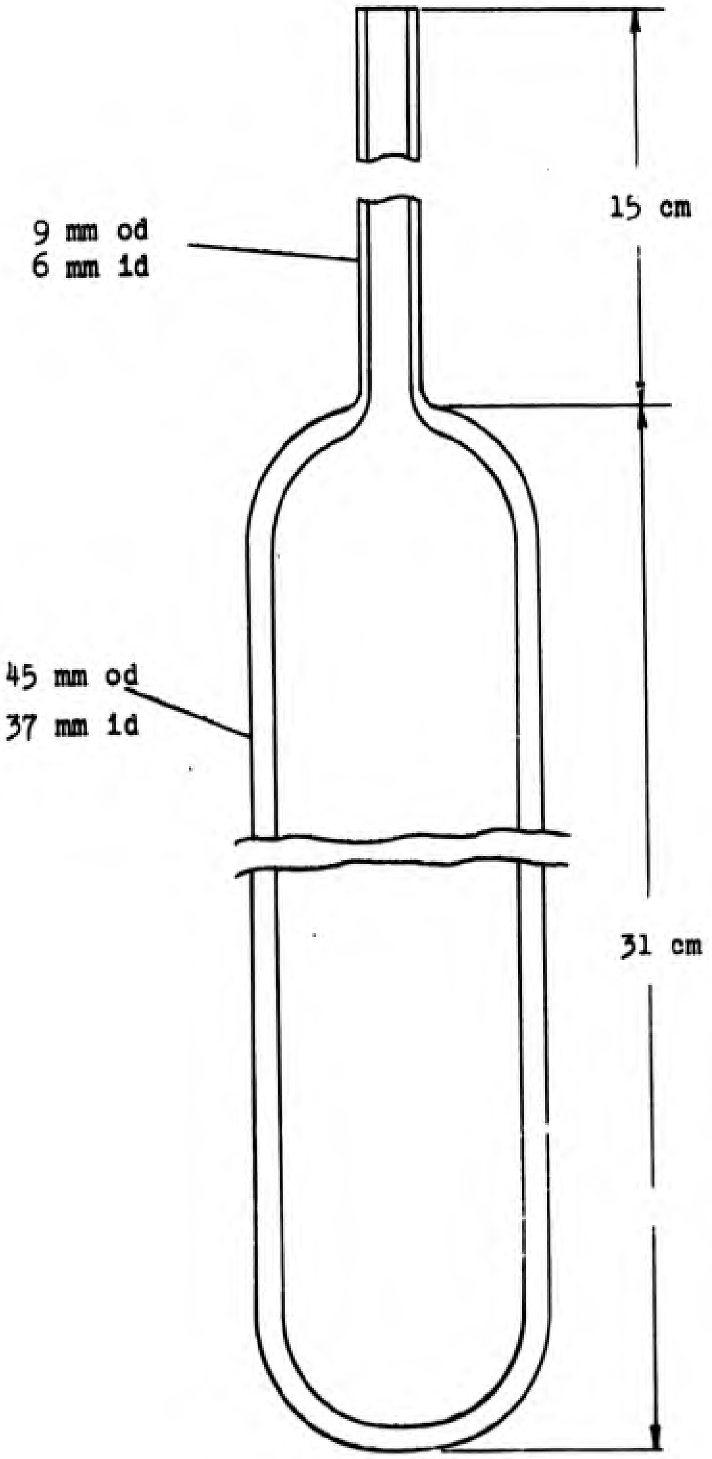


Figure 49. Carius Tube Used for Large Scale Porphin Synthesis

b. Porphin Purification Procedures

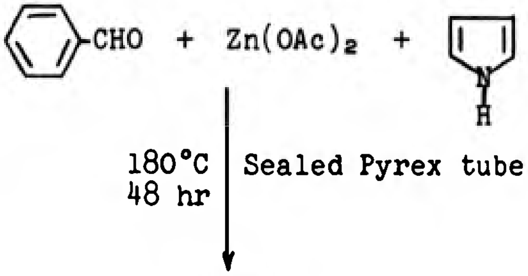
The classical zinc TPP purification method involved three tedious chromatographic separations over talc (ref. 2). A synthetic talc has also been used as a column packing (ref. 3). Sharp (ref. 4) has recently reported that alumina was suitable for zinc TPP purification. We have found that alumina has the following advantages over talc as a chromatographic substrate:

- Packed columns of alumina allow solvent to flow freely; with talc, the flow of solvent is very slow and often pressure is needed to force solvent through the column.
- Alumina can be obtained in various standardized chromatographic grades of known activity. This permits choice of the particular grade best suited for the separation to be performed.
- The use of alumina permits elution of the various bands off the column. With talc, once the bands have been resolved, the column packing is removed, the separated bands are mechanically separated, and each band is repacked in another column and then eluted.

The aluminas used were found to differ quite markedly in activity. Woelm neutral alumina was found to be more active than Matheson Coleman and Bell alumina, but it was also twice as expensive. Alcoa F-1 alumina was very active, but was ten times as expensive as the MC and B material.

It was found that a more efficient alumina to porphin ratio could be determined if the crude porphin mixture was extracted with chloroform to remove insoluble, non-porphin products before chromatography.

2. Synthesis of Zinc Tetraphenylporphin (M16T7a) (L, M=Zn^{+2})



M16T7a

a. Discussion

M16T7a was prepared as the first intermediate in the synthesis of the desired copper, cobalt, and iron chelates.

Both the "neat" or "no solvent" procedure of Sharp (ref. 4) and the pyridine solvent method of Rothemund and Menotti (ref. 1) were investigated as routes to M16T7a. The former method was found to be superior.

The quality of the tetraphenylporphin (M15T7a) obtained from the hydrolysis of M16T7a was found to depend greatly on the purity of the M16T7a used. It was found that the effort involved in preparing pure M16T7a by two chromatographic steps was justified by the quality of the M15T7a that could be obtained from the pure zinc chelate. Difficult emulsions and impure M15T7a were obtained if the crude or once chromatographed zinc chelate was hydrolyzed.

The overall yields of the zinc chelate (M16T7a) after two chromatographic purifications were 4 to 6%.

b. Proof of Structure-Spectra

The infrared spectrum of a porphin compound is of very little use in structure determination because of the nature of the molecule. Visible spectral data are of considerably greater use if literature values are available for comparison. The visible spectral data for M16T7a agrees with the values in the literature (Table 2).

c. Purity

The sample of M16T7a submitted to the Air Force was chromatographed twice over alumina and then recrystallized from chloroform-methanol solution in a Soxhlet apparatus.

The T.L.C. sample gave one spot on Woelm talc after elution with either benzene or acetone.

d. Air Force Sample

Two samples of M16T7a (1.5 and 0.5 grams, total 2.0 grams) under nitrogen were delivered to the Air Force on 18 December 1963. Although M16T7a was not a requested dye, it was submitted as a compound of possible future interest.

3. Synthesis of Tetraphenylporphin (M15T7a) (L, M = 2H)

$$\text{M16T7a} \xrightarrow[\text{(2) } NH_4OH]{\text{(1) } HCl} \text{M15T7a}$$

a. Discussion

This reaction proceeds in nearly quantitative yield if the zinc chelate (M16T7a) is pure. Attempts to hydrolyze the crude reaction mixture or the product of one chromatographic separation led to greatly decreased yields of M15T7a.

Since the hydrolysis is a heterogeneous reaction between aqueous dilute hydrochloric acid and a chloroform solution of M16T7a, efficient stirring is necessary. It was found in our work that the use of a Morton flask with creased sides and fast mechanical stirring was satisfactory.

Neutralization of the hydrolysis mixture to pH 7.0 with cooling is also important since, if the solution is not neutral, then some M15T7a will be lost in the washing procedure either as the hydrochloride salt if the solution is acid or as the Zn salt if the solution is basic. The neutralization and washing are advantageously done in the hydrolysis flask. This allows for stirring between additions of ammonium hydroxide to facilitate attainment of equilibrium.

The neutralized solution is washed many times with water to remove zinc salts. The product obtained must be recrystallized at least once from benzene to give spectrophotometrically pure M15T7a.

b. Proof of Structure

The visible spectrum of M15T7a is in general agreement with the literature data (Table 2).

c. Purity

The sample of M15T7a submitted to the Air Force was recrystallized twice from benzene.

The T.L.C. sample gave one spot on Woelm talc after elution with either benzene or acetone.

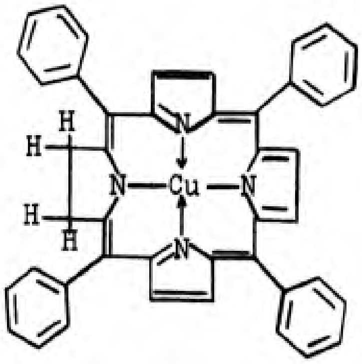
d. Air Force Sample

Two samples of M15T7a (1.5 and 0.5 grams, total 2.0 grams) under nitrogen were delivered to the Air Force on 18 December 1963. Although M15T7a was not a requested dye, it was submitted as a compound of possible future interest.

4. Synthesis of Copper (II) tetraphenylporphin (T7aM11) (L, M = Cu^{+2})

a. Discussion

The first attempt to prepare T7aM11 was a direct synthesis from benzaldehyde, pyrrole, and cupric acetate in the general manner found successful for the preparation of zinc tetraphenylporphin (M16T7a) (see II.L.2). The copper tetraphenylporphin produced in this manner was found to be contaminated by about 8% copper tetraphenylchlorin (L-1).



(L-1)

This impurity was identified by its visible spectral absorption at 617 mμ (ref. 2).

L-1 could not be removed by chromatography or by reaction with cupric acetate. The direct synthesis of T7aM11 was, therefore, abandoned in favor of a synthetic method that was found to produce chlorin-free T7aM11.

The new procedure involved the reaction of pure tetraphenylporphin (M15T7a), with cupric acetate (ref. 5).

$$\text{M15T7a} + \text{Cu(OAc)}_2 \longrightarrow \text{T7aM11}$$

The degree of reaction was followed spectrophotometrically by the disappearance of the tetraphenylporphin (M15T7a) bands at 590 and 647 mμ. The yield of T7aM11 was essentially quantitative after two hours. The chlorin impurity was not present in samples of T7aM11 prepared by this method.

b. Proof of Structure

(1) Infrared spectrum

While consistent with the assigned structure, the infrared spectrum is of little aid in the structure proof due to the nature of the molecule.

(2) Visible Spectrum

The visible spectral data are consistent with those given in the literature (Table 2).

(3) Elemental Analysis

The elemental analysis agrees with the values calculated for T7aM11 (see Experimental II.L.7). The structure of T7aM11 is that assigned.

c. Purity

The sample submitted for elemental analysis had been twice recrystallized and was taken directly from the sample submitted to the Air Force.

Thin layer chromatography on Woelm magnesium silicate (talc) showed only one spot after elution with benzene or acetone.

d. Air Force Samples

Two samples of T7aM11 (4.0 and 1.5 grams, total 5.5 grams) under nitrogen were submitted to the Air Force on 3 December 1963.

Two samples of the chlorin-containing direct synthesis product (T7aM11 -chlorin) (2.0 and 0.5 grams, total 2.5 grams) under nitrogen were submitted, as requested, on 8 January 1964.

5. Synthesis of Cobalt (II) tetraphenylporphin (T7aM12) (L, M = Co^{+2})

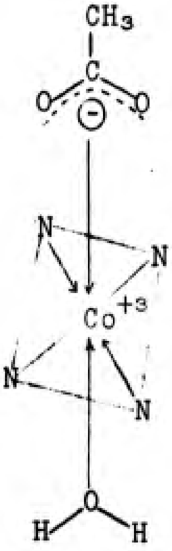
$$\text{M15T7a} + \text{Co(OAc)}_2 \longrightarrow \text{T7aM12}$$

a. Discussion

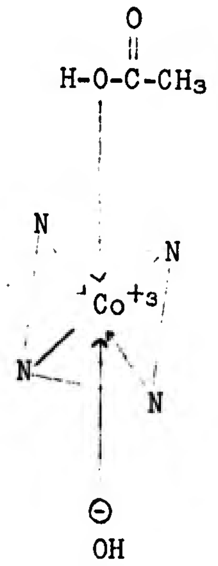
T7aM12 was prepared from M15T7a in much the same manner as the copper chelate (T7aM11). In one of the two T7aM12 preparations, the reaction did not go to completion. The reaction product was continuously extracted with hot methanol until the visible absorption bands of unreacted M15T7a no longer appeared in the spectrum of the product.

The cobalt chelate was initially obtained as fluffy purple needles. Recrystallization from ether (Soxhlet extraction) changed the crystal form to hard microcrystals that were much less soluble in ether than were the needles. After two weeks of continuous ether extraction, the second recrystallization yielded only one gram of product. Since the twice recrystallized material was spectrally identical with the once recrystallized product, no further purification was carried out. Although this sample proved to be analytically pure, it gave three spots (R_f 0.80, 0.45, and 0.00) by thin-layer chromatographic (T.L.C.) analysis on synthetic talc (1:1::benzene:chloroform). The compounds with R_f 0.80 and 0.45 were identified by their visible spectra as T7aM12 and starting material (M15T7a), respectively.

Chromatography of 4.9 grams of the above sample over 300 grams of Woelm alumina with benzene-chloroform in a one-inch diameter column gave (1) the sample of T7aM12 submitted to the Air Force, (2) a small amount of M15T7a, and (3) 0.073 grams of a dark solid obtained from a sharp band isolated in the fortieth 225-ml fraction. This compound is believed to be the cause of the R_f 0.00 T.L.C. spot. The infrared spectrum of this compound showed an absorption at 1658 cm^{-1}, which is not present in T7aM12. This, along with the low R_f value, led us to believe that the R_f 0.00 contaminant was cobalt (III) tetraphenylporphin acetate (L-2). The 1658 cm^{-1} band was assigned to the acetate ionized carboxyl absorption. Attempted recrystallization from chloroform resulted in the conversion of L-2 to L-3. The 1658 cm^{-1} L-2 absorption was raised to 1722 cm^{-1} in L-3. This higher absorption was consistent with unionized carboxyl. The proposed structures for L-2 and L-3 are given below.



(L-2)



(L-3)

b. Proof of Structure of T7aM12

(1) Visible Spectrum

The visible spectral data are consistent with those given in the literature (Table 2).

(2) Elemental Analysis

The elemental analysis agrees with the values calculated for T7aM12 (see Experimental II.L.7).

c. Purity

The analytical sample was taken directly from the sample submitted to the Air Force.

The T.L.C. sample showed two spots on Woelm talc with 1:1::benzene: chloroform (R_f 0.00 and 0.80). Whether the spot at the origin was real or imaginary could not be determined.

d. Air Force Sample

Two samples of T7aM12 (2.0 and 0.5 grams-Total 2.5 grams) were submitted to the Air Force on 28 February 1964.

6. Synthesis of Iron (III) tetraphenylporphin Chloride (T7aM13) (L, M = Fe^{+3}, Cl^{-})

a. Discussion

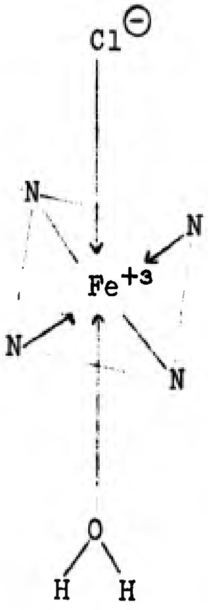
T7aM13 was prepared from tetraphenylporphin (M15T7a) and ferric acetate.

$$\text{Fe} + \text{HOAc} \longrightarrow \text{Fe(OAc)}_2 \xrightarrow[\text{HOAc}]{O_2} \text{Fe(OAc)}_3$$

$$\text{Fe(OAc)}_3 + \text{M15T7a} \xrightarrow[\text{CHCl}_3]{\text{NaCl}} \text{T7aM13}$$

The ferrous to ferric oxidation presumably takes place during the filtration step. T7aM13 was obtained in quantitative yield.

An analytically pure sample of T7aM13 could not be obtained by recrystallization. Column chromatographic purification of the sample gave two T7aM13 fractions with slightly different visible spectra. The elemental analyses of these samples gave low chlorine values and did not quite total 100% (see Experimental II.L.7). These samples may be hydrates of T7aM13 (L-4), i.e. hexa-coordinated iron (III) with structures similar to that postulated for cobalt (III) tetraphenylporphin acetate (L-2, L-3).



(L-4)

A water analysis is underway.

b. Proof of Sturcture - Visible Spectrum

The visible spectral data are similar to the literature values (see II.L.7.g).

c. Air Force Sample

A sample of T7aM13 will be delivered as soon as analytically pure material is obtained.

7. Experimental

a. Starting Materials

Benzaldehyde (Eastman, 500 g - $2.90) was redistilled at reduced pressure under nitrogen through an 8-inch Vigreux column [bp 75-76°C/16 mm; lit. (ref. 7), bp 62°/10 mm] and stored under nitrogen until used.

Pyrrole (Eastman, 500 g- $6.60) was redistilled under nitrogen through an 8-inch Vigreux column, [bp 130-131°C; lit. (ref. 7), bp 130-131°C] and stored under nitrogen until used.

Inorganic Reagents were reagent grade and were used without further purfication.

b. Materials, Procedures and Equipment

(1) Chromatographic Materials

Three different chromatography columns and three different substrates were used in the chromatographic procedures. They are described below.

Column	Inside Diameter, in.	Length, in.
A	1	36
B	1.5	36
C	2	30

Columns Band C were topped by a 4-in. sphere that served as a solvent reservoir.

The three types of alumina used in chromatographic procedures and described below are hereafter referred to by the short name indicated.

MCB Alumina, activated, chromatographic grade, 80-200 mesh, Matheson Coleman and Bell No. AX612, 5 lb - $15.75.

Woelm Alumina, neutral, activity grade 1 for chromatography, Alupharm Chemicals, Inc., 2 lb - $14.00.

F-1 Alumina, activated, Alcoa F-1, 80-100 mesh, Matheson Coleman and Bell AX612-4, 500 g - $32.15.

(2) Chromatographic Procedure

The column to be used was filled with solvent, and purified sand was poured to form a layer 1 in. thick above a plug of glass wool, which served to prevent the sand from interfering with operation of the stopcock. The alumina substrate was slowly poured into the column with gentle tapping. When the alumina had settled uniformly, a 1 in. layer of sand was placed on top. Solvent was removed from the bottom of the column until the level of solvent was even with the top of the sand. All chromatographic separations were performed on columns packed in this manner.

For best results, the material to be chromatographed should be dissolved in a minimum amount of chloroform and placed on the column so that the level of the solution is about even with the top level of sand. Then fresh solvent is carefully added to continue the elution. All the solution should be on the column before more solvent is added.

(3) Pyrolysis Equipment

Two different furnaces were used in the synthesis of the porphins.

The exploratory procedures using the small Carius tubes (Fig. 48) were performed in a 25-in. cylindrical furnace, which had four 1-in. holes running the length of the cylinder. Each hole held one small Carius tube. Both ends of the cylinder were equipped with baffle plates to minimize the danger from explosions. The furnace was also equipped with a thermocouple, electrical contacts to allow heating through a Powerstat, and a motor to rotate the cylinder during heating.

The large Carius tubes (Fig. 49) were placed in safety tube before heating. This tube consisted of a 2-in. steel pipe sealed at one end and fitted with a threaded steel cap at the other end. Methanol (100 ml) was added to the pipe to reduce the pressure differential on the Carius tube. The samples were heated in a stationary cylindrical furnace (8 x 28 in.). Three samples could be heated simultaneously. The temperature of the electrically heated furnace was controlled by an automatic temperature control unit attached to a large Variac.

c. Zinc tetraphenyl porphin (M16T7a) (Typical Large-scale Preparation

Three large Carius tubes (Figure 49) were flushed with nitrogen, and each was charged with benzaldehyde (34.00 ml, 34.80 g, 0.338 mole), pyrrole (22.00 ml, 20.85 g, 0.310 mole) and zinc acetate dihydrate (22.00 g, 0.092 mole). Each tube was sealed under nitrogen and placed within a 2-in. diameter pipe sealed at one end and fitted with a threaded steel cap on the open end. The pipe contained 100 ml of methanol to reduce the pressure differential on the Carius tube. The three bombs were then placed within a large Carius furnace and heated to 180°C ± 10°C for 48 hr. The furnace was cooled, and the Carius tubes were removed and cracked open. The brittle, dark solid was pulverized and extracted with chloroform in a Soxhlet apparatus until no color was observed in the chloroform extracts. Removal of chloroform in vacuo yielded 171.6 g of black solid that was chromatographed in 35 g quantities over MCB alumina (1 kg/35 g) in column C.

The ZnTPP that eluted as a maroon band and a wine red solution was collected and the solvent removed to give 43.2 g of bluish solid, which was rechromatographed in 10 g quantities over Woelm alumina (50 g/g dye) in column C. The maroon band was eluted with chlrorform. Removal of solvent in vacuo yielded 8.85 g of pure zinc tetraphenyl porphin (5.4% yield). (See Table 2 for spectral data). The second chromatrography and resulting low yield is justified by the purity of the product and the ease and rapidity of the chromatographic procedures. All the zinc tetraphenylporphin used to prepare tetraphenylporphin was obtained and purified in this manner.

The sample of zinc tetraphenylporphin submitted as M16T7a was prepared as above and recrystallized in a Soxhlet apparatus using chloroform-methanol (2:1 by volume, 120 ml/gram) and dried at 100°C/0.5 mm for 16 hrs. See Table 2 for spectral data.

Table 2

PORPHIN VISIBLE SPECTRAL DATA

	Reported[a]		Found[b,c]	
Compound	λ(mμ)	ϵ	λ(mμ)	ϵ
M16T7a	589	3,580	588	3,680
	545	22,100	539	22,900
	422	589,000	422	542,000
M15T7a	548	8,200	548	8,025
	514	19,000	514	19,500
	419	399,000	419	549,000
T7aM11	540	20,500	539	21,350
	417	470,000	417	482,000
T7aM11-chlorin			416	418,000
			539	18,200
			617	2,100
T7aM12	528	15,100	528	16,200
	403	243,000	403	243,000

---

[a] Reported data determined from curves in literature (ref. 6)

[b] Average of two determinations except for T7aM11-chlorin and T7aM12 (one determination)

[c] Benzene solution

d. Tetraphenylporphin (M15T7a)

The M16T7a from the above reaction (1.462 g, 2.2×10^{-3} mole) was dissolved in 100 ml of chloroform and vigorously stirred for 2 hr with 100 ml of 6N HCl in a 500-ml Morton flask. The mixture was neutralized with conc. NH_4OH to pH 7, and the aqueous layer was removed by pipette. The chloroform layer was washed 5 times with 125-ml portions of water in the same flask. The water was removed after each washing by pipette. The chloroform layer was dried over anhydrous sodium sulfate. Removal of desiccant and solvent yielded 1.305 g (98%) of pure M15T7a.

The tetraphenylporphin thus obtained was recrystallized once from benzene before being used in the preparation of other metallo-porphins. The sample of tetraphenylporphin submitted as M15T7a was prepared as above, recrystallized a second time from benzene and dried at 100°C/0.5 mm for 16 hrs. See Table 2 for spectral values.

e. Copper (II) tetraphenylporphin (T7aM11)(ref. 5)

(1) Method A - Chlorin-free T7aM11

To a stirred solution of tetraphenylporphin (2.674 g, 4.3 mmoles) in 250 ml of chloroform was added a solution of cupric acetate monohydrate (1.30 g, 6.5 mmoles) in 250 ml glacial acetic acid. The mixture was stirred at reflux for 2 hr, cooled and filtered. The product was dried at 80°C/15 mm for 2 hr to yield 2.711 g (93%) of deep blue crystals. This reaction was repeated twice on the same scale with an average yield of 95%.

The copper tetraphenylporphin obtained was recrystallized twice from chloroform-methanol and dried at 100°C/0.5 mm for 16 hrs. The visible spectrum agrees well with the reported spectrum (ref. 6). See Table 2.

Analysis for $C_{44}H_{28}N_4Cu$

	C	H	N	Cu
Calc'd.	78.12	4.18	8.29	9.41
Found	77.93	4.37	7.97	9.39

The absence of copper chlorin impurity was confirmed by the absence of any absorption above 600 mμ in the visible spectrum.

(2) Method B - Chlorin-Containing Chelate (T7aM11-chlorin)-Small Scale Reaction (Figure 48)

Into each of 4 Carius tubes were placed benzaldehyde (4.25 ml, 4.43 g, 0.042 mole), pyrrole (2.75 ml, 2.27 g, 0.040 mole), and cupric acetate monohydrate (10.0 g, 0.050 mole). The tubes were flushed with nitrogen and sealed. They were placed in a revolving Carius furnace and heated at 180-200°C for 48 hours. The tubes were cooled and opened. The water was decanted and the brittle solid was pulverized and extracted overnight with 500 ml of chloroform in a Soxhlet apparatus. Removal of solvent yielded 29.3 g of black solid whose visible spectrum indicated presence of porphin.

The solid obtained was chromatographed over 1 kg of MCB alumina in column C. No definite bands were visible on the column so fractions of 100 ml of chloroform were collected and the visible spectrum examined for the presence of T7aM11. The first 7 cuts exhibited spectra similar to that reported for T7aM11 (ref. 2,6). Removal of the solvent *in vacuo* gave 8.53 g of product.

A portion of this solid (4.00 g) was rechromatographed over 200 g of Woelm alumina in column B using chloroform solvent. A red-brown band was the first to elute. Removal of solvent yielded 0.750 g of T7aM11 whose visible spectrum was similar to that reported (ref. 6) except for an extra peak at 617 mμ characteristic of Cu tetraphenyl chlorin (ref. 2).

The remainder of the product from the first chromatography (4.53 g), was rechromatographed on 200 g of Woelm alumina and the red-brown band collected. Removal of solvent yielded 1.07 g of T7aM11 making a total yield of 1.82 g (27.0%). Recrystallization of 0.750 g of this material from chloroform-methanol yielded 0.540 g of T7aM11-chlorin.

The sample submitted was prepared as above and the dried at 100°C/ 0.5 mm for 16 hr. Spectral analysis of the final product indicated approximately 8% chlorin by comparison of the extinction coefficients for pure Cu tetraphenylchlorin (λ 617, ref. 2) and pure Cu tetraphenylporphin (λ 540, ref. 6).

(3) Attempted Removal of Chlorin Impurity

(a) Chromatography

The chlorin-containing T7aM11 (4.352 g) from Method B was chromatographed a third time over 200 g of Woelm alumina in Column A. The reddish brown band was collected after elution with chloroform. The solvent was removed *in vacuo* to give 4.256 g of material that still exhibited the 617 mμ chlorin peak in the visible spectrum. A further recrystallization of this compound from chloroform-methanol failed to remove this peak.

(b) Reaction with Excess Cupric Acetate (ref. 2)

A 1.00 g sample of copper tetraphenylporphin from Method B was refluxed with cupric acetate monohydrate (0.500 g) in glacial acetic acid (100 ml). Samples of the reaction mixture were withdrawn and examined spectroscopically for the chlorin peak at 617 mμ. After 48 hr at reflux, this peak was still present. The mixture was cooled and the copper tetraphenylporphin filtered and dried. The product was recovered in 92% yield and had a spectrum identical to the product of Method B.

f. Cobalt (II) tetraphenylporphin (T7aM12) (ref. 5)

To a stirred solution of tetraphenylporphin (2.679 g, 4.4 mmoles) in 250 ml of chloroform in a 1000-ml Morton flask was added a solution of cobaltous acetate tetrahydrate (1.54 g, 6.2 mmole) in 250 ml glacial acetic acid. The mixture was stirred at reflux for 3/4 hr. Examination of the visible spectrum at that time indicated complete reaction, i.e., absence of bands above 590 mμ due to M15T7a. The mixture was cooled in an ice bath and filtered. The deep blue fluffy solid was dried at 80°C/15 mm for 2 hr to yield 2.842 g (100%).

In a second preparation of cobalt tetraphenylporphin using slightly larger amounts of tetraphenylporphin (3.62 g, 5.9 mmoles) and cobaltous acetate tetrahydrate (2.10 g, 8.4 mmoles), unreacted tetraphenylporphin was detected by absorption at 647 mμ even after 4 hr at reflux. The mixture was cooled and filtered. The crystals were dried at 80°C/15 mm for 2 hrs to yield 3.74 g (95%) of product which was extracted in a Soxhlet apparatus with 250 ml of methanol for 16 hr to remove unreacted M15T7a. Examination of the visible spectrum of the residual T7aM12 in the thimble showed only a very small peak at 647 mμ. This peak was removed completely in the subsequent recrystallization.

The T7aM12 was extracted in a Soxhlet apparatus with anhydrous ether (250 ml/g). This recrystallization proceeded very slowly as it appeared that digestion of the blue solid in refluxing ether produced small lustrous crystals that are not as soluble in ether as the fluffy solid. The 6.23 g of microcrystalline T7aM12 obtained by cooling the Et_2O extracts were extracted a second time. After two weeks of continuous extraction, only 1.39 g of product was obtained from the ether extracts while 4.51 g still remained in the thimble. The spectrum of the twice recrystallized product was identical to that of the material in the thimble so the extraction was discontinued.

Sample	λ (mμ)	ϵ	Reported (ref. 6)
Twice recrystallized	527	16,800	15,400
Once recrystallized	527	16,800	

The combined product was dried at 100°/0.5 mm for 16 hr. The spectral data are given in Table 2.

The products from the thimble and the ether extract are combined and dried at 100°C/0.5 mm for 16 hr.

Analysis for $C_{44}H_{28}N_4Co$

	C	H	N	Co
Calcd	78.68	4.20	8.34	8.78
Found	79.05	4.22	8.05	8.62

Thin layer chromatographic analysis of the analytical sample on talc (benzene), using a double development, indicated three components.

The analytical sample (4.86 g) was then chromatographed over 300 g of Woelm alumina in column A. The column was initially eluted with benzene.

Fractions (225 ml each)	Sample	Eluent	Visible Absorptions,mμ	wt. g
1-12	A	C_6H_6	418,528	1.79
13-17	B	C_6H_6	418,528,635	0.908
18-25	C	C_6H_6	418,528,635	1.443
26-29	D	C_6H_6	418,528,550,590,635	0.331
30-39	E	1:1 C_6H_6-$CHCl_3$	418,516,548,589,650	—
40-42	F	$CHCl_3$	418,525,589,645	0.073

The visible spectrum indicates that samples D and E are mainly tetraphenylporphin. Sample F eluted as a sharp, dark ring with chloroform and probably has structure L-2.

Samples A, B, and C were combined and placed in a Soxhlet apparatus and continuously extracted with methanol to insure that all unreacted M15T7a was removed. The extraction was continuous for one week.

The T7aM12 remaining in the thimble was dried at 100°C/0.5 mm for 16 hr and re-analyzed. The visible spectrum is given in Table 2.

Analysis for $C_{44}H_{28}N_4Co$

	C	H	N	Co
Calcd	78.68	4.20	8.34	8.78
Found	78.18	4.08	8.31	8.94

Thin layer chromatographic analysis on talc using C_6H_6-$CHCl_3$ gave two spots (R_f 0.00 and 0.80) provided that the plate was spotted heavily enough. It is not known whether the 0.00 spot is real.

An attempt at further purification by chromatography on Alcoa F-1 alumina using benzene as eluent gave only a single band indicating the chromatographic purity of the sample submitted.

g. Iron (III) tetraphenylporphin chloride (T7aM13) (ref. 5)

A mixture of 3.0 g of iron filings in 300 ml of glacial acetic acid was refluxed for 2 hr. The hot saturated ferrous acetate solution was filtered into a mixture of M15T7a (1.15 g, 1.86 mmoles) and sodium chloride (0.440 g, 7.5 mmoles) in 100 ml of chloroform. The mixture was stirred at reflux in a Morton flask for 2 hr. The volume of liquid was reduced to ca. 100 ml *in vacuo*. After cooling in an ice bath, the product was filtered and dried at 80°C/15 mm to yield 1.260 g (97%) of deep blue solid. The above reaction was repeated six times with an average yield of 99%.

The crude products were recrystallized by continuous extraction with chloroform (50 ml/g). The solution was concentrated to ca. 20 ml/g and hot methanol (160 ml/g) slowly added. After slow cooling, the recrystallized product was filtered and dried at 100°C/0.5 mm for 16 hr to give 6.3 g of blue crystals.

Analysis for $C_{44}H_{28}N_4FeCl$

	C	H	N	Fe	Cl
Calcd	75.06	4.01	7.96	7.93	5.04
Found	73.49	3.90	7.38	7.49	6.86

Because of the poor elemental analysis, the FeTPPCl obtained above was recrystallized again in the same manner. The extinction coefficients of the visible spectrum were not greatly changed by this recrystallization so 3.85 g of product was chromatographed over 500 g Woelm alumina in column C. Fractions of 500 ml volume were taken. The first 13 fractions were eluted with benzene, the remaining 34 fractions were eluted with benzene 80%-$HCCl_3$ 20%. The forerun, consisting of the first 25 fractions was a broad yellow band that yielded 0.368 g of solid. The visible spectrum of this solid was similar to that of tetraphenylporphin. A definite black band was eluted in two parts. The product from the first half of this band (fractions 25-29) yielded 1.374 g of blue solid (Sample A) with a visible spectrum of $\lambda_{max}^{C_6H_6}$ 687, 655, 570, 507, and 420 mμ [λ T7aM13, lit. (ref. 6) $\lambda_{max}^{C_6H_6}$ 685, 660, 573, 508, and 420 mμ]. The second half of the dark band, fractions 30-33, yielded 2.31 g of blue solid (Sample B) whose visible spectrum was slightly different from that of Sample A [$\lambda_{max}^{C_6H_6}$ 685, 610, 570, 510 (sh), and 420 mμ].

The infrared spectra of Samples A and B are identical.

Analysis		C	H	N	Fe	Cl	Total (%)
Calcd	$C_{44}H_{28}N_4FeCl$	75.06	4.01	7.96	7.93	5.04	100
Calcd	$C_{44}H_{28}N_4FeCl \cdot H_2O$	73.4	4.16	7.76	7.76	4.92	98
Found	Sample A	74.89	4.53	7.50	7.39	4.20	98.51
	Sample B	74.75	4.53	7.40	7.89	4.02	98.59

The purification continues.

Visible Spectrum (benzene)

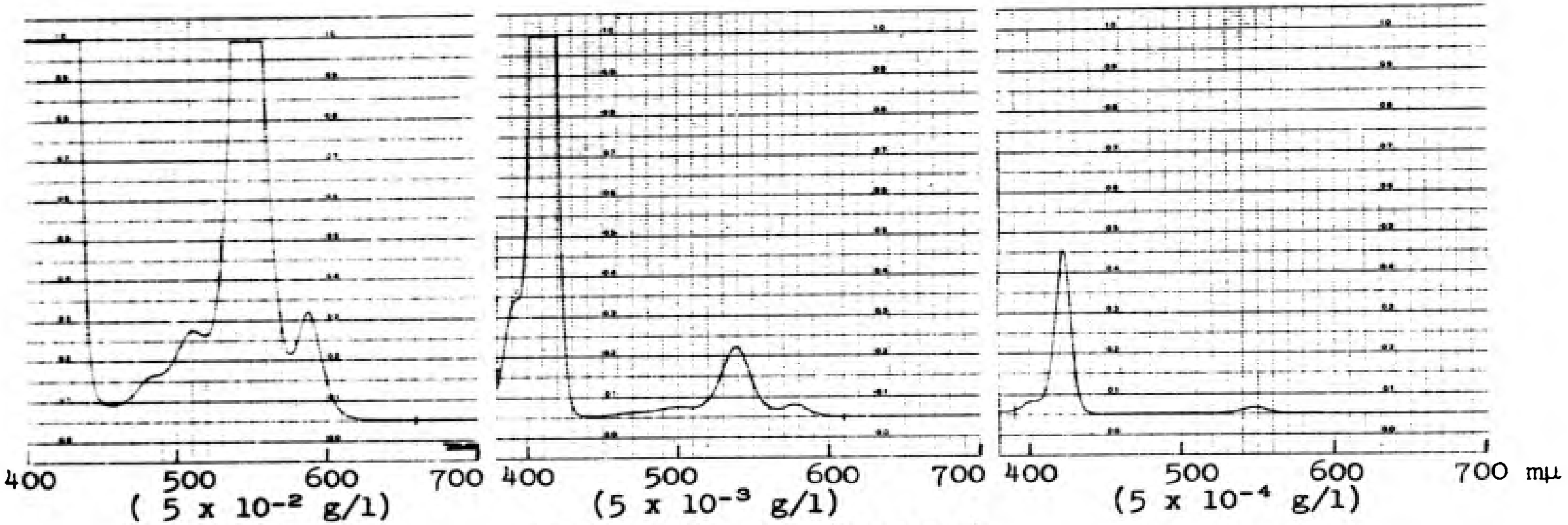
Sample A		Sample B		Reported (ref. 6)	
λ (mμ)	ϵ	λ (mμ)	ϵ	λ (mμ)	ϵ
690	3,060	611	3,200	685	2,960
656	Not calc.	–	–	656	2,600
573	3,900	571	6,850	574	3,340
508	11,800	502	6,850	511	11,000
418	104,000	412	93,900	419	94,000

8. References

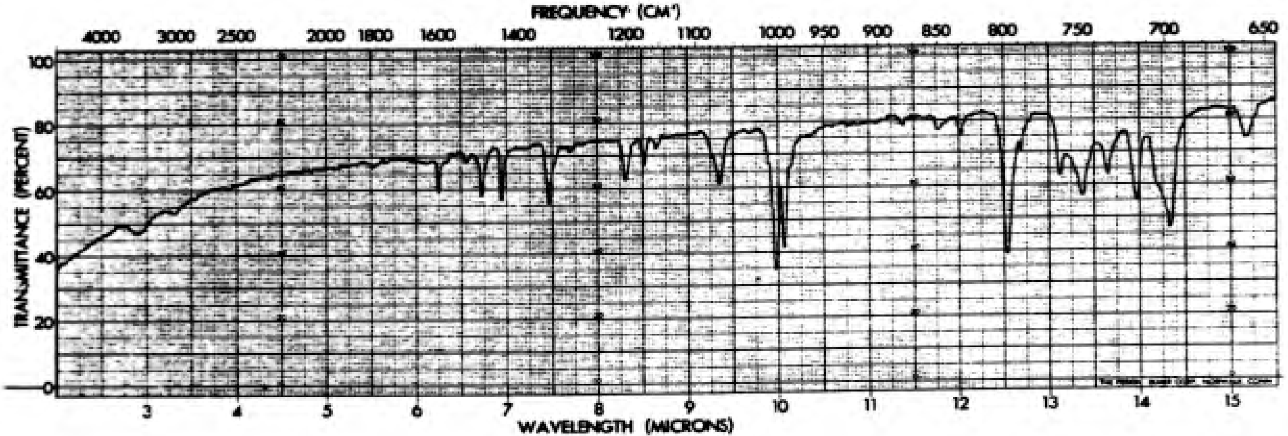
1. P. Rothemund and A. R. Menotti, J. Am. Chem. Soc., 63, 267 (1941).
2. R. H. Ball, G. D. Dorough and M. Calvin, J. Am. Chem. Soc., 68, 2278 (1946).
3. J. H. Priesthoff and C. V. Banks, J. Am. Chem. Soc., 76, 937 (1954).
4. D. B. Sharp, U. S. Patent, 2,950,237, Aug. 23, 1960. C.A., 52, 3290 (1962).
5. P. Rothemund and A. R. Menotti, J. Am. Chem. Soc., 70, 1808 (1948).
6. G. D. Dorough, J. R. Miller and F. M. Huennekens, J. Am. Chem. Soc., 73, 4315 (1951).
7. "Dictionary of Organic Compounds", I. Heilbron and H. M. Bunbury, Eds., Oxford, N.Y., 1953.

9. Spectra

Spectral data are given in Figures 50-59.

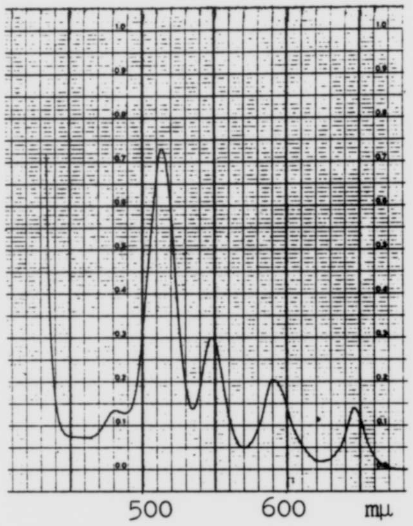


Visible Spectra (Benzene)

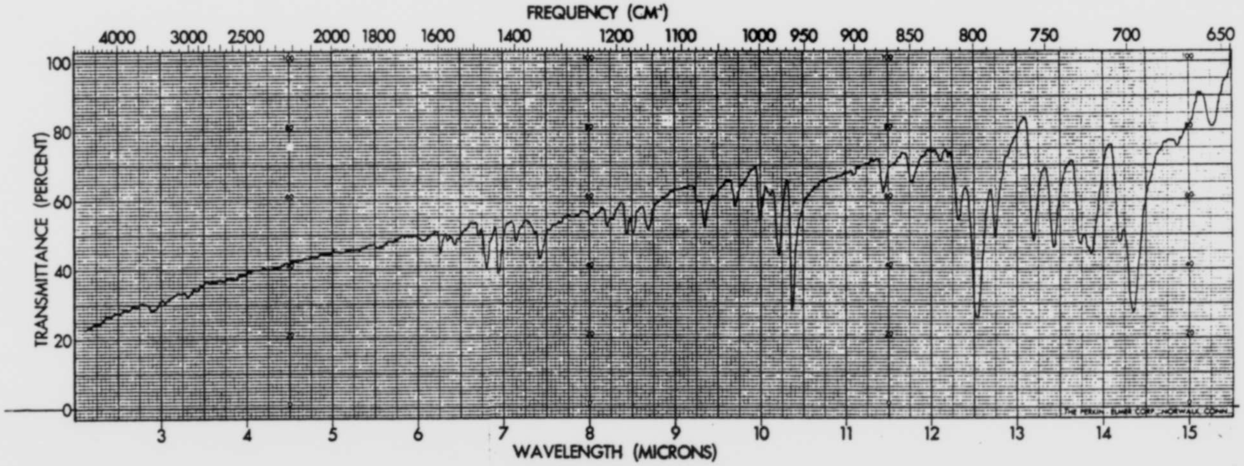


Infrared Spectrum (KBr Pellet)

Figure 50. Spectral Data on Zinc tetraphenylporphin (M16T7a)



Visible Spectrum (Benzene Solution)



Infrared Spectrum (KBr Pellet)

Figure 51. Spectral Data on Tetraphenylporphin (M15T7a)

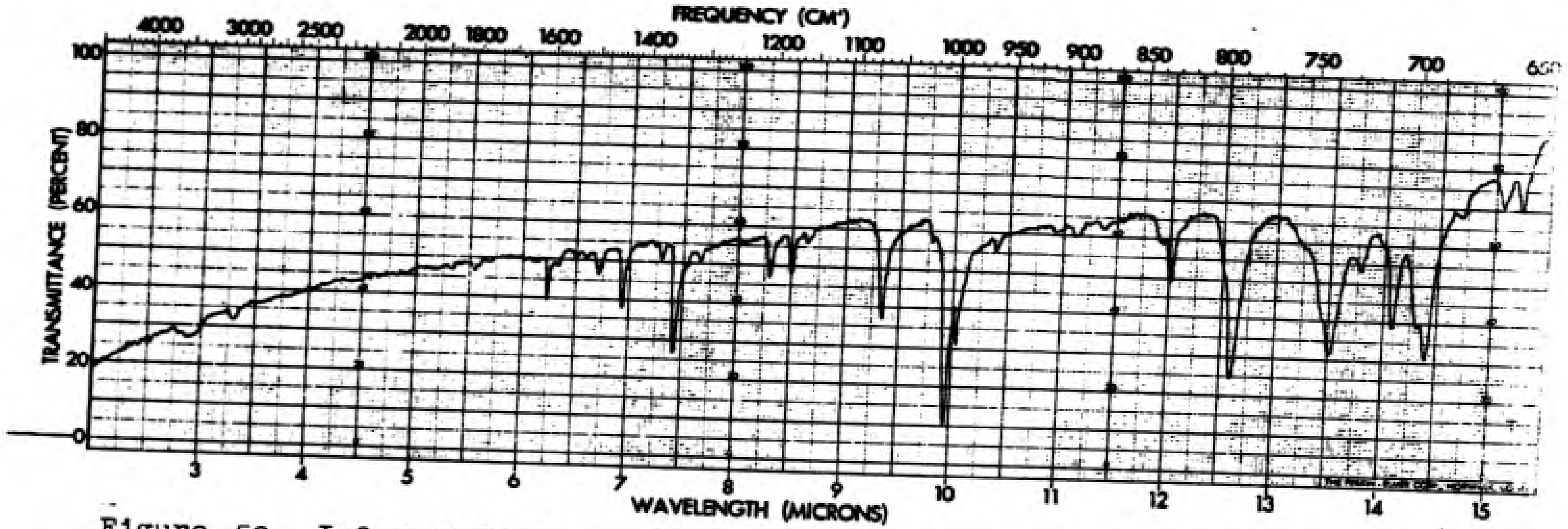
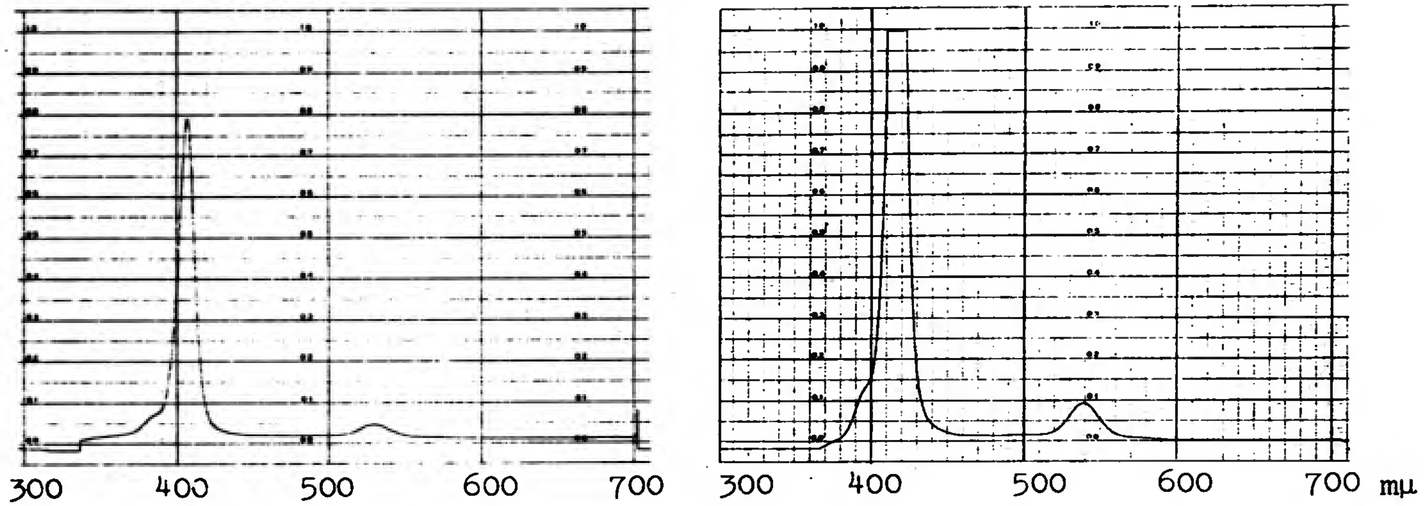
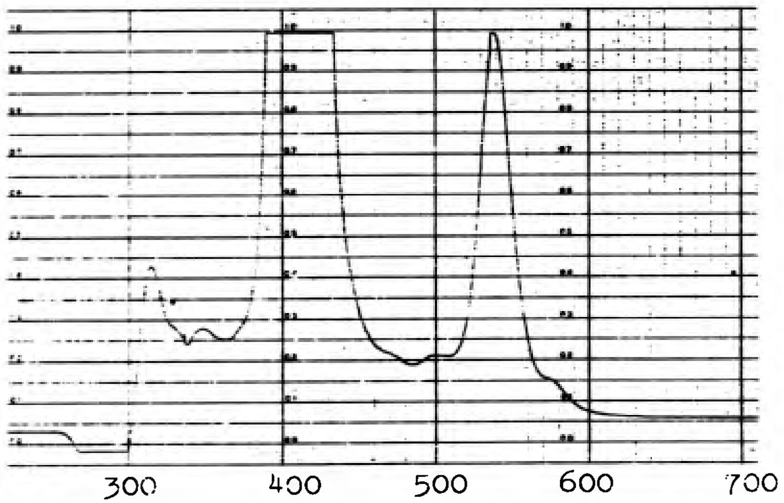


Figure 52. Infrared Spectrum (KBr Pellet) of Copper(II) tetraphenylporphin (T7aM11)



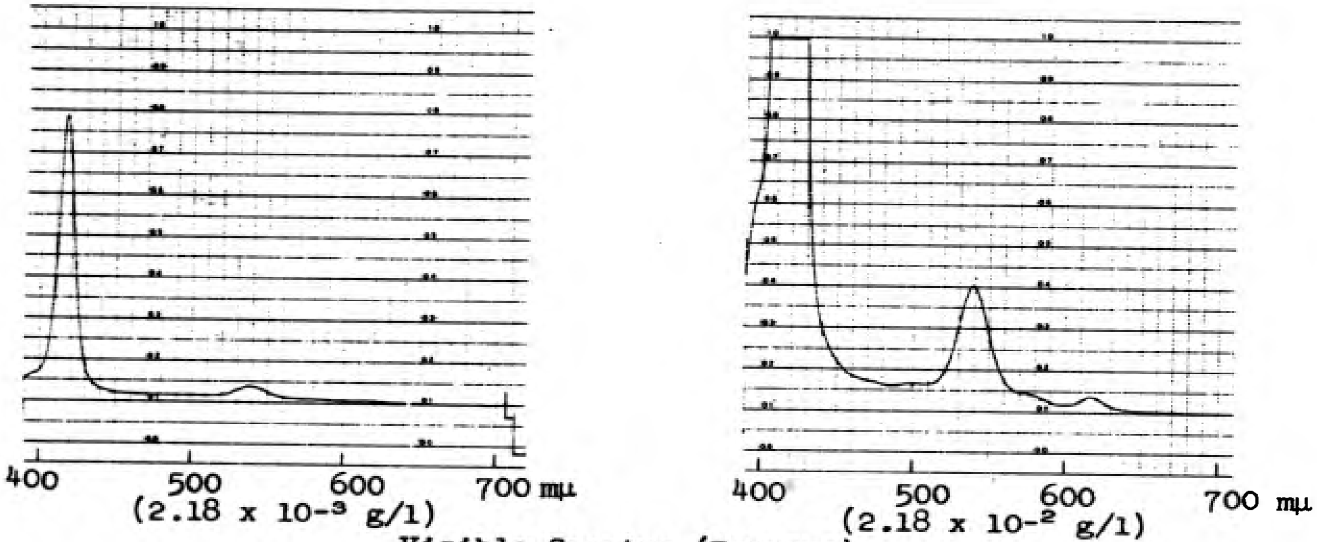
1 x 10^{-3} g/1

3 x 10^{-3} g/1

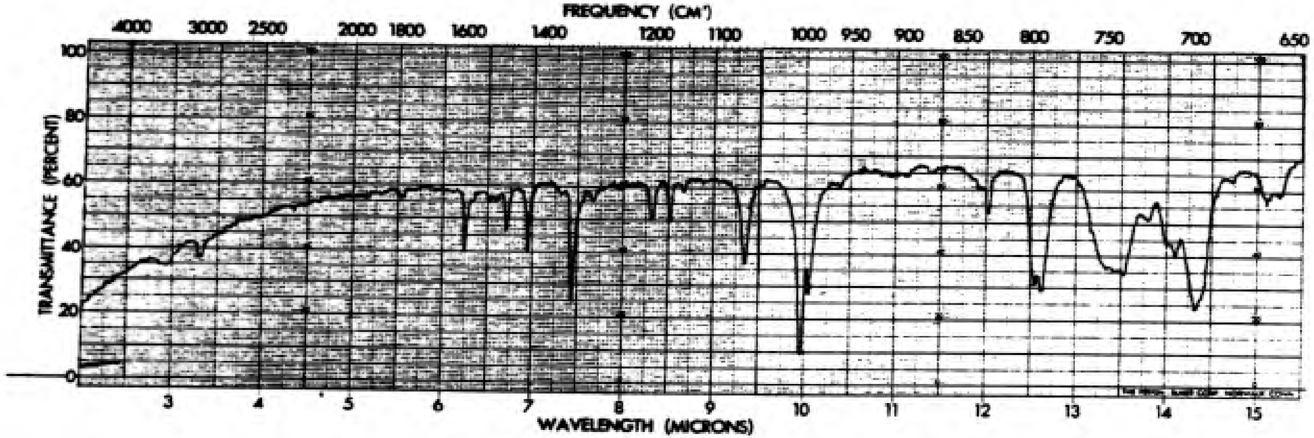


3 x 10^{-2} g/1

Figure 53. Visible and Near Ultraviolet Spectral Data (Benzene) on Copper (II) tetraphenylporphin (T7aM11)

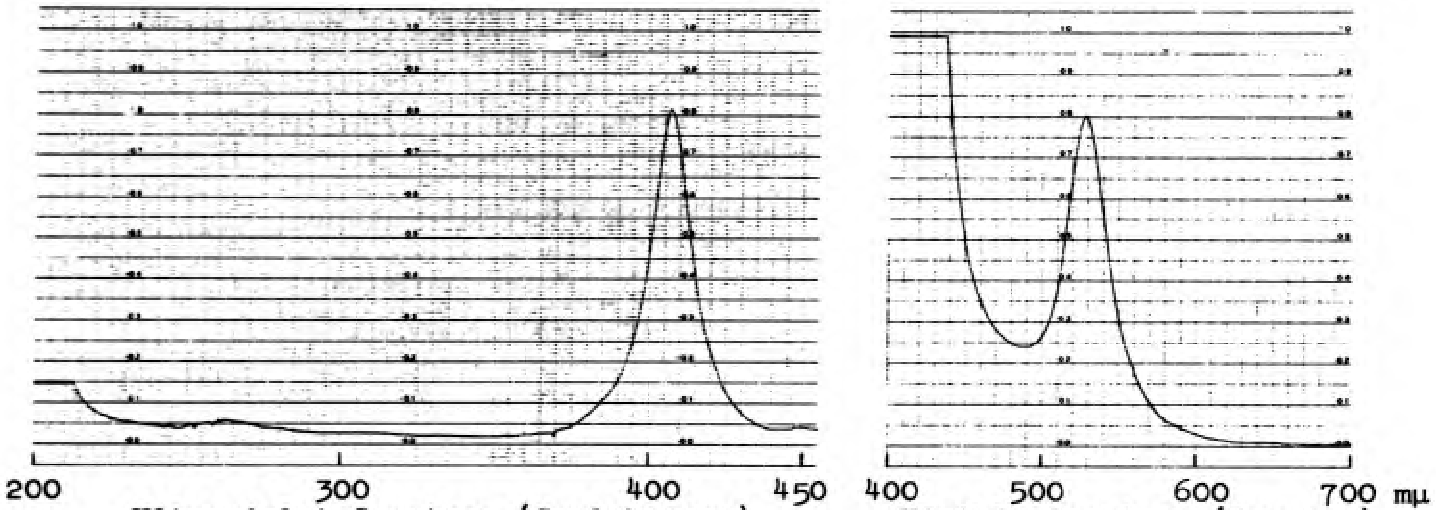


Visible Spectra (Benzene)



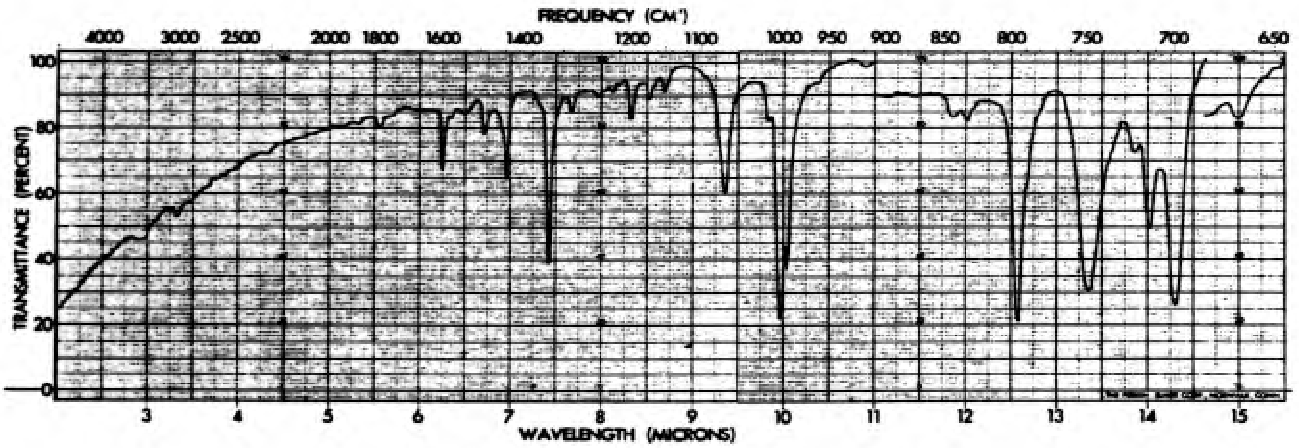
Infrared Spectrum (KBr Pellet)

Figure 54. Spectral Data on Copper (II) tetraphenylporphin-Chlorin



Ultraviolet Spectrum (Cyclohexane)

Visible Spectrum (Benzene)



Infrared Spectrum (KBr Pellet)

Figure 55. Spectral Data on Cobalt (II) tetraphenylporphin (T7aM12)

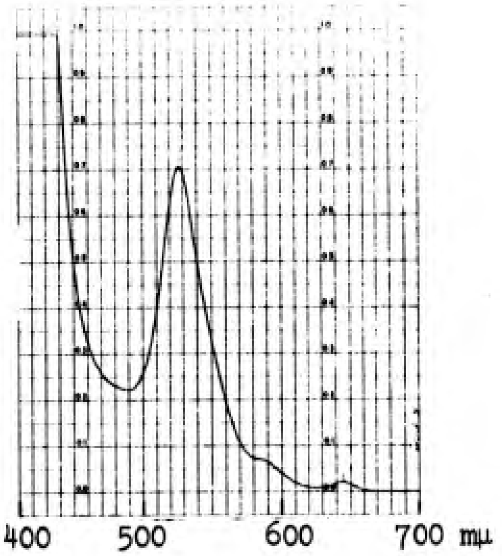


Figure 56. Visible Spectrum (Benzene) of Cobalt (III) tetraphenylporphin acetate hydrate (L-2)

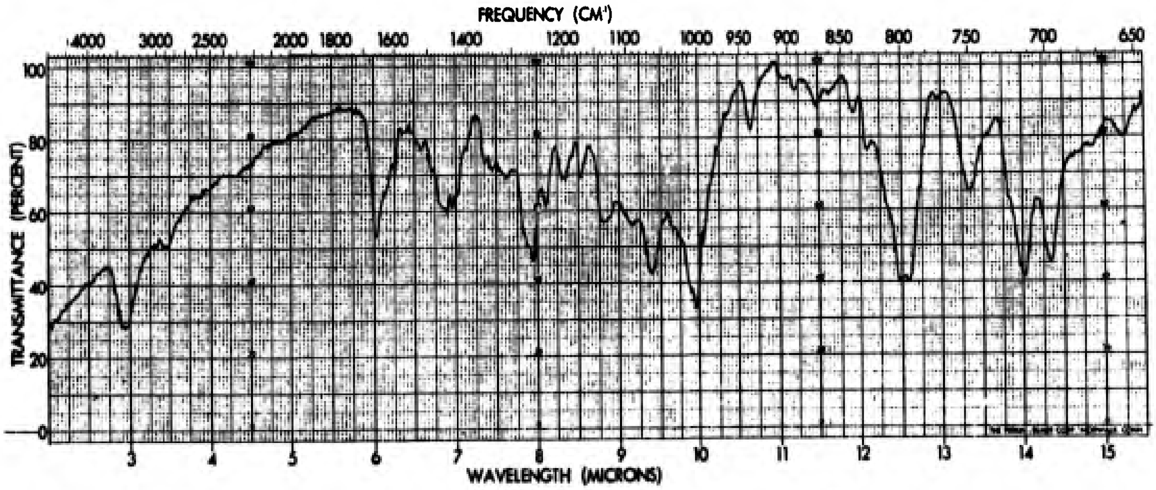


Figure 57. Infrared Spectrum (KBr Pellet) of Cobalt (III) tetraphenylporphin acetate hydrate (L-2)

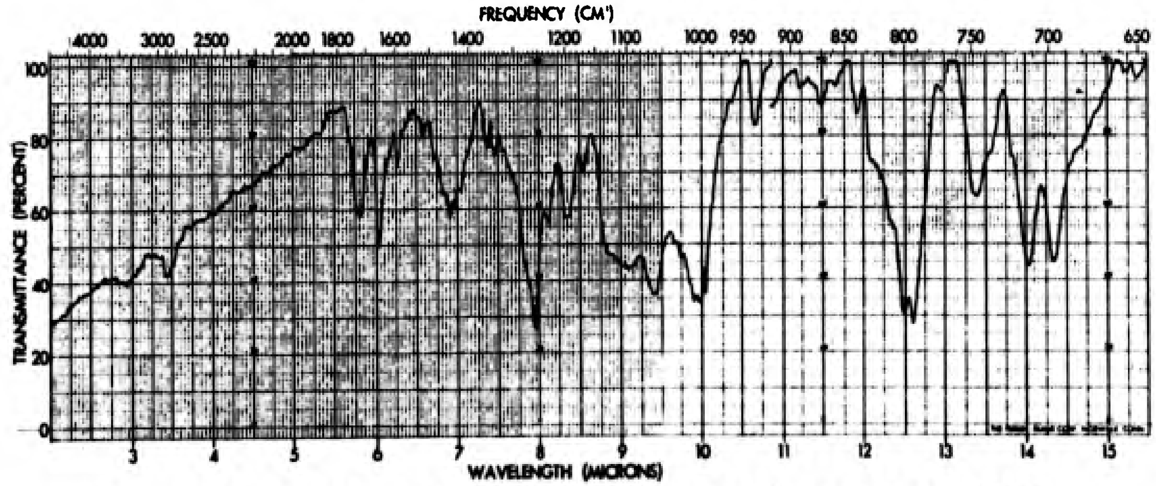
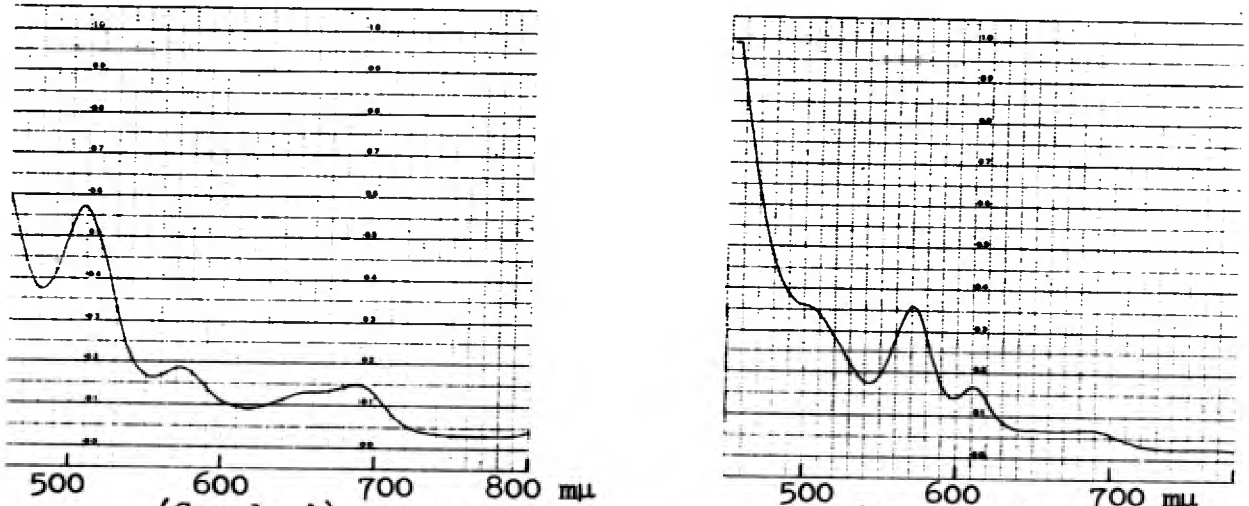


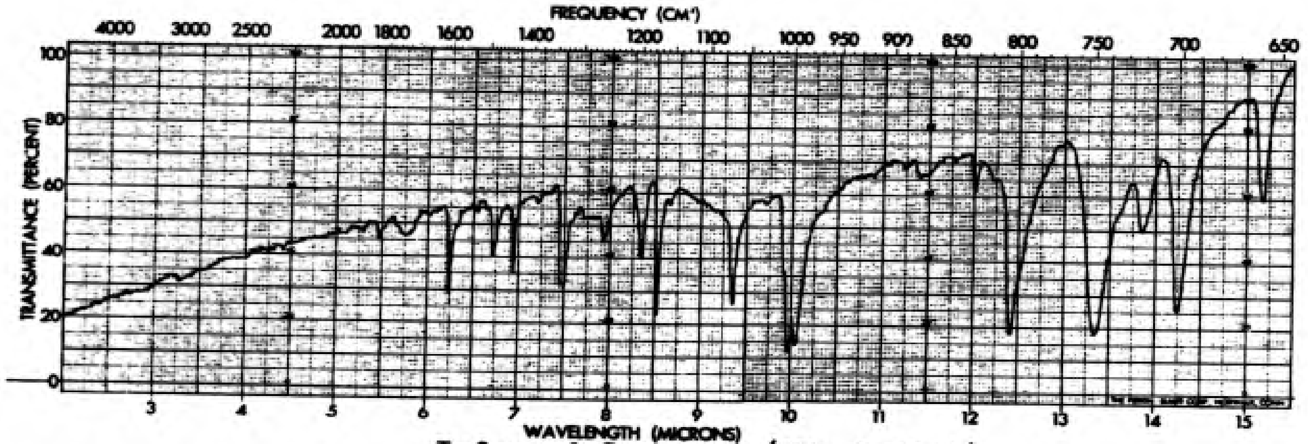
Figure 58. Infrared Spectrum (KBr Pellet) of Cobalt (III) tetraphenylporphin hydroxide-acetic acid complex (L-3)



(Sample A)

(Sample B)

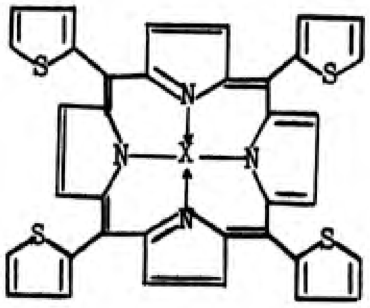
Visible Spectra (Benzene)



Infrared Spectrum (KBr Pellet)

Figure 59. Spectral Data on Iron (III) tetraphenylporphin chloride (T7aM13)

M. TETRATHIENYLPORPHIN CHELATES (M)



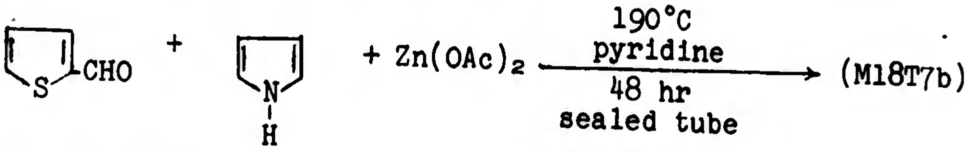
(M)

1. Discussion

The tetrathienylporphins (M) are less well known than the previously described tetraphenylporphins (II.L). The only known tetrathienylporphin reference is found in the patent literature (ref. 3). This reference discusses only tetrathienylporphin (M, X = 2H). The chelates are not described.

The route chosen to the requested copper, cobalt, and ferric tetrathienylporphins was through the zinc chelate and free base intermediates. This method was similar to the procedure used for the synthesis of the tetraphenylporphins (L).

2. Synthesis of Zinc tetrathienylporphin (M18T7b)(M, X = Zn^{+2})



a. Discussion

The use of pyridine as a reaction solvent appeared to yield better M18T7b samples than the "no solvent" method (see II.L). A large amount of a black, chloroform-soluble, benzene-insoluble side product was produced during the synthesis of M18T7b. It was found to be advantageous to extract the crude reaction product with benzene (rather than chloroform; see II.L) before chromatography in order to avoid adding the black, non-porphin material to the column.

Better quality tetrathienylporphin (M-1) was obtained if the zinc chelate (M18T7b) was chromatographed twice before hydrolysis. The yields of pure M18T7b were about 4%.

b. Proof of Structure

(1) Spectra

While the infrared spectrum is not of much use in the structure proof of M18T7b, it is not inconsistent with the structure.

There are no literature values for the visible absorption of M18T7b. The spectrum is, however, similar to that of zinc tetraphenylporphin (see II.L.9) and is that expected for a zinc porphin chelate.

(2) Reaction Product

The structure of M18T7b can be assumed to be that assigned since the known compound, tetrathienylporphin (M-1) is produced from M18T7b on hydrolysis.

c. Purity

The sample of M18T7b submitted to the Air Force had been chromatographed over alumina three times.

The T.L.C. sample showed two spots on talc with either acetone (R_f0.00 and 0.90) or 1:1 benzene-chloroform (R_f0.00 and 0.70). It is not known whether the spots at the origin are real.

d. Air Force Sample

Two samples of M18T7b (2.0 and 0.5 grams, total 2.5 grams) under nitrogen were submitted to the Air Force on 4 March 1964.

Although M18T7b was not a requested compound, it was submitted as a dye of possible future interest.

3. Synthesis of Tetrathienylporphin (M-1)(M, X = 2H)

$$\text{M18T7b} \xrightarrow[\text{(2) } NH_4OH]{\text{(1) HCl}} \text{(M-1)}$$

The crude M-1 obtained from the hydrolysis of twice-chromatographed M18T7b appears to be of high quality. Our M-1 extinction coefficients are slightly lower than the values previously reported (ref. 4). Chromatographic purification of M-1 results in large material losses.

If a sufficient amount of M-1 remains after the three requested chelates have been prepared, a sample of this dye will also be submitted to the Air Force.

4. Synthesis of Copper tetrathienylporphin (M-2)(M, X=Cu^{+2})

$$(\text{M-1}) + \text{Cu(OAc)}_2 \xrightarrow[\text{HOAc}]{\text{CHCl}_3} (\text{M-2})$$

M-2 is prepared from tetrathienylporphin and cupric acetate in yields of about 70%. The crude product contains unreacted M-1, although it cannot be detected in the visible spectrum of M-2. One chromatographic purification removed this impurity, but reduced the yield of M-2 by 50%. The analysis of the purified dye agrees with the theoretical values (see II.M.7.e). M-2 gives one thin-layer chromatographic spot on talc with benzene-chloroform. This compound will be submitted as soon as the data sheets are completed.

5. Synthesis of Cobalt tetrathienylporphin (M-3)(M, X = Co^{+2})

$$(\text{M-1}) + \text{Co(OAc)}_2 \xrightarrow[\text{HOAc}]{\text{CHCl}_3} (\text{M-3})$$

Poor yields and tetrathienylporphin contamination have plagued this reaction. The chromatographic purification of M-3 is not as clean as in the case of copper analog (M-2). This reaction is still under investigation.

6. Synthesis of Iron (III) tetrathienylporphin chloride (M-4) (M, X = Fe^{+3}, Cl^-)

$$(\text{M-1}) + \text{Fe(OAc)}_3 \xrightarrow[\text{HOAc}]{\substack{\text{CHCl}_3 \\ \text{NaCl}}} (\text{M-4})$$

This synthesis is still in the exploratory stage. The chromatographic behavior of M-3 appears to be similar to that of iron (III)tetraphenylporphin chloride.

7. Experimental

a. Starting Materials

Pyrrole (Eastman, 500 g - \$6.60) was redistilled under nitrogen through an 8-inch Vigreux column, [bp 130-131°C, lit. (ref. 1), bp 130-131°C] and stored under nitrogen until used.

2-Thienylcarboxaldehyde (Columbia Chemicals, 100 g - \$18.00) was redistilled at reduced pressure through an 8-inch Vigreux column, [bp 75°C/10 mm; lit. (ref. 2), bp 73.5°C/11 mm] and stored under nitrogen until used.

Inorganic Reagents and Solvents were reagent-grade and were used without further purification.

b. Chromatographic Materials, Procedures and Pyrolysis Equipment

These are described in section II.L.7 of this report.

c. Zinc tetrathienylporphin (M18T7b)

Three large Carius tubes (Fig. 49) were flushed with nitrogen and charged to approximately one-half their volume with pyrrole (20.0 ml, 19.4 g, 0.288 mole), 2-thienylcarboxaldehyde (40.0 ml, 48.6 g, 0.414 mole), zinc acetate dihydrate (20.0 g, 0.092 mole), and pyridine (40.0 ml). The tubes were sealed under nitrogen and heated at 190°C for 48 hr in the manner described for zinc tetraphenylporphin (M16T7a) (see II.L.7). The tubes were cooled and opened, and contents were poured into 1500 ml of distilled water. The dark semi-solid product was pulverized under water, and the black solid was filtered and dried *in vacuo* at 100°C/15 mm for 4 hr. The black powder was extracted in a *Soxhlet* apparatus with benzene until the extracts were colorless. The benzene extracts exhibited bands in the visible spectrum characteristic of porphins, i.e., Soret peak *ca.* 420 mμ plus minor peaks from 430 to 600 mμ. The solvent was removed *in vacuo* and the dark solid was dried at 80°C/15 mm for 2 hr to *yield* 123.6 g of black solid. This material was chromatographed in 30-g portions over MCB alumina (1 g/33 g alumina) in column C using benzene as eluant. The black solid was allowed to settle at the top of the column. It slowly dissolved as more benzene was added. The light yellow forerun was discarded. The broad, deep green band eluted as a maroon solution. An average of twenty-five 450-ml fractions was collected in each chromatography. Later fractions were quite dilute as evidenced by light coloration. All fractions exhibited the same general visible spectrum, i.e., $\lambda_{max}^{C_6H_6}$ Soret, 488 (sh), 520 (sh), 555 and 600 mμ. At times, the later fractions (22 to 25) also exhibited an extra peak at 630 mμ. The solvent was removed *in vacuo* and the blue solid dried at 70°C/15 mm for 2 hr. The yield *of M18T7b* obtained after one chromatography was 17.71 g. A total of 3.22 g of material was also obtained that had an extra peak at 630 mμ.

The combined product was rechromatographed in 10-g portions over Woelm alumina (1 g/50 g alumina) in column C using benzene as solvent. No forerun was obtained. Again, the green band was eluted as a maroon solution. The visible spectrum was the same as that of the earlier fractions of the first chromatography. No extra peak at 630 mμ was ever detected. The combined yield of M18T7b after two chromatographies was 6.61 g (4.3% yield). All the zinc tetrathienylporphin (M18T7b) used as starting material for tetrathienylporphin (M-1) was prepared in the above manner. The yield was 4 to 8% after two chromatographies.

The sample of zinc tetrathienylporphin submitted as sample M18T7b was prepared as above and chromatographed a third time on Woelm alumina using benzene in column B, $\lambda_{max}^{C_6H_6}$ 557 mμ (ε 18,000), 431 mμ (ε 362,000).

d. Tetrathienylporphin (M-1)

Zinc tetrathienylporphin (3.27 g, 4.65×10^{-3} mole), which had been twice chromatographed, was dissolved in 500 ml of chloroform and the solution rapidly stirred with 350 ml of 6N hydrochloric acid in a Morton flask for 2 hr. The flask was cooled in ice bath while the reaction mixture was neutralized to pH 7.0 with conc. ammonium hydroxide. The water layer was removed and the chloroform solution was washed with three 350-ml portions of distilled water. Chloroform was added as needed to keep the M-1 in solution. The chloroform solution was separated and dried over anhydrous sodium sulfate.

Filtration of the desiccant and evaporation of the solvent *in vacuo* yielded a purple-blue solid, which was dried at 80°C/15 mm for 2 hr to give 2.10 g (71%) of product. The M-1 thus prepared was sufficiently pure to be used in the preparation of the copper chelate. The visible spectrum, $\lambda_{max}^{C_6H_6}$ 657, 597, 560, 522, and 428 mμ, was similar to that reported by Sharp (ref. 4). M-1 (0.80 g), prepared as above, was chromatographed over 50 g of Woelm alumina (benzene) in column A. A single, dark green band was eluted as a maroon solution in eleven 200-ml fractions. Since the visible spectra of all fractions were identical, the fractions were combined and the solvent was removed *in vacuo*. The resulting product was dried at 70°C/15 mm for 2 hr to give 0.42 g of blue solid. The quantitative visible spectrum is reported below.

Wavelength, mμ	ε*	ε**
657	1,516	7,500
597	4,202	5,800
560	6,004	8,500
522	13,114	19,400
428	276,000	366,000

---

*found

**ref. 4

The difference in ε values is under investigation.

e. Copper(II) tetrathienylporphin (M-2)

To a stirred solution of tetrathienylporphin (2.27 g, 3.6×10^{-3} mole), in 250 ml of chloroform, was added a solution of cupric acetate monohydrate (1.44 g, 7.2×10^{-3} mole), in 250 ml of glacial acetic acid. The mixture was stirred at reflux for 2 hr, cooled in an ice bath, and filtered. The product was dried at 70°C/15 mm for 2 hr to yield

1.74 g (69%) of deep blue crystals. This reaction was repeated three times on the same scale with an average yield of 72%.

The copper tetrathienylporphin obtained (ca. 7 g) was chromatographed over Woelm alumina (1 g/150 g alumina) and eluted with a petroleum ether (30-60°C)-benzene mixture (1:3 by vol). The brown-red M-2 band was cleanly separated from a definite green band that remained in the top third of the column. Removal of solvent *in vacuo* and drying at 70°C/15 mm for 2 hr gave 3.34 g of M-2. This solid was dissolved in chloroform, and filtered to remove any alumina. The solvent was removed *in vacuo*, and the solid dried at 100°C/0.5 mm for 16 hr [$\lambda_{max}^{C_6H_6}$ 548 mμ (ϵ19,700), 424 mμ (ϵ350,000)].

Analysis for $C_{36}H_{20}N_4S_4Cu$

	C	H	N	S	Cu
Calcd	61.73	2.88	8.00	18.31	9.07
Found	61.93	3.36	7.76	18.36	8.83

f. Cobalt(II)tetrathienylporphin (M-3)

To a stirred solution of tetrathienylporphin (0.638 g, 1x10^{-3} moles) in 50 ml of chloroform was added a solution of cobaltous acetate tetrahydrate (0.374 g, 1.5x10^{-3} mole) in 50 ml glacial acetic acid. The mixture was stirred at reflux for 2 hr. At that time, the visible spectrum of the reaction mixture indicated no unreacted tetrathienylporphin. The solution was allowed to cool slowly for 30 minutes and then was chilled in an ice bath and filtered. The product was dried at 80°C/15 mm for 2 hr to yield 0.39 g (55%) of blue solid.

Attempts to increase this yield by (1) evaporating the chloroform layer, (2) using only glacial acetic acid as solvent, and (3) using pyridine as solvent were unsuccessful.

The M-3 obtained above was chromatographed over 50 g of Woelm alumina in column A and eluted with a mixture of 30-60°C petroleum ether-benzene (1:3 by vol). A broad red band was followed by a dark green band on the column. The red band was eluted as six 125-ml fractions. The visible spectrum of these fractions showed $\lambda_{max}^{C_6H_6}$ 535 and 420 mμ. Removal of solvent and drying at 80°C/15 mm for 2 hr yielded 0.19 g of blue solid.

Fractions 7-12 showed contamination with unreacted tetrathienylporphin.

g. Iron (III) tetrathienylporphin chloride (M-4)

To a stirred solution of tetrathienylporphin (0.500 g, 7.9x10^{-4} mole) and sodium chloride (0.200 g, 3.4x10^{-3} mole) in 50 ml of chloroform was added 150 ml of a hot filtered solution of ferric acetate, prepared by refluxing 150 ml of acetic acid over iron filings (1 g) for 3 hr. The reaction mixture was refluxed for 2 hr and then evaporated to dryness *in vacuo*. The reddish solid was extracted thoroughly with four 100-ml portions of benzene. Removal of the benzene *in vacuo* and drying of the product at 80°C/15 mm for 2 hr yielded 0.41 g (70%) of blue solid.

This sample of M-4 was chromatographed over 50 g of Woelm alumina and initially eluted with benzene. A light green band was very slowly eluted in the first fifteen 250-ml fractions, while the broad, dark band had traveled one-third of the way down the column. When the solvent was then changed to a (3:1 by vol) mixture of benzene-chloroform, the dark band was eluted completely in three 200-ml fractions. The solvent was removed and the resulting product dried at 80°C/15 mm for 2 hr to yield 0.08 g of black solid, tentatively identified as M-4.

8. References

1. "Dictionary of Organic Compounds", I. Heilbron and H. M. Bunbury, Eds., Oxford, N. Y., 1953.

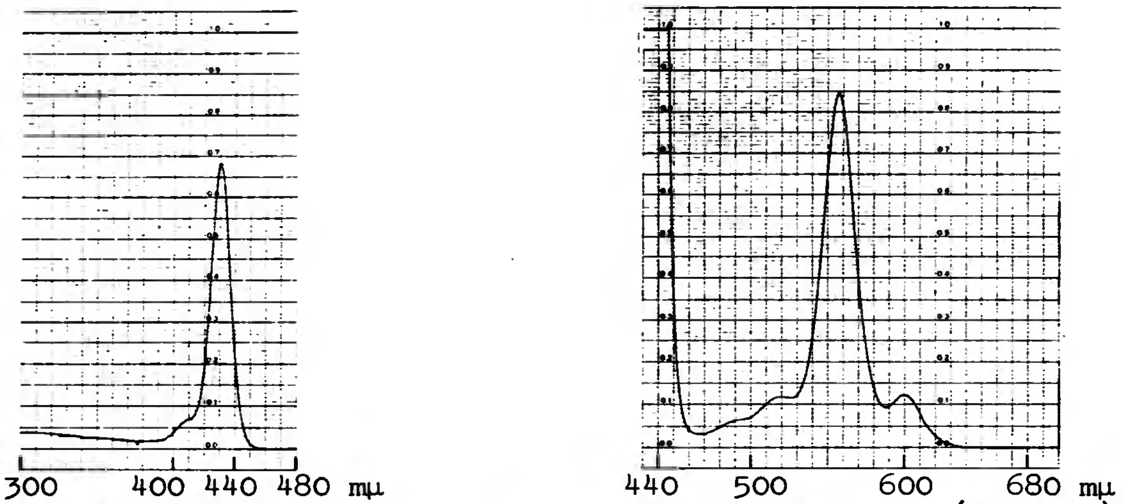
2. G. H. Jeffery, R. Parker and A. I. Vogel, *J. Chem. Soc.*, 570 (1961).

3. D. B. Sharp, U. S. Patent 2,950,237, Aug. 23, 1960, *C.A.*, *57*, 3289 (1962).

4. D. B. Sharp, private communication.

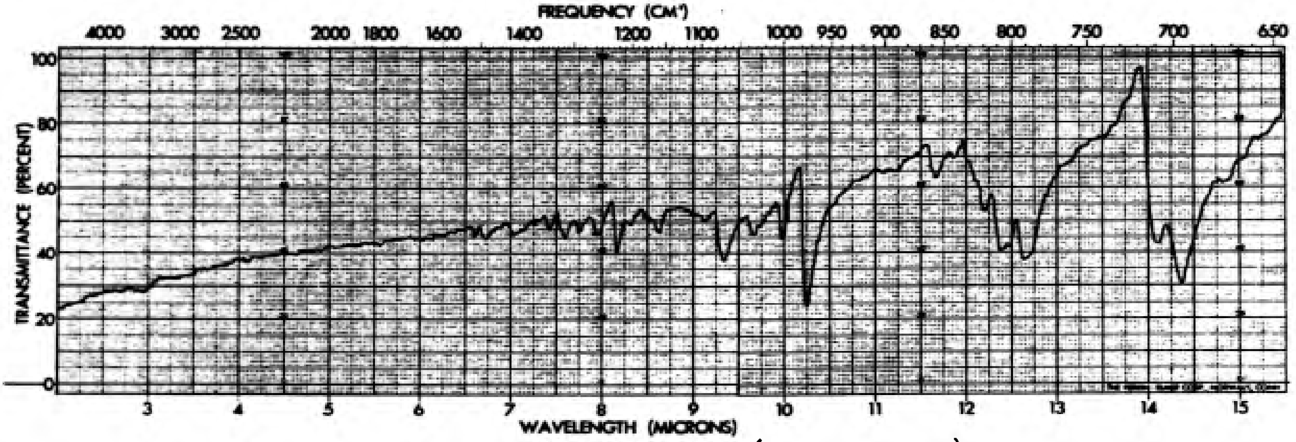
9. Spectra

Spectral data are given in Figures 60-64.



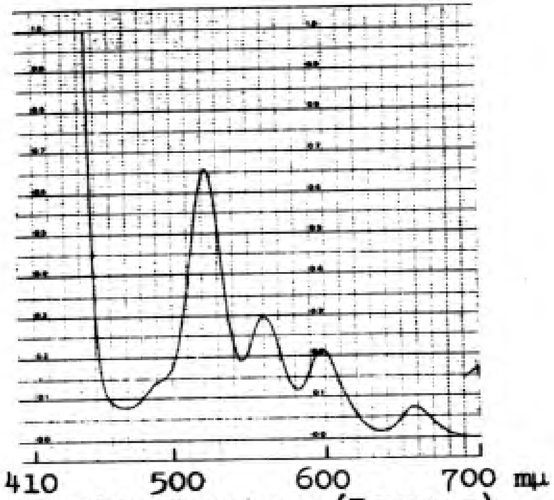
Ultraviolet Spectrum (Benzene) (1.32 x 10^{-3} g/l)

Visible Spectrum (Benzene) (3.3 x 10^{-2} g/l)

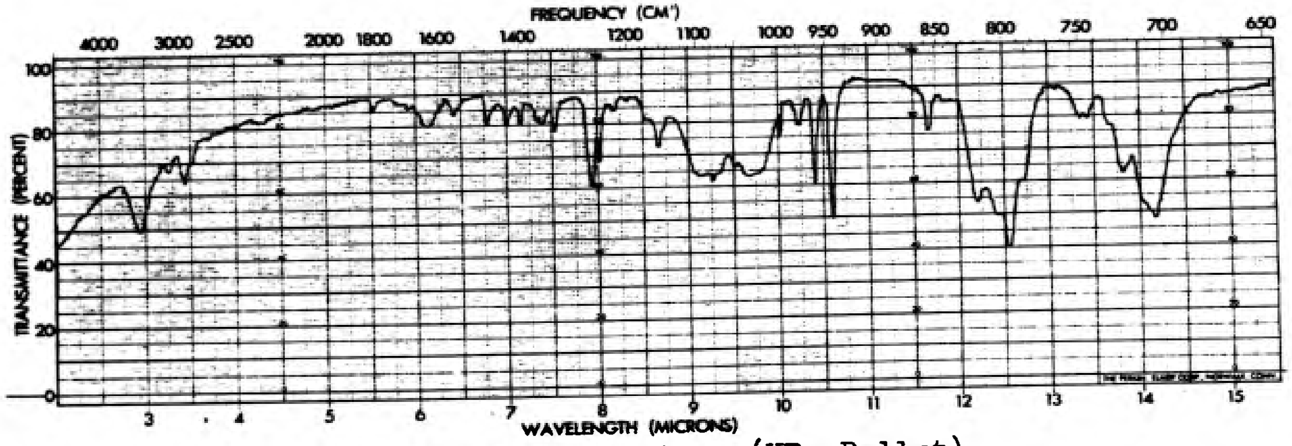


Infrared Spectrum (KBr Pellet)

Figure 60. Spectral Data on Zinc tetrathienylporphin (M18T7b)

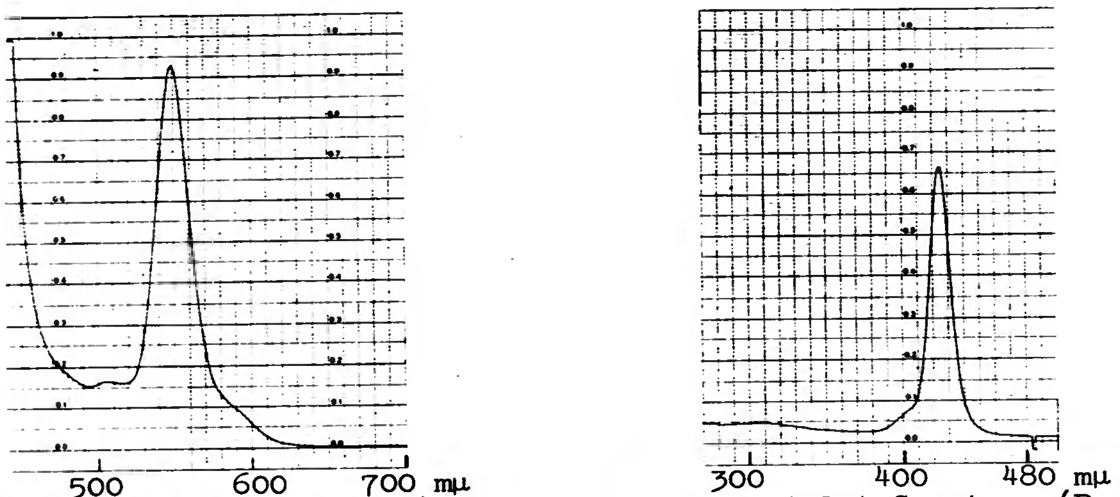


Visible Spectrum (Benzene)



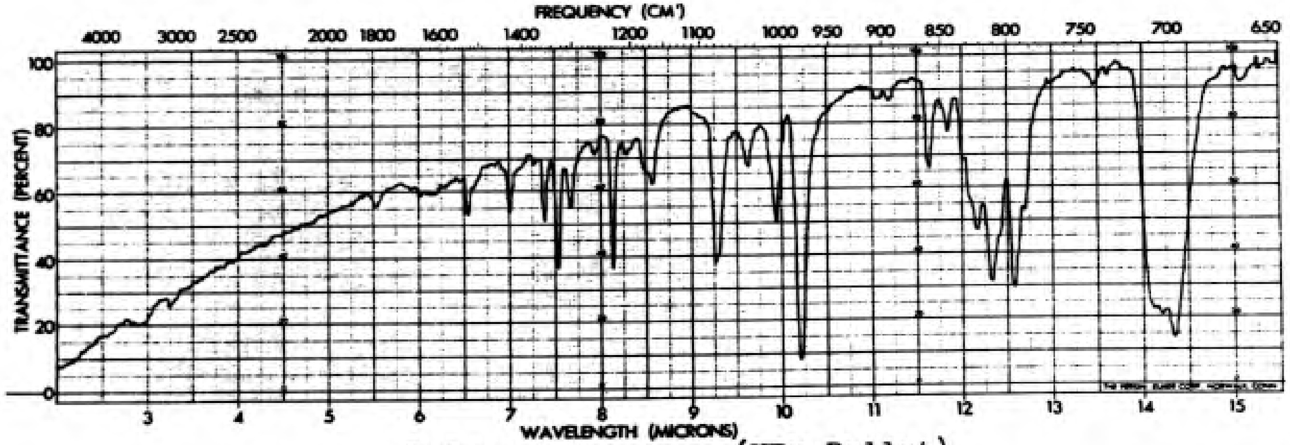
Infrared Spectrum (KBr Pellet)

Figure 61. Spectral Data on Tetrathienylporphin (M-1)



Visible Spectrum (Benzene)

Ultraviolet Spectrum (Benzene)



Infrared Spectrum (KBr Pellet)

Figure 62. Spectral Data on Copper (II) tetrathienylporphin (M-2)

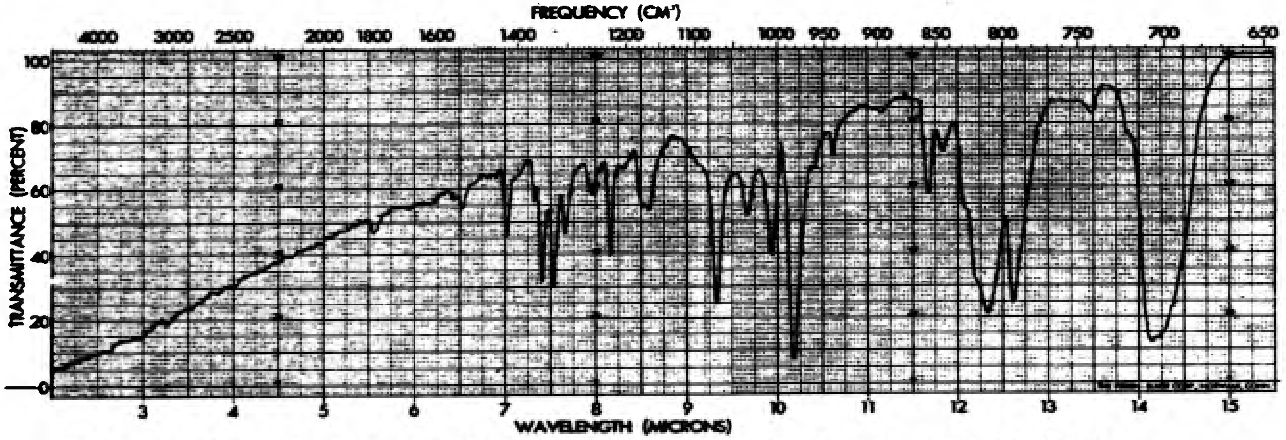


Figure 63. Infrared Spectrum (KBr Pellet) of Cobalt (II) tetrathienylporphin (M-3)

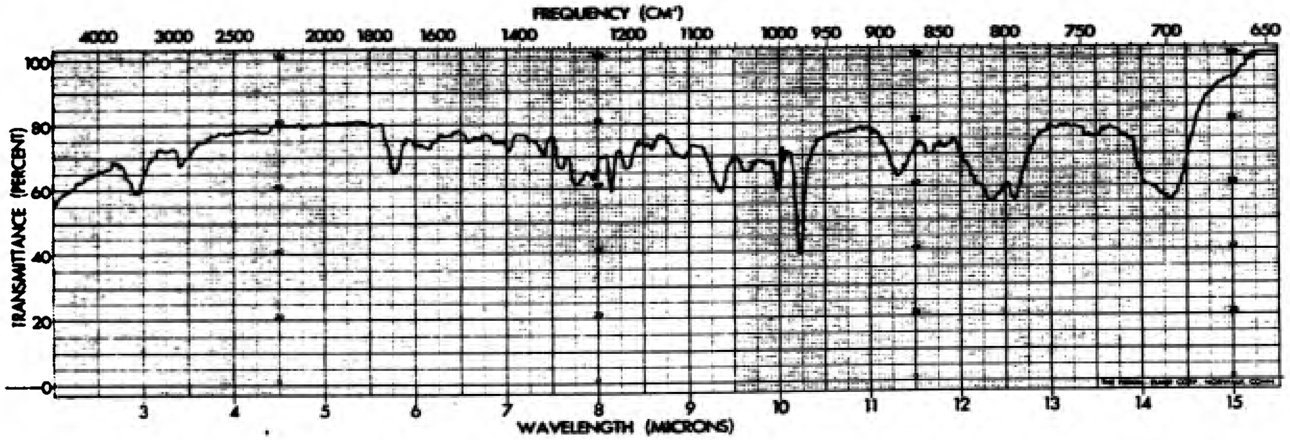
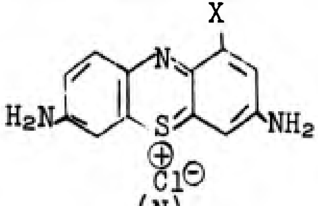


Figure 64. Infrared Spectrum (KBr Pellet) of Iron (III) tetrathienylporphin chloride (M-4)

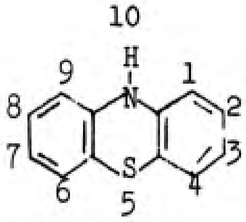
N. 1-SUBSTITUTED THIONINE DYES (N)


(N)

X = CH_2COOH, CH_2CH_2COOH,
CH_2CH_2OH, $CH_2CH_2NH_2$

1. Discussion

The object of this investigation is to provide analytically pure 3,7-diaminophenothiazonium salts that are substituted in the 1-position with the groups indicated above.


(phenothiazine numbering)

Two general synthetic methods were considered;

(1) the preparation and condensation of small molecules, i.e., anilines and thiophenols, to form N, and

(2) modification of phenothiazine (N-1) by substitution reactions.

The latter method was chosen after a review of the current phenothiazine (chloropromazine) contract literature (ref. 21) which illustrated the difficulties innerent in the first method.

The synthesis work to date has been directed towards the modification of phenothiazine by:

(1) placement of the amino groups in the proper positions (via nitration-reduction)

(2) introduction of a one-, two-, or three-carbon chain into the 1-position.

2. Introduction of Amino Groups into Phenothiazine (Table 3)

a. 3,7-Dinitrophenothiazine Sulfoxide (N-2)

N-2 was prepared by the method of Kehrmann (ref. 3). The initially-formed orange precipitate, originally identified as the "mononitroderivative" (ref. 3), was found to be identical with N-2, the dinitro compound.

The infrared spectrum of N-2 shows N-H and aromatic C-H stretching at 3247 and 3053 cm^{-1}, respectively. The C=C stretching bands are at higher frequencies than in phenothiazine (N-1) indicating the addition of nitro groups. Nitro absorptions are seen at 1515 and 1325 cm^{-1}. The strong absorptions at 750 and 735 cm^{-1} in N-1, which are assigned to the four adjacent ring hydrogen atoms, are not present in N-2, indicating substitution has taken place. The assignment of the 743 cm^{-1} absorption to a low frequency nitro vibration was confirmed by subsequent reduction reactions (see N-5). Bands at 843 and 830 cm^{-1} can indicate two adjacent ring hydrogens, but these absorptions do not distinguish between 2- and 3-position substitution. No 1050 cm^{-1} S-O absorption is seen, but a sulfoxide is suspected by analogy with N-11 (see II.N.3.d) and the incomplete, but indicative, analysis for N-2 (ref. 3).

b. 7-Amino-3-phenothiazime (N-4) and Hydrochloride (N-5) (Thionine)

The catalytic reduction of N-2 in methanol resulted in a light green solution, presumably containing 3,7-diaminophenothiazine (N-3), i.e., leucothionine. Exposure to the air resulted in an immediate color change, which indicated the oxidation of N-3 to N-4. Addition of hydrogen chloride to N-4 gave the hydrochloride, N-5, which was shown to be thionine by comparison of its visible and infrared spectra with that of an authentic sample. N-4, N-5 and commercially obtained thionine had identical visible spectra (λ_{max}^{EtOH} 604 mμ).

The infrared spectra of N-4 and N-5 are similar. N-5 does not show the nitro absorptions present in the starting material, N-2. The enhanced 3100-2400 cm^{-1} absorption in N-5 may be due to $=\overset{\oplus}{N}H_2$.

3. Introduction of a One-Carbon Chain into Phenothiazine (Table 4)

a. 1-Carboxyphenothiazine (N-7)

N-7 was prepared by the method of Gilman (ref. 4). The infrared spectrum of the product is in agreement with the structure proposed on the basis of an indirect structure proof (ref. 4).

The infrared spectrum indicates bonded O-H at 3000-2400 cm^{-1} and O-H deformation at 905 cm^{-1}. The carboxyl absorption at 1667 cm^{-1} is low for an aryl acid and indicates intramolecular hydrogen bonding. This finding also supports 1-substitution. The N-H stretch

Table 3

INTRODUCTION OF AMINO GROUPS INTO PHENOTHIAZINE

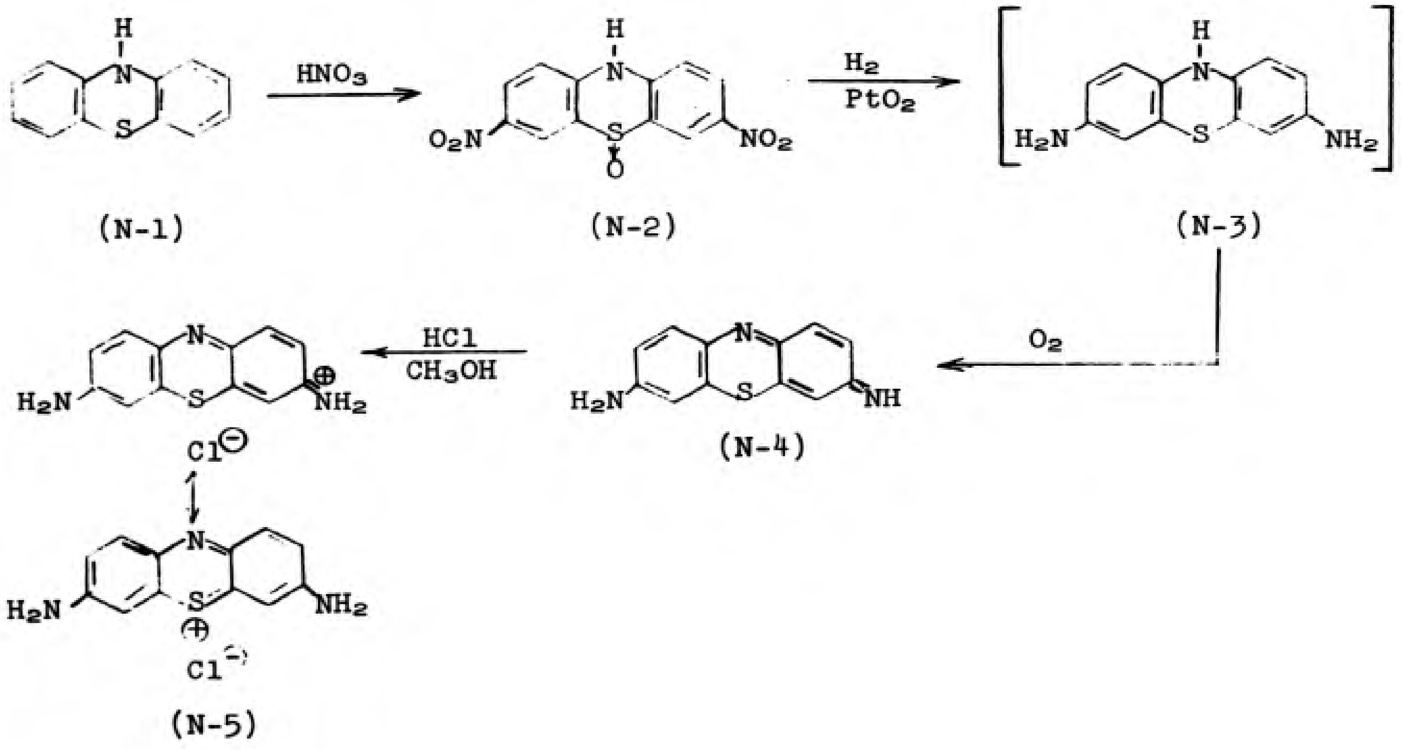
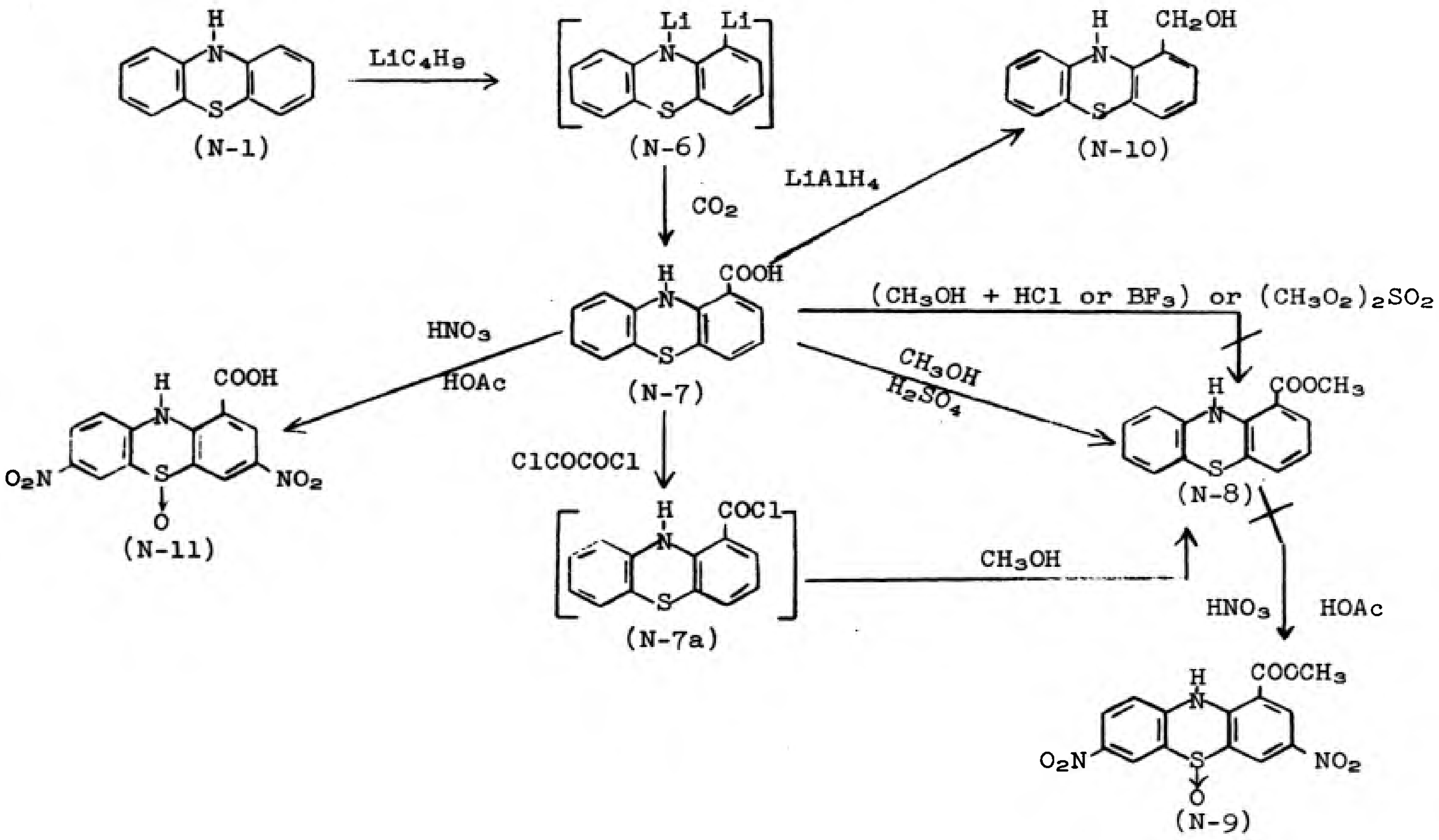


Table 4

INTRODUCTION OF A ONE-CARBON CHAIN INTO PHENOTHIAZINE



is similarly lowered from 3316 cm^{-1} in N-1 to 3289 cm^{-1} in N-7. The bands at 1433, 1274, 1256, and 1225 cm^{-1} are assigned to C-O stretching. Absorptions at 1597, 1565, 1502, and 1486 cm^{-1} are C=C stretching vibrations. Strong absorptions around 750 cm^{-1} can be assigned to the four adjacent hydrogen atoms on one ring and the three on the other.

Protection of the phenothiazine amino group by alkylation (benzylation) before carboxylation would have advantages in many of the routes devised for the preparation of N. Unfortunately, when a 10-alkyl substituent is present, phenothiazine carboxylates in the 4- rather than the 1-position (ref. 13,14) (see, however, ref. 23).

b. 1-Carbomethoxyphenothiazine (N-8)

A number of unsuccessful or only partially successful attempts were made to esterify N-7. The literature procedure (dimethylsulfate) (ref. 4) did not yield the desired product. The reaction of the acid chloride (N-7a) with methanol gave a mixture of N-7 and N-8. Oxalyl chloride (ref. 6) was used to prepare N-7a since thionyl chloride had been reported to cause the nuclear chlorination of 2-chlorophenothiazine (ref. 7). Attempted catalysis of the esterification with hydrogen chloride (ref. 8) or boron trifluoride (ref. 8) gave starting material. Sulfuric acid catalysis gave the desired ester, N-8, in yields of 40 per cent.

The carboxyl O-H absorptions (3000-2400 and 905 cm^{-1}) of the starting material, N-7, are not seen in the infrared spectrum of N-8. The ester carbonyl is seen at 1689 cm^{-1}, a reasonable frequency for an aryl ester. The bands at 748 and 755 cm^{-1} can be assigned to the four and three adjacent ring hydrogens, respectively. The N-H stretch is at 3257 cm^{-1} with aromatic C=C at 1600 (split), 1565, 1499, and 1486 cm^{-1}. The C-O stretch is at 1250 cm^{-1}. The attempted nitration of N-8 to produce N-9 was unsuccessful.

c. 1-Hydroxymethylphenothiazine (N-10)

N-10 was prepared as a possible precursor for lengthening the carbon chain at the 1-position.

$$\underset{R}{\overset{}{CH_2OH}} \xrightarrow{TsCl} \underset{R}{CH_2OTs} \xrightarrow{KCN} \underset{R}{CH_2CN} \xrightarrow{H_2O} \underset{R}{CH_2COOH}$$

Lithium aluminum hydride reduction of the acid, N-7, gave a compound with the correct elemental analysis for N-10. While the 2-hydroxymethyl compound is known (ref. 10), the 1-isomer is new.

All evidence for a carboxylic acid group has disappeared from the infrared spectrum of N-10. The absorption at 3356 cm^{-1} is probably a combination of free O-H and N-H. Aliphatic C-H stretching is seen at 2874 cm^{-1} while the band at 1004 cm^{-1} is assigned to C-O stretching. The spectrum is consistent with the structure.

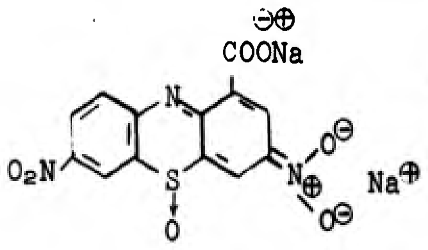
d. 1-Carboxy-3,7-dinitrophenothiazine sulfoxide (N-11)

The nitration of 1-carboxyphenothiazine (N-7) with nitric acid in acetic acid should give 3,7-substitution as was found for phenothiazine (Table 3). The influence of the 1-carboxylic acid group on the phenothiazine nucleus should be to decrease the reaction rate and direct substitution into the 3-position. A product was obtained that gave a correct elemental analysis for N-11.

The infrared spectrum of N-11 shows N-H and aromatic C-H stretching at 3226 and 3067 cm^{-1}, respectively. Bonded O-H is found at 2900-1800 cm^{-1}. The increase in the carboxyl carbonyl frequency from 1667 cm^{-1} in N-7 to 1695 cm^{-1} in N-11 indicates the introduction of a nitro group into the ring bearing the carboxyl group. The 985 cm^{-1} absorption is O-H deformation. Nitro absorptions are found at 1527, 1333, and 745 cm^{-1}.

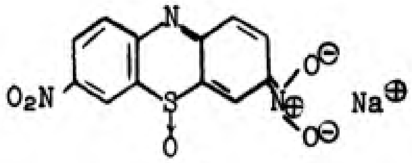
The 745 cm^{-1} band is assigned to a low frequency nitro absorption rather than four adjacent hydrogens (which would indicate mononitration) since this band disappears on reduction of the nitro groups (see N-13). A number of bands are noted in the 950-790 cm^{-1} region making the assignments for two adjacent hydrogen and a lone hydrogen deformation impossible. While the spectrum is consistent with the structure, it does not, alone, establish the positions of the substituents.

The visible and ultraviolet spectra of the di-anion of N-11 (see N-15) in 0.1N sodium hydroxide were similar to the spectra of the mono-anion of 3,7-dinitrophenothiazine sulfoxide (N-2a).



(N-15)

λ_{max} 500, 225 mμ

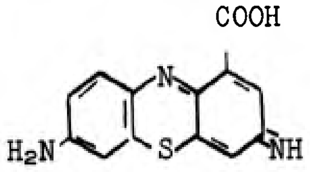


(N-2a)

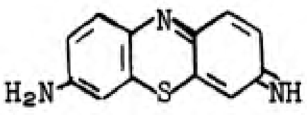
λ_{max} 485, 223 mμ

This evidence supports 3,7-dinitro-substitution.

The catalytic reduction of N-11 followed by air-oxidation of the resulting amino compound gave a dye (see N-13) with the same shaped curve and absorption maximum as found with 7-amino-3-phenothiazime (N-4).



(N-13)



(N-4)

These data, when considered with the spectral data of other dinitrophenothiazines (ref. 9), allow quite certain assignment of the nitro groups in N-11 to the 3,7-positions.

4. Reactions of 1-Carboxy-3,7-dinitrophenothiazine sulfoxide (N-11) (Table 5)

a. 1-Carboxy-7-amino-3-phenothiazime (N-13)

The catalytic reduction of N-11 was analogous to the reduction of N-2 in that the intermediate amino compound was air-oxidized to a thionine dye. The oxidation of N-12, however, was considerably slower than that of N-3.

The visible spectrum of N-13, which has been discussed previously (see II.N.3.d), offers good evidence for the proposed structure. The infrared spectrum of N-13 is very similar to the non-carboxyl-containing dye, N-4. The carboxyl absorption is not easily identified, but the band at 950 cm^{-1} may be O-H bonding. The spectrum favors the N-13 structure over the zwitter-ion, N-13a.

b. Mono- and Disodium Salts of N-11 (N-14 and N-15)

When slightly less than one equivalent of sodium hydroxide was added to N-11, a red monosodium salt (N-14) was formed. The infrared spectrum of N-14 has a 1626 cm^{-1} absorption that is probably an ionized carboxyl frequency. The nitro absorptions are in about the same positions as in the acid, N-11.

When more than one equivalent of sodium hydroxide is added, a purple solid is obtained that has an infrared spectrum in which the nitro absorptions are shifted relative to N-11. This is evidence for aci-nitro salt formation. The visible spectrum of N-15 has been discussed previously (see II.N.3.d).

c. Attempted Esterification of N-11

The methyl ester of N-11 was desired because it was felt that the ester group could be reduced to an alcohol with the proper metal hydride complex (ref. 11) without affecting the nitro groups. Nitro groups are preferable to amino groups during the cyanide chain extension reaction (see next page).

$$\text{R-OH} \longrightarrow \text{ROTs} \longrightarrow \text{RCN} \longrightarrow \text{R-COOH}$$

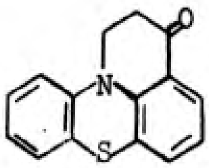
since phenothiazines with amino groups in the 3- and 7-positions are easily hydrolyzed and oxidized (ref. 12).

The esterification of N-11 is much more difficult than that of N-7. Sulfuric acid or boron trifluoride catalysis was unsuccessful. This is probably due to the electron withdrawing effect of the nitro groups on the character of the carboxyl carbonyl bond. The synthesis of the ester through the acid chloride with oxalyl chloride was probably hindered by the meta nitro group (ref. 6). However, preliminary results utilizing the sodium salt (N-14) for the preparation of the acid chloride are promising.

5. Introduction of a Two- or Three-Carbon Chain into the 1-Position of Phenothiazine (Table 6)

a. Discussion

A multicarbon chain can be introduced into the 2-position of the phenothiazine nucleus by the Friedel-Crafts reaction (ref. 15,16). The potential for a 3-carbon chain in the 1-position is available in 2,3-dihydro-3-keto-1H-pyrido[3,2,1-kl]phenothiazine (N-21) (ref. 17), but many steps are necessary to convert N-21 into N.



(N-21)

More reasonable as an intermediate is structure N-16. Alcoholysis would ring-open the cyclic amide giving rise to a 3-carbon β-keto-ester in the 1-position.

b. Introduction of a Three-Carbon Chain

The ease of carboxylation of 1,10-dilithiophenothiazine (N-6) with carbon dioxide suggested that a three-carbon bridge might be added by the reaction of N-6 with malonyldichloride. The reaction was carried out at low temperature, utilizing both modes of addition, since both addition methods have advantages. A similar product (N-16) was obtained in both instances.

The infrared spectrum of N-16 was very poor. This was probably caused by lithium chloride in the sample and the rigidity of the tetracyclic structure. The presence of lithium chloride was

Table 5

REACTIONS OF 1-CARBOXY-3,7-DINITROPHENOTHIAZINE SULFOXIDE (N-11)

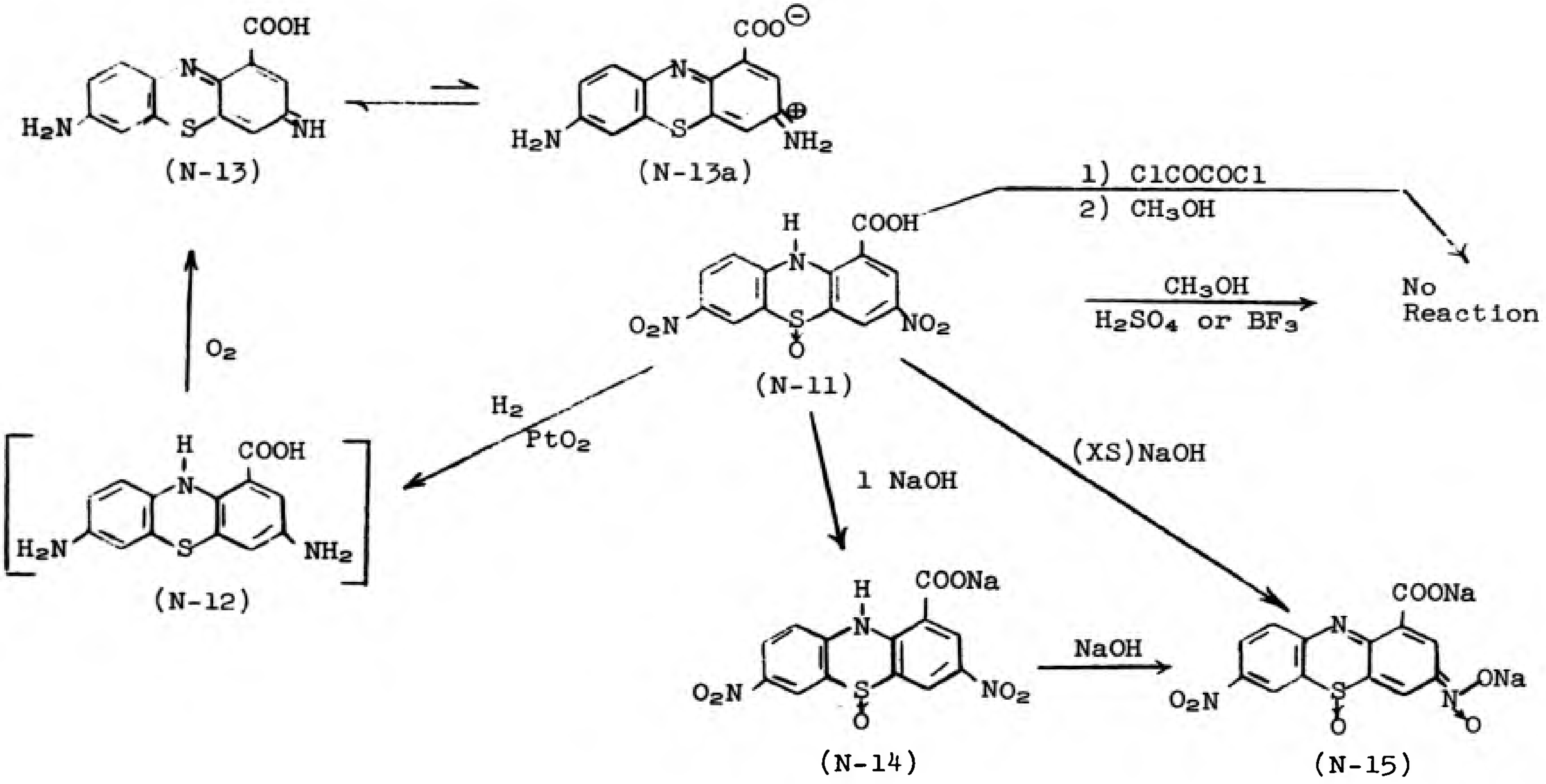
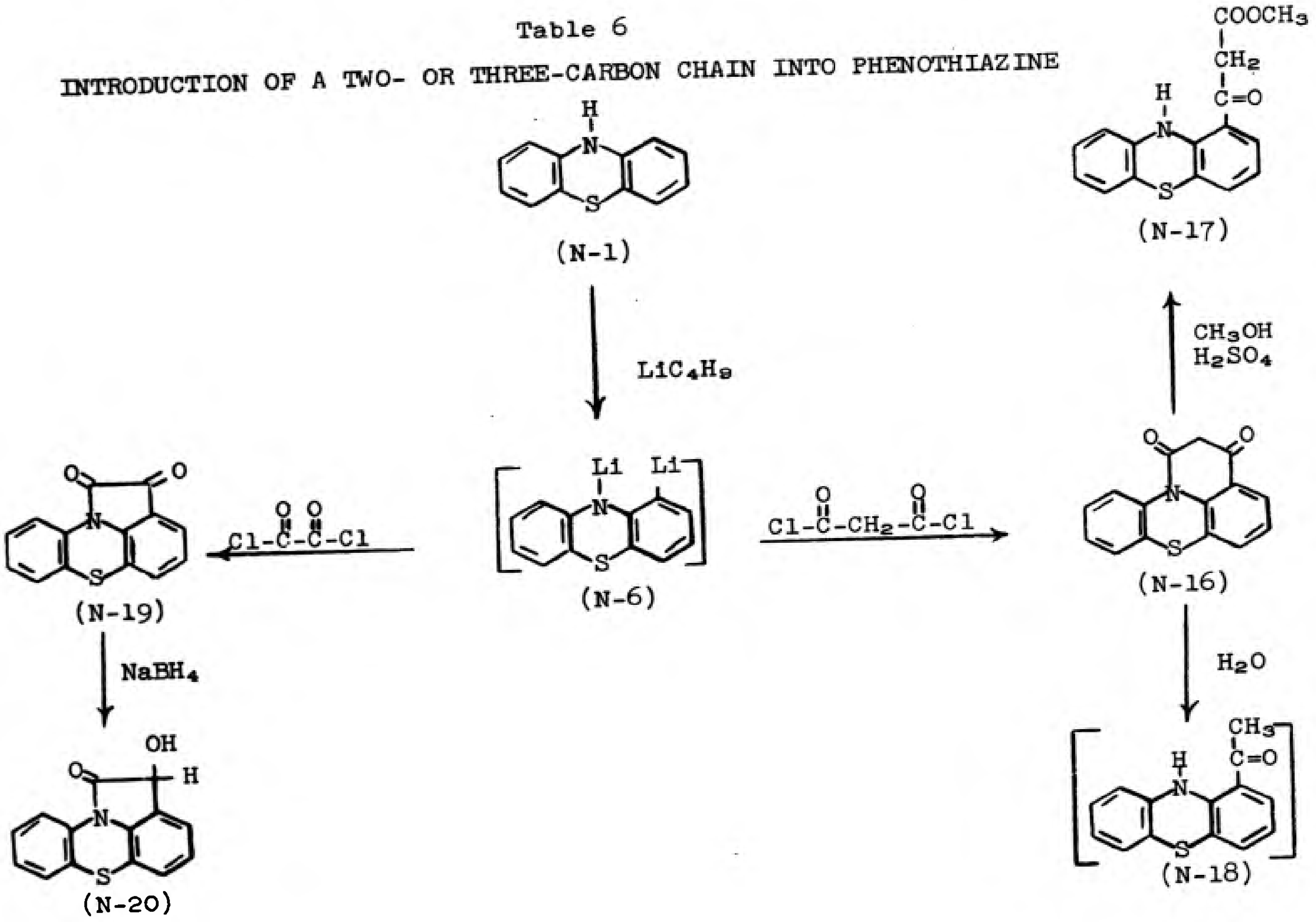


Table 6

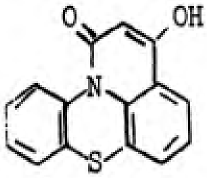
INTRODUCTION OF A TWO- OR THREE-CARBON CHAIN INTO PHENOTHIAZINE



confirmed by a flame test. Continuous extraction of the sample with ether did not completely remove the salt. When the sample was passed through a chloride ion-exclusion resin (ref. 18), the salt was removed, but N-16 could not be removed from the resin.

While a one-minute water extraction of the sample removed all the lithium chloride, it also caused a complete change in N-16. The product, postulated as N-18 from infrared data, probably resulted from the formation of a β-ketoacid that spontaneously decarboxylated to form N-18. The problem of complete removal of inorganics from N-16 has not been solved.

The very strong infrared O-H absorption of N-16 at 3380 cm^{-1} suggests the presence of water or an enol tautomer (N-16a)



(N-16a)

The broad absorptions at 1706 and 1613 cm^{-1} may result from a combination of dicarbonyl and enol-carbonyl absorptions. The bands at 1460 and 1439 cm^{-1} are also found in phenothiazine (N-1). The absorption at 755 cm^{-1} is in the correct region for four adjacent hydrogen atoms on the unsubstituted ring. The spectrum is not inconsistent with the structure.

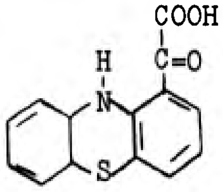
The methanolysis of N-16 in the presence of a sulfuric acid catalyst gave N-17. No reaction occurred in the absence of the catalyst.

The infrared spectrum of N-17 in nujol shows a weak absorption at 3376 cm^{-1} that can be assigned to either the N-H stretch or the bonded O-H of the enol of N-17. The potassium bromide spectrum gives evidence for both aliphatic and aromatic C-H.

The carbonyl absorptions, while similar in shape to those in N-16, are shifted to higher frequencies (1724 and 1686 cm^{-1}), as expected. The bands at 1582, 1460, and 1439 cm^{-1} are part of the phenothiazine spectrum, while the ortho substitution band is seen at 745 cm^{-1}. The spectrum is consistent with the structure.

c. Introduction of a Two-Carbon Chain

The reaction of N-6 with oxalyl chloride was expected to yield N-19 by analogy with N-16. The product of the reaction could not be changed (ring-opened) with alcohol or water, suggesting that the product may have the structure of an α-ketoacid (N-19a).



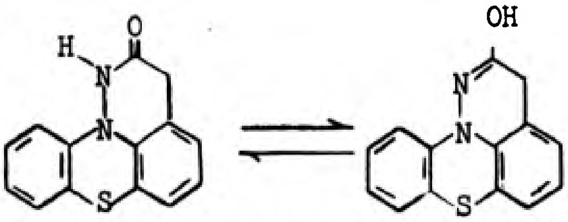
(N-19a)

The solubility of the product in benzene and chloroform, and its insolubility in 0.1N sodium hydroxide solution, suggests structure N-19, however.

The nmr spectrum shows no trace of a carboxyl proton absorption at δ=11 ppm.

The infrared spectrum of N-19 shows absorptions at 1745 and 1678 cm^{-1}, which could be due to the keto and amide carbonyl groups, respectively. The C-O stretching vibrations are seen at 1235 and 1160 cm^{-1} while the band at 755 cm^{-1} can be assigned to unresolved three and four adjacent-ring hydrogen absorptions. There is practically no evidence for a carboxyl group in the O-H stretching region nor is any O-H deformationseen near 900 cm^{-1}. These data further support the assignment of structure N-19 rather than N-19a.

A Wolff-Kishner reduction of N-19 gave a very small yield of a product. The infrared spectrum of this compound suggested that the desired reduction plus hydrazinolysis of the amide and ring closure had taken place to give N-22.



(N-22)

An attempted catalytic reduction (ref. 20) of the keto carbonyl of N-19 to a methylene group failed.

The reduction of N-19 with sodium borohydride gave N-20. The keto absorption at 1745 cm^{-1} in N-19 is not present in N-20. The O-H stretching intensity has also increased, indicating a successful reduction reaction.

6. Experimental

a. Starting Materials

Phenothiazine (N-1) (MC and B, 500 g - $2.90, crude mp 174-178°C) was twice dissolved in benzene (25 ml/g) and the solution refluxed in the presence of charcoal (1 g/20 g compound). The solution was filtered and the filtrates evaporated to dryness to give a gray-white solid [mp 181-182°C; lit. (ref. 1) mp 182°C] which was 100% pure by v.p.c. analysis.

n-Butyllithium (Foote Mineral Co., 64 g - $7.50) was a 15% solution in hexane.

Carbon dioxide from a commercial "Dry-Ice" source was used.

Oxalyl chloride (Eastman, 25 g - $6.55) was used as received.

Malonyl dichloride (Aldrich, 25 g - $16) was distilled under nitrogen [bp 57°C/29 mm; lit. (ref. 1), bp 58°C/26 mm].

Boron trifluoride etherate (Eastman, 250 g - $2.75) was distilled [bp 123°C; lit. (ref. 2), bp 125.7°C].

Chloride ion-exclusion resin (Baker, Dowex 1-X4 (Cl^- form), 50-100 mesh) was used as received.

Platinum oxide (MC and B, 1 g - $8.50)

b. 3,7-Dinitrophenothiazine sulfoxide (N-2) (ref. 3)

Phenothiazine (2.0 g, 0.01 mole) was dissolved in 30 ml of hot glacial acetic acid, and the solution was chilled and stirred until freezing occurred. The ice bath was removed and 16 ml of concentrated nitric acid (70%, d = 1.42 g/ml, 19.2 g, 0.3 mole) was added dropwise to the stirred slurry over a 15-min. period. An immediate black coloration occurred. An orange precipitate came out of the dark solution after about 1/3 of the HNO_3 had been added. After completion of the addition, the suspension was cautiously heated on a steam bath for 1 hr, and then cooled to room temperature. The resulting brown solid was filtered, washed with 250 ml of water, and dried at 60°C/15 mm to give 2.36 g (82%) of brown solid (mp 258-265°C dec). Extraction with acetone (10 ml/g) reduced the yield by 16% while giving yellow crystals [mp 268-269°C dec; lit. (ref. 3), mp not sharp, ca. 260°C dec] $\lambda_{max}^{0.1N\ NaOH}$ 485 and 223 mμ.

c. 7-Amino-3-phenothiazime (N-4)

3,7-Dinitrophenothiazine (0.50 g, 1.75 mmoles) and 0.10 g of platinum oxide were heated with 100 ml of reagent-grade methanol on a steam bath for 15 min. The suspension was cooled to 30°C and hydrogenated at room temperature in a Parr apparatus at 30 lb/in.^{2} for 2.3 hours. About 0.8 lb of hydrogen was taken up (calc. 0.96 lb). Upon filtration, the light green solution immediately became purple (air oxidation). Evaporation of the solvent *in vacuo* produced 0.35 g (90%) of purple crystals [mp spots 167°C, 221°C-?°C dec. (not sharp), λ_{max}^{EtOH} 604 mμ].

d. 7-Amino-3-phenothiazime hydrochloride (thionine) (N-5)

7-Amino-3-phenothiazime (0.10 g) was added to 50 ml of methanol and 2.0 ml of a solution of hydrogen chloride in methanol (0.1 g/ml) was added. The solution was filtered and the filtrates were evaporated to dryness to give 0.07 g (60%) of a dark maroon solid (mp >320°C). The visible absorption spectrum (shape and λ_{max}^{EtOH} 604 mμ) was identical with the spectrum of a commercial sample of thionin (MC and B).

e. 1-Carboxyphenothiazine (N-7)

All glass equipment was flamed out under nitrogen before use.

n-Butyllithium in hexane (320 ml, 0.50 mole) was added to 800 ml of dry ether under a nitrogen atmosphere. Phenothiazine (40.0 g, 0.20 mole) was added in small portions to the mechanically stirred solution under positive nitrogen pressure. Gas evolution resulted (C_4H_{10}). The yellow solution was stirred for 6 hr and allowed to stand 40 hr. When stirring was resumed, a yellow solid precipitated after 2 hr. The suspension was then stirred a total of 10 hr and allowed to stand 16 hr. The suspension was then cooled under nitrogen in a Dry-Ice-acetone bath, and the cold suspension was poured rapidly into a stirred mixture of 880 g (20 moles) of solid carbon dioxide in 300 ml of ether (4 liter beaker). After the suspension had warmed to room temperature, 1000 ml of water was added. After thorough mixing, the aqueous layer was separated and acidified with 100 ml of 6N hydrochloric acid (CO_2 evolution). The resulting yellow precipitate was filtered and washed with 300 ml of water. After drying at 90°C/15 mm for 16 hr, 39.17 g of crude product (mp 255-257°C dec) was obtained. The product was dissolved in warm solution of 140 g of sodium hydroxide in 1400 ml of water and the solution filtered through a sintered glass funnel. A concentrated aqueous sodium hydroxide solution (128 g in 200 ml) was added to the stirred filtrates causing the precipitation of the yellow-green sodium salt of the acid. The salt was filtered (glass funnel) and dissolved in 1600 ml of water. The solution was filtered (glass funnel) and 200 ml of 6N hydrochloric acid was added to the stirred filtrates. The resulting yellow solid was filtered (glass funnel) washed with 1000 ml of water, and dried at 90°C/15 mm for 24 hr to give 31.04 g (64%) of product [mp 267-268°C dec.; lit. (ref. 4), mp 264-264.5°C].

f. 1-Carbomethoxyphenothiazine (N-8)

Method A (ref. 4) (unsuccessful)

A mixture of 0.49 g (0.002 mole) of 1-carboxyphenothiazine, 3.0 ml of 0.1N sodium hydroxide, and 1.0 ml of dimethylsulfate was refluxed 17.5 hr. The solid was filtered and extracted with two 50-ml portions of ether, which were evaporated to dryness. The resulting 0.14 g of yellow solid (mp 169°C dec) had the infrared spectrum of impure starting material.

Method B

A suspension of 1-carboxyphenothiazine (0.45 g, 0.0018 mole), 10 ml of methanol, and 1.0 ml of conc. sulfuric acid was refluxed for 56 hr. The dark brown solution was filtered to remove a black gum. The yellow solid that precipitated from the filtrates upon cooling at 0°C was filtered and dried to yield 0.19 g (40%) of brown crystals (mp 110-112°C). Recrystallization from methanol (charcoal) gave golden crystals [mp soften 109°C, 111-113.5°C; lit. (ref. 4), mp 113-113.5°C].

Method C

A suspension of 2.00 g (0.008 mole) of 1-carboxyphenothiazine, 50 ml of methanol, and 1.0 ml of conc. sulfuric acid was heated in a pressure bottle for 70 hr on a steam bath. The resulting green crystals were filtered and recrystallized from methanol (charcoal) to yield 0.92 g (43%) of green-brown crystals (mp 110-112°C). The infrared spectrum of the solid was identical with that of the product of Method B.

Method D (unsuccessful)

A suspension of 1.0 g (0.004 mole) of 1-carboxyphenothiazine, 25 ml of methanol, and 2.0 ml of hydrogen chloride in methanol (0.12 g/ml) was heated in a pressure bottle on a steam bath for 96 hr. The infrared spectrum of the product (mp 243-257°C dec.) showed that only a minor amount of ester was present in the recovered starting material.

Method E (unsuccessful)

A suspension of 0.50 g (0.002 mole) of 1-carboxyphenothiazine, 10 ml of methanol, and 1.0 ml of freshly distilled boron trifluoride etherate was refluxed for 24 hr. The dark brown solution was evaporated to near dryness. Hot methanol (5 ml) was added and the suspension filtered. The filtrates were cooled and triturated to give 0.13 g of impure product (mp soften 132°C, 162-230°C). The infrared spectrum indicated partial ester formation.

Method F

1-Carboxyphenothiazine (1.2 g, 0.005 mole) was suspended in 5.0 ml of dry benzene and 1.26 ml (1.9 g, 0.015 mole) of oxalyl chloride was quickly added. The resulting slow gas evolution became more rapid as the stirred mixture was heated at reflux for 0.5 hr. The dark red solution was cooled to room temperature and 10.0 ml of methanol was added dropwise. A yellow solid precipitated. Filtration gave a total of 0.85 g (66%) of a mixture of starting material and ester identified by infrared spectral analysis and TLC (R_f 0.1 and 0.8; silica gel/methanol). Rf 0.8 indicates the ester.

g. 1-Hydroxymethylphenothiazine (N-10)

1-Carboxyphenothiazine (0.49 g, 0.002 mole) was extracted in a Soxhlet apparatus (ref. 5) for 6.5 hr with 15 ml of ether containing 0.19 g (0.005 mole) of lithium aluminum hydride. After cooling the suspension to room temperature, 5 ml of ether was added and the excess lithium aluminum hydride was cautiously decomposed with 5 ml of water. An emulsion was obtained. Water (50 ml) and 75 ml of ether were added and the layers thoroughly mixed. The ether layer was separated, dried with magnesium sulfate, and evaporated in vacuo to yield 0.31 g (68%) of a red-brown solid (mp 96-99°C). Recrystallization from 2:3::methanol:water in the presence of charcoal gave white needles (mp 100.5-101°C).

Analysis ($C_{13}H_{11}NOS$)

	Calcd.	Found
C	68.09	68.29
H	4.84	4.92
N	6.12	5.82

h. 1-Carboxy-3,7-dinitrophenothiazine sulfoxide (N-11)

A mixture of glacial acetic acid (500 ml) and 1-carboxyphenothiazine (12.02 g, 0.05 mole) was heated on a steam bath for 2 hr in a 2-liter, 4-necked flask equipped with a mechanical stirrer, reflux condenser (Drierite tube), thermometer, and dropping funnel.

The solution was allowed to remain at room temperature overnight and was then cooled to 5°C with an ice bath. Concentrated nitric acid (94 ml, 113 g, 1.8 mole) was added to the stirred, cooled suspension (1-2 drops/min) over a period of 26 min. An immediate black coloration developed. When the addition was complete, the ice bath was removed and the solution was allowed to stir at room temperature for 32 min. The mixture was then cautiously heated on a steam bath for 1 hr (the pot temperature rose to 92°C).

The suspension was cooled to 35°C over a 1.5-hr period and poured into 500 ml of water (stirring). The resulting brown precipitate was filtered and washed with 100 ml of water. The brown solid was stirred with 135 ml of acetone, filtered, and dried at 70°C/15 mm to give 5.02 g of crude yellow product (mp 250°C dec).

The original aqueous acidic filtrates were diluted with one liter of water resulting in precipitation of a brown solid. Addition of another two liters of water gave a third crop of solid after 2 days. The additional crops of brown solid were combined and extracted with 50 ml of acetone to yield an additional 2.15 g of yellow product (mp 247-249°C dec) which had an infrared spectrum identical with that of the first crop [total yield 7.15 g (41%)]. Two reprecipitations from 5% sodium hydroxide (20 ml/g) with 1.5N hydrochloric acid (15 ml/g) yielded a yellow solid [mp 260-262°C dec; $\lambda_{max}^{0.1N\ NaOH}$ 500 mμ (ε29,300) and 225 mμ (ε20,200)].

Analysis ($C_{13}H_7N_3O_7S$)

	Calcd	Found
C	44.70	44.8
H	2.00	2.0
N	12.03	11.9
S	9.17	9.2

i. Attempted Synthesis of 1-Carbomethoxy-3,7-dinitrophenothiazine Sulfoxide (N-9) (Unsuccessful)

The attempted nitration of 0.50 g (0.002 mole) of 1-carbomethoxyphenothiazine in 50 ml of glacial acetiac acid with 4.5 ml of nitric acid in a manner similar to the synthesis of N-11, produced a small amount (ca 0.5 ml) of an immiscible clear oil that would not crystallize.

j. 1-Carboxy-7-amino-3-phenothiazime (N-13)

Method A

A mixture of 0.50 g (0.0014 mole) of 1-carboxy-3,7-dinitrophenothiazine sulfoxide, 100 ml of methanol, and 0.10 g of platinum oxide was reacted in a Parr apparatus at 38 lb/in.^{2} H_2 pressure and 20°C for 3 hr. The catalyst and a small amount of starting material were removed by filtration. The brown filtrates became purple after standing overnight partially exposed to the atmosphere. The solution was evaporated in vacuo to yield 0.32 g (81%) of maroon product, (mp >320°C) whose visible spectrum was similar to that of thionine.

Method B (Unsuccessful)

To a dark red solution of 0.50 g (0.0014 mole) of 1-carboxy-3,7-dinitrophenothiazine sulfoxide in 100 ml of 0.1N sodium hydroxide was added 0.10 g of platinum oxide catalyst. The mixture was hydrogenated in a Parr apparatus at 35 lb/in.^{2} and 20°C for 1.5 hr. A 0.6 lb/in.^{2} take-up was noted. Filtration of the catalyst yielded a dark red-brown solution which was kept under a nitrogen atmosphere. Acidification of the solution with 50 ml of 6N hydrochloric acid (pH 1-2) gave only a small amount of brown precipitate which was not characterized.

Method C (Unsuccessful)

A suspension of 0.45 g (0.001 mole) of 1-carboxy-3,7-dinitrophenothiazine sulfoxide, and 0.10 g of platinum oxide in 100 ml of acetic anhydride was hydrogenated for 5 hr in a Parr apparatus (35 lb/in.^{2}, 22°C). There was no visible hydrogen uptake. No product was isolated from this reaction.

k. Mono- and Disodium Salts of 1-Carboxy-3,7-dinitrophenothiazine sulfoxide (N-14 and N-15)

To a stirred suspension of 2.00 g (5.74 meq) of 1-carboxy-3,7-dinitrophenothiazine sulfoxide in 75 ml of water was slowly added 55.0 ml of 0.0955N sodium hydroxide (5.24 meq.). Stirring was continued for 0.5 hr after complete addition. The solution was filtered to remove the 0.50 meq of unreacted starting material, and the amber aqueous filtrates were evaporated *in vacuo*. The resulting product was dried at 75°C/15 mm to give 1.79 g (91%) of red N-14 [mp >320°C, $\lambda_{max}^{H_2O}$ 388, 226 mμ]. N-14 forms a yellow aqueous solution that attains the blood-red color of the dianion (N-15) [$\lambda_{max}^{0.1N\ NaOH}$ 500, 225 mμ] upon the addition of excess aqueous sodium hydroxide.

l. Attempted Esterification of 1-Carboxy-3,7-dinitrophenothiazine sulfoxide

Method A

1-Carboxy-3,7-dinitrophenothiazine sulfoxide (0.50 g, 0.0014 mole) was suspended in a solution of 10 ml of methanol and 1.0 ml of conc. sulfuric acid in a pressure bottle. The mixture was heated for 48 hr on a steam bath, cooled, and filtered. After filtration, the red solid obtained had the infrared spectrum of starting material. The solid was extracted with 50 ml of ether. Water (50 ml) was added to the methanol-sulfuric acid filtrates and the solution was extracted with 25 ml of ether. The combined ether extracts were dried over magnesium sulfate and evaporated to dryness to give 0.03 g of red solid (mp 82-115°C dec.) which was shown to be a mixture of starting material and the desired ester by infrared spectral analysis.

When a similar reaction was carried out in refluxing methanol (20 hr), starting material was recovered in almost quantitative yield.

Method B

Oxalyl chloride (0.51 ml, 0.76 g, 0.006 mole) was added to a mixture of 1-carboxy-3,7-dinitrophenothiazine sulfoxide (0.66 g, 0.002 mole) in 5.0 ml of "Chromatoquality" benzene under a nitrogen atmosphere. Very slow gas evolution resulted. The mixture was heated at reflux for 24 hr. The volume of the dark red solution was reduced in vacuo by about two-thirds; 8 ml of benzene was added, and the volume reduced again to 5 ml. The red solution was transferred in a dry box to a dropping funnel and added dropwise to a stirred solution of 5.0 ml of methanol in 5.0 ml of pyridine. The resulting dark red solution was refluxed for 1 hr, cooled to room temperature and added to 50 ml of water. After stirring for 15 min, the emulsion was extracted with two 100-ml portions of ether. The ether layer was separated, dried over magnesium sulfate, and evaporated to yield 0.29 g of red-brown crystals (mp 161-168°C). The infrared spectrum indicated partial ester formation.

Method C (Unsuccessful)

A suspension of 0.10 g (0.3 mmole) of 1-carboxy-3,7-dinitrophenothiazine sulfoxide, 5.0 ml of methanol, and 2 drops of boron trifluoride etherate was refluxed for 65 hr. Starting material was recovered.

m. 1,3-Diketo-2H-pyrido-[3,2,1-kl]phenothiazine (N-16)

Phenothiazine (2.00 g, 0.01 mole) was added to a stirred solution of 13 ml (0.02 mole) of n-butyllithium in 100 ml of dry ether under a nitrogen atmosphere. The yellow solution was stirred for 4 hr. After allowing the solution to stand overnight the dark brown solution was stirred for an additional 5 hr and then cooled to -70°C with a Dry Ice-acetone bath. This dilithiophenothiazine solution was added dropwise over a 1-hr period to a stirred, -70°C solution of 1.40 g (0.01 mole) of malonyl dichloride in 225 ml of ether under nitrogen. The dark gray reaction mixture was allowed to warm to room temperature and stand overnight. The resulting blue-gray solid was filtered, washed with 210 ml of ether, and dried at 70°C/15 mm to yield 1.52 g of dark green solid (mp shrink 115°C, 119-130°C dec, ref. 22, mp 270-271°C). The presence of lithium chloride was indicated by a copper wire flame test (red).

(1) Attempted Lithium Chloride Ether Extraction

Soxhlet extraction of 0.1 g of N-16 for 5 hr with 20 ml of ether gave 0.05 g of ether-insoluble green solid (mp shrink 146°C, 172°-?°C dec), which still gave a LiCl flame test.

(2) Attempted Lithium Chloride Removal by Ion Exclusion

N-16 (0.1 g) was added to 11.5 g of Dowex 1-X4 (Cl^- form) ion exclusion resin in methanol in a 15 x 250 mm column and eluted with methanol. The first 10 ml of eluent gave a strong $AgNO_3$ test. After 40 ml, the test for chloride was very light. Attempts to remove the compound from the resin by elution with acetone (1000 ml) or continuous Soxhlet extraction with acetone (16 hr) gave no isolable product.

(3) Attempted Lithium Chloride Removal by Water Extraction-Formation of N-18

A mixture of 0.10 g of N-16 and 10 ml of water was stirred for 1 min. The suspension was filtered to yield 0.06 g of tan solid (mp 113-124°C dec; ref. 23, mp 100°C). A flame test showed practically no LiCl present.

n. 1-Carbomethoxyacetylphenothiazine (N-17)

A mixture of 0.50 g(0.0019 mole) of 1,3-diketo-2H-pyrido[3,2,1-kl]-phenothiazine, 25 ml of methanol, and 1 drop of concentrated sulfuric acid was refluxed for 3 hr. The suspension was cooled with an ice bath and filtered to yield 0.12 g (21%) of an olive colored solid (mp 170-?°C dec). No further precipitate could be obtained by refluxing the filtrates.

o. 1,2-Diketo-pyrrolo[3,2,1-kl]phenothiazine (N-19)

A solution of 16 ml (1.5 g, 0.025 mole) of n-butyllithium, 2.00 g (0.01 mole) of phenothiazine, and 40 ml of ether under nitrogen was stirred for 18 hr of a 50 hr reaction period. The resulting yellow suspension was quickly added to a stirred solution of 4.25 ml (6.35 g, 0.05 mole) of oxalyl chloride in 40 ml of ether, resulting in a brown precipitate. Water (100 ml) was cautiously added to the brown suspension (exotherm). The brown solid was filtered and dried at 70°C/15 mm to yield 1.87 g (74%) of product (mp 140-151°C dec).

(1) Attempted Methanolysis of N-19

Method A (Unsuccessful)

N-19 (0.10 g, 0.4 mmole), 10 ml of methanol, and 2 drops of concentrated sulfuric acid were heated in a pressure bottle at 100°C for 16 hr. The resulting brown solid was filtered. The infrared spectrum was that of starting material.

Method B (Unsuccessful)

A mixture of N-19 (0.10 g, 0.4 mmole), 10 ml of methanol, and 0.01 g of sodium methoxide was refluxed for 2.5 hr. The resulting brown solid had the infrared spectrum of starting material.

(2) Attempted Hydrolysis of N-19

Method A

A mixture of N-19 (0.10 g, 0.4 mmole) and 6N hydrochloric acid was refluxed for 21 hr. The resulting brown solid had an infrared spectrum almost identical with N-19. A low intensity absorption around 1710 cm^{-1} was noted, however.

Method B

A mixture of 0.10 g (0.4 meq) of N-19 and 10.0 ml of 0.0955N sodium hydroxide (0.95 meq) was refluxed for 17 hr. The turbid solution was filtered and the filtrates acidified with 2 ml of 6N hydrochloric acid. The resulting flocculant precipitate was filtered and dried to give 0.01 g of gray solid which had an infrared spectrum different from that of N-19. The spectrum was not interpretable.

p. 1-Keto-2-hydroxypyrrolo[3,2,1-kl]phenothiazine (N-20)

A solution of sodium borohydride (0.50 g, 0.13 mole) in 10 ml of methanol was added dropwise over a 10-min period to a stirred suspension of 1,2-diketopyrrolo[3,2,1-kl]phenothiazine (0.10 g, 0.004 mole) in 5 ml of methanol at room temperature. Water (15 ml) was then added to the light brown solution. Hydrochloric acid (1N) was added until the resulting orange solid ceased to precipitate. The solid was filtered and dried to yield 0.06 g (60%) of product (mp soften 140°C, 162-169°C dec).

q. Attempted Reductions of N-19

(1) Wolff-Kishner [Huang-Minlon (ref. 19)]

A mixture of 0.27 g (0.001 mole) of 1,2-diketopyrrolo[3,2,1-kl]phenothiazine, 0.28 g of potassium hydroxide, 1.0 ml of 65% hydrazine hydrate (0.013 mole), and 5.0 ml of diethyleneglycol was first heated for 1.5 hr at 106°C and then for 3 hr at 150°C. Water (25 ml) was added to the brown suspension and a very small amount of gray precipitate was filtered. Addition of 1N hydrochloric acid to the filtrates resulted in 0.02 g of brown solid (mp 73-80°C dec).

(2) Catalytic (Palladium on Carbon - ref. 20)

A suspension of 0.20 g (0.8 mmole) of N-19 and 0.20 g of 5% palladium on charcoal in 100 ml of absolute ethanol was reacted in a Parr apparatus at 35 lb/in.^{2} hydrogen pressure (24°C) for 2 hr. Filtration and evaporation of the solvent gave a brown solid that had an infrared spectrum almost identical with the starting material.

7. References

1. "Dictionary of Organic Compounds", I. Heilbron and H. M. Bunbury, Eds., Oxford, N. Y., 1953.
2. "The Merck Index", 7th Ed., Merck and Co., N. J., 1960.
3. F. Kehrmann and O. Nossenko, Ber., 46, 2809 (1913).
4. H. Gilman, D. A. Shirley and P. R. Van Ess, J. Am. Chem. Soc., 66, 625 (1944).
5. R. F. Nystrom and W. G. Brown, J. Am. Chem. Soc., 69, 2549 (1947).
6. R. Adams and L. H. Ulich, J. Am. Chem. Soc., 42, 599 (1920).
7. H. Kano and M. Fujimoto, Pharm. Bull. (Tokyo), 5, 393 (1957), C.A., 52, 5416i (1958).
8. S. G. Toole and F. J Sowa, J. Am. Chem. Soc., 59, 1971 (1937).
9. F. Kehrmann and Goldstein, Helv. Chim. Acta, 4, 27 (1921). Beilstein II, Vol. 27, p. 33.
10. A. Burger and J. B. Clements, J. Org. Chem., 19, 1113 (1954).
11. "The Mixed Hydrides", M. N. Rerick, Metal Hydrides, Inc., Congress St., Beverly, Mass.
12. "Chemistry of Carbon Compounds", E. H. Rodd, Ed., Vol. 4C, Elsevier, Amsterdam, 1960, 1517-1518.
13. H. Gilman, P. R. Van Ess and D. A. Shirley, J. Am. Chem. Soc., 66, 1214 (1944).
14. H. Gilman, et. al., J. Org. Chem., 19, 560 (1954).
15. R. Baltzly, M. Harfenist and F. J. Webb, J. Am. Chem. Soc., 68, 2673 (1946).
16. J. G. Michels and E. D. Amstutz, J. Am. Chem. Soc., 72, 888 (1950).
17. M. Harfenist, J. Org. Chem., 28, 1834 (1963).
18. "Ion-Exchange Resins", R. Kunin, 2nd Ed., Wiley, N. Y., 1958, 298.
19. Huang-Minlon, J. Am. Chem. Soc., 68, 2487 (1946).

20. W. H. Hartung and F. S. Crossley, *J. Am. Chem. Soc.*, **56**, 158 (1934).

21. Private communication, B. J. Gudzinowicz, Monsanto Research Corp., Boston

22. E. Ziegler, H. Junek and U. Rossmann, *Monatsh. Chem.*, **92**, 809 (1961), *C.A.*, **56**, 7310b (1962). E. Ziegler and F. Litvan, U. S. Patent 3,052,678, Sept. 4, 1962. *C.A.*, **58**, 3437g (1963).

23. G. Cauquil, A. Casadevall and E. Casadevall, *Compt. rend.*, **243**,159, 590 (1956). *C.A.*, **51**, 2797b,f (1957).

8. *Spectra*

Spectral data are given in Figures 65-79.

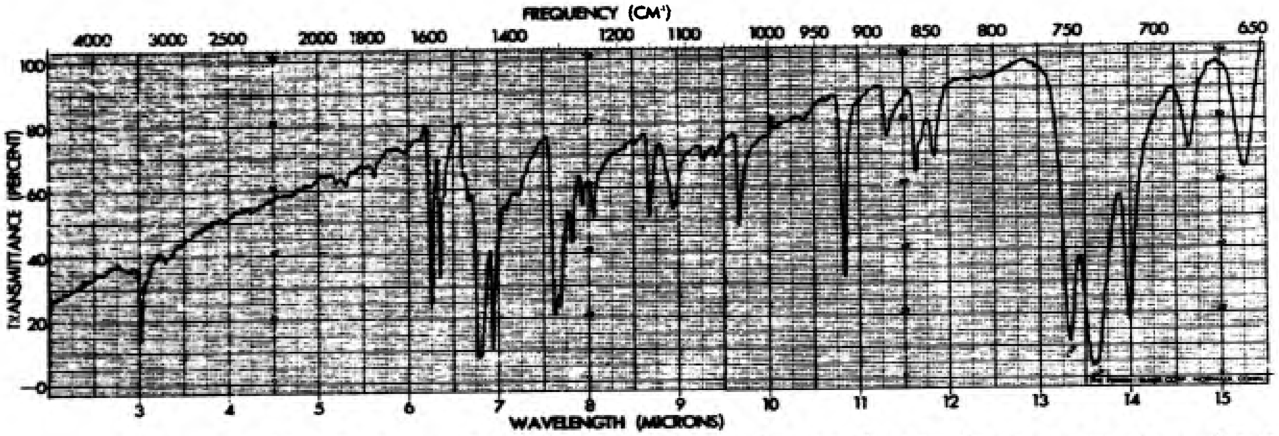


Figure 65. Infrared Spectrum (KBr Pellet) of Phenothiazine (N-1)

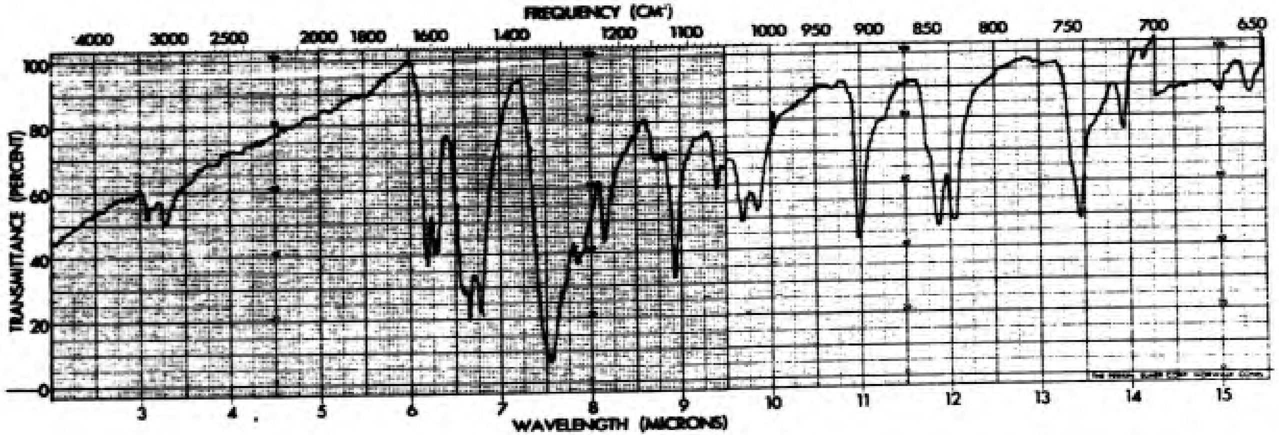
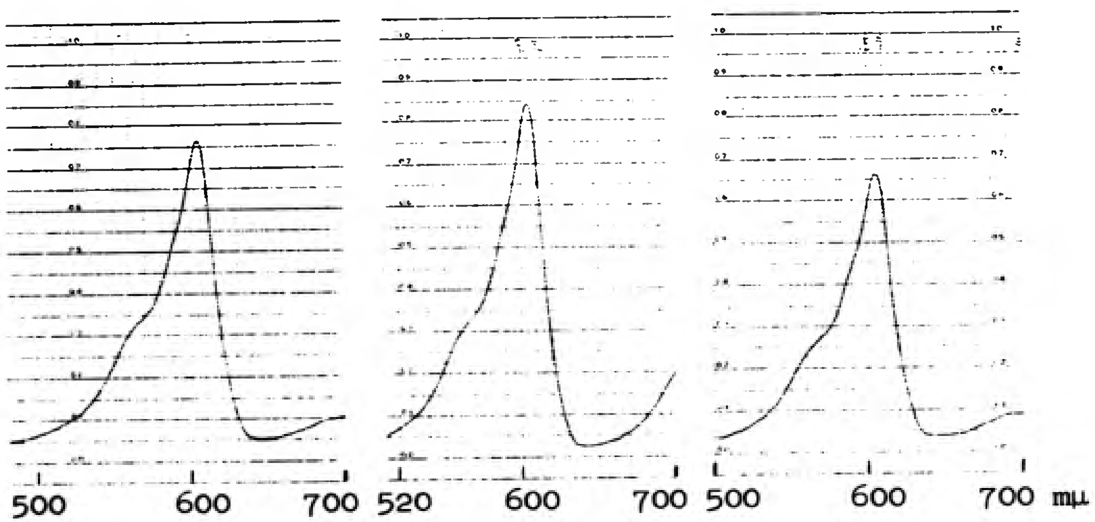


Figure 66. Infrared Spectrum (KBr Pellet) of 3,7-Dinitrophenothiazine sulfoxide (N-2)



7-Amino-3-phenothiazime (N-4)

7-Amino-3-phenothiazime hydrochloride (N-5)

Commercial Thionine

Figure 67. Visible Spectra of Thionine in Ethanol

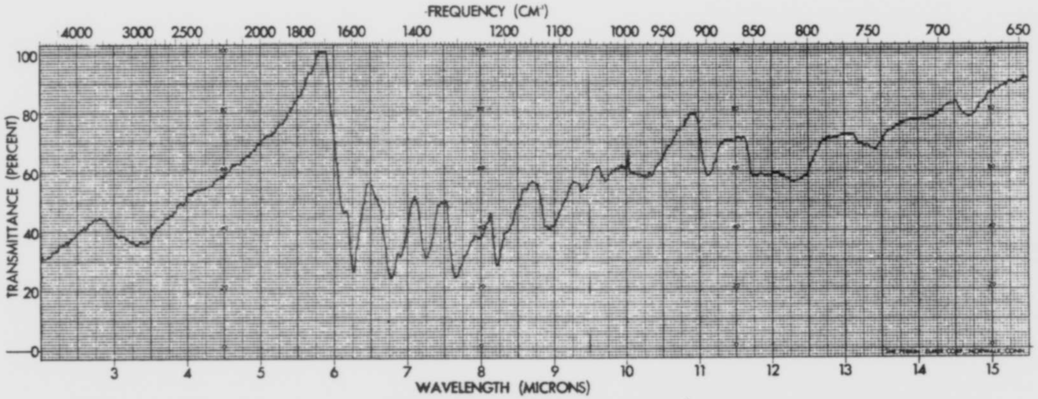


Figure 68. Infrared Spectrum (KBr Pellet) of 7-Amino-3-phenothiazime (N-4)

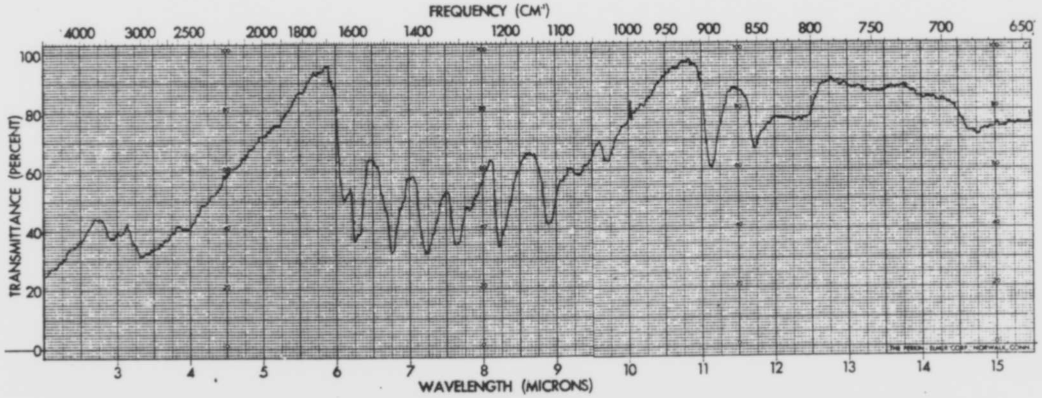


Figure 69. Infrared Spectrum (KBr Pellet) of 7-Amino-3-phenothiazime hydrochloride (N-5)

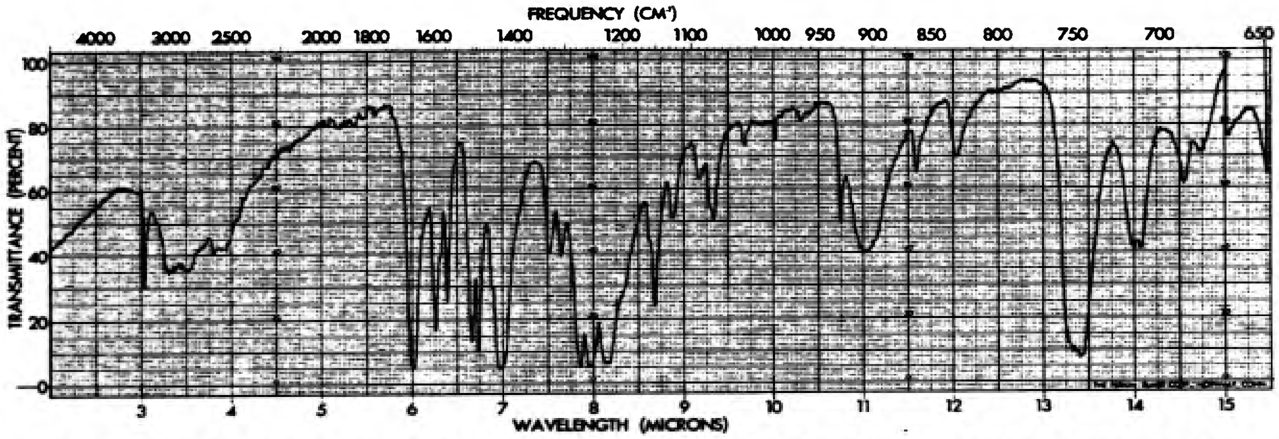


Figure 70. Infrared Spectrum (KBr Pellet) of 1-Carboxyphenothiazine (N-7)

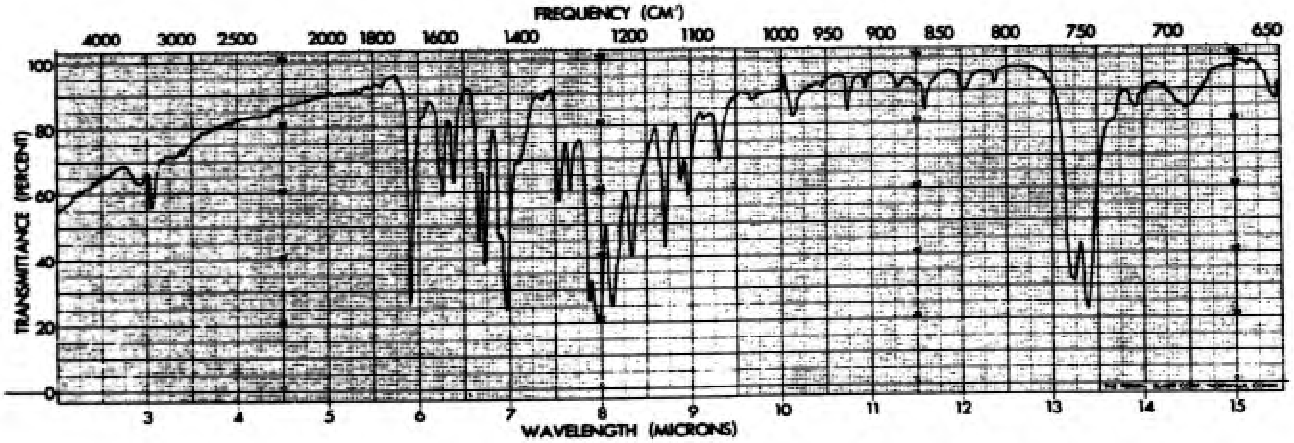


Figure 71. Infrared Spectrum (KBr Pellet) of 1-Carbomethoxyphenothiazine (N-8)

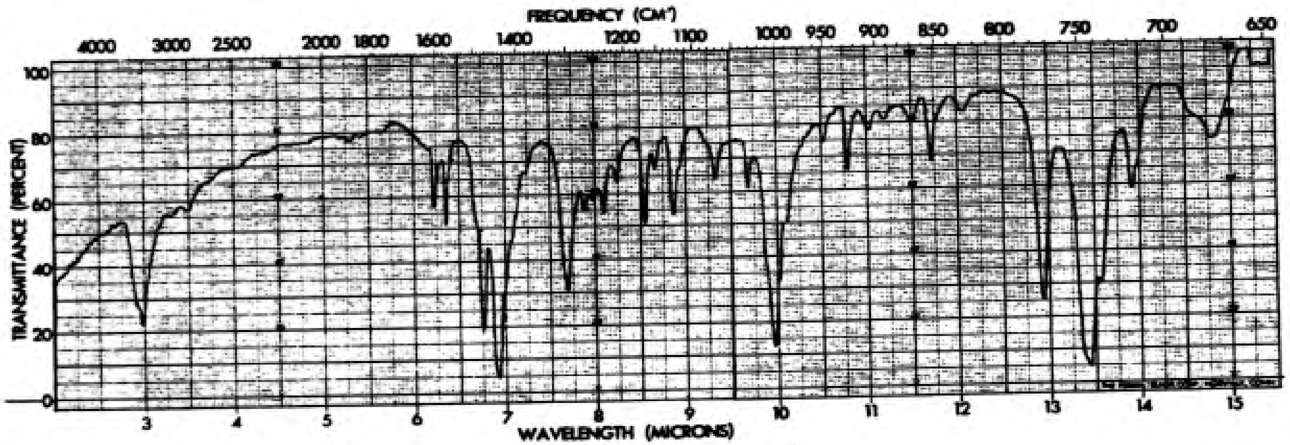
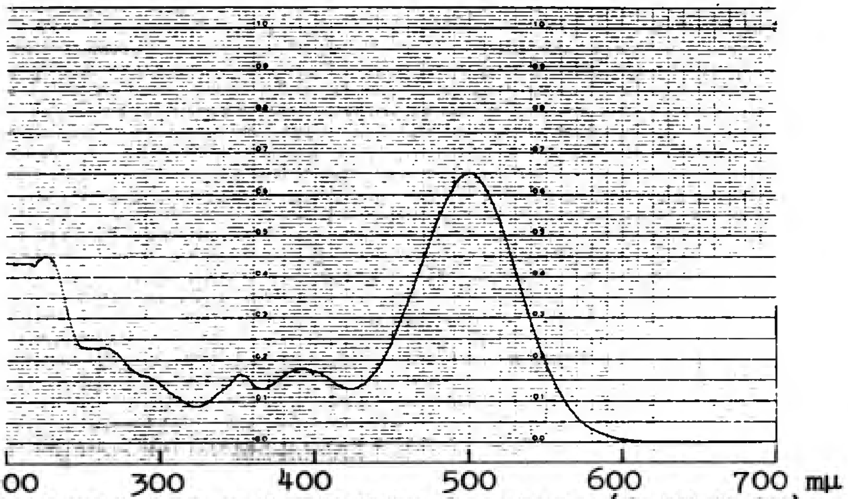
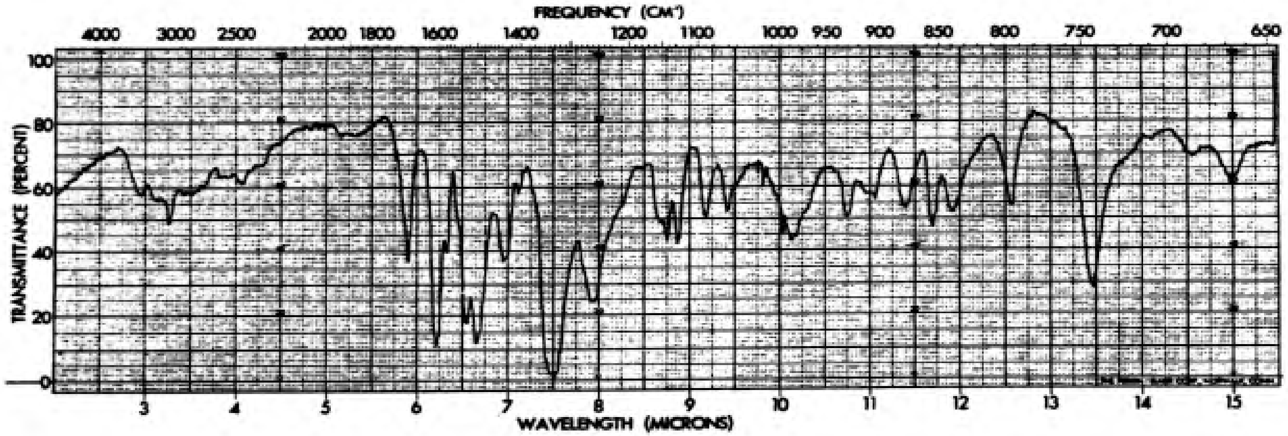


Figure 72. Infrared Spectrum (KBr Pellet) of 1-Hydroxymethylphenothiazine (N-10)

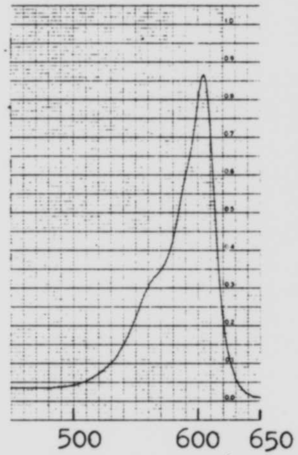


Ultraviolet and Visible Spectrum (0.1N NaOH)



Infrared Spectrum (KBr Pellet)

Figure 73. Spectral Data on 1-Carboxy-3,7-dinitrophenothiazine sulfoxide (N-11)



Visible Spectrum (Ethanol)

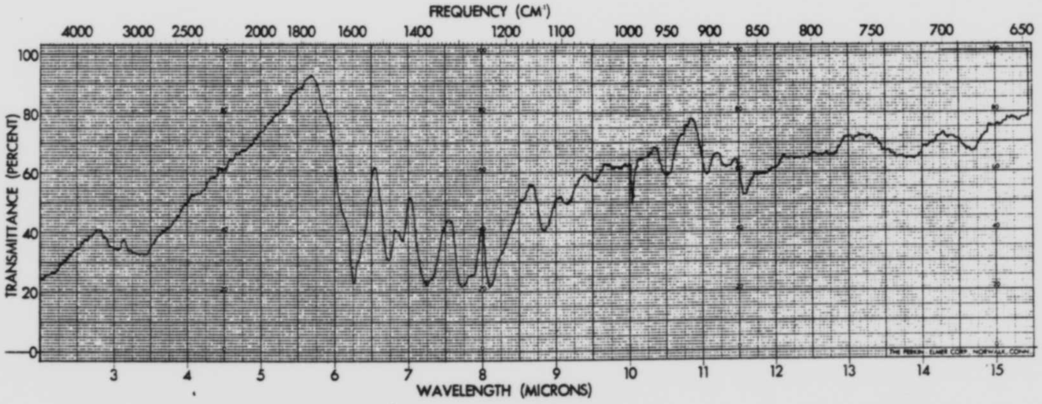
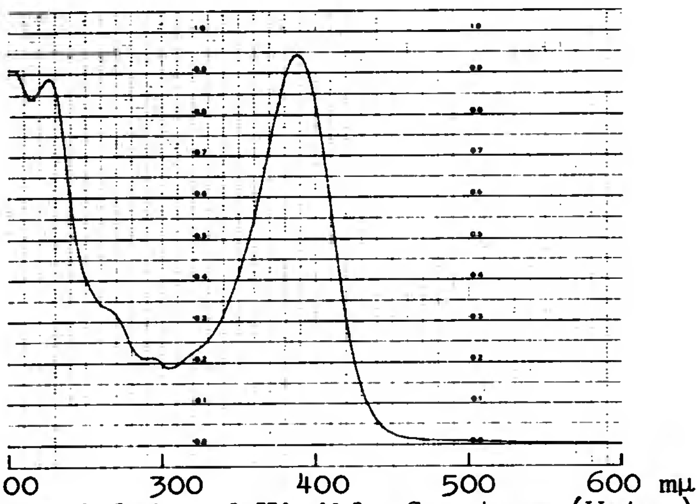
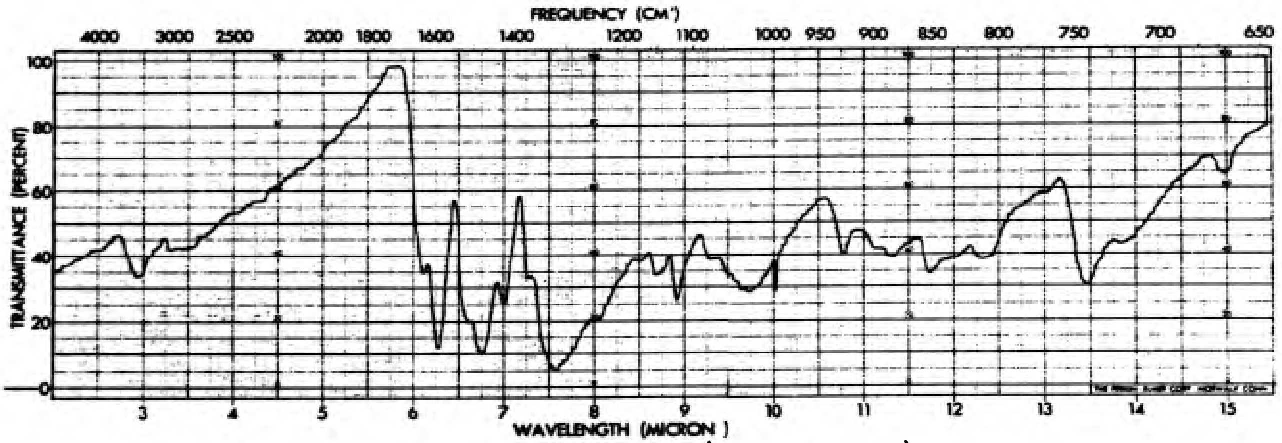


Figure 74. Spectral Data on 1-Carboxy-7-amino-3-phenothiazime (N-13)



Ultraviolet and Visible Spectrum (Water)



Infrared Spectrum (KBr Pellet)

Figure 75. Spectral Data on 1-Carboxy-3,7-dinitrophenothiazine sulfoxide mono-sodium salt (N-14)

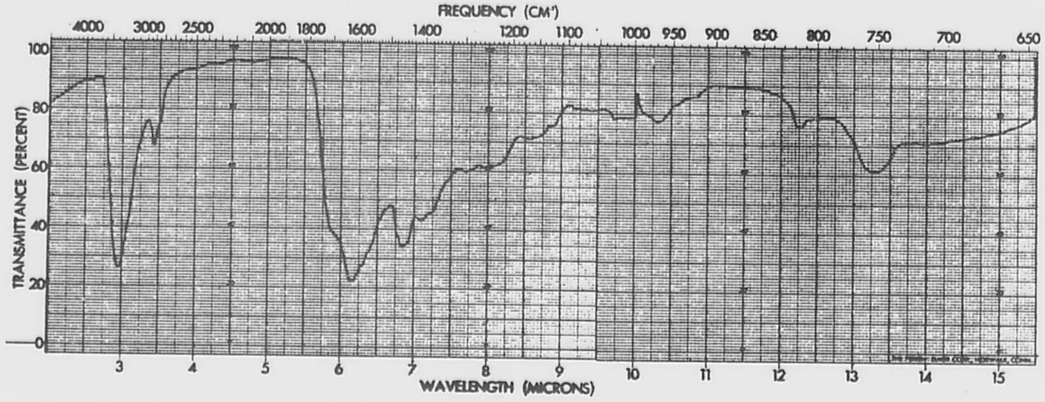


Figure 76. Infrared Spectrum (KBr Pellet) of 1,3-Diketo-2H-pyrido[3,2,1-kl]-phenothiazine (N-16)

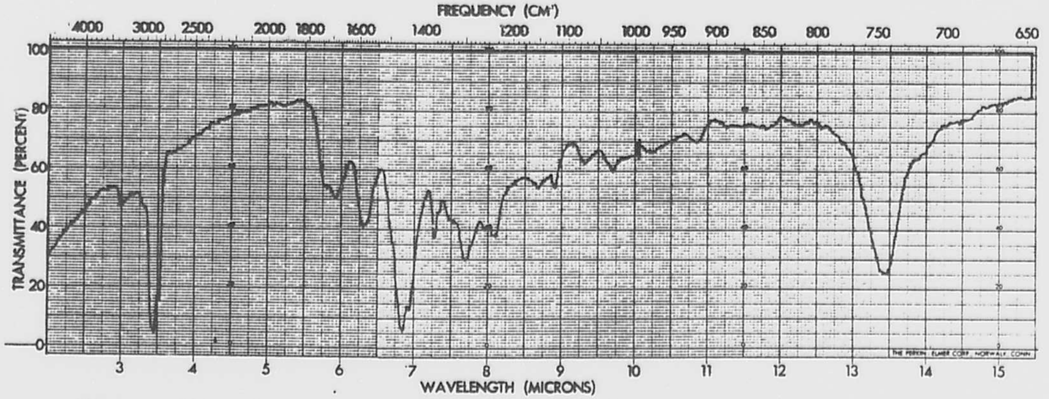


Figure 77. Infrared Spectrum (Nujol) of 1-Carbomethoxyacetylphenothiazine (N-17)

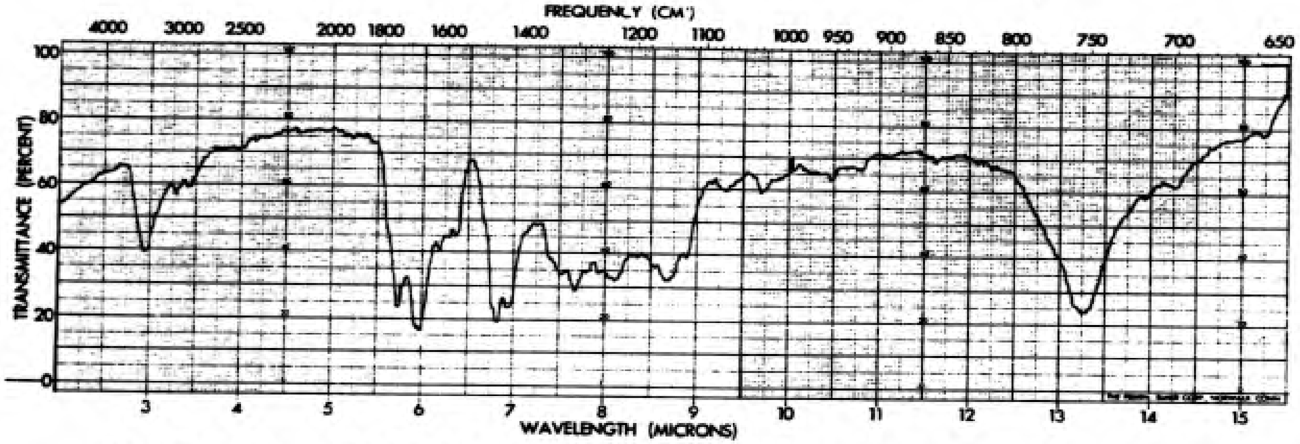


Figure 78. Infrared Spectrum (KBr Pellet) of 1,2-Diketopyrrolo-[3,2,1-kl]-phenothiazine (N-19)

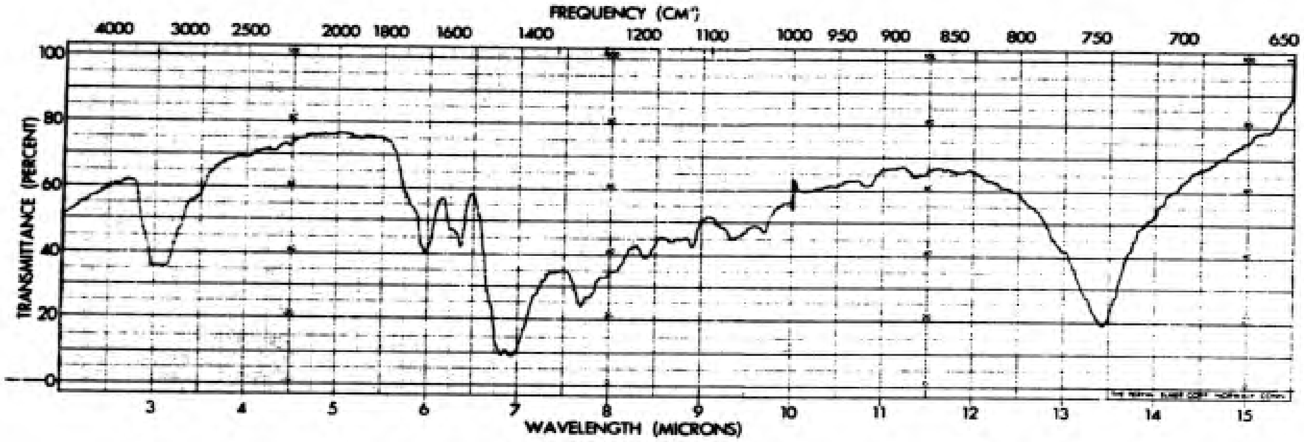
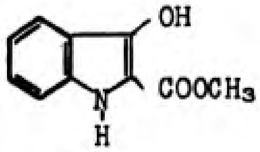


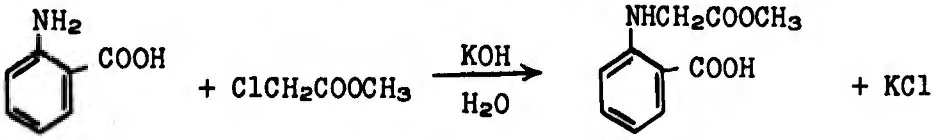
Figure 79. Infrared Spectrum (KBr Pellet) of 1-Keto-2-hydroxy-pyrrolo[3,2,1-kl]phenothiazine (N-20)

O. 2-CARBOMETHOXY-3-HYDROXYINDOLE (T6M8)



(T6M8)

1. Synthesis of Methyl-N-(o-carboxyphenyl)glycinate (O-1)

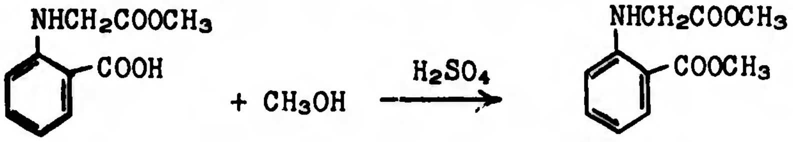


(O-1)

A mixture of light-yellow needles and brown solid was obtained from this reaction mixture upon cooling to room temperature. Both were O-1, the desired compound. The reaction mixture should not be chilled in an ice bath before filtration as this causes unreacted anthranilic acid to precipitate with the reaction product.

The infrared spectrum shows a broad absorption from 3000-2400 cm^{-1} which is probably bonded carboxyl O-H. This is further substantiated by the strong band at 900 cm^{-1} assigned to O-H deformation. The 3311 and 1575 cm^{-1} absorptions are assigned to N-H stretching and deformation modes, respectively. The 1739 cm^{-1} absorption is characteristic of an ester carbonyl while that at 1675 cm^{-1} is assigned to the carboxylic acid carbonyl. Both the acid and ester groupings have C-O stretching frequencies near 1220 cm^{-1}. The four adjacent hydrogen atoms on the benzene ring cause the band near 750 cm^{-1}. The spectrum is consistent with the structure.

2. Synthesis of Methyl-N-(o-carbomethoxyphenyl)glycinate (O-2)



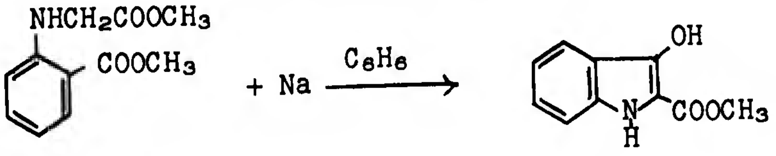
(O-1) (O-2)

During one reaction, a mixture of yellow crystals and a gray solid was obtained. These were shown to be the same material by a mixed melting point determination.

Yields of 52, 60, and 70% were obtained in three reactions.

As expected, the N-H stretching and deformation frequencies at 3311 and 1575 cm^{-1} are present in 0-2 as well as 0-1. Two ester carbonyl absorptions are noted: 1742 cm^{-1} for the aliphatic ester, and 1681 cm^{-1} for an anthranilate. The phenyl bands and bands for *ortho* substitution are the same as in 0-1. The band at 1225 cm^{-1} is C-O stretching. The infrared spectrum is consistent with the assigned structure.

3. 2-Carbomethoxy-3-hydroxyindole (T6M8)



(0-2) (T6M8)

a. Discussion

At least ten unsuccessful small-scale reactions were run before the critical variable in this reaction was determined.

When small pieces of sodium in benzene were used, the sodium became coated with a yellow material and the reaction stopped. Yields of 5% were obtained. Freshly distilled benzene (no water present) had been used. Dry toluene, xylene, tetrahydrofuran (THF), and diglyme were tried as reaction solvents along with sodium methoxide and sodium-potassium alloy as bases, all to no avail. A product (mp 173-179°C) other than T6M8 was formed in THF with sodium as base. It was then found that the particle size of sodium was the critical factor. When sodium sand was used, T6M8 yields increased to 41, 47, 57, 59, and 66%.

T6M8 can be purified by sublimation at 100°C/0.5 mm, but the process is slow. The melting points and spectra of sublimed and recrystallized products were identical. It is very simple to tell if a T6M8 sample contains di-ester (0-2) starting material by thin-layer chromatography. Both compounds fluoresce strongly under ultraviolet light, but the R_f value of T6M8 is about 0.1 while that of 0-2 is 0.8-0.9 after methanol or acetone elution.

b. Proof of Structure

(1) Infrared Spectrum

Two sharp bands are seen at 3401 and 3300 cm^{-1}. Ordinarily two such bands are indicative of a primary amine; a secondary amine exhibits only one. However, the frequencies for these bands do not fit the mathematical relationship for primary amines, i.e.,

$\nu_{sym} = (0.876 \nu_{asym}) + 345.53$. Also, no $-NH_2$ rocking frequency is seen at longer wavelengths. It is, therefore, reasonable to assign 3401 and 3300 cm^{-1} to O-H and N-H stretching frequencies, respectively. The 1692 cm^{-1} band is due to the ester carbonyl absorption, with ester C-O stretching seen at 1241 cm^{-1}. Bands at 1333 and 1198 cm^{-1} can be assigned to O-H deformation while the 740 cm^{-1} absorption is caused by the four adjacent hydrogens on the phenyl ring. The spectrum is consistent with the assigned structure.

(2) Elemental Analysis

The elemental analysis agrees with the values calculated for T6M8 (see Experimental II.O.4). The structure of the compound is that assigned.

c. Purity

The sample sent for analysis was taken directly from the sample, which had been recrystallized four times, that was submitted to the Air Force.

Thin layer chromatography on alumina showed one spot with methanol or acetone elution followed by ultraviolet light and iodine treatment.

d. Air Force Sample

Four 2.6-gram samples (total 10.4 grams) of T6M8 were submitted to the Air Force on 23 September 1963.

4. Experimental

a. Starting Materials

Anthranilic acid (Eastman, 500 g - $38) was recrystallized from hot water, [mp 145-146°C; lit. (ref. 1) mp 145°C).

Methylchloroacetate (Eastman, 1 kg - $5.80) was distilled [bp 128.5°C; lit. (ref. 2) bp 130°C].

Benzene was distilled and further dried with Linde 4A molecular sieves before use.

Xylene was dried with Linde 4A molecular sieves before use.

Miscellaneous - Sodium, methanol, and potassium hydroxide were of reagent grade quality.

b. Methyl-N-(o-carboxyphenyl)glycinate (0-1) (ref. 3)

Anthranilic acid (100.0 g, 0.73 mole) was added in small portions to a solution of 43.2 g (0.77 mole) of potassium hydroxide in 300 ml of water. The mechanically stirred tan solution was heated to reflux and 79.2 g (0.73 mole) of methylchloroacetate was dropped in over a 3-minute period. After a 1-hr reflux period, the mixture was allowed to cool overnight to room temperature. The yellow-gray solid was filtered and dried at 80°C/15 mm to give 127.6 g of crude product. Recrystallization from 500 ml of absolute ethanol with 5.0 g of activated charcoal gave 64.8 g (43%) of off-white solid [mp 157-160°C; lit. (ref. 3) mp 163°C].

Refrigeration of the reaction filtrates gave 6.7 g of crude unreacted anthranilic acid (mp 184-214° dec.) identified by its infrared spectrum.

c. Methyl-N-(o-carbomethoxyphenyl)glycinate (0-2) (ref. 3)

Methyl-N-(o-carboxyphenyl)glycinate (60.0 g, 0.29 mole) was dissolved in 120 ml of methanol containing 10.0 ml of concentrated sulfuric acid. The solution was refluxed for 69 hr, and the clear, red-brown solution was cooled in an ice bath. The light yellow product resulting was filtered, washed with two 100-ml portions of cold methanol, and dried at 65°C/15 mm. The light yellow crystals, (mp soften 89°C, 93-94°C) were accompanied by a gray solid with identical melting characteristics. A total of 45.12 g (70%) was obtained. One recrystallization from methanol (18 ml/g) with activated charcoal (16 g compound/g) gave off-white crystals [mp soften 93°C, 95-96°C; lit. (ref. 3) mp 94-95°C] with a 14% decrease in yield. Thin layer chromatography showed this purified product to contain a single component.

d. 2-Carbomethoxy-3-hydroxyindole (T6M8) (ref. 4)

Xylene (250 ml) was dried with Linde 4A molecular sieves and filtered into a 500-ml Morton type 3-necked, round-bottomed flask equipped with a reflux condenser (calcium sulfate tube) and a mechanical stirrer. Fresh sodium metal (2.40 g, 0.104 mole) was added to the xylene in about 10 pieces, and the unstirred mixture was heated to reflux with a flame. The flame was extinguished, and the boiling mixture was stirred at high speed until the xylene had cooled to near room temperature. The sodium was then present as hundreds of very small spheres (sodium sand). The xylene was decanted and 200 ml of benzene was rapidly added. Methyl-N-(o-carbomethoxyphenyl)glycinate (20.00 g, 0.088 mole) was added to the suspension along with 2 drops of anhydrous methanol. A vigorous reaction took place in the stirred reaction mixture after careful heating on a steam bath for 5-10 min. A brown precipitate began to form after 15 min. This reaction mixture was refluxed for 3 hr, cooled to room temperature, and filtered. The resulting tan solid was washed with 25 ml of dry benzene and dried at 70°C/15 mm for 2 hr to give 18.80 g of tan T6M8 sodium salt (mp >320°C).

This salt was added with stirring to 275 ml of cold water to give a brown solution and a blue-green solid that was very difficult to filter. Several filtrations were made to remove this impurity. The clear brown filtrates were warmed on a steam bath for 15 min with 4.0 g of activated charcoal. It was filtered, cooled to room temperature, and acidified (stirring) with 10 ml of 50% aq. acetic acid. The tan precipitate was filtered, washed with 25 ml water, and dried at 80°C/15 mm for 4 hr to give 11.10 g (66%) of light tan solid (mp 154-156°C). Recrystallization from a 7:3::methanol:water solution (20 ml/g) with charcoal (0.1 g charcoal/g) gave white crystals which were dried at room temperature/0.1 mm [mp 156.5-157.5°C; lit. (ref. 4) mp 157-158°C]; $\lambda_{max}^{CH_3OH}$ 245mµ (ϵ 19,100); no visible absorption].

Each recrystallization reduced the yield by 20%.

Analysis for $C_{10}H_9NO_3$

	C	H	N
Calc'd	62.82	4.74	7.33
Found	62.3	4.7	7.5

5. References

1. A. F. Isbell and H. R. Hezne, J. Am. Chem. Soc., 66, 2096 (1944).

2. Simon, Compt. rend., 176, 585 (1923).

3. K. Freudenberg, et al., Chem. Ber., 85, 641 (1952).

4. A. Robertson, J. Chem. Soc., 1927, 1939.

6. Spectra

Spectral data are given in Figures 80-82.

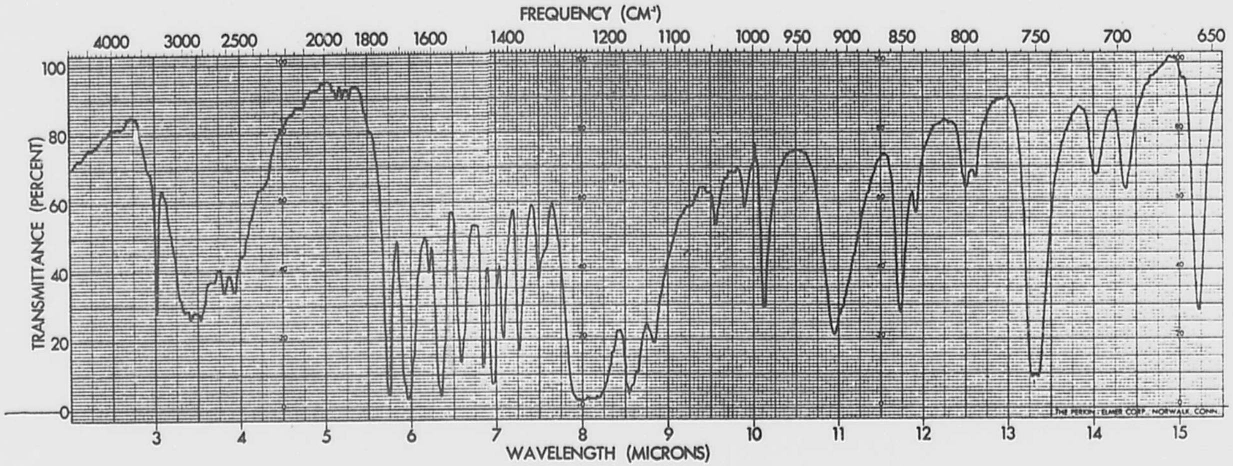


Figure 80. Infrared Spectrum (KBr Pellet) of Methyl-N-(o-carboxyphenyl) glycinate (O-1)

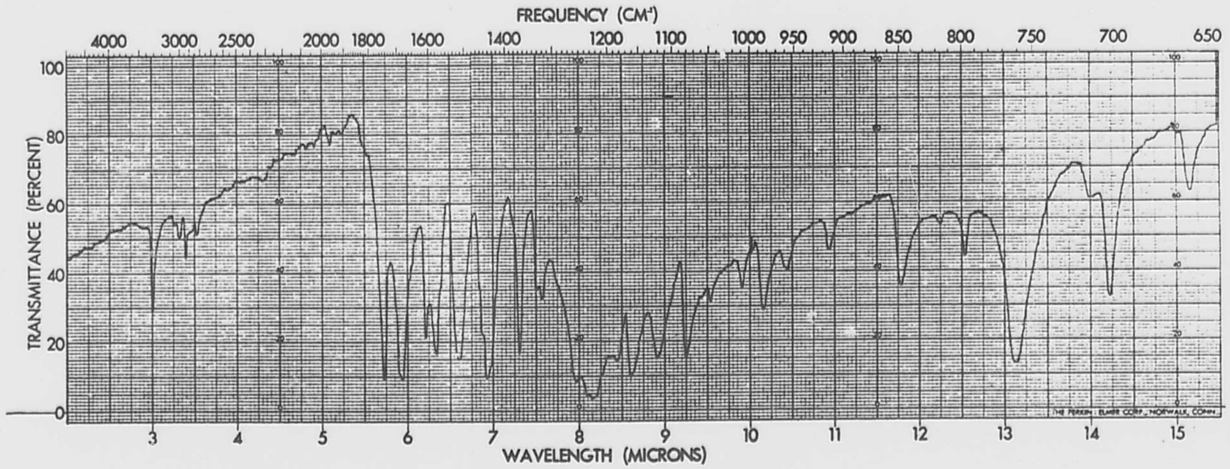
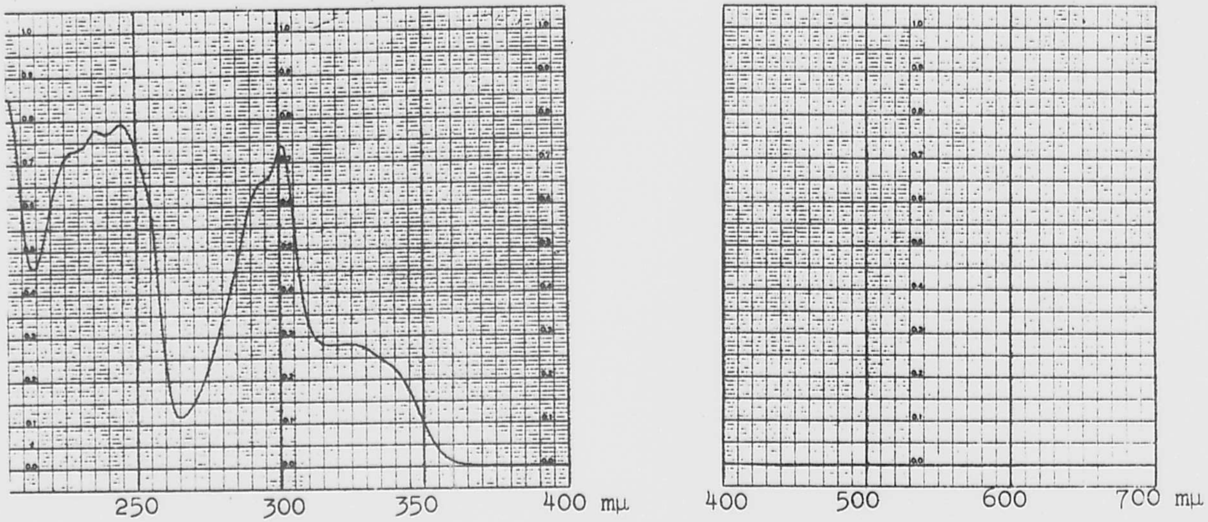
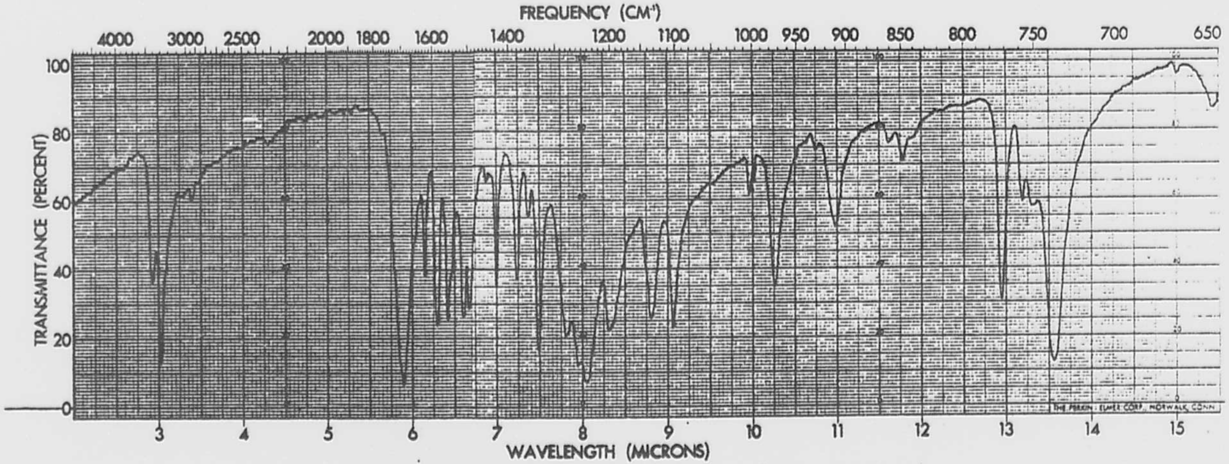


Figure 81. Infrared Spectrum (KBr Pellet) of Methyl-N-(o-carbomethoxyphenyl) glycinate (O-2)



Ultraviolet Spectrum
(Methanol)

Visible Spectrum
(Methanol)



Infrared Spectrum (KBr Pellet)

Figure 82. Spectral Data on 2-Carbomethoxy-3-hydroxyindole (T6M8).

III. ANALYTICAL TECHNIQUES

A. MELTING POINTS

Melting points were determined on a Thomas-Hoover Capillary Melting Point Apparatus (6406-H). This oil bath instrument was calibrated against melting point standards in the range 80-235°C and against a potentiometer (which in turn was checked at 0 and 100°C) in the range 60-330°C. The same calibration was obtained with both methods.

B. INFRARED SPECTRA

Infrared spectra were determined on a Perkin-Elmer Model 20 Double Beam Infrared Spectrophotometer and a Perkin-Elmer, Model 137, "Infracord", in KBr pellets, thin films, and nujol mulls.

C. VISIBLE AND ULTRAVIOLET SPECTRA

These spectra were recorded on a Cary Recording Spectrophotometer, Model 14.

D. NUCLEAR MAGNETIC RESONANCE SPECTRA

Proton n.m.r spectra were obtained with a Varian A-60 spectrometer.

E. VAPOR PHASE CHROMATOGRAMS

V.p.c. analyses were determined on an Aerograph, Model A-350, chromatograph with automatic temperature programming.

F. THIN-LAYER CHROMATOGRAPHY

T.l.c. analyses were performed on heat activated substrate layers 250 microns thick. The purity of the final dye products was determined, whenever possible, by two separate chromatograms with solvents of different polarities. Separated compounds were detected by visual color, iodine treatment, or ultraviolet light absorption.