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Lehigh University, Ph.D., 1971
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THE SYNTHESIS OF SOME NOVEL THIAPYRANO THIAPYRANS

by

Laurence J. Heitz

A DISSERTATION

Presented to the Graduate Faculty

of Lehigh University

in Candidacy for the Degree of

Doctor of Philosophy

Lehigh University

1971

CERTIFICATE OF PRESENTATION

This dissertation is respectfully submitted to the Graduate Faculty of Lehigh University, in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

Laurence J. Heitz

Laurence J. Heitz

CERTIFICATE OF APPROVAL

Approved and recommended for acceptance as a dissertation in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

Sept. 10, 1971
Date

Thomas E. Young
Professor in Charge

Special committee directing the work of Mr. Laurence J. Heitz.

Thomas E. Young Chairman

Ned D. Heindel

Charles D. Kraihanzel

James E. Sturm

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The author wishes to thank Dr. Thomas E. Young for suggesting the problem and for his concern and advice during the course of this research.

In addition, the author wishes to express his appreciation to the late Dr. Velmer B. Fish for performing much of the elemental analyses and to Dr. James Sturm for the mass spectra.

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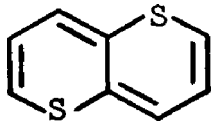
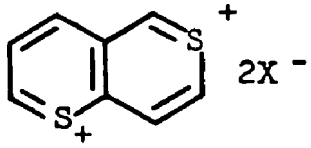
ABSTRACT

Theoretical arguments are presented to suggest that fully conjugated thiapyranothiapyrans having [3,2-b] and [4,3-b] modes of ring fusion (I and II, respectively) would comprise new classes of potentially aromatic heterocycles in which the opportunity for delocalization *via* the 3d-orbitals of sulfur should be optimized. Since even the primary skeletal structures of such compounds were previously unknown,



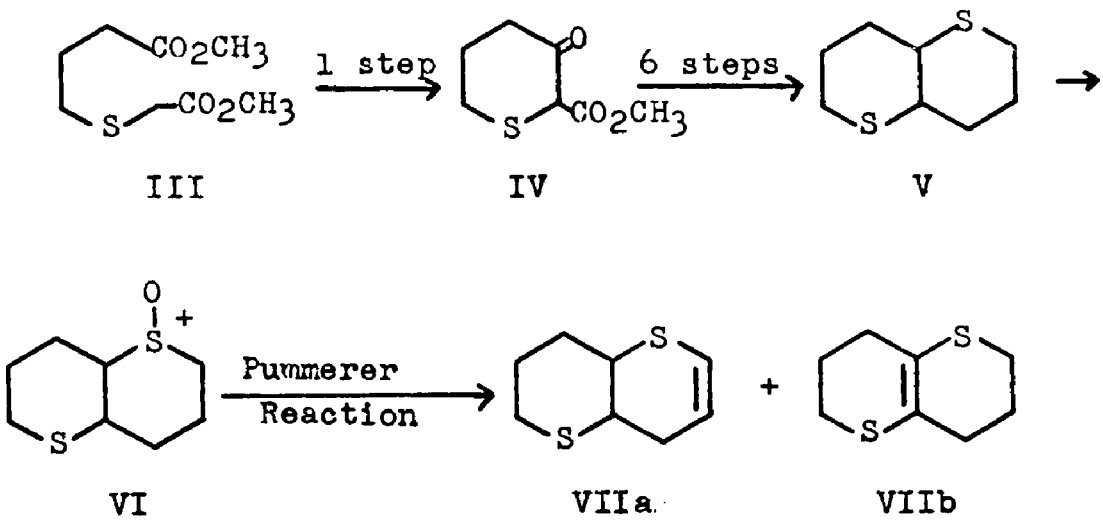
I



II

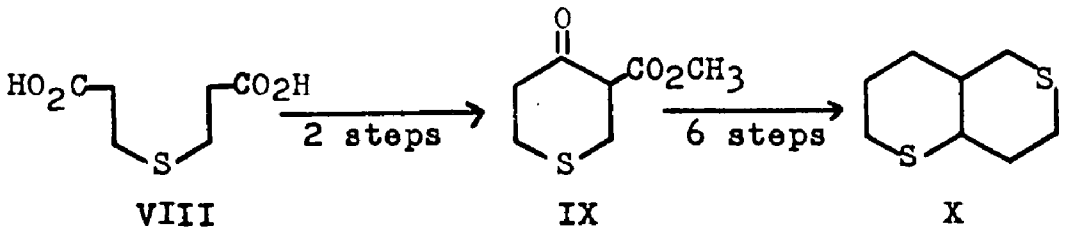
the present work was undertaken to provide suitable synthetic pathways leading to appropriate prototypical systems.

A somewhat laborious multistep synthesis of octahydrothiapyrano[3,2-b]thiapyran (V) was achieved in an overall yield of 2.6%, starting with methyl 4-(carbomethoxymethylmercapto)butyrate (III) and proceeding through the intermediate 2-carbomethoxythiacyclohexan-3-one (IV). This saturated thiapyranothiapyran (V) reacted readily with sodium meta-periodate to yield a well-defined mono-sulfoxide (VI), which underwent a Pummerer dehydration to a mixture of monoenes (VIIa and VIIb). However, attempts to introduce further unsaturation by reaction of these olefins with high potential

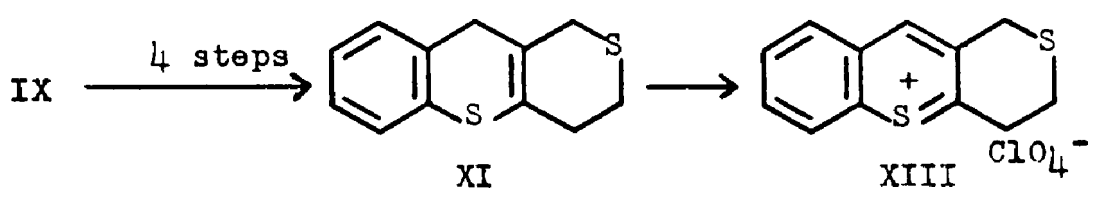


quinones yielded complex, intractable products, and it appeared that the overall conversion of (V) to (I) would require an intensive separate investigation.

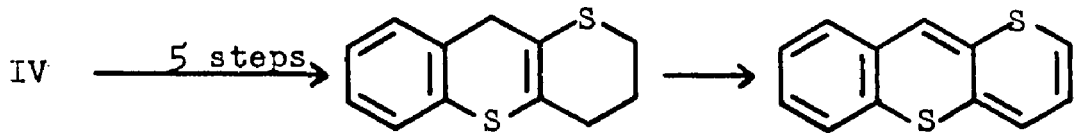
By a similar, eight-step sequence, thiodipropionic acid (VIII) was converted <u>via</u> 3-carbomethoxythiacyclohexan-4-one (IX) to octahydrothiapyrano[4,3-b]thiapyran (X) in an overall yield (1.5%) which precluded investigation of further transformations.



The benzologs, 1,3,4,10-tetrahydrothiapyrano[4,3-b]-1-benzothiapyran (XI) and 2,3,4,10-tetrahydrothiapyrano[3,2-b]-1-benzothiapyran (XII) were also obtained in 5% and 9% overall yields in extended sequences beginning with (IX) and (IV), respectively. A thiapyrylium perchlorate (XIII) was formed from (XI) and further attempts to dehydrogenate (XIII) and the thiapyran (XII) using trityl perchlorate, o-chloranil, and dichlorodicyanoquinone in addition to a series of strong bases are described.

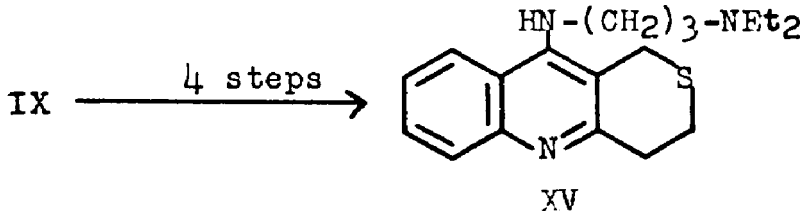


XI XIII



XII XIV

As a side issue, a four step scheme was undertaken to synthesize 10-(3-diethylaminopropylamino)-1H-3,4-dihydrothiapyrano[4,3-b]quinoline (XV) as a potentially active antimalarial agent. However, preliminary screening of (XV) indicated a lack of activity, thus further syntheses of similar structural types was not pursued.

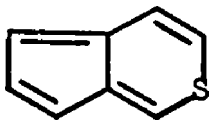


XV

All of the compounds described, including intermediates not illustrated, were fully characterized by elemental analyses, and by infrared and nmr spectral data consistent with the assigned structures.

INTRODUCTION

For years thiophenes and thiazoles have been considered the most significant of heteroaromatic sulfur compounds. In recent years, however, the interaction of theoretical and synthetic investigations has produced an interesting group of new structural types such as cyclopenta[c]thiapyran (1)[2], thiapyrylium ion (2)[3], 1-phenyl-1-thianaphthalene (3)[4], 1,3-dithiolium ion (4)[5], and 1,4-dithiin (5)[6]. In these diverse



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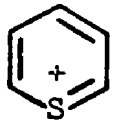

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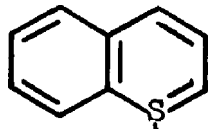

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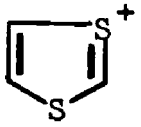

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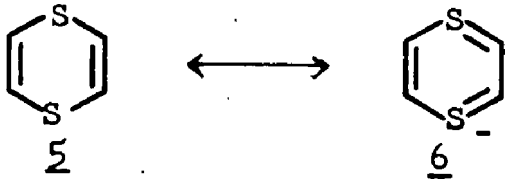


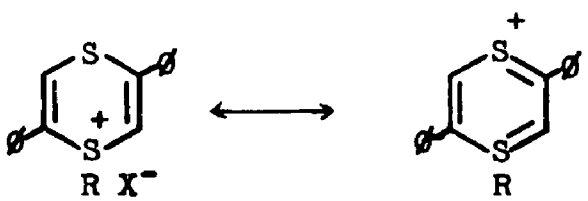
5 ⟷ 6

molecular environments sulfur possesses a varied opportunity for delocalization via the $3p_z$ and possibly the 3d-orbitals of sulfur.

Among these modern heterocyclic sulfur compounds Parham's 1,4-dithiin (5)[6,7] was of early interest because of possible sulfur d-orbital participation resulting in valence shell expanded forms such as 6. Single crystal x-ray analysis showed, however, that 1,4-dithiin exists in a boat form, and its chemical properties were found to be predominantly olefinic[7]. LCAO-MO calculations by Kreevoy[8], neglecting

d-orbital participation, were in essential agreement with the observed properties of dithiin, indicating virtually no contributions from structures such as 6. This conclusion is in accord with the theoretical arguments of Jaffe and others[9] that a sulfur atom may expand its valence shell only if, in the singly bonded structure, it bears a positive charge. Price's S-phenylthiaaromatics[4] (e.g. 3) are some of the few compounds that fulfill the stated structural requirement by means of σ-tervalent sulfur. But even here it is not certain that the cyclic conjugation truly involves carbon 2p to sulfur 3d overlap. In fact, in all but the 1,2,4,6-tetraphenylthiabenzene, Price suggests the utilization of sp^2-orbitals for σ-bonding, the $3p_z$-orbital for cyclic conjugation tion and one or more 3d-orbitals for the unshared pair of electrons. He further states that if indeed the unshared pair on sulfur is promoted to a 3d-orbital in thiabenzenes, then the intense color of these compounds may arise from atomic excitation of one of the electrons to another 3d-orbital of only slightly higher energy. All this could be done without very great influence on the cyclic conjugated π-electron system.

Recent work in this laboratory[10] has led to a series of 1-alkyl-1,4-dithiinium salts such as 7 which also fulfull the



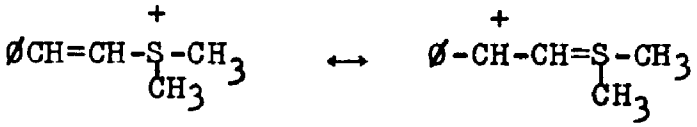
7 8

sulfonium requirement for possible d-orbital participation via a σ-tervalent sulfur. However, these dithiinium salts exhibit nmr spectra which are incompatible with cyclic conjugation via structures such as 8. The strong deshielding of the H-3 proton of these salts may be the consequence of d-orbital participation by the sulfonium atom.

Caserio[11] and her coworkers have investigated by nmr the electronic effects of dimethylsulfonium groups directly bonded to a carbon-carbon double bond. Compounds of the type $RCH=CHS^{+}(CH_3)_2\,^{-}BF_4$ were prepared and their nmr spectra recorded. By means of these compounds and their deuterium-labeled analogs, it was demonstrated unambiguously that the sulfonium center strongly deshielded selectively the protons β to the sulfonium atom. A specific example is given below.

	$\delta(H_\beta)$ ppm	$\delta(H_\alpha)$ ppm	$\delta(H_\beta) - \delta(H_\alpha)$ cps	Solvent
$\phi CH=CHSCH_3$	6.34	5.98	19.6	neat
$\phi CH=CHS^{+}(CH_3)_2\,^{-}BF_4$	7.82	6.52	78.0	CH_3NO_2

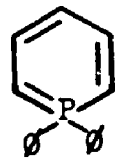
Furthermore, it was postulated that this deshielding in vinyl sulfonium salts (e.g. 9) was a consequence of d-orbital participation by the sulfonium atom.



9a ↔ 9b

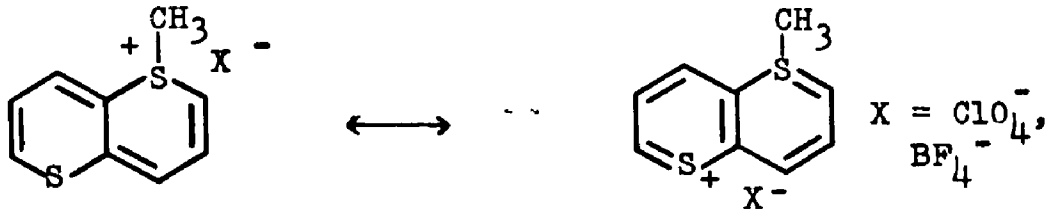
The lack of deshielding of H-6 in the dithiinium salts (7) indicates the absence of cyclic delocalization. This can

occur either because a folded ring conformation prevents fully effective p-orbital overlap around C_3-S-C_5, or that, if the d-orbitals are truly involved at S-1, as the nmr indicates they are, they individually overlap p-orbitals at carbons 2 and 6 but are themselves orthogonal and non-conducting. Märkl[12] has indicated a similar lack of through conjugation via the d-orbitals of phosphorus in 1,1-diphenyl-1-phosphabenzene (10).



10

Since the boat conformation of dithiin and its salts might be unfavorable to the expected resonance interaction, it was decided to investigate a structually related series of compounds such as 11. In these compounds it was hoped that

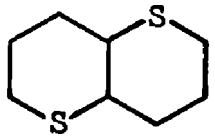


11a ⟷ 11b

X = ClO_4^-, BF_4^-

conjugation through a σ-tervalent sulfonium atom might be enhanced by the prerequisite coplanarity of the carbon skeleton π-system. Cation 11b is iso-π-electronic with 1-phenyl-1-thianaphthalene (3) and, like this compound, might be colored if Price's postulated bonding configuration about σ-tervalent sulfur is involved.

During the course of this research the thiapyrano[3,2-b] thiapyran (12) and its benzolog (13) were obtained.



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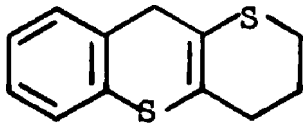

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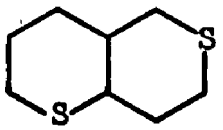

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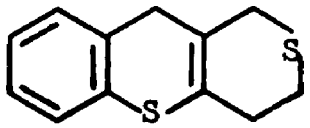
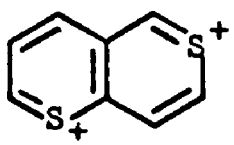
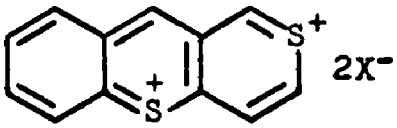


15

Dehydrogenation of 12 and 13 followed by known alkylation methods[10] would generate salts containing cation 11. The isomeric thiapyrano[4,3-b]thiapyran (14) and its benzolog (15) were also obtained and suggested as possible precursors to the potentially aromatic thiapyrano[4,3-b]thiapyrylium dication (16a) and its 1-benzolog (16b).



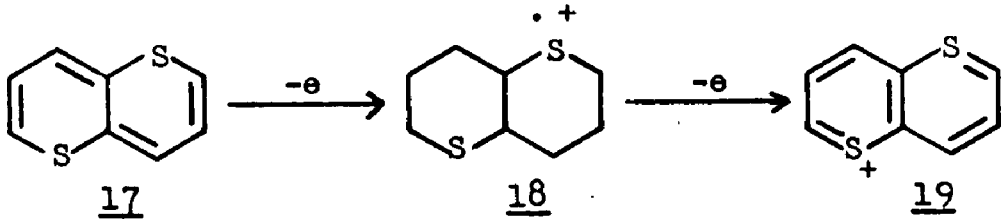
16a



16b

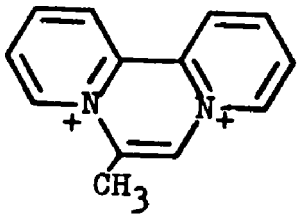
X = ClO_4^-, BF_4^-

Dithiin (5), benzodithiin and dibenzodithiin are known to lose one electron to form radical cations[1a], thus it appeared likely that thiapyranothiapyrans and their benzologs would do the same (e.g. 18 from 17). Oxidative removal of two electrons would form a dication such as 19. Although 19 is coulombically destabilized, it is iso-π-electronic



17 18 19

with naphthalene; i.e., it should possess aromatic stabiilization associated with 4N+2 π-electron delocalization. Structures similar to 19 have been reported by Calder[13] and Curphey[14] and are represented as 20 and 21 respectively.



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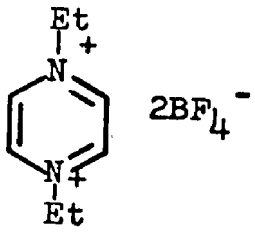
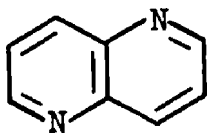


21

Bicyclic systems of the form C_5X-C_5X, where X represents the heteroatom, have been known for many years. The earliest compounds of this type had nitrogen as the heteroatom. Both 1,5-naphthyridine (22)[15] and 1,6-naphthyridine (23)[16] were reported in the early German literature. 5H-Thiapyrano-[4,3-b]pyridine (24) was also reported in 1925 by O. Mumm[17] and coworkers. A U.S. patent in 1963[18] also described 2H,5H-thiopyrano[4,3-b]thiopyran as part of a larger molecule, specifically, 5,8-etheno-2H,5H-thiopyrano[4,3-b]thiopyran. No other simple bicyclic systems of the type C_5X-C_5X where X=S have appeared in the literature to date.



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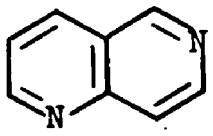

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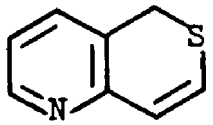
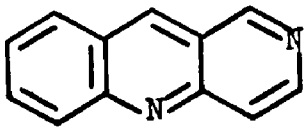


24

The first tricyclic systems of the form C_6-C_5X-C_5X also contained nitrogen as the heteroatom. In 1916, Rassow and Döhle[19] synthesized benzo-(b)-1,6-naphthyridine (25) and in 1927 Bobranski and Sucharda[20] prepared benzo-(b)-1,5-naphthyridine (26). More recently the syntheses of 10H[1]benzothiopyrano[3,2-b]pyridine (27)[21] and 10H-1-benzothiopyrano[3,2-c]pyridine (28)[22] have been reported.



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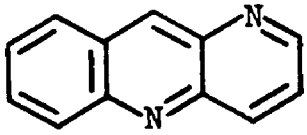

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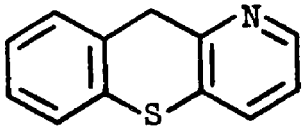

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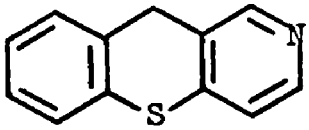
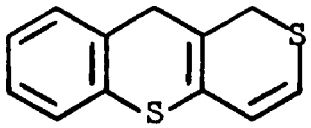


28

A British patent[23] described the synthesis of 1H,10H-thiapyrano[4,3-b]-1-benzothiapyran (29) in 1956 by means of a thiophenol condensation with the appropriate ∠-acyl fatty acid ester in the presence of poly phosphoric acid.

Finally, Bossert and Goennert[24] reported the synthesis of 1H,3,4-dihydro-6-methyl-9-(N-(2'-N,N-diethyl)ethyl)amino-thiapyrano[4,3-b]thiapyran-10-one (30).



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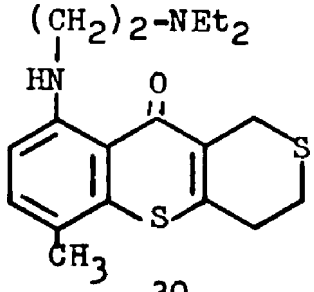

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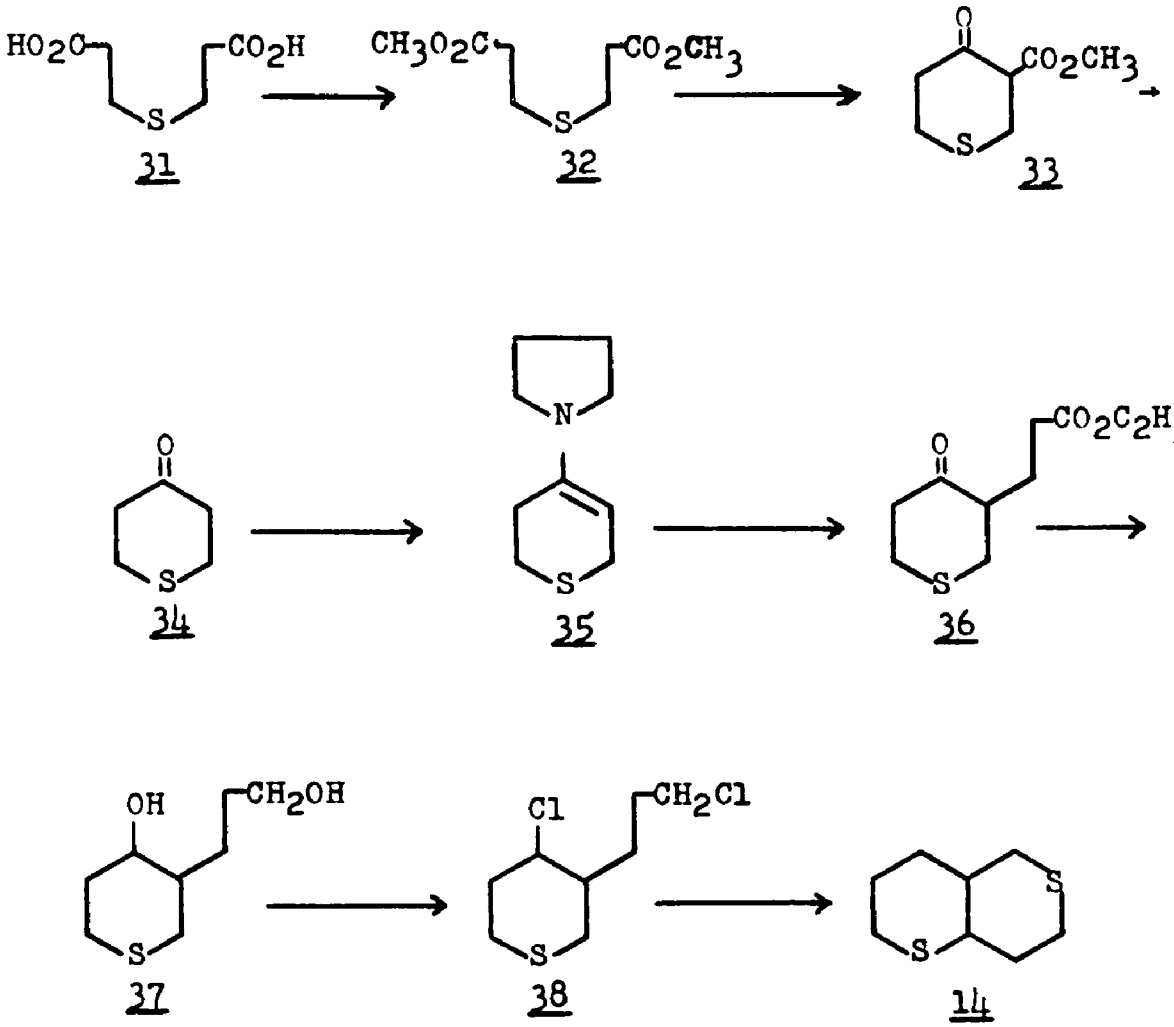
RESULTS AND DISCUSSION

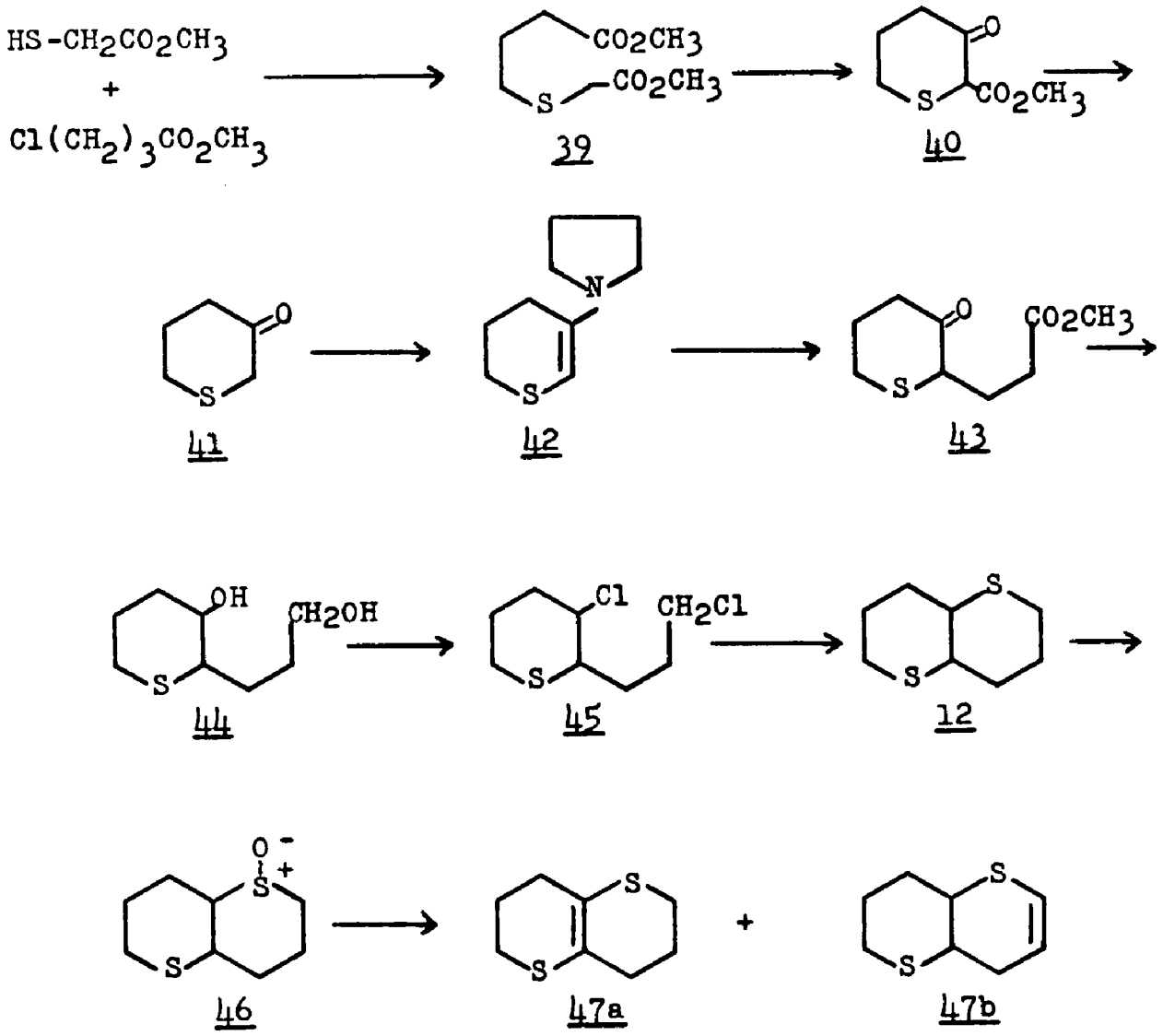
Summary of Synthetic Sequences

The problem of synthesizing the thiapyranothiapyrans and their 1-benzo derivatives involved initially substituting a sulfur atom for a carbon atom in the required position of the carbon skeleton.

Scheme I



Scheme II



The monocyclic rings containing one sulfur atom, (33) and (40), were generated essentially according to the method of Fehnel and Carmack[25] with the key reaction being a Dieckmann cyclization. Next an appropriate side chain was introduced in the desired position so that closing the second ring

while simultaneously inserting the second sulfur atom generated the target thiapyranothiapyrans, (12) and (14).

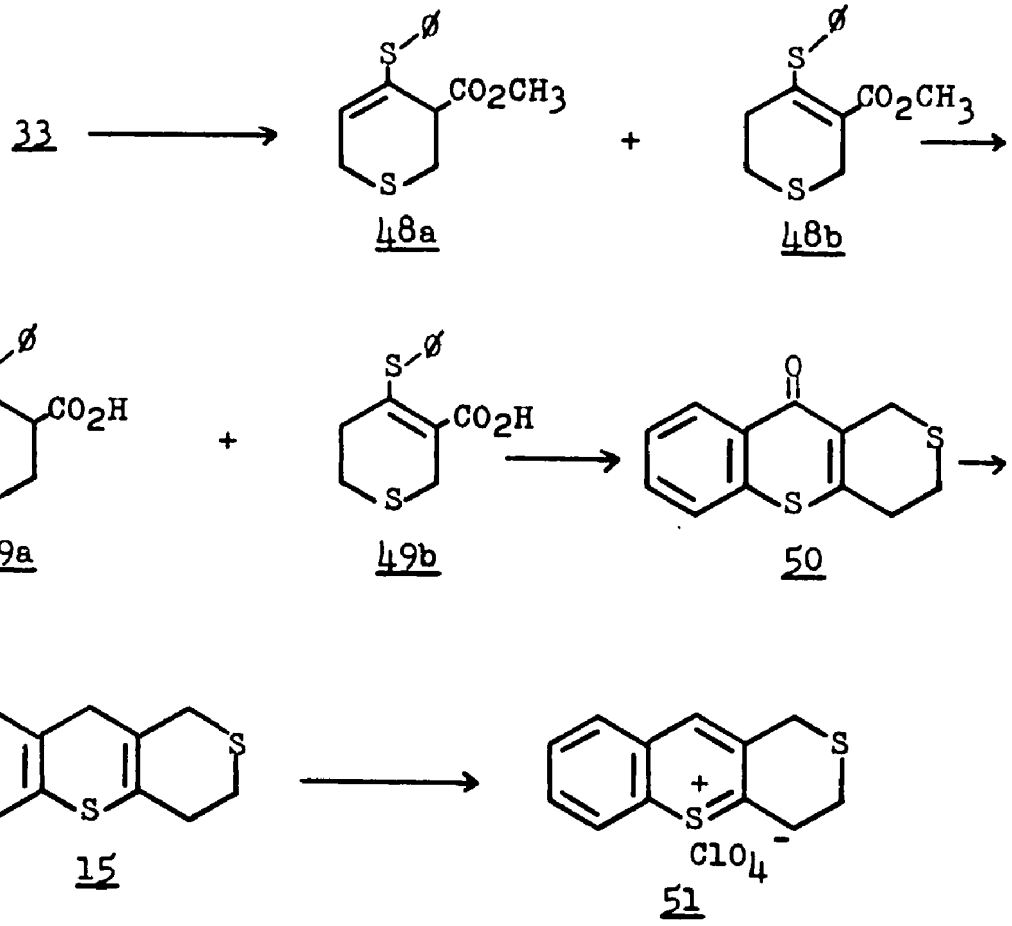
The Dieckmann products were decarbomethoxylated in aqueous acid to give thiacyclohexan-3-one (41) and thiacyclohexan-4-one (34). These two compounds were readily alkylated[26] via their pyrrolidino enamines, (35) and (42), to give the corresponding keto esters, (36) and (43). In Scheme I methyl 3-bromopropionate was the alkylating agent of choice while in Scheme II methyl acrylate worked adequately.

After introduction of the side chain a series of standard transformations led to the bicyclic compounds. The first step involved lithium aluminum hydride reduction[27] to the diols, (37) and (44). Treatment of the diols with thionyl chloride gave the corresponding dichlorides, (38) and (45). The final step involved closure of the second ring with Na_2S to give (12) and (14).

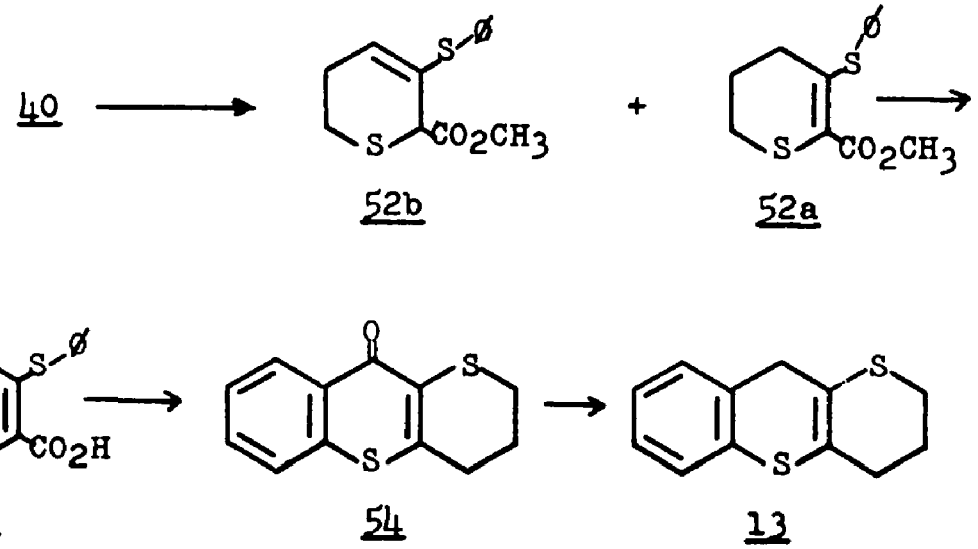
Although the [4,3-b] isomer sequence (Scheme I) was terminated at this point, the [3,2-b] sequence (Scheme II) was carried two steps further. The first step was the generation of the monosulfoxide (46)[28] using sodium meta-periodate as the oxidizing agent. The second step involved conversion to a mixture of olefins, (47a) and (47b), *via* a Pummerer-type reaction described by Parham[29].

The sequence of transformations leading to the corresponding 1-benzo-thiapyranothiapyrans, (13) and (15), started in each case with the Dieckmann cyclized keto esters, (33) and (40).

Scheme III



Scheme IV



The keto esters were condensed with thiophenol to give a mixture of the two possible α,β unsaturated sulfides[30]. In Scheme IV the desired sulfide (52a) was crystallized out of the mixture while in Scheme III no effort was made to separate the isomers, (48a) and (48b).

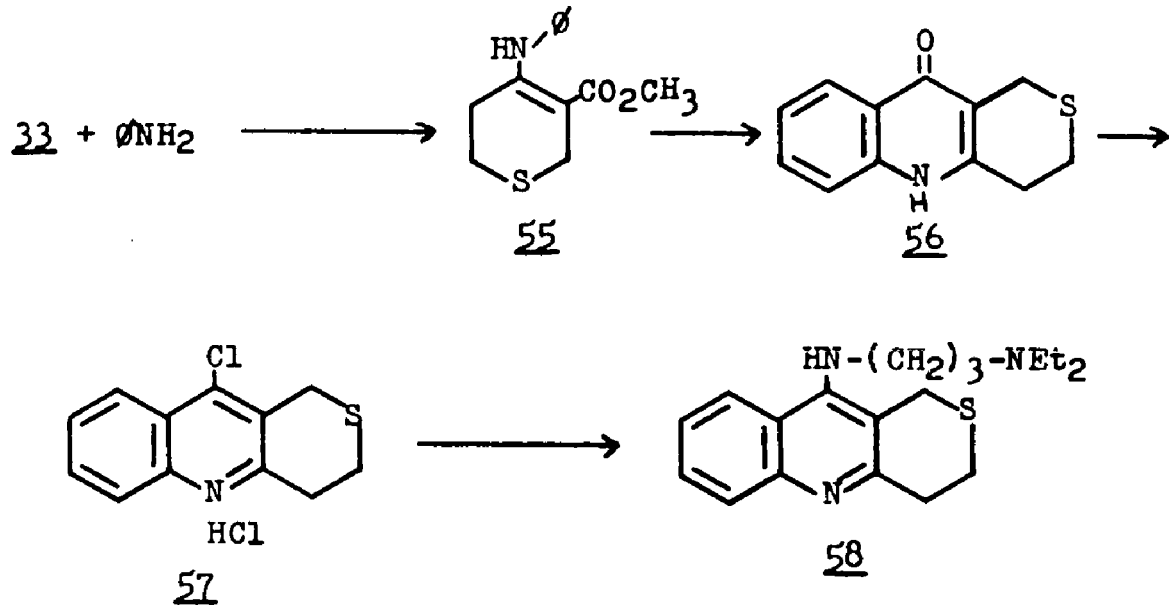
Simple aqueous saponification with sodium hydroxide yielded the carboxylic acid (53). Conversion to the acid chloride with thionyl chloride followed by treatment with stannic chloride gave the tricyclic system as the ketone (54). The acid chloride was never isolated in pure form, but instead was used crude in the ring closure.

Finally, the ketone (54) was converted to the methylene compound (13) in a mixed hydride reduction developed by Urberg and Kaiser[31].

In Scheme III the sulfide mixture, (48a) and (48b), was also saponified with aqueous sodium hydroxide, yielding a mixture of carboxylic acids, (49a) and (49b). The acid mixture was then easily ring closed to a single ketone (50) in cold concentrated sulfuric acid[32]. Again, as in Scheme IV the ketone (50) was converted to the corresponding methylene compound (15) in a mixed hydride reduction utilizing lithium aluminum hydride and aluminum chloride.

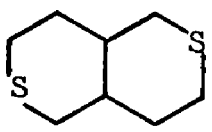
A quinoline derivative (58) of thiapyran was also synthesized as a potentially active anti-malarial agent (Scheme V).

Scheme V

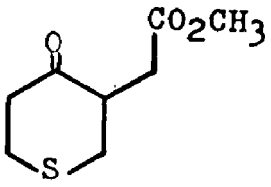


The sequence undertaken involved initial condensation of 3-carbomethoxythiacyclohexan-4-one (33) with aniline to give the α,β unsaturated amine (55). In this case only one olefin was obtained. The ester (55) was smoothly cyclized to the quinolone (56) in refluxing diphenyl ether. The sequence was completed first by conversion of (56) to the chloroquinoline hydrochloride (57) in phosphorus oxychloride followed by alkylation of (57) with the appropriate amine to give (58).

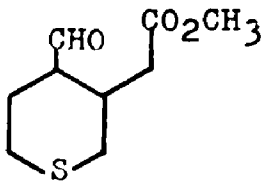
Efforts were also made to synthesize thiapyrano[4,3-c] thiapyran (59) in a manner analogous to Scheme I and II. Initially the pyrrolidino enamine (35) was alkylated with methyl bromoacetate to give (60). However, attempts to homologate the ketone site of (60) in a Wittig reaction with methoxymethylenetriphenylphosphorane[33] to give (61) were unsuccessful.



59



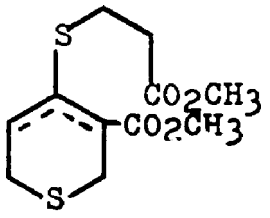
60



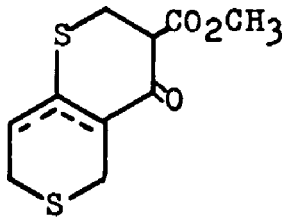
61

Both phenyl lithium[34] and dimsyl sodium[35] were used to initially generate the phosphonium ylid.

Finally, attempts were made to generate the thiapyrano [4,3-b]thiapyran system (14) by an alternate approach. 3-Carbomethoxythiacyclohexan-4-one (33) was thioalkylated with methyl 3-mercaptopropionate, yielding (62). A Dieckmann cyclization of (62) would have given the [4,3-b] system (63), possessing functional sites capable of reactions toward achieving a fully aromatic system.

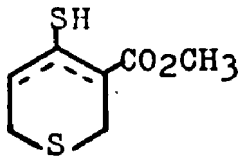


62a & b



63a & b

However, the Dieckmann precursor (62) proved to be unstable under the basic conditions necessary for ring closure and instead fell apart to give what appeared to be 3-carbomethoxy-4-mercaptothiacyclohexan-3-ene (4-ene) (64a and b). Further work in this area was suspended.

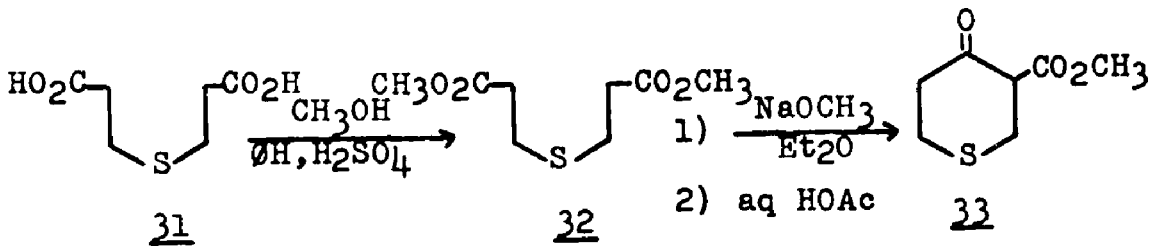


64a & b

Syntheses

Synthesis of Thiapyrano[4,3-b]thiapyran (14) - Scheme I

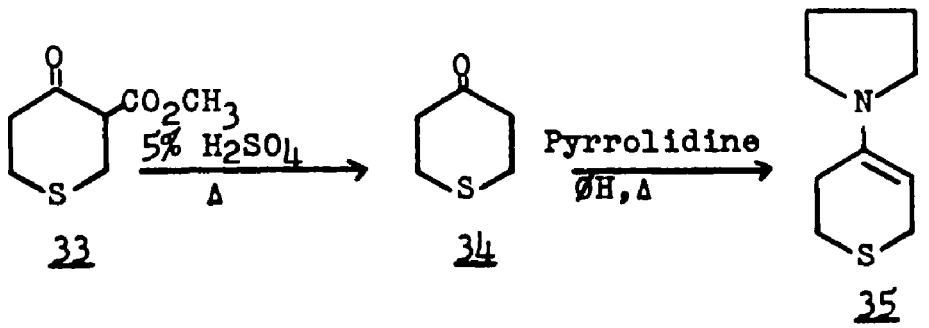
The sequence undertaken involved initial Fischer esterification of commercially available thiodipropionic acid (31) with methanol followed by Dieckmann cyclization[25] to 3-carbomethoxythiacyclohexan-4-one (33).



In the initial attempt to esterify the thiodipropionic acid, the reflux was carried out without stirring the reaction mixture. This resulted in substantial charring and a lower yield of product. In subsequent reactions, the mixture was mechanically stirred during the reflux period. The Dieckmann cyclization was carried out using dry commercial grade sodium methoxide and a freshly opened container of anhydrous diethyl ether. With small amounts of moisture present in either of these two materials, the reaction mixture failed to set up into a paste. This invariably resulted

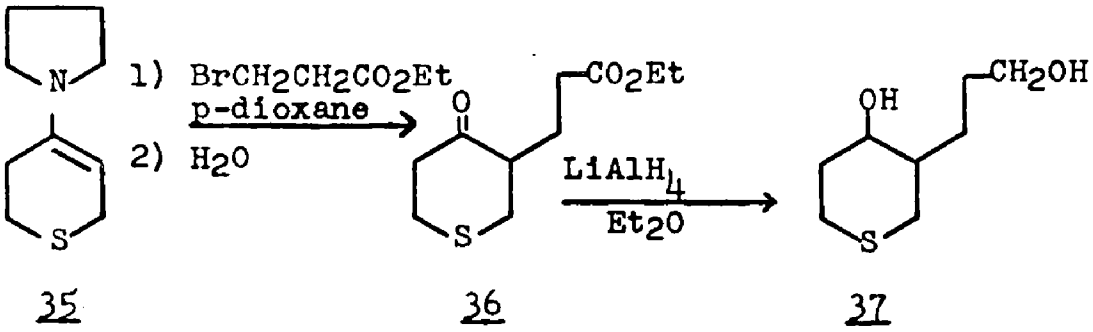
in little or no yield of 3-carbomethoxythiacyclohexan-4-one (33). The workup of the cyclization step required careful acid hydrolysis of the pasty mixture due to its highly exothermic nature. Finally, the ether extracts were tested for the presence of keto ester (33) with a ferric chloride solution. The sensitivity of this reagent toward enols made it difficult to obtain a negative test even after numerous extractions. The keto ester (33) had noteworthy infrared and nmr spectra. The infrared was characterized by an ester carbonyl at 1745 cm^{-1} and ketone at 1715 cm^{-1} plus a chelated ketone at 1660 cm^{-1} and finally a carbon-carbon double bond at 1615 cm^{-1}. These latter two peaks were a direct result of the high degree of enol character of (33). The nmr spectrum indicates the keto ester was ca. 67% enolic as determined by the strength of the hydroxyl proton resonance at δ 12.45 ppm.

The keto ester (33) was then decarbomethoxylated to thiacyclohexan-4-one (34) after a 4 hr reflux in a 5% aqueous sulfuric acid solution. Higher concentrations of acid resulted in substantially lower yields of product.



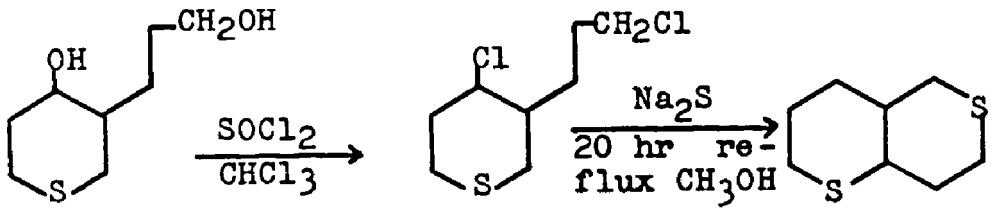
The ketone (34) was then converted to the corresponding pyrrolidino enamine (35) in refluxing benzene. A Dean-Stark trap was used to collect the water generated in the reaction. Invariably, more than the theoretical amount of water was collected due to the presence of water in the commercial grade of pyrrolidine utilized. The freshly distilled enamine (35) was darkened rapidly when exposed to air, but was relatively stable when refrigerated under a nitrogen atmosphere. The more stable morpholino enamine was also synthesized but proved to be less reactive in the subsequent alkylation reaction. The infrared of the enamine (35) possessed a strong carbon-carbon double bond absorption at 1635 cm^{-1} while its nmr spectrum showed a vinyl triplet resonance at δ 4.30 ppm.

4-Pyrrolidinothiacyclohex-3-ene (35) was subsequently alkylated with ethyl-3-bromopropionate in p-dioxane heated to 60-5° for 5 hours. It has been reported[36] that benzene and methanol are satisfactory solvents for enamine alkylations, however p-dioxane proved to be superior in this case. The reactants combined initially to form a pyrrolidinium salt which precipitated as a white solid. This salt then disappeared on hydrolysis to give the alkylated product (36). The infrared of (36) showed an ester carbonyl stretch at 1730 cm^{-1} and a ketone carbonyl stretch at 1710 cm^{-1}.



35 36 37

The alkylation product was reduced to the diol (37) with $LiAlH_4$ in refluxing dry diethyl ether. The workup procedure which proved most successful involved the following two steps: 1) addition of ethyl acetate to destroy the excess $LiAlH_4$ and 2) addition of 4X ml of water to coagulate the aluminum salts where X equals the weight in grams of $LiAlH_4$ used. This is a modification of a method described by Fieser and Fieser[27]. Again in this reduction efficient mechanical stirring was required to prevent clumping of the reaction mixture. The infrared of the diol (37) showed a strong broad hydroxyl absorption centered at 3360 cm^{-1}.

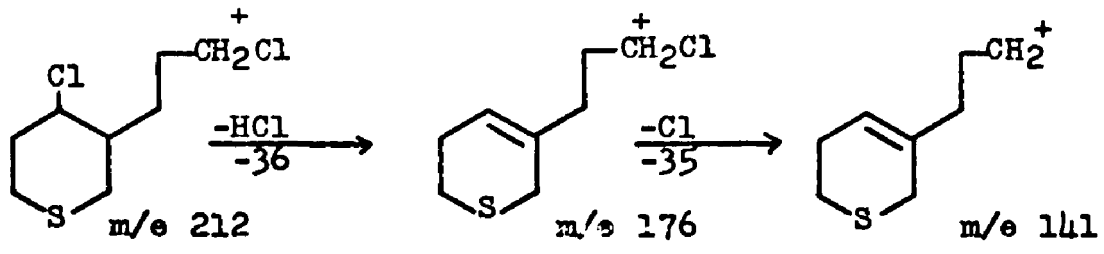


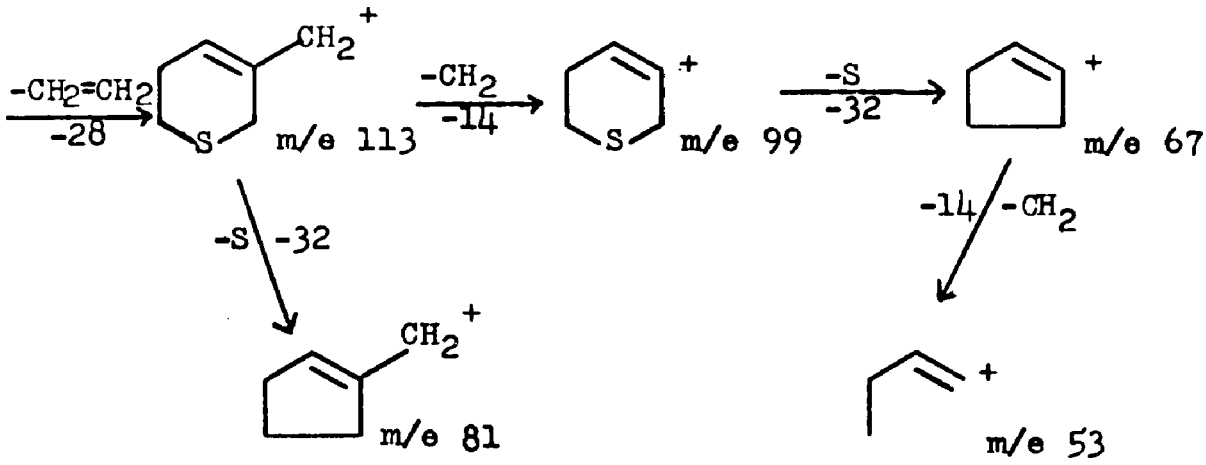
37 38 14

The pale yellow viscous diol (37) was converted to the corresponding dichloride (38) by refluxing with $SOCl_2$ in chloroform for 5 hours. Large quantities of HCl gas were

evolved during the reflux period. A substantial amount of degradation and partial chlorination occurred in addition to the desired reaction, thus accounting for the low yield of pure product. Numerous fractional distillations were required to produce an analytical sample. Again, as in the case of the enamine (35), the product darkened rapidly after several days even in the cold.

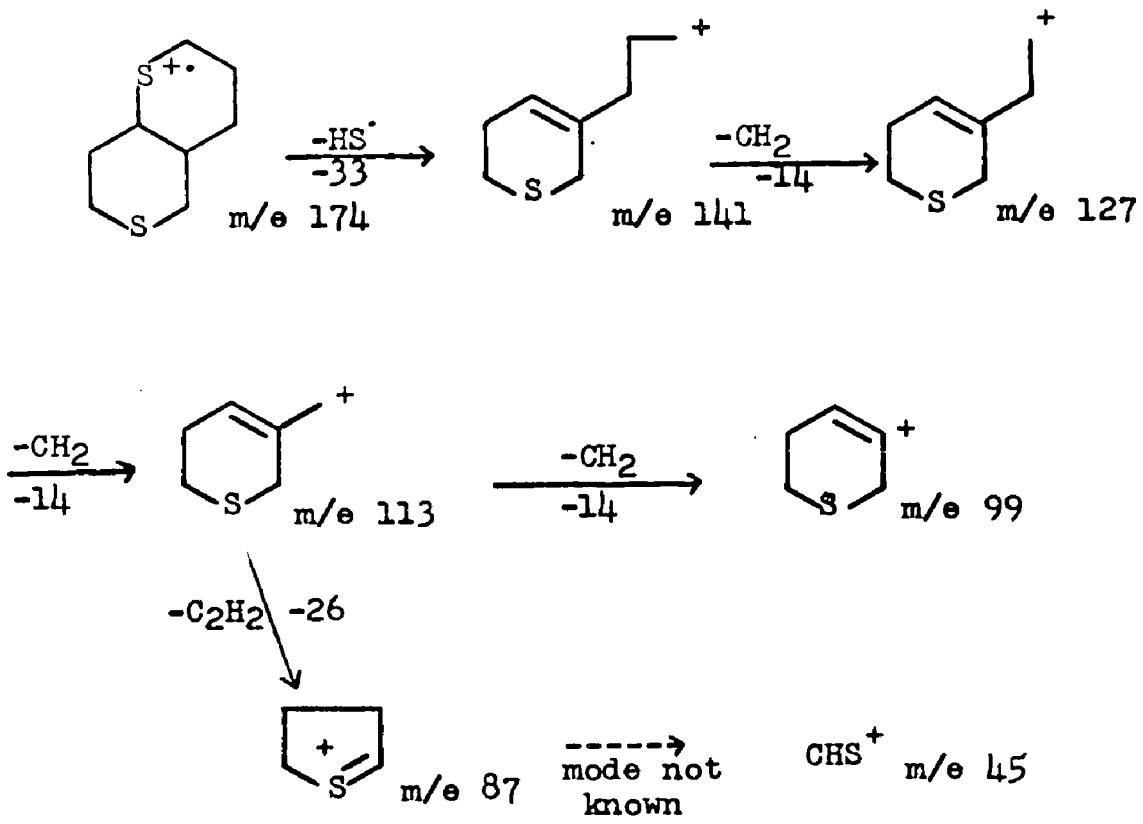
The mass spectrum of the dichloride (38) showed a small parent peak at m/e = 212 with the first major peak being the parent minus an HCl molecule at m/e = 176. Then loss of Cl gave a major peak at m/e = 141 followed by loss of C_2H_4 to give m/e = 113. Cleavage of a CH_2 unit from the 113 peak yielded the base peak at m/e = 99. Sulfur extrusion from the 113 species gave the m/e = 81 peak while a similar loss of sulfur from m/e = 99 yielded the m/e = 67 species. Finally, loss of another CH_2 unit gave a strong peak at m/e = 53.





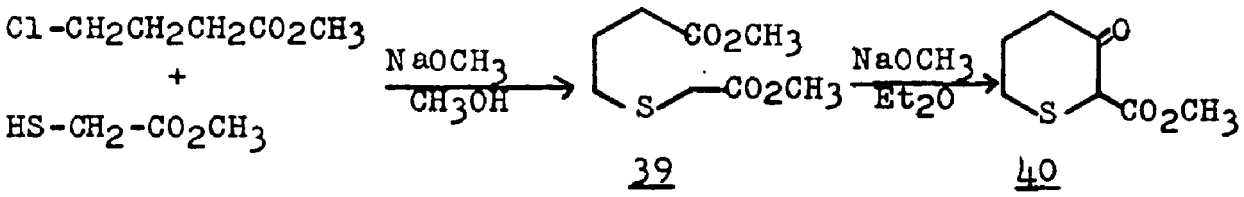
Ring closure of the dichloride (38) to the thiapyrano [4,3-b]thiapyran (14) was accomplished using freshly ground sodium sulfide in refluxing methanol over a period of 22 hours. Both the cis and trans ring fused products were obtained with one isomer, presumably the trans one, crystallizing out of the mixture on refrigeration. Recrystallization from absolute ethanol provided an analytical sample of white needles: mp 96.5-97° possessing a mint-like sulfur smell.

The mass spectral cracking pattern of (14) contains many of the same peaks as the dichloride (38). The stability of (14) is evident in the strong parent peak (66% of base peak) at m/e = 174. Loss of a sulfhydryl group gave a peak at m/e = 141 which then loses a CH_2 unit to yield m/e = 127. Loss of two more CH_2 units produces peaks at m/e = 113 and m/e = 99. The strong m/e = 45 is thought to be CHS^+ although its mode of formation is speculative[37]. The base peak at m/e = 87 is obtained by loss of C_2H_2 from the m/e = 113 species.



Synthesis of Thiapyrano[3,2-b]thiapyran (12) - Scheme II

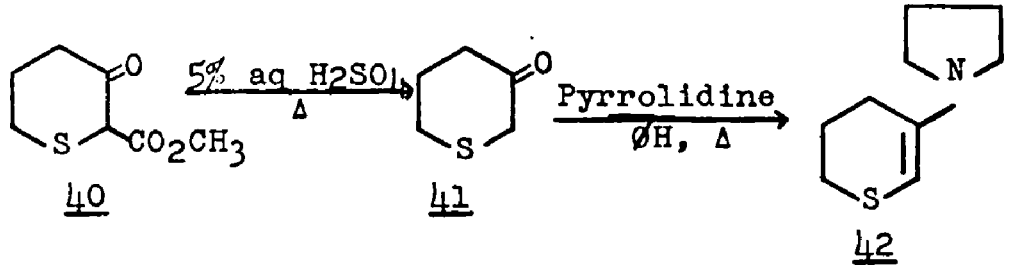
This sequence began with a nucleophilic displacement on methyl 4-chlorobutyrate by methyl mercaptoacetate in the presence of sodium methoxide. The displacement was mildly exothermic with the temperature rising from 5° up to a maximum of 41° in the course of about 2 hours. Most of the sodium chloride generated was suction filtered, with the remainder being removed by diluting the residual oil with an ether/water mixture after stripping off the methanol solvent. The yield of (39) was greater than 80%.



39 40

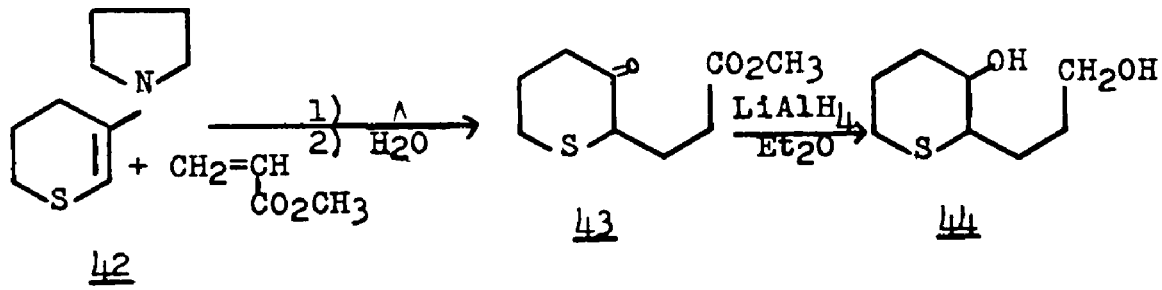
The Dieckmann ring closure was carried out using commercially available sodium methoxide in anhydrous diethyl ether. This reaction differs from its counterpart in Scheme I insomuch as the mixture never solidifies to the point where mechanical stirring becomes impossible. Finally, the exothermic nature of the hydrolysis step of the workup bears careful attention as in Scheme I. This keto ester (40) also showed enolic character. The infrared had an ester carbonyl at 1745 cm^{-1} and a ketone at 1715 cm^{-1} in addition to a chelated ketone stretch at 1645 cm^{-1} and a carbon-carbon double bond at 1600 cm^{-1}. The nmr showed a hydroxyl resonance at δ 12.30 ppm. Integration of the hydroxyl resonance indicated a 63% enol character for (40).

The keto ester (40) was converted to thiacyclohexan-3-one (41) in a refluxing 5% aqueous sulfuric acid solution. The product was collected by vacuum distillation through a Vigreux column. This was in contrast to the low melting solid collected in the similar step in Scheme I. The symmetrical nature of thiacyclohexan-4-one (34) apparently induces crystallization whereas the unsymmetrical thiacyclohexan-3-one (41) remains a liquid.



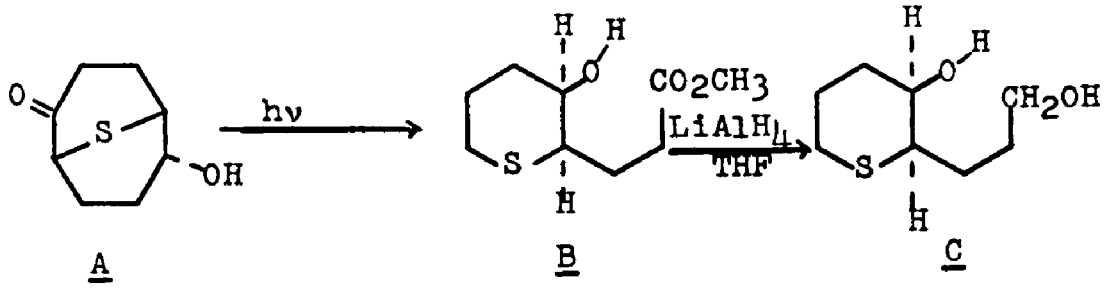
The ketone (41) was next converted to 3-pyrrolidino-thiacyclohex-2-ene (42) in 88% yield. The nmr spectrum of the product indicated exclusive formation of the 2-ene isomer with no trace of the isomeric 3-ene. The vinyl singlet resonance at δ 4.40 ppm integrated for a full proton. The infrared showed a strong carbon-carbon double bond absorption at 1600 cm^{-1}.

The enamine (42) was alkylated with methyl acrylate during a 4 hour reflux in p-dioxane. 2-Carbomethoxyethyl-thiacyclohexan-3-one (43) was collected in 38% yield after distillation at reduced pressure. Longer reflux periods produced no increase in the yield of product. The keto ester (43) displayed an ester carbonyl stretch at 1740 cm^{-1} and a ketone stretch at 1710 cm^{-1} in the infrared spectrum.



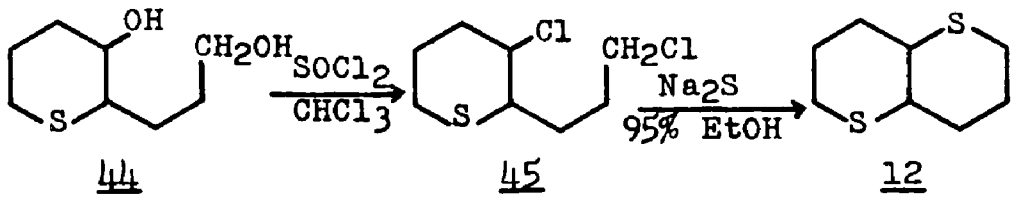
As in Scheme I a modified Fieser and Fieser procedure[27] was used to reduce the alkylation product to the corresponding diol (44). The yield of viscous oil product was 73% after vacuum distillation. There is a strong broad hydroxyl absorption centered at 3380 cm^{-1} in the infrared spectrum.

Ganter and Moser[38] reported the synthesis of the cis isomer of diol (44) which exists as a crystalline solid with mp 74-5° (C). The synthesis involved initial ultraviolet irradiation of the saturated β-ketosulfide (A) to give among other products the hydroxy ester (B).



A B C

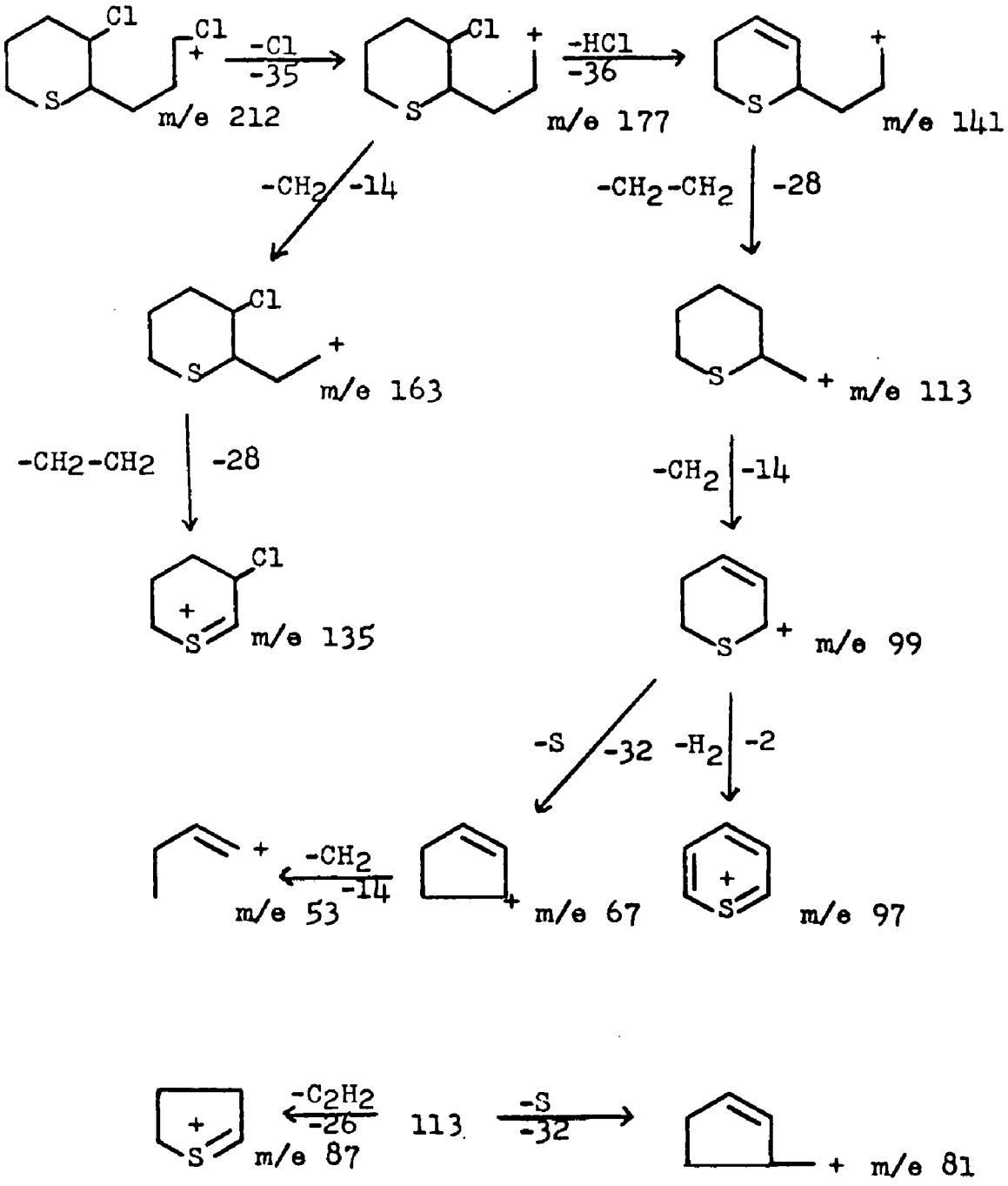
Compound (B) was then converted to the diol (C) by means of lithium aluminum hydride reduction in THF. The infrared of (C) showed a strong hydroxyl absorption at 3615 cm^{-1} and a weaker absorption at 3480 cm^{-1}. Based on the nmr spectral assignments of (C) the nmr spectrum of (44) showed the following: the H-3 proton occurred as a multiplet at δ 3.90 ppm while the H-2 proton was a multiplet at δ 2.85 ppm. The H-6 protons were a multiplet centered at δ 2.53 ppm while the rest of the spectrum consisted of a singlet worth 4 protons at δ 3.68 ppm and a multiplet worth 8 protons at δ 1.70 ppm.



44 45 12

Reaction of the diol (44) with thionyl chloride in chloroform afforded 2-(3-chloropropyl)-3-chlorothiacyclohexane (45) as a pale yellow liquid. Extensive fractional distillations yielded an analytical sample: bp 96-7° (0.07 mm). As in Scheme I the dichloride (45) proved to be unstable toward decomposition.

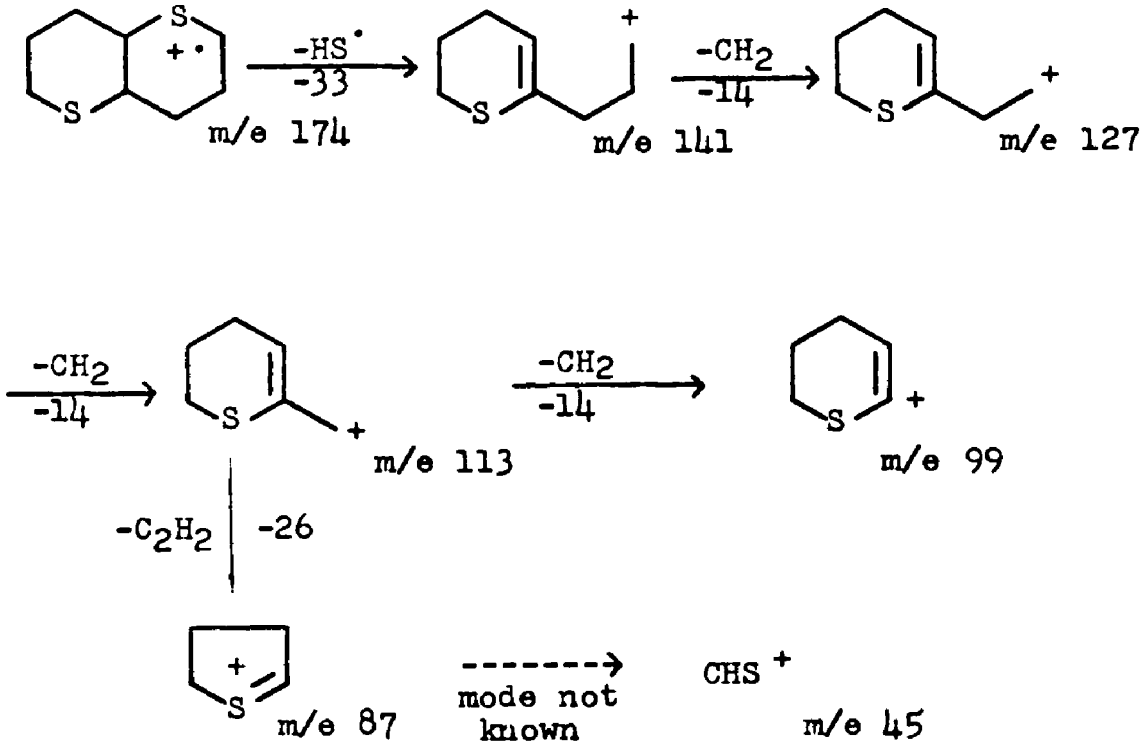
The mass spectrum of (45), however, was slightly different from that of dichloride (38). First, there was a substantial parent peak at m/e = 212 which then lost a Cl unit to give m/e = 177. From this point two different pathways appeared to be operative. One path generated the 141 and 113 peaks by loss of HCl and ethylene, respectively, while the other path produced the 163 and 135 peaks by the loss of a CH_2 unit followed by an ethylene unit. The pathways converge again at m/e = 99. The base peak (m/e = 87) could have been obtained by the loss of acetylene from m/e = 113. After this point the pathways became numerous and complex; however, peaks at m/e 81, 67 and 53 can be envisioned in the following scheme.



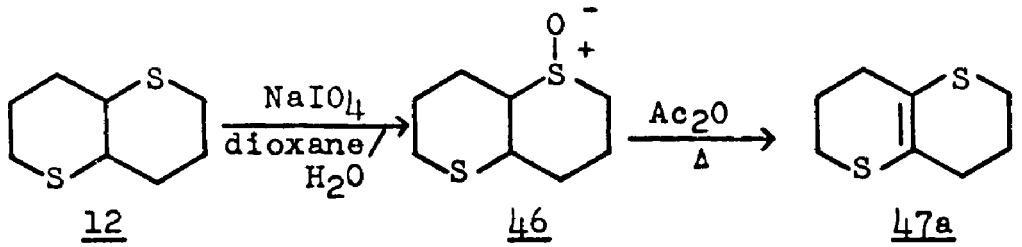
Ring closure of the dichloride (45) to the thiapyrano [3,2-b]thiapyran (12) was effected with sodium sulfide in refluxing 95% aqueous ethanol. The precipitation of sodium chloride was observed as the reaction proceeded. The product (12) was collected in 17% yield as white platelets: mp 68-70°

which gradually crystallized out of a mixture of the cis and trans ring fused isomers. Again, based on symmetry considerations, the crystalline isomer was thought to be the trans ring fused product.

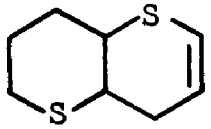
The mass spectrum of thiapyran (12) is virtually identical with that of the isomeric thiapyrano[4,3-b]thiapyran (14) except for the variation in relative intensities of the major peaks. A striking feature was the increased intensity of the parent peak relative to the base peak at m/e = 87 [94% of base compared with 87% of base for the isomeric thiapyran (14)]. The following scheme accounted for the major peaks.



Conversion of the thiapyrano[3,2-b]thiapyran (12) to the monosulfoxide (46) was achieved using sodium meta-periodate in a 50/50 p-dioxane/water solution. Sodium iodate precipitated from solution as the reaction proceeded during overnight stirring at room temperature. The white crystalline sulfoxide was characterized by its strong S-O stretch at 1030 cm^{-1} in the infrared.



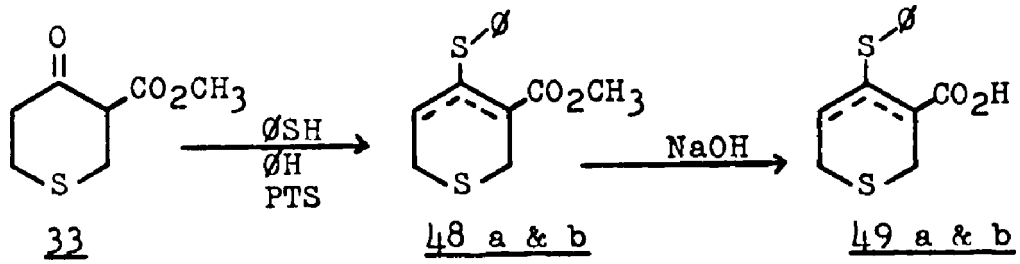
12 46 47a



47b

Heating the sulfoxide (46) in acetic anhydride at 100° for 72 hours effected a Pummerer-type conversion to a mixture of olefins (47a,b). The infrared showed a weak carbon-carbon double bond stretch at 1620 cm^{-1} while the nmr spectrum indicated a 3:1 ratio of internal to external double bonded product. The weak vinyl resonance occurred between δ 6.10 and 5.40 ppm.

Synthesis of 1H-3,4-Dihydrothiapyrano[4,3-b]-1-benzothiapyrylium Perchlorate (51) - Scheme III

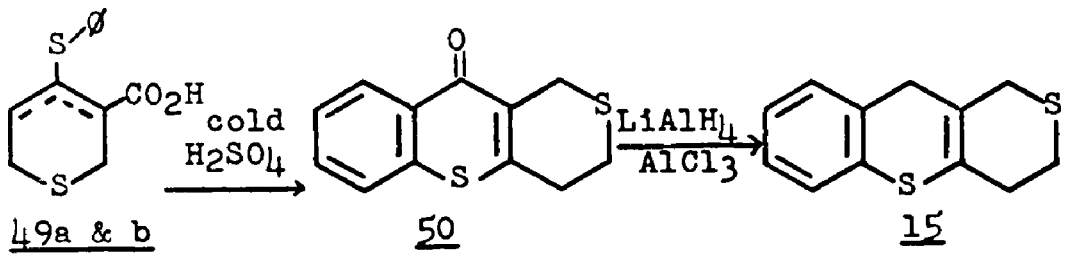


33 48 a & b 49 a & b

The sequence leading toward the tricyclic perchlorate began with a condensation reaction between 3-carbomethoxythiacyclohexan-4-one (33) and thiophenol in refluxing benzene. A Dean-Stark trap was again employed to collect the water produced as the reaction proceeded to completion. After much trial and error experimentation it was deemed necessary to include two grams of p-toluenesulfonic acid catalyst per 25 g of starting keto ester to achieve complete reaction. In the workup procedure it was found necessary to wash the solution with a 10% NaOH solution. Efforts to use a milder base wash led to incomplete removal of excess thiophenol and resultant severe decomposition of the residual oil on attempted distillation. The product was collected as a foul-smelling viscous amber oil in 64% yield. Both the 3-ene (48b) and 4-ene (48a) isomers were generated in the condensation as indicated by both the infrared and nmr data. The infrared showed the non-conjugated carbonyl stretch at 1735 cm^{-1} and the conjugated carbonyl at 1700 cm^{-1}. The carbon-carbon double bond

occurred as a broad peak centered at 1580 cm^{-1}. Comparison of the two methyl resonances at δ 3.60 and 3.70 ppm in the nmr indicated a virtual 50:50 distribution of the two isomers in the mixture.

The mixture of 3-ene and 4-ene isomers was saponified to the carboxylic acid (49a) and (49b) with sodium hydroxide. It was important in the workup to acidify to pH 1-2 in order to avoid working with the sodium carboxylate salt. The two isomeric acids are fractionally crystallized out of benzene to yield on purification (49b) with mp 142-4° and (49a) with mp 159-61°. The infrared spectrum of each isomer showed a broad carboxyl carbonyl centered at 1660 cm^{-1}.

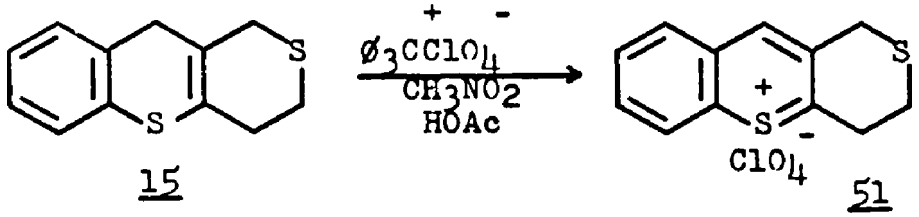


49a & b 50 15

The carboxylic acid mixture was easily converted to 1,3,4,10-tetrahydrothiapyrano[4,3-b]-1-benzothiapyran-10-one (50) by dissolution in cold concentrated sulfuric acid. The yield of tan plates: mp 114-16° was 57% after recrystallization from absolute ethanol. The nmr spectrum of (50) showed no vinyl resonance; i.e., the ring closure gave exclusively the internally double bonded ketone. A noteworth feature of the infrared was the carbonyl stretch at 1600 cm^{-1} and the

carbon-carbon double bond at 1570 cm^{-1}. Prior to this ring closure method, attempts had been made to convert the acid mixture to the acid chloride and then generate the ketone by treatment of the acid chloride with stannic chloride. This route met with little or no success as did phosphorus pentoxide ring closure procedures. These latter two methods usually gave tars or at best recovered starting materials.

The reduction of the ketone (50) to the methylene compound (15) was achieved by the method of Urberg and Kaiser[31]. This involved a mixed hydride reduction using aluminum chloride and $LiAlH_4$ to generate aluminum hydride. The 1,3,4,10-tetrahydrothiapyrano[4,3-b]-1-benzothiapyran (15) was isolated as pale green crystals: mp 62-4° from absolute ethanol. Normal reduction techniques utilizing hydrogenation, sodium borohydride or lithium aluminum hydride failed with this ketone.



15 51

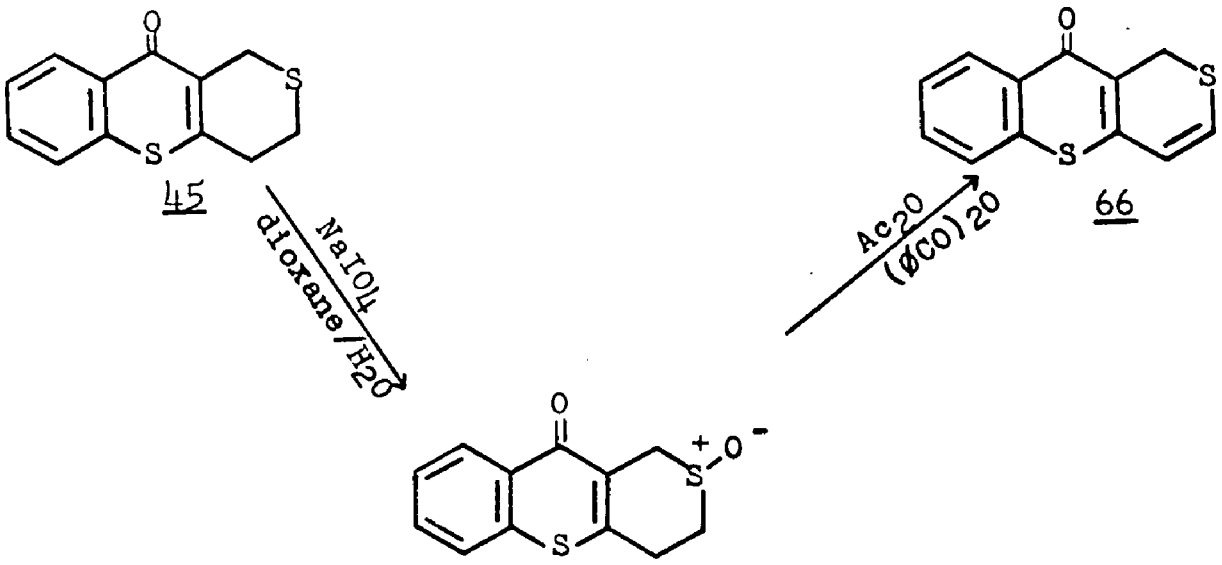
The methylene compound (15) was converted to 1H-3,4-dihydrothiapyrano[4,3-b]-1-benzothiapyrylium perchlorate (51) by treatment with trityl perchlorate[39] in a mixed nitromethane/glacial acetic acid solvent system. The reddish brown crystalline perchlorate salt (51) had a mp dec. >103° and was purified by recrystallization from CH_3NO_2/Et_2O. A

very strong perchlorate stretch occurred at 1050 cm^{-1} in the infrared. The nmr of the perchlorate salt showed the H-10 resonance as a spike at δ 9.20 ppm, the aromatic protons as a multiplet group between δ 7.50-8.80 ppm followed by the H-1 protons as a singlet at δ 4.25 ppm and the H-3 and H-4 protons as triplets centered at δ 3.90 and δ 3.25 ppm. These latter two methylene groups could not be specifically assigned to either of the triplets.

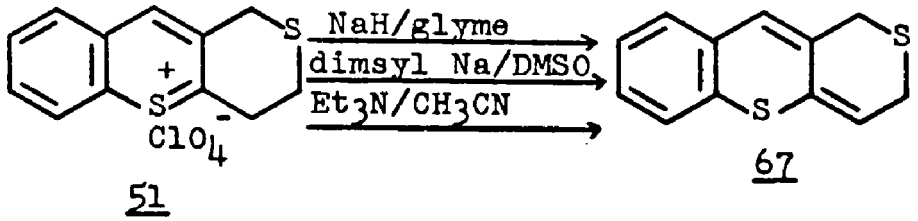
In an effort to introduce unsaturation into the terminal thiapyran ring the sulfoxide (65) was synthesized from (50) in the hope it would undergo a Pummerer-type reaction. As before, the ketone and sodium meta-periodate were stirred overnight at room temperature in a 50:50 dioxane/water solvent system. The 1,3,4,10-tetrahydrothiapyrano[4,3-b]-1-benzothiapyran-10-one-2-oxide (65) was obtained as pale yellow crystals from absolute ethanol with mp 157-60°. The infrared of the sulfoxide showed a very strong $S^{+}O^{-}$ stretch from 1050 to 1010 cm^{-1}. The attempted Pummerer reaction of (65) with acetic anhydride yielded an unworkable tarry material while the use of benzoic anhydride usually gave a quantitative recovery of starting sulfoxide.

On one occasion a small quantity of yellow needles: mp 227-9° was obtained on refluxing the sulfoxide (65) with benzoic anhydride in benzene for 72 hours. The analysis indicated a $C_{16}H_{12}S_2O$ formulation; i.e., the expected $C_{12}H_8S_2O$ (66) plus C_4H_4. The mass spectrum of the needles showed the expected 232 peak plus the dimer at 464. The synthesis of

this material could not be duplicated; hence, it was pursued no further.

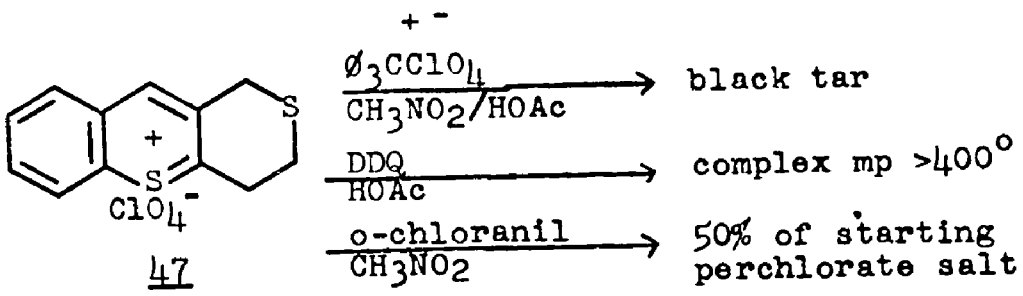


The perchlorate salt (51) was also reacted with a series of bases in the hope of introducing unsaturation into the terminal thiapyran ring to give (67). However, in each case a non-crystalline polymeric solid was obtained which decomposed in the neighborhood of 200°. The only useful information obtained about the product was the disappearance of



the perchlorate absorption at 1050 cm^{-1}. No further work was done along these lines.

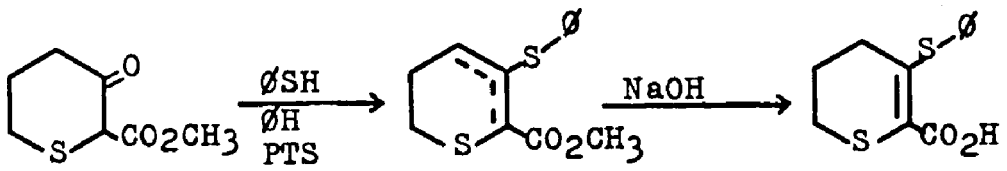
The perchlorate (51) was then subjected to various reaction conditions with high potential quinones and with more trityl perchlorate. Some examples are given below.



47

In general these reactions yielded either dark colored intractable tarry materials or very high melting black complex solids. Sometimes the starting material was recovered. Further work in this area was also stopped.

Synthesis of 2,3,4,10-Tetrahydrothiapyrano[3,2-b]-1-benzothiapyran (13) - Scheme IV

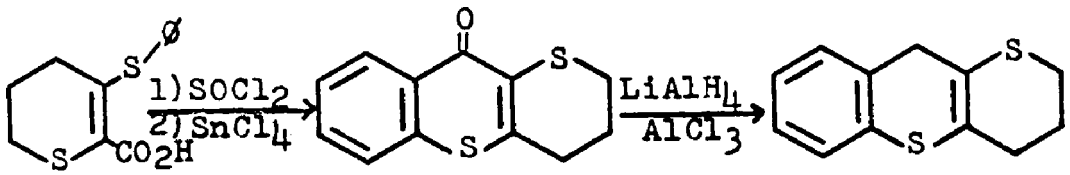


40 52a & b 53

The series of steps leading to 2,3,4,10-tetrahydrothiapyrano[3,2-b]-1-benzothiapyran (13) began with the condensation of 2-carbomethoxythiacyclohexan-3-one (40) with thiophenol in the presence of p-toluenesulfonic acid as a catalyst. Again it was found necessary to use approximately 2 g of catalyst for each 25 g of starting keto ester (40).

As with the isomeric keto ester (33) the reaction yielded two isomeric olefins, namely the 2-ene (52a) and 3-ene (52b) as a mixture. Fractional distillation of the mixture gave two cuts with bp 138-145°(0.1 mm) and bp 146-156° (0.1 mm). The higher boiling cut contained the desired 2-ene as the predominant species. This isomer gradually crystallized and gave white prismatic needles: mp 48-48.5° from n-hexane. The infrared of (52a,b) had a non-conjugated ester carbonyl stretch at 1730 cm^{-1} and a conjugated carbonyl at 1710 cm^{-1}.

Methyl 3-phenylmercaptothiacyclohex-2-ene-2-carboxylate (52a) was converted to (53) by refluxing (52a) for 5 hours in a 10% aqueous sodium hydroxide solution. Recrystallization from benzene provided 69% of a pale yellow solid: mp 122-5°. The nmr spectrum in deuterochloroform showed the carboxyl proton resonance as a singlet at δ 11.02 ppm, the aromatic resonances as a multiplet at δ 7.58 ppm, the H-6 resonance as a triplet at δ 2.87 ppm and H-4, 5 as a multiplet at δ 2.03 ppm.



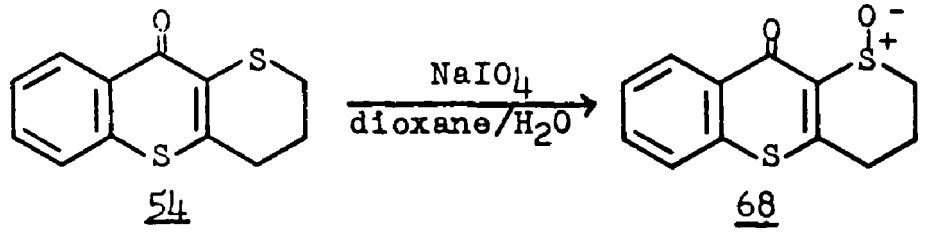
53 54 13

The carboxylic acid (53) was ring closed to the ketone (54) by conversion first to the acid chloride and then treatment with stannic chloride to give 2,3,4,10-tetrahydrothiapyrano [3,2-b]-1-benzothiapyran-10-one (54) as yellow crystals:

mp 178-80°. Polyphosphoric acid ring closure gave a much poorer yield of ketone and the concentrated sulfuric acid method proved totally unsuccessful. The striking feature of the infrared was the carbonyl stretch at 1600 cm^{-1}. The nmr showed the aromatic proton H-9 as a multiplet at δ 8.50 ppm, aromatic protons H-6, 7, 8 as a multiplet at δ 7.55 ppm, the H-2 and H-4 protons as triplets at δ 3.07 ppm and δ 2.78 ppm, and the H-3 protons as a multiplet at δ 2.20 ppm. The H-2 and H-4 protons could not be specifically assigned to either of the triplets.

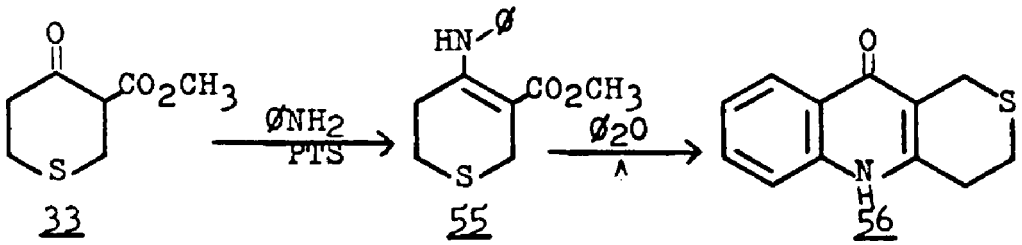
A mixed hydride reduction was successful in converting the ketone (54) to 2,3,4,10-tetrahydrothiapyrano[3,2-b]-1-benzothiapyran (13) in 76% yield. An attempted Huang-Minlon reduction of the ketone using 85% hydrazine hydrate to form the hydrazone, followed by cleavage with KOH to the methylene compound (14) gave only starting material. The methylene compound exhibits an olefinic double bond absorption at 1680 cm^{-1}. The nmr spectrum showed the four aromatic protons as a multiplet at δ 7.08 ppm, the H-10 protons as a singlet at δ 3.20 ppm, H-2 protons as a triplet at δ 2.75 ppm and the H-3, 4 protons as a multiplet centered at δ 2.08 ppm. Here again an attempt was made to utilize a Pummerer reaction to introduce unsaturation into the terminal thiapyran ring. Consequently, the ketone (54) was converted to its corresponding sulfoxide (68) with sodium meta-periodate. Treatment of the sulfoxide with acetic anhydride at 100° for 72 hours yielded an unidentified polymer product. On the

other hand, when (68) was subjected to $(\phi CO)_2O$ in refluxing benzene for 48 hours an 88% recovery of the sulfoxide was realized. Thus this pathway was abandoned.



54 68

Synthesis of 10-(3-Diethylaminopropylamino)-1H-3,4-dihydrothiapyrano[4,3-b]quinoline (58)

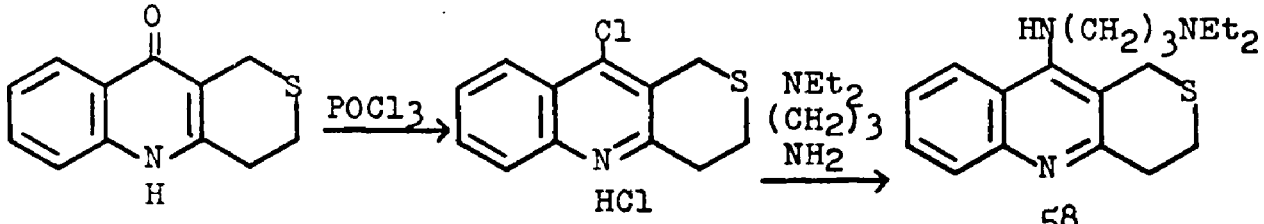


33 55 56

The first step in the generation of the quinoline thiapyran (58) involved the condensation of 3-carbomethoxythiacyclohexan-4-one (33) with aniline (distilled from Zn) in the presence of p-toluenesulfonic acid as a catalyst. The refluxing benzene solution became initially cloudy due to the precipitation of anilinium p-toluenesulfonate. The reaction differs from the previously mentioned thiophenol condensation in that only one isomer, namely 3-carbomethoxy-4-N-phenylaminothiacyclohex-3-ene (55) is formed. The infrared contained the ester carbonyl stretch at 1650 cm^{-1} (conjugated) and the carbon-carbon double bond frequency at 1600 cm^{-1}. The nmr spectrum run in carbon tetrachloride shows the following: N-H resonance as a singlet at 10.95 ppm, aromatic resonance

as a multiplet at δ 3.73 ppm; the H-2 protons at a singlet at δ 3.47 ppm, and the H-5, 6 protons as a singlet at δ 2.63 ppm.

The ester (55) was then converted in one step to the ring closed ketone (56) in refluxing diphenyl ether. The ketone precipitated out of the hot solvent after only 0.5 hour as tan plates: mp 330-5°. The carbonyl absorbs at 1630 cm^{-1} and the carbon-carbon double bond at 1590 cm^{-1} in the infrared. The H-9 aromatic proton occurs as a doublet at δ 7.70 ppm while H-6, 7, 8 occur as a multiplet at 7.20 ppm. The H-1 protons form a singlet at δ 3.27 ppm and the H-3, 4 protons form a pair of triplets at δ 2.80 and 2.35 ppm. The nmr spectrum was run in trifluoroacetic acid



56 57 58

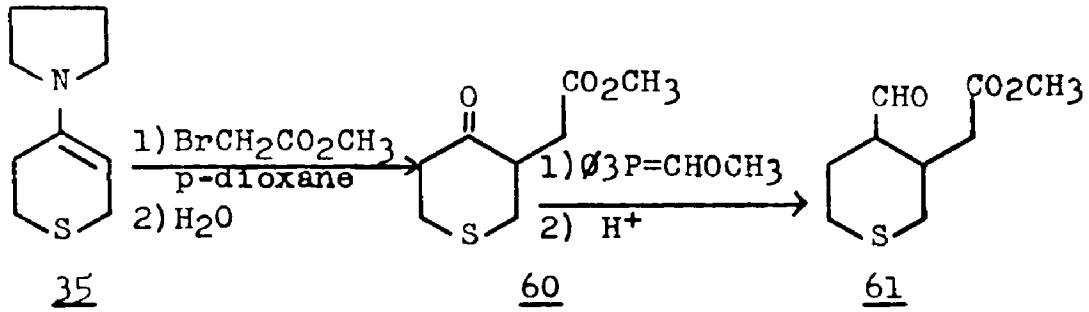
The ketone (56) was rapidly converted to the quinoline hydrochloride (57) in refluxing phosphorous oxychloride. The hydrochloride was obtained in 70% yield as yellow crystals: mp dec. >215°. Neutralization of the hydrochloride produced the free quinoline base as tan plates: mp 102-4°.

The quinoline hydrochloride was then alkylated with N,N-diethyl-1,3-n-propyl diamine at reflux temperature for 20 hours. Distillation yielded 66% of the alkylated quinoline (58); bp 228-32° (0.3 mm). The analytical sample had

a bp 209-11° (0.08 mm). The infrared possesses an N-H absorption at 3270 cm^{-1}. The nmr is quite cluttered due to the presence of numerous aliphatic protons. The aromatics form a multiplet running from δ 8.05 to 7.10 ppm, the N-H is an ill-defined triplet at δ 5.75 ppm and the methyl groups form a well defined triplet at δ 1.05 ppm. The rest of the aliphatic protons form a multiplet of lines from δ 3.60 to 2.30 ppm and a small resonance centered at δ 1.75 ppm. This final compound in the series was sought after in the hope it might show some antimalarial activity. However, such was not the case, so further work with these compounds was terminated.

Miscellaneous Syntheses

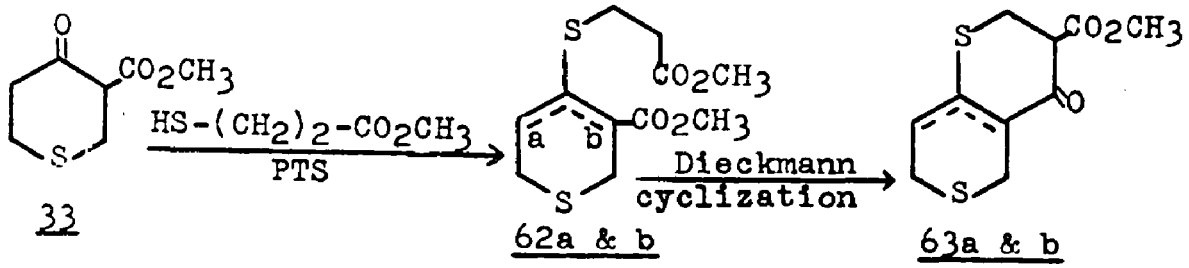
An effort was made at one time to carry out a sequence of steps leading to the thiapyrano[4,3-c]thiapyran (59). The first step was the alkylation of the pyrrolidino enamine (35) with methyl bromoacetate in p-dioxane heated to 50-5° for a total of 2.5 hours. The distilled product solidified after overnight refrigeration to give a 20% yield of 3-carbomethoxymethylthiacyclohexan-4-one (60) as white needles with mp 58-61° when crystallized from petroleum ether. The infrared showed the ester carbonyl frequency at 1730 cm^{-1} and the ketonic stretch at 1700 cm^{-1}. The nmr spectrum showed the methyl resonance as a singlet at δ 3.66 ppm and the rest of the protons as a multiplet grouped between δ 3.2 to 2.0 ppm.



35 60 61

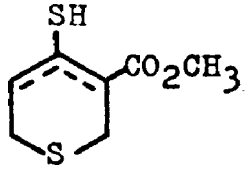
Then a series of unsuccessful attempts were made to homologate the ketonic site using methoxymethylenetriphenylphosphorane [33] in a Wittig reaction. Both phenyl lithium[34] and dimsyl Na[35] were tried as bases to generate the phosphonium ylid. The ylid indeed was generated as evidenced by the blood red color of the solution, however the keto ester (60) failed to react. Since cyclohexanone was found to react in the desired manner under these conditions, it was concluded that the side chain in (60) somehow interferred with the ketonic site, thus preventing the Wittig reaction.

In an attempt to generate the thiapyrano[4,3-b]thiapyran (14) by a slightly different route the following sequence was undertaken.



33 62a & b 63a & b

It was hoped to synthesize the bicyclic system (63a,b) and still retain functional groups necessary for further reactions leading to a fully aromatic system. In the first step, the keto ester (33) was condensed with methyl 3-mercaptopropionate in the presence of some p-toluenesulfonic acid catalyst. The product was collected in 41% yield by vacuum distillation. The infrared of (62a,b) showed a very strong ester carbonyl at 1735 cm^{-1} and a moderate conjugated carbonyl at 1700 cm^{-1}. The nmr spectrum of the mixture (62a) and (62b) in carbon tetrachloride indicated the ratio of (62a):(62b) to be 64:36 based on the strength of the vinyl triplet at δ 6.19 ppm. The rest of the spectrum showed two finely split methyl singlets at δ 3.68 and 3.72 ppm and a grouping of methylene protons as a multiplet from δ 3.5 to 2.4 ppm. No attempt was made to separate the two isomeric α,β unsaturated sulfides. Dieckmann cyclization of the mixture (62a) and (62b) using $NaOCH_3$ as the base produced on distillation a red oil: bp 78-80° (0.08 mm). The infrared of this oil indicated a -SH stretch from 2520-2480 cm^{-1} in addition to an ester carbonyl at 1735 cm^{-1} and a conjugated carbonyl at 1695 cm^{-1}. There is also a carbon-carbon double bond frequency at 1590 cm^{-1}. A possible structure for the red oil might be (64a,b).

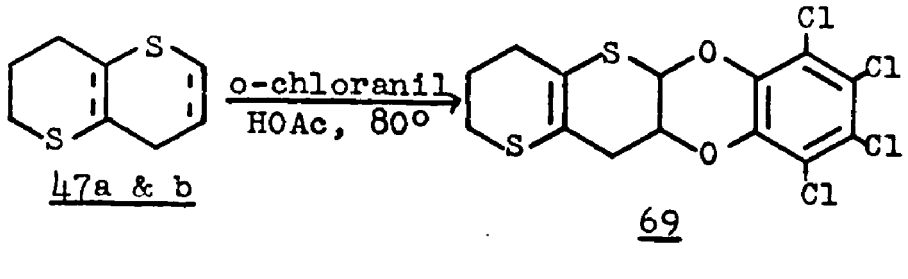


64a & b

Elemental analysis of the red oil indicates a molecular formula of $C_8H_{12}O_2S_2$, i.e., (64a,b) plus a CH_2 group. The nmr spectrum of the oil provided no enlightenment as to the nature of the compound. It consisted of a very small broad resonance at δ 6.10 ppm and a spread of multiplets from δ 3.9 to 2.2 ppm with major singlet spikes at δ 3.68 ppm ($-CH_3$ group) and at δ 2.20 ppm.

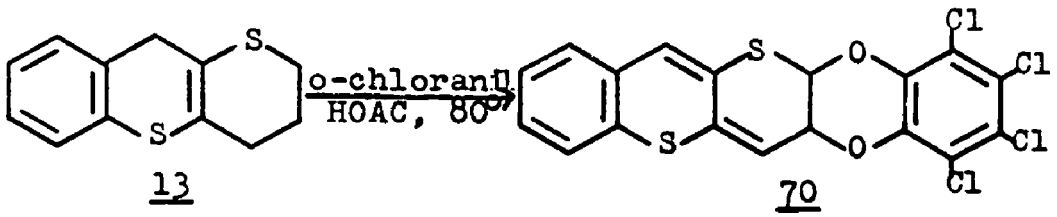
The same red oil was also obtained when cyclization was attempted in glyme with NaH. When run at dry ice/acetone temperatures this particular reaction yielded only the starting diester (62a) and (62b). When an aqueous H_2SO_4 ring closure was tried the only compound isolated was 3-carbomethoxythiacyclohexan-4-one (33). This reaction sequence was thus terminated at this point.

Two final reactions involved the treatment of the thiapyrano[3,2-b]thiapyran olefin (47a) and (47b) and 2,3,4,10-tetrahydrothiapyrano[3,2-b]-1-benzothiapyran (13) with ortho-chloranil in acetic acid.



47a & b

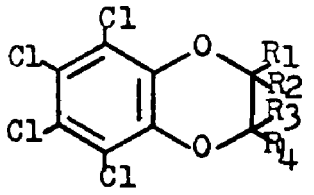
69



13

70

Compound (69) was a black solid which did not melt up to 400° while (70) was a white non-crystalline solid which decomposed above 265°. The elemental analysis of (69) and (70) combined with their mass spectral data indicated that (69) was a structure containing one o-chloranil molecule plus one molecule of (47a,b) which had undergone one dehydrogenation step, while (70) contained one o-chloranil molecule plus one molecule of (13) which had undergone two dehydrogenation steps. The mass spectrum of (69) showed a parent peak at m/e = 416, while the spectrum of (70) indicated the parent peak as m/e = 462. Finally, the infrared spectra of (69) and (70) contained very strong absorptions in the 1450 to 1425 cm^{-1} region. Jackman[40] has reported that o-chloranil undergoes an addition reaction with olefins to form a dioxin structure, e.g. (71). He further stated that the dioxin is

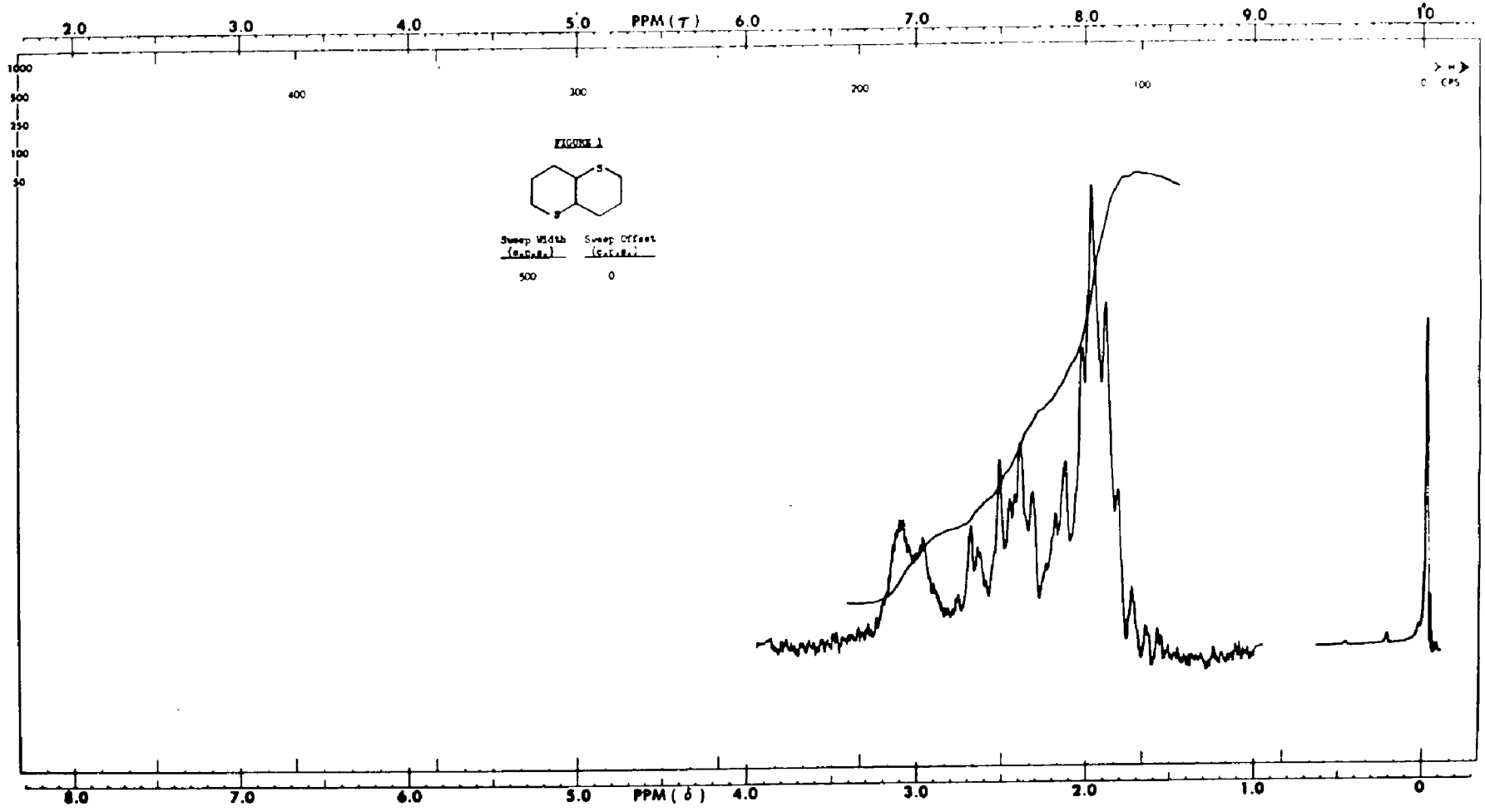


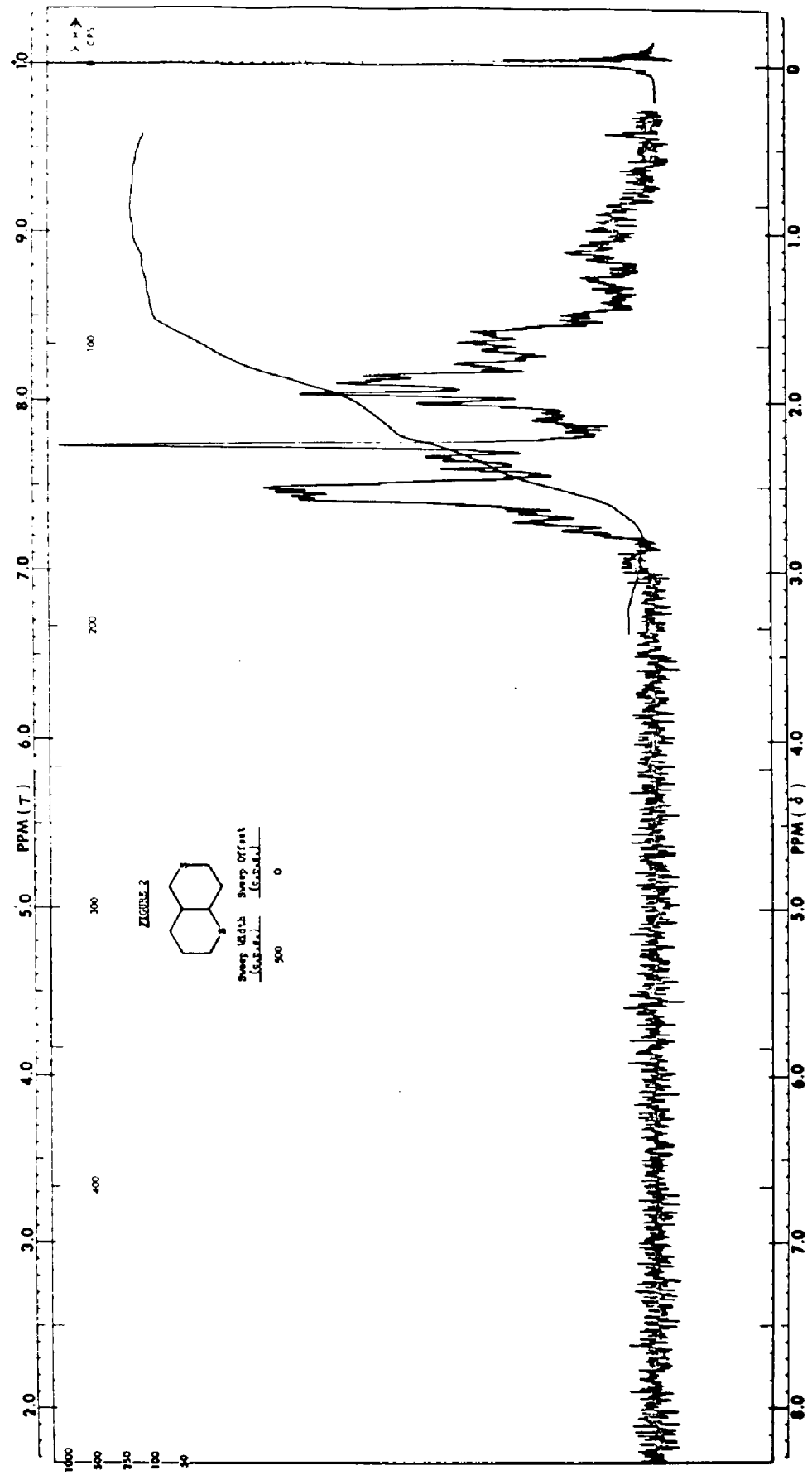
71

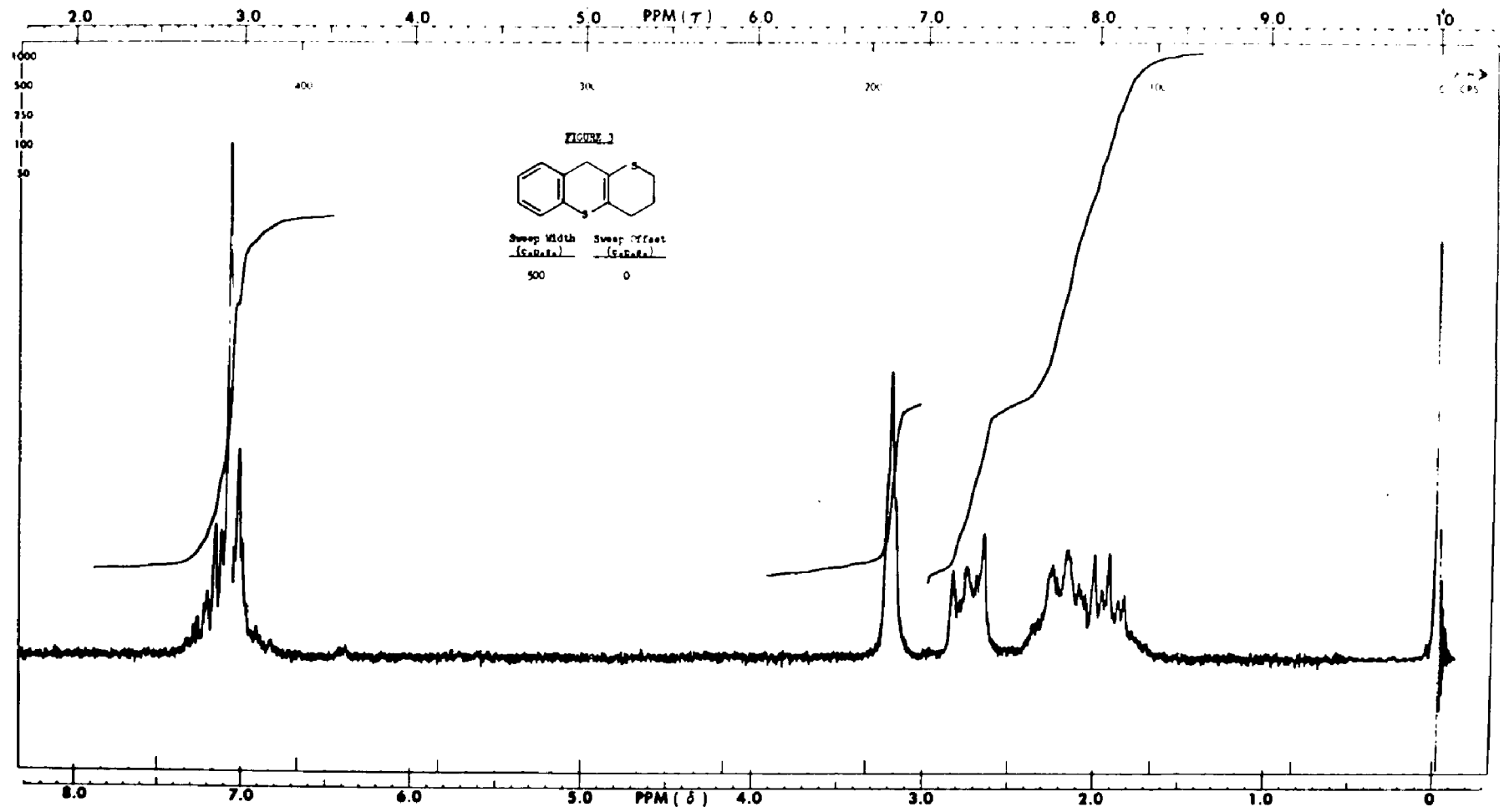
characterized by a very intense band at 1428 cm^{-1} in the infrared which is associated with the C-O-C stretching frequency.

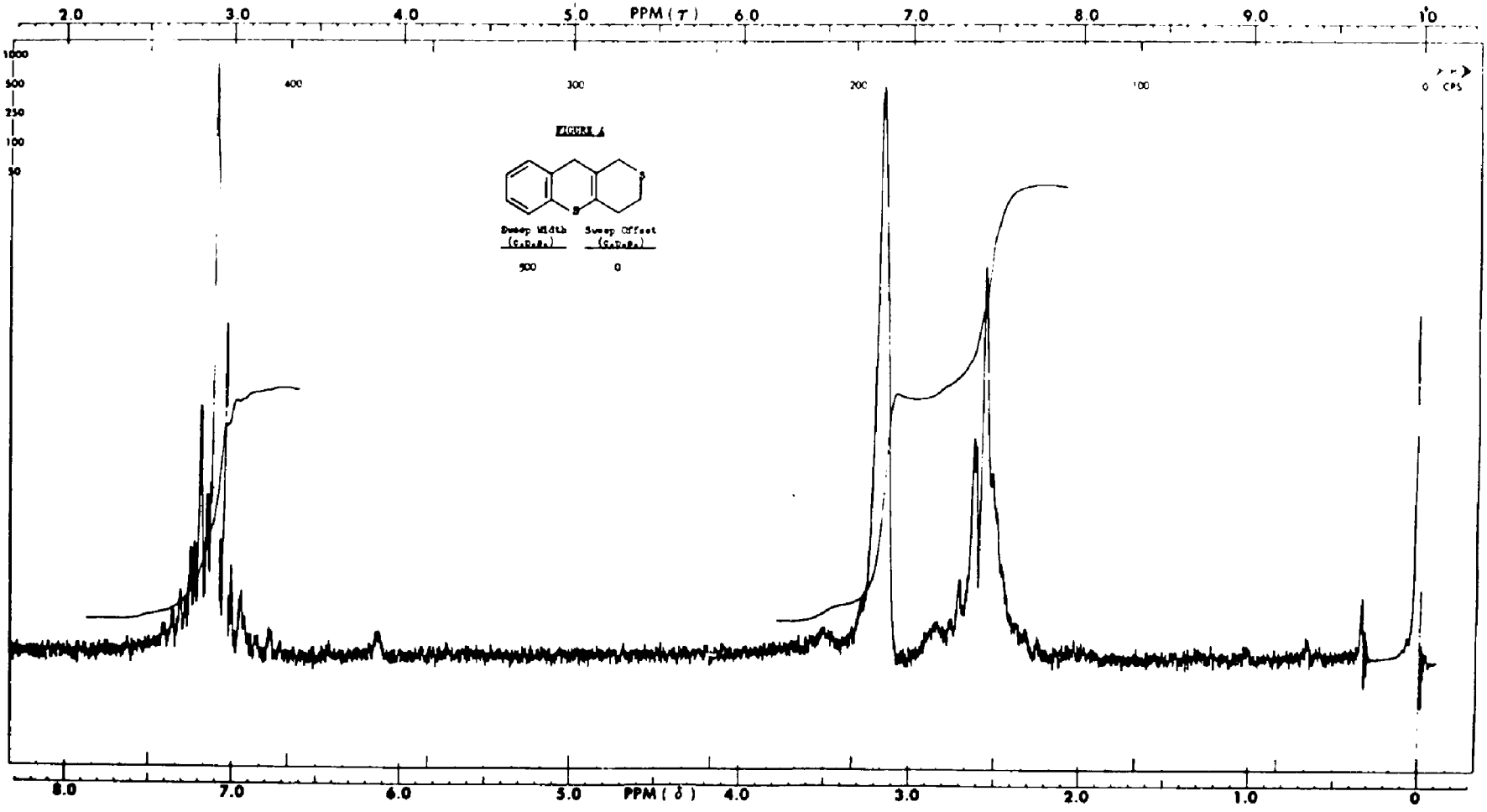
Useful nmr spectra could not be obtained for (69) or (70) due to their extreme insolubility in the available solvents. In addition, an attempted Raney nickel reduction of

(70) produced no characterizable product. Nevertheless, a dioxin-like structure for (69) and (70) is possible based on the data obtained.


2.0
3.0
4.0
5.0
PPM (τ)
6.0
7.0
8.0
9.0
10
1000
500
250
100
50
400
300
200
100
0 CPS
FIGURE 1
S
S
Sweep Width
(CPS/cm)
Sweep Offset
(CPS/cm)
500
0
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0


PPM(τ)
PPM(δ)
FIGURE 2
Sweep Width (cps/div)
500
Sweep Offset (cps/div)
0


2.0
3.0
4.0
5.0
PPM (τ)
6.0
7.0
8.0
9.0
10
1000
500
250
100
50
400
300
200
100
0 CPS
FIGURE 3
S
S
Sweep Width (CPS/cm)
Sweep Offset (CPS/cm)
500
0
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0


2.0
3.0
4.0
5.0
PPM (τ)
6.0
7.0
8.0
9.0
10
1000
500
250
100
50
400
300
200
100
0 CPS
FIGURE 4
Sweep Width
Sweep Offset
500
0
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

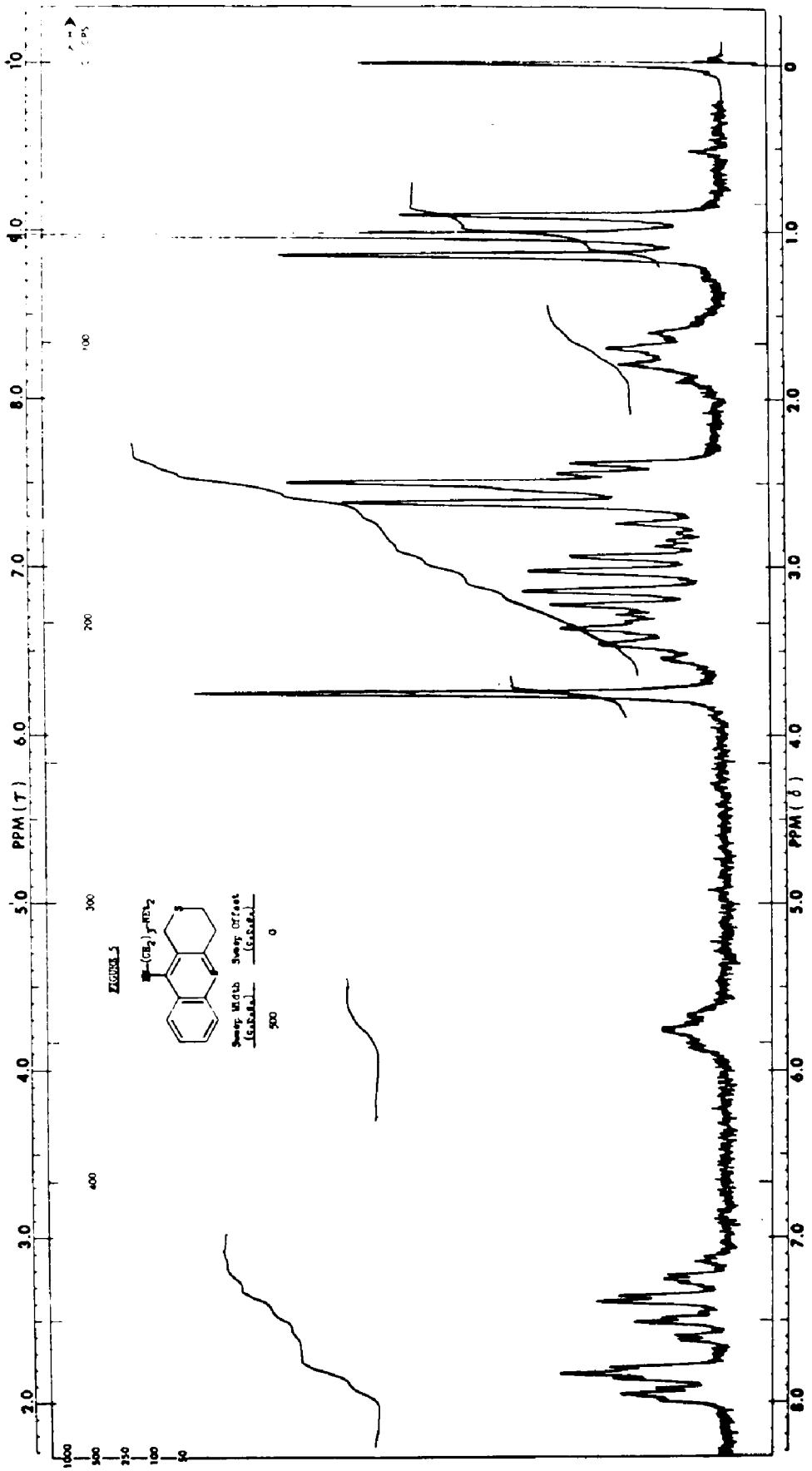
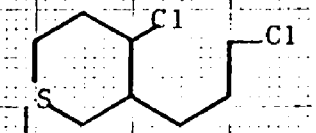
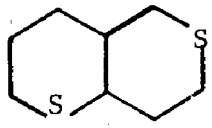

PPM (τ)
PPM (δ)
Sweep Width (Cps/sec)
Sweep Offset (Cps/sec)
900
0

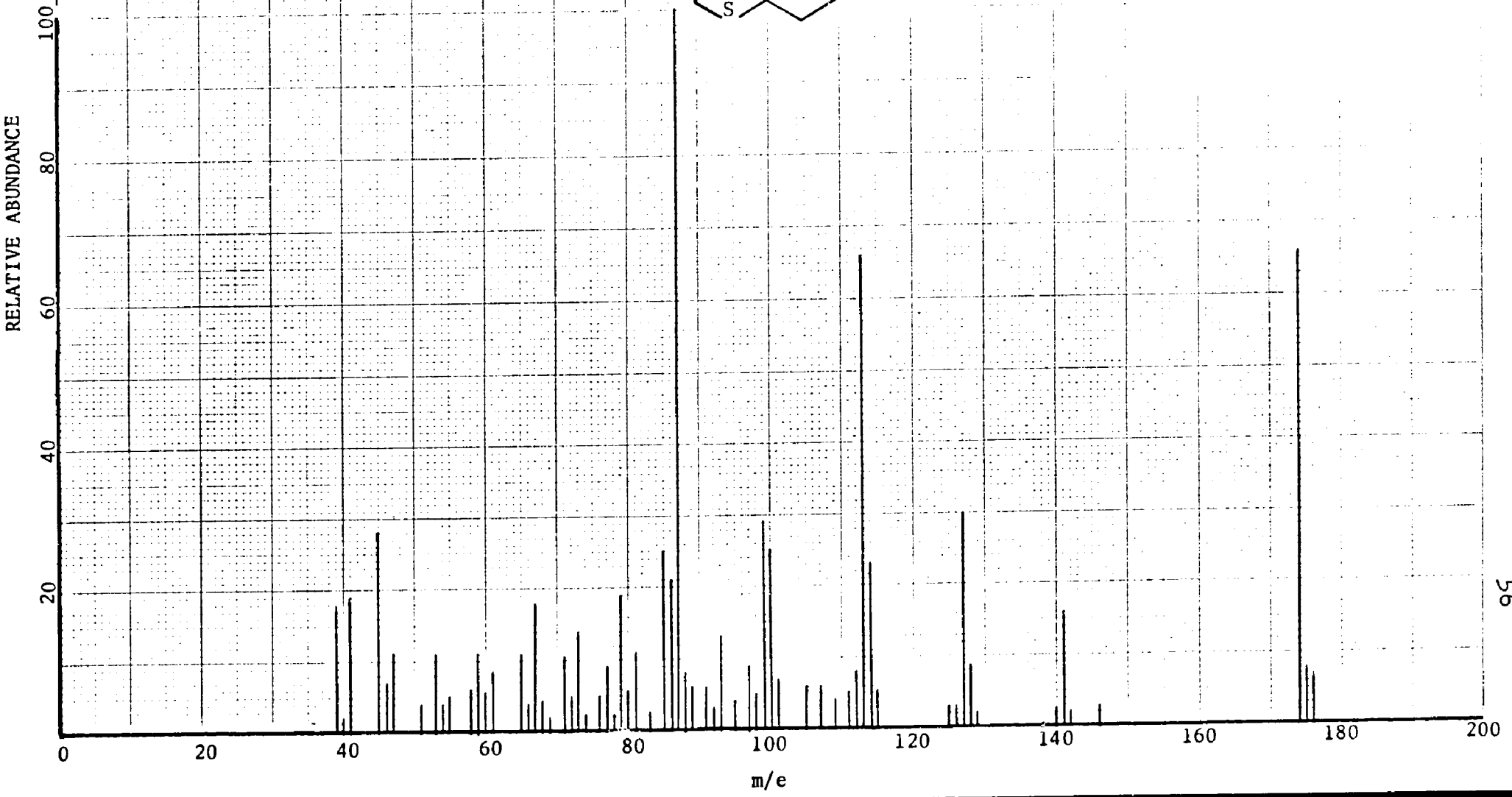
FIGURE 6


Cl
Cl
S

RELATIVE ABUNDANCE
100
80
60
40
20
20
40
60
80
100
120
140
160
180
200
220
m/e

FIGURE 7


S
S


RELATIVE ABUNDANCE
100
80
60
40
20
0
20
40
60
80
100
120
140
160
180
200
m/e

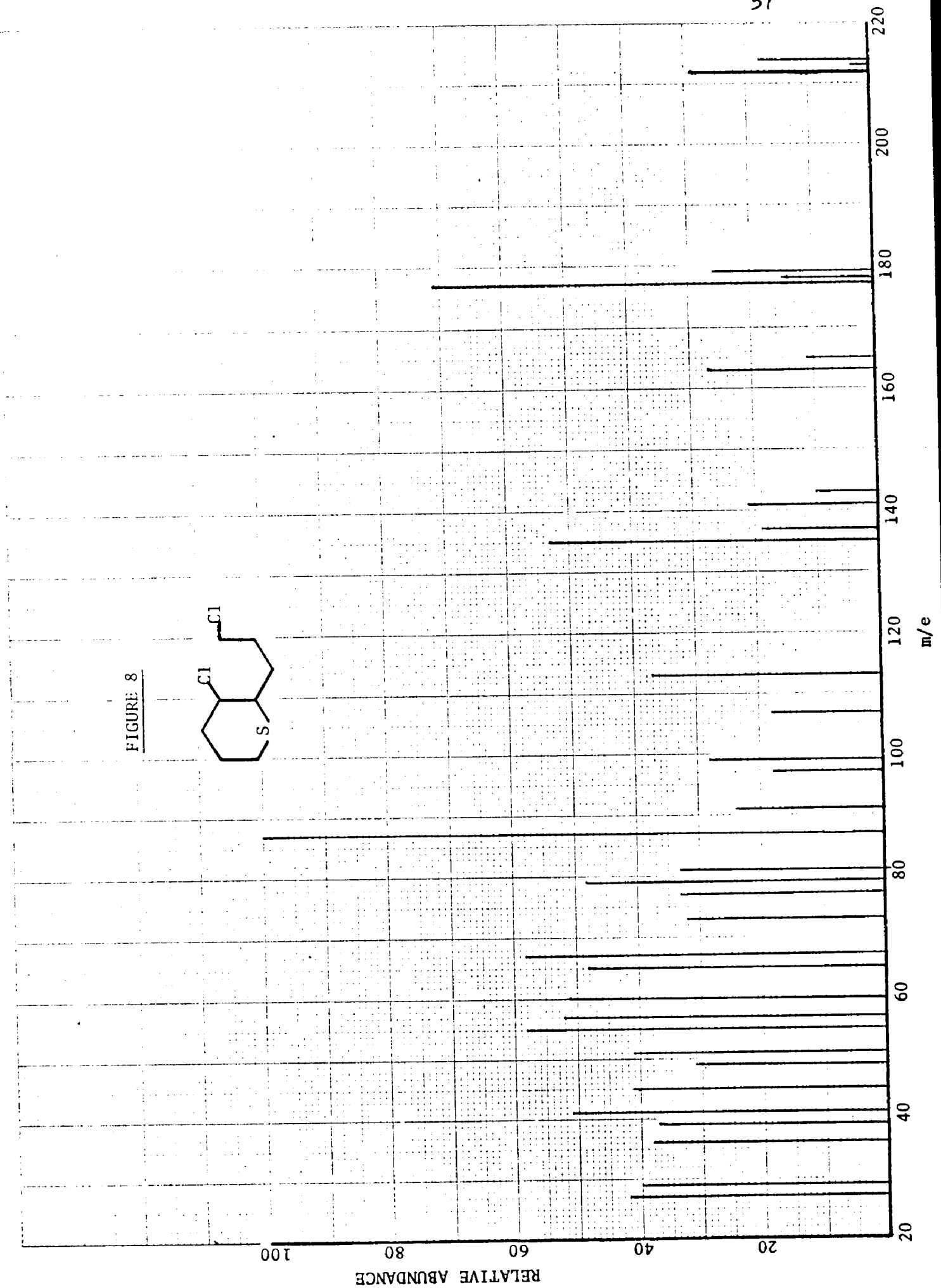
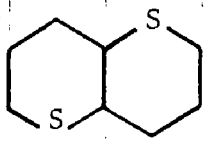

RELATIVE ABUNDANCE
100
80
60
40
20
m/e
220
200
180
160
140
120
100
80
60
40
20
Cl
Cl
S

FIGURE 8

FIGURE 9


S
S

RELATIVE ABUNDANCE
100
80
60
40
20
0
20
40
60
80
100
120
140
160
180
200
m/e

EXPERIMENTAL

Melting points were determined in Kimax capillary tubes using a Mel-Temp apparatus (Laboratory Devices, Cambridge, Mass.) which was calibrated with a standard series of compounds having known corrected melting points. The microanalyses were performed by the late Dr. V. B. Fish (Lehigh University), Galbraith Microanalytical Laboratories, Knoxvill, Tenn. and by George I. Robertson, Florham Park, New Jersey.

Infrared spectra were recorded on a Perkin-Elmer Model 257 instrument. Solid samples were run at approximately 2% concentration by weight, in potassium bromide disks. Liquid samples were run neat between sodium chloride plates.

NMR spectra were determined on a Varian A-60 or Perkin-Elmer R20A spectrometer using tetramethylsilane as the internal standard. Data are presented in the order δ (multiplicity, number of protons, assignment).

The mass spectra were run by Dr. J. E. Sturm (Lehigh University) on a Hitachi 6E high resolution instrument equipped with a double focusing sector.

Methyl 3-(2-carbomethoxyethylmercapto)propionate (32)

To 500 g (2.80 mol) of thiodipropionic acid (31) in 500 ml of anhydrous methanol and 850 ml of anhydrous benzene was added slowly 100 ml of concentrated sulfuric acid. The resulting solution was mechanically stirred and refluxed for 10 hours, cooled, and poured onto water. After separation,

the benzene layer was washed with 5% sodium bicarbonate solution then water and the benzene dried ($MgSO_4$). The benzene was removed on a rotary evaporator and the residual oil distilled through a 4" Vigreux column to yield 519 g (90%) of water white methyl 3-(2-carbomethoxyethylmercapto)propionate (32): bp 152-7° (10 mm); lit.[41] bp 161-2° (18 mm); ir (neat) 2950, 1735 (ester C=O), 1435, 1355, 1250, 1200, 1170.

3-Carbomethoxythiacyclohexan-4-one (33)

To a mechanically stirred slurry of 156 g (2.90 mol) of commercial sodium methoxide in 800 ml of dry ether and 5 ml of methanol was added 236 g (1.14 mol) of methyl 3-(2-carbomethoxyethylmercapto)propionate (32) over a period of 40 minutes. After the addition was complete the mixture solidified to the point where stirring had to be stopped. The mixture was then refluxed for 3 hours, cooled and treated with 1 l. of ice water containing 150 ml of acetic acid. The layers were separated and the aqueous layer extracted with ether until a negative test was given to ferric chloride solution. The combined ether extracts were dried ($MgSO_4$) and the ether removed on a rotary evaporator. The residual oil was distilled through a 4" Vigreux column to give 102 g (52%) of water white 3-carbomethoxythiacyclohexan-4-one (33): bp 94.8° (0.8 mm); lit.[25] bp 120-25° (5 mm); ir (neat) 2950, 2900, 1745 (ester C=O), 1715 (ketone C=O), 1655 (chelated C=O), 1610 (C=C), 1440, 1410, 1380, 1350, 1310, 1260, 1225, 1200, 1070, 835; nmr (CCl_4) δ 12.45 (s, .65, -O-H), 3.75 (s, 3, CH_3), 3.7-2.5 (m, 6, H's, 2,3, 5, 6).

Thiacyclohexan-4-one (34)

A slurry of 50 g (0.287 mol) of 3-carbomethoxythiacyclohexan-4-one (33) in 370 ml of 5% sulfuric acid was stirred and refluxed for 4 hours. The mixture was cooled in an ice bath and slowly neutralized with 10% sodium hydroxide to pH=7. The precipitated product was removed by extraction with four 100 ml portions of ether. The combined ether extracts were dried ($MgSO_4$) and the solvent removed on a rotary evaporator to yield 20.7 g (62%) of thiacyclohexan-4-one (34): mp 60-3° after one recrystallization from pet ether; lit.[41] mp 65-6°; ir (KBr) 2950, 2925, 1700 (C=O), 1440, 1425, 1410, 1320, 1300, 1280, 1250, 1220, 1130, 990, 980, 940, 660.

4-Pyrrolidinothiacyclohex-3-ene (35)

A solution of 20.0 g (0.172 mol) of thiacyclohexan-4-one (34) and 24.5 g (0.345 mol) of pyrrolidine in 150 ml benzene was refluxed in a round bottomed flask fitted with a Dean-Stark trap until no more water was collected (ca. 2 hours). The solution was then cooled and the solvent removed on a rotary evaporator. The residual oil was distilled through a 4" Vigreux column to give 24.4 g (84%) of 4-pyrrolidinothiacyclohex-3-ene (35) as a pale yellow oil; bp 96-8° (0.07 mm); ir (neat) 2960, 2900, 2860, 2805, 1635 (C=C), 1420, 1390, 1350, 1300, 1170; nmr (CCl_4) δ 4.31 (t, 1, C=C-H), 3.30-2.20 (m, 10, ring CH_2's), 2.10-1.70 (m, 4, ring CH_2's).

Anal. Calcd for $C_9H_{15}NS$: C, 63.85; H, 8.93, N, 8.27; S, 18.94. Found: C, 63.55; H, 8.71; N, 8.49; S, 18.68.

3-Carbomethoxymethylthiacyclohexan-4-one (60)

To a mechanically stirred solution of 101.0 g (0.66 mol) of methyl bromoacetate in 500 ml of dioxane heated to 50-5° was added dropwise 101.5 g (0.60 mol) of 4-pyrrolidinothiacyclohex-3-ene (35) over a period of 1.5 hours. After continued heating for 1 hour the mixture was cooled and 50 ml of water added. After 0.5 hour another 50 ml portion of water was added and the mixture stirred for a final 0.5 hour at room temperature. The mixture was then diluted with 1 l. of water and extracted with four 150 ml portions of benzene. The combined benzene extracts were dried ($MgSO_4$) and the solvent removed on a rotary evaporator. The residual oil was distilled through a 4" Vigreux column and the fraction boiling at 95-110° (0.25-0.40 mm) collected. After overnight refrigeration, the fraction solidified and was recrystallized from petroleum ether to give 23.0 g (20%) of 3-carbomethoxymethylthiacyclohexan-4-one (60) as white needles: mp 58-61°. Three more recrystallizations from petroleum ether gave an analytical sample: mp 60-2°; ir (KBr) 2960, 1730 (ester C=O), 1700 (ketone C=O), 1430, 1375, 1350, 1300, 2130, 1190, 1155, 1110; nmr (CCl_4) δ 3.66 (s, 3, $-CH_3$), 3.20-2.00 (m, 9, $-CH_2$'s, C-H).

Anal. Calcd for $C_8H_{12}O_3S$: C, 51.04: H, 6.43; S, 17.03. Found: C, 51.31; H, 6.72; S, 17.26.

3-Carboethoxyethylthiacyclohexan-4-one (36)

To a mechanically stirred solution of 27.7 g (0.164 mol) of 4-pyrrolidinothiacyclohex-3-ene (35) in 300 ml of

dioxane heated to 60-5° was added dropwise 32.6 g (0.18 mol) of ethyl 3-bromopropionate over a period of 0.75 hour. The temperature was maintained for 5 hours. The solution was cooled and two 20 ml portions of water added at 15 minute intervals. The mixture was then diluted with 500 ml of water and extracted with three 75 ml portions of benzene. The combined benzene extracts were dried ($MgSO_4$) and the solvent removed on a rotary evaporator. The residual oil was distilled through a 4" Vigreux column to give 13.55 g (38%) of 3-carboethoxyethylthiacyclohexan-4-one (36) as a pale yellow oil: bp 120-4° (0.1 mm). Redistillation on a short path column gave an analytical sample: bp 130-2° (0.55 mm); ir (neat) 2980, 2960, 2905, 1730 (ester C=O), 1710 (ketone C=O), 1445, 1425, 1375, 1310, 1270, 1185, 1120, 1030; nmr (CCl_4) δ 4.09 (q, 2, $-C\underline{H}_2-CH_3$), 3.10-2.17 (m, 11, $-CH_2$'s, CH), 1.25 (t, 3, $-CH_2-C\underline{H}_3$).

Anal. Calcd for $C_{10}H_{16}O_3S$: C, 55.52; H, 7.46; S, 14.82. Found: C, 55.35; H, 7.39; S, 15.01.

3-(3-Hydroxypropyl)thiacyclohexan-4-ol (37)

To a mechanically stirred suspension of 15.2 g (0.40 mol) of lithium aluminum hydride in dry ether (distilled from sodium hydride) was added dropwise 42.3 g (0.20 mol) of 3-carboethoxyethylthiacyclohexan-4-one (36) over a period of 3/4 hour. The resulting thick suspension was refluxed 1 hour. The excess lithium aluminum hydride was inactivated with approximately 35 ml of ethyl acetate followed by the

dropwise addition of 60 ml of water to coagulate the solids. The mixture was filtered and the white solids washed thoroughly with ether. The combined ether fractions were dried ($MgSO_4$) and the solvent removed on a rotary evaporator. The viscous residual oil was then distilled through a 4" Vigreux column to give 26.0 g (75%) of 3-(3-hydroxypropyl)thiacyclohexan-4-ol (37): bp 160-3° (0.8 mm); ir (neat) 3360 (hydroxyl), 2920, 1425, 1280, 1050, 930; nmr ($CDCl_3$) δ 4.20-1.00 (m, 16).

Anal. Calcd for $C_8H_{16}O_2S$: C, 54.51; H, 9.15; S, 18.19. Found: C, 54.28; H, 8.90; S, 18.45.

4-Chloro-3-(3-chloropropyl)thiacyclohexane (38)

To a mechanically stirred solution of 22.0 g (0.125 mol) of 3-(3-hydroxypropyl)thiacyclohexan-4-ol (37) in 340 ml chloroform was added dropwise 44.6 g (0.375 mol) of thionyl chloride in 75 ml of chloroform over a period of 20 minutes. The mixture was refluxed for 5 hours, cooled, poured onto 1 l. of ice water and stirred for 20 minutes. The layers were separated, the chloroform layer dried ($MgSO_4$) and the solvent removed on a rotary evaporator. The residual oil was distilled through a 4" Vigreux column to give 19.7 g (74%) of 4-chloro-3-(3-chloropropyl)thiacyclohexane (38): bp 110-120° (0.4-0.8 mm). Extensive redistillation produced an analytical sample: bp 102.5-103.5° (0.08 mm); ir (neat) 2940, 1450, 1430, 1300, 1280, 1250, 940, 730, 705, 655; nmr (CCl_4) δ 5.60 (d of t, 1, -CHCl), 3.48 (t, 2,

CH_2Cl), 2.97 (d, 2, S-CH_2), 2.80-1.50 (m, 9, CH_2's, C$\underline{H}$).

Anal. Calcd for $C_8H_{14}SCl_2$: C, 45.08; H, 6.62; S, 15.04; Cl, 33.26. Found: C, 45.35; H, 6.74; S, 14.81, Cl, 32.97.

Octahydrothiapyrano[4,3-b]thiapyran (14)

To a mechanically stirred solution of 21.1 g (0.088 mol) of $Na_2S \cdot 9H_2O$ in 250 ml of methanol heated to reflux was added 15.0 g (0.0705 mol) of 4-chloro-3-(3-chloropropyl)thiacyclohexane (38) in 250 ml of methanol over a period of 1 hour. The resultant mixture was refluxed for 22 hours, cooled, and concentrated to 150 ml. The concentrated solution was then diluted with 400 ml water and extracted with four 75 ml portions of benzene. The combined benzene extracts were dried ($MgSO_4$) and the solvent removed on a rotary evaporator. The residual oil was distilled through a 4" Vigreux column and the fraction with bp 95-107° (0.4 mm) collected. After overnight refrigeration, the fraction solidified and was recrystallized from absolute ethanol to give 2.0 g (16%) of an oily white solid, mp 91-5°. Three more recrystallizations from absolute ethanol gave an analytical sample of octahydrothiapyrano[4,3-b]thiapyran (14): mp 96.5-7°; nmr (CCl_4) δ 2.40 (m, 7), 1.80 (m, 7).

Anal. Calcd for $C_8H_{14}S_2$: C, 55.12; H, 8.10; S, 36.79. Found: C, 55.22; H, 8.28; S, 37.02.

Methyl 4-(carbomethoxymethylmercapto)butyrate (39)

To 1.5 l. of anhydrous methanol cooled to ice

bath temperature was added 210 g (3.75 mol) of commercial grade sodium methoxide over 30 minutes. Then 400 g (3.78 mol) of methyl mercaptoacetate was added over a period of 30 minutes followed by 500 g (3.66 mol) of methyl 4-chlorobutyrate over 30 minutes. The ice bath was removed, a thermometer inserted in place of the dropping funnel and the stirring continued. After the temperature rose to its maximum (41°) the solution was stirred another 2 hours and then left to stand overnight. The precipitated NaCl was filtered off and washed with anhydrous methanol. The combined filtrates were concentrated by rotary evaporation and the viscous residue (containing more precipitated NaCl) taken up in 1.5 l. of a 1:1 ether-water mixture. The ether layer was separated, washed with water, dried ($MgSO_4$) and filtered. The solvent was removed by rotary evaporation and the residual oil distilled through a 4" Vigreux column to give a small forerun: bp 40-107° (0.15 mm) followed by 634 g (84%) of water white methyl 4-(carbomethoxymethylmercapto)butyrate (39): bp 108-15° (0.1 mm). Redistillation gave an analytical sample: bp 118° (0.15 mm); ir (neat) 3000-2850, 1740 broad (C=O), 1440, 1370, 1300-1120, 1010.

Anal. Calcd for $C_8H_{14}SO_4$: C, 46.58; H, 6.84; S, 15.55. Found: C, 46.81; H, 7.11; S, 15.66.

2-Carbomethoxythiacyclohexan-3-one (40)

To a mechanically stirred, ice-cooled suspension of 54 g (1.0 mol) of commercial grade sodium methoxide in 500 ml of

dry ether (over Dri-Na) was added 103 g (0.500 mol) of methyl-4-(carbomethoxymethylmercapto)butyrate (39) over 10 minutes. The reaction mixture partially coagulated when approximately half of the diester had been added but gradually turned to a fine suspension by the end of the addition period. After the addition was complete, the mixture was stirred 1 hour at ice bath temperature followed by 2 hours at room temperature. Then the mixture was hydrolyzed with 200 ml of water containing 60 ml of glacial acetic acid. The ether layer was separated, washed with sodium bicarbonate solution, dried ($MgSO_4$), filtered, and the solvent removed on a rotary evaporator. The residual oil was distilled through a 4" Vigreux column to give 49.7 g (57%) of water white 2-carbomethoxythiacyclohexan-3-one (40): bp 80-4° (0.15 mm). Redistillation gave an analytical sample: bp 84° (0.15 mm); ir (neat) 2940, 1745 (ester C=O), 1715 (ketone C=O), 1645 (chelated C=O), 1600 (C=C), 1435, 1370, 1330, 1295, 1280, 1220, 1175, 1075; nmr (neat) δ 12.13 (s, 0.6, -O<u>H</u>), 4.20 (s, 0.4, H-2), 3.80 (s [split], 3, C<u>H</u>$_2$), 2.80 (m, 2, C<u>H</u>$_2$), 2.30 (m, 4, CH_2's).

<u>Anal</u>. Calcd for $C_7H_6SO_3$: C, 48.26; H, 5.79; S, 18.41. Found: C, 48.21; H, 5.96; S, 18.24.

<u>Thiacyclohexan-3-one (41)</u>

A mechanically stirred solution of 156 g (0.90 ml) of 2-carbomethoxythiacyclohexan-3-one (40) in 500 ml of 5% H_2SO_4 solution was refluxed for 10 hours, cooled and carefully

neutralized to pH=6 with a 10% NaOH solution. This mixture was extracted with several portions of ether and the combined ether extracts washed with water. The ether solution was then dried ($MgSO_4$), filtered, and the solvent removed on a rotary evaporator. The residual oil was distilled through a 4" Vigreux column to give 76.1 g (73%) of thiacyclohexan-3-one (41): bp 55-60° (0.10 mm); lit.[42] bp 101-102° (18 mm). An infrared spectrum of the product proved to be identical with that of an authentic sample; ir (neat) 2920, 1720-1710 (C=O), 1440-1410, 1325, 1235; nmr (CCl_4) δ 4.84 (s, 2, H-2), 4.62 (m, 2, CH_2), 4.07 (m, 4, CH_2's).

3-Pyrrolidinothiacyclohex-2-ene (42)

A mixture of 11.6 g (0.10 mol) of thiacyclohexan-3-one (41) and 8.5 g (0.12 mol) of pyrrolidine in 150 ml of benzene was refluxed for 2 hours during which time 2.5 ml of water was collected in a Dean-Stark trap. The solvent was removed on a rotary evaporator and the residual oil distilled through a 4" Vigreux column to give 13.92 g (88%) of 3-pyrrolidinothiacyclohex-2-ene (42): bp 98-103° (0.10 mm). Redistillation gave an analytical sample: bp 100° (0.10 mm); ir (neat) 2960-2800, 1600 (C=C), 1385, 1350, 1265; nmr (neat) δ 4.39 (s, 1, H-2), 2.95 (t, 4, CH_2's), 2.63 (m, 2, CH_2), 2.17 (m, 4, CH_2's), 1.80 (m, 4, CH_2's).

Anal. Calcd for $C_9H_{15}NS$: C, 63.85; H, 8.93; N, 8.28; S, 18.94. Found: C, 63.62; H, 8.91; N, 8.25; S, 19.04.

2-Carbomethoxyethylthiacyclohexan-3-one (43)

To a stirred solution of 10.0 g (0.0591 mol) of 3-pyrrolidinothiacyclohex-2-ene (42) in 50 ml of p-dioxane at room temperature was added dropwise 5.6 g (.065 mol) of methyl acrylate. The mixture was refluxed for 4 hours, cooled, and 25 ml of water added; stirring was continued for 0.5 hour and then another 25 ml of water was added at which point an oil phase appeared. The mixture was extracted with benzene, the benzene extracts washed with water, dried ($MgSO_4$) and filtered. The solvent was removed on a rotary evaporator and the residual oil distilled through a 4" Vigreux column to give 4.5 g (38%) of 2-carbomethoxyethylthiacyclohexan-3-one (43): bp 118-123° (0.15 mm). Redistillation gave an analytical sample: bp 123-4° (0.15 mm); ir (neat) 2950, 1740, 1710 (C=O), 1440, 1265, 1200, 1170; nmr (CCl_4) δ 3.64 (s, 3, CH_3), 3.55 (m, 1, H-2), 2.80 (m, 2, CH_2), 2.42 (m, 8, CH_2's).

Anal. Calcd for $C_9H_{14}O_3S$: C, 53.44; H, 6.98; S, 15.85. Found: C, 53.71; H, 6.96; S, 15.74.

2-(3-Hydroxypropyl)thiacyclohexan-3-ol (44)

To a mechanically stirred slurry of 21.2 g (0.56 mol) of $LiAlCl_4$ in 600 ml of dry diethyl ether (distilled from NaH) was added dropwise 75.4 g (0.373 mol) of 2-carbomethoxyethylthiacyclohexan-3-one (43) over a period of 50 minutes. The mixture was refluxed for 1 hour, cooled, and 40 ml of ethyl acetate carefully added dropwise to destroy the excess $LiAlCl_4$. Then enough water was slowly added so as to coagulate

the solids. Then the solution was filtered and the solids washed thoroughly with several portions of diethyl ether. The combined ether extracts were dried ($MgSO_4$), filtered, and the solvent removed on a rotary evaporator. The residual oil was distilled through a 4" Vigreux column to give 47.9 g (73%) of 2-(3-hydroxypropyl)thiacyclohexan-3-ol (44): bp 137-43° (0.08 mm). Redistillation gave an analytical sample: bp 150° (0.25 mm); ir (neat) 3380 broad (-OH), 2930-2860, 1950-1150, 1050, 940, 900; nmr ($CDCl_3$) δ 3.90 (m, 1), 3.68 (s, 4), 2.85 (m, 1), 2.53 (m, 2), 1.70 (m, 8).

Anal. Calcd for $C_8H_{12}SO_2$: C, 54.51; H, 9.15; S, 18.19. Found: C, 54.31; H, 8.94; S, 18.15.

2-(3-Chloropropyl)-3-chlorothiacyclohexane (45)

To a mechanically stirred solution of 59 g (0.50 mol) of $SOCl_2$ in 250 ml of chloroform was added dropwise 39.3 g (0.223 mol) of 2-(3-hydroxypropyl)thiacyclohexan-3-ol (44) in 50 ml of chloroform over a period of 0.5 hour. The resulting mixture was refluxed for 5.5 hours, cooled, and left to stand overnight. The solution was then poured onto 1 l. of ice water and stirred for 20 minutes. The layers were separated and the chloroform layer dried ($MgSO_4$), filtered, and the solvent removed on a rotary evaporator. The residual oil was distilled through a 4" Vigreux column to give 32.0 g (67%) of 2-(3-chloropropyl)-3-chlorothiacyclohexane (45): bp 108-12° (0.35 mm). Several redistillations were necessary to give analytical material: bp 96-7° (0.07 mm);

ir (neat) 2950, 2860, 1450, 1285, 790, 740, 650; nmr (CCl_4) δ 3.58 (m, 3), 2.70 (m, 3), 1.95 (m, 8).

Anal. Calcd for $C_8H_{14}SCl_2$: C, 45.08; H, 6.62; S, 15.04; Cl, 33.26. Found: C, 45.29; H, 6.65; S, 15.35; Cl, 33.00.

Octahydrothiapyrano[3,2-b]thiapyran (12)

A stirred solution of 34.7 g (0.163 mol) of 2-(3-chloropropyl)-3-chlorothiacyclohexane (45) and 39.0 g (0.163 mol) of $Na_2S \cdot 9H_2O$ in 300 ml of 95% ethanol was refluxed for 19 hours, cooled, and diluted with an equal volume of water. This mixture was extracted with four 100 ml portions of benzene, the benzene extracts washed with a saturated NaCl solution, then with water and the solution dried ($MgSO_4$) and filtered. The solvent was removed on a rotary evaporator and the residual oil distilled through a 4" Vigreux column. The combined fractions, bp 70-83° (0.4 to 0.12 mm), solidified to a great extent after overnight refrigeration. Recrystallization from petroleum ether gave 5.0 g (17%) of octahydrothiapyrano[3,2-b]thiapyran (12): mp 60-6°. A portion was sublimed and recrystallized to give an analytical sample: mp 68-70°; ir (neat) 2930, 2850, 1440, 1100, 1065, 725; nmr (CCl_4) δ 3.05 (m, 2), 2.40 (m, 4), 1.98 (m, 8).

Anal. Calcd for $C_8H_{14}S_2$: C, 55.12; H, 8.10; S, 36.79. Found: C, 54.91; H, 7.92; S, 36.56.

Octahydrothiapyrano[3,2-b]thiapyran-1-oxide (46)

A solution of 2.00g (0.0115 mol) of octahydrothiapyrano [3,2-b]thiapyran (12) in 50 ml of p-dioxane was added to 2.45

g (0.0115 mol) of $NaIO_4$ in 50 ml of water. The resulting mixture became immediately cloudy and a white fluffy solid precipitated. The mixture was stirred at room temperature for 24 hours, the solid filtered off and the filtrate diluted with 150 ml of water. This solution was extracted with chloroform and the chloroform extracts dried ($MgSO_4$) and filtered. Removal of the solvent on the rotary evaporator gave approximately 1.8 g of an orange solid which was recrystallized from petroleum ether to give 1.0 g (46%) of octahydrothiapyrano[3,2-b]thiapyran-1-oxide (46): mp 100-6°. Three more recrystallizations gave an analytical sample: mp 112-14°; ir (KBr), 2920, 1430, 1060, 1030 (S^+-O^-), 1000, 930.

Anal. Calcd for $C_8H_{14}S_2O$: C, 50.49; H, 7.41; S, 33.69. Found: C, 50.64; H, 7.47; S, 33.45.

2,3,4,6,7,8-Hexahydrothiapyrano[3,2-b]thiapyran (47a) and 4,4a,6,7,8,8a-Hexahydrothiapyrano[3,2-b]thiapyran (47b)

A mixture of 0.75 g (0.00394 mol) of octahydrothiapyrano[3,2-b]thiapyran-1-oxide (46) and 2 ml of acetic anhydride was heated at 100° for 72 hours. The solvent was then removed on a rotary evaporator and the residual oil distilled on a short path apparatus to give a few drops of an oil, bp 77° (0.03 mm), whose infrared was consistent with the desired product (47a) and (47b); ir (neat) 2930, 2840, 1620 (C=C), 1440, 1295, 1255, 1185, 940, 780S, 690, 670; nmr (CCl_4) δ 5.93 (d, 0.25, S-C(H)=CH), 5.55 (multiplet, 0.25,

S-C=C-H), 2.70 (m, 5), 2.08 (m, 7).
H

Anal. Calcd for $C_8H_{12}S_2$: C, 55.76; H, 7.02; S, 37.22. Found: C, 56.03; H, 7.30; S, 36.97.

3-Carbomethoxy-4-phenylmercaptothiacyclohex-3-ene (48a) and 3-Carbomethoxy-4-phenylmercaptothiacyclohex-4-ene (48b)

A solution of 25.0 g (0.144 mol) of 3-carbomethoxythiacyclohexan-4-one (33), 15.8 g (0.144 mol) of thiophenol and 2.0 g (0.0116 mol) of p-toluenesulfonic acid in 150 ml of benzene was refluxed for 18 hours in a round bottomed flask fitted with a Dean Stark trap. A total of 2.5 ml of water was collected. The solution was cooled and washed with four 50 ml portions of a 10% sodium hydroxide solution followed by two 50 ml portions of water. The solvent was dried ($MgSO_4$) and then removed on a rotary evaporator. The residual viscous amber colored oil was distilled through a 4" Vigreux column to give 24.26 g (64%) of 3-carbomethoxy-4-phenylmercaptothiacyclohex-3-ene (48a) and -4-ene (48b): bp 147-53° (0.2 mm). Two more redistillations produced an analytical sample: bp 155-7° (0.3 mm); ir (neat) 3060, 2950, 1735 (ester C=O), 1700 (conj. ester C=O), 1585, 1480, 1440, 1285, 1235, 1200, 1155, 1060, 1030, 950, 750, 700; nmr (CCl_4) τ 7.30 (m, 5, Ar-H), 6.32 (t, 1, H-5), 3.70 and 3.60 (two S, 3, $-CH_3$), 3.50-3.10 (m, 2, H-2 or H-6), 2.90 (t, 1, H-3), 2.70-2.10 (m, 2, H-2 or H-6).

Anal. Calcd for $C_{13}H_{14}O_2S_2$: C, 58.62; H, 5.30; S, 24.07. Found: C, 58.90, H, 5.64; S, 24.00.

3-Carboxy-4-(phenylmercapto)thiacyclohex-3-ene (49a) and 3-Carboxy-4-(phenylmercapto)thiacyclohex-4-ene (49b)

A mechanically stirred solution of 132.5 g (0.498 mol) of 3-carbomethoxy-4-phenylmercaptothiacyclohex-3-ene (48a) and -4-ene (48b) and 19.9 g (0.498 mol) of sodium hydroxide in 400 ml of water was refluxed for 2 hours. At this point the two phases had become one phase. The solution was cooled in an ice bath and carefully acidified to pH=1-2 with a 10% HCl solution. The precipitated carboxylic acid mixture (49a) and (49b) was then extracted with four 100 ml portions of benzene. The combined benzene extracts were dried ($MgSO_4$) and the solution gradually concentrated to precipitate the product. A series of concentration and filtration steps were utilized to collect the product. A total of 77.0 g (62%) of a mixture of (49a) and (49b) was obtained with a broad mp 130-50°. Extensive recrystallization from benzene/petroleum ether yielded the two possible isomeric acids (49a) with mp 142-4° and (49b) with mp 159-61°; (49a) ir (KBr) 3300-3100 (-OH), 3040, 2920, 3830, 1660 (C=O), 1570 (C-C), 1550, 1430, 1410, 1275, 1250, 1175, 870, 760, 750, 690; (49b) ir (KBr) 3300-3100 (-OH), 3040, 2920, 2800, 1660 (C=O), 1550, 1405, 1280, 1250, 950, 940, 760, 720, 700, 690.

Anal. Calcd for $C_{12}H_{12}O_2S_2$: (49a) C, 57.12; H, 4.79; S, 25.41. Found: C, 57.29; H, 4.98; S, 25.12.

1,3,4,10-Tetrahydrothiapyrano[4,3-b]-1-benzothiapyran-10-one (50)

To 75 ml of precooled (3°C) concentrated sulfuric acid in a 200 ml beaker in an ice bath was dissolved 5.0 g (0.02 mol) of 3-carboxy-4-(phenylmercapto)thiacyclohex-3-ene (and -4-ene) (49a) and (49b) with stirring. After overnight refrigeration the solution was poured onto 500 ml of cracked ice to hydrolyze the product. The precipitated 1,3,4,10-tetrahydrothiapyrano[4,3-b]-1-benzothiapyran-10-one (50) was extracted with four 75 ml portions of chloroform. The combined extracts were dried ($MgSO_4$), filtered, and the solvent removed on a rotary evaporator to give 2.6 g (57%) of tan plates of (50) after one recrystallization from absolute ethanol. Two more recrystallizations gave an analytical sample: mp 114-16°; ir (KBr) 3050, 2880, 1600 (C=O), 1570, 1540, 1430, 1350, 1320, 740; nmr ($CDCl_3$) δ 8.50 (m, 1, H-9), 7.58 (m, 3, H-6, 7, 8), 3.82 (s, 2, H-1), 2.95 (t, 4, H-3, 4).

Anal. Calcd for $C_{12}H_{10}OS_2$: C, 61.50; H, 4.30; S, 27.37. Found: C, 61.68; H, 4.24; S, 27.20.

1,3,4,10-Tetrahydrothiapyrano[4,3,b]-1-benzothiapyran (15)

To a mechanically stirred slurry of 4.25 g (0.112 mol) of lithium aluminum hydride in 75 ml of dry diethyl ether (distilled from sodium hydride) was added slowly a solution of 29.8 g (0.224 mol) of $AlCl_3$ in 100 ml of dry ethyl ether. After cooling the mixture in an ice bath, 15.0 g (0.064 mol) of 1H-3,4-dihydrothiapyrano[4,3-b]-1-benzothiapyran-10-one

(50) was added as a solid over a period of 10 minutes. The resultant solution was refluxed for 1/2 hour, cooled, and the excess lithium aluminum hydride carefully destroyed by the addition of ethyl acetate. Then water was added dropwise to coagulate the solids. The solution was filtered and the solids washed with three 75 ml portions of ethyl ether. The combined ether extracts were dried ($MgSO_4$), filtered, and the solvent removed on a rotary evaporator. An analytical sample, bp 124-8° (0.07 mm), was obtained after two successive distillations through a 4" Vigreux column of the initially isolated residual oil. The analytical sample solidified and was recrystallized from absolute ethanol to give 6.0 g (43%) of 1,3,4,10-tetrahydrothiapyrano[4,3-b]-1-benzothiapyran (15) as pale green crystals: mp 62-4°; ir (KBr) 3050, 2870, 2810, 1470, 1450, 1420, 1400, 1290, 1270, 1260, 1120, 1005, 970, 755; nmr (CCl_4) δ 7.10 (m, 4, Ar-H), 3.17 (s, 4, H-1, 10), 2.57 (m, 4, H-3, 4).

Anal. Calcd for $C_{12}H_{12}S_2$: C, 65.41; H, 5.49; S, 29.10. Found: C, 65.69; H, 5.35; S, 29.21.

1H-3,4-Dihydrothiapyrano[4,3-b]-1-benzothiapyrylium Perchlorate (51)

To a magnetically stirred, refluxing solution of 1.0 g (0.0045 mol) of 1,3,4,10-tetrahydrothiapyrano[4,3,b]-1-benzothiapyran (15) in 15 ml of glacial acetic acid was added 1.55 g (0.0045 mol) of trityl perchlorate in 16 ml of nitromethane over a period of 2 minutes. The solution immediately turned deep red. The solution was refluxed for 15 minutes and then

cooled to room temperature ambiently with stirring. Removal of the solvent on the rotary evaporator gave a two phase oil which solidified on cooling. Trituration with ethyl ether removed the triphenyl methane and left a reddish brown solid which was recrystallized from nitromethane-ethyl ether to give 1.0 g (70%) of 1H,3,4-dihydrothiapyrano[4,3-b]-1-benzothiapyrylium perchlorate (51): mp dec. >80°. Five more recrystallizations from CH_3NO_2/Et_2O produced an analytical sample: mp dec. >103°; ir (KBr) 1480, 1420, 1370, 1250, 1100, 1050 (ClO_4^-), 775; nmr (D_3CCN) δ 9.23 (s, 1, H-10), 8.40 (m, 3, Ar-H), 7.48 (s, 1, Ar-H), 4.18 (s, 2, H-1), 3.83 (t, 2, H-3 or 4), 3.17 (t, 2, H-3 or 4).

Anal. Calcd for $C_{12}H_{11}O_2SCl$: C, 45.21; H, 3.48; S, 20.12; Cl, 11.12. Found: C, 45.49; H, 3.49; S, 20.17; Cl, 11.15.

1,3,4,10-Tetrahydrothiapyrano[4,3-b]-1-benzothiapyran-10-one-2-oxide (65)

To a magnetically stirred solution of 4.7 g (0.022 mol) of sodium meta-periodate in 100 ml of water was added in one portion a solution of 5.0 g (0.0214 mol) of 1,3,4,10-tetrahydrothiapyrano[4,3-b]-1-benzothiapyran-10-one (50) in 100 ml of p-dioxane. The solution became immediately cloudy with precipitation of a white solid occurring after a few minutes. Stirring was continued overnight at room temperature. The mixture was then diluted with 150 ml water and extracted with three 100 ml portions of chloroform. The combined chloroform extracts were dried ($MgSO_4$), filtered, and the solvent removed on a rotary evaporator. The resulting crude

solid was recrystallized from absolute ethanol to give 5.0 g (94%) of 1,3,4,10-tetrahydrothiapyrano[4,3-b]-1-benzothiapyran-10-one-2-oxide (65): mp 157-60°. Two more recrystallizations gave an analytical sample: mp 162-4°; ir (KBr) 1605 (C=O), 1585 (C=C), 1550, 1430, 1405, 1355, 1320, 1050-1010 (S-O), 990, 745.

Anal. Calcd for $C_{12}H_{10}S_2O_2$: C, 57.57; H, 4.03; S, 25.62. Found: C, 57.51; H, 4.31; S, 25.59.

Methyl 3-phenylmercaptothiacyclohex-2-ene-2-carboxylate (52a) and Methyl 3-phenylmercaptothiacyclohex-3-ene-2-carboxylate (52b)

A solution of 87 g (0.500 mol) of 2-carbomethoxythiacyclohexan-3-one (40), 55.1 g (0.510 mol) of thiophenol and 6.0 g (0.0348 mol) of p-toluene sulfonic acid in 500 ml of benzene was refluxed for 18 hours in a round bottomed flask fitted with a Dean-Stark trap. A total of 9.0 ml of water was collected. The solution was cooled and washed with four 150 ml portions of 10% NaOH solution followed by two 150 ml portions of water. The benzene fraction was dried ($MgSO_4$), filtered, and the solvent removed on a rotary evaporator. The residual viscous straw-yellow oil was distilled through a 4" Vigreux column to give two large fractions with a combined weight of 60.5 g (45.5%). The fraction with bp 138-45° (0.1 mm) contained both the 2-ene (52a) and 3-ene (52b) isomers. The 3-ene was the predominant isomer in this fraction. The fraction with bp 146-56° (0.1 mm) contained mainly the

2-ene isomer. The fraction solidified to a yellow-white solid which was recrystallized from n-hexane to give white prismatic needles: mp 48-48.5°; (52a) ir (neat) 2950-2920, 1730-1710 (C=O), 1585 (C=C), 1480, 1440, 1290-1210, 1190, 1055, 1030, 750, 695; nmr (CCl_4) δ 7.30 (m, 5, Ar-H), 3.83 (s, 3, CH_3), 2.90 (t, 2, H-6), 2.05 (m, 4, H-4, 5).

Anal. Calcd for $C_{13}H_{14}O_2S_2$: C, 58.61; H, 5.30; S, 24.08. Found: C, 58.40; H, 5.21; S, 24.32.

3-Phenylmercaptothiacyclohex-2-ene-2-carboxylic acid (53)

A mechanically stirred solution of 165 g (0.619 mol) of methyl 3-phenylmercapto thiacyclohex-2-ene-2-carboxylate (52a) and 600 ml of a 10% aqueous NaOH solution was refluxed for 5 hours. At this point the two phase system had become one phase. The solution was cooled in an ice bath and carefully acidified to pH = 1-2 with a 10% HCl solution. The foul-smelling brown precipitate was filtered and air dried. Recrystallization from 600 ml of benzene yielded 108 g (69.1%) of a pale yellow solid (53): mp 122-5°; nmr ($CDCl_3$) δ 11.02 (s, 1, CO_2H), 7.58 (d, 5, Ar-H), 2.87 (t, 2, H-6), 2.03 (m, 4, H-4, 5).

Anal. Calcd for $C_{12}H_{12}S_2O_2$: C, 57.11; H, 4.79; S, 25.41. Found: C, 57.40; H, 4.83, S, 25.51.

2,3,4,10-Tetrahydrothiapyrano[3,2-b]-1-benzothiapyran-10-one (54)

To a mechanically stirred solution of 23.2 g (0.092 mol) of 3-phenylmercaptothiacyclohex-2-ene-2-carboxylic acid (53)

in 250 ml of anhydrous diethyl ether was added 34.5 ml (0.52 mol) of $SOCl_2$ plus 5 drops of pyridine. A condenser and drying tube were then attached and the mixture refluxed for 2 hours. The solution was then cooled and the ether and excess $SOCl_2$ removed on a rotary evaporator leaving the crude acid chloride as a dark brown oil. The acid chloride was dissolved in 250 ml of anhydrous benzene, cooled in an ice bath and 23.4 ml (0.200 mol) of $SnCl_4$ slowly added. The addition was accompanied by gas evolution and the formation of a heavy brown solid. The mixture was allowed to come to room temperature for 2 hours after which it was poured into 250 ml of conc. HCl in 700 g of ice. The resultant mixture was well stirred and the solid filtered off. Benzene extraction of the mother liquor yielded more brown solid upon removal of the solvent. The combined solids were recrystallized from absolute ethanol to give 8.6 g (40%) of 2,3,4,10-tetrahydrothiapyrano[3,2-b]-1-benzothiapyran-10-one (54) as yellow crystals: mp 174-6°. Further recrystallization produced an analytical sample: mp 178-80°; ir (KBr) 1600 (C=O), 1580, 1560, 1530, 1430, 1320, 1145, 830, 810, 750; nmr ($CDCl_3$) δ 8.50 (m, 1, H-9), 7.55 (d, 3, H-6, 7, 8), 3.07, 2.78 (t, 4, H-2,4), 2.20 (m, 2, H-3).

Anal. Calcd for $C_{12}H_{10}S_2O$: C, 61.50; H, 4.30; S, 27.27. Found: C, 61.30; H, 4.48; S, 27.28.

2,3,4,10-Tetrahydrothiapyrano[3,2-b]-1-benzothiapyran (13)

To a mechanically stirred slurry of 1.29 g (0.034 mol) of lithium aluminum hydride in 50 ml of dry diethyl ether (distilled from NaH) was added slowly a solution of 9.1 g

(0.0685 mol) of $AlCl_3$ in 75 ml of dry ethyl ether. After cooling the mixture in an ice bath, 4.0 g (0.0171 mol) of 2,3,4,10-tetrahydrothiapyrano[3,2-b]-1-benzothiapyran-10-one (54) was added as a solid over a period of 10 minutes. The resultant solution was refluxed for 1/2 hour, cooled, and the excess lithium aluminum hydride carefully destroyed by the addition of ethyl acetate. Then water was added dropwise to coagulate the solids. The solution was filtered and the solids washed with three 50 ml portions of ethyl ether. The combined ether extracts were dried ($MgSO_4$), filtered and the solvent removed on a rotary evaporator. The residual oil was distilled through a short path column to give 2.85 g (76%) of 2,3,4,10-tetrahydrothiapyrano[3,2-b]-1-benzothiapyran (13) as a pale yellow oil: bp 133-6° (0.15 mm); ir (neat) 3060, 2920, 1680 (C=C), 1590, 1575 (C=C), 1470, 1450, 1440, 750; nmr (CCl_4) δ 7.08 (m, 4, Ar-H), 3.20 (s, 2, H-10), 2.75 (t, 2, H-2), 2.08 (m, 4, H-3, 4).

Anal. Calcd for $C_{12}H_{12}S_2$: C, 65.41; H, 5.49; S, 29.10. Found: C, 65.50; H, 5.58; S, 28.90.

2,3,4,10-Tetrahydrothiapyrano[3,2-b]-1-benzothiapyran-10-one-1-oxide (68)

To a magnetically stirred solution of 2.72 g (0.0128 mol) of sodium meta-periodate in 50 ml of water was added in one portion a solution of 3.0 g (0.0128 mol) of 2,3,4,10-tetra hydrothiapyrano[3,2-b]-1-benzothiapyran-10-one (54) in 50 ml of p-dioxane. The solution immediately became cloudy with

precipitation of a white solid occurring after a few minutes. Stirring was continued overnight at room temperature. The mixture was then diluted with 100 ml of water and extracted with three 75 ml portions of chloroform. The combined chloroform extracts were dried ($MgSO_4$), filtered, and the solvent removed on a rotary evaporator. The resulting crude solid was recrystallized from absolute ethanol to give 2.6 g (81%) of 2,3,4,10-tetrahydrothiapyrano[3,2-b]-1-benzothiapyran-10-one-1-oxide (68): mp dec. >166°. Two more recrystallizations gave an analytical sample of tan crystals: mp dec. >166°; ir (KBr) 3050, 2900, 1610 (C=O), 1590 (C=C), 1565, 1530, 1440, 1315, 1050, 1030 ($S^{+}-O^{-}$), 990, 750; nmr (CF_3CO_2D) δ 8.55 (m, 1, H-9), 7.83 (m, 3, H-6,7,8), 4.2-2.2 (m, 6, H-2,3,4).

Anal. Calcd for $C_{12}H_{10}S_2O_2$: C, 57.57; H, 4.03; S, 25.62. Found: C, 57.36; H, 4.19; S, 25.41.

3-Carbomethoxy-4-N-phenylaminothiacyclohex-3-ene (55)

To 10.0 g (0.058 mol) of 3-carbomethoxythiacyclohexan-4-one (33) in 100 ml of benzene was added 5.35 g (0.058 mol) of aniline (freshly distilled from Zn) and 1.0 g of p-toluenesulfonic acid as a catalyst. The mixture immediately became cloudy due to the formation of the anilinium p-toluene sulfonate. The solution was refluxed 4 hours and the water generated was collected in a Dean-Stark trap. Approximately 1 ml of water was collected. The precipitated sulfonate was then filtered off, the benzene solution cooled and washed with four 50 ml portions of 10% $NaHCO_3$ solution. The benzene

solution was then dried ($MgSO_4$) and the solvent removed on a rotary evaporator to give 12.0 g (84%) of 3-carbomethoxy-4-N-phenylaminothiacyclohex-3-ene (55): mp 60-70. Three recrystallizations from cyclohexane gave an analytical sample: mp 85-7°; ir (KBr) 1650 (C=O), 1600 (C=C), 1590, 1570, 1490, 1420, 1260-1150, 1060, 765, 740, 710, 700; nmr (CCl_4) δ 10.95 (s, 1, N-H), 7.16 (m, 5, Ar-H), 3.73 (s, 3, CH_3), 3.47 (s, 2, H-2), 2.63 (s, 4, H-5, 6).

Anal. Calcd for $C_{13}H_{15}O_2NS$: C, 62.63; H, 6.06; N, 5.62; S, 12.86. Found: C, 62.61; H, 6.05; N, 5.62; S, 12.80.

1,3,4,10-Tetrahydrothiapyrano[4,3-b]quinoline-10-one (56)

To 75 ml of refluxing dipheny ether in a three-necked flask equipped with a mechanical stirrer and an air condenser was added 5.0 g (0.02 mol) of 3-carbomethoxy-4-N-phenylaminothiacyclohex-3-ene (55) in one portion. The solution turned yellow, then red, and finally reddish brown during the 20 minute reflux. The product began to precipitate near the end of the reflux period. The solution was cooled and the precipitated solid filtered and washed with petroleum ether to give 3.32 g (77%) of 1,3,4,10-tetrahydrothiapyrano[4,3-b]quinoline-10-one (56) as tan plates: mp dec. >330°. Three recrystallizations from methanol gave an analytical sample: mp dec. >330°; ir (KBr) 3260-3240 (N-H), 3050, 2900-2800, 1630 (C=O), 1590 (C=C), 1540, 1490, 1470, 1410, 3150, 1330, 1250, 750; nmr (F_3CCO_2D) δ 7.70 (d, 1, H-9), 7.20 (m, 3, H-6, 7, 8), 3.27 (s, 2, H-1), 2.80 (t, 2, H-3 or H-4), 2.35 (t, 2, H-3 or H-4).

Anal. Calcd for $C_{12}H_{11}ONS$: C, 66.33: H, 5.10; N, 6.45; S, 14.76. Found: C, 66.26; H, 5.06; N, 6.44; S, 14.73.

10-Chloro-1H-3,4-dihydrothiapyrano[4,3-b]quinoline Hydrochloride (57)

To 5.0 g (0.023 mol) of 1,3,4,10-tetrahydrothiapyrano [4,3-b]quinoline-10-one (56) was added 25 ml of $POCl_3$. The solid immediately went into solution to give a dark oil. The product then precipitated and the solution was refluxed for 0.5 hours. The solution was cooled, the solid portion filtered and washed with petroleum ether to give 3.8 g (70%) of 10-chloro-1H-3,4-dihydrothiapyrano[4,3-b]quinoline hydrochloride (57) as yellow crystals: mp dec. >215°.

Anal. Calcd for $C_{12}H_{11}NSCl_2$: C, 52.95; H, 4.07; N, 5.15; S, 11.78; Cl, 26.05. Found: C, 53.07; H, 4.14; N, 5.16; S, 11.84; Cl, 25.89.

Neutralization of the hydrochloride salt gave the free base which was recrystallized from absolute ethanol, giving tan plates: mp 102-4°; ir (KBr) 2260 (HCl), 1920, 1630, 1475, 1360, 1265.

10-(3-Diethylaminopropylamino)-1H-3,4-dihydrothiapyrano[4,3-b]quinoline (58)

A mixture of 5.1 g (0.022 mol) of 10-chloro-1H-3,4-dihydrothiapyrano[4,3-b]quinoline hydrochloride (57) and 57.0 g (0.44 mol) of N,N-diethyl-1,3-n-propyldiamine was refluxed for 20 hours, cooled, and poured onto 600 ml of water. The resultant mixture was extracted with four 100 ml portions of ethyl ether. The combined ether extracts were dried ($MgSO_4$)

and the solvent removed on a rotary evaporator. The residual reddish oil was distilled through a short path column to give 4.8 g (66%) of 10-(3-diethylaminopropylamino)-1H-3,4-dihydrothiapyrano[4,3-b]quinoline (58): bp 228-32° (0.3 mm). Two more distillations gave an analytical sample: bp 209-11° (0.08 mm); ir (neat) 3270 (N-H), 3040, 2950-2800, 1610, 1560, 1490, 1410, 1360, 1280, 1190, 1160, 1125, 1075, 755; nmr (CCl_4) δ 8.05-7110 (m, 4, Ar-H), 5.75 (t, 1, N-H), 3.75 (s, 2, H-1), 3.60-2.30 (m, 12, CH_2's), 1.75 (t, 2, -CH_2), 1.05 (t, 6, CH_3).

Anal. Calcd for $C_{19}H_{27}N_3S$: C, 69.26; H, 8.26; N, 12.75; S, 9.73. Found: C, 69.32; H, 8.11; N, 12.74; S, 9.62.

3-Carbomethoxy-4-(carbomethoxyethylmercapto)thiacyclohex-3-ene (62a) and 3-Carbomethoxy-4-(carbomethoxyethylmercapto)thiacyclohex-4-ene (62b)

A mixture of 50.0 g (0.287 mol) of 3-carbomethoxythiacyclohexan-4-one (33), 34.6 g (0.287 mol) of methyl 3-mercaptopropionate and 5.0 g of p-toluenesulfonic acid (catalyst) in 500 ml of benzene was refluxed in a round bottomed flask equipped with a Dean-Stark trap to collect the water generated. Reflux was continued until no more water came over. Approximately 5.0 ml of water was collected. The benzene solution was cooled and washed with two portions of a 10% Na_2CO_3 solution followed by a washing with water, dried ($MgSO_4$), and the solvent removed on a rotary evaporator. Distillation of the residual oil through a 4" Vigreux column gave 32.0 g (41%) of 3-carbomethoxy-4-(carbomethoxyethylmercapto)thiacyclohex-3-ene (62a) and -4-ene (62b): bp 155-60°

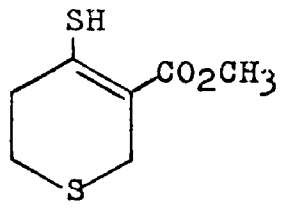
(0.1 mm). Redistillation gave analytical material: bp 135-7° (0.04 mm); ir (neat) 2950, 1735 (C=O), 1700, 1430, 1360, 1280, 1240-1150, 1020; nmr (CCl_4) δ 6.20 (t, 0.65, H-5), 3.72, 3.68 (two s [fine split], 6, CH_3's), 3.30 (t, 2, H-6), 2.76 (m, 8, rest of aliphatic H).

Anal. Calcd for $C_{11}H_{16}O_4S_2$: C, 47.81; H, 5.84; S, 23.20. Found: C, 48.00; H, 5.94; S, 23.30.

Attempted Dieckmann Cyclization of 3-Carbomethoxy-4-(carbomethoxyethylmercapto)thiacyclohex-3-ene (62a) and 3-Carbomethoxy-4-(carbomethoxyethylmercapto)thiacyclohex-4-ene (62b)

To a slurry of 4.9 g (0.09 mol) of commercial grade sodium methoxide in 30 ml of dry Et_2O (distilled from NaH) plus 1 ml of methanol was added 10.0 g (0.0362 mol) of 3-carbomethoxy-4-(carbomethoxyethylmercapto)thiacyclohex-3-ene (62a) and -4-ene (62b) over a period of 35 minutes. The mixture was then refluxed for 3 hours, during which time the solution became pasty. After cooling the mixture was hydrolyzed with 40 ml of ice water containing 7 ml of glacial acetic acid. The ether layer was separated and the aqueous layer extracted with ether until the extracts gave a negative test with $FeCl_3$ solution. The combined ether extracts were dried ($MgSO_4$), filtered, and the solvent removed on the rotary evaporator. The residual oil was distilled through a 4" Vigreux column to give 4.3 g of a red oil: bp 78-80° (0.08 mm). Spectral data were not consistent with the desired product; ir (neat) 2950, 1735, 1695, 1585, 1430, 1340, 1280, 1240, 1190, 1165, 1060,

1025, 960, 760; nmr (CCl_4) δ 4.96 (s, 1, -S<u>H</u>), 3.77 (s, 3, $C\underline{H}_3$), 3.42 (s, 2, H-2), 2.75 (s, 4, H-5, 6), appears to be



Methoxymethylenetriphenyl Phosphonium Chloride

A mixture of 38.2 g (0.146 mol) of triphenyl phosphine and 12.5 g (0.155 mol) of chloromethyl methyl ether in 300 ml of dry benzene (distilled from NaH) was heated to 50° for 72 hours. The solution was then cooled and the precipitated product suction filtered to give 45.6 g (91%) of methoxymethylenetriphenyl phosphonium chloride. Recrystallization from chloroform:ethyl acetate gave 40.8 g of off-white crystals: mp 186-91°; lit.[33] mp 201-2°; nmr ($CDCl_3$) δ 7.75 (m, 15, Ar-<u>H</u>), 5.90 (d, 3, $C\underline{H}_2$), 3.72 (s, 3, $C\underline{H}_3$).

Trityl Perchlorate

Triphenyl carbinol, 5.0 g (0.0192 mol), was dissolved in 75 ml of acetic anhydride with heating. The solution was then cooled to 20° in an ice water bath, the mixture stirred and 6.25 ml of $HClO_4$ added dropwise so as to maintain the temperature. Trityl perchlorate began precipitating before the addition was complete. After the $HClO_4$ was added, the solution was cooled to <10° and stirred for 0.5 hour. The product was then collected by suction filtration on a

sintered glass funnel and washed with several portions of cold diethyl ether. The product was dried in a vacuum desiccator over KOH pellets, yielding 6.2 g (95%) of trityl perchlorate as bright yellow crystals: mp 135-9°; lit.[39] mp 143°.

Attempted Dehydrogenation of 2,3,4,10-Tetrahydrothiapyrano [3,2-b]-1-benzothiapyran (13)

To a magnetically stirred, refluxing solution of 2.2 g (0.01 mol) of 2,3,4,10-tetrahydrothiapyrano[3,2-b]-1-benzothiapyran (13) in 30 ml of glacial acetic acid was added dropwise 4.9 g (0.02 mol) of o-chloranil in 20 ml of glacial acetic acid over a period of 15 minutes. After the addition was complete, the resultant mixture was refluxed for 2 hours. The solution was then cooled to room temperature and the precipitate collected by suction filtration to give 4.0 g of a white non-crystalline solid: mp dec. >260°. The very low solubility of this material in all solvents dictated purification by extraction of impurities with refluxing xylene to give an analytical sample of white powder: mp dec. >265°. The elemental analysis agrees with a $C_{18}H_8Cl_4S_2O_2$ formulation (70); i.e., an adduct of an o-chloranil molecule plus a dehydrogenated molecule of the thiapyran (13). The mass spectrum parent peak of 462 agrees with the above formulation; ir (KBr) 1600, 1445, 1385, 1310, 1285, 1230, 1165, 1110, 1090, 1010, 1000, 865, 835, 755.

Anal. Calcd for $C_{18}H_8Cl_4S_2O_2$: C, 46.78; H, 1.74; S, 13.87; Cl, 30.68. Found: C, 47.03; H, 2.06; S, 14.17; Cl, 30.45.

Attempted Dehydrogenation of Hexahydrothiapyrano[3,2-b]thiapyran-2-ene (47a) and Hexahydrothiapyrano[3,2-b]thiapyran-9-ene (47b)

To a magnetically stirred, refluxing solution of 1.0 g (0.0058 mol) of (47a) and (47b) in 30 ml of glacial acetic acid was added dropwise 4.28 g (0.0175 mol) of o-chloranil in 20 ml of glacial acetic acid over a period of 15 minutes. The resultant mixture was then refluxed another 2.25 hours, cooled and 0.85 g of a purple solid was obtained: mp >410°. Without purification the elemental analysis was not far from a $C_{14}H_{10}Cl_4S_2O_2$ formulation (69); i.e., an adduct of an o-chloranil molecule plus a dehydrogenated molecule of (47a) or (47b). The mass spectrum parent peak of 416 agrees with the above formulation; ir (KBr) 1670, 1450, 1425, 1395.

Anal. Calcd for $C_{14}H_{10}Cl_4S_2O_2$: C, 40.80; H, 1.48; S, 15.56. Found: C, 41.16; H, 1.99; S, 17.34.

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