A NOVEL SYNTHESIS OF 1,5-DITHIOCINS

by

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This thesis reports a novel synthetic method for the formation of 6,12-imino-6*H*,12*H*-dibenzo[b,f]-1,5-dithiocin. Dithiocins are a new and interesting class of conformationally rigid, cleft-shaped molecules, which may be useful in molecular recognition problems and supramolecular chemistry. These molecules are also chiral, locking two aromatic rings in an almost perpendicular fashion. The preparation of these compounds was accomplished by the formation of a requisite aldehyde through *ortho*-lithiation followed by treatment with ammonium acetate to form the desired bicyclic compounds in excellent yields. N-Alkylated dithiocins have also been prepared in a similar manner using a variety of different primary amines and amino acids. Functionalized derivatives of 1, 5-dithiocins by methods which acylate and phenylate at the N-site are also outlined. The naphthalene analogues as well as the tricyclo compounds have been prepared, which provide even larger V-shaped cavities. Due to the chiral nature of this compound, an attempt to resolve the 1, 5-dithiocin was undertaken and the results have been reported. The complexation of these compounds with heavy metals was also examined.

TO IAN PREYRA

Whose generosity and support will always be remembered.

I want to extend my sincerest gratitude to Prof. I.W.J. Still for his unfailing good nature, guidance and friendship during this project. His advice and encouragement during those down periods, which were often too close in between, has especially been helpful.

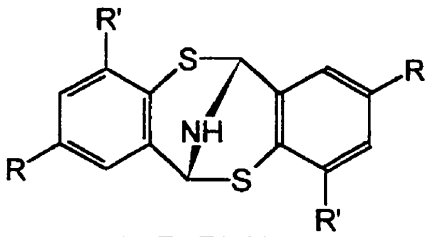
I would also like to thank Dean Toste, whose work much of this study was built upon. Thanks is also extended to my past and present colleagues on the fifth floor, especially to Jim Martyn for his suggestions, conversations and his successful efforts at making me a coffee addict. Special thanks to Kim Demetriou, Catherine Rolland, Natalie Venus, Guenaelle Martin and Francis Panosyan for their companionship and conversations about life and everything under the sun. Pamela Newman and Samia Awadallah for keeping the FTIR in working order and their generosity when I beg for chemicals and, to Alex Young for running the mass spectra.

I am particularly indebted to Ian for his understanding and support, for sharing with me both the happy and frustrating times I may have encountered in research, and for all his help and encouragement.

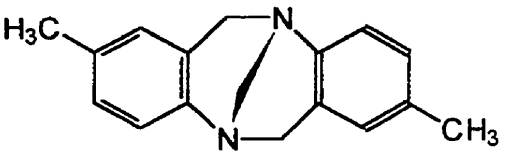
Finally to my family, without their support this would have never been possible.

Boc	*tert*-butoxycarbonyl
CSA	D-10-camphorsulfonic acid
DEPT	Distortionless enhancement by polarization transfer (^{13}C-NMR)
DMF	N,N-dimethylformamide
DNA	deoxyribonucleic acid
ee	enantiomeric excess
EIMS	electron impact mass spectrometry
FAB	fast atom bombardment mass spectrometry
FTIR	Fourier transform infrared
HMPA	hexamethylphosphoric triamide
HRMS	high-resolution mass spectrometry
LAH	lithium aluminum hydride
TBAF	tetrabutylammonium fluoride
TBDMS-Cl	*tert*-butyldimethylsilyl chloride
THF	tetrahydrofuran
TIPS	triispropylsilyl
TLC	thin layer chromatography
TMEDA	N,N,N',N'-tetramethyl-1,2-ethylenediamine
TMS	trimethylsilyl

Dithiocins (**1**) are a new and interesting class of conformationally rigid, cleft-shaped molecules. It has been found that compounds containing such well defined molecular clefts have potential applications in molecular recognition, self assembly and catalysis.[1] Tröger's base (**2**), which patterns the molecular shape of a dithiocin, was synthesized well over a century ago.[2] It has been used in diverse applications and have become the subject of renewed recent interest in chemical research as DNA probes[3] due to their different modes of interaction with DNA and the chiral properties that they possess. The structure of Tröger's base was determined by Spielman[4] in 1935, and contains a methano[1,5]diazocine bridge which locks two aromatic rings in an almost perpendicular fashion. Tröger's base is chiral[5] and is considered a very stable compound. Wilcox and Rebek and co-workers[6] have elegantly used this as a structural module in the construction of cyclic as well as acyclic molecular receptors.



1a R=R'=H
1b R=CH_3 R'=H
1c R=CH_3 R'=S^{t}Bu

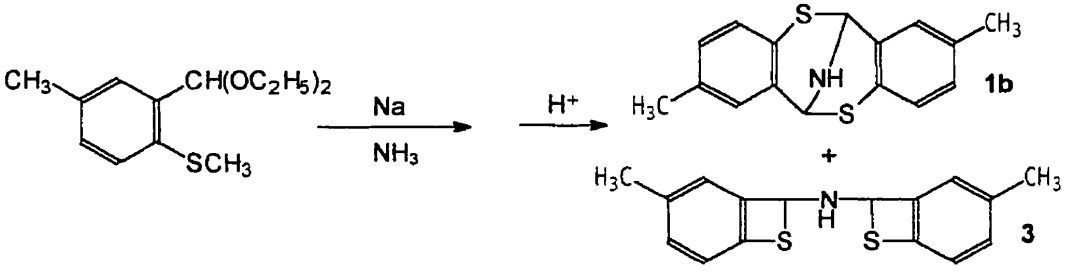


2

Wilen and co-workers[7] have reported Tröger's base to be a chiral solvating agent. Quaternary Tröger's base salts have been shown to form inclusion complexes with aliphatic and aromatic solvents by Weber *et al.*,[8] and by Bond and Scott.[9] Since their structure is similar to that of the

investigated in the future. We have made a series of dithiocins by a method adapted from the facile preparation of **1a** (6, 12-imino-6*H*, 12*H*-dibenzo [b,f]-1,5-dithiocin). These range from analogues with substituted aromatic rings to those with substituents on the imino position. Such molecules, it was expected, would provide interesting cavities for molecular recognition sites as well as for catalytic and supramolecular chemistry.

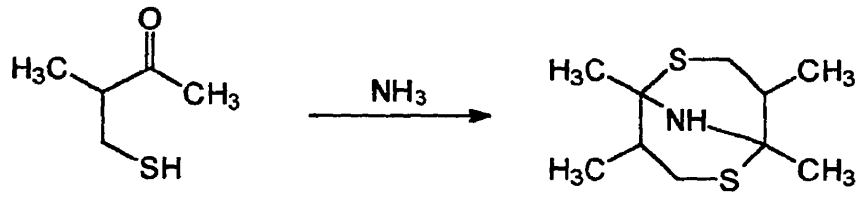
Historically, Gol'dfarb *et al.*[10] were the first to have synthesized the 1,5-dithiocin system using aromatic diethyl acetal compounds in sodium and liquid ammonia (Scheme 1). Due to insufficient spectral data, however, these structures were not rigorously established. The dithiocin **1b** and its isomer **3** were believed to have been obtained from the above reaction; all the data obtained were acquired from chemical analysis and this ratio was never disclosed.



Scheme 1

Using a similar approach, Theil *et al.*[11] had prepared the fully saturated parent ring 1, 5 dithia-2, 6-iminocycloctane, by treatment of 4-mercapto-3-methyl-2-butanone with ammonia (Scheme 2). The preparation of the 1,5-dithiocin in this laboratory by a different route and confirmation

by X-ray crystallographic (Figure 1) structure **1b** has proven that Gol'dfarb's original postulate was correct.



Scheme 2

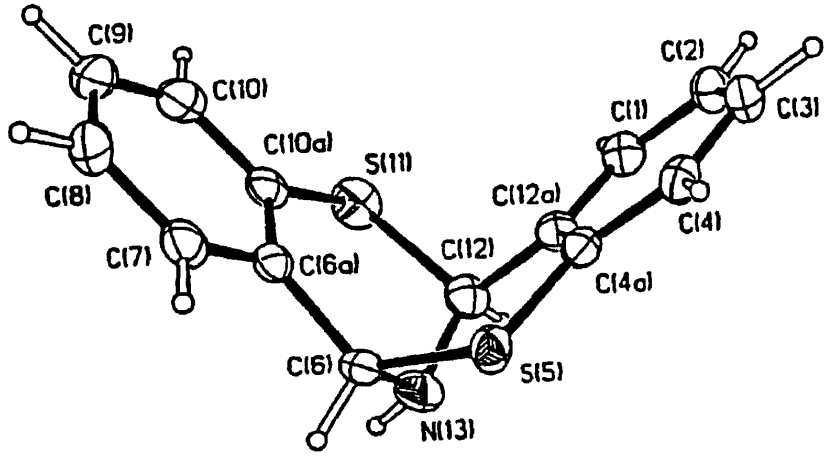
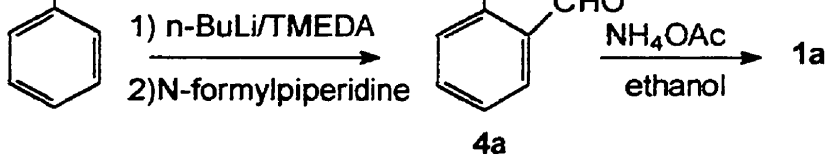


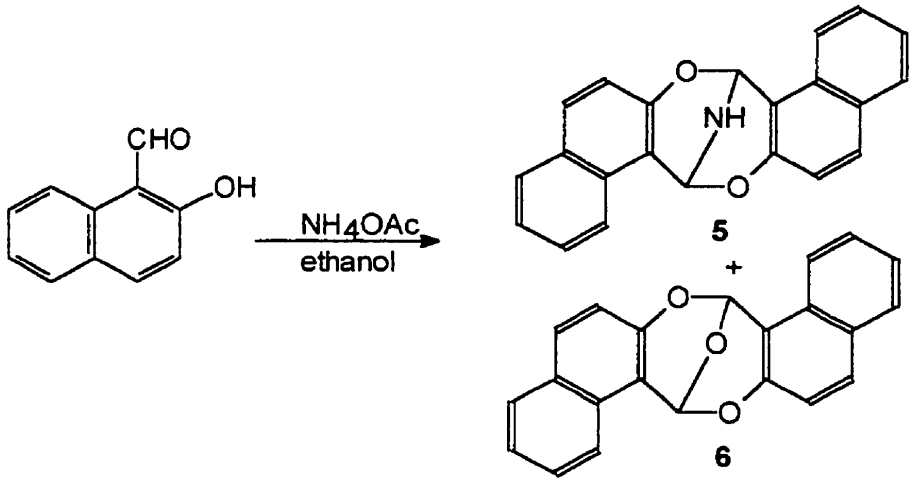
Figure 1

The dithiocins have been prepared in two steps involving initial formation of a salicylaldehyde by trapping of the organolithium intermediate from thiophenol[13] with N-formylpiperidine, followed by the condensation of the aldehyde with an amine compound (Scheme 3).[12]



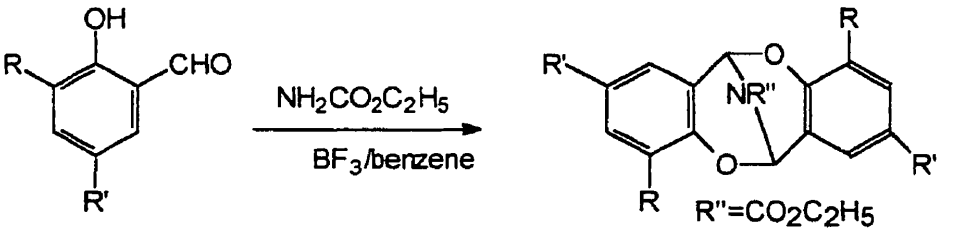
Scheme 3

After our study was well under way a similar type of structure was synthesized in the dinaphtho series (8,16-imino-8*H*,16*H*-dinaphtho[2,1-b:2, 1:f]-1,5-dioxocin) by Biehl *et al.*[14] (Scheme 4) in 53% yield. Condensation of 2-hydroxy-1-naphthaldehyde and ammonium acetate in refluxing ethanol for 2 h resulted in the dioxocin (**5**) and a trace amount of an oxa-derivative (**6**) (<5%).



Scheme 4

Merten and Muller[15] had unexpectedly obtained a dioxocin compound by condensation of salicylaldehyde **7** with a carbamic ethyl ester and boron trifluoride (Scheme 5).

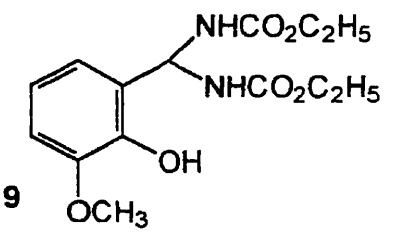


7a R=OCH_3 R'=H
7b R=R'=Cl

8a R=OCH_3 R'=H
8b R=R'=Cl

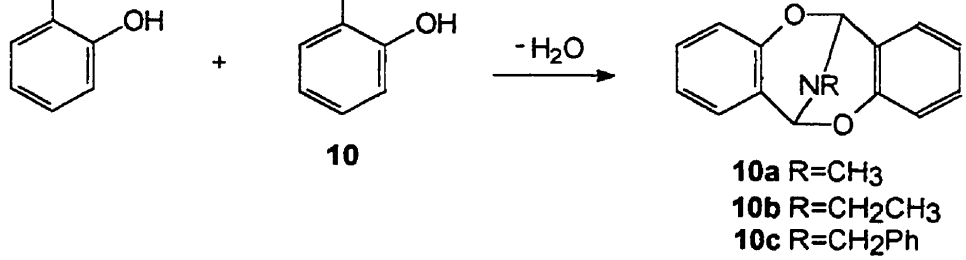
Scheme 5

It was found that if small amounts of carbamic ester were added only the bisurethane **9** would form, but if larger quantities of the carbamic ester were used the bicyclic compound formed more readily. Merten and Muller wanted compound **9** for their studies since it was the intermediate required for the formation of chromane derivatives.



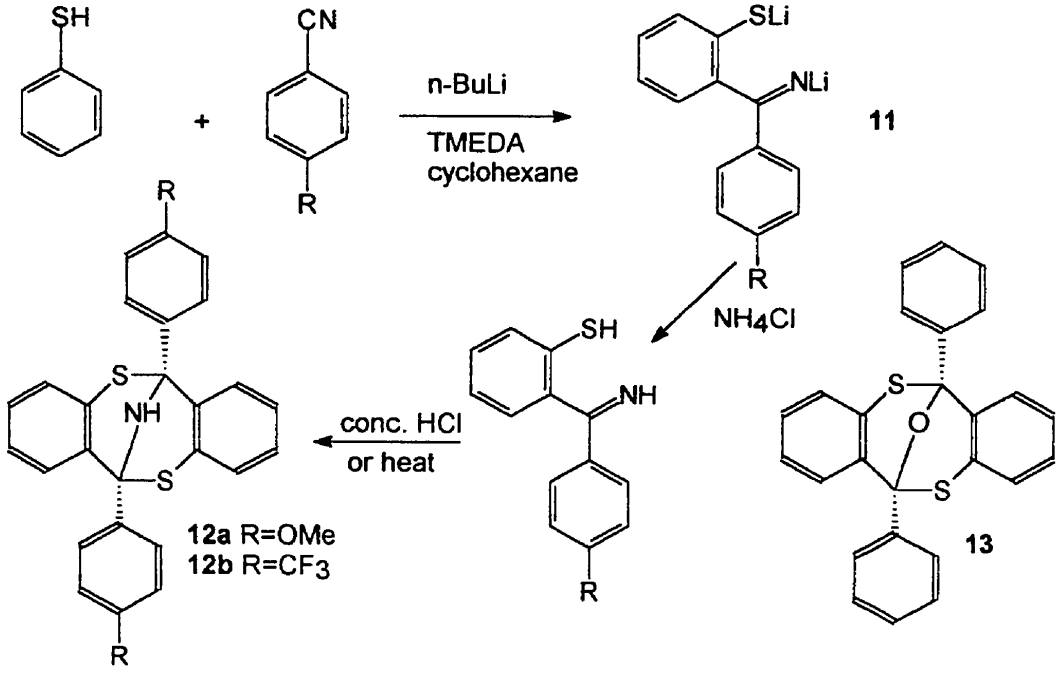
9

Subsequently Appel and co-workers[16] had shown that reaction of the salicylaldehyde with various imines (**10**) formed 1,5-dibenzo-dioxocins in less than 48% yield (Scheme 6). Appel and co-workers had also shown that these compounds possess chirality by the use of a chiral shift reagent.



Scheme 6

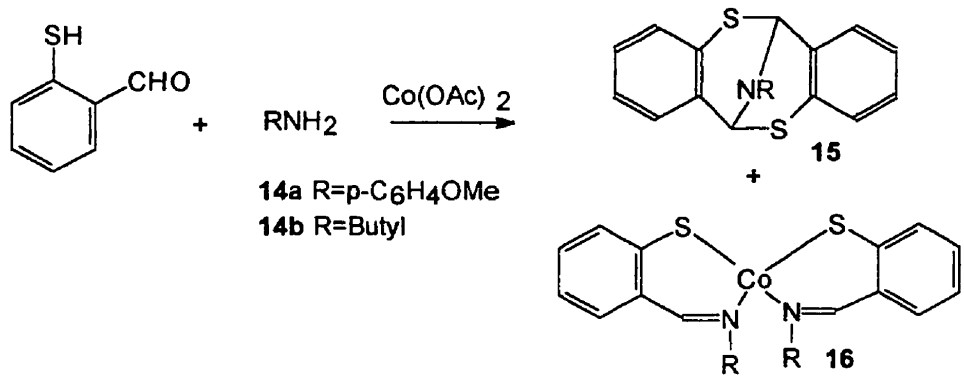
More recently Brieaddy and Donaldson[17] unexpectedly formed the 1,5-dithiocins by treatment of the dilithio salt (prepared by *ortho*-lithiation) of thiophenol with benzonitrile to give the thioimine **11** (Scheme 7).



Scheme 7

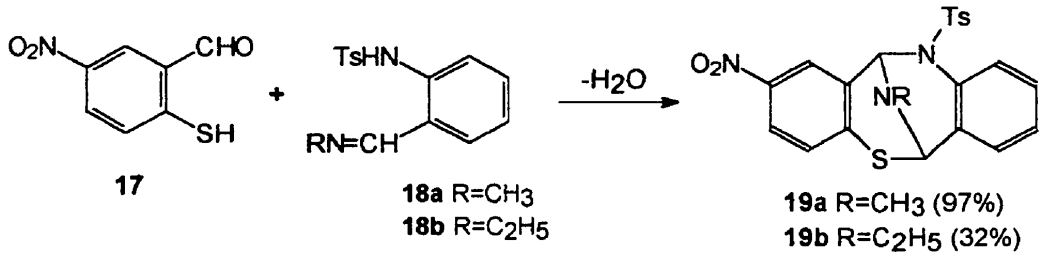
extensive heating resulted in **12**. A series of analogues was prepared and, in addition, an oxygen-bridged compound **13**. The mechanism proposed for these reactions assumes that the thioimine is highly reactive, and undergoes a bimolecular reaction with itself under either strong acid conditions or thermally to yield **11**. Brieaddy and Donaldson had originally thought that this method would form 2-thiobenzophenone but due to the work up conditions it led instead to the formation of the dithiocin.

A series of N-alkylated dithiocins was synthesized by West and Corrigan.[18] The condensation of *o*-mercaptobenzaldehyde with a primary amine in ether formed an imine, and this was followed by the addition of cobalt(II) acetate in ethanol to afford a 1:1 mixture of the dithiocin (**15**) and the metal complex (**16**) of interest (Scheme 8). Unfortunately, the organometallic product required by West and Corrigan was heavily contaminated with the dithiocin and it proved to be very difficult to isolate the cobalt complexes for their studies.



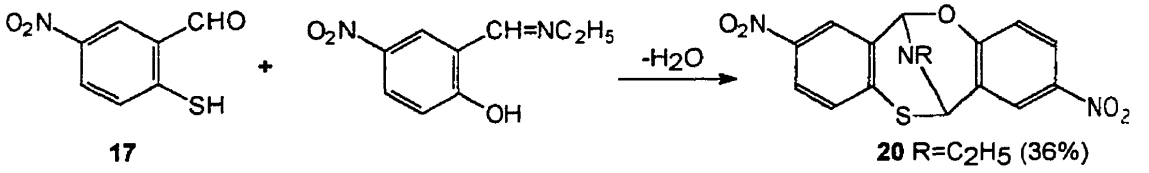
Scheme 8

thiazocin and oxathiocin types, with yields ranging between 30-90%. The most important information emerging from these condensations is the facile reactivity between the aldehyde and azomethine components to form an unsymmetrical bicyclic structure with imine bridges, which results in the generation of new heterocyclic systems with different heteroatoms in the macrocycle. It was observed, for example, that 5-nitro-2-mercaptobenzaldehyde (**17**) reacted with the azomethines (**18**) at room temperature to afford N-(13)-substituted 6,12-imino-2-nitro-11-tosyl-6*H*,12*H*-dibenzo[b,f]-1,5-thiazocines (Scheme 9).



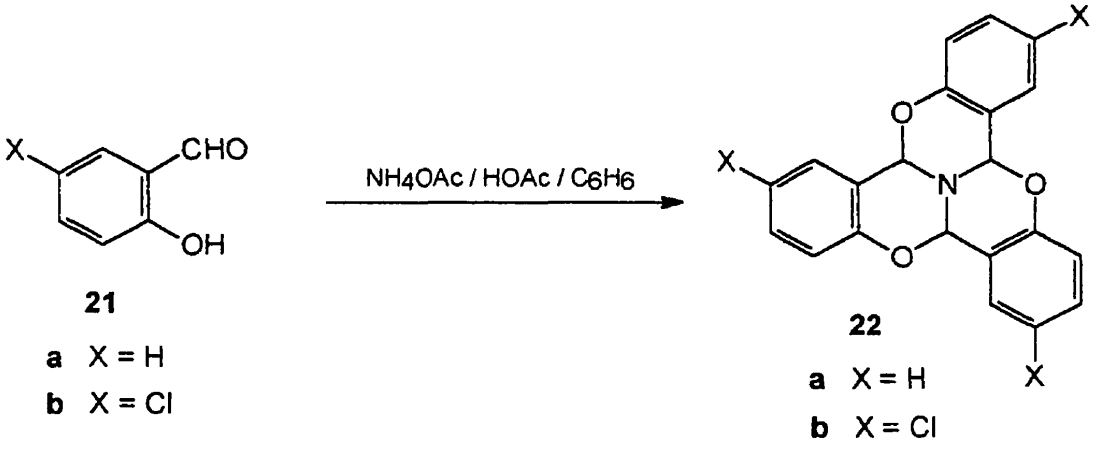
Scheme 9

A series of hydroxy-substituted azomethines (derived from 2-hydroxybenzaldehyde, 5-bromobenzaldehyde and 5-nitro-2-hydroxybenzaldehyde) was also condensed with the thiosalicylaldehyde (**17**) but only the N-(5-nitro-2-hydroxybenzylidene)ethylamine proved to be reactive under mild conditions (Scheme 10). This is probably attributable to the presence of a strong electron withdrawing group *para* to the hydroxyl group, which appears to be necessary for the condensation to take place.



Scheme 10

The formation of the so-called "tricyclo-compounds" provides molecules with even larger cavities which serve as interesting probes and molecular recognition sites. Kanakarajan *et al.*[20] have earlier synthesized a series of 1,3-benzoxazins from *o*-hydroxybenzaldehydes with ammonium acetate and acetic acid (Scheme 11). The IR shows the absence of OH and C=O bands and the mass spectrum has a molecular ion at 329 (**22a**).



21

a X = H

b X = Cl

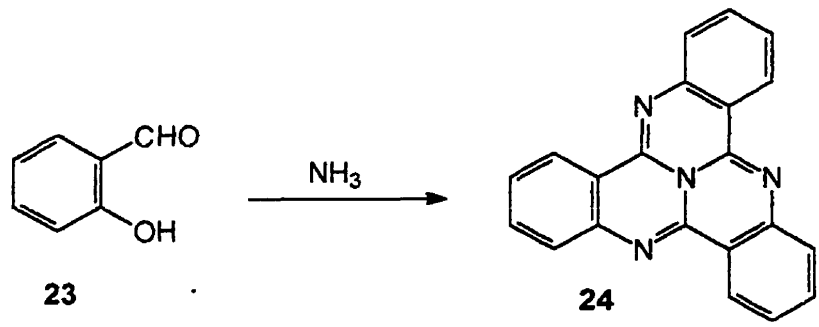
22

a X = H

b X = Cl

Scheme 11

A striking much earlier, parallel example of structure **22** is the condensation of *o*-aminobenzaldehyde **23** with ammonia to yield the tricycloquinazoline **24** (Scheme 12), as reported by Cooper and Partridge.[21]

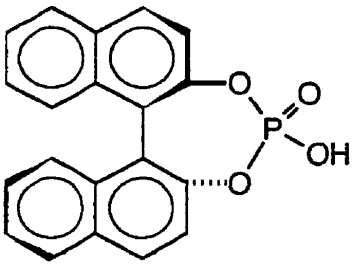


23 **24**

Scheme 12

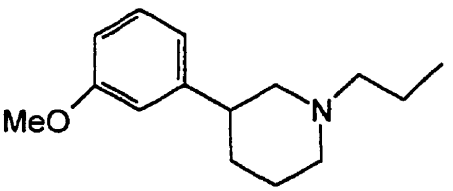
Of particular interest is the molecular chirality possessed by the 1,5-dithiocins, due to the 6,12-imino bridge locking the two aromatic rings into roughly perpendicular planes (cf. Tröger's base). Several methods have been explored to resolve the enantiomers of the dithiocin. The chirality demonstrated by Prelog for Tröger's base,[5] results from the blocked conformation of the nitrogens giving a C2 axis of symmetry across the methylene bridge. The resolution of the mixture of enantiomers was initially realized by Prelog using a chiral column of lactose, followed by successive recrystallizations. The absolute configuration of Tröger's base was proposed to be *S*, *S* by Cervinka *et al.*.[22] and later revised to *R*, *R* by Mason *et al.*,[23] through circular dichroism (CD) analysis. Recently compound **2** has been resolved via a second-order asymmetric transformation[7] by the formation of a diastereomeric salt with the base and 1,1'-binaphthalene-2-2'-

diyl hydrogen phosphate (**25**).[24] This has confirmed that Tröger's base has in fact the *S*, *S* configuration by the X-ray structure of the diastereomeric salt.



25

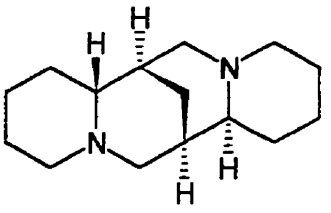
Another amine that has been resolved with **25** was 3-(3-methoxyphenyl)-N-propylpiperidine (**26**). This tertiary amine has been claimed to be the first selective dopaminergic autoreceptor agonist reported.[25] In order to understand its mechanism on the molecular level, separation of its enantiomers was investigated.



26

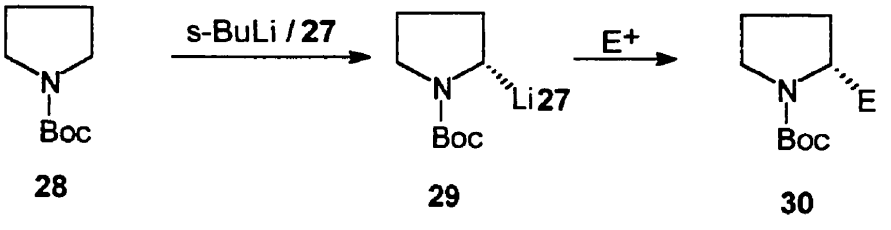
Similar methods to form diastereomeric salts between a variety of different chiral acids and the 1,5-dithiocins prepared in our work have been studied and will be discussed later. Ultimately, the purpose of this resolution is to use the resolved amine as a chiral base in simple reactions which involve deprotonation and to examine if there is any asymmetric selectivity in the product. Early reports by Nozaki *et al.*[26] established that sparteine (**27**), a readily available alkaloid, could be used as a ligand for

enantioinduction at the carbanionic centre in a lithiation-substitution sequence: unfortunately, with very poor selectivity.



27

Very recently, Beak *et al.*[27] have since used this chiral base (**27**) in the reactions of N-Boc pyrrolidine (**28**) with *sec*-BuLi to afford **29,** which reacts with electrophiles to provide enantioenriched products (**30**) (Scheme 13). Work has progressed on this dual BuLi, sparteine combination for the induction of asymmetry in lithiation-substitution of benzylic, *ortho* aromatic and other α-heteroatom hydrogens.[28]



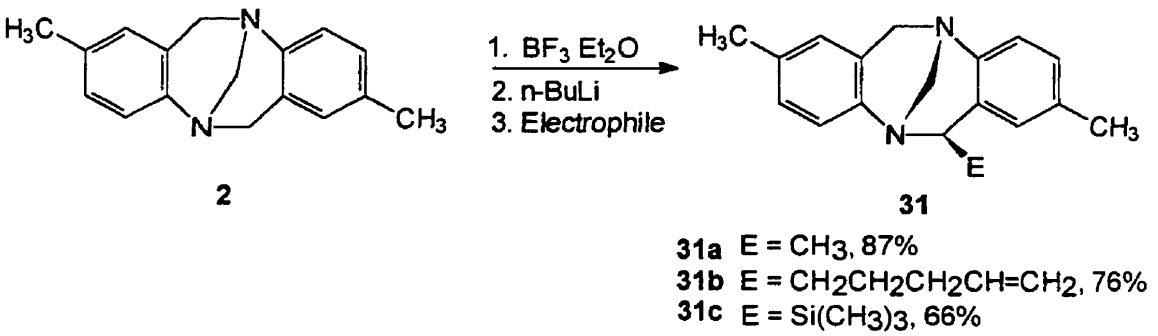
28 **29** **30**

E = CO_2H, 55%, 88% ee
E= $(C_6H_5)_2COH$, 77%, 90% ee
E = $Si(CH_3)_3$, 71%, 94% ee

Scheme 13

Recently, the development of chiral species from Tröger's base by metallating the benzylic site was examined by Harmata and co-workers.[29] Based on Kessar's[30] work, which reported that the metallation of amines such as tetrahydroisoquinolines could be facilitated by the pre-complexation

of the amine with boron trifluoride, Harmata's method was applied to Tröger's base, followed by treatment with n-BuLi. The lithiated species was then reacted with a series of electrophiles stereoselectively to give products **31 a-c** in good to excellent yields (Scheme 14).



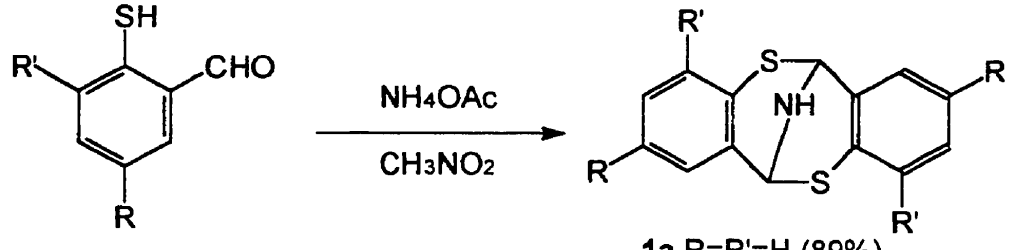
Scheme 14

There has also been potential for the bicyclic compounds in our study to be used as complexing ligands for heavy metals. Preliminary investigations by Still and Toste[12] had shown positive tests using copper and platinum metals. Tröger's base has only a few examples containing metal complexes reported in the literature. Transition metal complexes (rhodium(III) or iridium(III)) of Tröger's base have been used, for example, to catalyze the hydrosilylation of alkynes.[31] It was proposed that Tröger's base forms a complex with two metal atoms, coordinated with the two nitrogens of the diazocine unit. Crossley *et al.*[32] have shown that the porphyrin analogues chelate different metal ions such as palladium(II), zinc(II), cobalt(II), nickel(II) and copper(II). An examination of the attempted complexation of several metal acetates with the dithiocin complex will be discussed and outlined later in the results and discussion section.

of several dithiocin compounds, most interestingly the naphthalene and amino acid analogues, as well as many other N-substituted derivatives. It will present new routes and several novel chemical transformations which were developed to optimize the synthesis of the 1,5-dithiocin compounds.

Dithiocins are structurally well defined molecules with V-shaped molecular clefts. These molecules possess chirality[5], resulting from the locking of the two aromatic rings in an almost perpendicular fashion. We have carried out the facile preparation of a series of racemic 6, 12-imino-6*H*, 12*H*-dibenzo[b,f]-1,5-dithiocins, which may have potential application towards molecular recognition and supramolecular chemistry.

Formation of these bicyclic compounds results from the treatment of thiosalicylaldehydes with ammonium acetate in refluxing ethanol for 3.5 h to provide excellent yields (Scheme 15).



4a R=R'=H
4b R=CH_3 R'=H
4c R=CH_3 R'=S^{t}Bu

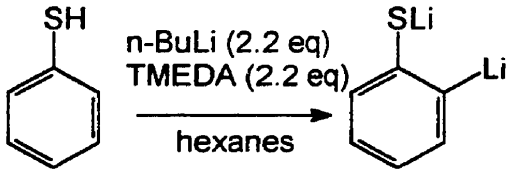
1a R=R'=H (89%)
1b R=CH_3 R'=H (91%)
1c R=CH_3 R'=S^{t}Bu (90%)

Scheme 15

I. *ortho*-Lithiation of Thiophenolates

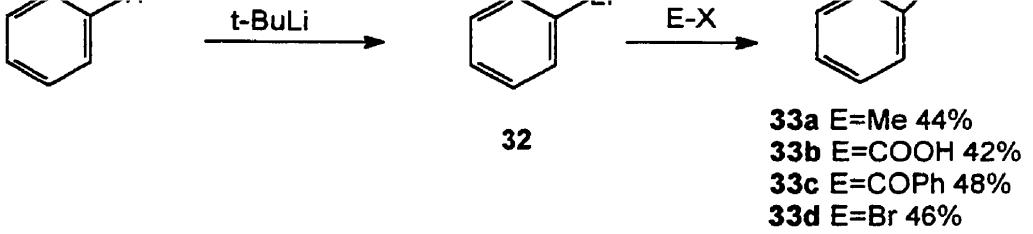
The initial step taken was the formation of the aldehyde by treating the appropriate thiophenol with n-BuLi in the presence of hexanes and

fair yields with the use of 2.2eq of both n-BuLi and TMEDA (Scheme 16).



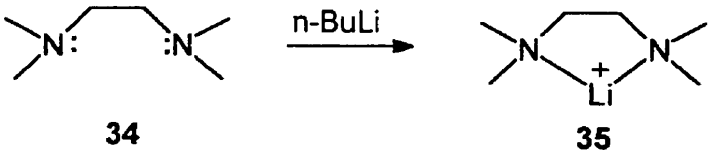
Scheme 16

Lithiation of aromatic compounds is often directed *ortho* to substituents that possess oxygen, nitrogen or sulfur atoms.[13] *ortho*-Lithiation involves heteroatom metallation prior to ring *o*-metallation, to yield a dimetallated species. Other functional groups that encourage *ortho*-metallation include SO_2NR_2, $CONR_2$, $OCONR_2$, CH_2NMe_2, OCH_2OMe, and OMe.[13c] Initial work on *ortho*-lithiation procedures was outlined by Gilman *et al.*,[33] using monobrominated thiophenols, via a halogen-metal exchange, but very low yields were obtained. A more recent literature statement implied that lithiation *ortho* to a simple thiol group was possible, but gave no details.[34] Posner and Canella have optimized the yield to provide an experimental procedure which generates the *o*-lithiophenolate **32** effectively (Scheme 18).[35] It was found that adding 2.8 eq of *tert*-butyl-lithium in pentane to 1.0 eq of phenol in 4.2 eq of tetrahydropyran (THP) at 25°C was the most effective way of converting the phenol instantaneously into the lithium phenoxide. Quenching the *ortho*-lithiated phenolate **32** with various electrophiles led to yields between 42-48% (Scheme 17).



Scheme 17

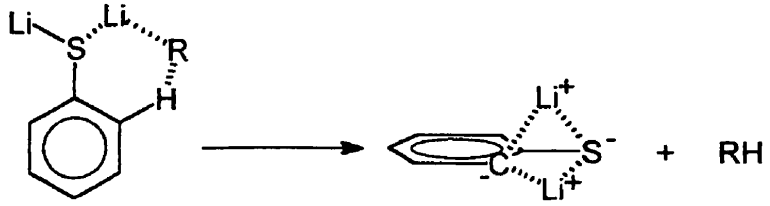
A similar technique was used in our case to direct lithiation *ortho* to a simple thiol group as a means of producing *ortho*-substituted arenethiols. It is also worth noting that electrophilic addition occurs exclusively at the carbanionic centre in the dimetallated species since the lithium cations stabilize the anionic oxygen and carbon (by kinetic effect), which facilitates the dianion formation. The dianion associated with two lithium cations could be considered as an ion triplet, which belongs to a class of ionic clusters having surprisingly high relative stability.[34] This is due to the Coulombic attraction of each lithium cation to both proximate ion centres. The reactivity of the organolithium compounds may be increased by the addition of TMEDA (**34**). This tertiary amine chelates lithium and effectively accelerates the rate of deprotonations.[36] Similar effects were expected to operate in the thiophenol series.



34 **35**

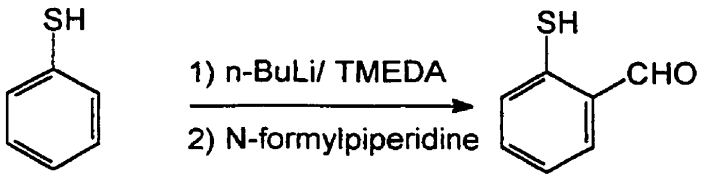
The success of directed *ortho*-lithiation is also partly attributable to the choice of hexane as a solvent. This non-polar solvent favours

the benzenethiolate anionic sulfur. The dilithiated species **37** could be formed via a transition state similar to **36,** as Streitwieser has suggested.[34] The Coulombic interactions of the two cations and a dicarbanion are favourable in geometry. As well, the weak C-S bond of **37** provides an antibonding σ* orbital low in energy to provide a stabilizing interaction with the adjacent carbanion lone pair of electrons in the plane of the benzene ring,[37] which may significantly contribute to the efficiency of this reaction.



36 **37**

Once we had converted the thiophenolates to the organolithium intermediates, the aldehydes were prepared with the addition using N, N-dimethylformamide.[12] The yields were subsequently optimized by using a better electrophile, N-formylpiperidine (Scheme 18).



1a

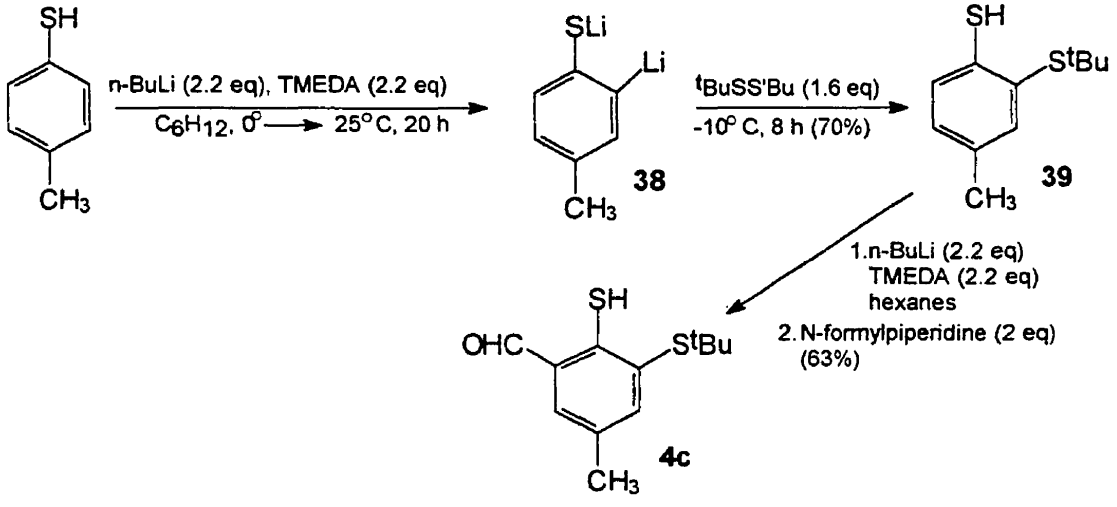
Scheme 18

The use of N-formylpiperidine has doubled the yields obtained by the original method (Table 1). This is due to the structural nature of N-

conjugation and hence the carbonyl group is more reactive. Subsequent preparations of the dithiocins **1a-1c** have shown the potential for the preparation of highly functionalized derivatives. Two sequential *ortho*-lithiation steps were used to convert 4-methylbenzenethiol to **4c**. The initial lithiation and trapping with *t*-butyl disulfide[38] introduced the *t*-butyl sulfide moiety to form **39**, followed by the required aldehyde functionality by trapping with N-formylpiperidine after a second lithiation step (Scheme 19).

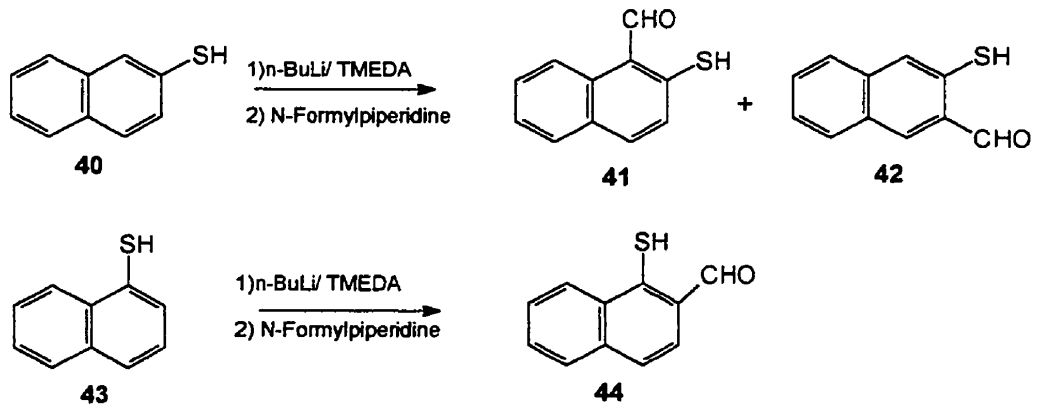
Salicylaldehyde	DMF	N-Formylpiperidine
4a	45%	81%
4b	41%	75%
4c	34%	63%

Table 1



Scheme 19

aldehydes from 1- and 2-naphthalenethiol, utilizing the same methodology (Scheme 20). Interestingly, formylation resulted both at the C-1 and C-3 positions for 2-naphthalenethiol. A slightly higher ratio of n-BuLi and TMEDA mixture to substrate was required to observe any formylation in the product (Table 2).



Scheme 20

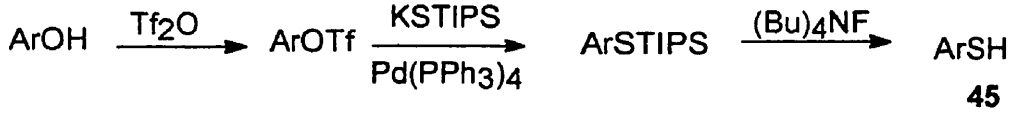
2-Naphthalenethiol (eq.)	n-BuLi (eq.)	TMEDA (eq.)	Yield**
1.0	2.2	2.2	0%
1.0	2.3	2.3	0%
1.0	2.4	2.4	34%
1.0	2.5	2.5	75%
1.0	2.6	2.6	77%
1.0	2.5	0	23%
1.0	2.5*	2.5	51%
1.0	2.5*	0	10%

*t-BuLi was used to test the relative yields of these reactions.

** the yield is a mixture of products **41** and **42**

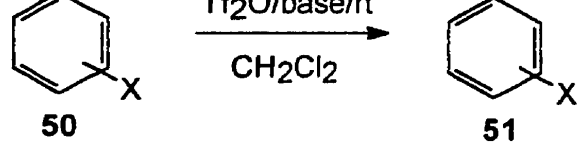
Table 2

It was found that 2.5 equivalents of n-BuLi and TMEDA produces the best results, since the increase to 2.6 equivalents resulted only in a 2 percent increase in yield. The use of a more reactive butyllithium as metallating agent did not result in an increase in the yield but rather a decrease (note that this was only tested with only 2.5 equivalents of t-BuLi), which was similar to findings by Smith *et al.*[13c] The overall yield, 75%, is comprised of a mixture of two products: **41**, **42** as 2-mercapto-1-naphthaldehyde and 3-mercapto-2-naphthaldehyde, in 60% and 40% yield, respectively. The spectral data for the mixture of products obtained from 2-naphthalenethiol had ^{1}H-NMR signals at δ 11.03 and 10.05, which result from the aldehyde protons. To determine which peak is attributable to which product, a new synthetic route was established to prove the position of the aldehyde functionality unambiguously. Using a method by Arnould *et al.*,[39] the conversion of 2-hydroxy-1-naphthaldehyde to 2-mercapto-1-naphthaldehyde was undertaken. The key reaction is the palladium catalyzed coupling reaction of a corresponding triflate with potassium triisopropylsilanethiolate (KSTIPS) and subsequent deprotection of the silyl function to give **45** (Scheme 21).



Scheme 21

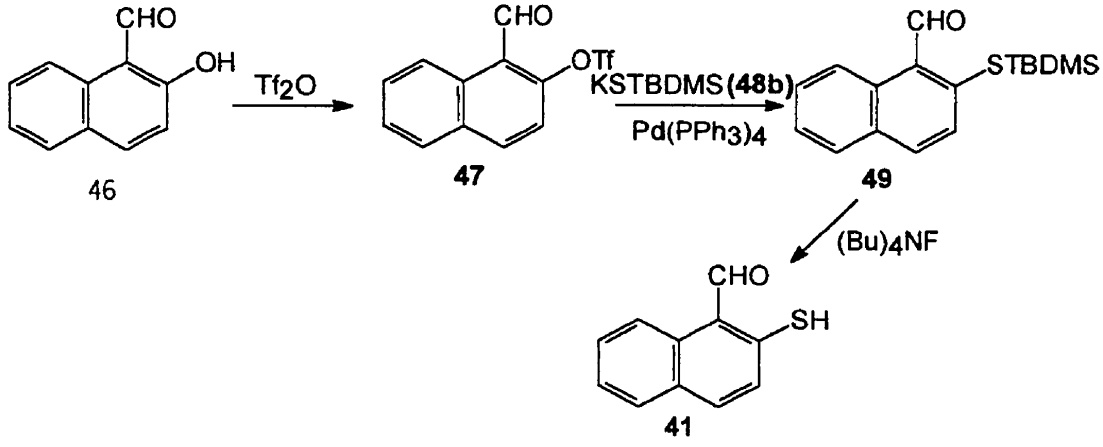
With this in mind, the 2-hydroxy-1-naphthaldehyde (**46**) was converted into the triflate **47** in 75% yield (Scheme 22). Aryl triflates are usually prepared from phenols in excellent yield by treating them with triflic anhydride in the presence of a base such as pyridine or triethylamine (Table 3).[40]



50 51

X	% Yield (**51**)
4-CHO	85%
4-Br	92%
4-OCH_3	93%
4-NO_2	85%
2-NHTos	75%

Table 3



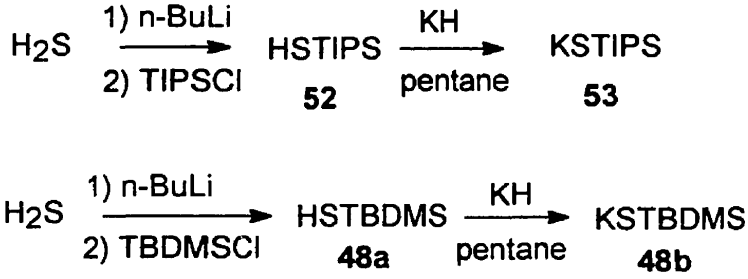
46 47 49 41

Scheme 22

The triflate **47** was reacted with potassium *tert*-butyldimethyl-silanethiolate (KSTBDMS) (**48b**) and tetrakis(triphenylphosphine) palladium(0) to give the silylated thiol **49**, which was then deprotected by

treatment with tetrabutylammonium fluoride (TBAF) to yield **41** (Scheme 22).

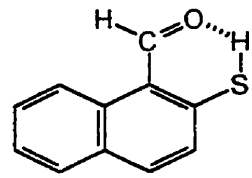
Our method for the formation of the potassium salt was taken from the work of Soderquist and co-workers[41] on the preparation of unsymmetrical thiols and thioacetals from triisopropylsilanethiol. A simple conversion of H_2S to its monotriisopropylsilyl (TIPS) derivative **52** using n-BuLi, followed by the addition of KH, gave the stable crystalline salt **53** in 95% yield (Scheme 23). With only *tert*-butyldimethylsilyl chloride (TBDMSCl) on hand, conversion to the analogous potassium salt by Soderquist's method resulted in an overall yield of 50% (Scheme 23). The ^{1}H-NMR for the *tert*-butyldimethylsilanethiol (**48a**) showed a singlet at δ 0.11 for the SH, which is quite upfield from its usual position. This is due to the silicon atom shielding the SH proton; a chemical shift at higher field is observed as a result.



Scheme 23

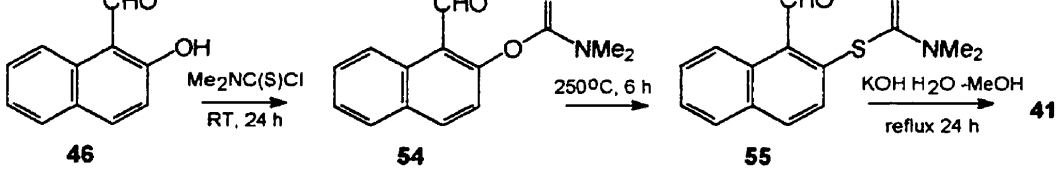
The next step was a palladium-catalyzed coupling reaction of the naphthaldehyde triflate (**47**) and the potassium salt (KSTBDMS) to form **49**, in 52% yield. This idea was drawn from the report of Stille and Echavarren[42] on palladium coupling reactions of aryl triflates with

organostannanes. The final step was the deprotection of the silyl group with TBAF[43] to give the 2-mercapto-1-naphthaldehyde **41** in 76% yield (Scheme 22). The chemical shift for the aldehydic proton was 11.03 ppm, which coincided with the 11.05 ppm peak observed for the *ortho*-lithiation method. This confirmed that the aldehyde group in this product is at the C-1 site. It is somewhat surprising that the chemical shift difference between the two isomeric aldehydes is approximately 1 ppm. Typically, aromatic aldehyde proton signals are found at about 10.0 ppm. Thus, 3-mercapto-2-naphthaldehyde does not show a great deviation from the theoretical value but the peak at δ 11.05 does. To explain this phenomenon, there must be more pronounced hydrogen bonding between the oxygen of the carbonyl substituent and the proton of the thiol to shift the peak slightly downfield (**41a**).



41a

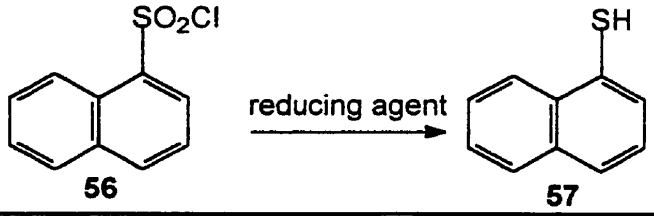
Another method we have experimented with for the conversion of the hydroxy to a thiol substituent is a procedure reported by Topping *et al.*[44] The naphthaldehyde **46** is treated with dimethylthiocarbamoyl chloride to acylate the phenol **54**, followed by a thermolytic isomerization to give **55**, and finally hydrolysis to the desired thiol precursor **41** (Scheme 24). Unfortunately, the isomerization reaction (thermolysis) did not provide us with encouraging results.



Scheme 24

II. Reductions of 1-Naphthalenesulfonyl Chloride

Since 1-naphthalenethiol was an expensive reagent, we felt it was necessary to generate this compound from 1-naphthalenesulfonyl chloride **(57)** as it is easier to reduce than the parent sulfonic acids. Our initial efforts to reduce directly to the thiol were not promising. A series of methods was tried and these are listed in Table 4.

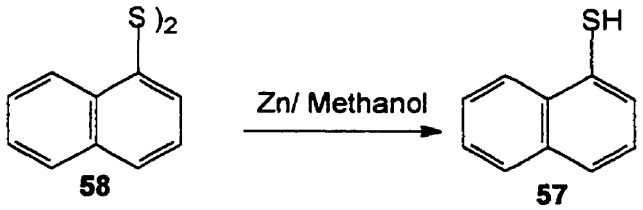


METHOD	% YIELD
Zn/ H_2SO_4[45]	0%
Zn (Hg)/ H_2SO_4[46]	62%*
Zn (Hg)/HCl	26%
LAH/THF[47]	12%
Sn/HCl	89%

* mainly the disulfide obtained

Table 4

Our efforts with zinc looked encouraging once the zinc was activated with $HgCl_2$ but only a small amount of the free thiol was obtained. The majority of the product was the disulfide **58** (62% yield), characterized by its yellow, crystalline appearance. This was reduced with zinc in methanol to obtain 1-naphthalenethiol in 93% yield (Scheme 25).

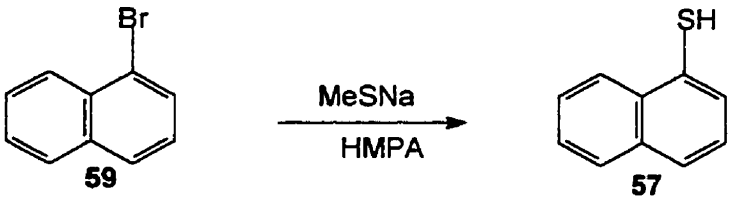


Scheme 25

Even though the desired product was obtained, we wanted to reduce the 1-naphthalenesulfonyl chloride in a single step. Unfortunately, during work-up procedures the thiol appeared to complex with the zinc and was lost. Other methods were sought: the use of LAH formed only 12% of the thiol, which was not feasible for our purposes. Finally, the reaction with tin and aqueous HCl gave the best results. The 1-naphthalenesulfonyl chloride was refluxed for 6 h, turning the solution from a yellow to a clear one and affording the thiol in 89% yield. ^{1}H-NMR showed a singlet at δ 3.71 for the SH proton and the IR revealed an absorbance at 2571 cm^{-1} for the thiol. This thiol was subsequently used for the lithiation reactions to form the necessary naphthaldehydes (*vida supra*).

Another useful reduction leading to the 1-naphthalenethiol starts with 1-bromonaphthalene, which is also fairly inexpensive. Testaferri *et al.*[48] have also shown very encouraging results, with yields greater than 90% reported

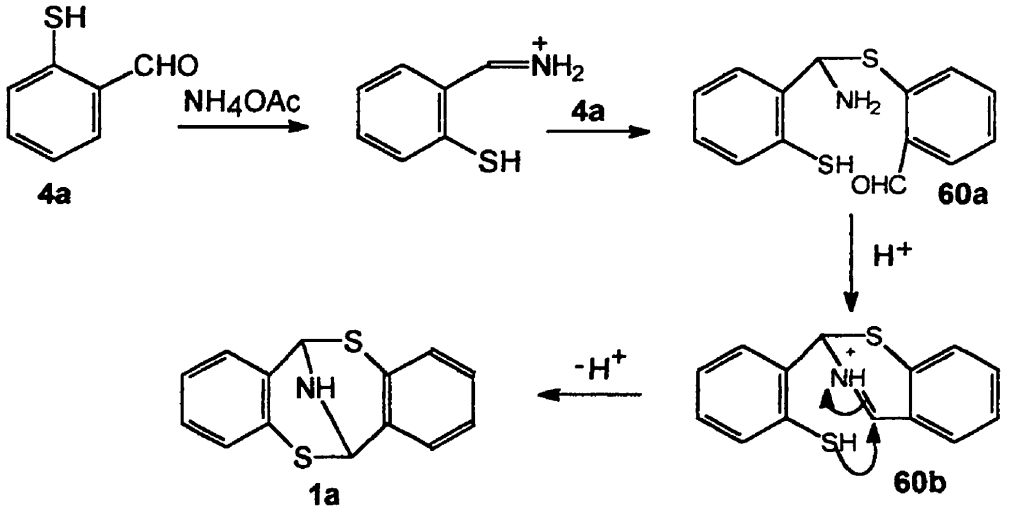
been another simple route towards 1-naphthalenethiol.



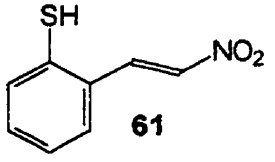
Scheme 26

III. Formation of 1,5-Dithiocins

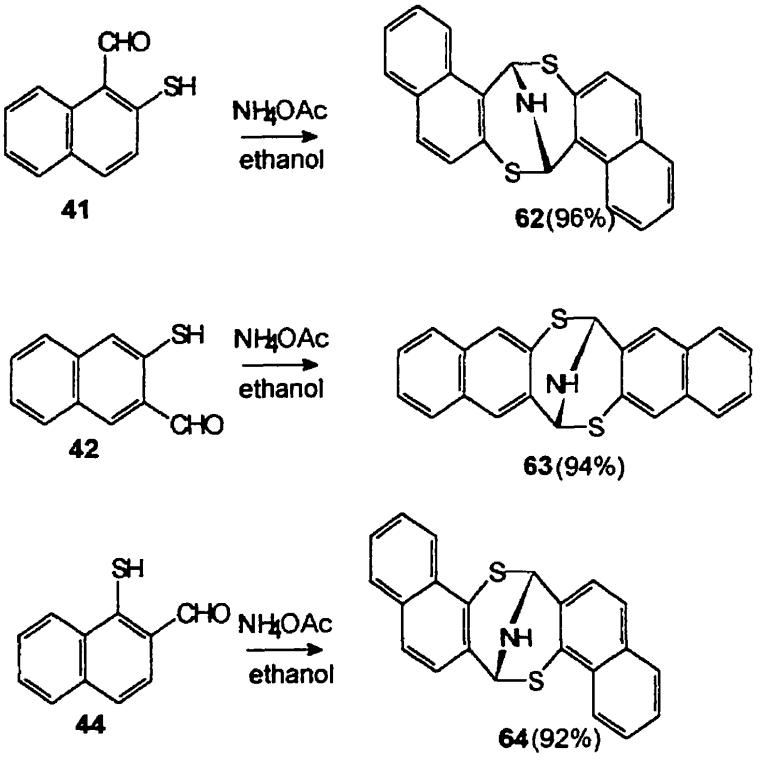
The second major step in the formation of the desired bicyclic compounds is treatment of the thiosalicylaldehyde (**4a**) with ammonium acetate in refluxing ethanol for 3.5 h. A possible mechanism for this transformation is outlined in Scheme 27. The aldehyde initially forms a Schiff base with the amine or ammonium salt, which enhances the electrophilicity of the carbonyl group. A second equivalent of the thiosalicylaldehyde (**4a**) provides a thiol nucleophile and attacks the iminium species. The intramolecular condensation of the more complex aldehyde **60a** with the newly generated primary amine leads to the formation of a cyclic iminium species **60b**, which is intramolecularly trapped by the remaining thiol to give the 1,5-dithiocin **1a**. Originally, the solvent used was nitromethane[12] and the expected product is nitroethene **61**, but before the traditional Knoevenagel (Henry) carbanion nucleophile attacks, the thiol intercepts the iminium intermediate. Consequently, very little **61** is formed.



Scheme 27



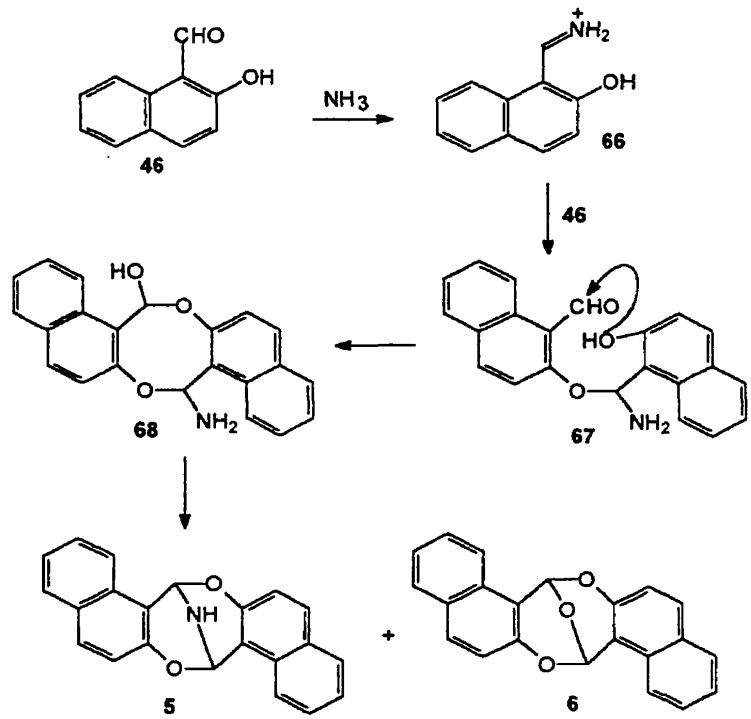
We have since used a different solvent, ethanol, which not only enhances the rate of formation of the dithiocin but eliminates any possibility of forming the nitroethene product **61**. ^{1}H-NMR showed chemical shifts for the methine peaks from δ 5.66-5.73 for compounds **1a-c**. The NH shift for **1c** (δ 4.33), however, slightly deviates from the shifts observed for **1a** and **1b** (δ 2.88 and 2.83, respectively). This may be due to the S^{t}Bu substituents on **1c**, which shield the NH proton, resulting in a downfield shift. We have also reduced the number of equivalents of ammonium acetate to 0.55 from the original 1.1. Similar methods have been used for the formation of the analogous naphtho-dithiocins (Scheme 28) in excellent yields. These compounds are attractive molecules for molecular recognition sites because of the additional fused rings and larger V-shaped clefts.



Scheme 28

In a study reported by Biehl after our work was well under way, the formation of dioxocin **5** by the method outlined in Scheme 29 provided a yield of only 64%.[14] The lower yield may be attributable to the weaker nucleophilicity of the hydroxyl group in comparison to the thiol, making cyclization less facile than in the formation of the dithiocins. In their proposed mechanism (Scheme 29), they suggest that **65** reacts with the free ammonia to form the imine **66**. The Schiff base then condenses with another molecule of **65** forming **67**, which cyclizes to give the amino alcohol (**68**). Intermediate **68** then undergoes a further intramolecular cyclization yielding **5**. The order of the final steps differs from our mechanistic Scheme 27.

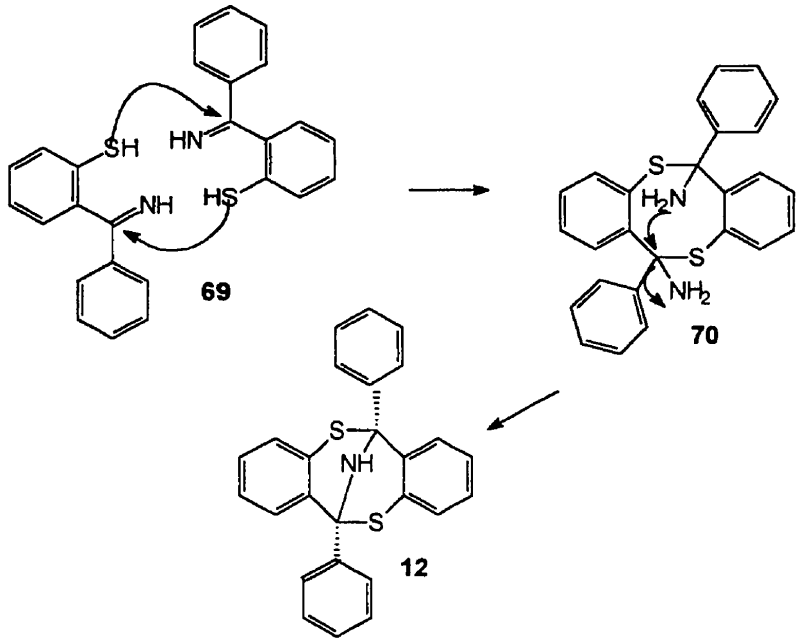
We disagree with a few steps outlined in this mechanism. We believe that an imine would initially form in preference to the O attacking the carbonyl site (**67** → **68**). Nitrogen is known to be more nucleophilic than oxygen because of its less electronegative character. The nucleophilicity would also depend on the degree of solvation. In protic solvents like



Scheme 29

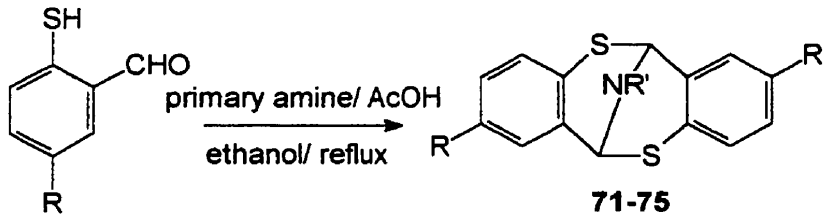
ethanol, nucleophilic sites are subject to strong interaction through hydrogen bonding. Hard nucleophiles like OH are more strongly solvated and become less nucleophilic. We believe that Biehl may have suggested this mechanism to explain the oxa derivative **6**, which results from attack of the hydroxyl at the benzylic site. A close re-investigation of this reaction was undertaken in the lab and we did not find any compound **6**. Biehl and co-

owing to the methine protons for compound **6** was observed. How is this possible if there is an oxygen which bridges the two protons unless there is long range coupling observed? There were, however, no results supporting this hypothesis. Brieaddy and Donaldson[17] proposed a similar mechanism to the one Biehl suggested (Scheme 30). They believed that the thioimine was a very reactive substrate which was capable of undergoing a bimolecular reaction with itself under strong acidic conditions or thermally to give **12**. It was proposed that a self-condensation of the thioimine by nucleophilic attack of the thiol to the thioimine carbon initially forms the 8-membered ring (**70**). One of the amines then attacks the benzylic position opposite to their site to form the bicyclic compound **12**. This proposed mechanism is similar to Biehl's hypothesized mechanism since the 8-membered ring is initially formed instead of the bridged intermediate, as we have suggested.



Scheme 30

Our attempts to modify the secondary amine unit in the dithiocins by use of a primary amine in place of ammonium acetate have been quite successful. A series of N-alkylated 1,5-dithiocins has been synthesized (Table 5). Originally these reactions were performed using nitromethane but, as stated earlier, a competition between the production of the nitroethene product and the 1,5-dithiocin resulted, so the solvent was changed to ethanol to form exclusively the N-alkyl dithiocin.



71-75

R	Amine	R'	% Yields
H	$C_6H_5CH_2CH_2NH_2$	$C_6H_5CH_2CH_2$	**71** 84%
H	$(CH_3)_2CHCH_2NH_2$	$(CH_3)_2CHCH_2$	**72** 91%
H	$(CH_3)_3CNH_2$	$(CH_3)_3C$	**73** 87%
CH_3	$C_6H_5CH_2CH_2NH_2$	$C_6H_5CH_2CH_2$	**74** 83%
CH_3	$(CH_3)_2CHCH_2NH_2$	$(CH_3)_2CHCH_2$	**75** 86%

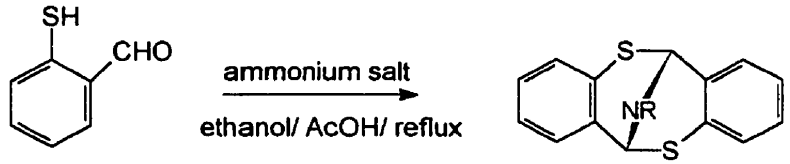
Table 5

Acetic acid was also found to be necessary for the reaction to go to completion. The reaction conditions were optimized to afford the best yields (Table 6). It was found that 1.0 eq of thiosalicylaldehyde (**4b**), 0.55 eq of the primary amine and 2.0 eq of the AcOH were the most favourable conditions for the formation of the N-alkylated 1,5-dithiocins.

1.00	1.10	0.50 mL	62%
1.00	0.55	0.50 mL	75%
1.00	0.55	0.30 mL	84%
1.00	0.55	-	27%

Table 6

Cyclization with the free amine to form the 1,5-dithiocin is possible without using a counter-ion but a very low yield was obtained. Therefore, it is necessary for a counter-ion to be present for best results. We believe this must interact with the solvent in some way to enhance the initial intermolecular condensation between the primary amine and thiosalicylaldehyde. The pH of this reaction also played an important role since acidic conditions were necessary in the formation of 1,5-dithiocins. The use of other ammonium salts was also tested and yields obtained are outlined in Table 7.



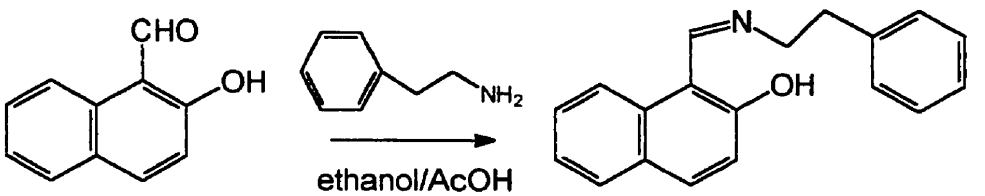
4a

Ammonium Salt	% Yield
NH_4Oac	95%
NH_4SCN	76%
NH_4HCO_3	91%
NH_4Cl	85%

Table 7

These results have proven that while the acetate is not the only salt which forms the dithiocin product, it is a superior counterion compared to other common ammonium salts.

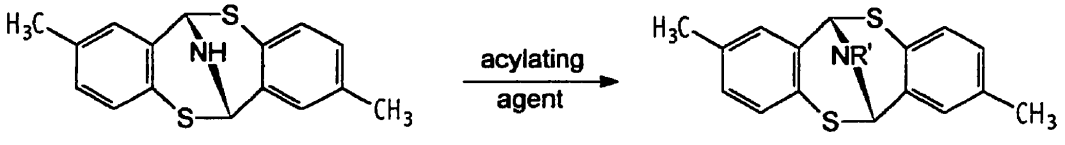
Preparation of N-alkyl analogues in the dioxocin series was also attempted but has so far been unsuccessful. Thus, 2-hydroxy-1-naphthaldehyde was treated with phenethylamine and AcOH in refluxing ethanol for 3.5 h but no bicyclic compound was obtained. The imine (**76**) was the only product isolated from the reaction mixture (Scheme 31). ^{1}H-NMR showed no signal for the characteristic methine protons in the expected dioxocin. It is possible that the hydroxyl group is not nucleophilic enough to attack the substituted imine. Increases in temperature or reaction time resulted in no change in the product. A change in the solvent may have an effect on the outcome of the reaction. Since ethanol is a protic solvent it is possible that there is a strong solvating interaction with the 2-hydroxy-1-naphthaldehyde (**46**), which prevents any further attack on the imine. Solvents such as toluene, benzene or pyridine may lead to more hopeful results but we have not yet investigated these possibilities.



46 **76**

Scheme 31

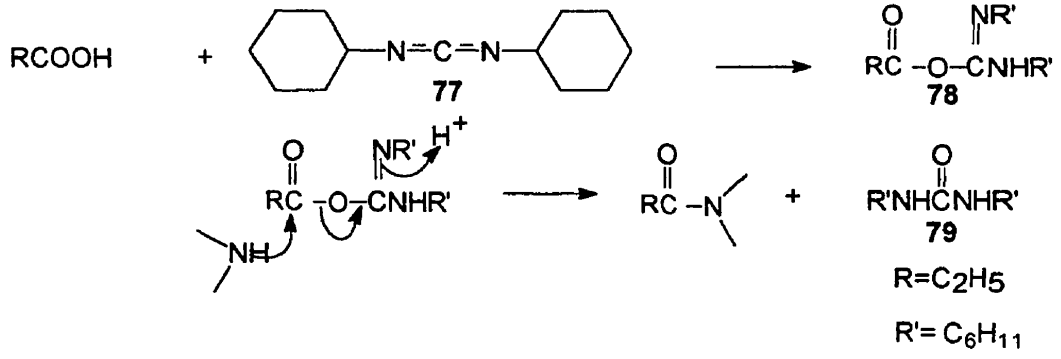
A number of methods have been investigated to find the best approach to acylate the 1,5-dithiocin at the N-site (Table 8). This allows for new functionalized analogues and would open a new class of derivatives for the dithiocins. Some success was observed but yields obtained were acceptable only in the carbamate formation.



Method	R'	% Yield
10% NaOH/ benzoyl chloride	C_6H_5CO-	0%
Methyl chloroformate/ K_2CO_3 reflux	MeOOC-	55%
Methyl chloroformate/ Cs_2CO_3 reflux	MeOOC-	67%
C_2H_5COOH/ DCC CH_2Cl_2 4 h 25°C	C_2H_5CO-	0%
C_2H_5COOH/ DCC CH_2Cl_2 24 h 25°C	C_2H_5CO-	11%

Table 8

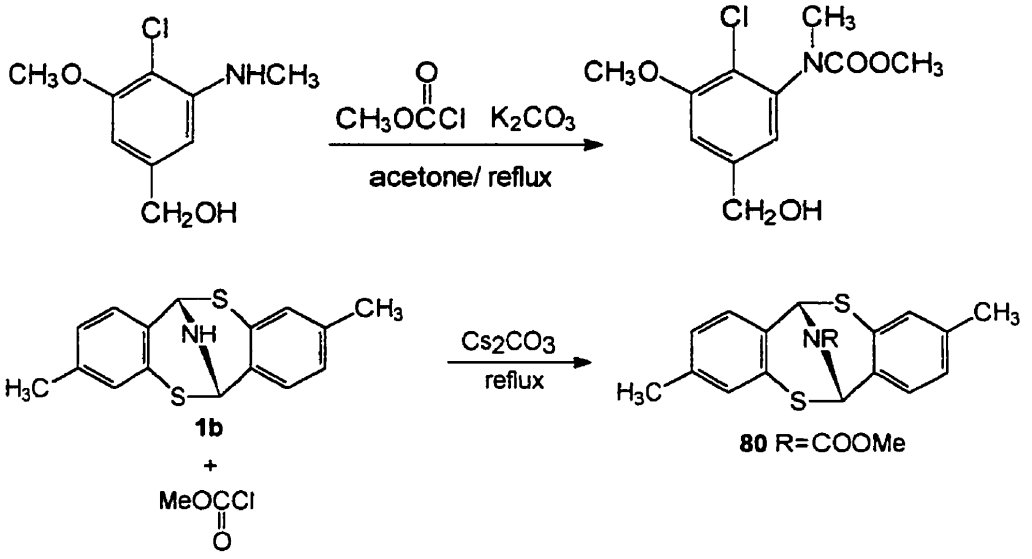
was isolated. Normally this type of reaction works best for acyl halide and alcohols or phenols to form carboxylic esters. We then turned to methods using a carboxylic acid (propionic acid) and 1,3-dicyclohexylcarbodiimide (DCC). DCC (**77**) is a reagent which activates the acid to enhance its reactivity as an acylating agent. This has been widely applied in the acylation step for the synthesis of polypeptides from amino acids.[49] The reactive species is an acyl isourea (**78**) because the cleavage of the acyl-oxy bond converts its carbon-nitrogen double bond to the more stable urea carbonyl group (**79**) (Scheme 32).[50] In our hands, however, this reaction only provided an 11% yield of the desired product, even after stirring for 24h.



Scheme 32

Possibly the addition of 4-dimethylaminopyridine (DMAP) would further catalyze this reaction and form the amide in a better yield. The most successful acylating method (Table 8) was taken from the procedure of Corey and co-workers[51] for the synthesis of a key intermediate in maytansine, an anti-tumour agent (Scheme 33). Recently, the formation of carbamate esters by Butcher[52] has shown that the use of cesium carbonate

of potassium carbonate and sodium carbonate. Applying this method to our system has optimized the yield of **80** to 67%. A white powdery solid was obtained, the ^{1}H-NMR of which showed singlets at δ 6.74 and 6.57 for the methine protons, which result from conformational effects involving the ester substituent. Since the nitrogen is blocked by the carboxy functional group of the bulky molecule, rotation around the nitrogen-CO_2Me is slow, thus, methine protons are not equivalent. Proton NMR, therefore, observes each methine peak in different chemical environments.

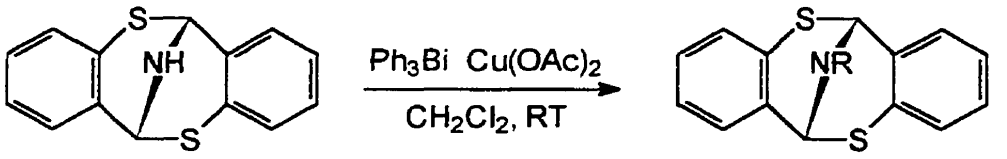


Scheme 33

V. The Phenylation of 1,5-Dithiocin

We have shown that the dithiocins can be both N-alkylated and acylated, the next challenge was to phenylate the secondary amine.

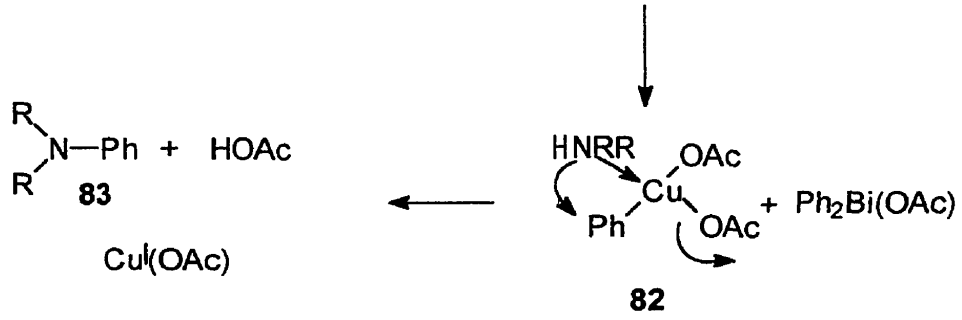
workers[53] to arylate aliphatic and aromatic amines in the presence of metallic copper or a copper(II) salt under mild conditions. The dithiocin was subjected to this method but only very little of the N-phenyldithiocin was obtained, isolated as a mixture with the unreacted dithiocin (Scheme 34).



1b **81** R=C_6H_5

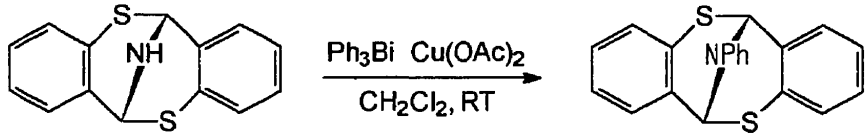
Scheme 34

During the course of the phenylation process (it is presumed that a transient high valent copper species results from an *in situ* oxidation by Bi^V) the concomitant liberation of the acid salt originally bound to the bismuth is observed. The $Cu(OAc)_2$ reacts with the Ph_3Bi to give $Ph_3Bi(OAc)_2$, which reacts with a copper(I) species to give a phenylcopper(III) species **82** (via transmetallation), and the phenylation of the amine **83** then follows (Scheme 35).[54]



Scheme 35

Recently, Chan[55] has reported a modified procedure for arylating amines in the presence of Ph_3Bi and $Cu(OAc)_2$. This modification is proposed to enhance the solubility and reactivity of cupric acetate and various copper species involved in product formation. In addition to this, it may also help buffer the reaction, since acetic acid is presumably generated as a product. We performed a series of experiments to attempt to optimize the conditions of this reaction (Table 9).



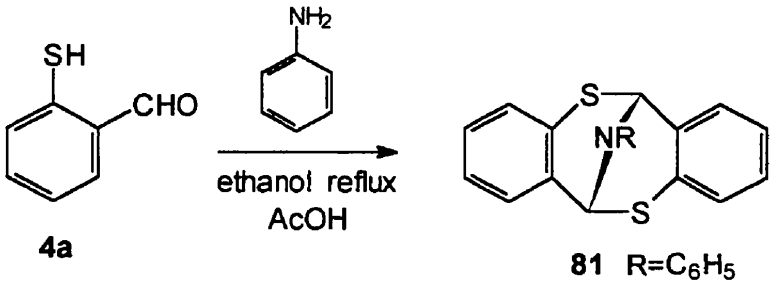
1b **81**

Amine (eq)	$Cu(OAc)_2$ (eq)	Ph_3Bi (eq)	NEt_3 (eq)	Temp.	% Yield
1.0	0.5	1.2	1.0	25°C	0%
1.0	1.0*	1.2	-	25°C	25%
1.0	1.0	1.2	1.0	25°C	15%
1.0	1.0	1.2	-	40°C**	17%

*This reaction was tested using anhydrous $Cu(OAc)_2$ as well as the more readily available monohydrate. Similar results were obtained.
** This reaction was carried out in $CHCl_3$

Table 9

unreacted dithiocin and the N-phenyldithiocin. It is evident from these results that the addition of triethylamine as promoter did not greatly assist the reaction. A possible problem that might have been encountered depended on the pH values of the acetic acid, which may protonate the starting amine and thus prevent any N-phenylation from occurring. Due to the complexity and low yields of this reaction a completely different approach was tried. Since primary aliphatic amines when treated with thiosalicylaldehyde readily cyclize to form the N-alkyl 1,5-dithiocins, it did not seem unreasonable to try the same procedure using aniline. This reaction afforded a very good yield of 75% of the N-phenyldithiocin (Scheme 36). The ^{1}H-NMR spectrum of the product **81** showed a singlet at δ 6.15 for the methine protons. A comparison between the two methods has shown clearly that the preferred route for the formation of N-phenyldithiocins is that outlined in Scheme 36.



4a **81** R=C_6H_5

Scheme 36

We have been interested in the chirality of the dithiocins, since we felt that once the amine is resolved it has the potential to act as a chiral base for stereoselective transformations. This is similar to the concept that Beak *et al.*[27] demonstrated by asymmetric deprotonation of N-Boc-pyrrolidine using sec-BuLi/(-)-sparteine. The resolution of two enantiomers which constitute a racemate is carried out in one of three ways:

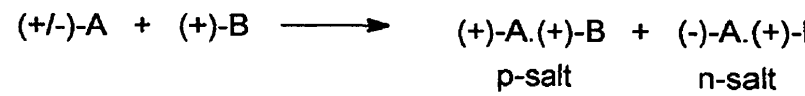
i) Chromatographic separation employing a homochiral stationary phase. In the 1980's separation with high performance liquid chromatography (HPLC) became a common practice.[56] In recent years there has been a growing interest in separating racemates by capillary zone electrophoresis, which appears also to be a versatile method for the determination of enantiomeric excess (ee).[57]

ii) Kinetic resolution, whereby the difference in reaction rates between two enantiomers and an optically pure reagent results in an enantiomeric enrichment of the starting material and/or the reaction product.[58]

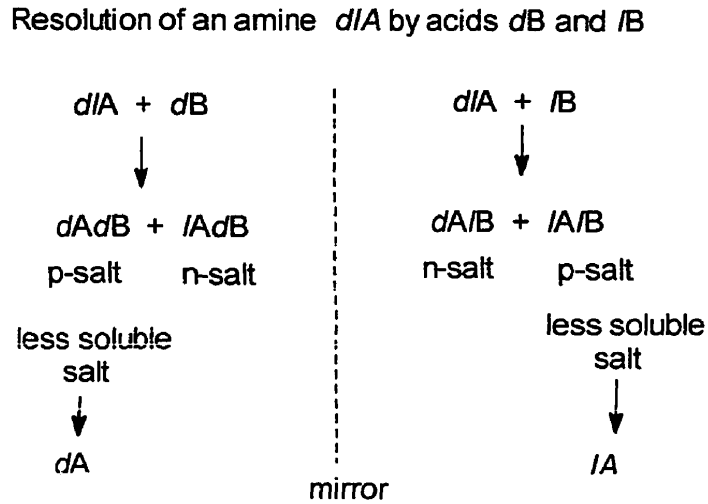
iii) Resolution of a racemate by selective crystallization, which can be subdivided into two groups: direct crystallization of enantiomers and the crystallization of diastereomers.

The most frequently applied method for the separation of enantiomers involves formation of a pair of diastereomers with an optically pure resolving agent. In contrast to enantiomers, diastereomers have different physical properties and can be separated by chromatography or by crystallization techniques. This method was first performed by Pasteur[59]

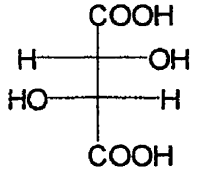
applied to the separation of diastereomeric salts.



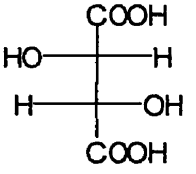
For example, racemic acid A reacts with an optically pure base B and a mixture of the two diasteromeric salts results. The p-salt (positive) denotes the salt resulting from the enantiomers with the same sign of optical rotation and n-salt (negative) from those with opposite signs. In practice, classical resolution usually involves the formation of diastereomeric salts between acids and bases and subsequent selective crystallization of one of the stereoisomers, based on solubility differences. In principle, the resolving agent can readily be recycled by acid-base extractions. When both enantiomers of the resolving agent are available, then both enantiomers of the resolved substrate are obtainable. This is known as the Marckwald principle.[60]



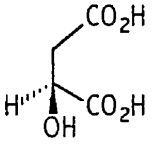
via diastereomeric crystallization involves the search for a suitable resolving agent but this method remains an important industrial source of optically active compounds, simply because it is economically the most attractive method. A series of chiral acids was used as resolvants for the 1,5-dithiocins (Fig. 2). Each acid was treated with the amine to form a diastereomeric salt. The results of salt formation are outlined in Table 10. It is important to note that acetonitrile and chloroform were only used with selected chiral acids, since the other acids were insoluble in these solvents.



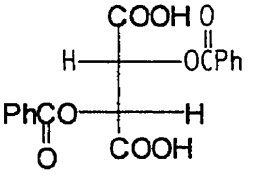
84 L-(+)-Tartaric acid



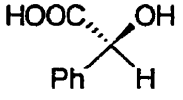
85 D-(-)-Tartaric acid



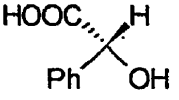
86 (-)-*S*-Malic acid



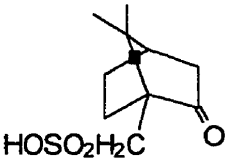
87 (+)-*R,R*-Dibenzoyl -L-Tartaric aci



88 (+)-*S*-Mandelic acid

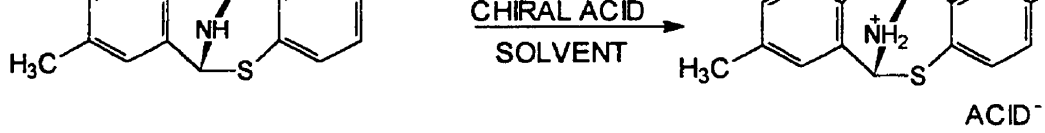


89 (-)-*R*-Mandelic acid



90 (+)-1*S*-Camphor-10-sulfonic acid

Figure 3

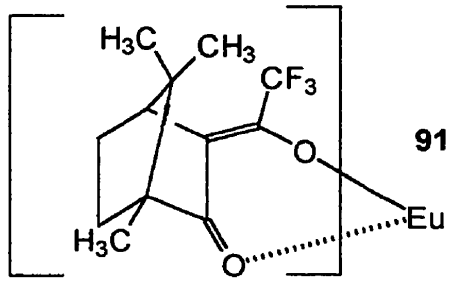


Chiral Acid	Solvent	Observations
D-(-)-Tartaric acid	Acetone	Small suspension
D-10-CSA	Acetone	White solid
D-(-)-Mandelic acid	Acetone	No ppt.
L-(+)-Mandelic acid	Acetone	No ppt.
L-(-)-Malic acid	Acetone	Small suspension
L-DBTA	Acetone	No ppt.
D-10-CSA	Ethyl acetate	Yellow solid
D-(-)-Mandelic acid	Ethyl acetate	Small ppt.
L-(+)-Mandelic acid	Ethyl acetate	Small ppt.
L-(-)-Malic acid	Ethyl acetate	No ppt.
L-DBTA	Ethyl acetate	No ppt.
D-10-CSA	Acetonitrile	Yellow solid
L-(+)-Tartaric acid	THF	Small suspension
D-(-)-Tartaric acid	THF	Small suspension
D-10-CSA	THF	Yellow solid
D-(-)-Mandelic acid	THF	No ppt.
L-(+)-Mandelic acid	THF	No ppt.
L-(-)-Malic acid	THF	Small ppt.
L-DBTA	THF	Small ppt.
L-DBTA	Chloroform	No ppt.

Table 10

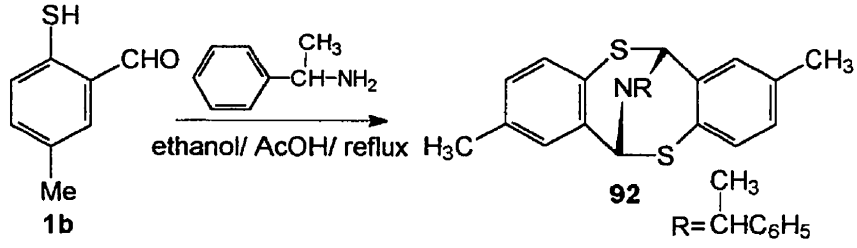
any selective precipitation with the dithiocin. Kinbara *et al.*[61] have recently reported that similarity in molecular size between the target racemate and the resolving agent is one of the most important factors for achieving successful optical resolution. It was revealed that there was a correlation of efficiencies of the optical resolutions of the amines with the resolving reagents and the crystal structure of the salts. A characteristic hydrogen bonding layer, consisting of stable columnar structures having a planar boundary surface, was found to be common to the less-soluble salt crystals. In contrast, in the corresponding more-soluble salts and those diastereomeric salts which could not be separated by crystallization, no such stabilized crystal structure was formed. The most promising result from our studies was the salt formation between *D*-camphor-10-sulfonic acid (*D*-10-CSA) and the dithiocin. Other salts also formed precipitates, but the reaction with *D*-10-CSA was the most favourable, since precipitation occurred spontaneously and thus, was the only salt that provided a yield close to 50%. The isolated salt **90a** afforded a 48% yield and led us to believe that the separation of a pure diastereomer was achieved. The specific rotation was found to be +19.0 ($CHCl_3$, c.0.50). The amine was converted to its free base by addition of alkali and a chiral shift reagent was used to determine whether a single enantiomer was formed. When a racemate resides in a chiral environment, diasteromeric interactions are created which may differ sufficiently in energy so as to permit the two species to be separately observed by NMR spectroscopy. Chiral lanthanide shift reagents which were described nearly simultaneously by Whitesides[62], Fraser[63] and Goering[64] and their co-workers have proven very useful in enantiomer composition determinations by NMR techniques. It has been found that chiral shift reagents generate separate signals for

strongly with europium or praseodymium, such as alcohols, esters, amines, ketones and others. Returning to our case, if selective diastereomeric salt crystallization had resulted, the use of europium tris[3-(trifluoromethyl-hydroxymethylene)-(+)-camphorate] ($Eu(tfc)_3$) (**91**), a chiral shift reagent should result in a ^{1}H-NMR spectrum of single peaks for all protons of the enantiomerically pure dithiocin. To our disappointment this was not observed, but rather a doublet for each peak was noted. Other reactions involving N-alkylated dithiocins (N-*t*-butyl and N-phenethyl) were also conducted with several chiral acids but attempts to crystallize or separate by column chromatography gave no encouraging results.



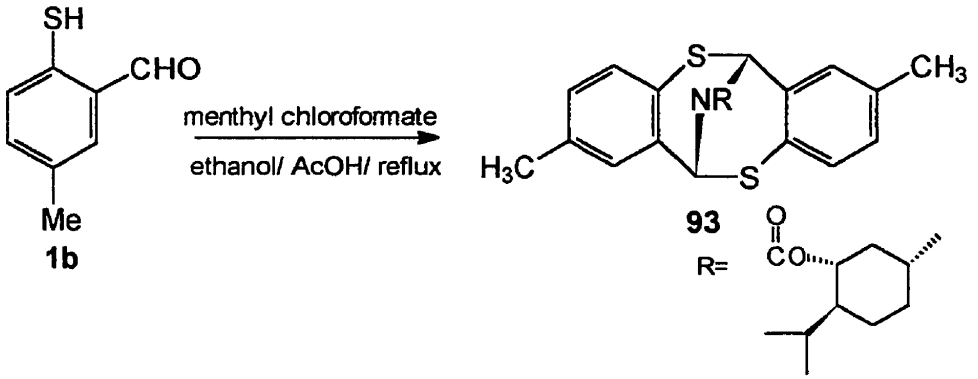
91

Moving along to another approach, we decided to attempt to synthesize a diastereomer of the 1,5-dithiocin using a chiral derivatizing agent, *R*-α-methylbenzylamine (Scheme 37).



Scheme 37

NMR spectrum showed a splitting pattern for all peaks. Attempts to separate the diastereomers, however, by column chromatography were unsuccessful because the R_f values ran too closely together, such that separation even on the scale of 200:1 of silica gel to product was not effective. Formation of another pair of diastereomers by acylating the secondary amine with (-)-menthyl chloroformate (Scheme 38) resulted in similar observations. Had the diastereomers been separable by this method, a convenient procedure was available to remove the (-)-menthyloxycarbonyl group with HBr in hot acetic acid in good yield.[65] These attempts to resolve the dithiocins were reluctantly abandoned.

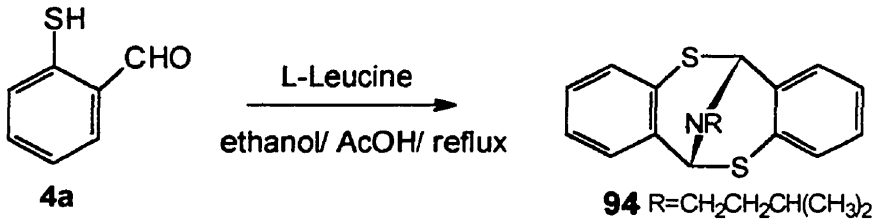


Scheme 38

VI. The use of Amino Acids in the Formation of 1,5-Dithiocins

Our original aim in using the amino acids was to assist in the resolution problem discussed above. It was thought that the product would consist of diastereomers which may be easily separated but, to our surprise,

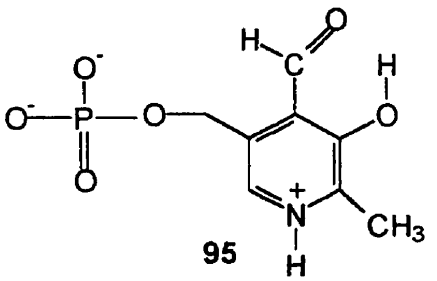
observation was noted when the thiosalicylaldehyde **1b** was condensed with various amino acids. A decarboxylation resulted to form the corresponding N-alkylated 1,5-dithiocins (Scheme 39).



4a **94** R=$CH_2CH_2CH(CH_3)_2$

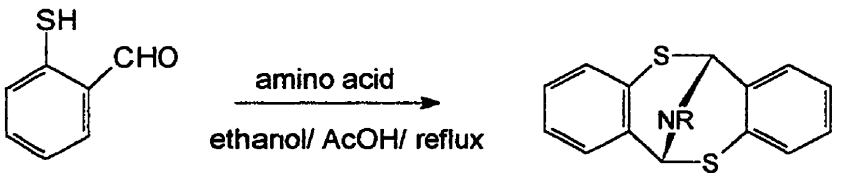
Scheme 39

The ^{1}H-NMR gives no evidence of a carboxylic acid peak but a singlet was observed at δ 5.41 for the methine protons: the IR reveals no carbonyl or OH stretch as well. Decarboxylation reactions are important for metabolic interconversions. Analogous to this reaction is the known enzymatic reaction of pyridoxal phosphatase (**95**), which helps to catalyze the α-decarboxylation of amino acids.[66] In the pyridoxal phosphatase mechanism, an initial formation of a Schiff base results. The pyridine ring in the Schiff base acts as an electron sink which effectively stabilizes the negative charge and allows for facile decarboxylation (Scheme 40).



95

Other amino acids, as their methyl esters, were treated in the same manner (Table 11) and complete loss of the methyl ester group was observed in these cases, in synthetically acceptable yields.

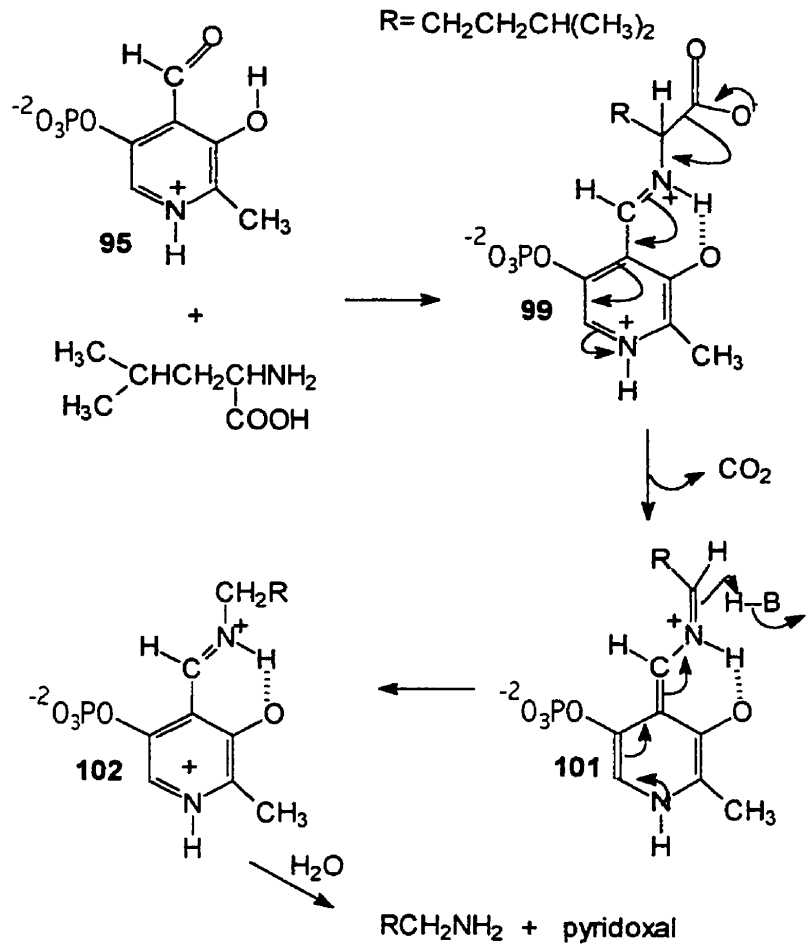


4a **94, 96-98**

Amino acid	R	% Yield
Leucine	$(CH_3)_2CHCH_2CH_2$-	**94** 68%
Serine methyl ester	$HOCH_2CH_2$-	**96** 75%
Phenylalanine methyl ester	$C_6H_5CH_2CH_2$-	**97** 63%
Leucine*t*-butyl ester	$(CH_3)_2CHCH_2CHCO_2{}^tBu$-	**98** 71%

Table 11

As predicted, the product obtained from the phenylalanine methyl ester gave exactly the same results as when the thiosalicylaldehyde was subjected to phenethylamine. In sharp contrast, the *t*-butyl ester of leucine did not result in the loss of the carboxy substituent. The ^{1}H-NMR spectrum of the product showed a doublet at δ 1.20 for the *t*-butyl protons and 5.73 for the methine protons.

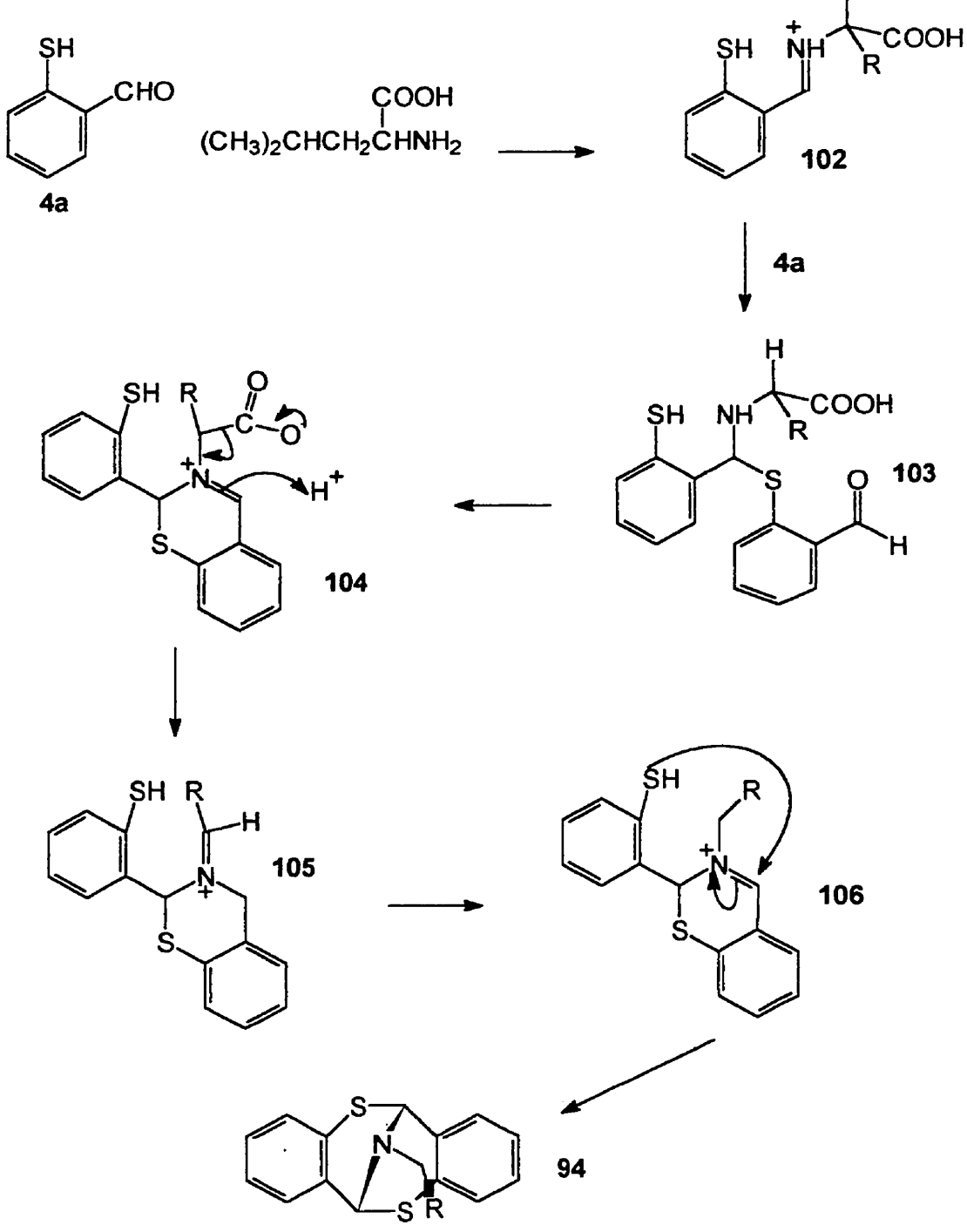


Scheme 40

A possible mechanism for the original reaction with leucine is outlined in Scheme 41. Initial formation of a Schiff base (**102**), followed by the attack of a second equivalent of thiosalicylaldehyde produces intermediate **103**. Another Schiff base forms and decarboxylation of the acid results to produce **105**. Rearrangement of the double bond to form a thermodynamically more stable compound (due to a conjugated system), followed by the attack of the imine by the free thiol will form **94**. We

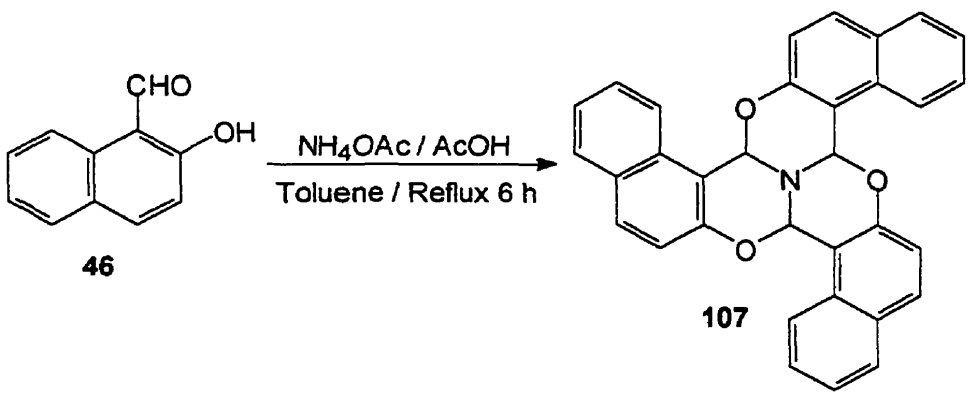
an ArS^-, which will remove the methyl group then follow the decarboxylation step as outlined above. This ArS^- is able to nucleophilically attack the CH_3 of the methyl ester, which allows the decarboxylation to occur. However, such attack on the *t*-butyl of the *t*-butyl ester does not occur. This provides a new method for amino acid decarboxylation, but a more detailed investigation of this reaction is required.

One notable feature in the formation of the diastereomers was the chemical shift observed for the methine protons. In each case, two peaks were observed for the benzylic protons, which gave good evidence that a resolution may be achieved in this way. In **92** and **93**, as well as in compound **98** (see pages 78-82) the benzylic protons showed increasing separation (**93**> **98** > **92**) ranging from $\Delta\delta$ 0.03 to δ 0.21 ppm, corresponding to the varying nature of the auxiliary chiral site (or sites as in the case of **93**). Once separation of these diastereomers has been attained, the removal of the chiral auxiliary may then be attempted in such a way that only unsubstituted (at the N-site) 1,5-dithiocins will be obtained. Alternatively, especially in the case of compounds **92** and **98**, the N-substituted diastereomeric amine bases themselves may prove to have a future role in base-catalyzed enantioselective reactions.


SH
CHO
4a
COOH
(CH3)2CHCH2CHNH2
SH
NH
COOH
R
102
4a
H
SH
NH
COOH
R
S
O
H
103
SH
R
O
C
O
N
H+
S
104
SH
R
H
N
S
105
SH
R
N
S
106
S
N
S
R
94
R = CH2CH(CH3)2

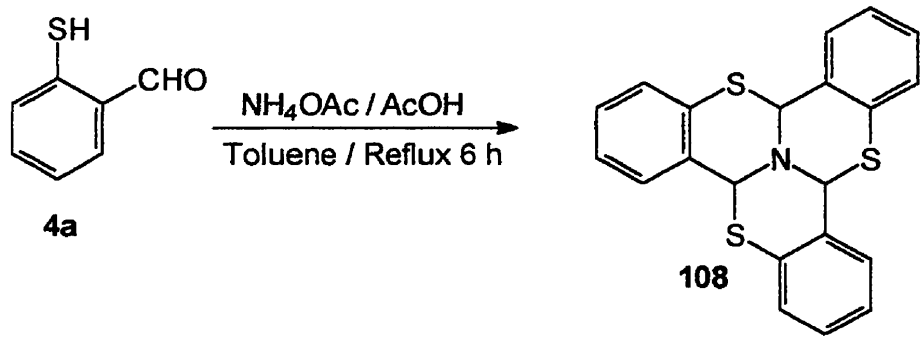
Scheme 41

We have recently completed the syntheses of tricyclo-benzoxazine analogues of the dithiocins. These compounds form molecular clefts even larger than those of the 1,5-dithiocins, which may suggest some useful applications as DNA recognition sites. Using the method suggested by Kanakarajan *et al.*,[20] tricyclo-naphthoxazine **107** has been formed by treating 2-hydroxy-1-naphthaldehyde with ammonium acetate and acetic acid in refluxing toluene for 6 h (Scheme 42). When the reaction mixture was concentrated to half its volume, yellow crystals were formed. The mass spectrum showed a molecular ion at m/z=479, which corresponds to the mass of the expected tricyclo-naphthoxazine. A proton NMR was not obtained due to solubility problems of the compound, but an IR spectrum confirmed the loss of the OH and carbonyl bands, to prove that the condensation has taken place. Solvent effects may play an important role in the formation of these compounds.



Scheme 42

The tricyclo-benzothiazine **108** has been synthesized in a similar manner (Scheme 43). The ^{1}H-NMR showed a peak at δ 6.59 for the methine protons and the mass spectrum showed a molecular ion at m/z=377, corresponding to **111**.



Scheme 43

It has been reported by Meier *et al.*[67] that tricyclo-benxoxazines are stable to weak acid but heating with 98% trifluoroacetic acid hydrolyzes the compound back to the starting materials.

IX. Complexation of Heavy Metals to the 1,5-Dithiocins

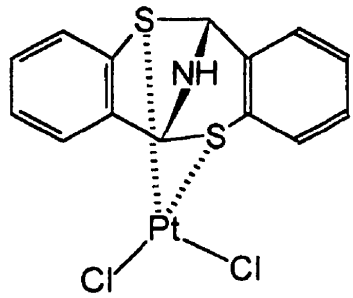
We are currently exploring the potential of 1¬5-dithiocins as complexing ligands for heavy metals. A variety of metals have been reacted with **1b**. Of the metals examined, the most interacting is lead acetate in anhydrous THF, which resulted in the formation of a yellow precipitate. Unfortunately, in spite of extensive efforts, we were unable to obtain suitable crystals from this yellow solid for X-ray analysis. When the solid was dissolved in dichloromethane, the lead acetate precipitated out of solution and only the dithiocin (**1b**) remained. It is possible that a weak

disturbed. Likewise, the reaction with mercury(II) acetate in THF afforded a dark grey precipitate, but due to recrystallization problems no suitable crystal was obtained (Table 12).

Heavy metals	Observations
$Hg(OAc)_2$	Dark grey ppt.
$Pb(OAc)_2$	Yellow ppt.
$Cu(OAc)_2$	Blue solution; no ppt
$Pd(OAc)_2$	Clear solution; no ppt

Table 12

Toste and Still[12] have reported the formation of a yellow precipitate using **1a** and Pt(II) chloride-dimethyl sulfide complex, prepared by the method reported by Kauffman *et al.*[68] The exchange of dimethyl sulfide ligands of Pt(II) complex for sulfides of the bidentate ligand **1a**, is



apparently an entropically favourable transformation (chelate effect). This transformation could be monitored by ^{1}H-NMR because of the coupling observed at H-6/H-12 and the Pt (II) site. ^{195}Pt makes up only 33% of

signals observed for *H*-6 and *H*-12 should appear as a 1:4:1 triplet, assuming that the Pt is coordinated to the ligand **1a**. We are currently investigating whether any interactions occur between the 1,5-dithiocins and metal complexes, either by ^{1}H-NMR or X-ray analysis. Yet another interesting investigation would be to examine the formation of the dithiocins in the presence of a metal with chiral ligands. Hopefully, coordination of the sulfur ligands to the metal will be observed and perhaps diastereomeric dithiocins would be formed. This would be an attractive transformation to study since it offers insight to the complexation as well as to the resolution of these compounds.

We have described the methods for the preparation and manipulation of the 1,5-dithiocins. The reaction of thiosalicylaldehydes with ammonium acetate in refluxing ethanol results in excellent yields of the desired bicyclic compounds. The requisite aldehydes were prepared by trapping the organlithium intermediate, formed by *ortho*-lithiation, with N-formylpiperidine. In the same manner we have also shown *ortho*-lithiation of naphthalenethiol to form regio-isomeric aldehydes in moderate yields. Interestingly, the formylation of 2-naphthalenethiol resulted in two products, which were condensed with ammonium acetate to provide a new class of 1,5-dithiocins analogues with an additional fused ring. In addition, the tricyclo compounds were formed which contain an even larger cleft. It was essential to use toluene as the solvating agent in order to isolate the tricyclo compound as the main product. However, use of protic solvents such as ethanol in the condensation between the amine and thiosalicylaldehyde has afforded almost exclusively the 1,5-dithiocins.

Our attempts of modifying the bridging secondary amine by the use of primary amines have proven successful in the formation of **71-75**. We have found that the presence of a counterion (acetic acid) was crucial in the cyclization to form the 1,5-dithiocins. Reactions of the bridging amine with acylating agents have also been outlined and a yield of 67% using methyl chloroformate and cesium carbonate in refluxing acetone was the most effective method. Functionalizing the 1,5-dithiocin at the N-site with a phenyl substituent has also proven successful. This was carried out by using $Cu(OAc)_2$ and Ph_3Bi but rather low yields were obtained. Another method

from primary amines was adapted. In this case, aniline was employed as the amine and condensed with thiosalicylaldehyde **4a** to form the N-phenyl-dithiocin with excellent yields (75%).

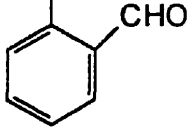
Our efforts in resolving the enantiomers of 1,5-dithiocins appear encouraging but this requires more extensive investigation. Ultimately, our goal is to resolve these enantiomers and examine the usefulness of these amines as chiral bases.

Some preliminary work has also been done on the complexation between the dithiocin **1b** and heavy metals. The most promising results were obtained from using $Pb(OAc)_2$ and $Hg(OAc)_2$ with the 1,5-dithiocin. For future studies, a more detailed inquiry into how the non-functionalized derivatives compare with functionalized ones in complexing with heavy metals is required.

General Methods

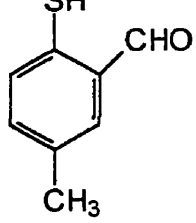
For all anhydrous reactions, glassware was dried in the oven overnight at 120°C prior to its use. Reactions were carried out using a one-neck or three-neck round-bottom flask and mixing was carried out using a magnetic stirring bar. All anhydrous reactions were run under argon atmosphere. DMF and nitromethane were distilled from P_2O_5 and stored over 3A sieves. Methanol was distilled from magnesium turnings and stored over activated 3A sieves. Hexanes, THF, toluene and diethyl ether were distilled from sodium/benzophenone ketyl. Triethylamine and TMEDA were distilled from calcium hydride prior to use. Alkyllithium solutions were obtained from Fluka and were titrated.[69] Purification was initially carried out by column chromatography, using Merck 40-60μ silica gel or aluminum oxide and an appropriate solvent system (q.v.)

Infrared spectra were obtained on a Nicolet 5-DXB Fourier transform infrared spectrometer as neat films on NaCl disks or as KBr pellets, as indicated, and data were recorded in wavenumbers (cm^{-1}). Proton NMR (200 MHz) were obtained on a Varian Gemini XL 200 spectrometer. NMR spectra were run in $CDCl_3$ unless otherwise stated. ^{13}C-NMR and DEPT spectra were run at 100.6MHz on a Varian XL 400 instrument. High resolution (HR-EIMS) and electron impact (EIMS) mass spectra were obtained on a VG11-25OS instrument at 70 eV. Elemental analyses were performed by the Guelph Chemical Laboratories Ltd., Guelph, Ontario.



2-Mercaptobenzaldehyde (**4a**)

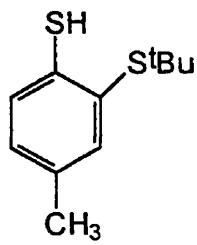
To a solution of thiophenol (2.00mL, 19.47mmol) in 45mL of dry hexanes under Ar atmosphere, TMEDA (6.43mL, 42.83mmol) was added via addition funnel. The clear solution was stirred for 5 min and was cooled to 0°C. The 2.2M n-BuLi (19.47mL, 42.83mmol) was added with a syringe over a period of 20 min, giving the solution a yellow colour. The mixture was stirred for an additional 0.5 h at 0°C and was warmed to room temperature and stirred for 17 h. The resulting solution turned white and became very thick in appearance. On cooling to 0°C N-formylpiperidine (4.34mL, 38.94mmol) was slowly added, forming a red solution and an orange paste-like precipitate. The reaction mixture was stirred at 25°C for 18 h, then acidified with 1M HCL (2x25mL), extracted with CH_2Cl_2 (4x25mL), and washed with sat'd NaCl (25mL). The solution was dried (Na_2SO_4) and concentrated to afford a dark orange-brown oil (2.77g, 93%). Flash chromatography, eluting with CH_2Cl_2 (R_f=0.35) afforded an oil (2.42g, 81% yield); IR (film): ν 3085, 2839, 2750, 1680, 1590, 1560, 1485, 1440, 1215, 850, 750; ^{1}H-NMR: δ 10.25 (s, 1H, *CHO*), 7.89 (dd, J=7.5, 1.6Hz, 1H, *H-6*), 7.80 (dd, J=7.8, 1.6Hz, 1H, *H-3*), 7.5 (td, J=7.8, 1.6Hz, 1H, *H-4*), 7.39 (td, J=7.5, 1.6Hz, 1H, *H-5*), 5.49 (s, 1H, *SH*).



2-Mercapto-5-methylbenzaldehyde (**4b**)

The salicylaldehyde was prepared according the same procedure for the preparation of **4a.**

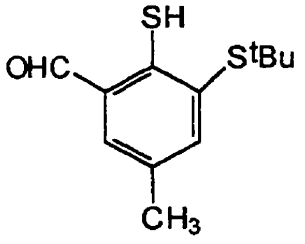
A crude orange-brown oil (1.19g, 88%) was obtained from the solution. Flash chromatography, eluting with CH_2Cl_2 (R_f=0.39) afforded a yellow oil (1.01, 75% yield); IR (film): ν 3018, 2925, 2875, 2545, 1665, 1461, 1245, 1176, 1075, 815, 780; ^{1}H-NMR: δ 9.99 (s, 1H, *CHO*), 7.52 (d, J=2.6Hz, 1H, *H-6*), 7.19 (m, 2H, *H-3, H-4*), 5.31 (s, 1H, *SH*), 2.37 (s, 3H, *$ArCH_3$*).



2-(*tert*-Butylsulfanyl)-4-methylbenzenethiol (**39**)

To a solution of p-thiocresol (0.30g 2.40mmol) in 30mL of dry hexanes under Ar atmosphere, TMEDA (0.80mL, 5.32mmol) was added via addition funnel. The clear solution was stirred for 5 min and was cooled to 0°C. The 1.6M n-BuLi (3.32mL, 5.32mmol) was added with a syringe, over

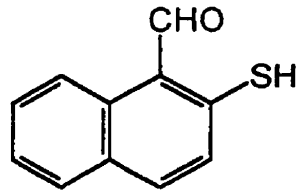
stirred for an additional 0.5 h at 0°C and was warmed to room temperature and stirred for 17 h. The resulting solution turned white and, was cooled to -10°C. Slow addition of freshly distilled *tert*-butyl disulfide (0.74mL, 3.84mmol) turned the mixture red in colour and stirring was continued for 16 h. The solution was washed with 1M HCl (2 x 20mL), saturated NaCl (20mL), dried (Na_2SO_4) and condensed to afford a brown oil (0.38g, 81%). Kugelrohr distillation collected **39** (0.33g, 70%), bp 130-134°C/7 mm; IR (film): ν 2961, 2934, 2518, 1450, 1358, 1164, 1028, 818; ^{1}H-NMR; δ 7.41 (d, J=1.5Hz, 1H, *H-3*), 7.29 (d, J=7.8Hz, 1H, *H-6*), 7.04 (dd, J=7.8, 1.5Hz, 1H, *H-5*), 4.77 (s, 1H, *SH*), 2.33 (s, 3H, CH_3), 1.39 (s, 9H, $SC(CH_3)_3$) .



3-(*tert*-Butylsulfanyl)-2-mercapto-5-methylbenzaldehyde **(4c)**

Compound **39** (0.20g, 0.94mmol) was lithiated in dry hexanes (20mL) and TMEDA (0.33mL, 2.17mmol), using 2.2M n-BuLi (0.98mL, 2.17mmol) as in the procedure for the preparation of **4a**. The resulting orange mixture was treated with N-formylpiperidine (0.21mL, 1.88mmol) at 25°C. The mixture turned yellow and was stirred for 18 h. The solution was washed with 1M HCl (2 x 15mL), saturated NaCl (15mL), dried (Na_2SO_4) and concentrated to afford a brown oil (0.159g, 74%). Flash chromatography, eluting with CH_2Cl_2 (R_f=0.45), yielded a yellow oil (0.13g, 63%). IR (film): ν 2960, 2925, 2893, 2480, 1684, 1672, 1459, 1430, 1363, 1156, 769; ^{1}H-

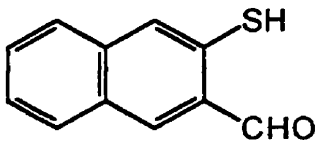
1H, *H-4*), 6.98 (s, 1H, *SH*), 2.15 (s, 3H, CH_3), 1.33 (s, 9H, $SC(CH_3)_3$).



2-Mercapto-1-naphthaldehyde (**41**)

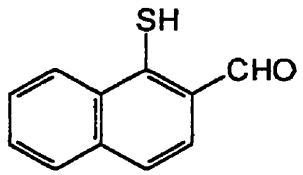
2-Naphthalenethiol (2.00g, 12.48mmol) was ground and dissolved in dry hexanes (80mL), under Ar atmosphere and TMEDA (4.69mL, 31.20mmol) was added to the mixture. The mixture was cooled to 0°C and 1.6M n-BuLi (19.50mL, 31.20mmol) was added dropwise. The solution initially turned a cloudy white colour and eventually became yellow and clear. The mixture was then stirred for 0.5 h at 0°C and warmed to room temperature to stir for an additional 16 h. N-formylpiperidine (2.78ml, 24.96mmol) was added via syringe and a dark red paste resulted. Vigorous stirring for 10 h formed a yellow mixture which was then washed with 1M HCl (2x30mL) and extracted with CH_2Cl_2 (4x30mL). Washing with saturated NaCl (30mL), drying (Na_2SO_4) and concentration afforded a brown oil (1.76g, 75%). Chromatography on aluminum oxide, eluting with CH_2Cl_2 /MeOH (95:5) (R_f=0.64), resulted in compound **41** (0.70g, 45%), mp 122-124°C. IR (film): ν 2957, 2924, 2851, 2725, 2555, 1722, 1463, 1433, 1345, 774; ^{1}H-NMR: δ 11.03 (s, 1H, *CHO*), 8.66 (d, J=7.5 Hz, 1H, *H-8*), 7.84 (d, J=7.6 Hz, 1H, *H-3*), 7.63 (m, 1H, *H-7*), 7.48 (m, 1H, *H-6*), 7.34 (d, J=7.5 Hz, 1H, *H-4*), 7.31 (d, J=7.7 Hz, 1H, *H-5*), 4.85 (s, 1H, *SH*); EIMS:

188.0285; calculated for $C_{11}H_8OS$, 188.0288.



3-Mercapto-2-naphthaldehyde (**42**)

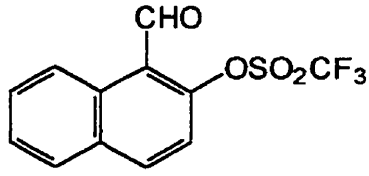
The same procedure as above provided an orange/brown oil (75%); column chromatography separated the two salicylaldehydes **41** and **42**; Chromatography on aluminum oxide, eluting with CH_2Cl_2 /MeOH (95:5) (R_f=0.33), results in **42** (0.79g, 30%) mp 134-136°C. IR (film): ν 2970, 2930, 2850, 2578, 1708, 1525, 1463, 1363, 1259, 1150, 925, 734; ^{1}H-NMR: δ 10.15 (s, 1H, *CHO*), 8.26 (s, 1H, *H-1*), 7.89 (d, 3.9Hz, 1H, *H-4*), 7.73 (m, 1H, *H-7*), 7.68 (m, 1H, *H-6*), 7.52 (d, 7.6 Hz, 1H, *H-5*), 7.45 (dd, 3.8, 7.6 Hz, 1H, *H-8*), 5.48 (s, 1H, *SH*); EIMS: m/z(%) 188 (100), 154 (24), 126 (52), 115 (60), 79 (15); HR-EIMS: found 188.0281; calculated for $C_{11}H_8OS$, 188.0288.



1-Mercapto-2-naphthaldehyde (**44**)

1-Naphthalenethiol (0.94g, 5.87mmol) was dissolved in dry hexanes (50mL) under Ar atmosphere and TMEDA (2.20mL, 14.67mmol) was added to the mixture. The reaction was cooled to 0°C and 1.6M n-BuLi (9.17mL, 14.67mmol) was added dropwise. The solution initially turned cloudy white

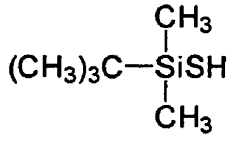
0.5 h at 0°C and warmed to room temperature before stirring for an additional 16 h. N-Formylpiperidine (1.11mL, 9.98mmol) was added via syringe and a dark red paste resulted. Vigorous stirring for 10 h formed a yellow mixture which was then washed with 1M HCl (2x25mL) and extracted with CH_2Cl_2 (4x25mL). Additional washing with saturated NaCl (25mL), drying (Na_2SO_4) and concentration yielded a brown oil (0.62g, 56%). Chromatography on aluminum oxide, eluting with CH_2Cl_2 /MeOH (95:5) (R_f=0.45), gave a yellow oil (0.47g, 43%), bp 139-142°C/7mm. IR (film): ν 3050, 2924, 2864, 2360, 1682, 1495, 1216, 1067, 825, 753; ^{1}H-NMR: δ 9.82 (s, 1H, *CHO*), 8.33 (m, 2H, *H-3*, *H-8*), 7.95 (m, 2H, *H-4*, *H-5*), 7.66 (m, 1H, *H-7*), 7.31 (m, 1H, *H-6*), 5.31 (s, 1H, *SH*) .



2-Trifluoromethylsulfonyloxy-1-naphthaldehyde (**47**)

To a solution of 2-hydroxy-1-naphthaldehyde (1.00g, 5.81mmol), in 16mL of pyridine at 0°C, triflic anhydride (1.09mL, 6.45mmol), was slowly added. Evolution of a white gas occurred and the resulting mixture was stirred at 0°C for an additional 5 min. The mixture was then warmed to room temperature and stirred for 24 h. Water (15mL) was added to the solution, which was extracted with diethyl ether (2x15mL), washed with H_2O (15mL), 10% aqueous HCl, then saturated NaCl (15mL). The organic layer was dried (Na_2SO_4) and concentrated to obtain a brown, foamy solid (1.32g, 75%). Recrystallization from CH_2Cl_2/hexanes afforded a beige solid

1075, 856, 784; ^{1}H-NMR: δ 10.81 (s, 1H, *CHO*), 8.45 (d, J=6.3Hz, 1H, *H-3*), 8.25-7.17 (m, 5H).



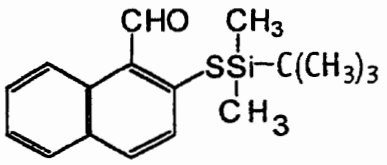
tert-Butyldimethylsilanethiol (**48a**)

Dry THF (25mL) was saturated with H_2S gas, and the reaction vessel was then cooled to –78°C. The 1.6M n-BuLi (8.00mL, 13.00mmol), was added dropwise to the above solution, which was allowed to warm to 0°C, with stirring for 0.5 h. The mixture was then re-cooled to –78°C and the TBDMSCl (1.68g, 11.11mmol) was added portion-wise with a spatula. The yellow mixture was warmed to room temperature and was partitioned between pentane (50mL) and H_2O (25mL). The organic layer was extracted and was washed with H_2O (20mL), dried (Na_2SO_4) and concentrated to afford a clear oil (83%). IR (film): ν 2737, 2560, 1463, 1250, 1160, 1070, 1026, 839, 789; ^{1}H-NMR: δ 0.97 (s, 9H, *$(CH_3)_3$*), 0.29 (s, 6H, *$(CH_3)_2$*), 0.11 (s, 1H, *SH*).

Potassium *tert*-butyldimethylsilanethiolate (**48b**)

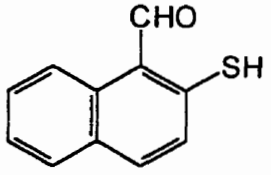
Potassium hydride (0.31g, 7.69mmol), was initially washed with dry pentane (3x20mL) and was placed in a flask with 10mL of pentane. The silanethiol **48a** (1.13g, 7.63mmol) was added slowly to the reaction mixture at 0°C and stirring was continued for 2 h. Solvent was removed and a white solid was obtained (0.98g, 69%). The salt was recrystallized from toluene to

spectrum was not obtained.



2-*tert*-Butyldimethylsilylsulfanyl-1-naphthaldehyde (**49**)

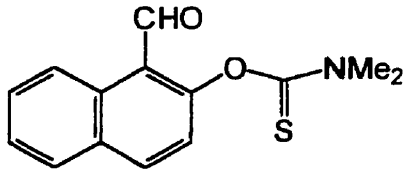
A solution of the salt **48b** (0.12g, 0.66mmol) in dry THF (15mL), was added to tetrakis(triphenylphosphine) (0.06g, 0.05mmol) and the triflate **47** (0.20g, 0.66mmol) in toluene (20mL). The brown solution was refluxed for 5 h, after which it was partitioned between H_2O (25mL) and ethyl acetate (25mL). The organic layer was washed with H_2O (2x15mL), dried (Na_2SO_4) and concentrated to afford a brown oil (0.14g, 73%). Flash chromatography, eluting with CH_2Cl_2 (R_f=0.44), afforded a yellow oil (0.10g, 52%). IR (film): ν 2990, 2946, 2856, 2725, 1722, 1597, 1517, 1263, 1148, 1085, 997, 917, ^{1}H-NMR: δ 10.85 (s, 1H, CHO), 8.35 (d, J=8.2Hz, 1H, *H-3*), 7.98 (d, J=7.1Hz, *1H*, *H-8*), 7.78 (dd, J=4.0, 8.1Hz, 1H, *H-4*), 7.60 (m, 1H, *H-7*), 7.41 (m, 1H, *H-6*), 7.17 (dd, J= 3.9, 7.0Hz, 1H, *H-5*), 1.05 (s, 9H, $(CH_3)_3$,), 0.48 (s, 6H, $(CH_3)_2$).



2-Mercapto-1-naphthaldehyde (Alternative preparation) (**41**)

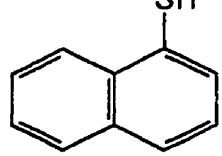
To a solution of the protected thiol **49** (0.53g, 0.18mmol) in THF (10mL) at 0°C, tetrabutylammonium fluoride (0.20mL, 0.19mmol) was

yellow colour. The reaction vessel was washed with saturated NH_4Cl (10mL) and was extracted with CH_2Cl_2 (3x10mL), dried (Na_2SO_4) and concentrated to afford a brown oil (0.03g, 89%). Flash chromatography, eluting with CH_2Cl_2 (R_f=0.48), resulted in a yellow solid (76% yield); mp 124-126°C.



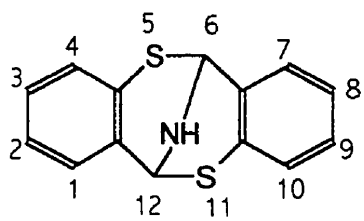
2-(N,N-Dimethylthiocarbamoyloxy)-1-naphthaldehyde (**54**)

Triethylamine (0.81mL, 5.81mmol) was added to a solution of 2-hydroxy-1-naphthaldehyde (1.00g, 5.81mmol) dissolved in CH_2Cl_2 (25mL) and stirred for 5 min. Crushed dimethylthiocarbamoyl chloride (0.86g, 6.97mmol) was added to the above mixture portion-wise with a spatula. The brown solution was stirred for 3 h at room temperature. The solution was washed with 1M HCl (2x20mL), saturated NaCl (20mL), dried (Na_2SO_4) and concentrated to give a brown oil (1.11g, 73%). The dark mass was stirred with charcoal, filtered and recrystallized from CH_2Cl_2 (0.93g, 61%). IR(KBr): ν 3356, 2840, 2798, 1654, 1510, 1384, 1191, 933, 839; ^{1}H-NMR: δ 10.80 (s, 1H, *CHO*), 8.36 (d, J=8.5Hz, 1H, *H-3*), 7.95 (d, J=7.1Hz, 1H, *H-8*), 7.82 (d, J=8.5Hz, 1H, *H-4*), 7.60 (t, J=7.1Hz, *H-7*), 7.41 (t, J=7.2Hz, 1H, *H-6*), 7.08 (d, J=7.1Hz, 1H, *H-5*), 3.40 (s, 6H, CH_3).



1-Naphthalenethiol (**57**)

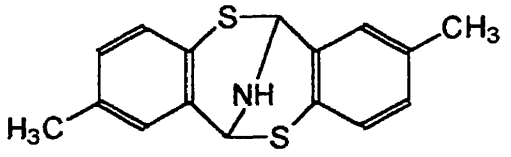
Concentrated hydrochloric acid (11.40mL) was added to crushed ice (30g) in a round bottom flask, with stirring. 1-Naphthalenesulfonyl chloride (1.00g, 4.41mmol) was added portion-wise via spatula, making sure that the solution was kept below 0°C. Tin (6.30g, 53.04mmol) was added to the vessel, turning the solution yellow. The mixture was refluxed for 6 h and the solution became clear. The solution was then extracted with CH_2Cl_2 (2x20mL), washed with saturated NaCl solution, dried (Na_2SO_4) and concentrated to yield a yellow oil (0.63g, 89%), bp 138-140°C/7mm, lit. bp[70] 131-132°C/5mm; IR (film): ν 3057, 2571, 1566, 1504, 1381, 1258, 978; ^{1}H-NMR: δ 8.30 (d, 1H), 7.94 (d, 1H), 7.80 (d, 1H), 7.70 (m, 3H), 7.44 (dd, 1H) 3.71 (s, 1H, *SH*).



6,12-Imino-*6H,12H*-dibenzo[b,f]- 1,5-dithiocin (**1a**)

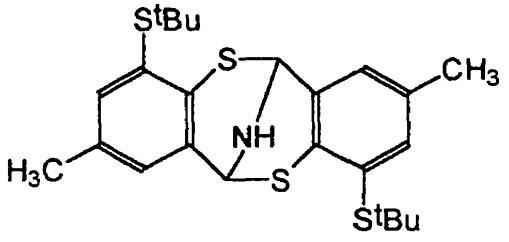
The thiosalicylaldehyde **4a** (0.90g, 6.52mmol) dissolved in absolute ethanol (30mL) was treated with ammonium acetate (0.55g, 7.17mmol), turning a yellow colour. The solution was refluxed for 3.5 h and cooled to room temperature, resulting in the formation of a white precipitate. Filtration and drying afforded a yield of (0.75g, 89%), mp 131-133°C lit.

763; ^{1}H-NMR: δ 7.28 (m, 2H, *H-4*, *H-10*), 7.04 (m, 6H), 5.73 (s, 2H, *H-6*, *H-12*), 2.88 (br s, 1H, *NH*).



2,8-Dimethyl-6,12-imino-*6H,12H*-dibenzo[b,f]-1,5-dithiocin (**1b**)

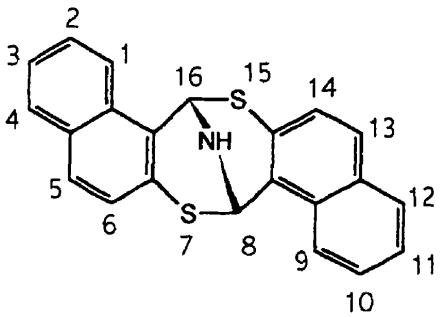
The same procedure as that used above for the preparation of **1a** was employed. A white solid was obtained from the reaction mixture (0.85g, 91%), which was filtered and dried in a desiccator; mp 205-206°C, lit mp[71] 206-206.5°C. IR (KBr): ν 3358, 3056, 2965, 1482, 1398, 1084, 1038, 953, 796; ^{1}H-NMR: 7.08 (s, 2H, *H-4*, *H-10*), 6.91 (s, 4H), 5.67 (s, 2H, *H-6*, *H-12*), 2.83 (br s, 1H, *NH*), 2.25 (s, 6H, CH_3).



4,10-Bis(*tert*-butylsulfanyl)-2,8-dimethyl-6,12-imino-*6H,12H*-dibenzo[b,f]-1,5-dithiocin (**1c**)

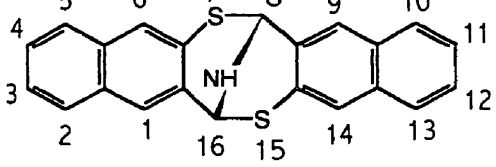
The same procedure as that used above for the preparation of **1a** was employed. A yellow solid was obtained from the reaction mixture (0.05g, 90%), filtered and dried in the desiccator. Mp 45-47°C, lit mp[71] 44-46°C. IR

4H), 5.66 (s, 2H, *H-6*, *H-12*), 4.33 (br s, 1H, *NH*), 2.24 (s, 6H, $ArCH_3$), 1.22 (s, 18H, $SC(CH_3)_3$).



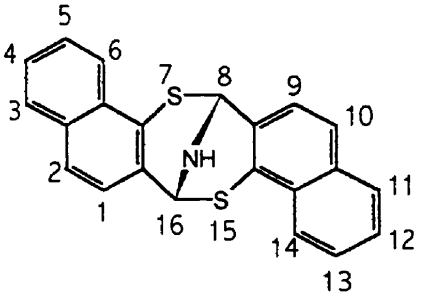
8,16-Imino-8*H*, 16*H*-dinaphtho [2,1-b,f]-1,5-dithiocin (**62**)

A mixture of the naphthaldehyde **41** (0.04g, 0.20mmol) and ammonium acetate (0.02g, 0.20mmol) in absolute ethanol (15mL) was refluxed for 3.5 h. The yellow solution was cooled and the ethanol was removed. The yellow solid was recrystallized from methanol to give **62** (0.03g, 94%), mp 160-163°C; IR (KBr): ν 3356, 2952, 1583, 1472, 1210, 1131, 835, 806; ^{1}H-NMR: δ 7.83 (dd, J=8.2, 8.4Hz, 4H), 7.62 (m, 4H), 7.48 (t, J=8.4Hz, 2H, *H-5*, *H-13*), 7.02 (d, J=8.5Hz, *H-2*, *H-10*), 6.45 (s, 2H, *H-8*, *H-16*), *NH* buried under aromatic protons; EIMS: m/z (%) 357 (100), 324 (74), 203 (18), 171 (49), 128 (31), 115 (19), 77 (6); HR-EIMS: found, 357.0647; calculated for $C_{22}H_{15}NS_2$ 357.0646.



8,16-Imino-8*H*, *16H*-dinaphtho [2,3-b,f]-1,5-dithiocin (**63**)

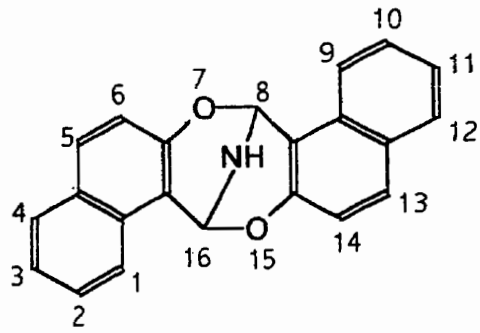
The same procedure outlined for compound **62** was used for the formation of **63**. Yellow crystals were obtained, recrystallized from methanol (0.04g, 96%), mp 170-172°C; IR (KBr): ν 3197, 2953, 1590, 1495, 1492, 1228, 1153, 1074, 805; ^{1}H-NMR: δ 7.76 (m, 4H), 7.62 (m, 5H, *ArH, NH*), 7.38 (m, 4H), 6.03 (s, 2H, *H-8, H-16*); EIMS: m/z (%) 357 (79), 324 (30), 203 (53), 172 (100), 115 (45), 77 (10); HR-EIMS: found, 357.0640 calculated for $C_{22}H_{15}NS_2$ 357.0646.



8,16-Imino-*8H*, *16H*-dinaphtho [1,2-b,f]-1,5-dithiocin (**64**)

The same procedure outlined for compound **62** was used for the formation of **64**. Yellow crystals were obtained (0.03g, 92%) mp 168-170°C; IR (KBr): ν 3033, 2953, 2846, 1529, 1389, 1164, 1062, 818; ^{1}H-NMR: δ 7.95 (m, 4H), 7.78 (d, J=6.9Hz, 2H), 7.75 (m, 2H), 7.53 (d, J=7.5, 2H), 7.44 (m, 2H) *NH* buried under aromatic protons 6.05 (s, 2H, *H-8, H-*

EIMS: found, 357.0643; calculated for $C_{22}H_{15}NS_2$ 357.0646.



8,16-Imino-8*H*,16*H*-dinaphtho[2,1-b,f]-1,5-dioxocin (**5**)

A mixture of 2-hydroxy-1-naphthaldehyde (1.72g, 10.00mmol), and ammonium acetate in 15mL of ethanol was refluxed for 4.5 h, then cooled to room temperature. The ethanol was partially evaporated and the yellow solid was recrystallized to yield **5** (1.55g, 95%), mp 241-243°C lit. mp[14] 240-242°C; IR (KBr): ν 3332, 1616, 1468, 1391, 1222, 1061, 955; ^{1}H-NMR: 8.18 (d, J=6.0Hz, 2H, *H-6*, *H-14*), 7.72 (t, J=5.8Hz, 4H, *H-2*, *H-3*, *H-10*, *H-11*), 7.59 (d, J=6.0Hz, 2H, *H-5*, *H-13*), 7.36 (d, J=5.8Hz, 2H, *H-4*, *H-12*), 7.05 (d, J=5.8Hz, 2H, *H-1*, *H-9*), 6.63 (d, J=2.5Hz, 2H, *H-8*, *H-16*), 3.00 (br s, 1H, *NH*); ^{13}C-NMR:δ 150.3 s, 131.5 s, 131.0 d, 128.9 s, 128.4 d, 127.2 d, 123.7 d, 121.9 d, 118.3 d, 112.4 s, 75.6 d. EIMS: m/z (%) 325 (100), 296 (10), 169 (26), 157(32), 128 (46), 83 (12); HR-EIMS: found, 325.1093; calculated for $C_{22}H_{15}NO_2$ 325.1101.

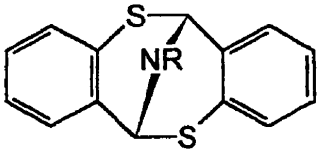
R=$CH_2CH_2C_6H_5$

N-(2'-Phenylethyl)-6,12-imino-*6H,12H*-dibenzo[b,f]-1,5-dithiocin (**71**)

To a solution of thiosalicylaldehyde **4a** (0.04g, 0.28mmol) in absolute ethanol (10mL), 0.5mL of AcOH was added. Addition of the phenethylamine (0.02mL, 0.15mmol) to the above reaction vessel immediately turned the yellow solution orange in colour. The mixture was refluxed for 3.5 h, quenched with H_2O (5mL) and extracted with CH_2Cl_2 (2x10mL). The organic layer was dried (Na_2SO_4) and condensed to afford a brown oil. Flash chromatography, eluting with CH_2Cl_2/hexanes (4:1) (R_f=0.52), yielded a light yellow solid, (0.04g, 84%), mp 147-150°C. IR (KBr): ν 3116, 3032, 2996, 1625, 1487, 1223, 1083, 815; ^{1}H-NMR: δ 7.25 (m, 7H), 7.05 (m, 6H), 5.45 (s, 2H, *H-6*, *H-12*), 3.01 (m, 4H); EIMS: m/z (%) 361(100), 328 (43), 256 (56), 224 (36), 242(33), 153 (43), 121 (61), 77(35); HR-EIMS: found 361.0954, calculated for $C_{22}H_{19}NS_2$ 361.0959. Anal. Found: C, 71.46; H, 5.19; S, 18.14. Calcd. for $C_{22}H_{19}NS_2$: C, 73.09; H, 5.30; S, 17.74.

An alternate route was carried out using a similar procedure to obtain the same product. A mixture of thiosalicylaldehyde **4a** (0.14g, 1.03mmol), *L*-phenylalanine methyl ester hydrochloride (0.09g, 0.57mmol) and absolute ethanol (15mL) was refluxed for 2.5 h. The solution was clear yellow, cooled to room temperature and the solvent was condensed to yield a yellow-brown oil. The oil was then dissolved in CH_2Cl_2 (15mL) and the organic layer was washed with saturated sodium bicarbonate (15mL). Drying (Na_2SO_4) and concentration afforded a white powdery solid (0.12g,

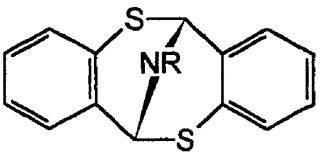
(R_f=0.57) gave white crystals (0.10g, 51%), mp 149-151°C.



R=$CH_2CH(CH_3)_2$

N-(Isobutyl)-6,12-imino-*6H,12H*-dibenzo[b,f]-1,5-dithiocin (**72**)

To a solution of thiosalicylaldehyde **4a** (0.05g, 0.35mmol) in absolute ethanol (8mL), 0.5mL of AcOH was added. Addition of the isobutylamine (0.02mL, 0.19mmol) to the above reaction vessel immediately turned the yellow solution orange in colour. The mixture was refluxed for 3.5 h, quenched with H_2O (5mL) and extracted with CH_2Cl_2 (2x10mL). The organic layer was dried (Na_2SO_4) and condensed to afford a brown oil (0.05g, 91%). Flash chromatography, eluting with CH_2Cl_2/hexanes (4:1) (R_f=0.52), yielded a yellow solid (0.04g, 83%). IR (film): ν 3053, 2456, 1515, 1489, 1075, 792, 743; ^{1}H-NMR: δ 7.25 (m, 2H, *H-4*, *H-10*), 7.00 (m, 6H), 5.38 (s, 2H, *H-6*, *H-12*), 2.87 (dd, J=6.3, 12.4Hz, 1H), 2.48 (dd, J=6.5, 12.3Hz, 1H), 1.96 (m, 1H), 0.98 (d, J=7.0Hz, 6H); EIMS: m/z (%) 313 (100), 280 (43), 256 (56), 224 (36), 153 (43), 121 (61), 77 (35); HR-EIMS: found 313.0956, calculated for $C_{18}H_{19}NS_2$ 313.0958.

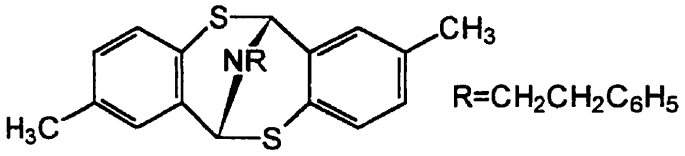


R=$C(CH_3)_3$

N-(*t*-Butyl)-6,12-imino-*6H,12H*-dibenzo[b,f]-1,5-dithiocin (**73**)

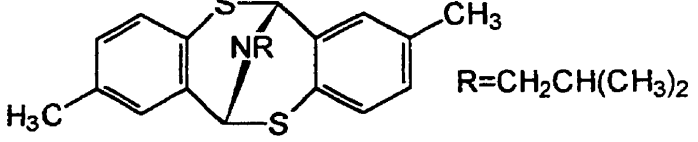
To a solution of thiosalicylaldehyde **4a** (0.06g, 0.40mmol) in absolute ethanol (10mL), 0.5mL of AcOH was added. Addition of the *t*-butylamine

yellow solution orange in colour. The mixture was refluxed for 3.5 h, quenched with H_2O (5mL) and extracted with CH_2Cl_2 (2x10mL). The organic layer was dried (Na_2SO_4) and condensed to afford a brown oil (0.05g, 92%). Flash chromatography, eluting with CH_2Cl_2/hexanes (4:1) (R_f=0.56), yielded a yellow solid (0.04g, 87%). IR (film): ν 3322, 3057, 2970, 2924, 1695, 1589, 1463, 1191, 1068, 819; ^{1}H-NMR: δ 7.28 (m, 2H, *H-4*, *H-10*), 6.69 (m, 6H), 5.87 (s, 2H, *H-6*, *H-12*), 1.30 (s, 9H, *CH_3*); EIMS: m/z (%) 313(37), 256 (100), 223 (43), 166 (32), 153 (37), 137 (61), 121 (64), 77(35); HR-EIMS: found 313.0968, calculated for $C_{18}H_{19}NS_2$ 313.0958.



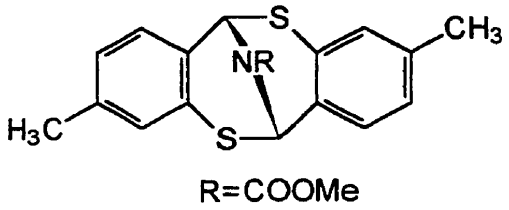
N-(2'-Phenylethyl)-2,8-dimethyl-6,12-imino-*6H,12H*-dibenzo[b,f]-1,5-dithiocin (**74**)

The same procedure as **71** was used for the formation of **74**. A crude yellow oil was obtained in 0.06g, 96% yield. Flash chromatography, eluting with CH_2Cl_2/hexanes (4:1) (R_f=0.58) yielded a beige solid (0.05g, 83%), mp 132-134°C. ^{1}H-NMR: δ 7.26 (s, 5H), 7.04 (s, 2H), 6.88 (s, 4H), 4.92 (s, 2H, *H-6*, *H-12*), 2.94 (m, 4H), 2.23 (s, 6H); EIMS: m/z (%) 389 (100), 356 (45), 284 (58), 270 (30), 252 (40), 167 (38), 135 (50), 105 (34), 91(38); HR-EIMS: found 389.1263, calculated for $C_{24}H_{23}NS_2$ 389.1272.



N-Isobutyl-2,8-dimethyl-6,12-imino-*6H,12H*-dibenzo[b,f]-1,5-dithiocin (**75**)

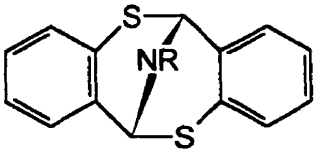
The same procedure as **71** for the formation of **75** was used. A crude yellow oil was obtained in 0.07g, 93% yield. Flash chromatography, eluting with CH_2Cl_2/hexanes (4:1) (R_f=0.60), yielded a yellow oil (0.06g, 86%). ^{1}H-NMR: δ 7.05 (s, 2H, *H-4*, *H-10*), 6.89 (s, 4H, *H-3*, *H-1*), 5.31 (s, 2H, *H-6*, *H-12*), 2.83 (m, *1H*), 2.46 (m, 1H), 2.27 (s, 6H, *Ar-CH$_3$*), 1.95 (m, 1H), 0.98 (d, J=7.6Hz, 6H, *CH$_3$*); EIMS: m/z (%) 341 (100), 308 (62), 284 (63), 252 (40), 167 (44), 135 (50), 91(29); HR-EIMS: found 341.1270, calculated for $C_{20}H_{23}NS_2$ 341.1272



N-(Methoxycarbonyl)-2,8-dimethyl-6,12-imino-*6H,12H*-dibenzo[b,f]-1,5-dithiocin (**80**)

The amine **1b** (0.20g, 0.70mmol) was dissolved in acetone (15mL), then cesium carbonate (1.37g, 4.20mmol) was added to the solution, which was stirred for 5 min. Slow addition of methyl chloroformate (0.22mL, 2.80mmol) with a syringe resulted in a red-coloured solution. The mixture was refluxed for 16 h under Ar. Removal of the Cs_2CO_3 by gravity filtration and evaporation of the acetone solution yielded an orange oil. A solution of

2 h. A white precipitate was obtained (0.16g, 67%), which was filtered off and recrystallized from CH_2Cl_2-hexanes (0.12g, 50%). IR (KBr): ν 3347, 2975, 2846, 2254 1698, 1503, 1464, 1255, 1164, 1060, 731; ^{1}H-NMR: δ 7.18 (d, J=7.2Hz, 2H, *H-4, H-10*), 6.93 (d, J=7.1Hz, 4H, *H-1, H-3, H-7, H-9*), 6.74 (s, 1H, *H-6*), 6.57 (s, 1H, *H-12*), 3.84 (s, 3H, *OCH_3*) 2.36 (s, 6H, *Ar-CH_3*). EIMS: m/z (%) 343 (100), 284 (79), 268 (73), 252 (33), 167 (96), 135 (35), 91 (30); HR-EIMS: found 343.0702, calculated for $C_{18}H_{17}NO_2S_2$ 343.0700.



R=C_6H_5

N-Phenyl-6,12-imino-*6H,12H*-dibenzo[b,f]-1,5-dithiocin (**81**)

Method A

A mixture of thiosalicylaldehyde **4a** (0.23g, 1.64mmol), aniline (0.08g, 0.90mmol) acetic acid (0.5mL) and absolute ethanol (15mL) was refluxed for 6.5 h. The clear yellow solution was cooled to room temperature and the solvent was evaporated to yield a brown oil (0.24g, 87%). Flash chromatography, eluting with CH_2Cl_2/hexanes (4:1) (R_f=0.58), resulted in a white solid (0.20g, 75%), mp 70-72°C. IR (KBr): ν 3075, 2961, 1449, 1455, 1362, 1168, 835; ^{1}H-NMR: δ 7.32 (m, 4H, *H-1, H-4, H-7, H-10*), 7.13 (m, 9H), 6.15 (s, 2H, *H-6, H-12*); ^{13}C-NMR: δ 147.1 s, 133.3 s, 130.3 d, 129.5 d, 128.6 d, 128.0 d, 127.9 d, 125.0 d, 123.0 s, 119.5 s, 61.1 d. EIMS: m/z (%) 333 (100), 300 (59), 268 (24), 240 (42) 153 (59), 77 (45); HR-EIMS: found 333.0651, calculated for $C_{20}H_{15}NS_2$ 333.0645. Anal.

72.12; H, 4.54; N, 4.20; S, 19.25.

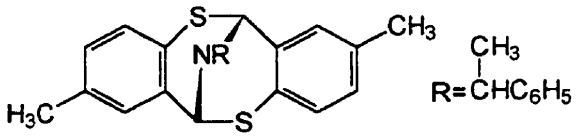
Method B

A mixture of triphenylbismuth (0.17g, 0.42mmol), $Cu(OAc)_2$ (0.07g, 0.35mmol) and CH_2Cl_2 (5mL) was stirred for 10 min under Ar giving a blue-green colour. A solution of the amine **1b** (0.10g, 0.35mmol) in CH_2Cl_2 (5mL), was added dropwise to the mixture resulting in a series of colour changes from blue to green to light brown. The mixture was stirred for 4.5 h and was filtered through Celite, washed with H_2O (5mL) and extracted with ether (3x10mL). The organic layer was dried (Na_2SO_4) and concentrated to afford a red brown oil (0.06g, 54%). Flash chromatography, eluting with hexanes/ethyl acetate (3:2) (R_f=0.44), yielded a yellow oil (0.02g, 15%).

Attempted resolution of 2,8-dimethyl-6,12-imino-*6H,12H*-dibenzo[b,f]-1,5-dithiocin using D-camphorsulfonic acid (**90a**)

A solution of D-camphor-10-sulfonic acid (0.36g, 1.54mmol), was dissolved in 5mL acetone and added dropwise to a solution of the amine **1b** (0.40g, 1.40mmol) dissolved in 10mL of acetone. The mixture became yellow and was gently heated for 10 min. This was cooled, and white crystals precipitated from the solution. Stirring was continued at room temperature for an additional 10 h. The white solid was collected by suction filtration, washed with acetone (3x5mL) and dried in the desiccator overnight. (0.33g, 48% yield). A sample of the salt (0.32g, 0.06mmol) **90a** was converted to its free base and partitioned between 10% NaOH (20mL) and EtOAc/hexanes (2:1) at 0°C. After 15 min of stirring, the aqueous layer was separated from the organic layer, extracted with EtOAc/hexanes (3x15mL) and washed with H_2O (2x15mL), dried (Na_2SO_4) and

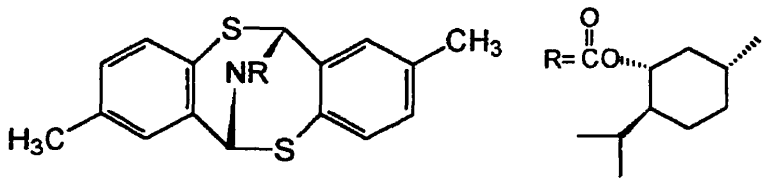
converted 3 additional times to the salt and back to its free base, with an overall yield of 61%. Mp 204-206^{0}C; $[\alpha]_D$= + 19.0 ($CHCl_3$, c 0.50). Chiral shift reagents were used, europium tris[3-(trifluoromethyl-hydroxymethylene)-(+)-camphorate] and praseodymium tris[3-(trifluoromethyl-hydroxymethylene)-(+)-camphorate] to determine if the diastereomeric salts were resolved.



N-(1'-Phenylethyl)-6,12-imino-*6H,12H*-dibenzo[b,f]-1,5-dithiocin (**92**)

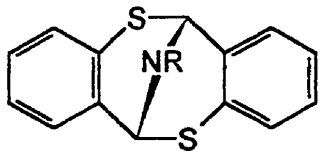
To thiosalicylaldehyde **4b** (0.11g, 0.69mmol) dissolved in 20mL of absolute ethanol and 1mL of acetic acid, the *R*-(+)-1-phenylethylamine (0.05mL, 0.38mmol) was added dropwise. The solution turned an orange colour and was then refluxed for 4.5 h. The mixture was washed with H_2O (10mL), extracted with CH_2Cl_2 (3x15mL), dried and concentrated to yield a brown oil (0.12g, 86%). Flash chromatography, eluting with ethyl acetate/hexanes (1:1) (R_f=0.57) gave a foamy beige solid (0.10g, 77%), mp 91-83°C. IR (KBr): ν 3367, 2949, 1485, 1363, 1250, 1162, 1043; ^{1}H-NMR: δ 7.39 (m, 4H, *H-4*, *H-10*, *H-2'*, *H-4'*), 6.92 (m, 7H, *H-1*, *H-3*, *H-7*, *H-9*, *H-1'*, *H-3'*, *H-5'*), 5.53 (d, J=6.0Hz, 2H, *H-6*, *H-12*), 4.17 (m, 1H, *α-CH*), 2.08 (s, 6H, *Ar-CH$_3$*), 1.38 (d, 3H, *CH$_3$*); ^{13}C-NMR: δ 143.2 s, 134.3 s, 133.1 d, 129.8 d, 129.2 d, 127.6 s, 127.5 d, 127.4 s, 127.2 s, 126.5 s, 60.0 d, 59.3 d, 22.5 q, 20.9 q. EIMS: m/z (%) 389 (13), 284 (100), 270 (11), 251 (11), 167

$C_{24}H_{23}NS_2$ 389.1272.



N-Menthyloxycarbonyl-2,8-dimethyl-6,12-imino-*6H,12H*-dibenzo[b,f]-1,5-dithiocin (**93**)

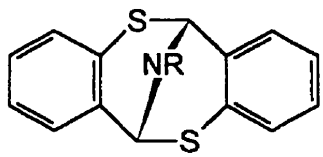
To a solution of the amine **1b** (0.60g, 0.21mmol) in 15mL of acetone, cesium carbonate (0.41g, 1.26mmol) was added and the mixture was stirred for 5 min. The (1*R*)-(-)-menthyl chloroformate (0.18ml, 0.84mmol) was added dropwise to the solution, which was refluxed for 6 h, the mixture turning from white to red in colour. The Cs_2CO_3 was filtered off and the mixture was evaporated to afford a light brown oil (0.07g, 76%). Flash chromatography, eluting with CH_2Cl_2/hexanes (9:1) (R_f=0.55), resulted in a yellow oil (0.06g, 68%). IR(film):ν 3364, 2977, 2254, 1673, 1503, 1267, 1175, 1038, 724; ^{1}H-NMR: δ 7.19 (d, J=6.1Hz, 2H, *H-4*, *H-10*), 6.92 (d, J=6.1Hz, 4H, *H-1*, *H-3*, *H-7*, *H-9*), 6.74 (d, J=2.5Hz, 1H, *H-12*), 6.53 (d, J=2.5Hz, 1H, *H-6*), 4.76 (td, J=7.2, 7.7, 8.3Hz, 1H, *H-1'*), 2.29 (s, 6H, *Ar-CH$_3$*), 2.11 (m, 2H), 1.70 (m, 2H), 1.48 (m, 4H), 1.03 (m, 1H), 0.86 (m, 3H), 0.75 (d, 6H). EIMS: m/z (%) 467 (44), 285 (100), 252 (45), 167 (24), 135 (48), 83 (82) 69 (43); HR-EIMS: found 467.1960, calculated for $C_{27}H_{33}NO_2S_2$ 467.1952.



R=$CH_2CH_2CH(CH_3)_2$

N-(3'-Methylbutyl)-6,12-imino-*6H,12H*-dibenzo[b,f]-1,5-dithiocin (**94**)

A mixture of thiosalicylaldehyde **4a** (0.12g, 0.85mmol), *L*-leucine (0.06g, 0.469mmol) and absolute ethanol (30mL) was refluxed for 4.5 h. The clear yellow solution was cooled to room temperature and the solvent was evaporated to yield a yellow oil (0.09g, 68%). Flash chromatography, eluting with CH_2Cl_2/hexanes (85:15) (R_f=0.52), gave a yellow oil (0.08g, 60%). IR (film): ν 3057, 2945, 2853, 1461, 1426, 1325, 830, 742; ^{1}H-NMR: δ 7.28 (m, 2H, *H-1*, *H-7*), 7.0 (m, 6H, *H-2*, *H-3*, *H-4*, *H-8*, *H-9*, *H-10*), 5.41 (s, 2H, *H-6*, *H-12*), 2.98 (m, 1H, *H-3'*), 1.62 (m, 4H, *H-1'*, *H-1'*, *H-2'*, *H-2'*), 0.91 (d, 6H, *CH_3*)); EIMS: m/z (%) 327 (100), 294 (56), 271 (28), 256 (70), 238 51), 153 (49), 121 (68), 77 (38); HR-EIMS: found 327.1112, calculated for $C_{19}H_{21}NS_2$ 327.1115.

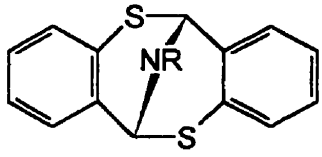


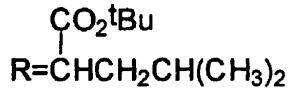
R=CH_2CH_2OH

N-(2'-Hydroxyethyl)-6,12-imino-*6H,12H*-dibenzo[b,f]-1,5-dithiocin (**96**)

A mixture of thiosalicylaldehyde **4a** (0.14g, 1.03mmol), *L*-serine methyl ester hydrochloride (0.09g, 0.57mmol) and absolute ethanol (15mL) was refluxed for 4.5 h. The clear yellow solution was cooled to room temperature and the solvent was evaporated to yield a yellow-brown oil.

washed with saturated sodium bicarbonate (15mL). The organic layer was dried (Na_2SO_4) and concentrated to afford a yellow oil (0.14g, 88%). Flash chromatography, eluting with CH_2Cl_2/hexanes (85:15) (R_f=0.57), gave white needle crystals (0.11g, 75%), mp 165-167°C; IR (film): ν 3395, 2993, 1626, 1505, 1451, 1353, 1278, 1134, 971, 806; ^{1}H-NMR: δ 7.82 (dd, J=7.6, 7.8Hz, 4H, *H-1*, *H-4*, *H-7*, *H-10*), 7.32 (dt, J=7.7, 7.8Hz, 4H, *H-2*, *H-3*, *H-8*, *H-9*), 6.21 (s, 2H, *H-6*, *H-12*), 4.35 (m, 2H, *CH_2*), 3.50 (m, 3H, *CH_2 and OH*); EIMS: m/z (%) 286 (53), 257 (70), 241 (33), 166 (46), 153 (42), 137 (100), 122 (68), 104 (60) 77 (35).

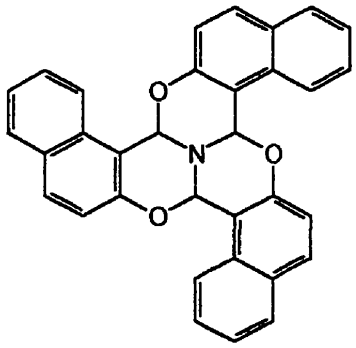




N-((1'-*tert*-Butyloxycarbonyl)-6,12-imino-*6H,12H*-dibenzo[b,f]-1,5-dithiocin (**98**)

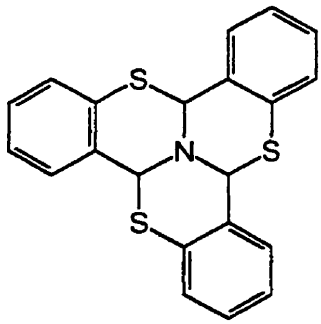
A mixture of thiosalicylaldehyde **4a** (0.22g, 1.60mmol), *L*-leucine *t*-butyl ester (0.19g, 0.88mmol) and absolute ethanol (15mL) was refluxed for 4.5 h. The clear yellow solution was cooled to room temperature and the solvent was evaporated to yield a yellow oil. The oil was dissolved in CH_2Cl_2 (15mL) and the organic layer was washed with saturated sodium bicarbonate. Flash chromatography, eluting with CH_2Cl_2/hexanes (85:15) (R_f=0.67), gave a yellow solid (0.24g, 71%), mp 154-156°C; ^{1}H-NMR: δ 7.33 (m, 4H, *H-1*, *H-4*, *H-7*, *H-10*), 7.01 (m, 4H), 5.73 (d, J=9.0Hz, 2H, *H-6*, *H-12*), 3.65 (t, J=9.1, 1H, *H-1'*), 1.82 (m, 1H, *H-3'*), 1.64 (m, 2H, *H-2'*), 1.20 (d, J=11.5Hz, 9H) 0.90 (d, J=9.4Hz, 6H). EIMS: m/z (%) 427 (40), 371

found 427.1644, calculated for $C_{24}H_{29}NO_2S_2$ 427.1639.



5,10,15-Imino-5*H*,10*H*,15*H*-trinaphtho[1,5,9-b,f,j]trioxazine (**107**)

A mixture of 1-hydroxy-2-naphthaldehyde (1.00g, 5.81mmol), ammonium acetate (0.30g, 3.87mmol), acetic acid (0.30mL) and dry toluene (30mL) was refluxed for 5 h using a Dean-Stark trap. The mixture was reduced to half its volume by vacuum removal of the solvent; on cooling a pale yellow, spongy solid precipitated. It was filtered and washed successively with toluene (10mL) and water (10mL) and dried in the desiccator (1.02g, 90%). A quick swirl in CH_2Cl_2 dissolved any dithiocin present in the solid, and the remainder was then recrystallized from toluene to give a crystalline yellow solid (0.78g, 84%); mp 240-242°C; IR (KBr): ν 2464, 1625, 1590, 1489, 1452, 1376; no NMR spectra was obtained due to solubility problems. EIMS: m/z (%) 479 (87), 462 (28), 325 (45), 308 (100), 281 (98), 252 (30), 169 (63), 128 (75), 11(52), 57 (45); HR-EIMS: found 479.1513, calculated for $C_{33}H_{21}NO_3$ 479.1521. An unsatisfactory elemental analysis obtained for **107** was attributed to contamination with the dithiocin **5**.



5,10,15-Imino-5H,10H,15H-tribenzo[1,5,9-b,f,j]-trithiazine (**108**)

A mixture of thiosalicylaldehyde **4a** (0.11g, 0.77mmol), ammonium acetate (0.04g, 0.52mmol), acetic acid (0.1mL) and dry toluene (20mL) was refluxed for 6.5 h using a Dean-Stark trap. The mixture was evaporated to yield a yellow oil (0.07g, 73%). Flash chromatography, eluting with CH_2Cl_2/hexanes (4:1) (R_f=0.47), resulted in a yellow oil (0.06g, 64%), bp 198-200°C/12mm. IR (film): ν 3094, 2947, 2573, 1658, 1586, 1483, 1353, 1167, 1056, 943, 812; ^{1}H-NMR: δ 7.89 (m, 3H, *H-4*, *H-10*, *H-16*), 7.55 (m, 3H, *H-1*, *H-7*, *H-13*), 7.46 (m, 3H, *H-3*, *H-9*, *H-15*), 7.15 (m, 3H, *H-2*, *H-8*, *H-14*), 6.59 (s, 3H, *H-6*, *H-12*, *H-18*); EIMS: m/z (%) 377 (28), 344 (35), 310 (10), 257 (29), 240 (55), 153 (100), 137 (72), 109 (50), 77 (55); HR-EIMS: found 377.0375, calculated for $C_{21}H_{15}NS_3$ 377.0367.

$Pb(OAc)_2$ (0.03g, 0.08mmol) in 5mL of THF was added to the dithiocin **1b** (0.02g, 0.07mmol) dissolved in THF (5mL). The clear mixture instantaneously turned yellow and was stirred at room temperature for 1h. Formation of a yellow precipitate resulted and this was filtered off. ^{1}H-NMR: δ 7.14 (d, J=8.0Hz, 2H, *H-4*, *H-10*), 7.00 (d, J=10.5Hz, 2H, *H*-1, *H*-7), 6.8 (d, J=7.0Hz, 2H, *H*-3, *H*-9), 6.30, 6.61 (d, J=2.5Hz, 1H, *NH*), 5.71 (d, J=10Hz, 2H, *H-6*, *H-12*), 2.25 (m, 6H, CH_3). Mass spectrometric (FAB) examination proved inconclusive and recrystallization was difficult due to the insolubility of the lead acetate complex .

Other heavy metal acetates e.g. $Cu(OAc)_2$ and $Pd(OAc)_2$ were also tested, but the results obtained were not as promising as those with the lead or mercury acetate complex.

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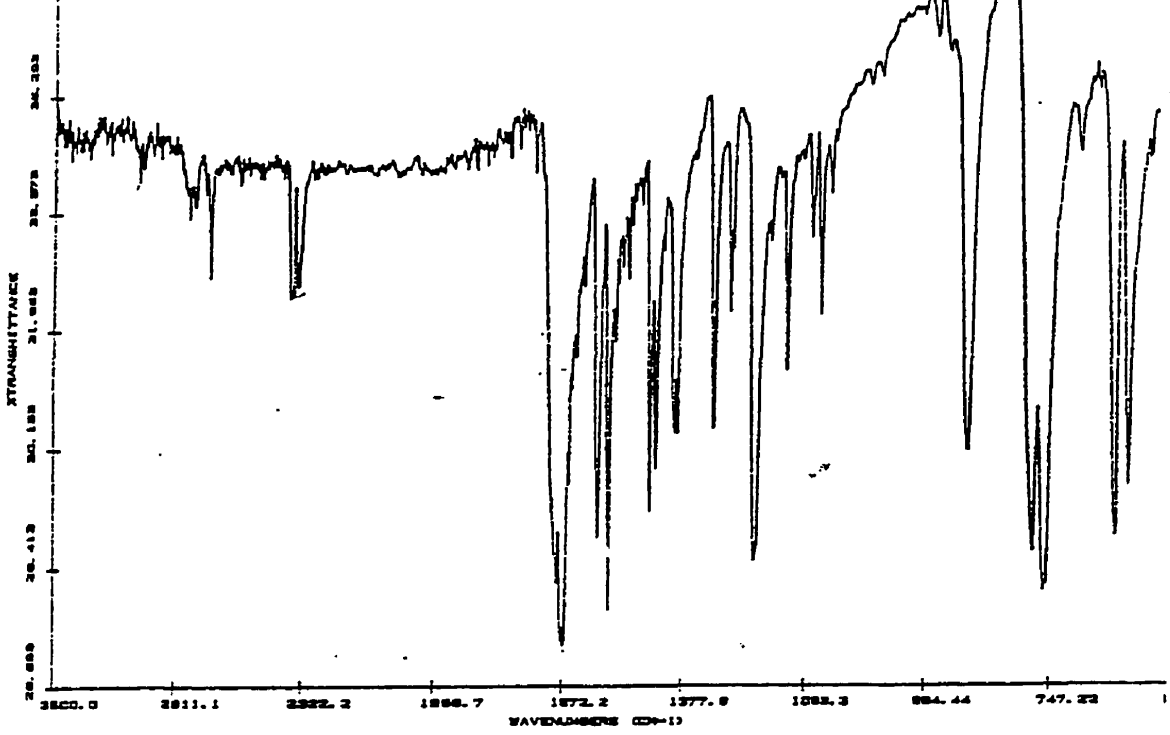
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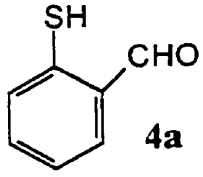
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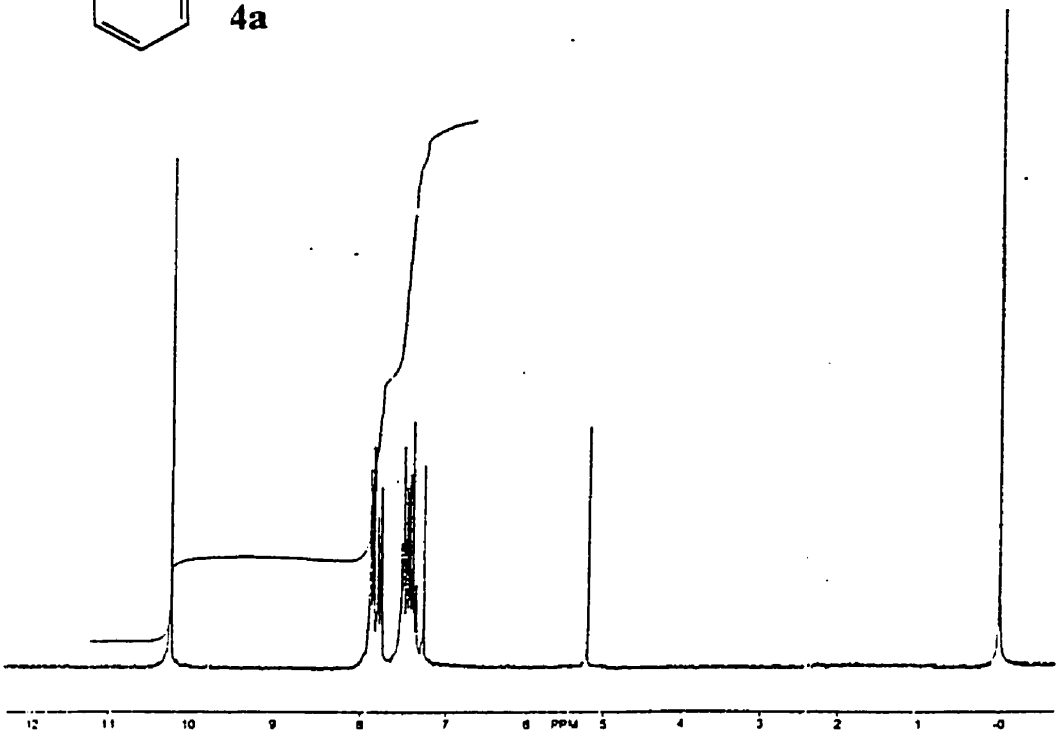
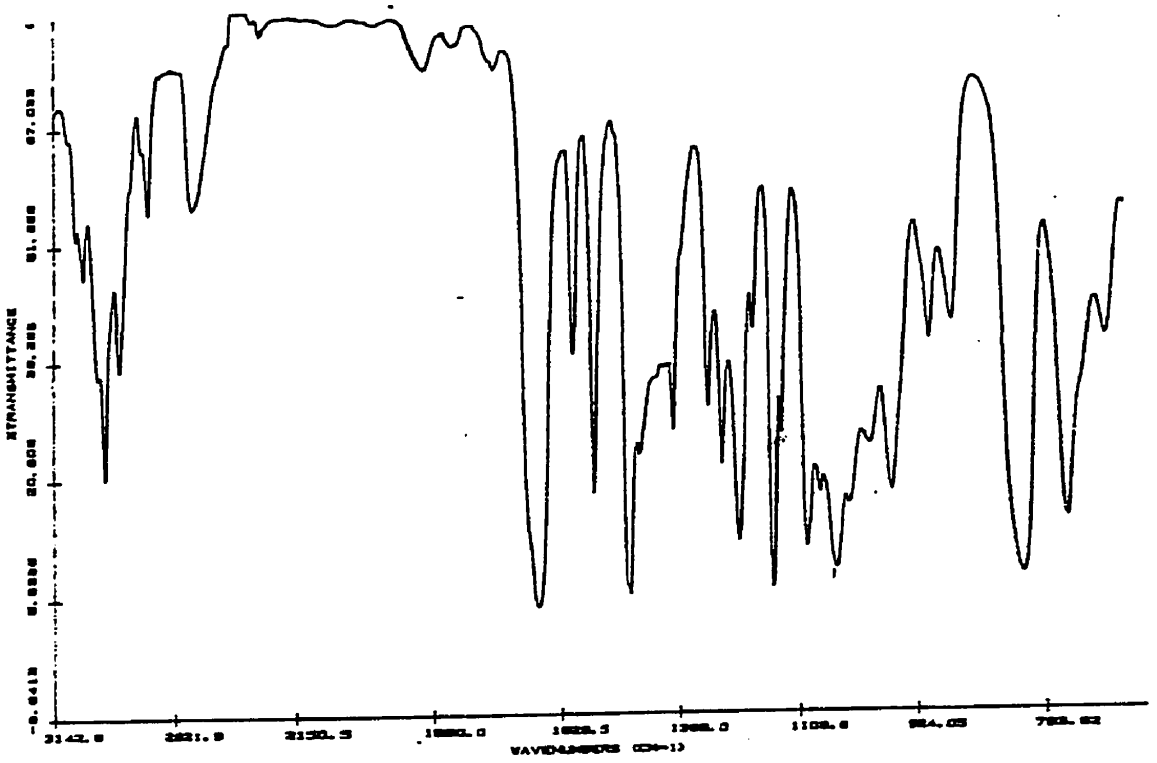
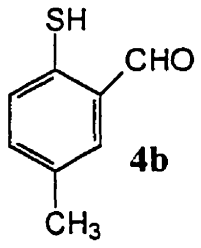
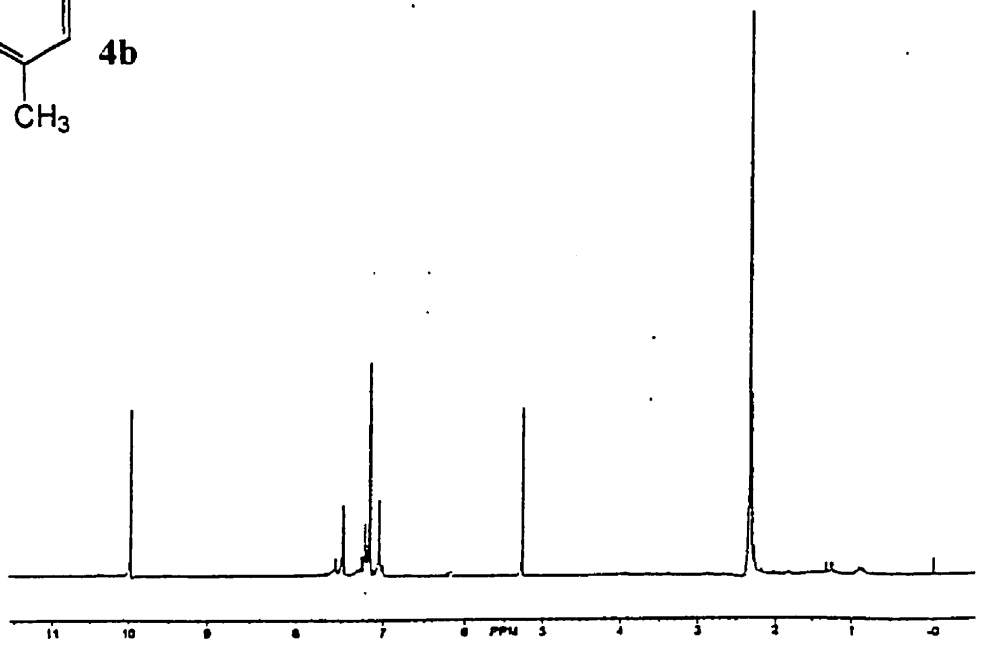
4a

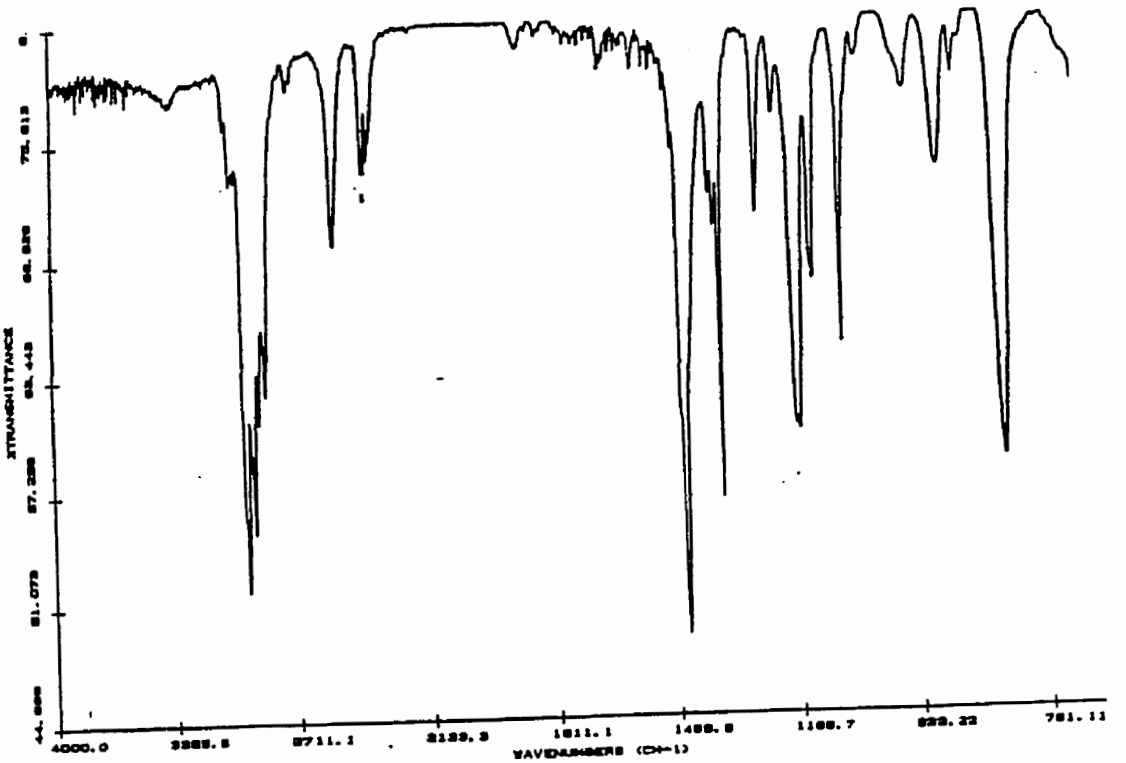

12
11
10
9
8
7
6
PPM
5
4
3
2
1
0

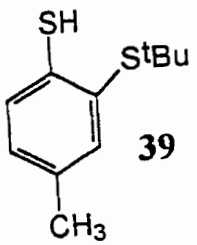




4b

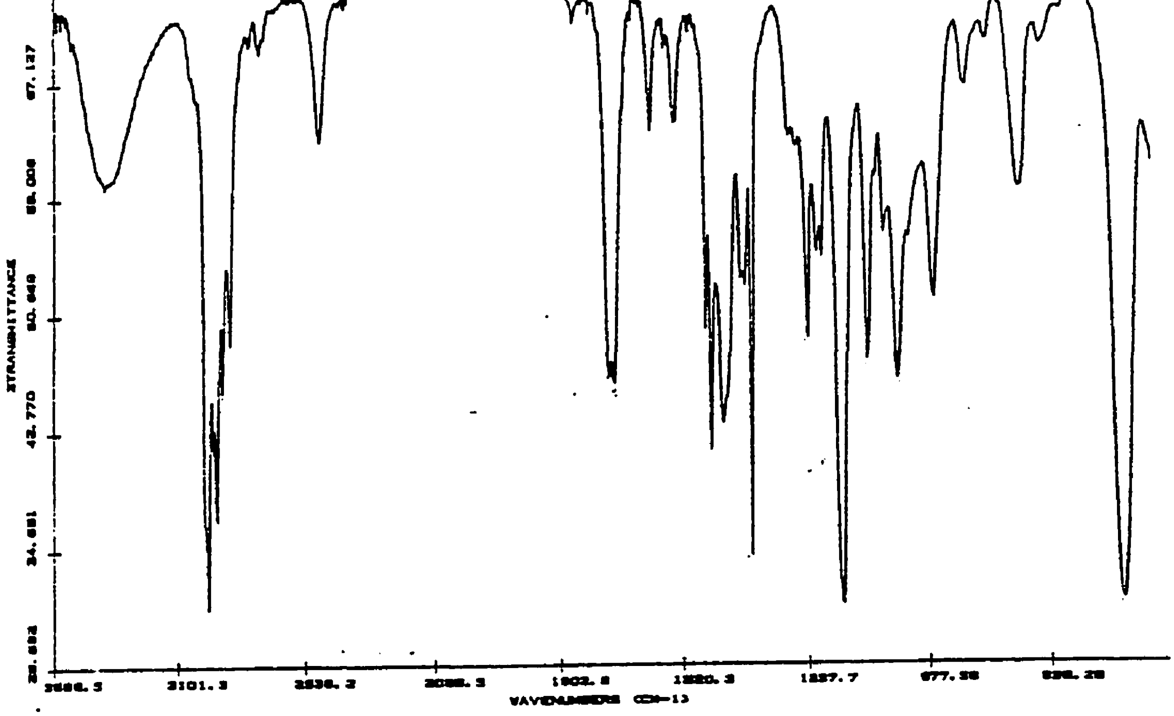



%TRANSMITTANCE
4000.0
3355.5
2711.1
2133.3
1811.1
1499.8
1188.7
922.22
781.11
WAVENUMBERS (CM-1)


SH
StBu
CH3

39

12
11
10
9
8
7
6
PPM
5
4
3
2
1
0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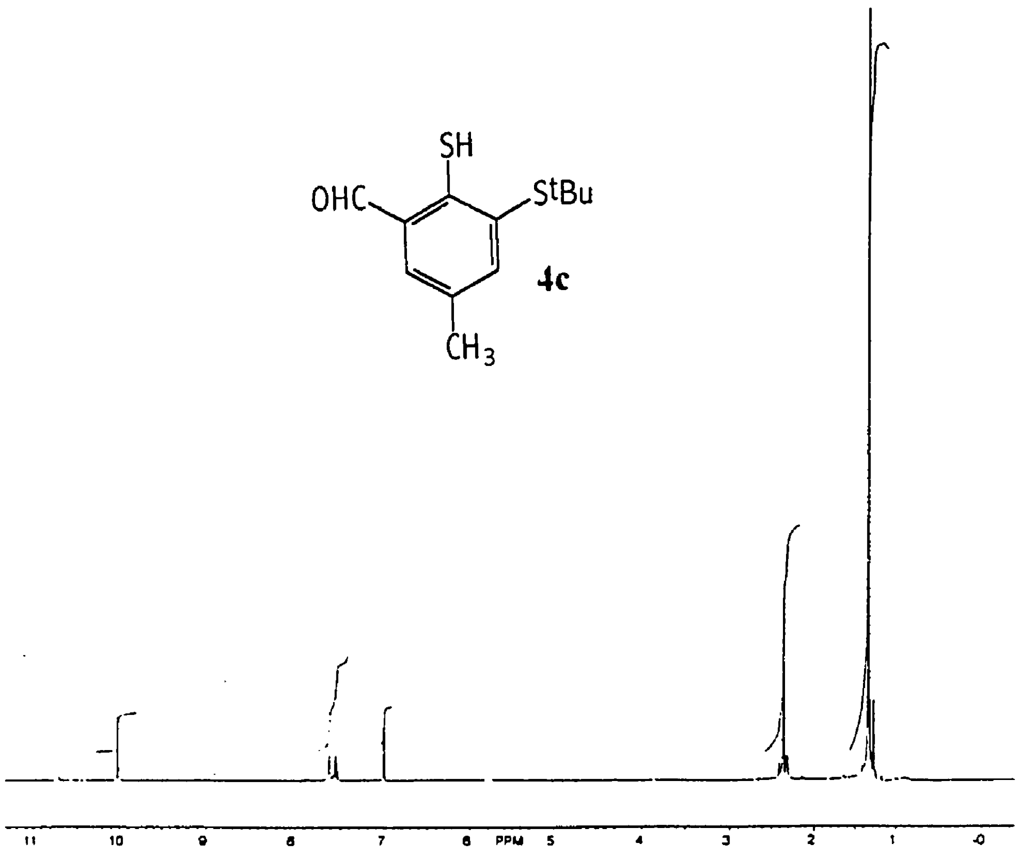
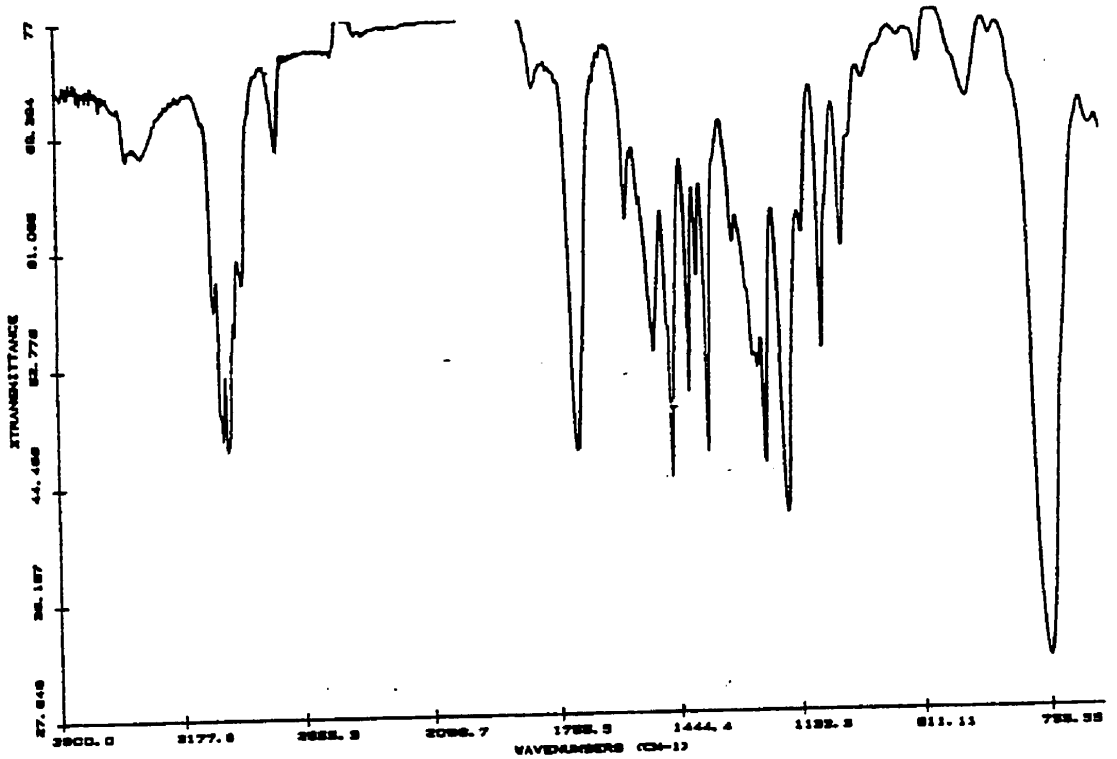
WAVENUMBERS CM-1


SH
OHC
StBu
CH3
11
10
9
8
7
6
PPM
5
4
3
2
1
0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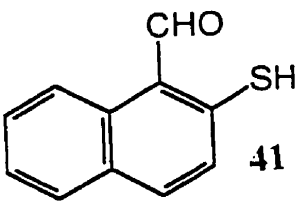
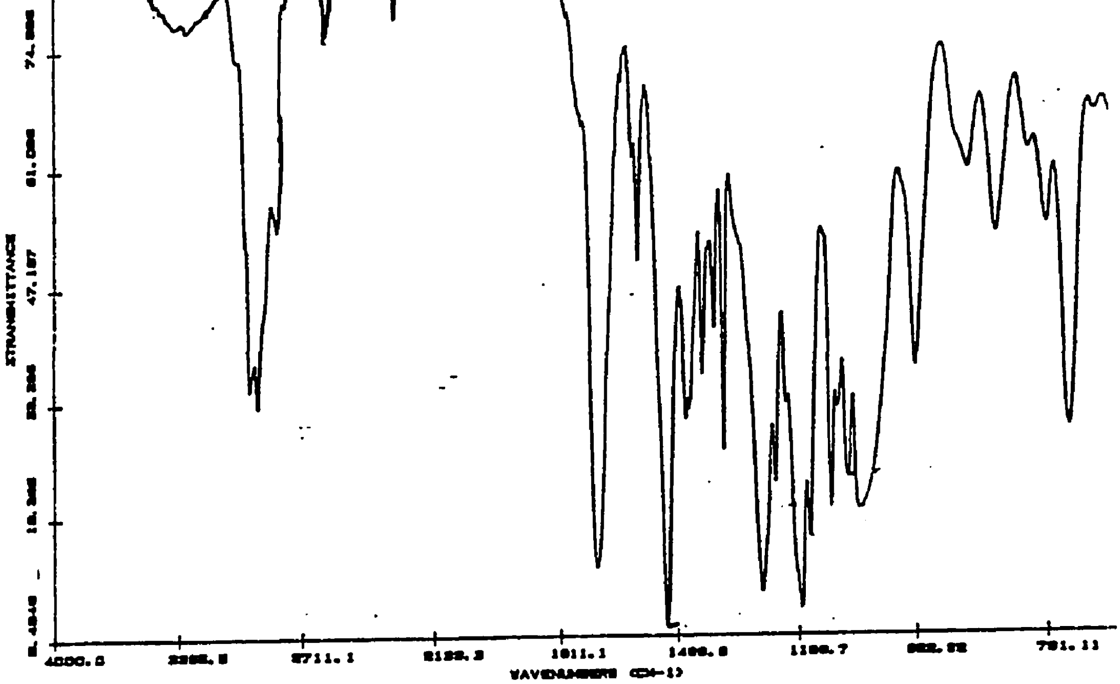
3900.0
3177.8
2655.3
2098.7
1788.5
1444.4
1132.3
811.11
733.55
WAVENUMBERS (CM-1)


CHO
SH

41

12
11
10
9
8
7
6
PPM
5
4
3
2
1
0



%TRANSMITTANCE
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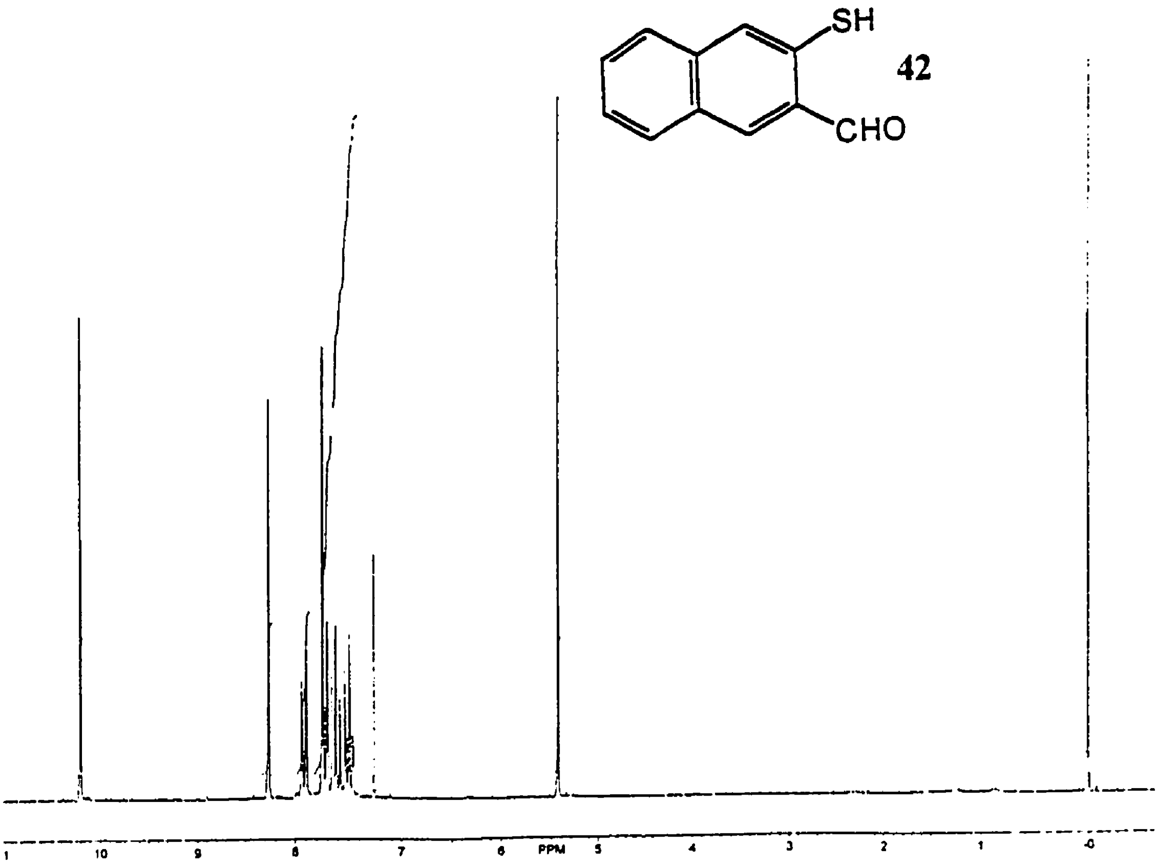
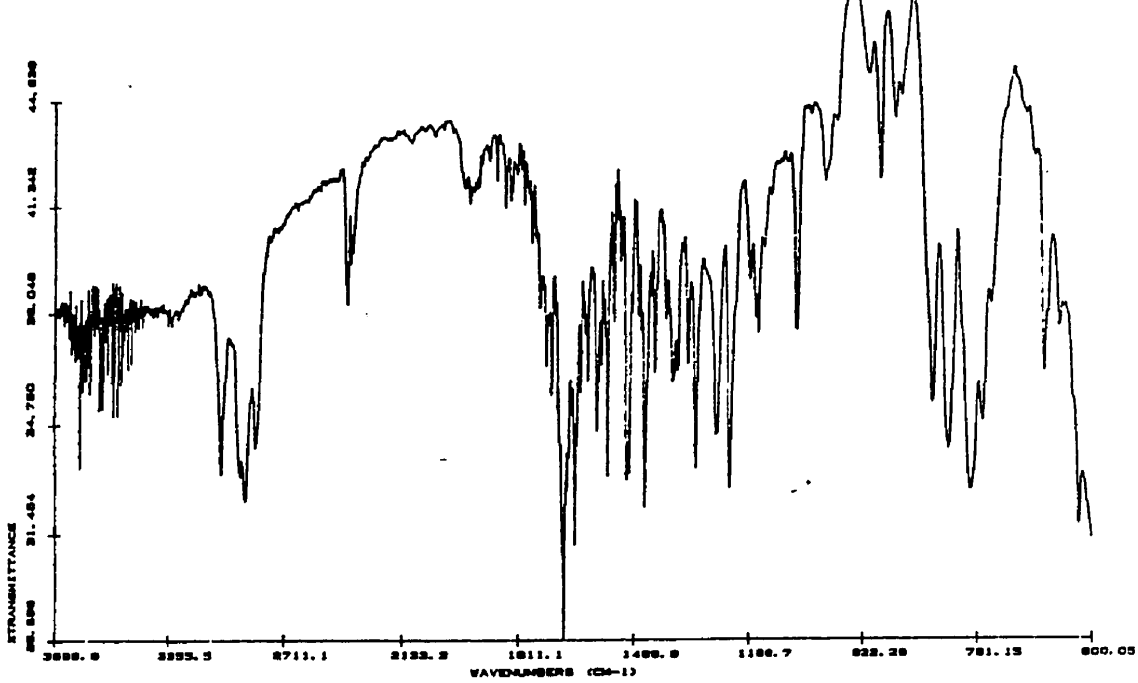
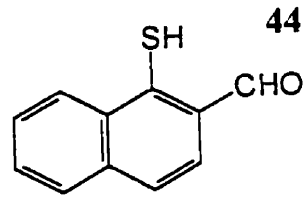
WAVENUMBERS (CM-1)

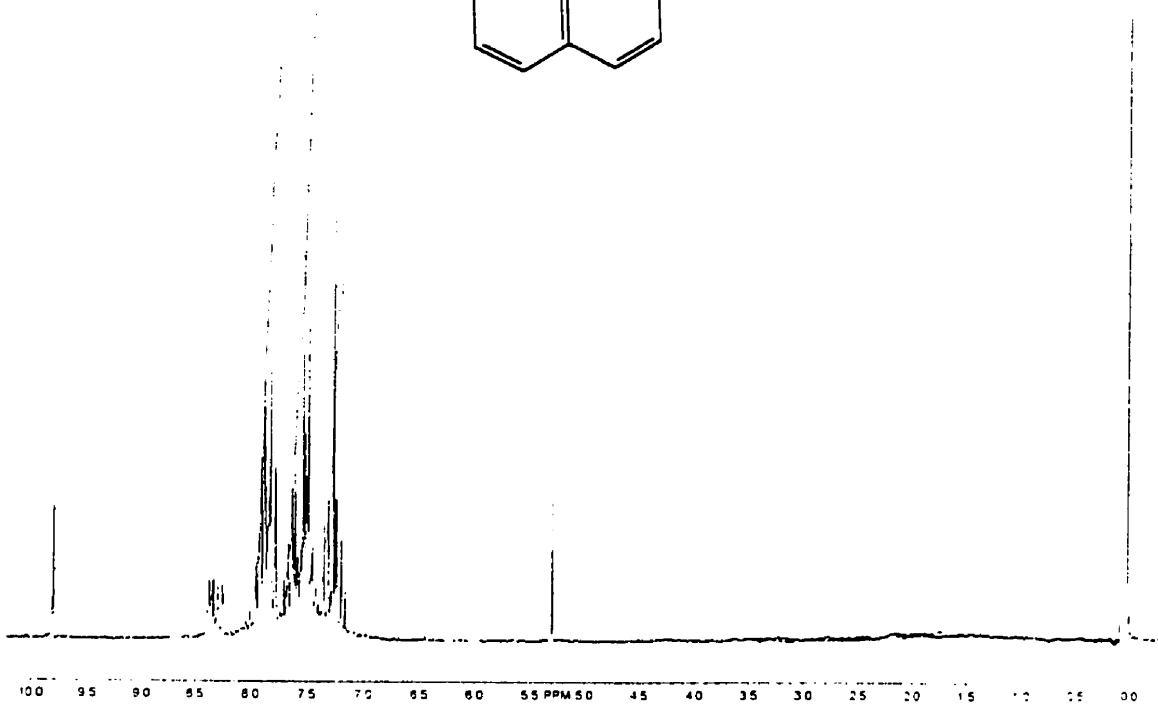


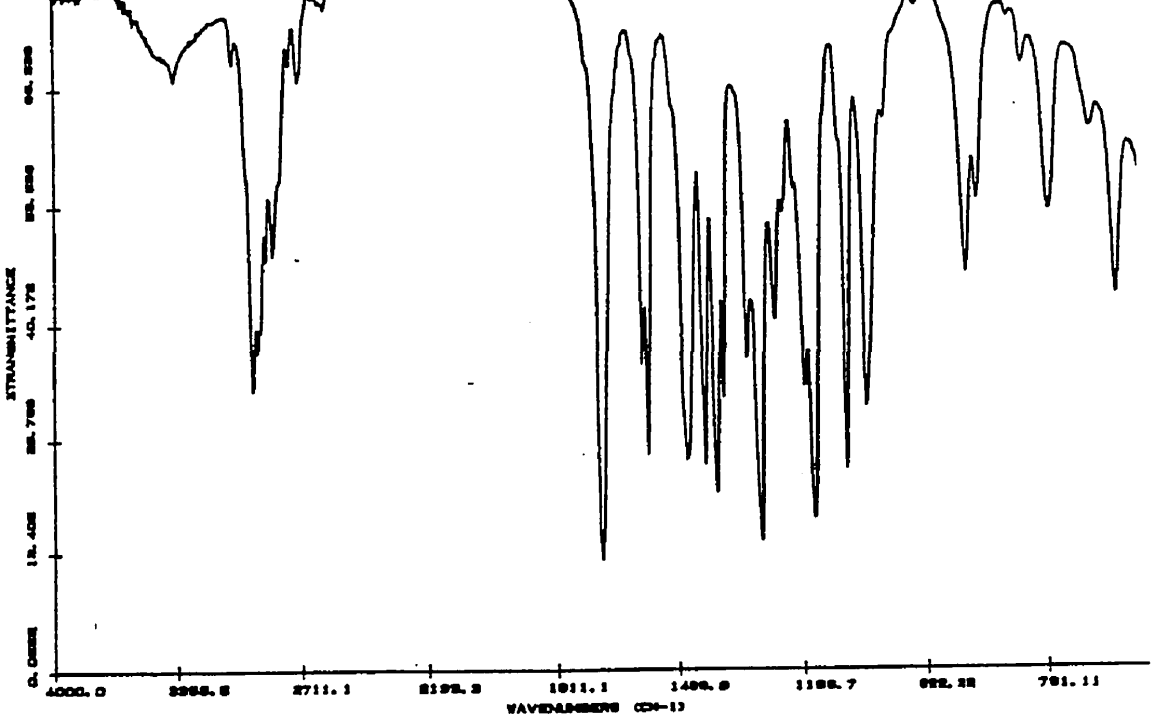
SH
42
CHO
10
9
8
7
6
PPM
5
4
3
2
1
0

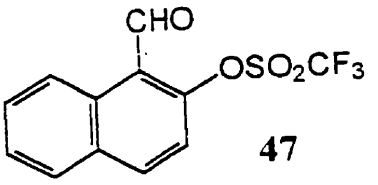

TRANSMITTANCE
WAVENUMBERS (CM-1)

44

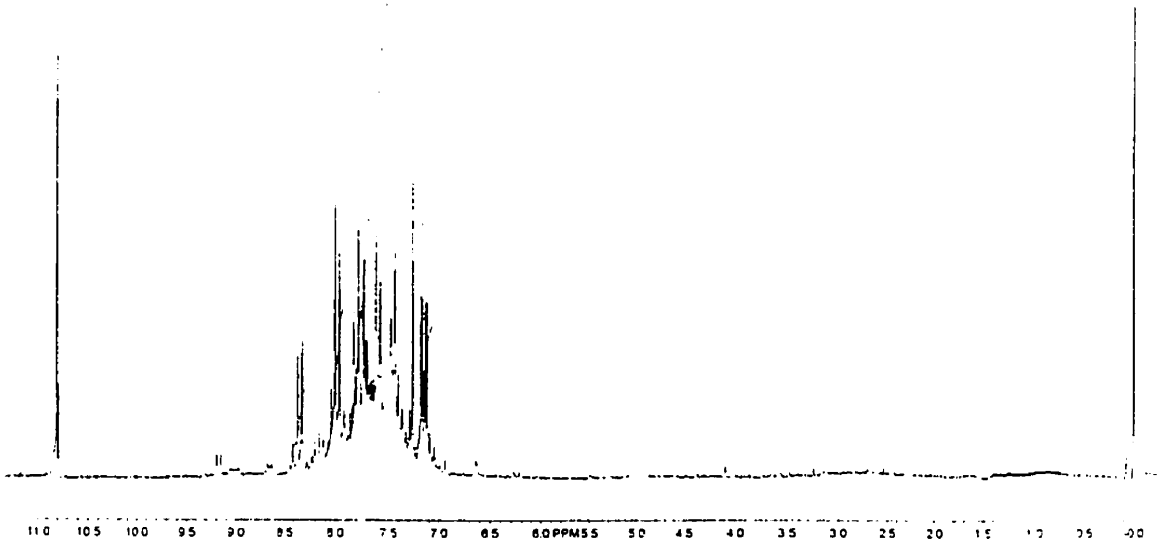

SH
CHO

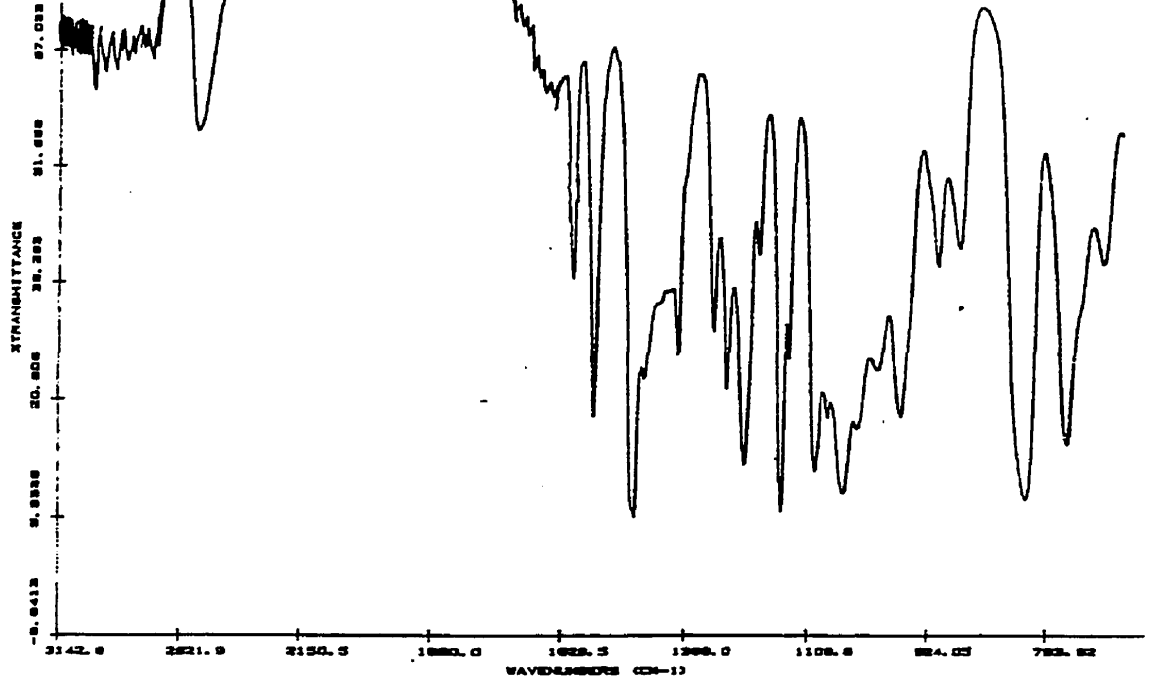

100 95 90 85 80 75 70 65 60 55 PPM 50 45 40 35 30 25 20 15 10 05 00

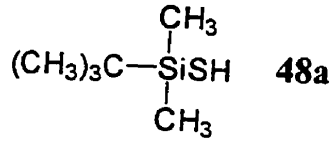

TRANSMITTANCE
4000.0
3268.8
2711.1
2195.2
1811.1
1498.0
1198.7
992.28
781.11
WAVENUMBERS (CM-1)


CHO
OSO2CF3

47

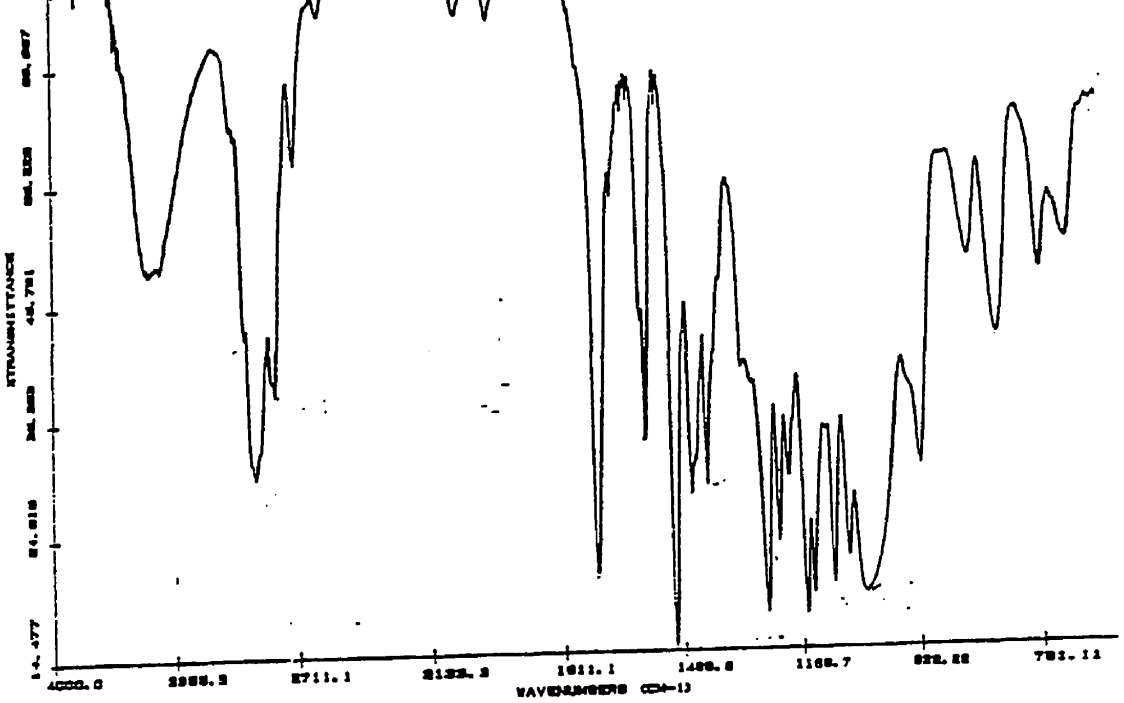

110
105
100
95
90
85
80
75
70
65
60PPM55
50
45
40
35
30
25
20

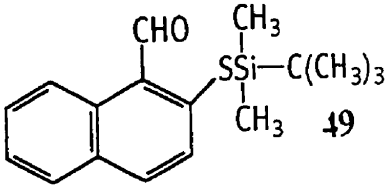

%TRANSMITTANCE
3142.0
2821.9
2150.5
1628.5
1396.0
1108.6
924.05
783.82
WAVENUMBERS (CM-1)


CH3
(CH3)3C—SiSH
CH3

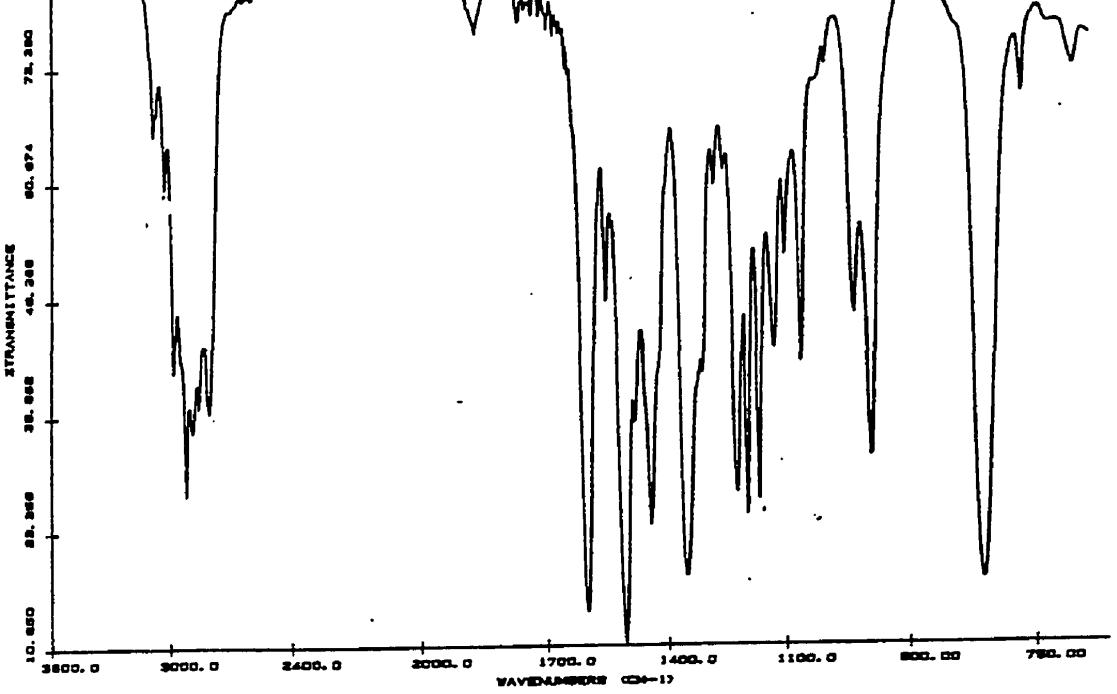
48a

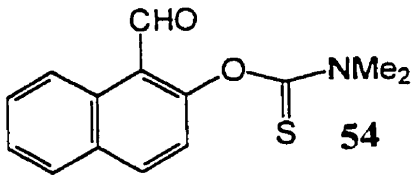
1.7
1.6
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0.8
0.7 PPM 0.6
0.5
0.4
0.3
0.2
0.1
0.0
-0.1


TRANSMITTANCE
4000.0
2355.2
1711.1
1011.1
1168.7
922.68
783.11
WAVENUMBERS (CM-1)

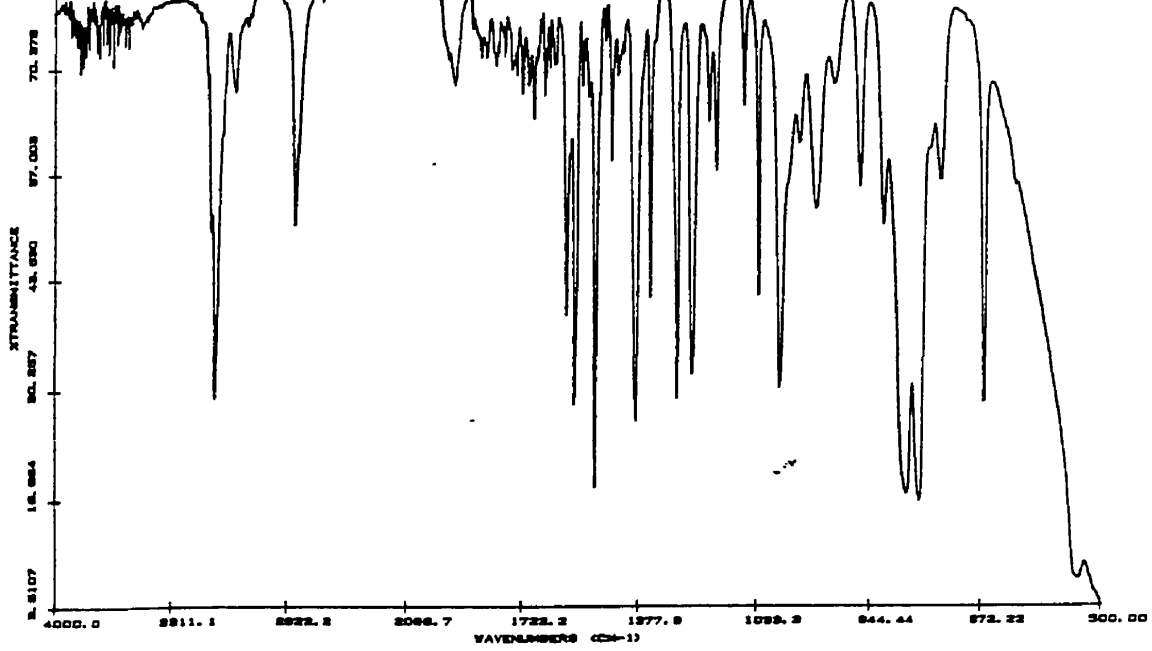

CHO
CH3
SSi—C(CH3)3
CH3

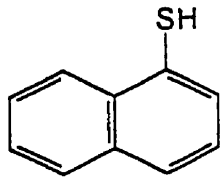
49


%TRANSMITTANCE
3600.0
3000.0
2400.0
2000.0
1700.0
1400.0
1100.0
800.00
750.00
WAVENUMBERS (CM-1)

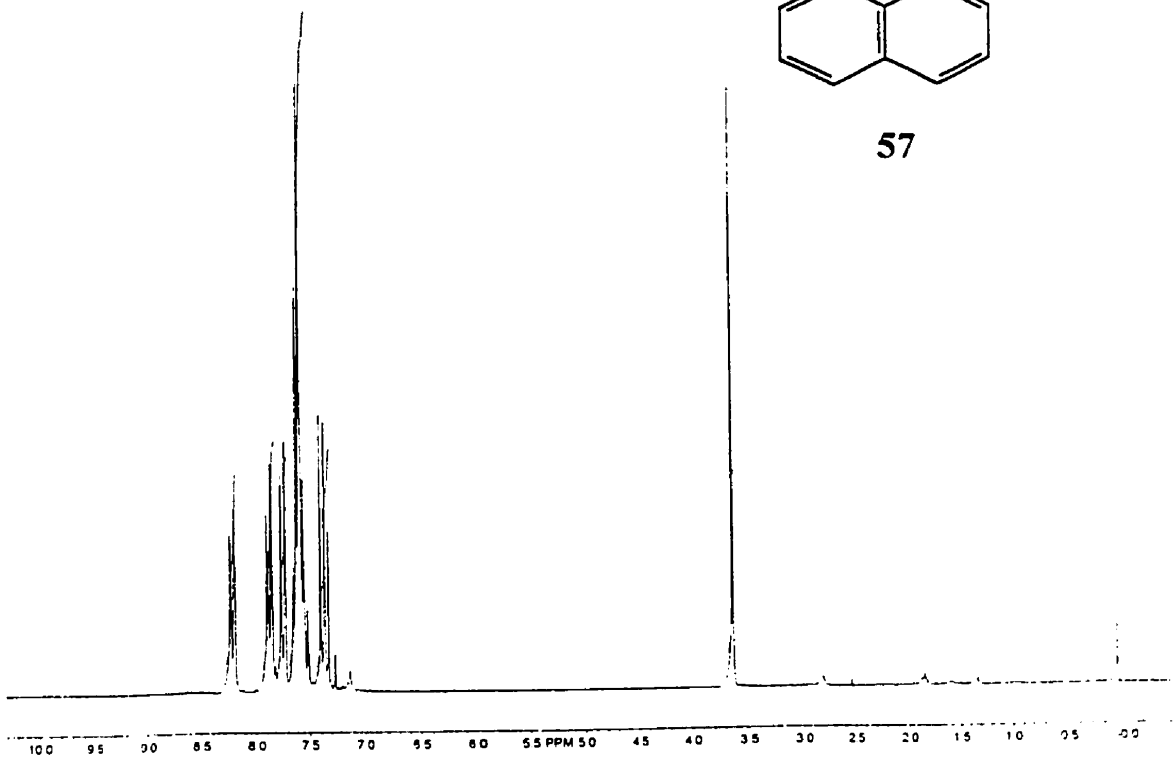

CHO
O
NMe2
S

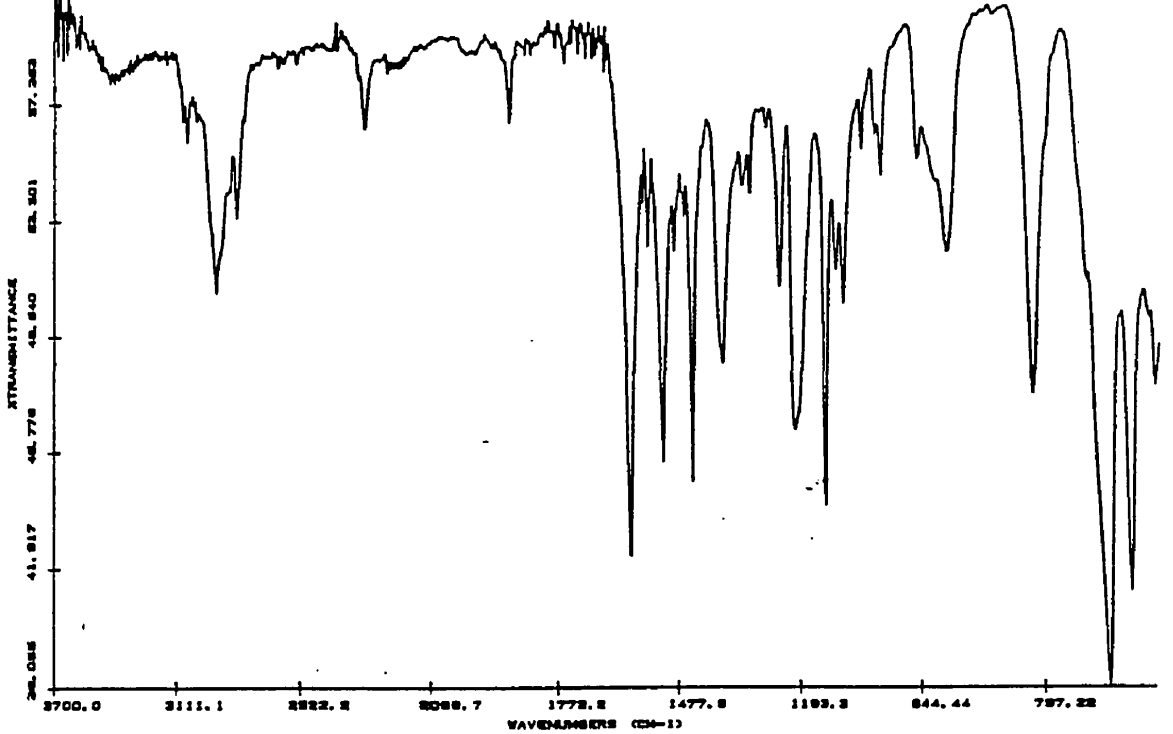
54


%TRANSMITTANCE
4000.0
3311.1
2922.2
2066.7
1722.2
1377.9
1033.2
844.44
672.22
500.00
WAVENUMBERS (CM-1)


SH

57


100
95
90
85
80
75
70
65
60
55 PPM 50
45
40
35
30
25
20
15
10
05
00


%TRANSMITTANCE
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53.301
49.840
46.778
41.917
38.055
3700.0
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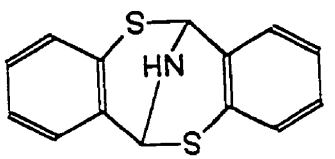
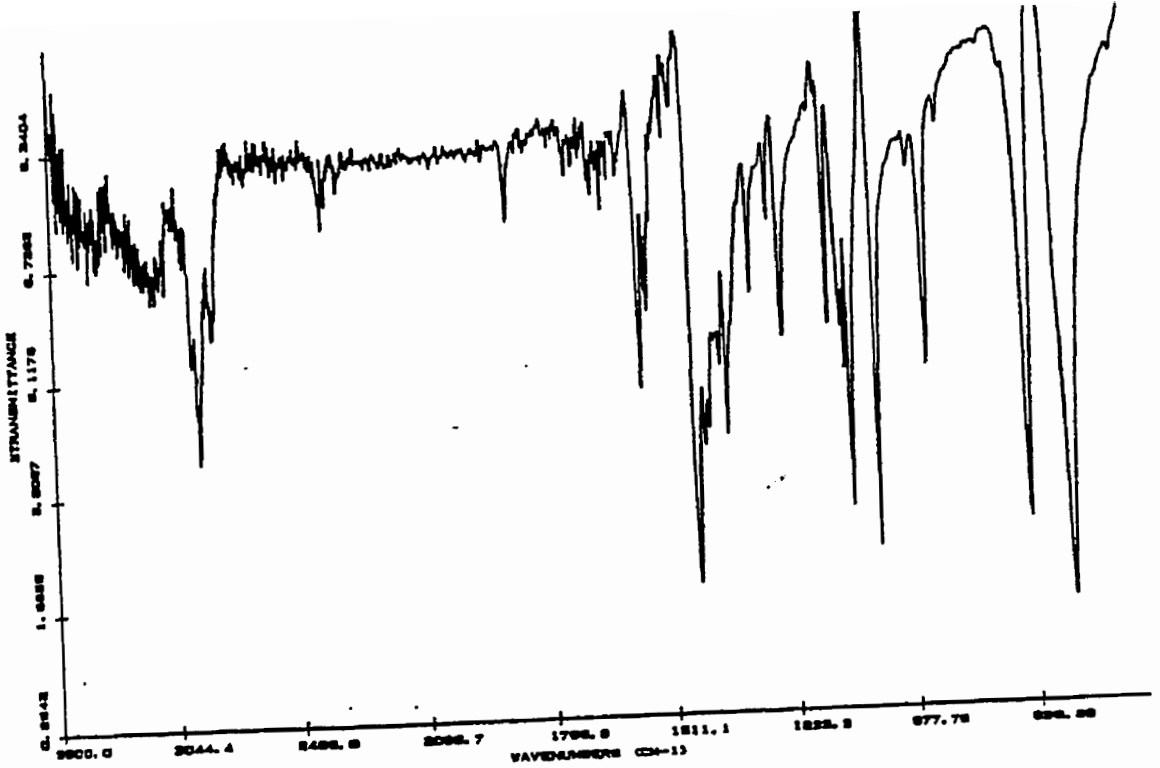
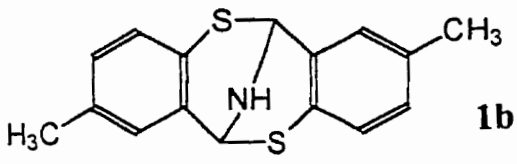
2522.2
2088.7
1772.2
1477.8
1193.3
844.44
787.22
WAVENUMBERS (CM-1)


S
HN
S

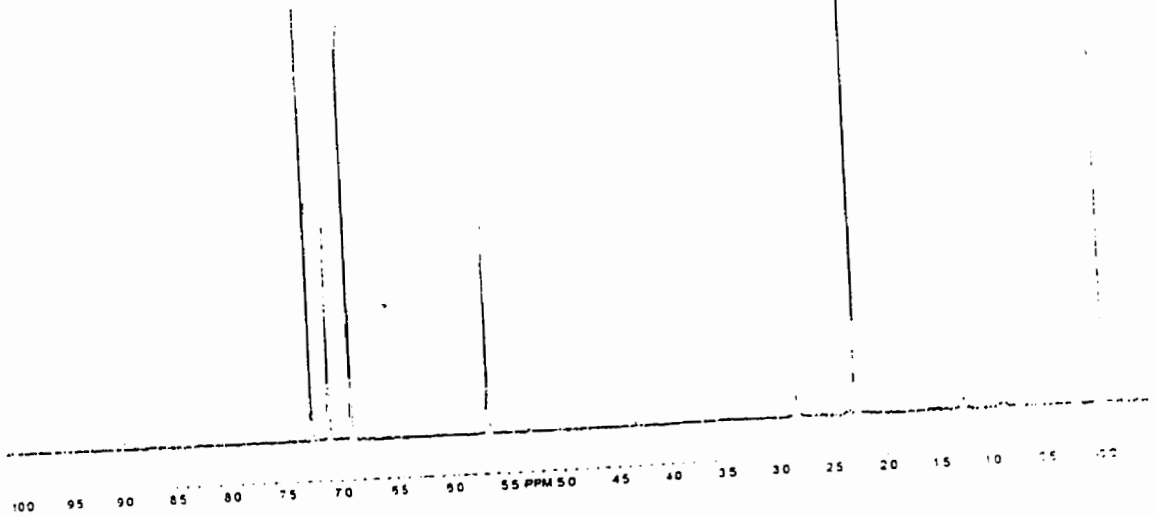
1a

9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0 PPM 5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0


TRANSMITTANCE
WAVENUMBERS (CM-1)


S
CH3
NH
H3C
S

1b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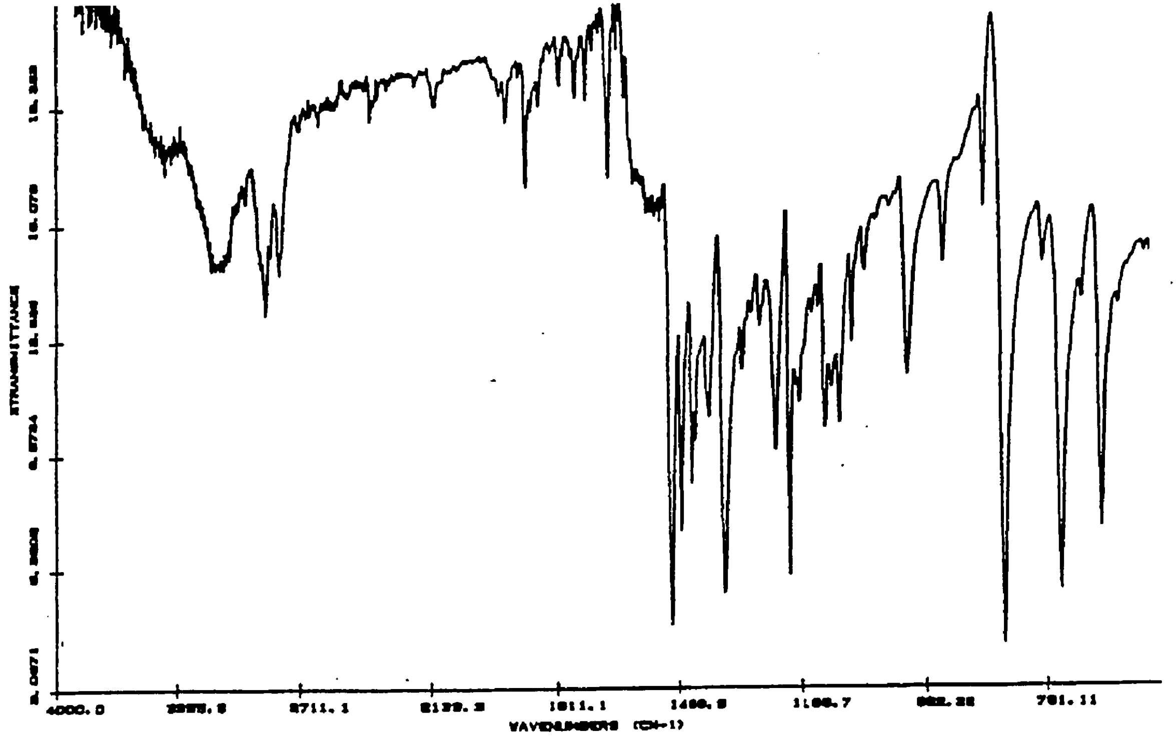
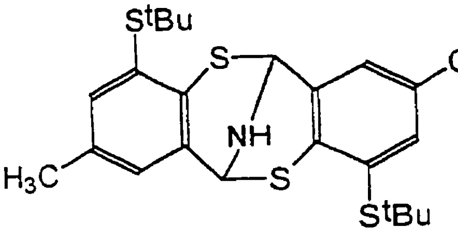
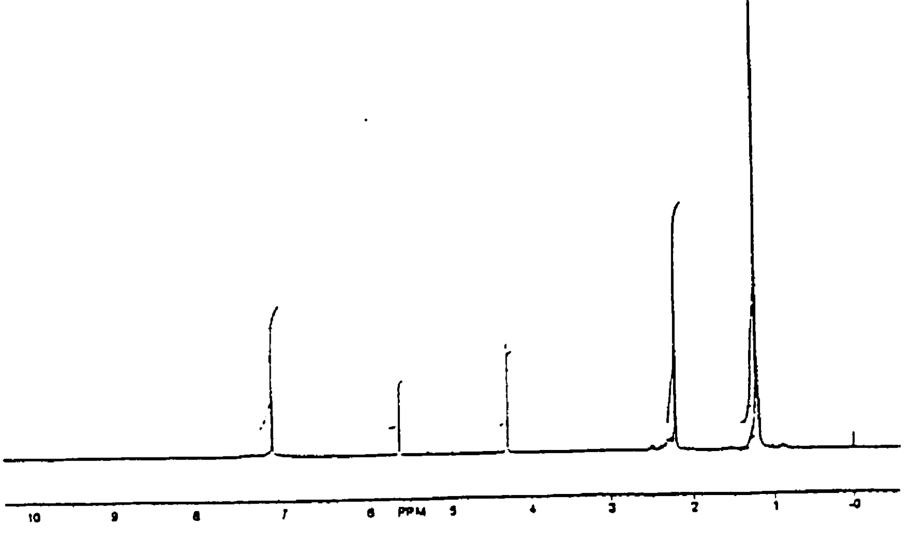


4000.0
2711.1
1811.1
WAVENUMBERS (CM-1)
701.11

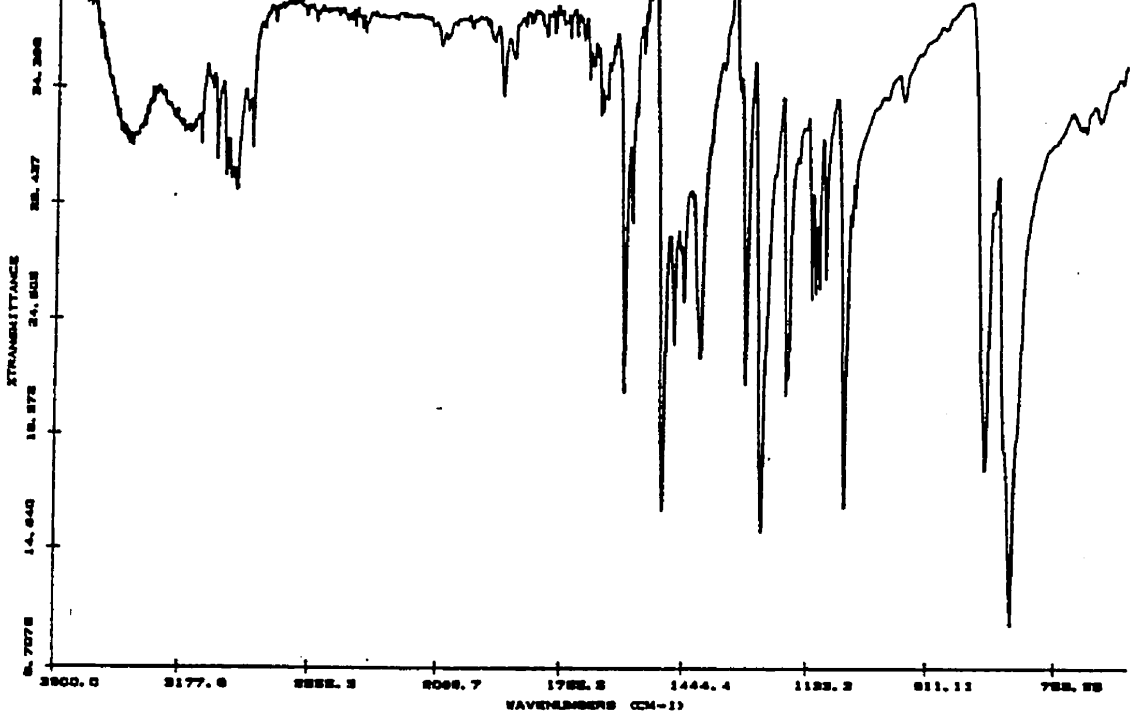


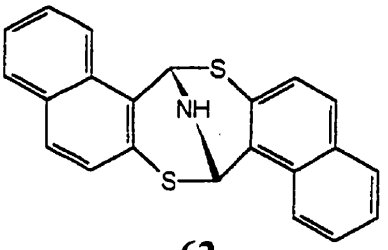
StBu
S
NH
S
CH3
H3C
StBu

1c



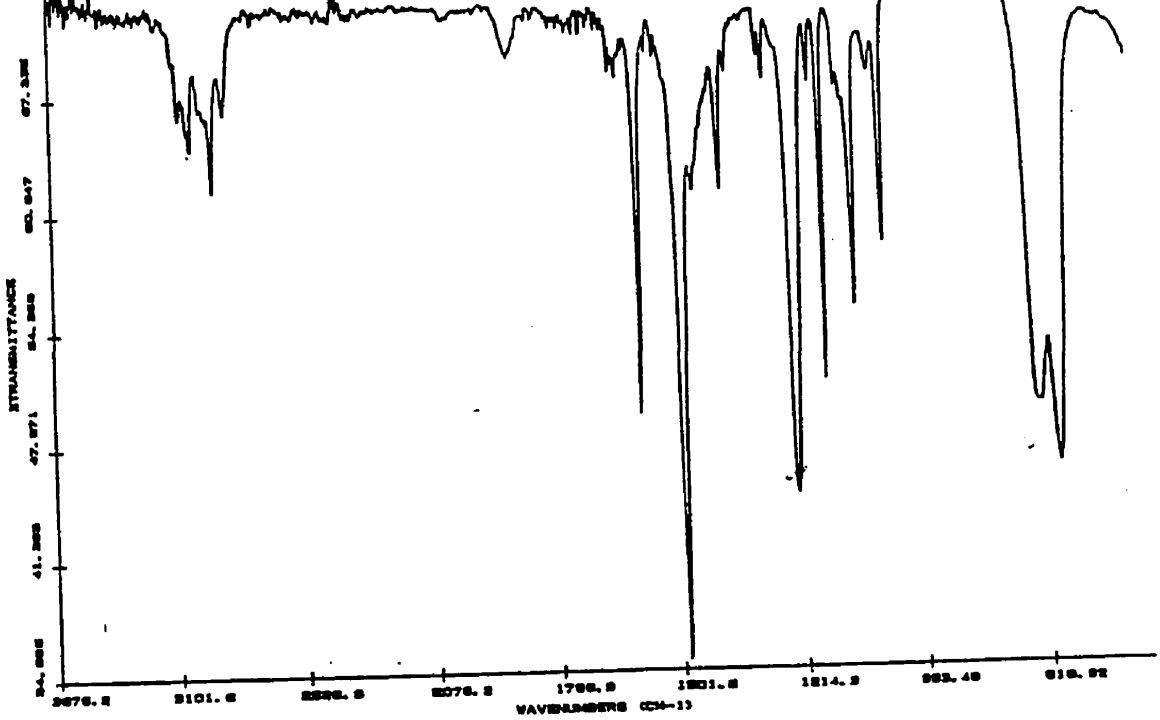
10
9
8
7
6
PPM
5
4
3
2
1
0

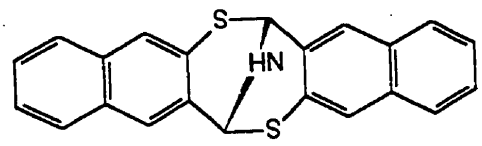

%TRANSMITTANCE
3900.0
3177.6
2666.3
2068.7
1782.2
1444.4
1123.2
811.11
WAVENUMBERS (CM-1)


S
NH
S

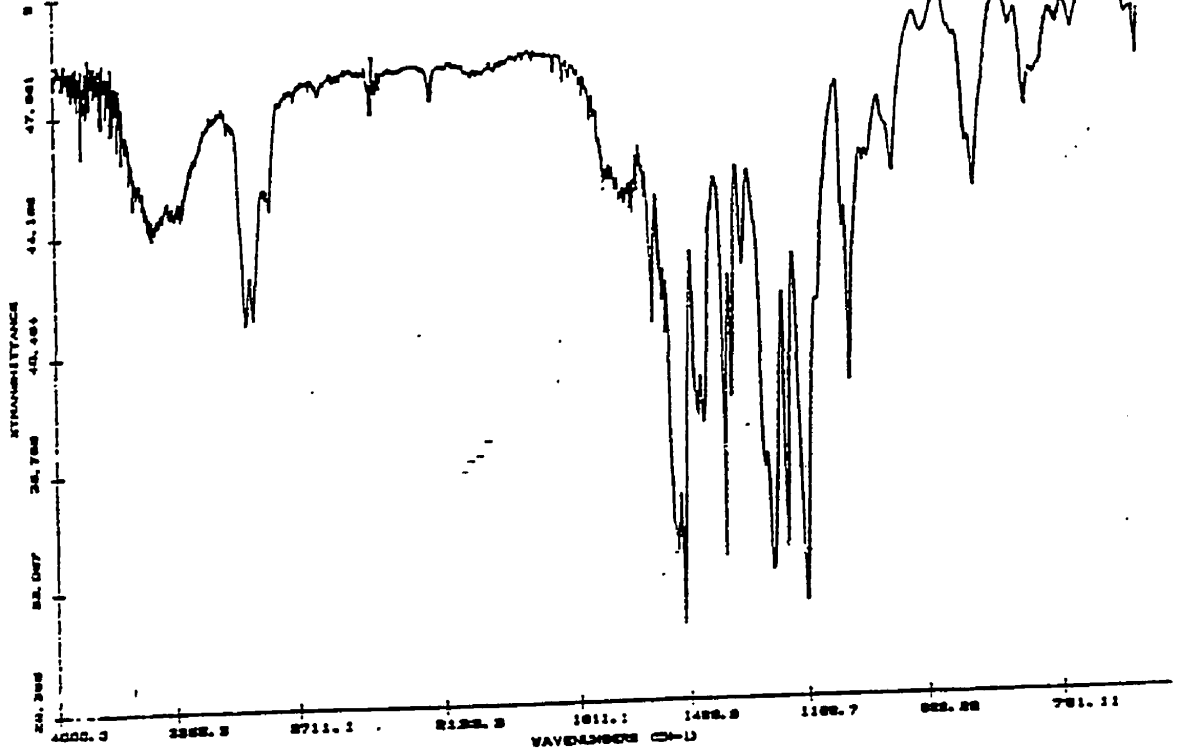
62

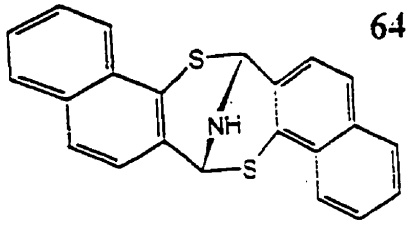
85
80
75
70
65
60
55
50
45 PPM 40
35
30
25
20
15
10
5
0



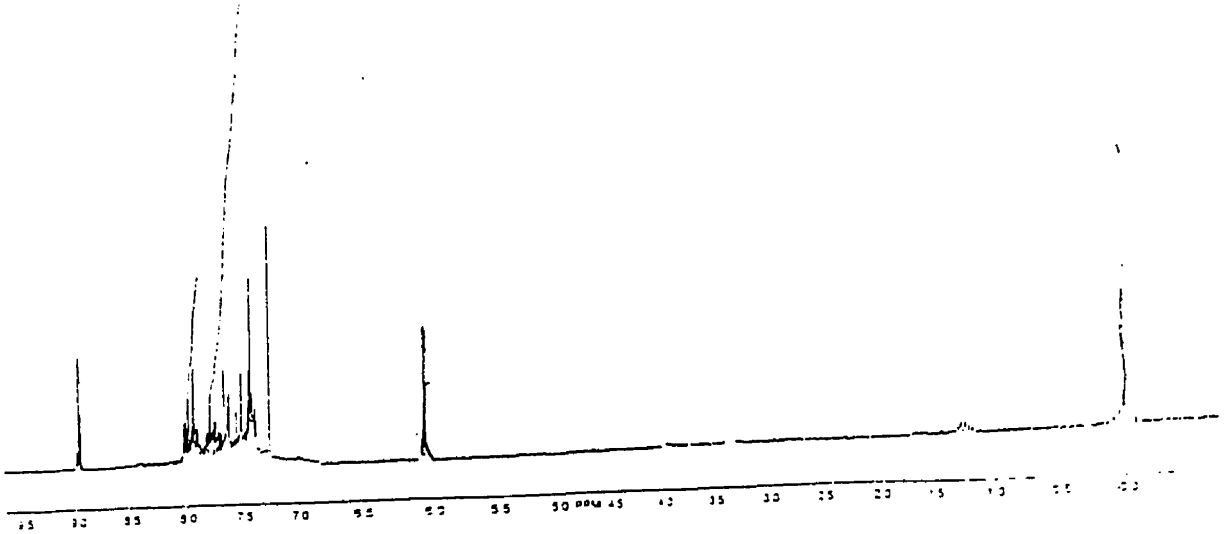


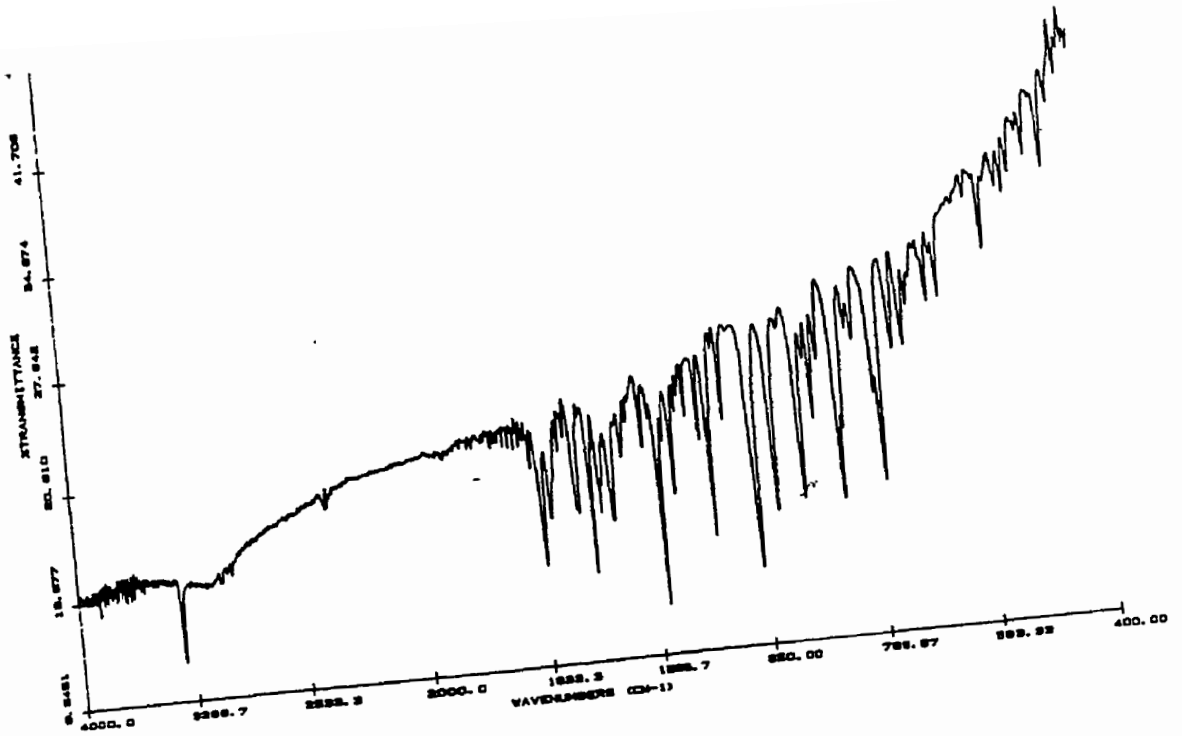
63

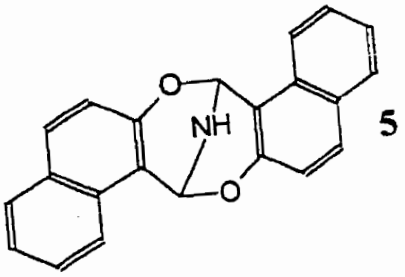




64



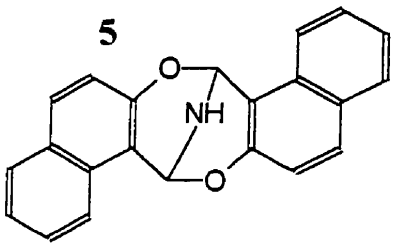

TRANSMITTANCE
41.708
34.674
27.640
20.610
13.577
6.545
4000.0
3200.7
2400.3
2000.0
1600.2
1200.7
800.00
700.67
600.33
400.00
WAVENUMBERS (CM-1)

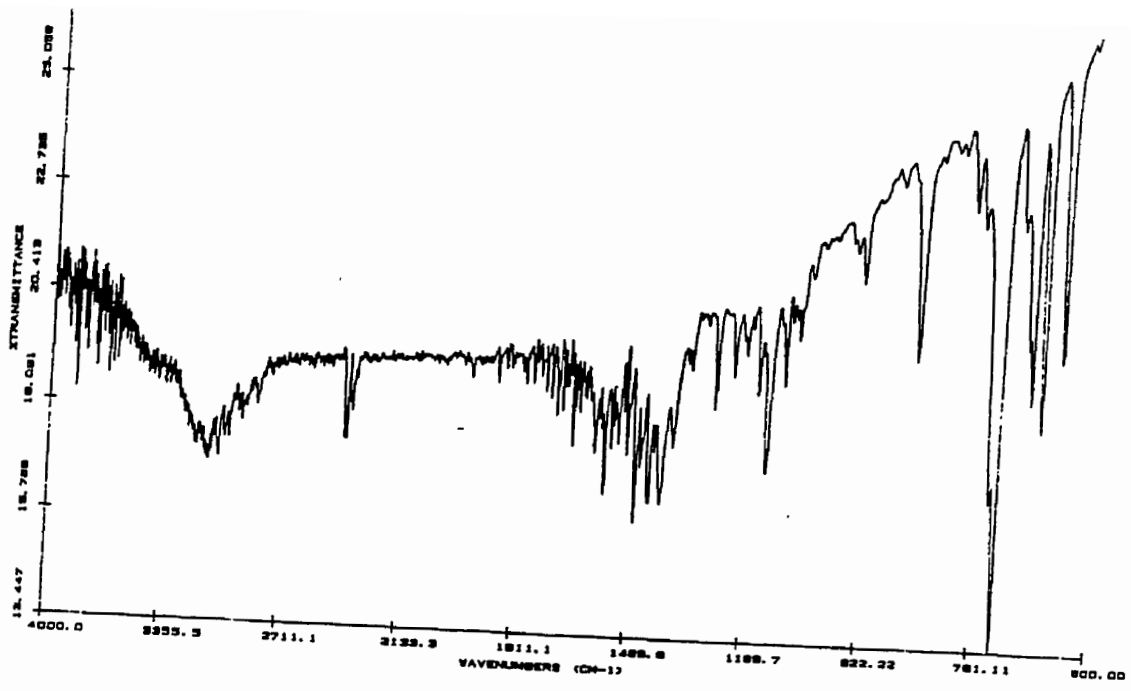

O
NH
O

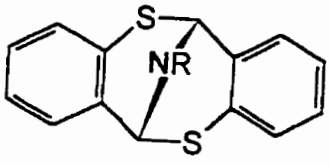
5

95
90
85
80
75
70
65
60
55
50
45 PPM 40
35
30
25
20
15
10
05
00
05

5

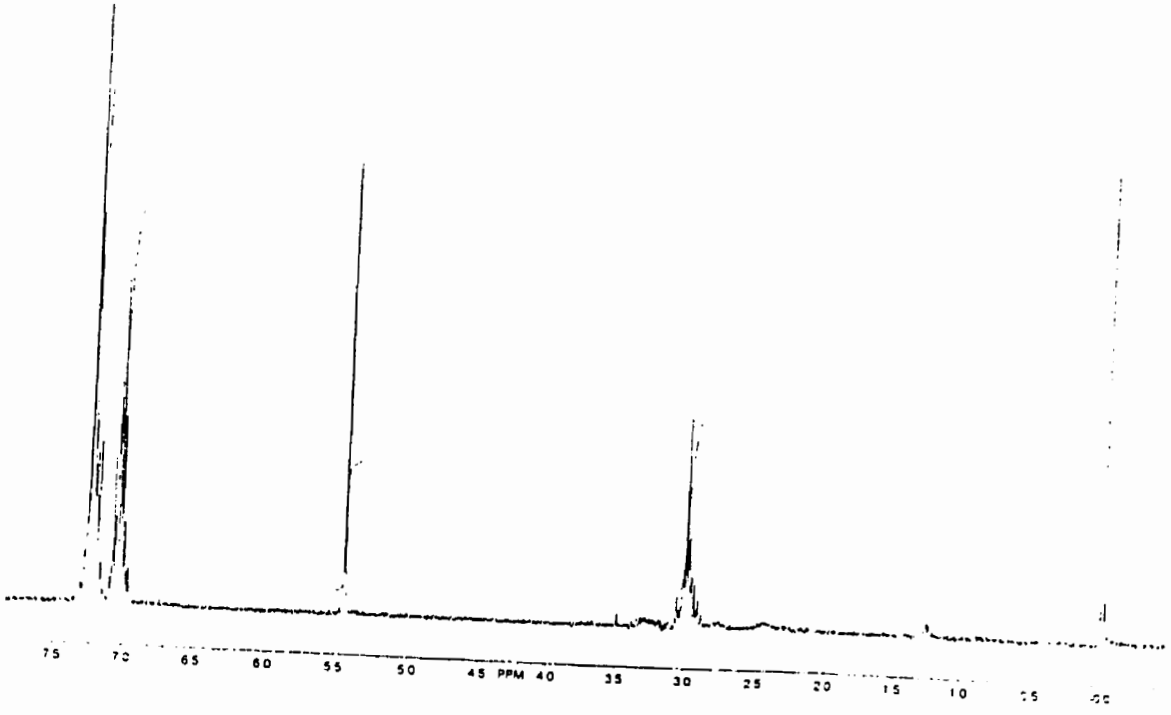


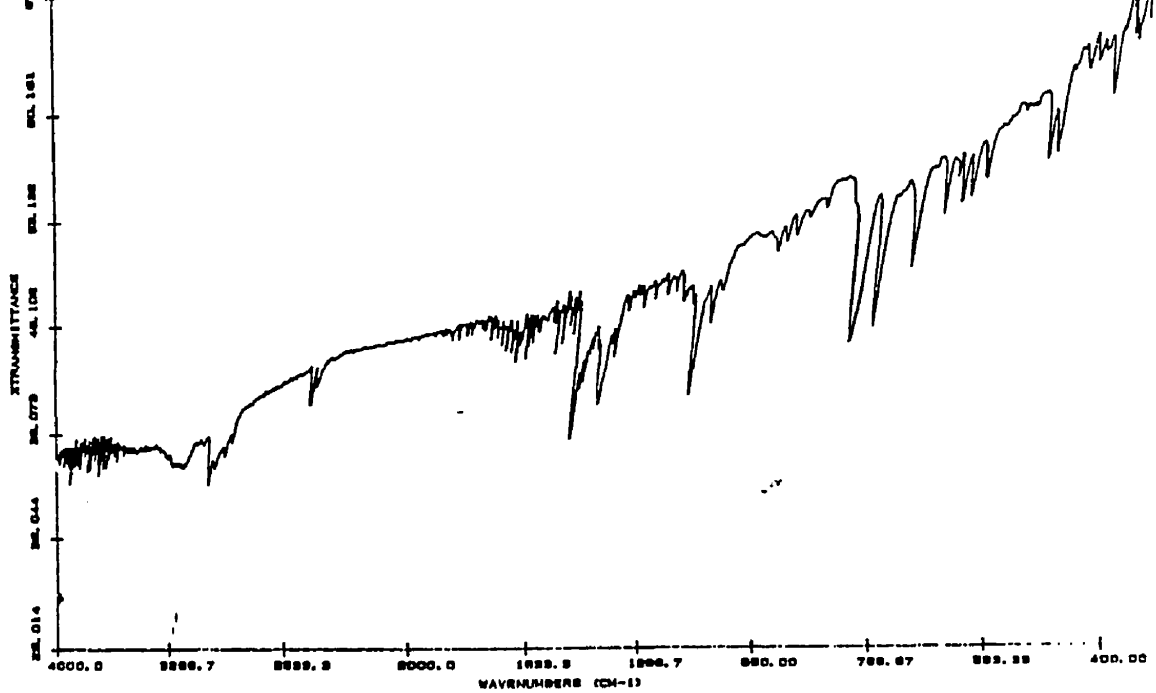


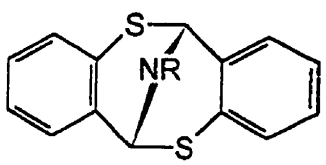


71

R=$CH_2CH_2C_6H_5$

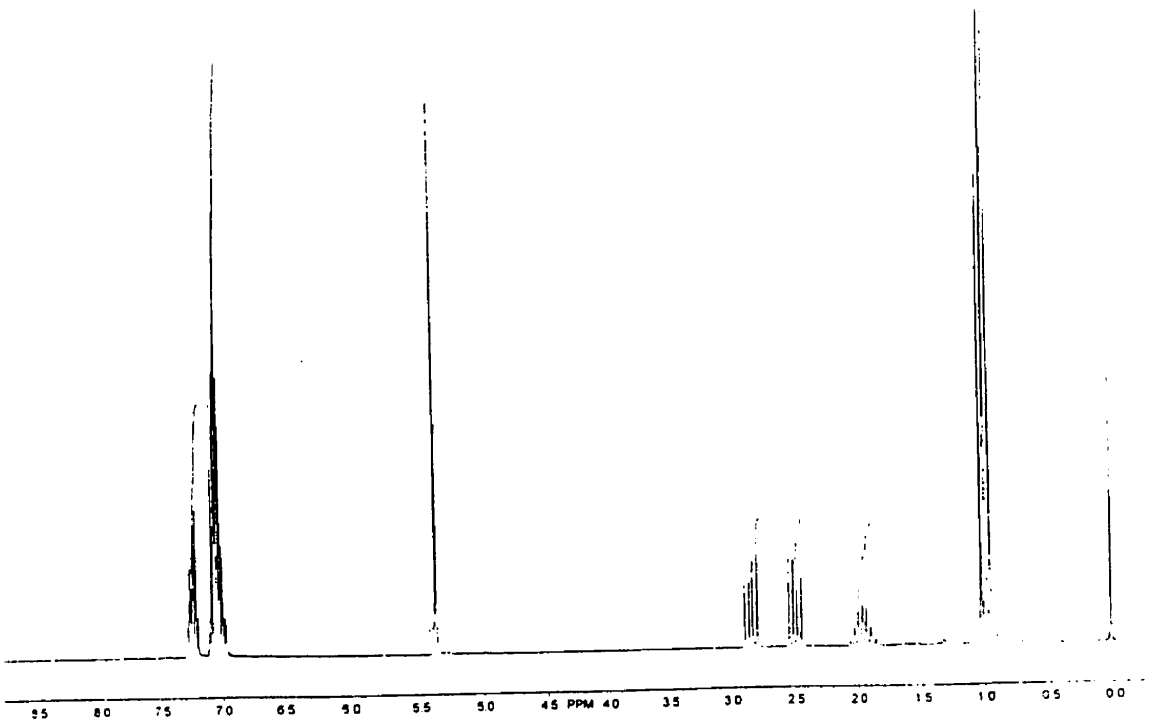


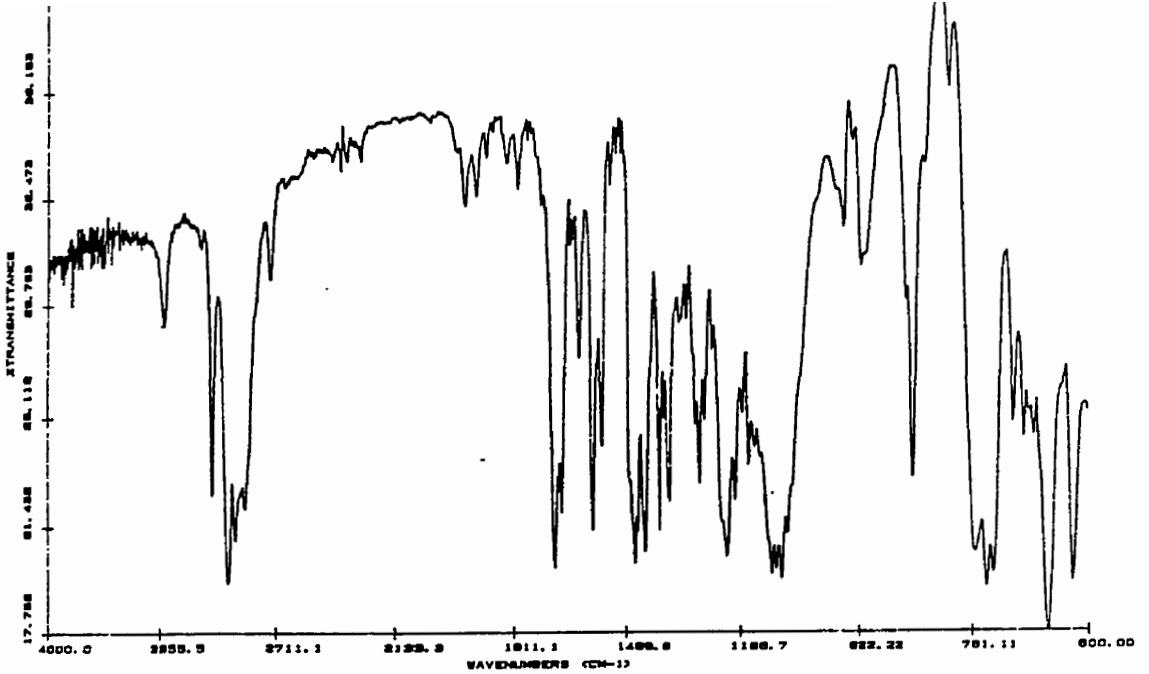




72

$R=CH_2CH(CH_3)_2$

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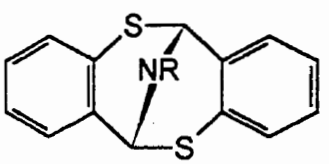
WAVENUMBERS (CM-1)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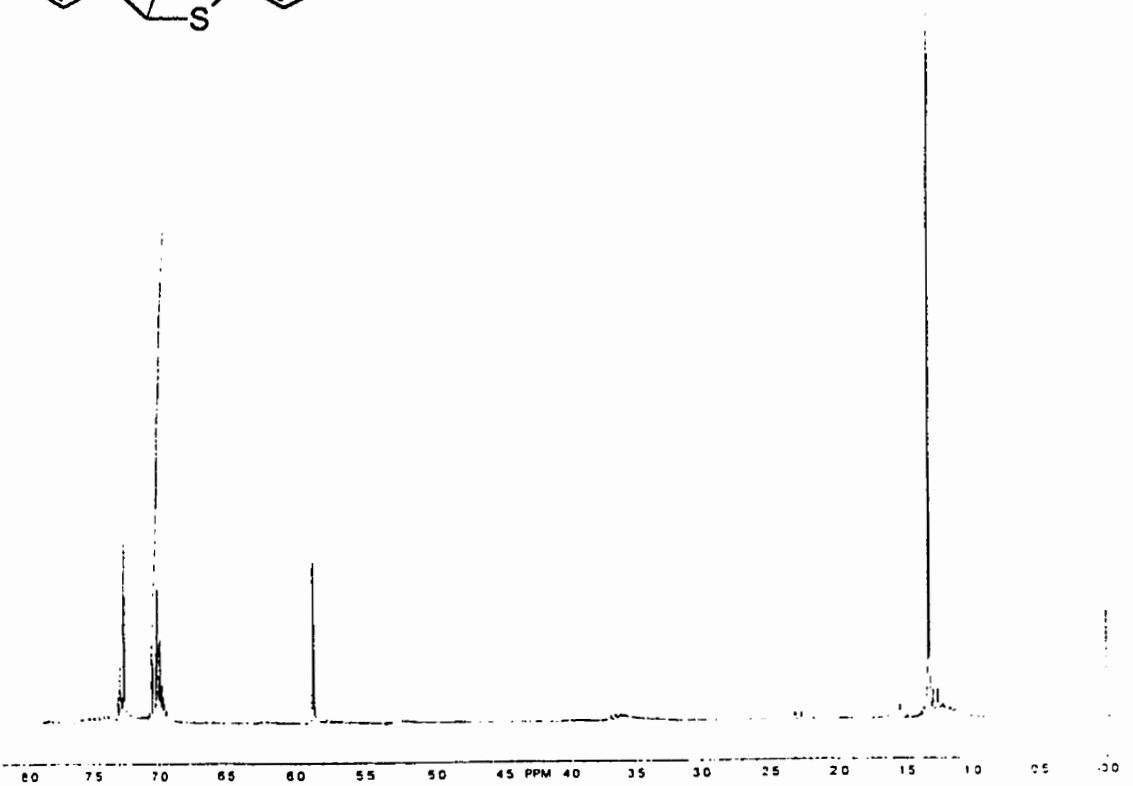
NR
S

73

R=C(CH$_3$)$_3$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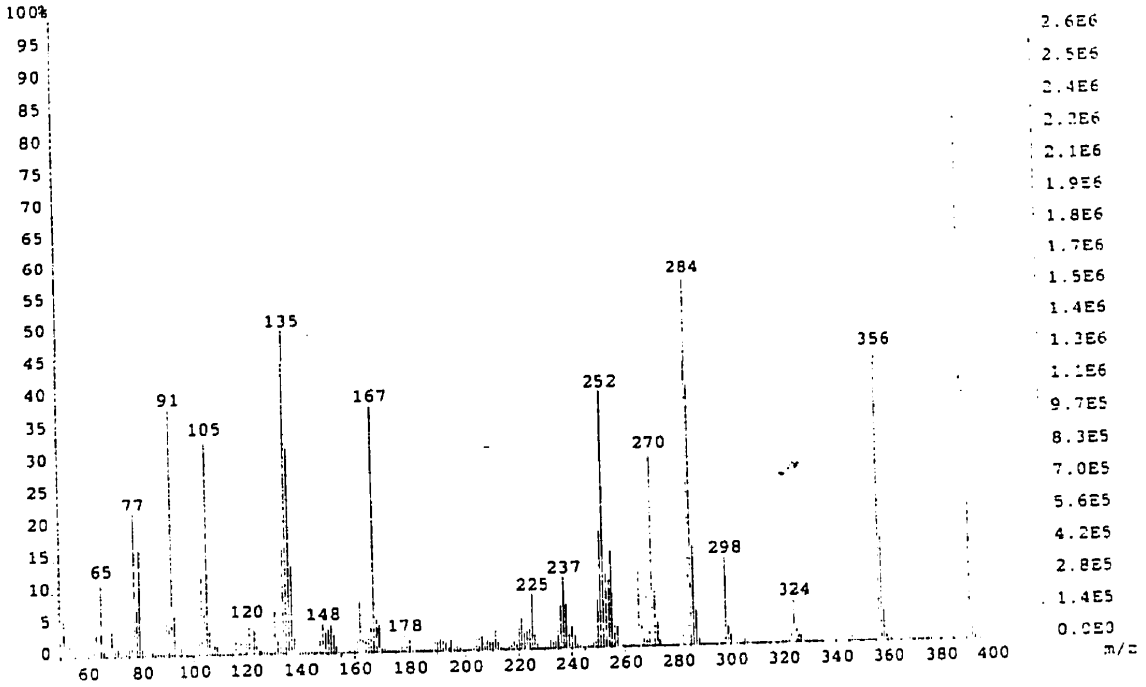
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40
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25
20
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10
5
0
2.6E6
2.5E6
2.4E6
2.3E6
2.1E6
1.9E6
1.8E6
1.7E6
1.5E6
1.4E6
1.3E6
1.1E6
9.7E5
8.3E5
7.0E5
5.6E5
4.2E5
2.8E5
1.4E5
0.0E0
m/z
65
77
91
105
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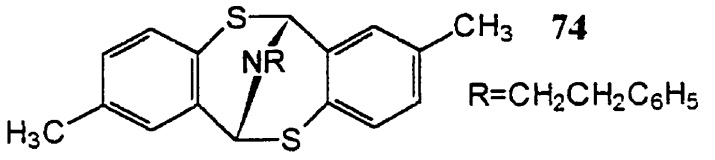
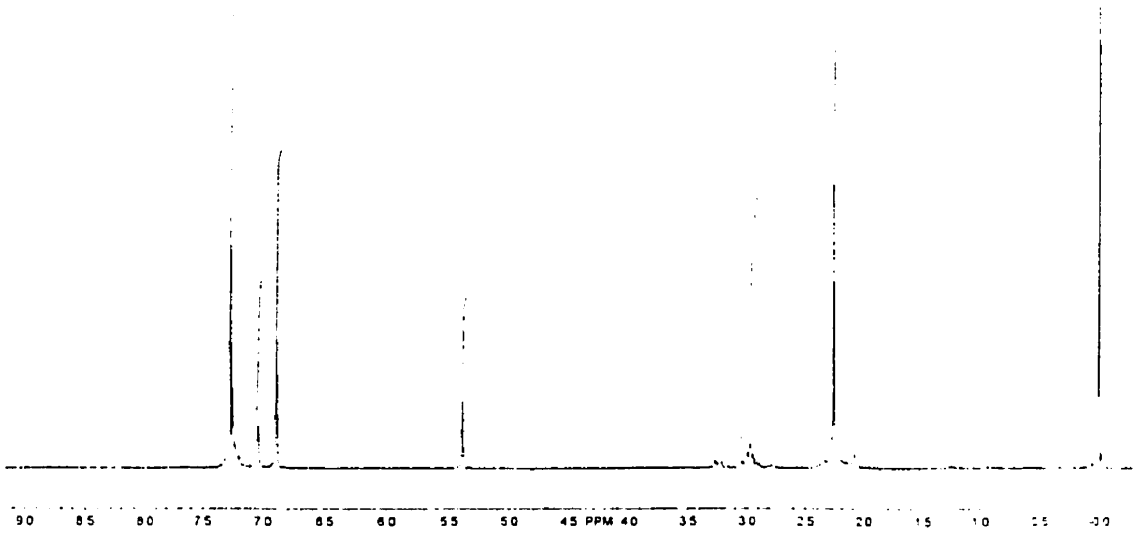

S
NR
S
CH3
H3C
74
R=CH2CH2C6H5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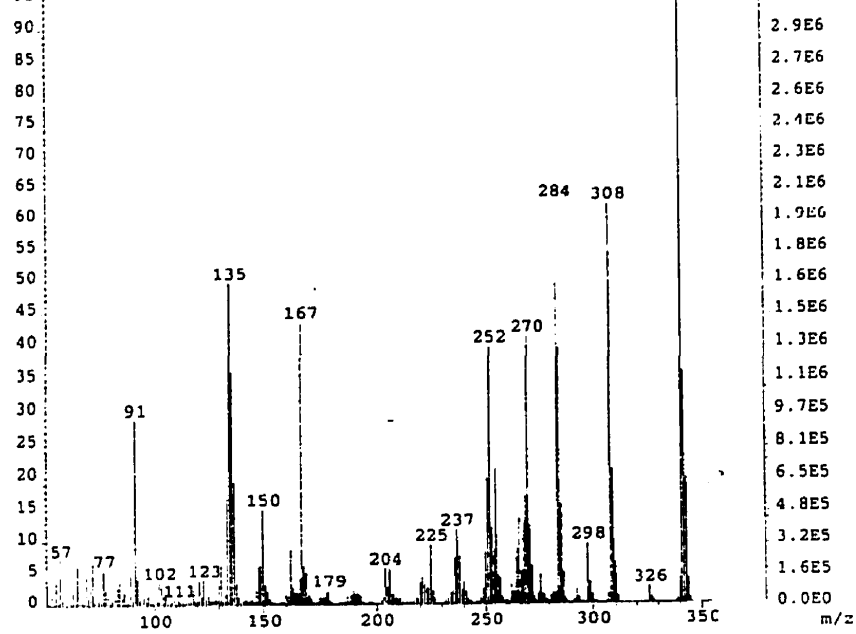
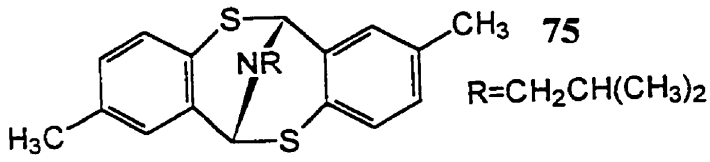
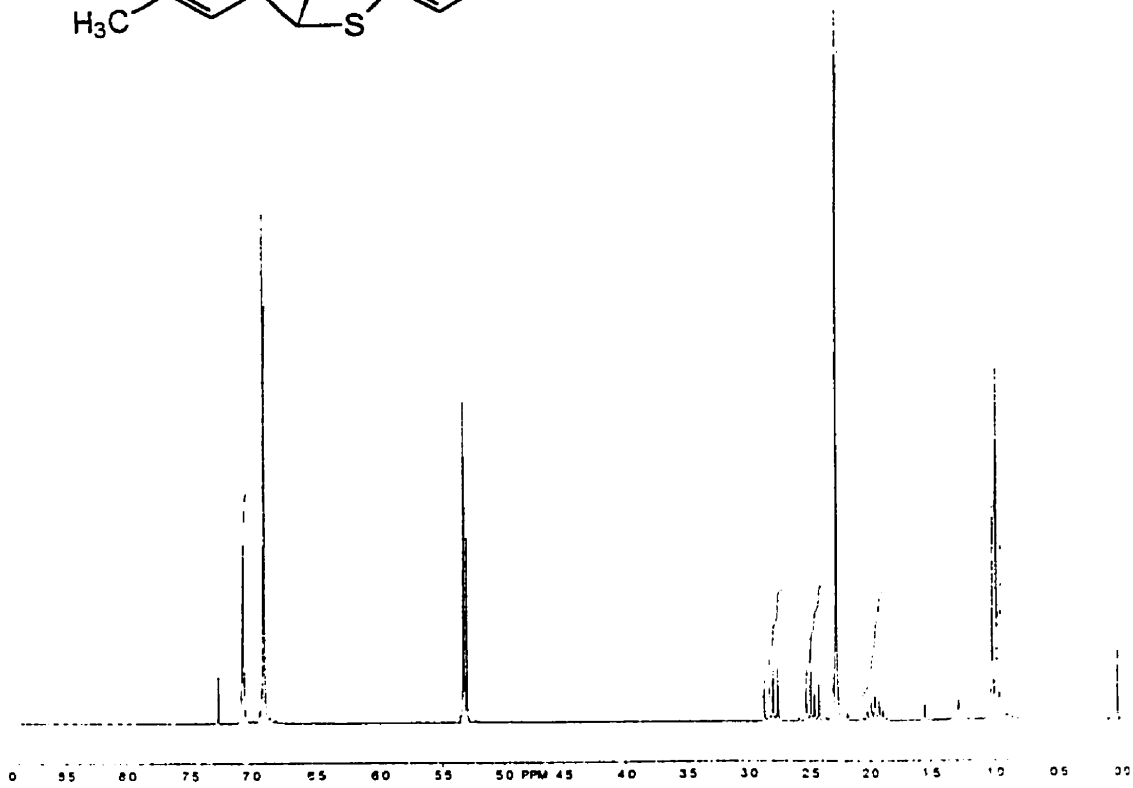
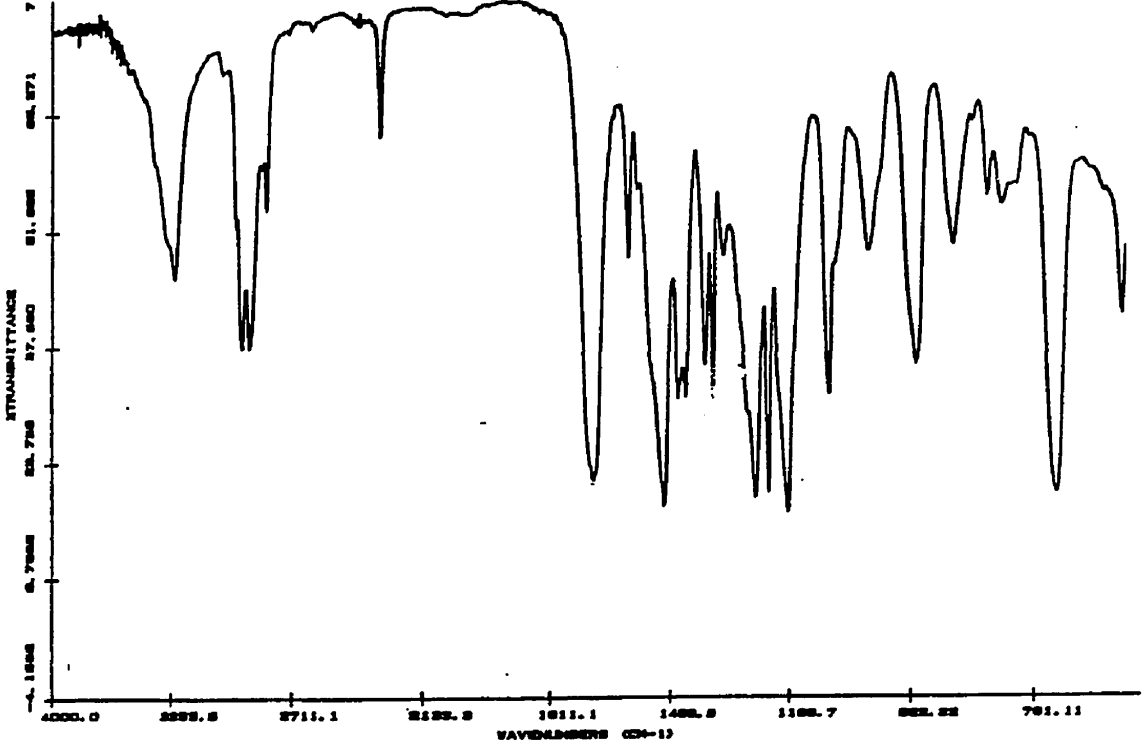


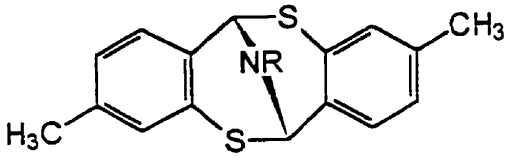


75

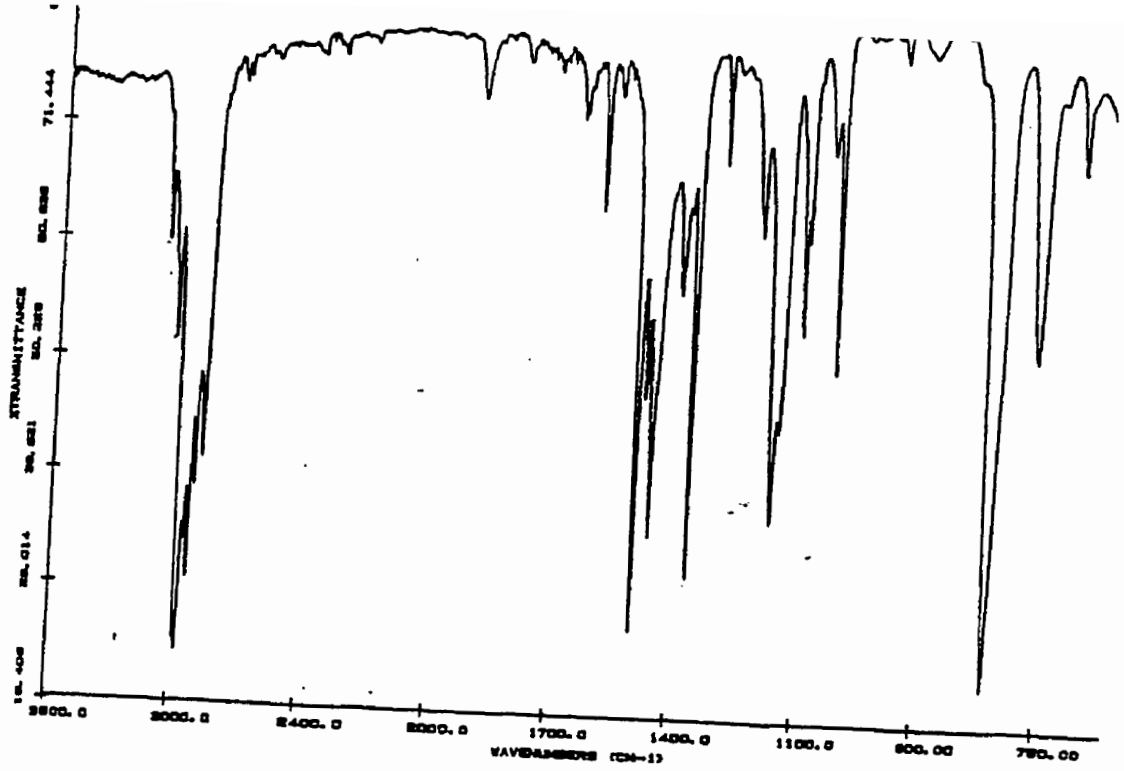
R=$CH_2CH(CH_3)_2$







80 R=COOMe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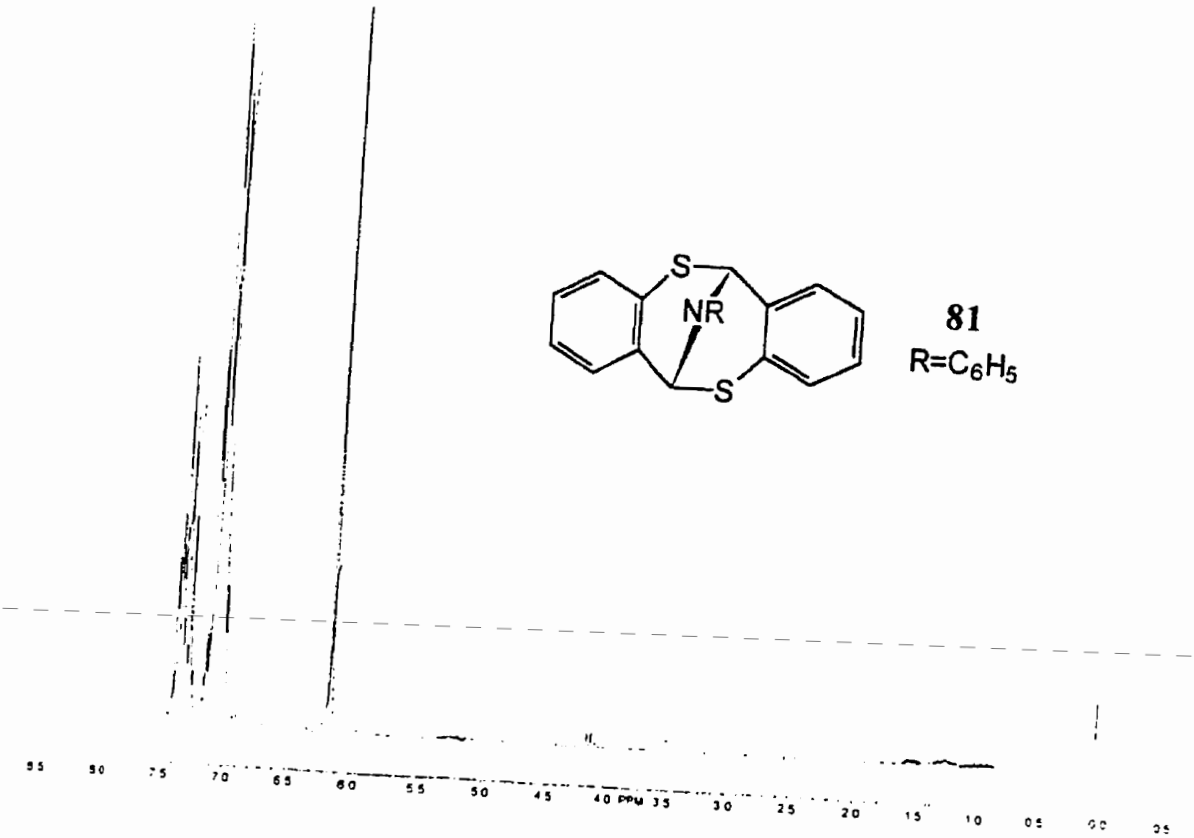
700.00


95
90
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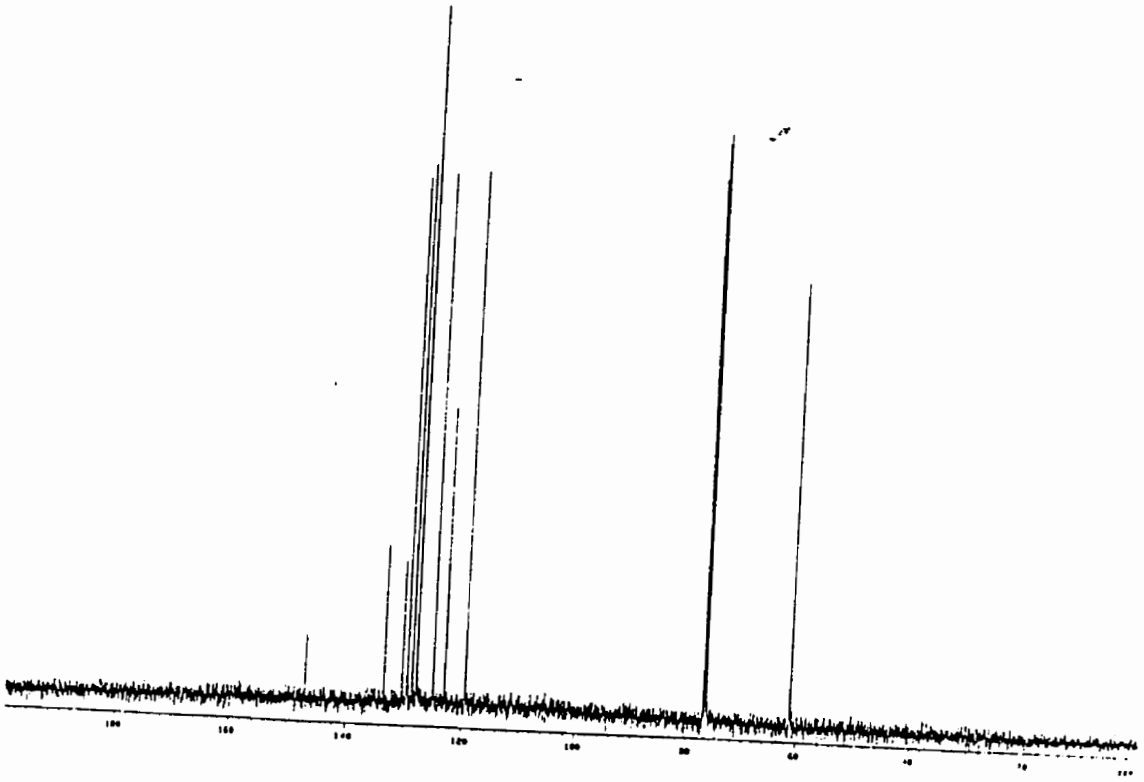
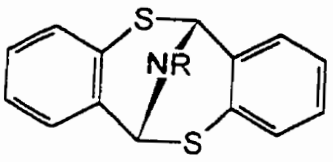
70
65
60
55
50
45
40 PPM
35
30
25
20
15
10
05
00
05

S
NR
S

81

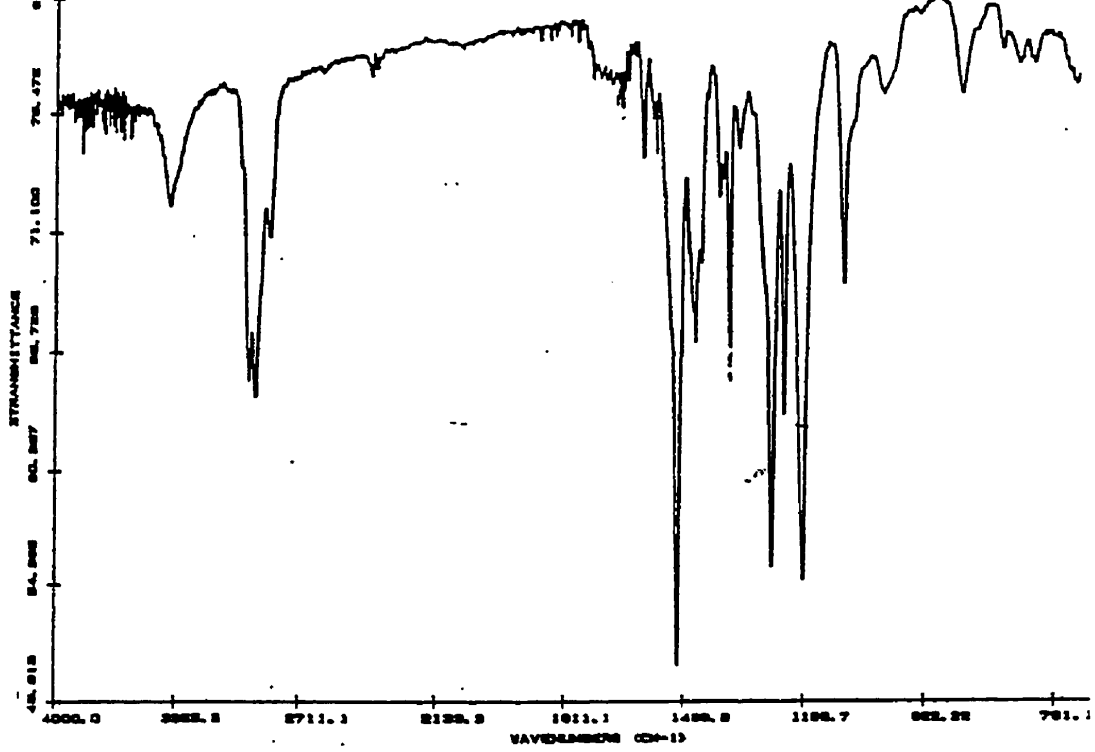
$R=C_6H_5$

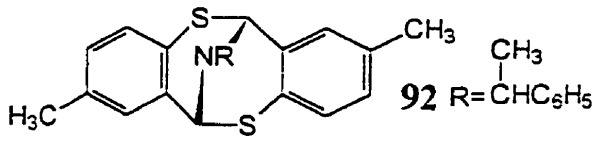




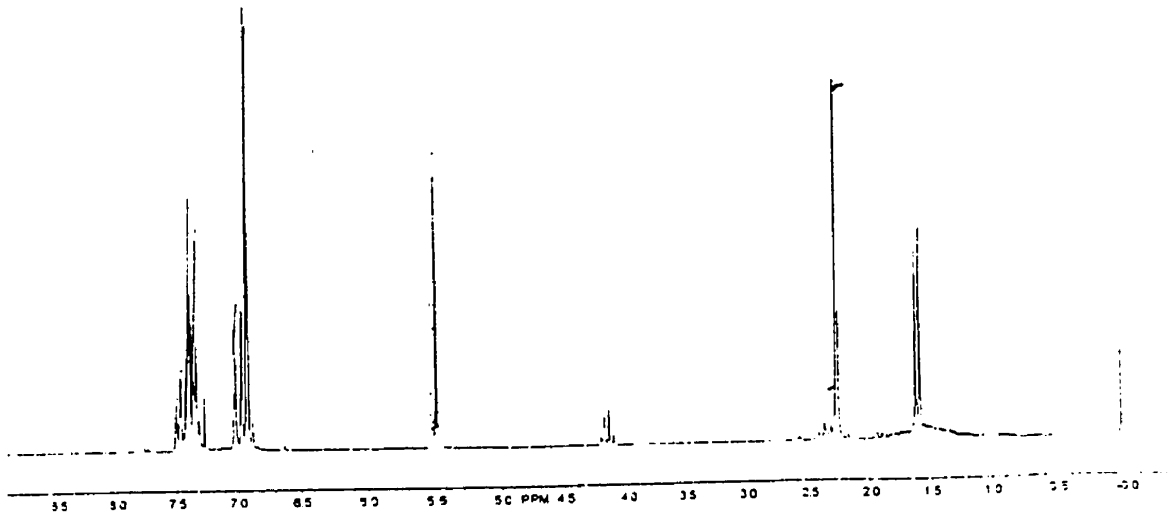
81

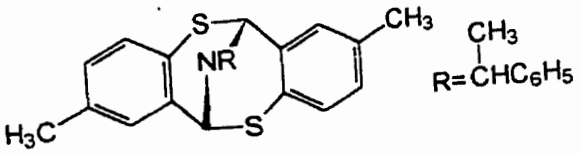
$R=C_6H_5$

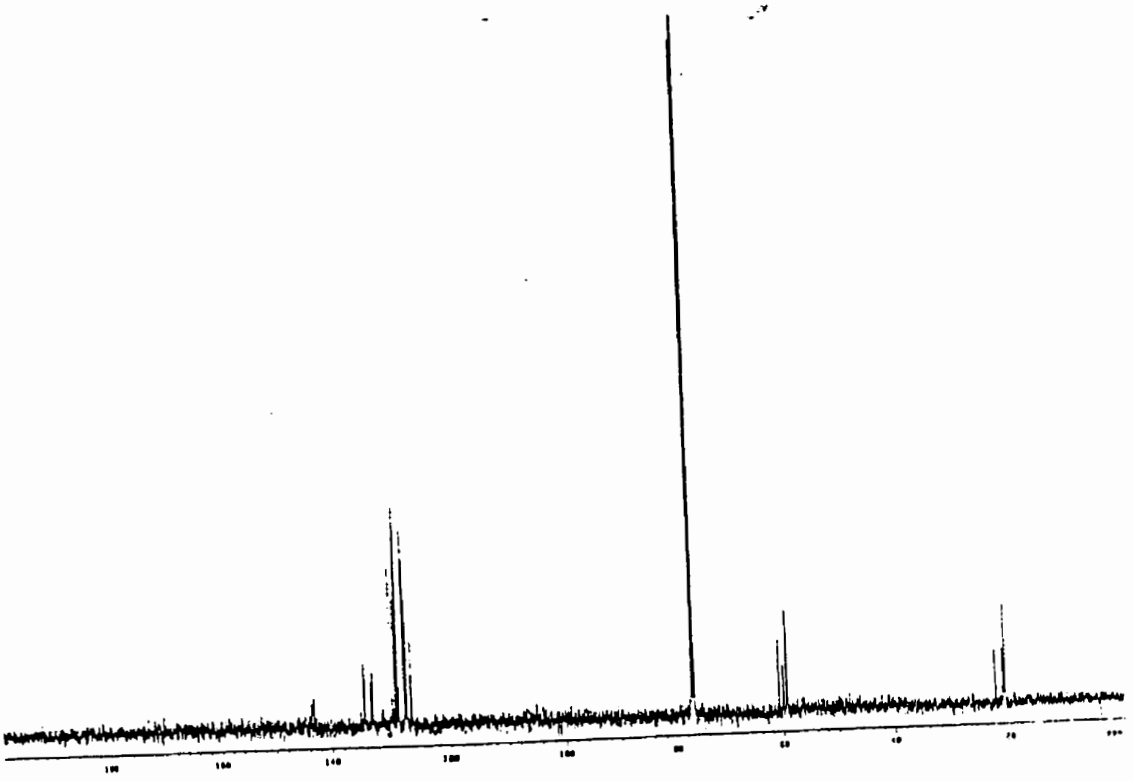


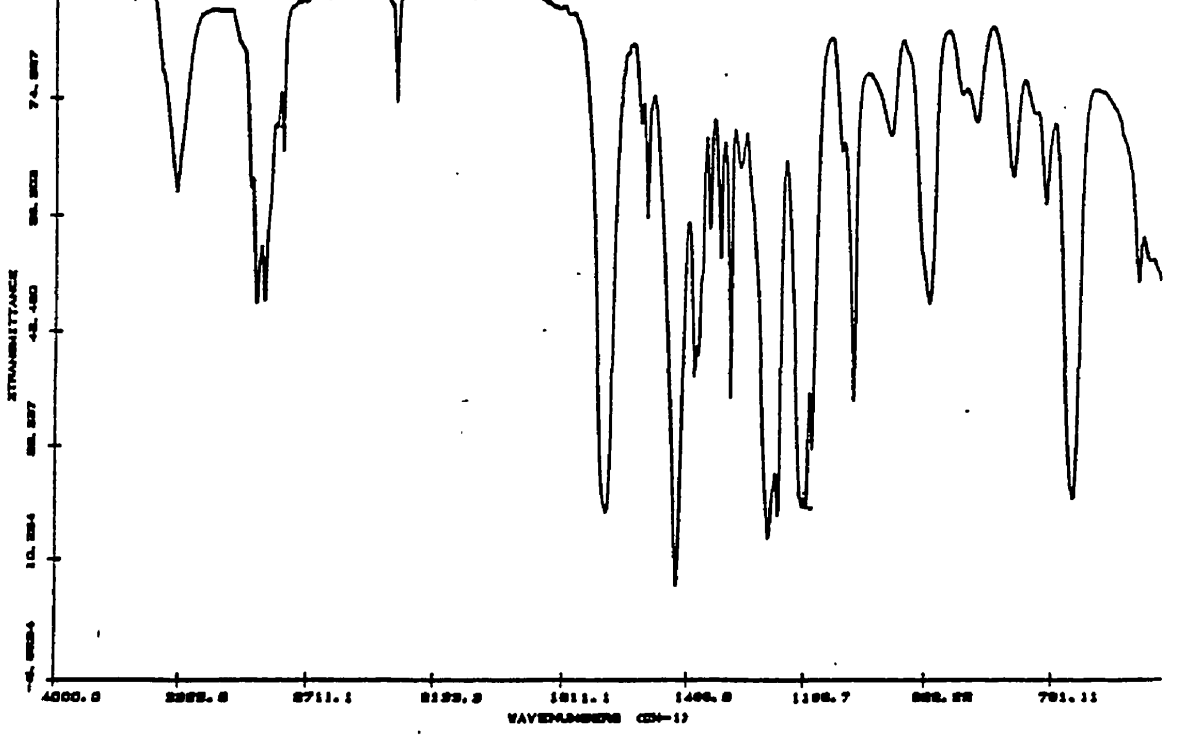


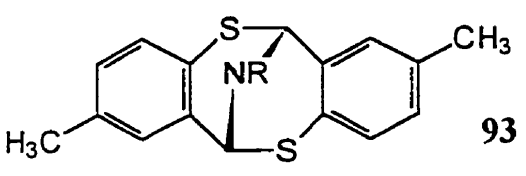
92 R=




S
NR
S
CH3
H3C
CH3
R=CHC6H5



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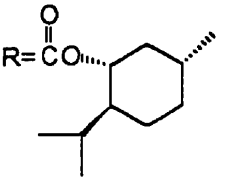
NR
S
CH3
H3C

93


O
R= CO

85
80
75
70
65
60
55
50
45 PPM 40
35
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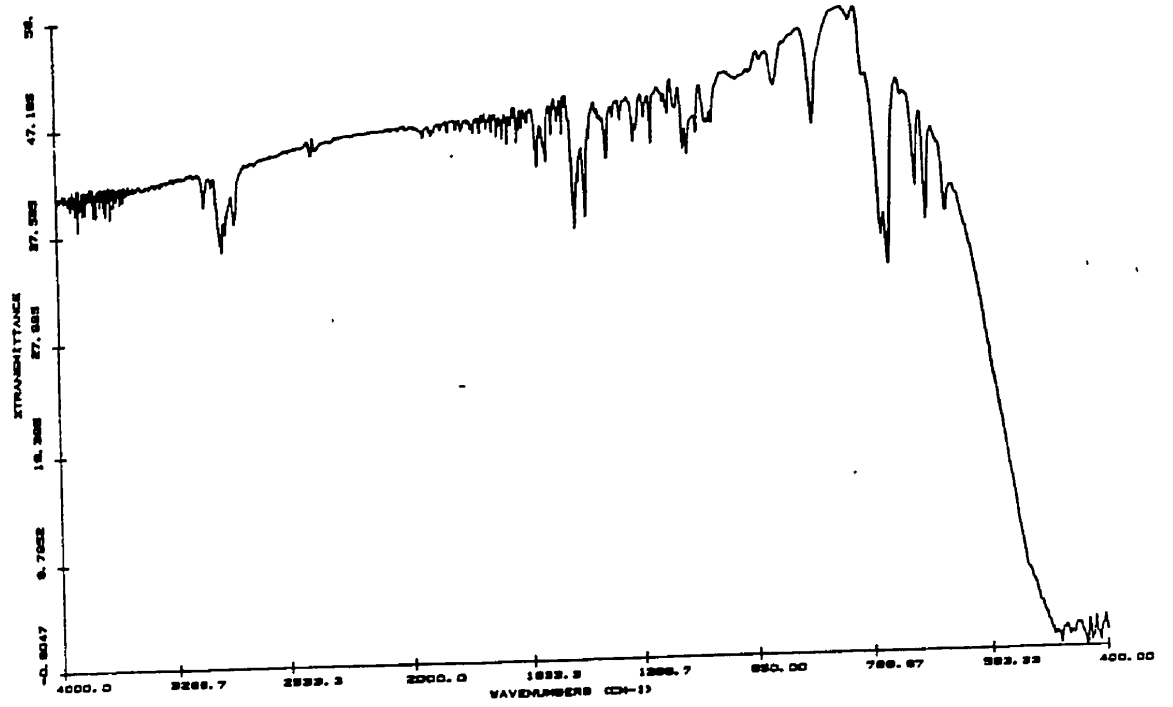
00



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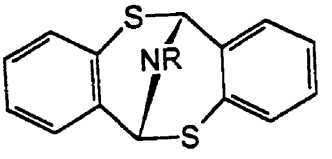
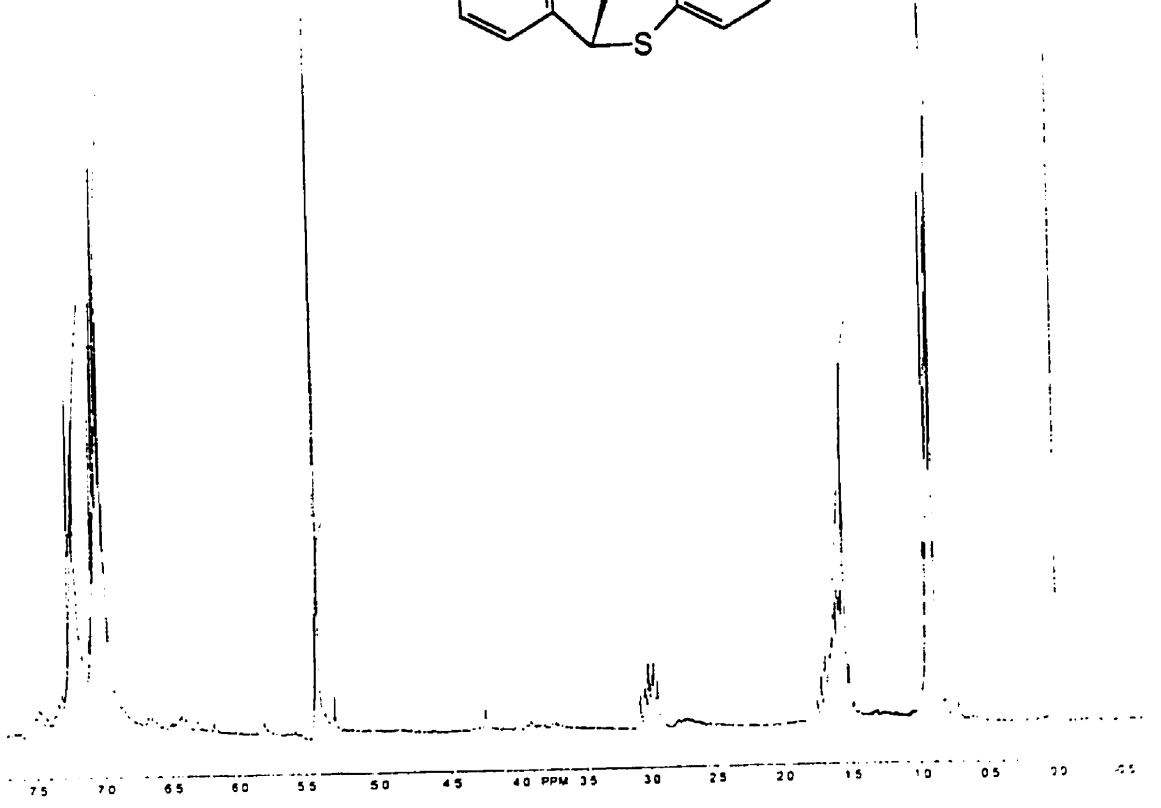
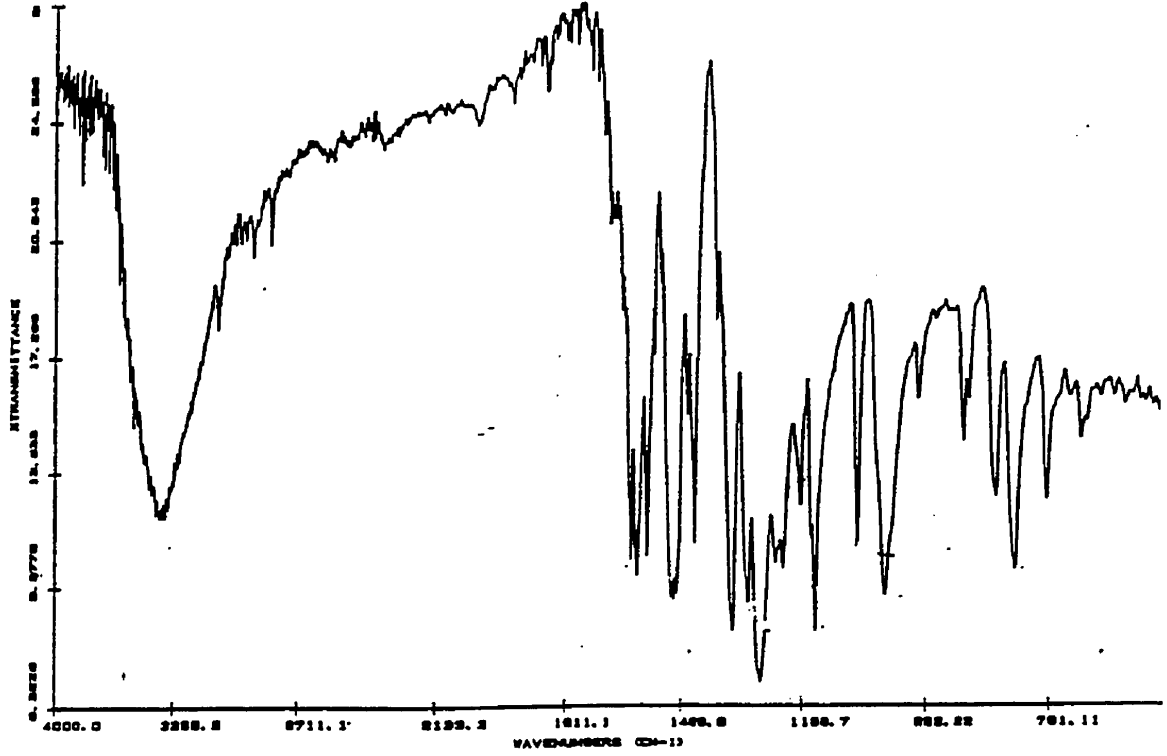
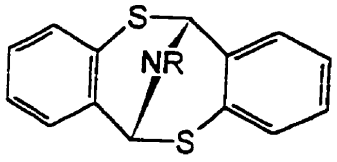


R=$CH_2CH_2CH(CH_3)_2$

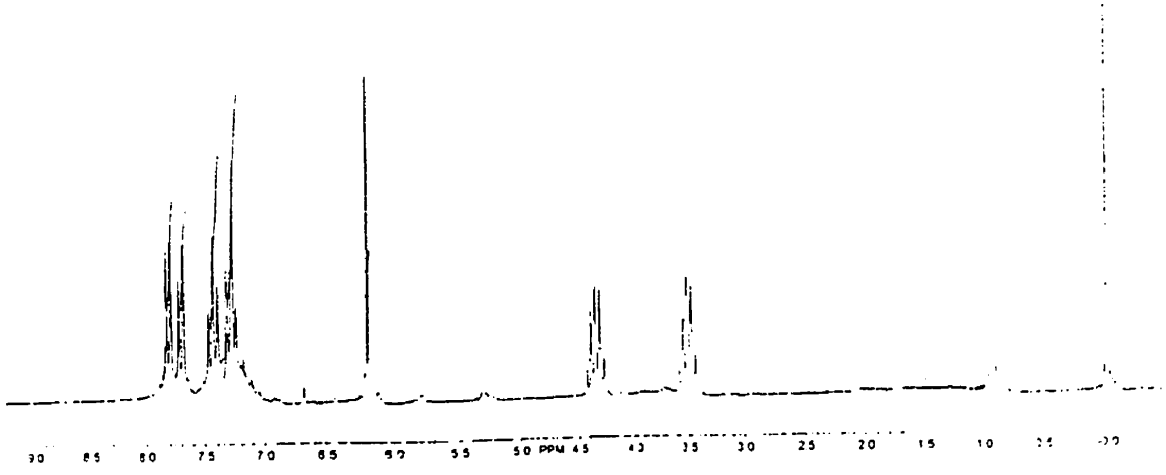


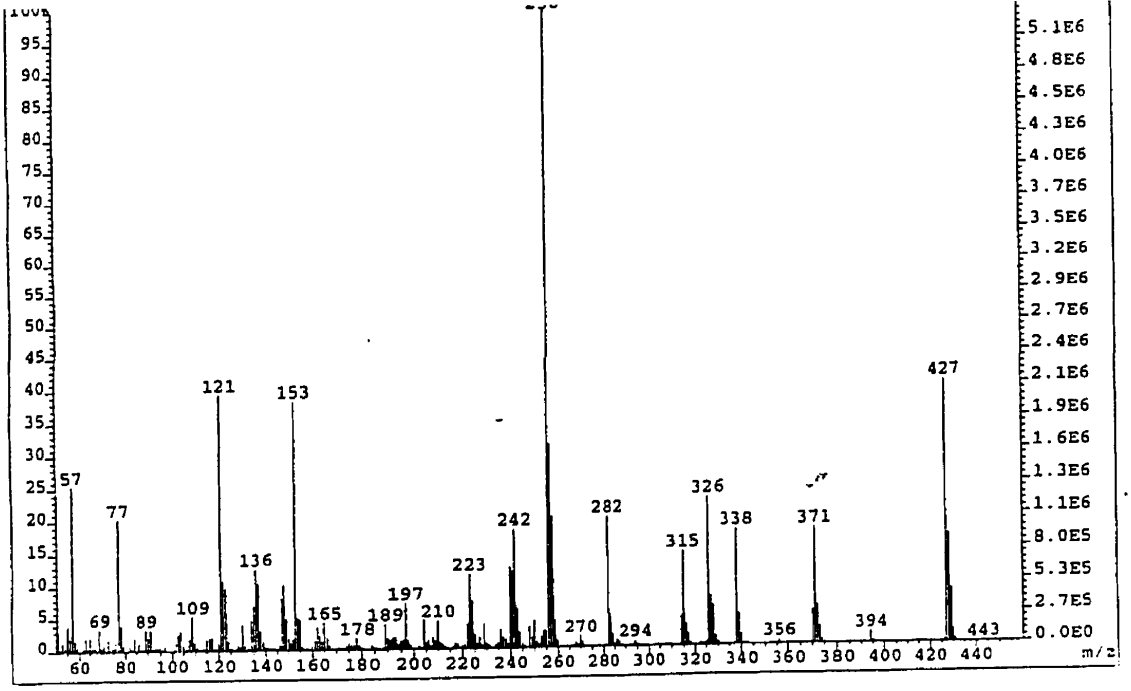


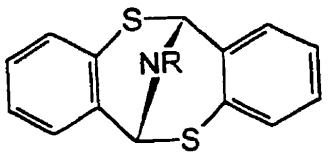


96

R=CH_2CH_2OH

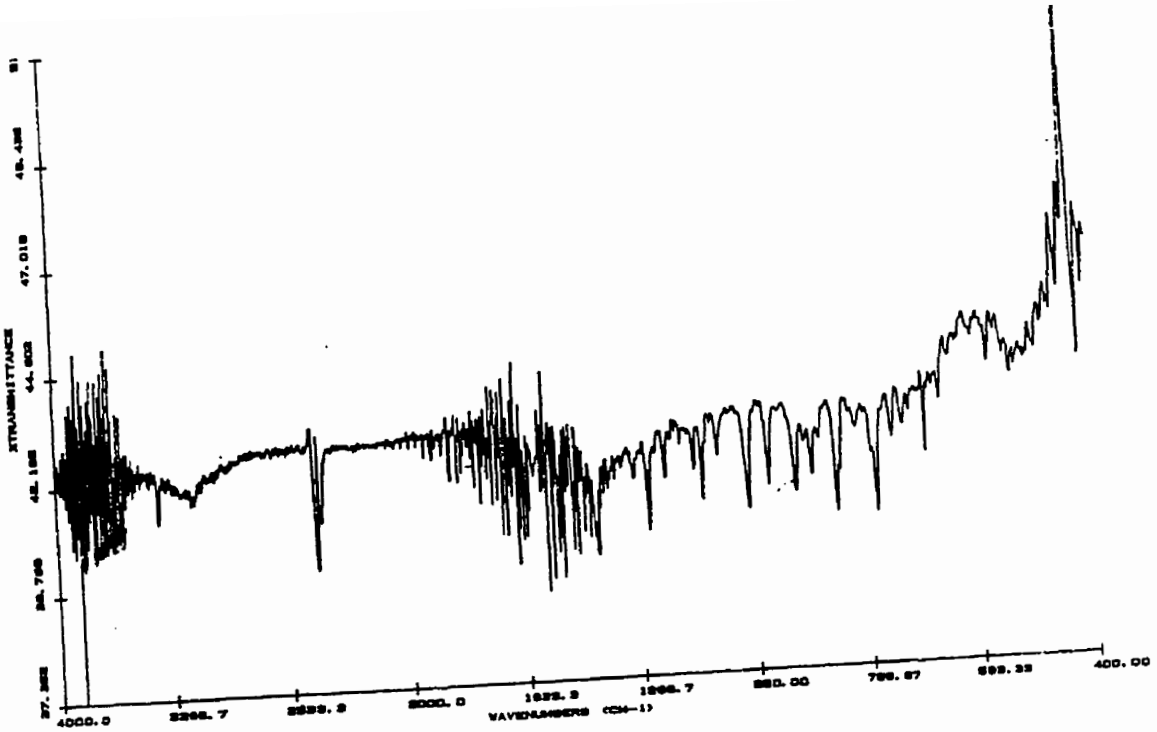






CO_2tBu **98**

$R=CHCH_2CH(CH_3)_2$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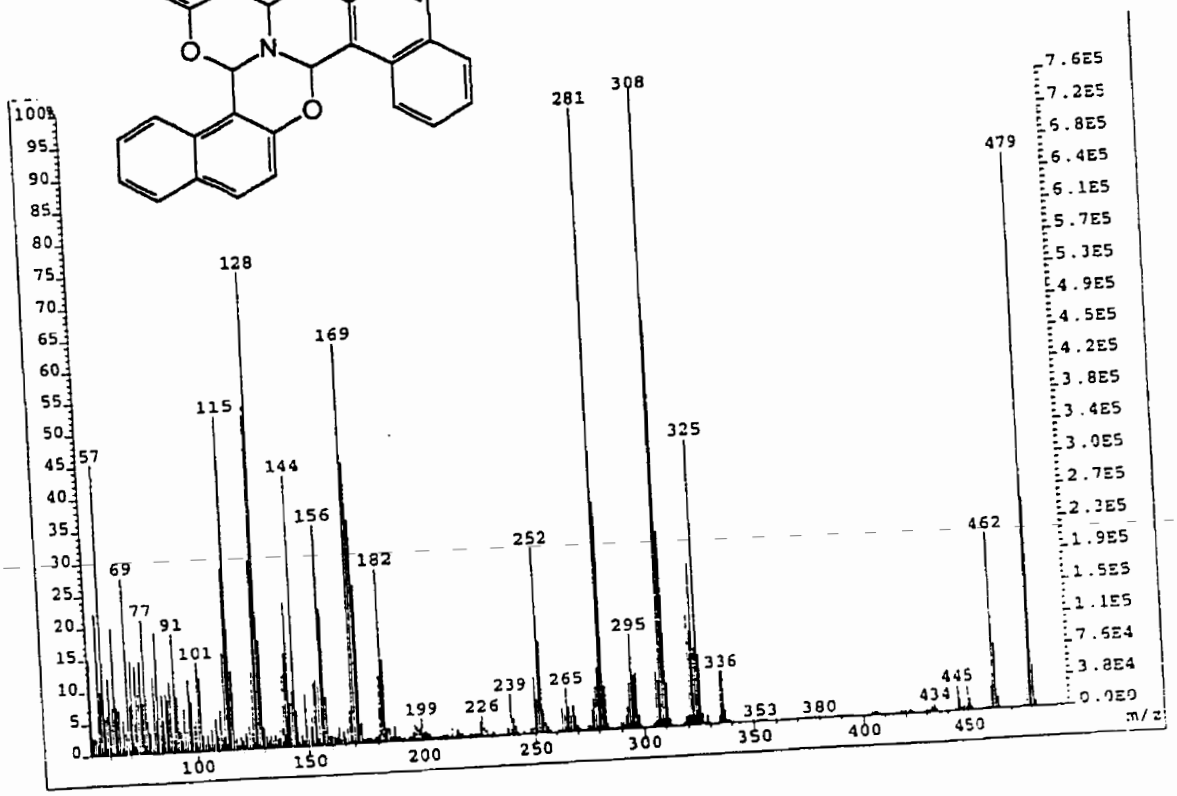
400.00
WAVENUMBERS (CM-1)

107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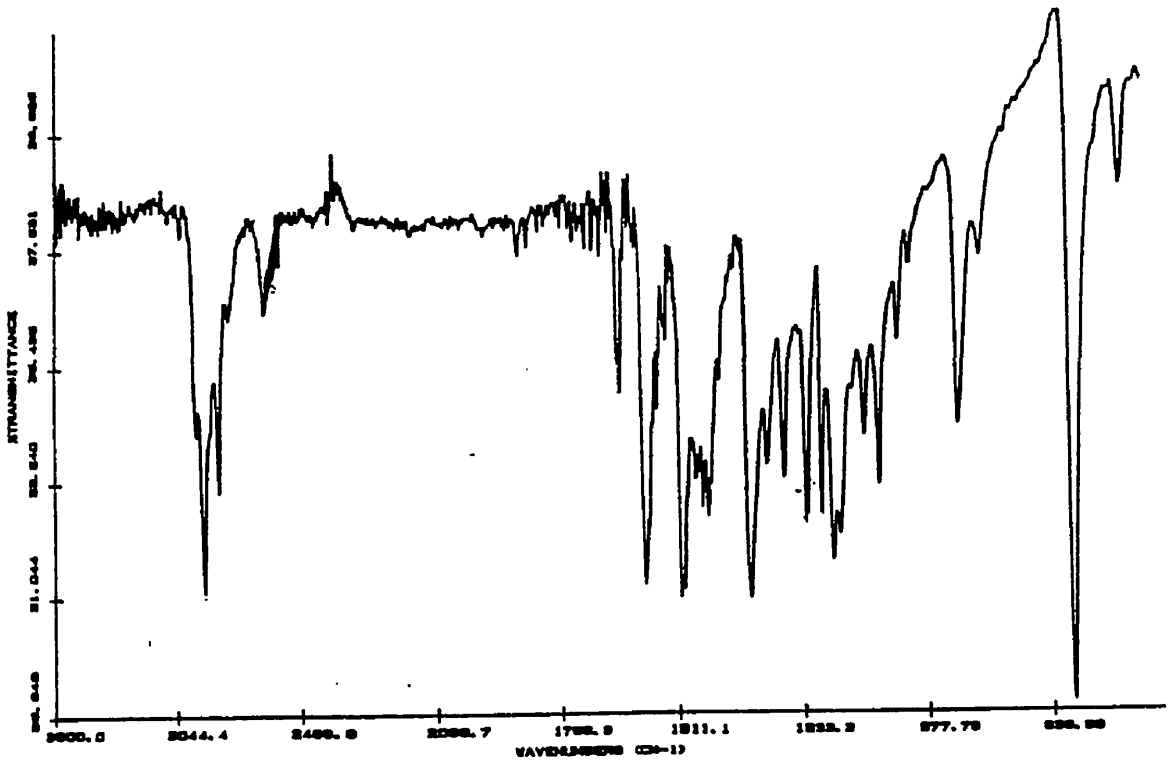
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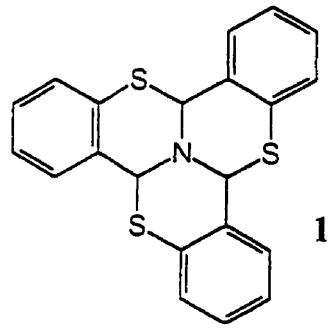
WAVENUMBERS (CM-1)


S
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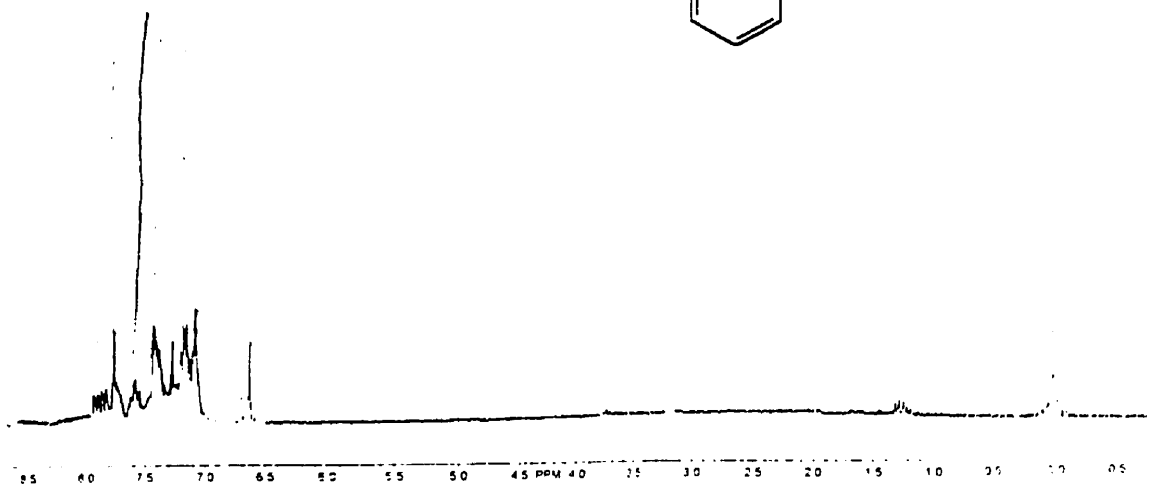
S
S

108


85
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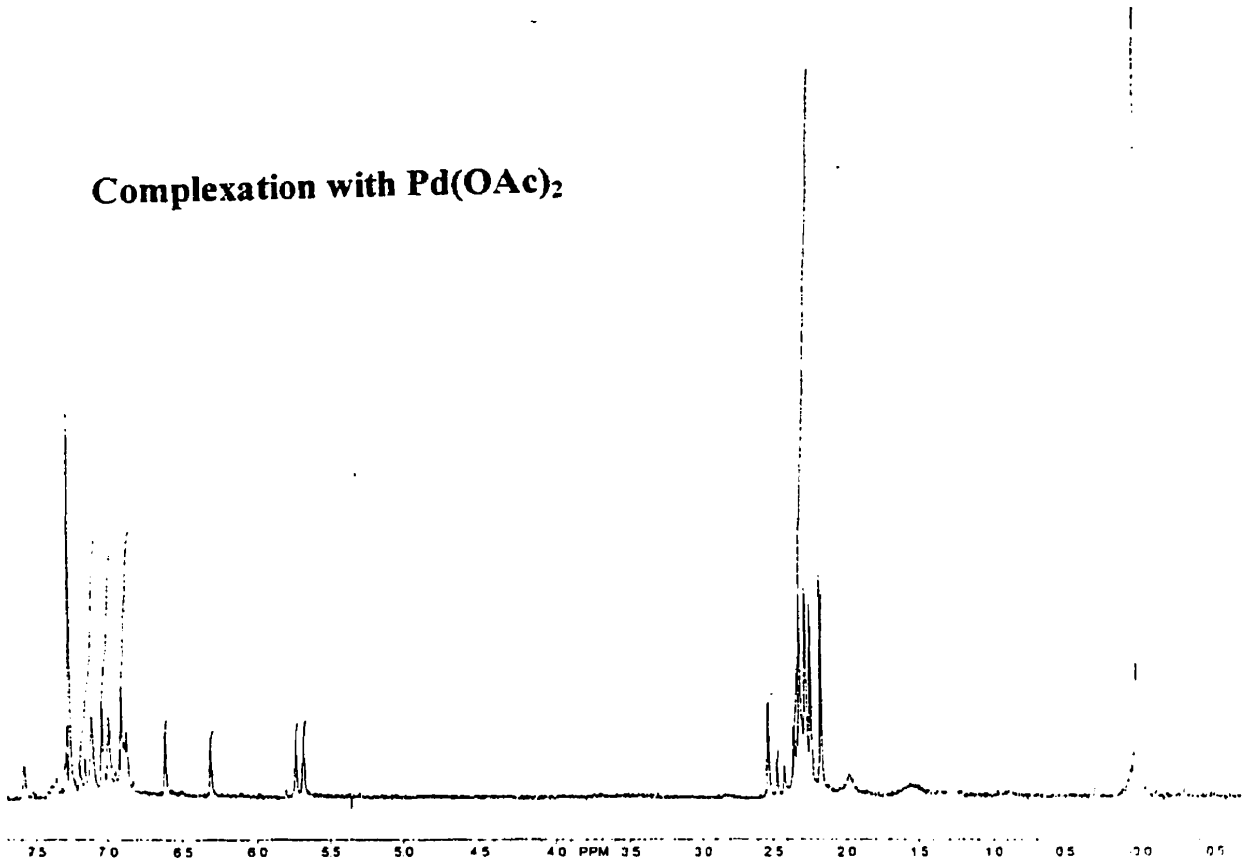
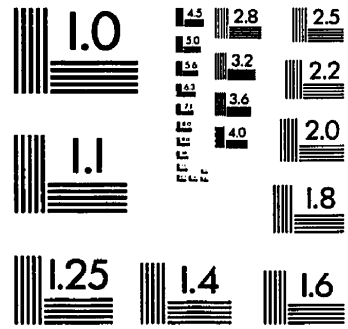
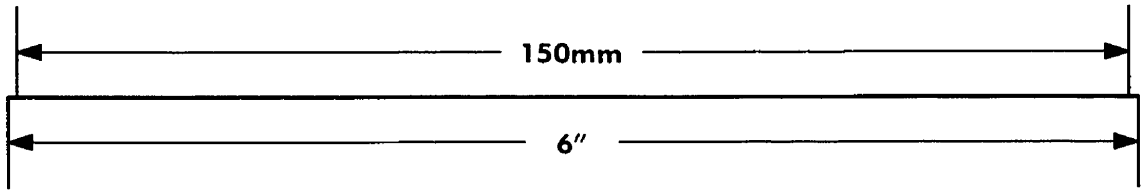
-05

Complexation with $Pd(OAc)_2$







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