STUDIES ON SOME BENZISOTHIAZOLE DERIVATIVES

by

Azza A. Abouzeid

A Thesis submitted to

The Faculty of Graduate Studies

of the University of Manitoba

in partial fulfilment of

the requirements of the degree of

Doctor of Philosophy

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Acknowledgement

I would like to express my deepest gratitude to my supervisor, Dr. David McKinnon for his patience, motivation and skillful guidance throughout the course of this work. I would also like to thank Mr. Kirk Marat and Mr. Terry Wolowiec for performing the pmr spectra and Mr. Wayne Buchannon for performing the mass spectra. I am very thankful to Mrs. Cheryll Armstrong for typing this thesis, her effort is greatly appreciated.

"Organic chemistry nowadays almost drives me mad. To me it appears like a primeval tropical forest full of the most remarkable things, a dreadful endless jungle into which one does not dare enter for there seems to be no way out."

-Friedrich Wohler, 1835.

ABSTRACT

This work describes the preparation and properties of some benzo[*d*,*d*′]*bis*-isothiazole and benzo[*c*,*d*′]*bis*-isothiazole derivatives which have not been previously synthesized.

Four examples of the five possible benzo[*d*,*d*′]*bis*-isothiazole system have been prepared namely the 3,7-dimethylbenzo[1,2-*d*:4,5-*d*′]*bis*-isothiazole (**167**), 3,5-dimethylbenzo[1,2-*d*:5,4-*d*′]*bis*-isothiazole (**174**), 3,6-dimethylbenzo[1,2-*d*:6,5-*d*′]*bis*-isothiazole (**191**) and 3,6-dimethylbenzo [1,2-*d*:3,4-*d*′]*bis*-isothiazole (**198**) systems. Several approaches toward the synthesis of the benzo[1,2-*d*:4,3-*d*′]*bis*-isothiazole (**141**) were attempted none of which were successful.

Two isomers of the benzo[*c*,*d*′]*bis*-isothiazole series have been synthesized namely the 3-methylbenzo[1,2-*c*:- 5,6-*d*′]*bis*-isothiazole (**232**) and 3-methylbenzo[1,2-*c*:- 6,5-*d*′]*bis*-isothiazole (**243**). Approaches towards the synthesis of the 3-methylbenzo[1,2-*c*:4,5-*d*′]*bis*-isothiazole (**249**) have been pursued and are discussed.

Electrophilic substitution on benzisothiazole derivatives in terms of charge distribution and resonance stabilization of the intermediates has been discussed.

Possible fused isothiazole and related systems where the sulfur atom might allow "bridging" have been investigated and the synthesis of 7-acetyl-3-methyl-1,2-benzisothiazole (**255**) was accomplished.

Potential approaches towards the synthesis of isothiazole analogues of ellipticine have been investigated. The 5-H-isothiazolo[4,3-*c*]carbazole (**153**) was synthesized. However attempts to prepare the [3,4-*c*](**152**), the [4,5-*d*](**154**) and the [5,4-*d*](**155**) 5-H-isothiazolocarbazole have not been successful.

FOREWORD

The following abbreviations are used throughout this text:

Alk	alkyl
Ar	aryl
B^-	base
DEM	diethyl malonate
EWG	electron withdrawing group
ERG	electron releasing group
Fe[II]ox	ferrous oxalate
ir	infrared
pmr	proton nuclear magnetic resonance
py	pyridine

THE REFERENCE SYSTEM

The reference system used throughout this thesis is based on that used previously in the series "Comprehensive Heterocyclic Chemistry" (A. R. Katritzky, C. W. Rees, Editors, Pergamon Press Ltd., Oxford, 1984).

Under this system, the references are designated by codes consisting of letters and digits. The first two characters of the code denote the last two digits of the year of publication of the reference. Following this is a one to three letter code denoting the name of the journal and finally a series of digits denoting the page of the reference.

The reader should note the following:

1. A list of journals (in alphabetical order) and the code assigned to each is given immediately following these notes.
2. All references cited in this thesis are listed on page 186 in full and are arranged in the following order:
   a) year
   b) journal in alphabetical order of journal code
   c) page number
3. For non-twentieth century references, the last three digits of the year are given.
4. Less common journals and books are given the code "MI" for miscellaneous.
5. Where journals have changed names, the same code is used throughout, e.g., CB refers to both Chem. Ber. and to Ber. Dtsch. Chem. Ges.

Journals	Codes
Ann.	A
Antimicrob. Ag. Chemother.	AAC
Ann. Chim., (Paris)	AC(P)
Ann. Chim., (Rome)	AC(R)
Acta. Chem. Scand.	ACS
Angew. Chem. Int. Ed. Engl.	AG(E)
Aust. J. Chem.	AJC
Acta Nat.	AN
Anales Real Soc. Espan. Fis. Quim.	ARE
Biophys. Chem.	BC
Bull. Chem. Soc. Jpn.	BCJ
Bull. Soc. Chim. Fr.	BSF
Chem. Ber.	CB
Chem. Commun.	CC
Chem. Ind.	CI
Can. J. Chem.	CJC
Chem. Pharm. Bull.	CPB
Farmaco, Ed. Sci.	FES
Gazz. Chim. Ital.	G
Ger. offen.	GO
Helv. Chim. Acta	HCA
Indian J. Chem.	IJC
Itsuu kenkyusho Nempo	IKN
J. Am. Pharm. Assoc.	JAA
J. Am. Chem. Soc.(C)	JAS
J. Chem. Phys.	JCP

J. Chem. Res. Synop.	JCR(S)
J. Chem. Res. Miniprint	JCR(M)
J. Chem. Soc.	JCS
J. Chem. Soc.(C)	JCS(C)
J. Chem. Soc. Perkin Tran., 1	JCS(P1)
J. Heterocycl. Chem.	JHC
J. Med. Chem.	JMC
J. Mol. Structure	JMS
J. Org. Chem.	JOC
J. Phys. Chem.	JPC
J. Prakt. Chem.	JPC
J. Mol. Spec.	JS
Khim. Khim. Tekhnol.	KKT
Proc. Chem. Soc.	PCS
Prog. Med. Chem.	PMC
Phosphorus Sulphur	PS
C.R. Acad. Sci. C	RAS(C)
Ric. Sci., Ser. B	RS(B)
Russ. Chem. Rev.	RCR
Synthesis	S
Tetrahedron	T
Tetrahedron Lett.	TL
Theor. Chim. Acta	TCA
Z. Chem.	ZC
Z. Naturforsch, Teil B	ZN(B)

Book Series

"Academic, New York"	A(NY)
"Advances in Heterocyclic Chemistry"	AHC
"Chemistry of Heterocyclic Compounds"	HC
"Comprehensive Heterocyclic Chemistry	CHC
"Harvey Lect. Ser."	HL
"Organic Reactions"	OR
"Organic Synth. Coll."	OS(C)
"Organic compounds of sulphur, selenium and tellurium	SST

Patent

German Patent	GP
U.S. Patent	USP

Thesis

Ph.D. Thesis, University of N. Carolina	PD(NC)

CONTENTS

1. INTRODUCTION

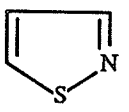
Among simple heterocycles containing both sulfur and nitrogen atoms, there are two main series. These are the 1,2-system, called isothiazole, and the 1,3-system, called thiazole. The isothiazole system (studies on derivatives of which will form the body of this thesis) is rather unusual in that it has a stable sulfur nitrogen bond. This feature is rather uncommon in the aliphatic series. While the monocyclic thiazole series has been recognized for over a century [887CB(20)3118], the monocyclic isothiazole ring has not been prepared until 1956, (see below). Isothiazole itself is reported to be water soluble and have a pyridine like odor [56CI1232].

Because of the limited number of suitable preparative methods for isothiazoles and their benzo-derivatives, little attention has been paid to compounds of industrial or pharmaceutical importance, at least in comparison to other simple heterocycles such as pyridines, thiophenes and thiazoles. However, more recently, some compounds have merited attention and a wide range of biological activity has been reported for isothiazoles. Thus some isothiazoles have been reported to have hypoglycemic, antiinflammatory and adrenergic β-blocker activity [75SST(3)541, 80JMC(23)65].

1,2-Benzisothiazole derivatives have been reported to possess antibacterial, diuretic, fungicidal, antiinflammatory, antithrombic [81PMC(18)117] and analgesic activity [83AN(19)35]. 2,1-Benzisothiazoles have also been reported to possess biological activity e.g.antifungal [76AN(12)123], antiinflammatory [78USP4122105], anticoagulant [85AHC(38)105], hypotensive and CNS-depressant activity [71USP3560512].

However, despite this recent work, the isothiazoles and their benzo derivatives still offer much scope for investigations on their synthesis and reactions. Some work on systems containing the isothiazole ring will form the body of the work in this thesis.

The isothiazole system (1), which contains three carbon atoms and adjacent sulfur and nitrogen atoms, is an aromatic system with 6π electrons. It may be regarded either as an isostere of pyridine, an aza analogue of thiophene, or a sulfur analogue of isoxazole with the sulfur atom contributing two electrons and the nitrogen and three carbons one electron each. There are two series of fused bicyclic compounds incorporating both an isothiazole and a benzene ring. These two ring systems are known as 1,2-benzisothiazole (2) and 2,1-benzisothiazole (3). Other names have also been used; thus 2 has been described as benzo[*d*]isothiazole and 3 as benzo[*c*]isothiazole.



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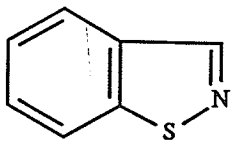

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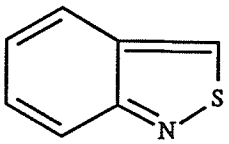


3

The isothiazole nucleus is also found in other forms e.g. as isothiazolium salts, isothiazolinethiones, isothiazolinones and their benzo derivatives.

As isothiazoles [65AHC(4)107, 72AHC(14)1, 79RCR(48)289], and their benzo derivatives [52HC(4)225, 72AHC(14)43, 85AHC(38) 105] have been extensively reviewed, this introduction is intended to cover the chemistry of isothiazoles and their benzo derivatives only briefly. Moreover, attention here has been focused on recent developments in the chemistry of benzisothiazoles.

1.1 Monocyclic Isothiazoles

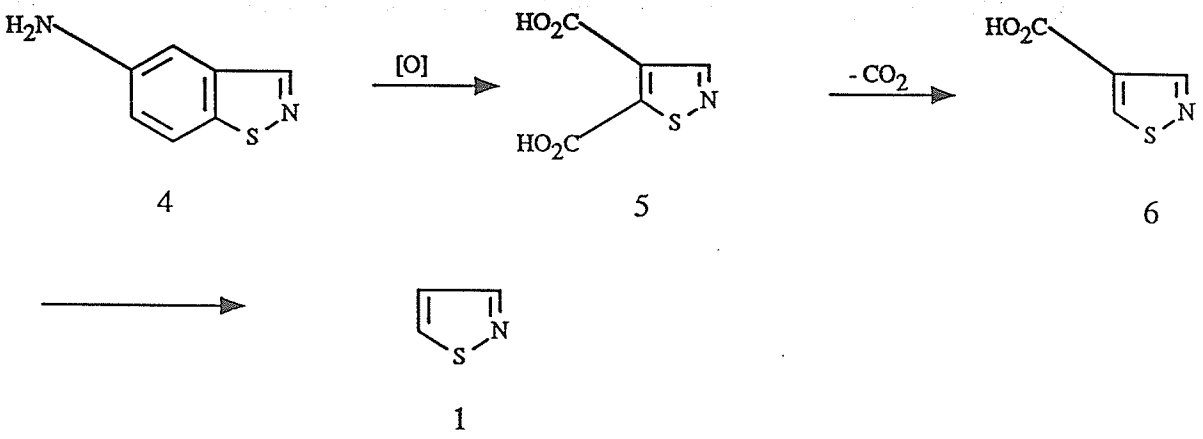
1.1.1 Synthesis

1.1.1.1 Synthesis from cyclic starting material

Isothiazole was first prepared by Adams and Slack [56CI 1232, 59JCS3061] by oxidation of 5-amino- 1,2-benzisothiazole (4) to isothiazole-4,5-dicarboxylic acid (5), which was decarboxylated to the isothiazole (1) (Scheme 1). This preparation is however of little practical value. Isothiazoles can also be formed from 1,2-dithiolium salts on treatment with ammonia (Scheme 2) [60PCS252, 65JCS32, 66T(22)2119, 67CC353, 66G(96)1000].

1.1.1.2 Synthesis from acyclic starting material

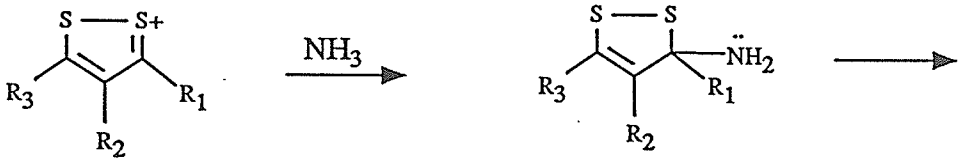
While the preparation of isoxazoles may be accomplished from β-diketones and equivalents by reaction with hydroxylamine, this approach is not applicable to isothiazoles as "thiohydroxylamine" does not exist. Fortunately an approach is available involving the oxidative formation of a sulfur-nitrogen bond and there are several synthesis of isothiazoles which depend on the oxidation of compounds that may be represented by "imino-enethiols" (10) (Scheme 3). Oxidation may be carried out by a variety of methods, e.g. peracids, high potential quinones, sulfur or halogens. Suitable intermediates may be obtained by reduction of isoxazoles and treatment of the resulting enaminoketones (12) with phosphorus pentasulfide to give the enaminothione derivatives which can be oxidized to the corresponding isothiazole (Scheme 4) [69T(25)389].



4 5 6

1

Scheme 1



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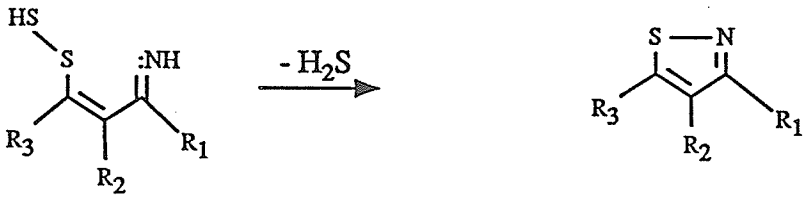

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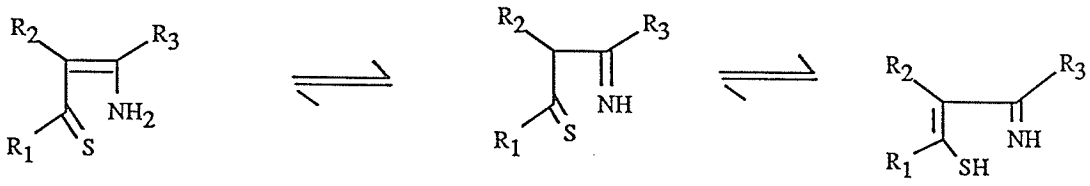
Scheme 2



Scheme 3

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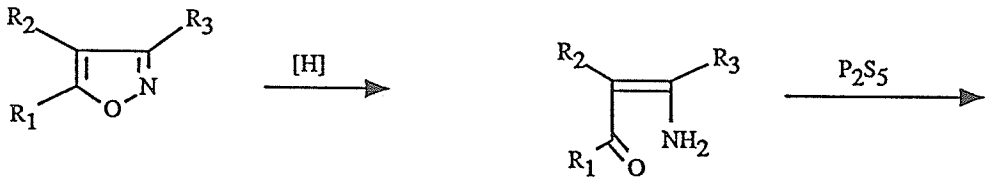

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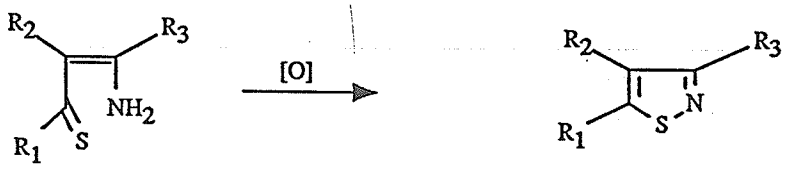


13

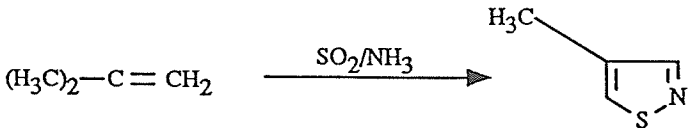
Scheme 4

In another approach, Hubenett and his colleagues observed that treatment of olefins with sulfur dioxide and ammonia in the presence of a catalyst at 200°C gave isothiazoles (Scheme 5) [62AG(E)(1)508, 63AG(E)(2)714] and in 1962 Wille and his collaborators [62AG(E)(1)335] devised a synthesis of isothiazole from acetylenes, sodium thiosulfate and liquid ammonia (Scheme 6). A number of important isothiazole syntheses depend on oxidative cyclization of substituted β-mercaptoacrylonitriles by chlorine (Scheme 7) [63JOC(28)2163].

1.1.2 Chemical Properties

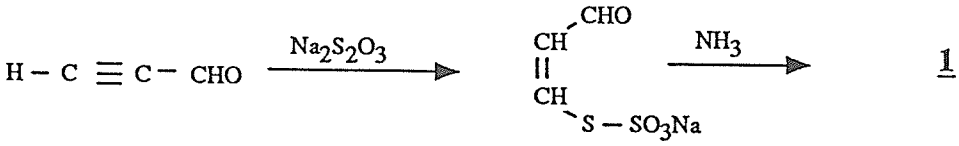
1.1.2.1 Electrophilic Substitution

Being aromatic systems, it would be expected that isothiazoles should undergo electrophilic substitutions, and in fact it is found that monocyclic isothiazoles undergo electrophilic substitution at the 4-position. This may be due to the low stability of the intermediate resonance structures for electrophilic attack in the 3- and 5-positions, i.e. they have an unfavourable  structure (Scheme 8). The theoretical methods also agree in placing most of the charge density on the C(4) atom of the heterocyclic ring and the least on the C(3) atom [65AHC(4)107, 74CJC(52)833, 79RCR(48)289]. Isothiazole and its 3- or 5-alkyl derivatives undergo nitration to give the 4-nitroisothiazole derivatives in high yield [63AG(E)(2)714]. Isothiazole can be brominated at the 4- position but low yields have been obtained [63JCS2032]. When the isothiazole ring contains an electron releasing group, the yield of bromination product is increased, e.g. high yields have been reported for isothiazoles with amino- [59JCS3061, 68CPB(16)148, 68JMC(11)159, 68JMC(11)70], alkoxy- [71JCS(C)1314] or hydroxy-[63CB(96)944] substituents in the 3- or 5-position. Isothiazoles are sulfonated readily with oleum [65JCS7283] or sulfur trioxide [66GP1 208 303] at the 4-position, but formylation and acylation under Friedel-Crafts conditions failed [63JCS2032].



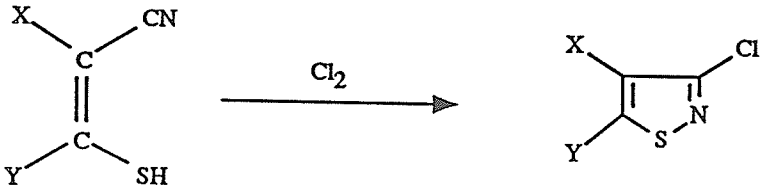
14 15

Scheme 5



16 17 1

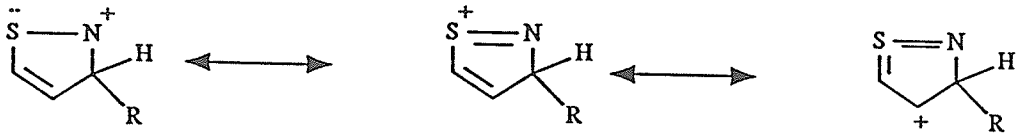
Scheme 6



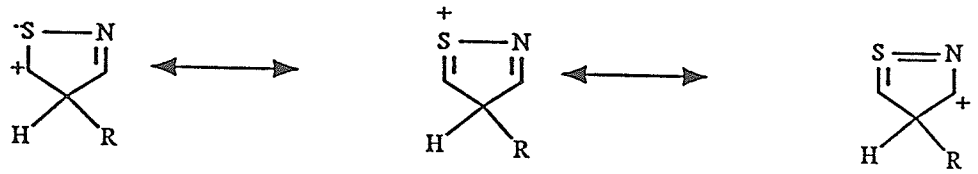
18 19

Scheme 7

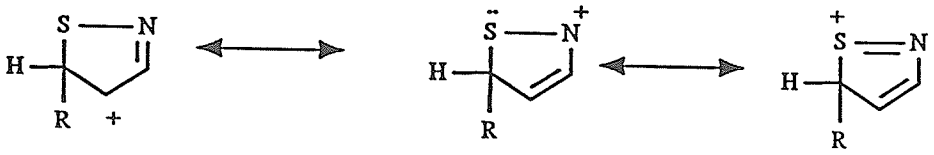
Intermediate resonance structures for electrophilic attack:



in the 3-position



in the 4-position



in the 5-position

Scheme 8

1.1.2.2 Nucleophilic substitution

(a) At the 3-position.

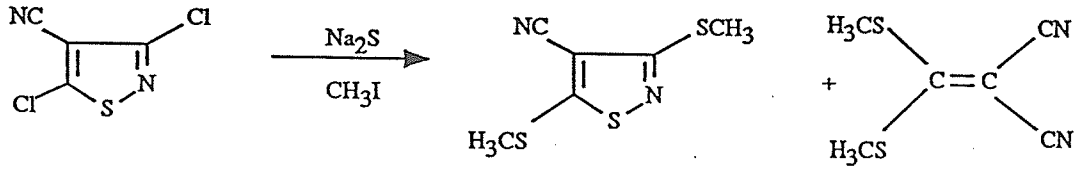
Like 2- or 4-halogenated pyridines, it would be expected that 3- or 5-halogenated isothiazoles should undergo nucleophilic substitution. Both positions are reactive but 3-halogenoisothiazole was found to be less reactive than the 5-halogeno derivative toward nucleophilic substitution. In addition nucleophilic replacement of the 3-halogen may be accompanied by ring cleavage (Scheme 9) [64JOC(29)660].

(b) At the 4-position.

Halogens in the 4-position have the greatest similarity in reactivity to aromatic halogens. Thus, a 4-haloatom resists nucleophilic attack with the exception of (i) the formation of nitriles with cuprous cyanide [68CPB(16)148, 63JCS2032, 68JMC(11)159, 68AAC(94)162] and, in another case, (ii) the formation of a lithium derivative [68CPB(16)148].

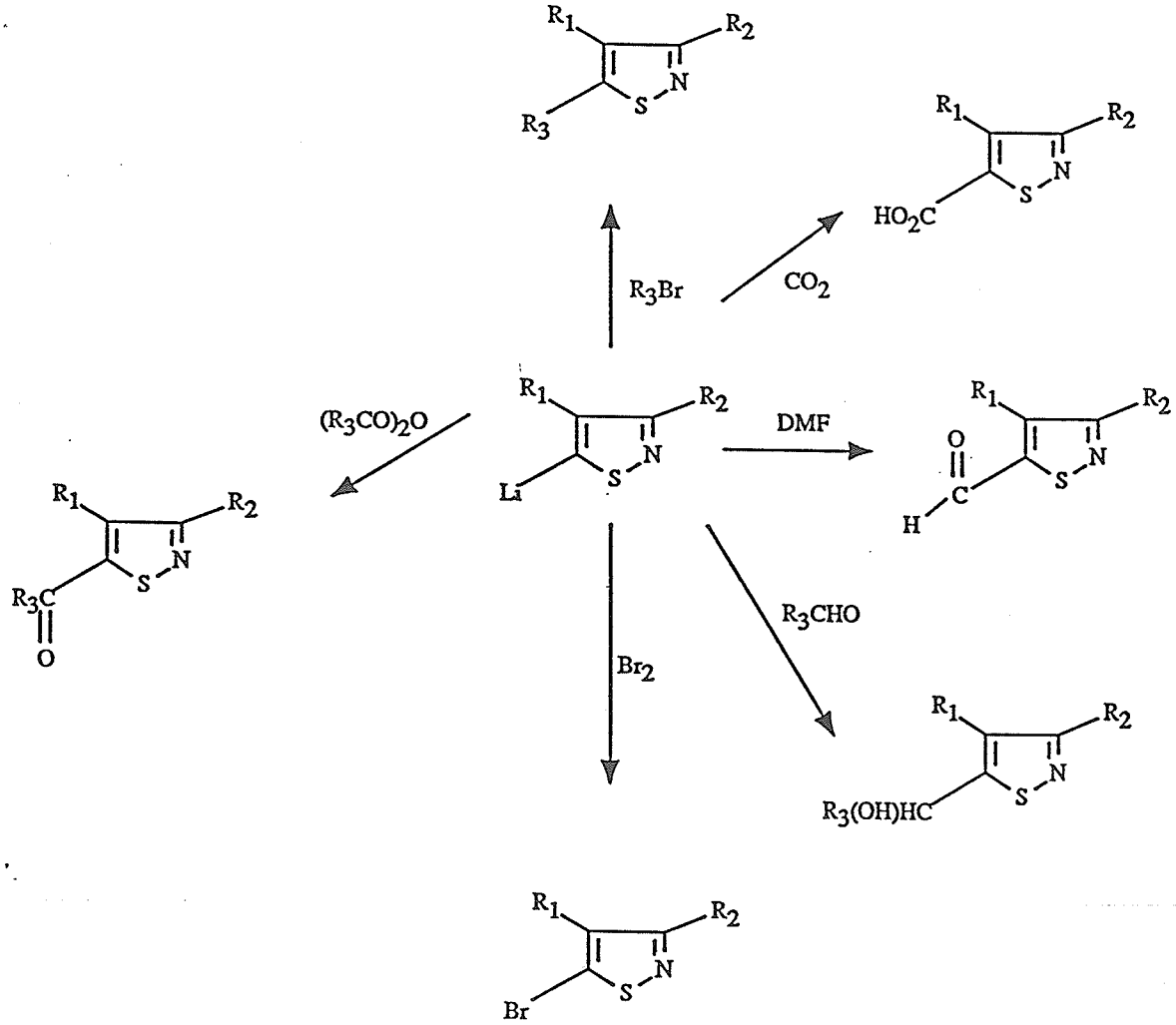
(c) At the 5-position.

5-Halogenoisothiazole readily undergoes nucleophilic displacement, particularly when activated by an electron withdrawing group in the 4-position, to give isothiazoles with substituents such as hydroxy-, alkoxy- [71JCS(C)1314], alkylthio-[68CPB(16)148, 64JOC(29)660, 68AAC(94)162], amino-[66PD(NC), 64JOC(29)660], cyano-[65JCS7277] and hydrazino- groups [71JCS(C)776]. Isothiazoles form lithium derivatives, which are of considerable preparative value, leading to a wide variety of substituents in the 5-position, usually in good yield (Scheme 10) [68CPB(16)148, 66HCA(49)2466, 69IJC(7)103, 64JCS446, 68JMC(11)159, 68AAC(94)162, 68JCS611, 68CJC(46)1057, 70CJC(48)2006].



20 21 22

Scheme 9



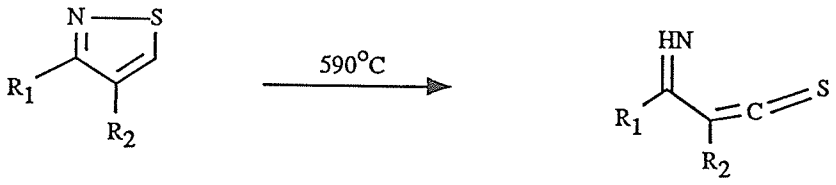
Scheme 10

1.1.2.3 Ring cleavage

Although the isothiazole nucleus is remarkably stable to chemical attack, there are instances in which cleavage occurs. Thus, thermolysis of isothiazoles causes ring fission forming thioketenes (24) (Scheme 11) [84CHC(6)131, 81SST(6)271].
3-Chloroisothiazoles with blocked 4- and 5-positions undergo attack on the ring sulfur by nucleophiles leading to ring-opened products (Scheme 12) [66PD(NC), 64JOC(29)660].

The rearrangement of isothiazoles to other heterocyclic systems has been well documented. Thus 3,5-dimercaptoisothiazoles on standing in the dark in ethanolic solution for several days [65ACS(19)549, 70ACS(24)228] or by acid treatment [66JPC(31)214] give high yields of amino-1,2-dithiole-3-thiones (Scheme 13).

Treatment of quaternary isothiazoles with hydrazine or phenyl hydrazine gives pyrazoles. This reaction involves nucleophilic attack, ring opening and recyclization (Scheme 14) [66T(22)2135]. Treatment of diazotized 4-aminoisothiazoles with thiourea gives 1,2,3-thiadiazoles (Scheme 15) [70JHC(7)415]. Rearrangements of isothiazoles to thiazoles have been well documented [80A(NY)(3)501]. Thus, treatment of 2-(E)styryl-5-phenylisothiazoline-3-thione (33) with trimethyloxonium tetrafluoroborate gave thiazole derivative (34) in 61% yield [88JOC(53)5374]. The mechanism proposed for this transformation is shown in Scheme 16.



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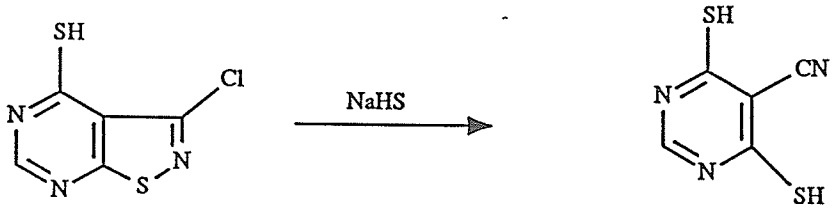
Scheme 11



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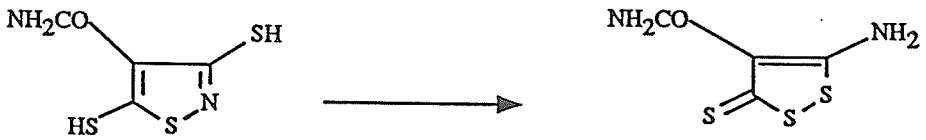
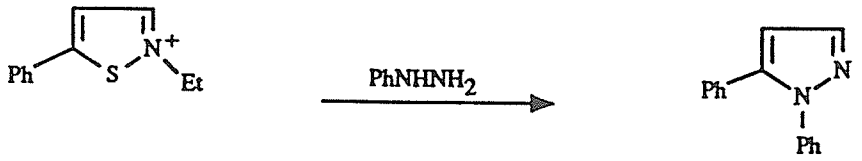
Scheme 12



27 28

Scheme 13



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Scheme 14

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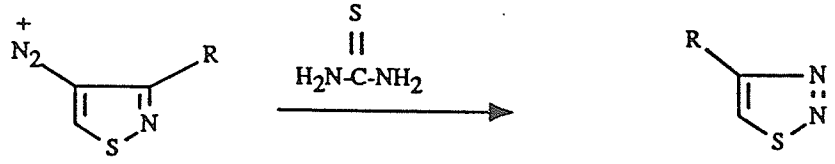


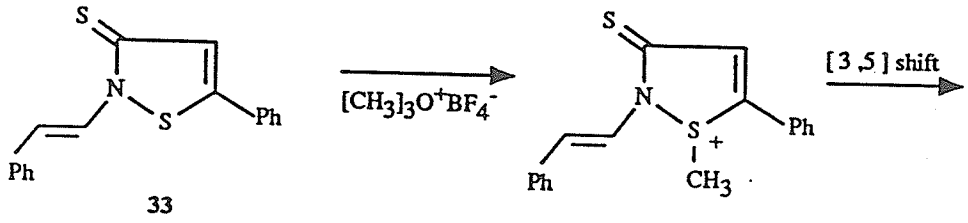
31

R = CH_3

32

R = $COCH_3$

Scheme 15



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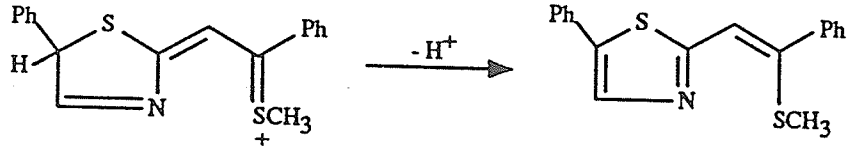

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Scheme 16

1.2 Monocyclic Isothiazolinones

1.2.1 Synthesis

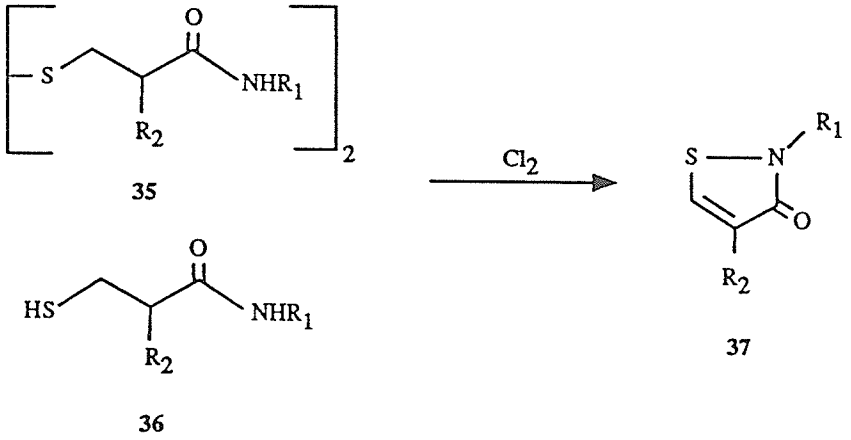
1.2.1.1 Synthesis of isothiazolin-3-ones

These forms are somewhat analogous to pyridones in structure and properties. Like isothiazoles, oxidative methods provide a useful synthesis. Thus N-substituted isothiazolin-3-ones can be prepared in high yields by cyclization of 3,3′-dithiopropionamides (**35**) or 3-mercaptopropionamides (**36**) with chlorine (Scheme 17) [71JHC(8)571, 71JHC(8)581].

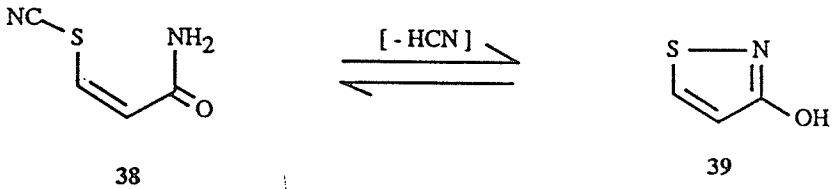
Crow and Leonard [64TL1477, 65JOC(30)2660] prepared isothiazolin-3-ol (a tautomer of isothiazoline-3-one) by reversible cyclization of *cis*-3-thiocyanoacrylamide (Scheme 18). Substitution on the amide nitrogen led to N-substituted isothiazolin-3-ones. Addition of sodium thiocyanate to N-substituted propiolamides gave a cyano intermediate which cyclised to yield isothiazolinones (Scheme 19) [64TL1477, 65JOC(30)2660]. When treated with base, certain penicillin sulfoxides were converted to isothiazolin-3-ones (Scheme 20) [84CHC(6)131].

1.2.1.2 Synthesis of isothiazolin-5-ones

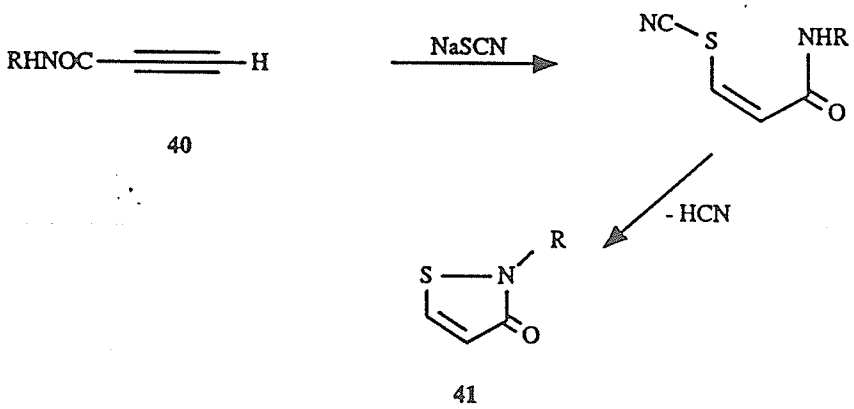
N-Substituted isothiazolin-5-ones can be prepared from dithiolium salts [77SST(4)339]. Thus cleavage of 3-ethoxy-1,2-dithiolium salts (**44**) by primary amines yields thioesters which on oxidation to isothiazolium salts (**46**), followed by dequaternization, give the N-substituted isothiazolin-5-ones (**47**) (Scheme 21).



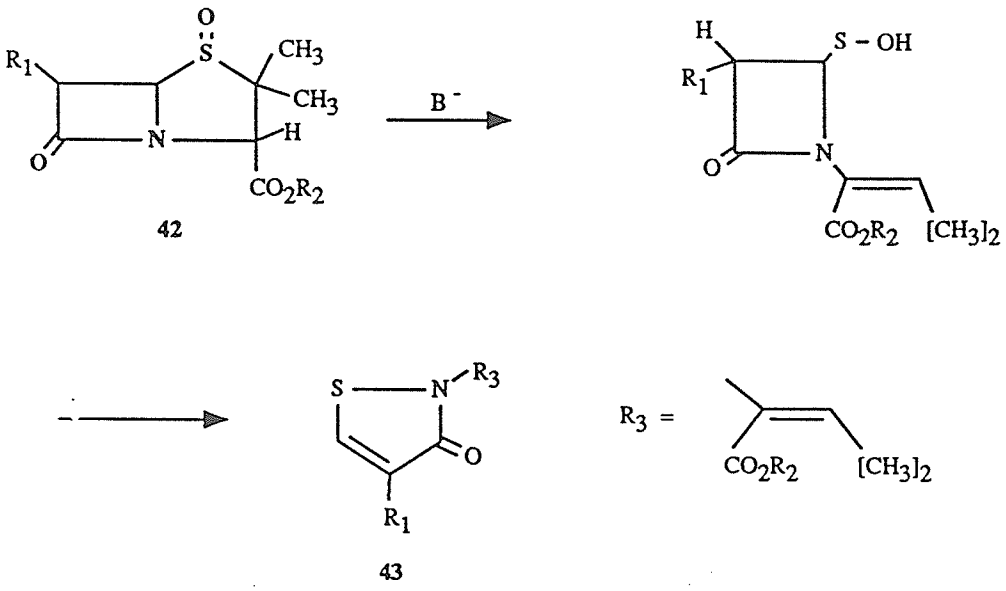
Scheme 17



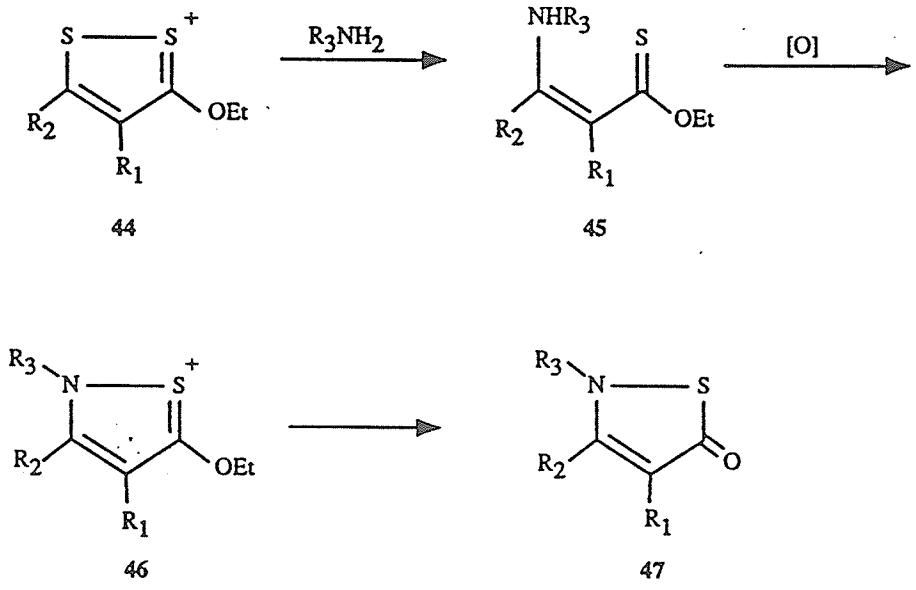
Scheme 18



Scheme 19



Scheme 20



Scheme 21

1.2.2 Chemical properties

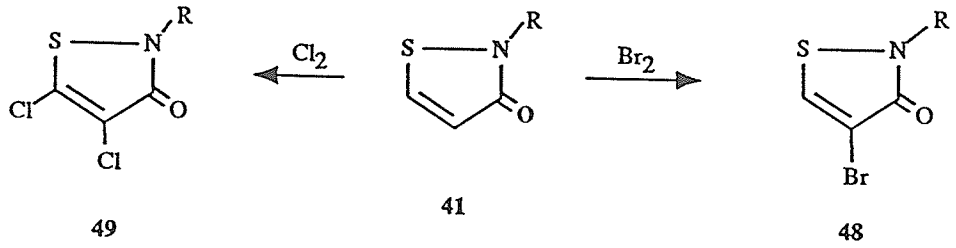
1.2.2.1 Electrophilic reactions

(a) Halogenation

N-Substituted isothiazolin-3-ones (**41**) are brominated at the 4-position while chlorination, even under mild conditions, gives primarily the 4,5-dichloro derivatives (**49**) (Scheme 22) [79SST(5)345, 84CHC(6)131]. N-Substituted isothiazolin-3-ones (**50**) react with oxalyl chloride to give 3-chloroisothiazolium chlorides [68ZC(8)170] which are useful synthetic intermediates (Scheme 23).

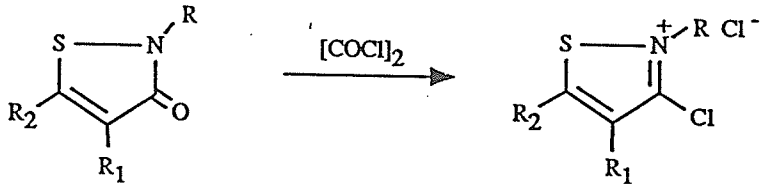
(b) Alkylation

N-Unsubstituted isothiazolinones are potentially tautomeric with hydroxy isothiazoles and could either react on nitrogen or on oxygen. The ultraviolet (uv) spectra of isothiazolin-3-ones in different solvents suggest that the compounds exist predominantly in the enol form in non-polar solvents, with increasing contributions from the keto form in solvents with high polarity, while isothiazolin-5-ones exist predominantly in the keto form in the solid state and in solution. [70T(26)2497, 71JCS(C)1314]. Isothiazolin-3-ones usually alkylate at the nitrogen while the isothiazolin-5-ones alkylate predominantly at the oxygen position [77AJC(30)1815, 71JCS(C)1314]. The ratio of products of O- and N-acylation and alkylation depends on the relative rates of reaction of the two tautomers rather than on their relative proportions [70T(26)2497].



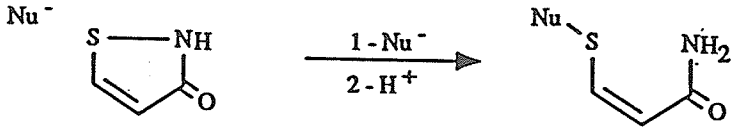
49 41 48

Scheme 22



50

Scheme 23



Scheme 24

1.2.2.2 Ring cleavage

(a) Ring cleavage by nucleophilic attack

An interesting feature of the reactivity of various isothiazoles is their succeptibility towards nucleophilic attack on the ring sulfur atom. Thus cleavage of the sulfur-nitrogen bond in isothiazolin-3-ones has been achieved by a variety of nucleophiles e.g. cyanide ion [65JOC(30)2660, 66AJC(19)1693, 67AJC(20)2729], resonance stabilized carbanions [69AJC(22)765, 70T(26)1463], benzenethiolate and t-butylthiolate anions [65JOC(30)2660]. The reaction involving nucleophilic attack on ring sulfur, is outlined in Scheme 24.

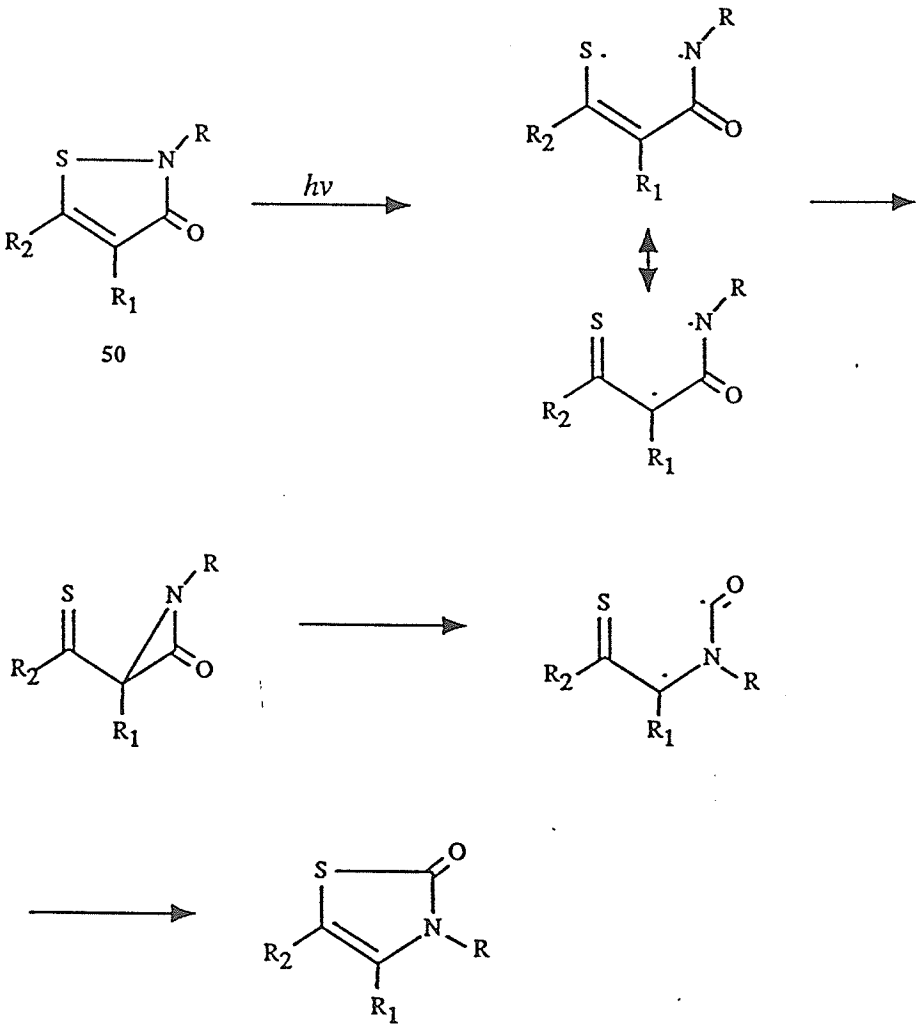
(b) Ring cleavage by photolysis

Photolysis of 2-substituted isothiazolin-3-ones affords 3-substituted thiazolin-2-ones (51). The mechanism proposed for the reaction is shown in Scheme 25. Again, the initial reaction is by cleavage of the sulfur-nitrogen bond [79CC786].

1.3 Monocyclic Isothiazolinethiones

1.3.1 Synthesis

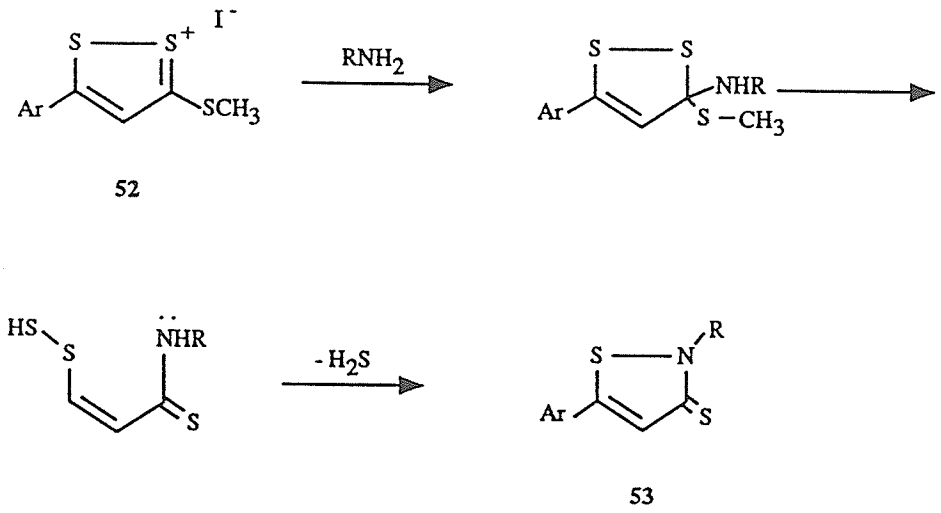
N-Alkyl-5-arylisothiazoline-3-thiones (53) can be prepared by reaction of 5-aryl-3-methylthio-1,2-dithiolium iodides (52) with aliphatic amines (Scheme 26) [70BSF3076], while reaction of primary aromatic amines with 3-bromothiodithiolium bromides (54), where the 5-position is not sterically hindered (e.g. $R^2 = H$), affords N-arylisothiazoline-5-thiones (55) (Scheme 27) [72CJC(50)2568, 74CJC(52)1738].



50

51

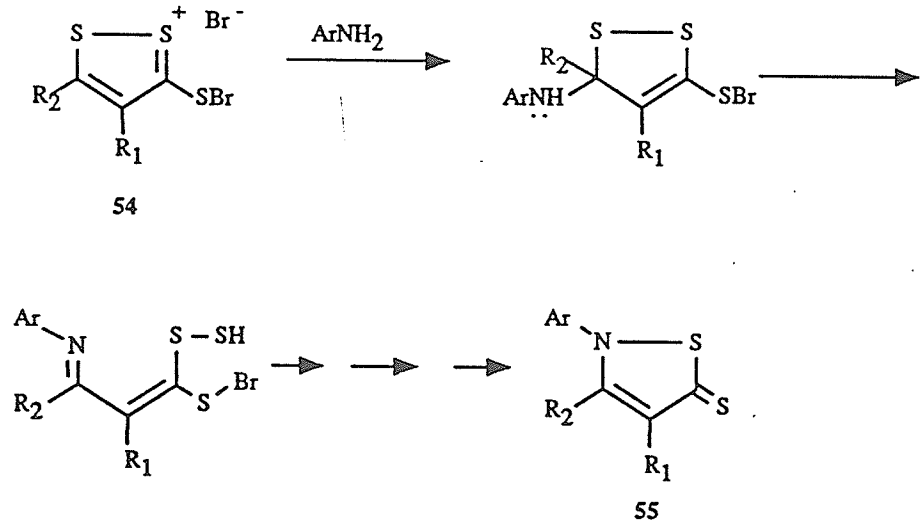
Scheme 25



52

53

Scheme 26



54

55

Scheme 27

1.3.2 Chemical properties

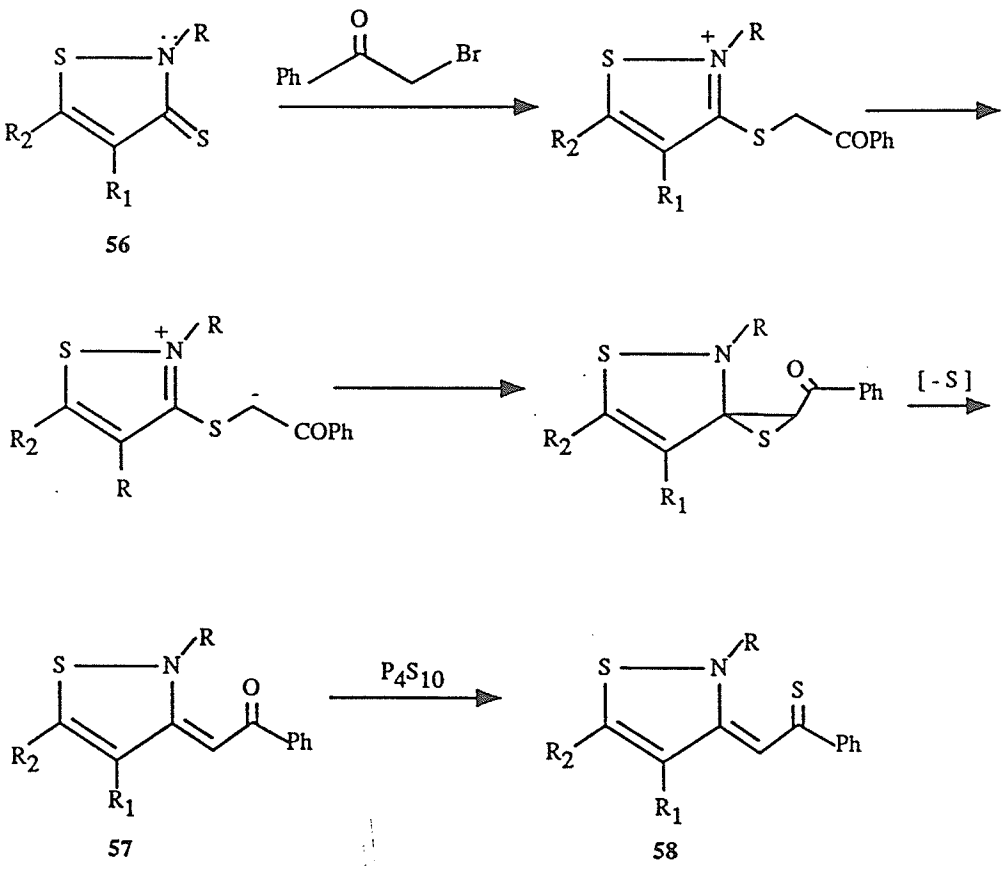
1.3.2.1 Electrophilic substitution

Like 1,2-dithiole-3-thiones and related heterocycles [66AHC(7)39], N-substituted isothiazoline-3- and 5-thiones are methylated on sulfur and yield the fully aromatic methylthioisothiazolium salts [66JPC(31)312, 68CJC(46)1855]. A modification of this method was used for the preparation of some thioacylmethylene isothiazoles. Thus reaction of isothiazoline-3-thiones (**56**) with phenacyl bromide in base affords the ketone **57** through alkylation on the exocyclic sulfur atom followed by sulfur extrusion. Thionation of the resulting ketone affords 3-thiophenacylideneisothiazoles (Scheme 28) [79CJC(57)207].

1.3.2.2 Miscellaneous reactions

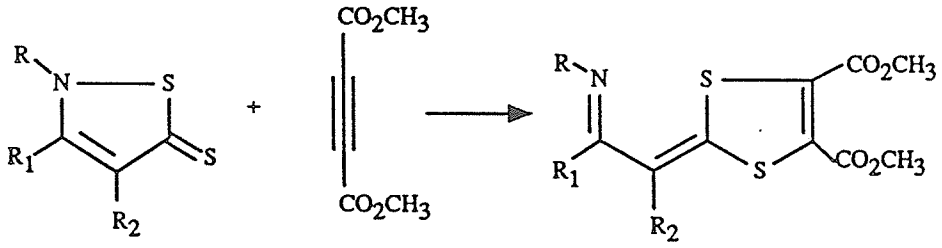
Isothiazoline-5-thiones (**59**) react with acetylenic reagents to give 1,3-dithioles (Scheme 29) [84CHC(6)131, 77SST(4)339], while isothiazoline-3-thiones produce diadducts [74CJC(52)1738].

N-alkyl and N-arylisothiazoline-3-and 5-thiones react with hydrogen peroxide in acetic acid to give the corresponding isothiazolium salts (Scheme 30) [74CJC(52)3021]. This reaction is similar to that observed for 1,2-dithiole-3-thiones and related compounds [66AHC(7)39, 80AHC(27)151].



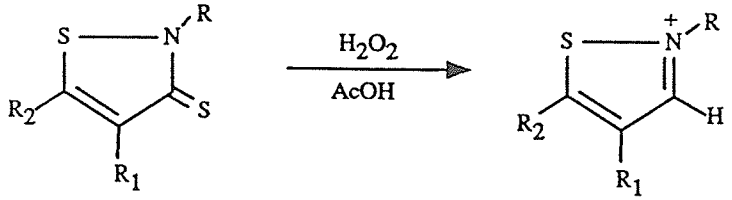
56 57 58

Scheme 28

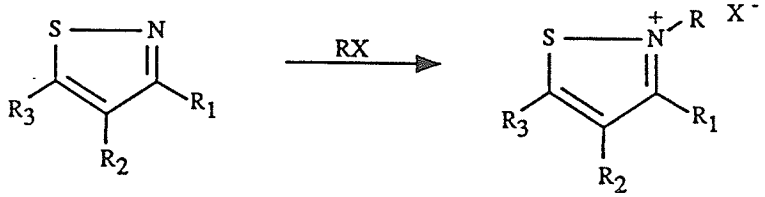


59 60 61

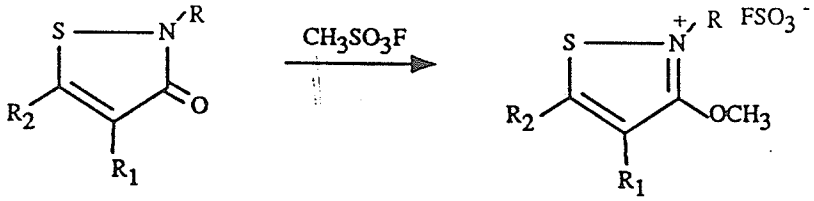
Scheme 29



Scheme 30

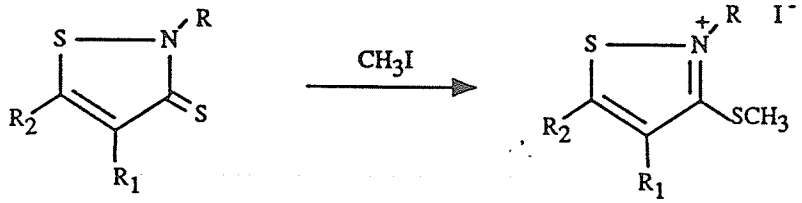


Scheme 31



50 62

Scheme 32



56 63

Scheme 33

1.4 Monocyclic Isothiazolium Salts

1.4.1 Synthesis

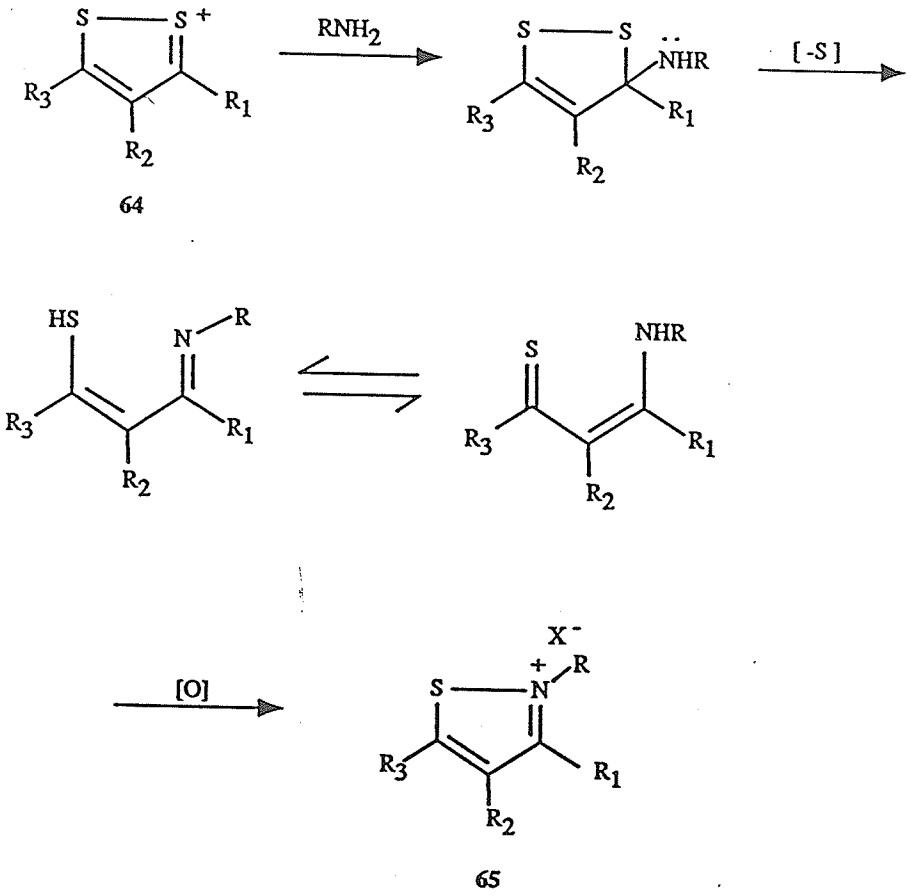
1.4.1.1 Using alkylating agents

The lone pair of electrons on the isothiazole nitrogen is not involved in the aromaticity of the ring and is then available for donation to suitable electrophiles. Thus isothiazoles can be alkylated by agents such as alkyl halides, alkaline dimethyl sulfate, methyl and benzyl halides (Scheme 31) [72AHC(14)1, 84CHC(6)131].

3-Methoxy- and 3-methylthioisothiazolium salts are synthesised by alkylation of the corresponding N-substituted isothiazolin-3-ones (**50**) and isothiazoline-3-thiones (**56**) (Scheme 32 and 33) [72AHC(14)1, 84CHC(6)131].

1.4.1.2 From other heterocycles

The reaction of 1,2-dithiolium salts (**64**) with primary amines affords the aminopropenethiones which are readily oxidised to N-substituted isothiazolium salts (**65**) by hydrogen peroxide or iodine (Scheme 34) [72AHC(14)1, 84CHC(6)131]. These salts are also available from isothiazoline-3- and 5-thiones (Scheme 30), and N-substituted isothiazolin-3-ones (**50**) react with phosgene or oxalyl chloride to yield the corresponding 3-chloroisothiazolium chlorides (Scheme 23) [68ZC(8)170].


S
S +
R3
R1
R2
RNH2
S
S
NHR
R3
R1
R2
[-S]
64
HS
N
R
R3
R1
R2
S
NHR
R3
R1
R2
[O]
X -
+
R
S
N
R3
R1
R2
65

Scheme 34

1.4.2 Chemical properties

1.4.2.1 Deprotonation

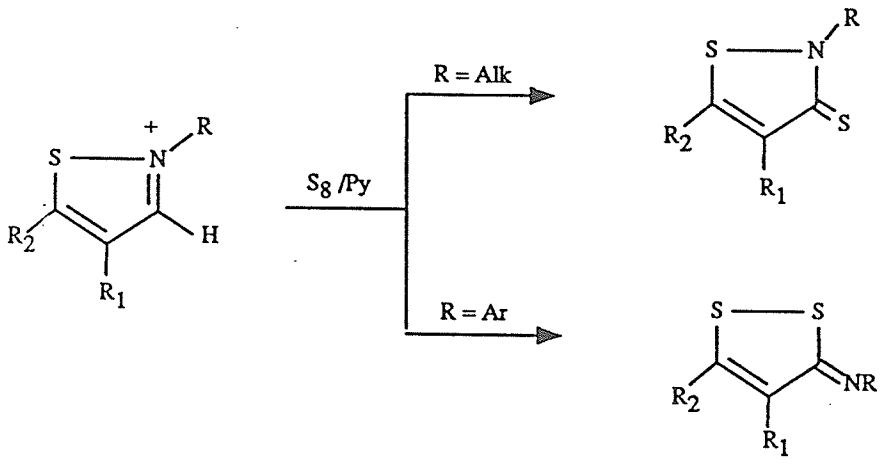
On treatment with elemental sulfur in boiling pyridine, isothiazolium salts form isothiazoline-3-or 5-thiones. Initial deprotonation at C(3) or C(5) has been suggested in the mechanism.

N-Substituted isothiazolium salts which are unsubstituted at the 3-position give isothiazoline-3-thiones when R is an alkyl group, and 3-arylimino-1,2-dithioles when R is an aryl group (Scheme 35) [72CJC(50)2568]. The reaction mechanism suggested is initial deprotonation at C-3, to form a carbene. This then undergoes ring opening to a thioketoketimine which may further react to form either systems. Isothiazolium salts which are unsubstituted at the 5-positions give the corresponding 5-thiones [72CJC(50)2568]. When both carbons 3 and 5 are unsubstituted, N-phenylisothiazolium salts give the 5-thiones, possibly due to greater stabilization of the carbanion formed at 5-position by the sulfur atom [72CJC(50)2568].

1.4.2.2 Nucleophilic reactions

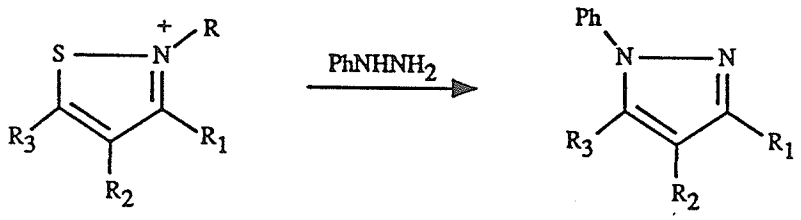
(a) Nucleophilic attack on C-3 or C-5

When treated with phenylhydrazine isothiazolium salts yield pyrazoles (67) (Scheme 36) 66T(22)2135 via nucleophilic attack, ring opening and recyclization.



66

Scheme 35

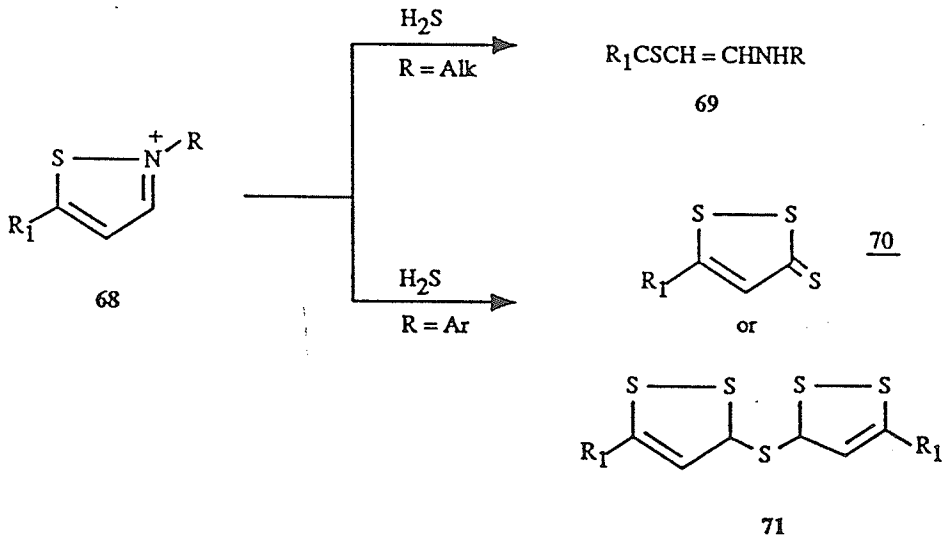


67

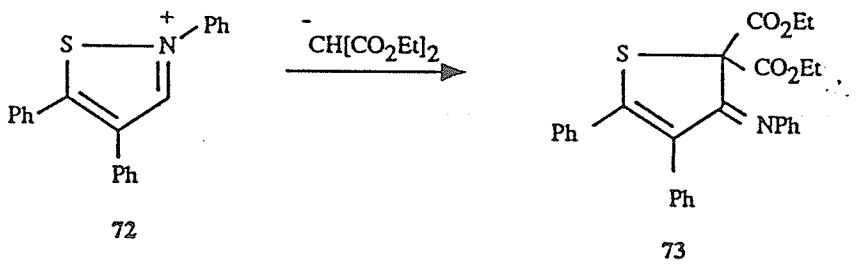
Scheme 36

(b) Nucleophilic attack on the sulfur

2-Alkylisothiazolium salts (68) undergo ring cleavage when treated with hydrogen sulfide or thiophenol to form acyclic products (69), but 2-aryl compounds give 1,2-dithioles (70,71) (Scheme 37) [75SST(3)541, 77SST(4)339]. Isothiazolium salts react with many stabilized carbanions by i) initial attack on sulfur, ii) ring opening and iii) recyclization to thiophenes. Thus diethyl malonate reacts with the 2,4,5-triphenyl isothiazolium ion to produce the thiophene 73 (Scheme 38) [77CJC(55)1123, 82CJC(60)440].



Scheme 37



Scheme 38

1.5 1,2-Benzisothiazoles

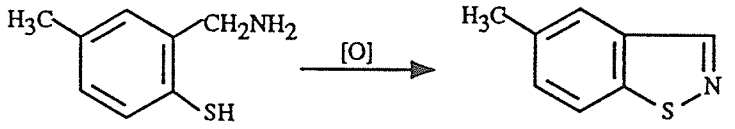
1.5.1 Synthesis

1.5.1.1 Synthesis from acyclic starting materials

Oxidation of the aminothiol 74 with iodine, bromine, or alkaline ferricyanide affords an excellent yield of 5-methyl-1,2-benzisothiazole (Scheme 39) [59CB(92)1679, 66RAS(C)(262)596].

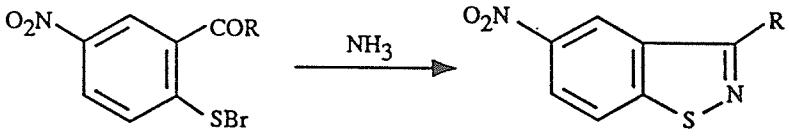
Aldehydes and ketones with *o*-halosulfenyl groups react with ammonia to form 1,2-benzisothiazoles (Scheme 40) [23CB(56)1630, 27A(454)264].

One of the most convenient methods for the synthesis of 1,2-benzisothiazoles is the cyclization of *o*-mercaptothiobenzaldoximes or ketoximes. Ricci and Martani [63AC(R)(53)577, 62RS(B)117] found that *o*-mercaptobenzaldoximes and ketoximes could be cyclized by treatment with hot polyphosphoric acid (PPA). Thioethers underwent a similar reaction on treatment with polyphosphoric acid [73JCS(P1)356], *p*-toluenesulfonyl chloride [66JOC(31)1655] or thiocarbamoyl chloride [82PS(12)357], the extra alkyl group on the sulfur being eliminated during the reaction (Scheme 41). This reaction has developed into a general synthetic method for 1,2-benzisothiazoles. Chloramine has been found to be a valuable alternative to hydroxylamine in these reactions [83JCS(P1)2973]. Another variation in the preparation of 1,2-benzisothiazoles through ketoximes has recently been developed by McKinnon and Lee who converted the oximes of 2-acylthioanisole derivatives into the 1,2-benzisothiazoles using acetic anhydride in pyridine. This method is more convenient for synthesis and separation of the products [88CJC(66)1405].



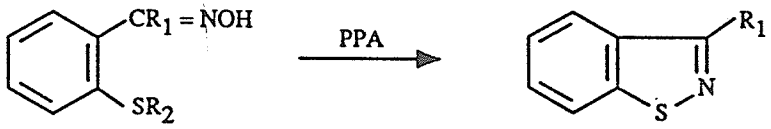
74 75

Scheme 39



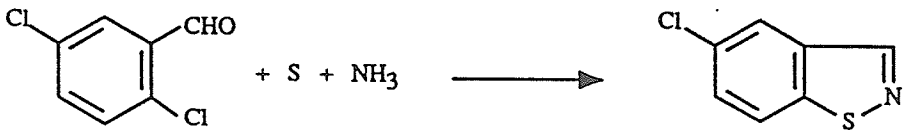
76

Scheme 40



77

Scheme 41



78

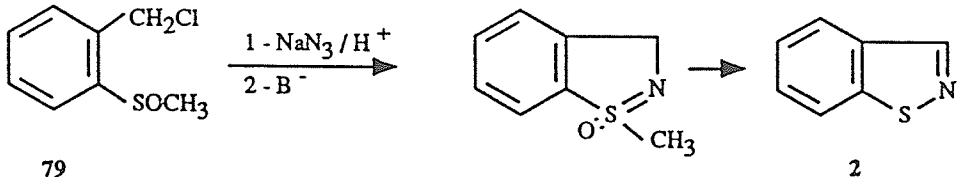
Scheme 42

1,2-Benzisothiazoles can be prepared from *o*-chlorobenzylidene dichloride [69A(729)146], *o*-chlorobenzonitriles [77,GO2 609 864], *o*-chlorobenzaldehydes [76 GO2 503 699], and *o*-chlorophenacyl compounds [80A768] on treatment with sulfur and ammonia. An example is shown in Scheme 42.

Rynbrandt and Balgoyen obtained 1,2-benzisothiazole from the benzyl chloride **79**, sodium azide and sulfuric acid on neutralizing the product and heating it at 155°C (Scheme 43) [78JOC(43)1824]. This unusual reaction involves a hypervalent sulfur intermediate.

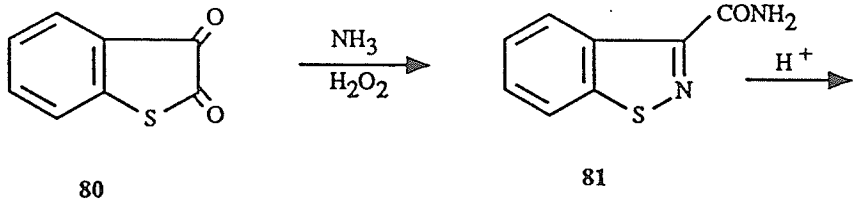
1.5.1.2 Synthesis from heterocyclic starting materials

1,2-Benzisothiazoles have also been synthesised from different heterocyclic systems involving some deep seated rearrangements. Thus, the parent compound **2** was first prepared by the treatment of thioisatin (**80**) with aqueous ammonia and hydrogen peroxide. The product **81** was hydrolysed to the acid which on subsequent decarboxylation gave the 1,2-benzisothiazole (Scheme 44) [52HC(4)225]. Treatment of thiochromanone (**82**) with *o*-mesitylenesulfonylhydroxylamine and base afforded the 1,2-benzisothiazole derivative (Scheme 45) [80TL(21)533]. Reaction of 3-acetamido-2-nitrobenzothiophene (**84**) with ferrous oxalate afforded the 1,2-benzisothiazole derivatives, **85** and **86** as the major products (Scheme 46). The mechanism of this unusual reaction is uncertain [67JCS(C)2364]. Treatment of 1,2-benzisothiazolinone (**87**) with phosphorus pentachloride [28CB(61)1680], phosphoryl chloride [69FES(24)440], phosgene, or oxalyl chloride [65ZN(B)(20)712, 68ZC(8)170] affords 3-chloro-1,2-benzisothiazole (**88**) (Scheme 47). This product is a valuable source of other 1,2-benzisothiazoles, as the chlorine atom is readily replaced by nucleophiles and thus a variety of 3-substituted 1,2-benzisothiazoles can be obtained [69FES(24)440].

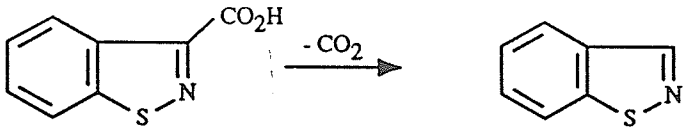


79 2

Scheme 43

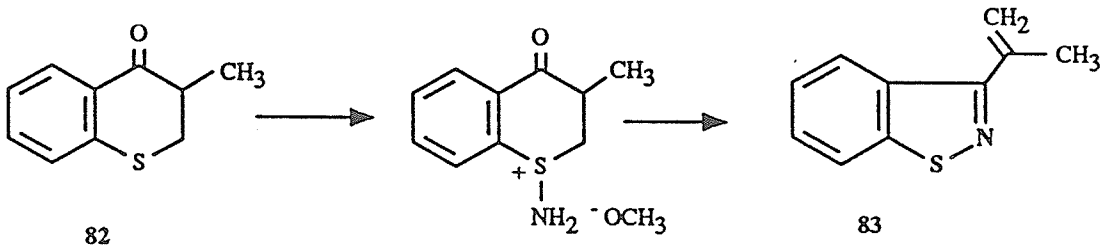


80 81



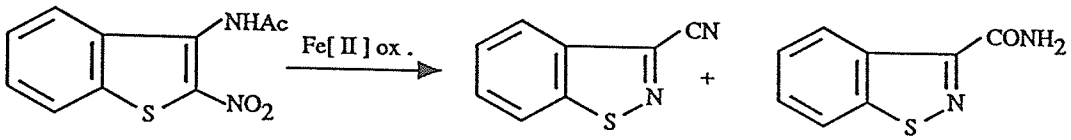
2

Scheme 44



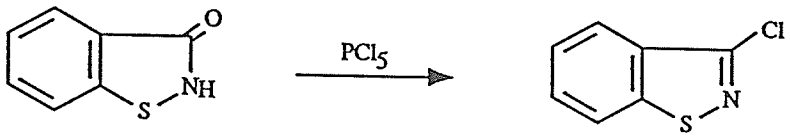
82 83

Scheme 45



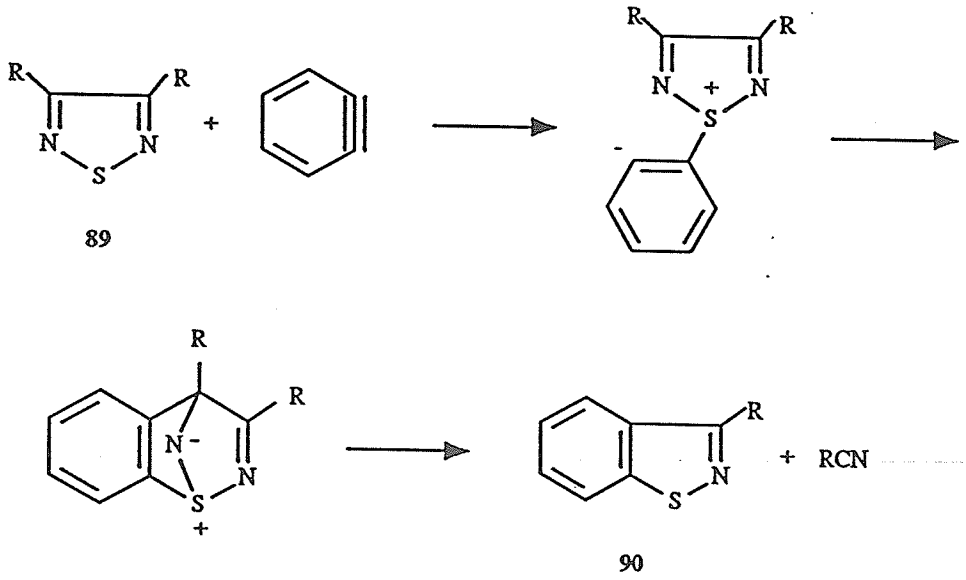
84 85 86

Scheme 46



87 88

Scheme 47



89 90

Scheme 48

In an approach to the benzisothiazole system via a cycloaddition reaction, it has been found that benzyne adds to the 1,2,5-thiadiazole **89** yielding the 1,2-benzisothiazole **90** [82CC299]. Recently Vernon and his colleagues have made an extensive study of the reaction of benzyne with a series of 1,2,5-thiadiazoles [88JCS(P1)2141]. The mechanism suggested to account for the formation of the 1,2-benzisothiazoles is shown in Scheme 48.

1.5.2 Chemical properties

1.5.2.1 Electrophilic substitution

(a) Electrophilic substitution on 1,2-benzisothiazole

As would be expected, the isothiazole ring is less reactive to electrophilic attack than the benzenoid ring since isothiazoles were found to nitrate in the 4-position ~ 10^4 times slower than benzene. Thus, 1,2-benzisothiazole undergoes nitration at its 5- and 7-positions [72AHC(14)43]. Bromination reactions proceed similarly. 4-Chloro-1,2-benzisothiazole nitrates only at the 7-position [84CHC(6)131].

(b) Electrophilic substitution on 1,2-benzisothiazole derivatives

Electrophilic substitution reactions on 5- substituted 1,2-benzisothiazole have been examined in detail [80JCR(S)197, 80JCR(M)2845]. In the case of electron releasing substituents at the 5-position e.g. 5-amino, 5-acetamido, 5-hydroxy and 5-methoxy-1,2-benzisothiazole, electrophilic substitutions were found to go in the 4-position.

1.5.2.2 Nucleophilic substitution

While nucleophilic displacement reactions on 3-chloro-1,2-benzisothiazole (88) have already been mentioned, in some cases this displacement is accompanied by rearrangement. Boshagen has shown that treatment of 3-chloro-1,2-benzisothiazole with thioacetic acid yields an N-acyl-3H-1,2-benzodithiole (91). The mechanism of the reaction is outlined in Scheme 49 [68CB(101)2472].

1.6 1,2-Benzisothiazolin-3-ones

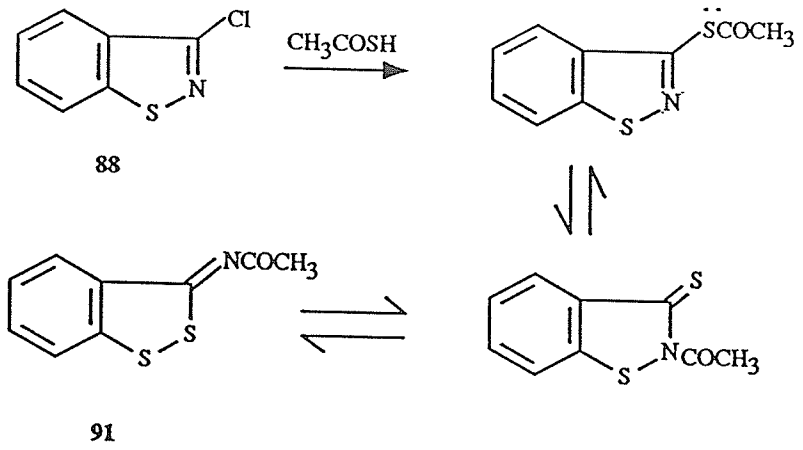
1.6.1 Synthesis

1.6.1.1 From acyclic starting materials

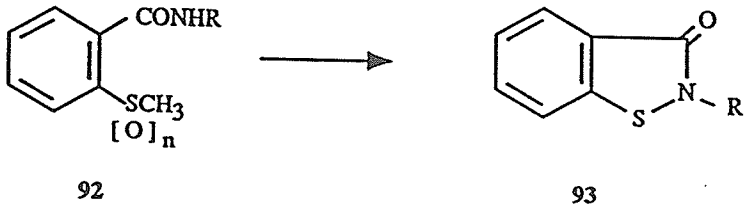
2-Methylsulfenyl- or 2-methylsulfinylbenzamides (92;n=0,1) can be cyclized using thionyl chloride. The reaction affords the 2-substituted-1,2-benzisothiazolin-3-ones (Scheme 50) [81CC510, 82BCJ(55)1183].

1.6.1.2 From cyclic starting material

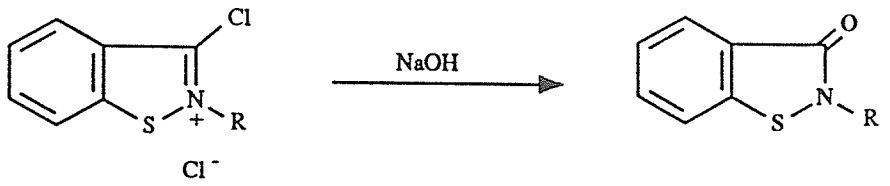
1,2-Benzisothiazolin-3-ones can also be produced by reaction of the benzisothiazolium salts 94 with sodium hydroxide (Scheme 51) [72AHC(14)43], and like many other heterocyclic thiones 1,2-benzisothiazoline-3-thiones can be converted by mercuric acetate into the corresponding 1,2-benzisothiazolin-3-ones (93) (Scheme 52) [72AHC(14)43].



Scheme 49

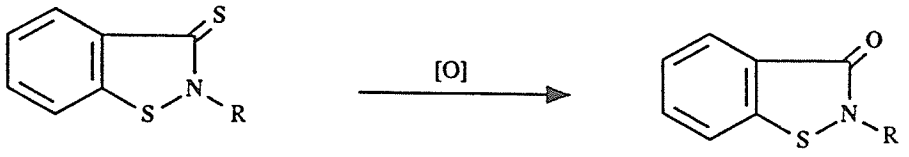


Scheme 50



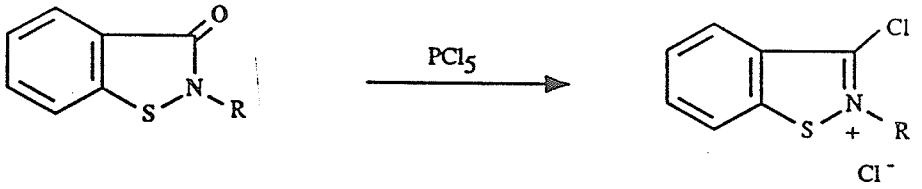
94 93

Scheme 51



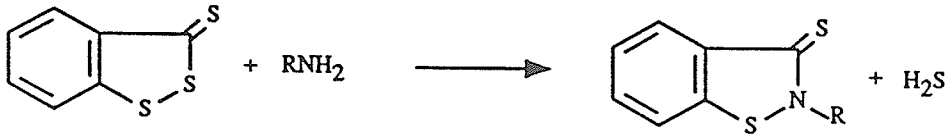
93

Scheme 52



93 94

Scheme 53



95 96

Scheme 54

1.6.2 Chemical properties

1.6.2.2 Electrophilic substitution

While N-unsubstituted 1,2-benzisothiazolinones could either react on the oxygen or nitrogen atom, in fact alkylation, acylation and sulfonylation reactions on 1,2-benzisothiazolin-3(2H)-ones produce the N-substituted derivatives [72AHC(14)43]. Treatment of 1,2-benzisothiazolin-3(2H)-one with phosphorus pentachloride, phosphoryl chloride, phosgene or oxalyl chloride affords 3-chloro-1,2-benzisothiazole (**88**) while N-substituted 1,2-benzisothiazolin-3-ones afford the 3-chloro-1,2-benzisothiazolium salts (**94**) (Scheme 53) [72AHC(14)43].

1.7 1,2-Benzisothiazoline-3-thiones

1.7.1 Synthesis

1,2-Benzisothiazoline-3-thiones (**96**) have been prepared by the reaction between benzo-1,2-dithiole-3-thione (**95**) and a primary amine (Scheme 54) [68FES(23)3, 68FES(23)583].

1.7.2 Chemical properties

1.7.2.1 Electrophilic substitution

Like 1,2-benzisothiazolin-3(2H)-ones (**87**), N-unsubstituted 1,2-benzisothiazoline-3(2H)-thiones undergo alkylation, acylation and sulfonylation on the nitrogen atom rather than on the sulfur atom of its thiol tautomer [72AHC(14)43].

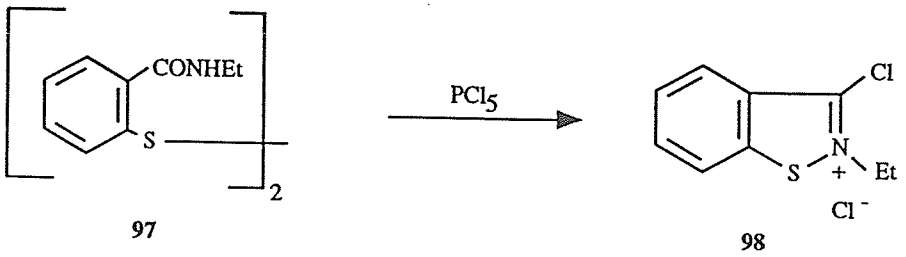
1.8 1,2-Benzisothiazolium Salts

1.8.1 Synthesis

Reaction of N-substituted 1,2-benzisothiazolin-3-ones (**93**) with phosphorus pentachloride [28CB(61)1680], phosphoryl chloride, phosgene or oxalyl chloride [65ZN(B)(20)712, 68ZC(8)170] affords 3-chloro-1,2-benzisothiazolium salts (**94**) (Scheme 53). Treatment of N,N′-diethyldithiosalicylamide (**97**) with phosphorus pentachloride yields 3-chloro-2-ethyl-1,2-benzisothiazolium chloride (Scheme 55) [66CB(99)2566].

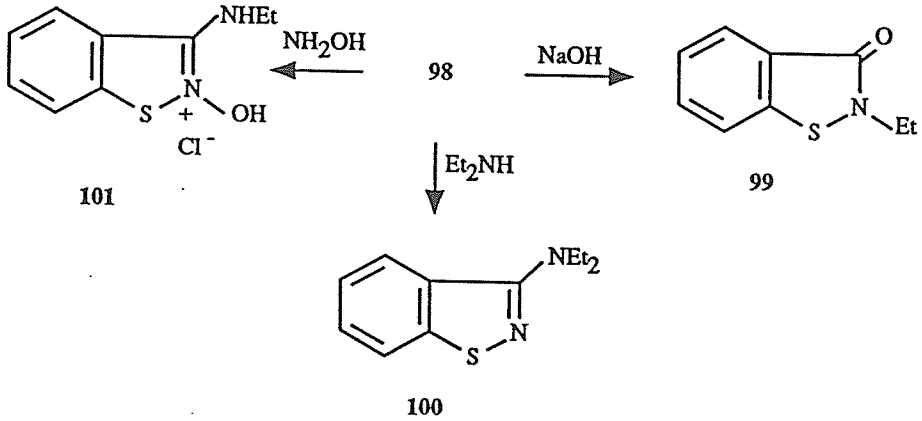
1.8.2 Chemical properties

As with the monocyclic series, the halogen atom at the 3-position of a benzisothiazole is labile, and reaction of 3-chloro-2-ethyl-1,2-benzisothiazolium chloride (**98**) with base yielded 2-ethyl-1,2-benzisothiazolinone (**99**) (Scheme 56) [66CB(99)2566]. Heating this salt with diethylamine gave 3-diethylamino-1,2-benzisothiazole (**100**). When the isothiazolium salt (**98**) was heated with hydroxylamine, the product was an N-oxide derivative, which was isolated in the form of its hydrochloride (Scheme 56) [70CB(103)3166]. Benzisothiazolium salts afford 3-arylimino-3H-1,2-benzodithioles (**102**) when treated with thioacetic acid, if R is an aryl group. When R is an alkyl group, the product is the benzisothiazoline-3-thione (**96**) (Scheme 57) [67CB(100)2435].



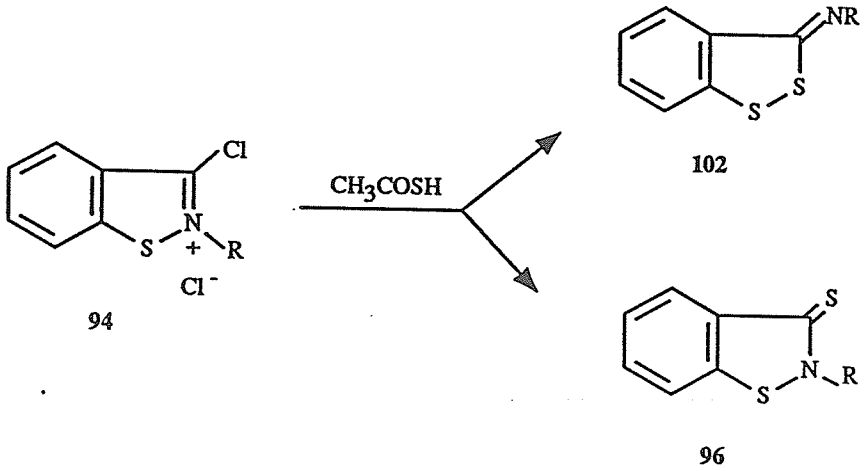
97 98

Scheme 55



101 99 100

Scheme 56



94 102 96

Scheme 57

1.9 2,1-Benzisothiazoles

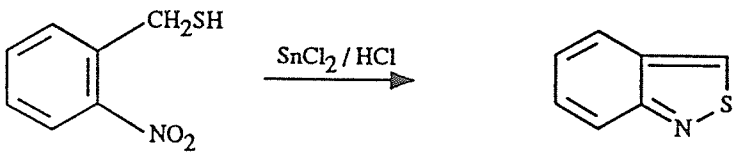
1.9.1 Synthesis

1.9.1.1 From *o*-nitro- and *o*-amino-α-toluenethiol

Gabriel and co-workers first prepared 2,1-benzisothiazole in the 1890's by reduction of *o*-nitro-α-toluenethiol with stannous chloride and hydrochloric acid followed by steam distillation (Scheme 58) [895CB(28)1025, 896CB(29)160]. Oxidation of the *o*-amino-α-toluenethiol yielded the same product [59CB(92)1679]. Careful control of the pH of this reaction is essential, otherwise the yield of the 2,1-benzisothiazole is low and that of the disulfide **104** is correspondingly high (Scheme 59).

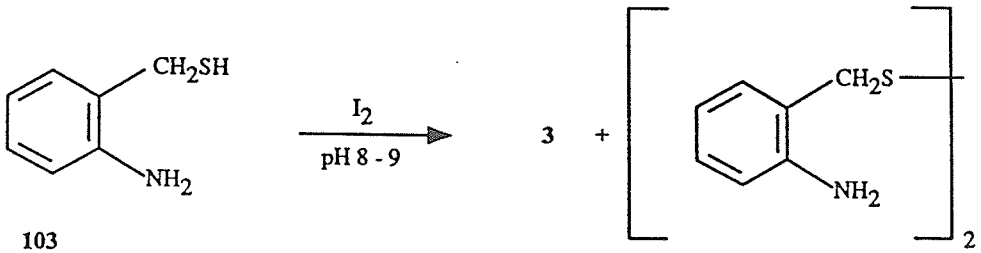
1.9.1.2 From *o*-nitro and *o*-aminothiobenzamide

In one of the variations on formation of isothiazoles by oxidative cyclization, hydrogen peroxide oxidation of *o*-aminothiobenzamide has been reported to yield the 3-amino-2,1-benzisothiazoles (**106**) (Scheme 60) [65JMC(8)515]. These are also available by reduction of *o*-nitrothiobenzamides with stannous chloride and hydrochloric acid (Scheme 61). These compounds can be diazotized (when R = H) and thus converted into a range of other 3-substituted compounds [71AJC(24)2405].



3

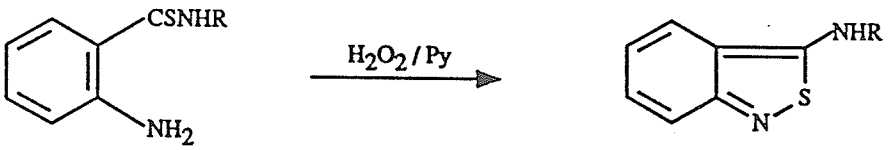
Scheme 58



103

104

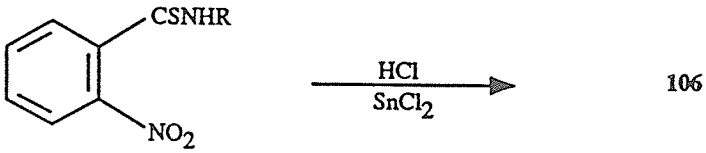
Scheme 59



105

106

Scheme 60



107

106

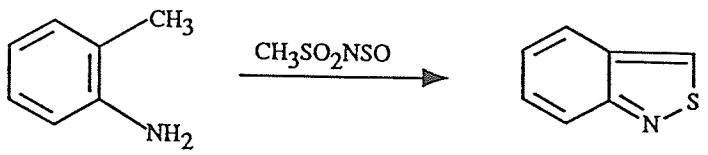
Scheme 61

1.9.1.3 From *o*-toluidine

In many ways superseding some tedious or inconvenient oxidative cyclization methods to 2,1-benzisothiazoles, a useful method was developed by Davis who showed that reaction between an *o*-toluidine and thionyl chloride in a high-boiling inert solvent afforded 2,1-benzisothiazoles in moderate yields [68CC1547, 69JOC(34)2985]. However, chlorinated products were also formed, e.g. an extensive study of this reaction [71IKN53] showed that, in addition to 1,2-benzisothiazole, 3-chloro-, 5-chloro- and 3,5-dichloro-1,2-benzisothiazoles were formed in considerable quantity. Singerman [75JHC(12)877] made a significant advance in this reaction by replacing thionyl chloride with N-sulfinylmethanesulfonamide (**109**). Better yields are usually obtained than by the thionyl chloride procedure, and chlorinated by-products are not formed (Scheme 62).

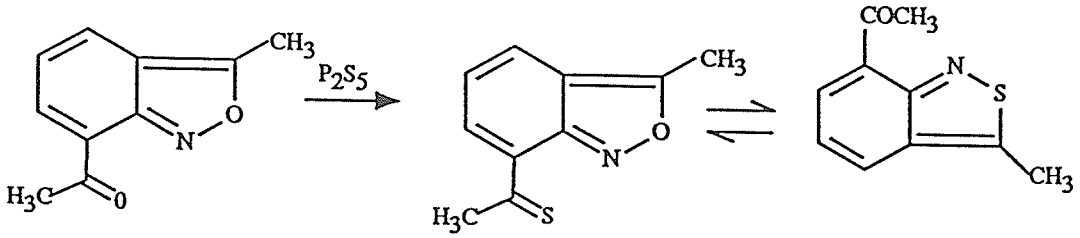
1.9.1.4 From benzisoxazole

A 7-acyl derivative of 2,1-benzisothiazole can be synthesized from the related 2,1-benzisoxazole on treatment with phosphorus pentasulfide [71CJC(49)2018, 72CPB(20)2372, 75CJC(53)1336] (Scheme 63). This reaction may proceed by rearrangement with a [1,9] sigmatropic mechanism similar to that observed by Rees in 7-acetyl-3-methylanthranil (**110**) where the pmr signals of the two methyl groups coalesced as a result of valence tautomerism [71CC833].



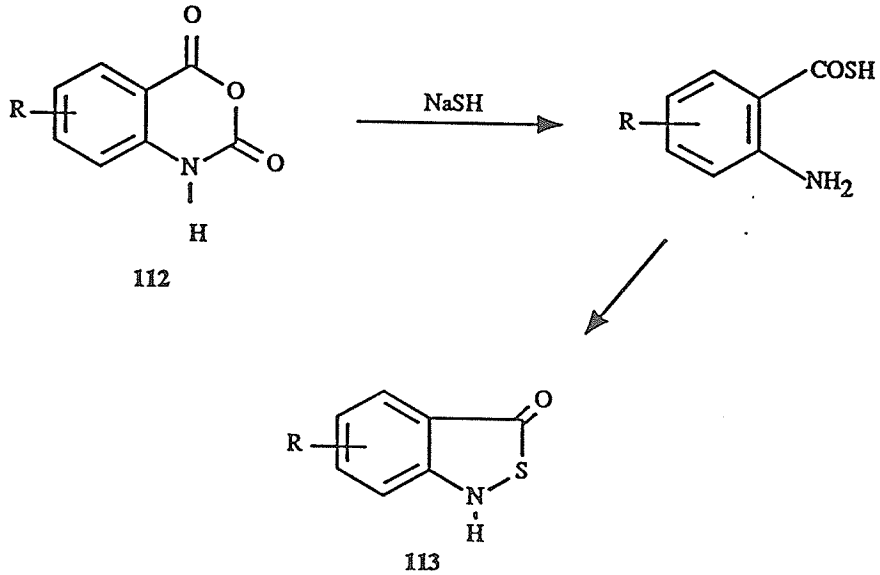
108 3

Scheme 62



110 111

Scheme 63



112 113

Scheme 64

1.9.2 Chemical properties

1.9.2.1 Electrophilic substitution

Electrophilic substitution on the 2,1-benzisothiazole ring affords mainly the 5- and 7-substituted derivatives. Thus bromination of 2,1-benzisothiazole gives a mixture of equal quantities of 5-bromo- and 7-bromo-2,1-benzisothiazole [69JCS(C)2189], while nitration affords mainly 5-nitro-2,1-benzisothiazole, with smaller quantities of 7-nitro and 4-nitro isomers [69JCS(C)2189]. In general, the direction of nitration in 2,1-benzisothiazoles already substituted in the benzenoid ring is controlled by the nature of that substituent rather than by the residual effect of the heterocyclic ring.

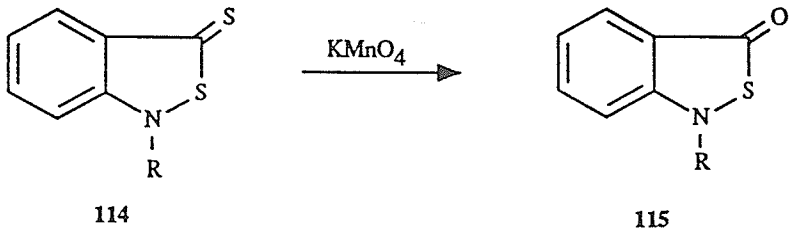
1.9.2.2 Nucleophilic substitution

3-Chloro-2,1-benzisothiazole [71AJC(24)2405] is readily attacked by nitrogen, oxygen, sulfur and carbon nucleophiles at the 3-position with displacement of the chloride ion. This provides a good route for synthesis of 3-substituted 2,1-benzisothiazoles [75AJC(28)129, 75AJC(28)2051, 78JHC(15)529].

1.10 2,1-Benzisothiazolin-3-one

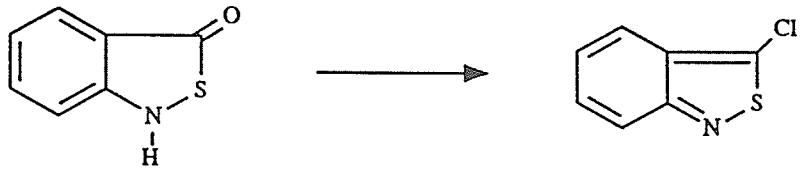
1.10.1 Synthesis

A useful approach to 2,1-benzisothiazolinones starts from N-alkyl isatoic anhydrides. These can be converted with sodium hydrogen sulfide into thioanthranilic acids, which then undergo oxidative cyclization to 2,1-benzisothiazolinones (113) (Scheme 64) [73JHC(10)413]. Oxidation of 2,1-benzisothiazoline-3-thiones with potassium permanganate yielded the corresponding benzisothiazolinone (115) (Scheme 65) [69BSF1170, 69BSF1173].



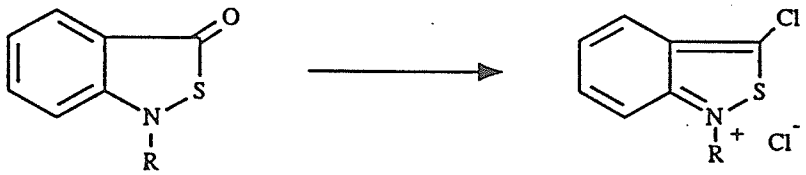
114 115

Scheme 65



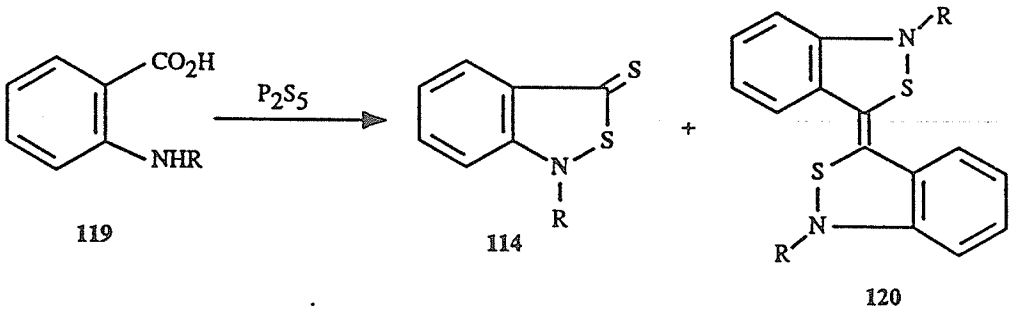
116 117

Scheme 66



115 118

Scheme 67



119 114 120

Scheme 68

1.10.2 Chemical properties

1.10.2.1 Electrophilic substitution

Electrophilic substitution of N-methyl-2,1-benzisothiazolin-3-one gives the 5-substituted derivatives, i.e. substitution also takes place on the aromatic ring. Thus bromination, nitration and chlorosulfonation of 2,1-benzisothiazolin-3-one yields the 5-bromo, 5-nitro and 5-chlorosulfonyl derivatives respectively [78JHC(15)529].
2,1-Benzisothiazolin-3(1H)-one exists in the keto form and alkylates on nitrogen [75AJC(28)129], but acylation occurs on oxygen to form O-acyl derivatives [81AJC(34)755, 85AHC(38)105].

1.10.2.2 Nucleophilic substitution

Treatment of 2,1-benzisothiazolin-3(1H)-one (**116**) with phosphoryl chloride yields 3-chloro-2,1-benzisothiazole (Scheme 66) [78JHC(15)529] while the N-substituted derivative (**115**) yields the 3-chloro-2,1-benzisothiazolium chloride when treated with oxalyl chloride (Scheme 67) [76JPC(318)161].

1.11 2,1-Benzisothiazoline-3-thiones

1.11.1 Synthesis

The reaction between an N-alkyl or N-aryl substituted anthranilic acid (**119**) and phosphorus pentasulfide affords a mixture of 2,1-benzisothiazoline-3-thione (**114**) and Δ-3,3′-*bis*-2,1-benzisothiazolylidene (**120**) (Scheme 68) [69BSF1170, 69BSF 1173].
Treatment of 3-chloro-2,1-benzisothiazolium chloride with hydrogen sulfide produces 2,1-benzisothiazolinethione [76JPC(318)161].

1.12 2,1-Benzisothiazol-2-oxides

1.12.1 Synthesis

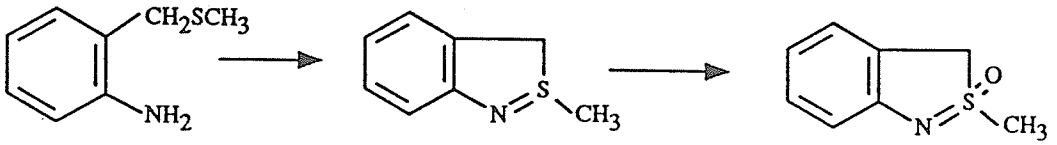
Derivatives of 2,1-benzisothiazol-2-oxide **122** can be prepared by oxidation of 2-methylthiomethylaniline (**121**) with N-chlorosuccinimide and alkali, followed by further oxidation with *m*-chloroperbenzoic acid (Scheme 69) [77USP4 031 227].

In a rather unusual approach to the synthesis of an isothiazole ring involving a carbon to carbon bond formation, the sulfonamide **123** is readily cyclized by potassium amide in liquid ammonia, affording 1-methyl-2,1-benzisothiazoline-2,2-dioxide (**124**) (Scheme 70) [63JOC(28)1, 73JHC(10)249, 74JHC(11)73]. Contri and Chiarino prepared 2,1-benzisothiazoline-2,2-dioxides (**127**) by cyclization of 2-chlorophenylmethanesulfonamide (**125**) or the sodium salt of 2-aminophenylmethanesulfonic acid (**126**) (Scheme 71) [86JHC(23)1645].

1.13 2,1-Benzisothiazolium salts

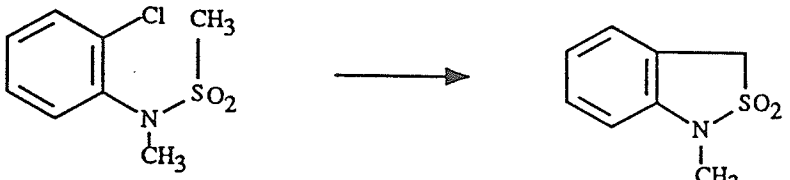
1.13.1 Synthesis

N-Alkyl or N-benzyl-2,1-benzisothiazolium salts are easily formed from 2,1-benzisothiazole and its derivatives by treatment with alkyl or benzyl halides [85AHC(38)105].



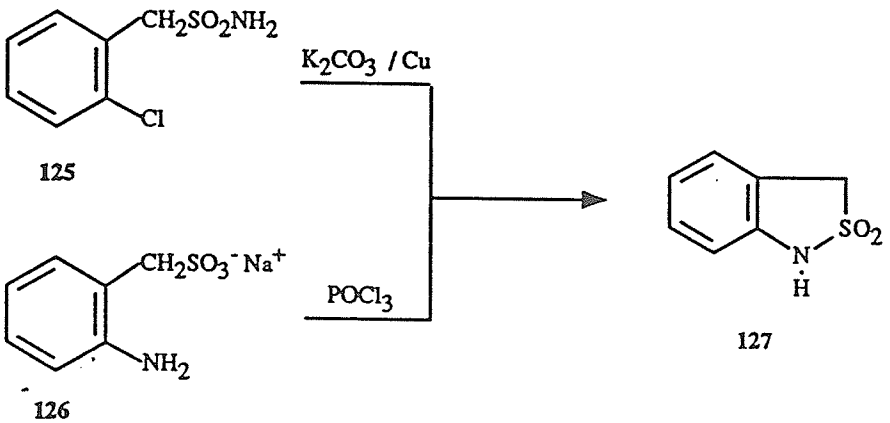
121 122

Scheme 69



123 124

Scheme 70



125 126 127

Scheme 71

1.13.2 Chemical properties

1.13.2.1 Reaction with base

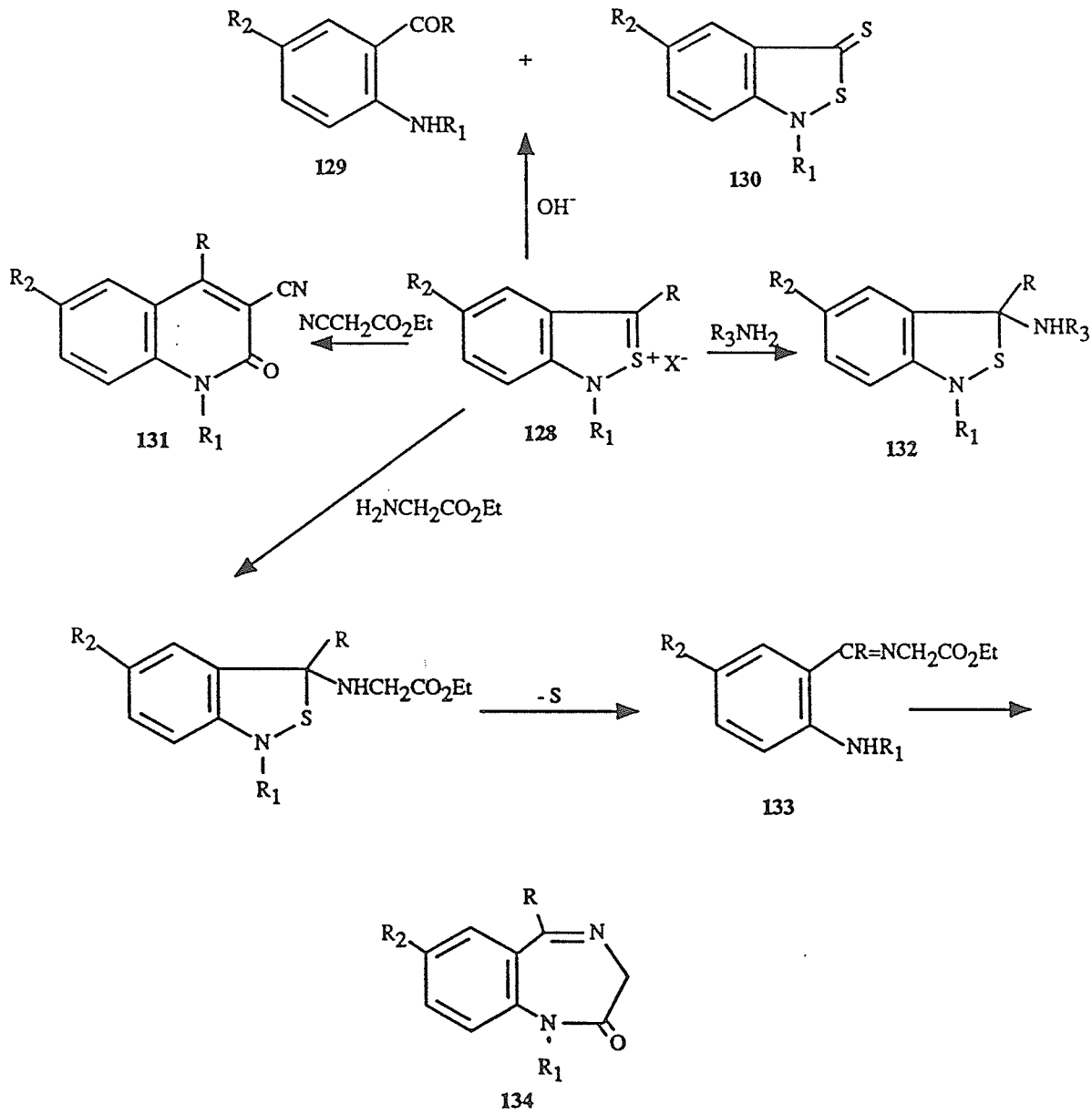
N-Substituted-2,1-benzisothiazolium salts **128** decompose in aqueous base producing *o*-aminobenzaldehydes and 2,1-benzisothiazoline-3-thiones (**130**). The reaction proceeds through initial nucleophilic attack at C-3 followed by sulfur elimination (Scheme 72) [73JCS(P1)1863, 82CJC(60)440].

1.13.2.2 Reaction with carbanions

Treatment of the salt **128** with ethyl cyanoacetate in hot pyridine affords 3-cyano-2-quinolones (**131**), probably by attack of the ethyl cyanoacetate anion on the heterocyclic carbon atom, ring opening with loss of sulfur and closure of the quinolone ring with expulsion of ethoxide ion (Scheme 72) [82CJC(60)440, 83JHC(20)1707].

1.13.2.3 Reaction with amines

2,1-Benzisothiazolium salts react with amines to afford 2,1-benzisothiazoline derivatives. These are formed by direct addition of the nucleophile without further ring opening. A synthesis of 1,4-benzodiazepines results by attack of ethyl aminoacetate at C-3 in this case, ring opening follows with loss of sulfur to form the aminoimino ester **133**, which recyclises to the 1,4-benzodiazepin-2-one derivative (**134**) (Scheme 72) [72CPB(20)2372].


R2
COR
NHR1
129
+
R2
S
S
N
R1
130
OH-
R
R2
CN
NCCH2CO2Et
O
N
R1
131
R2
R
S+ X-
N
R1
128
R3NH2
R2
R
NHR3
S
N
R1
132
H2NCH2CO2Et
R2
R
NHCH2CO2Et
S
N
R1
-S
R2
CR=NCH2CO2Et
NHR1
133
R
N
R2
N
O
R1
134

Scheme 72

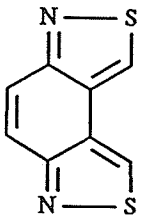
2. OBJECT OF RESEARCH

Due to the biological activity of benzisothiazoles in a number of areas as stated in the introductory section, synthesis and studies of the chemical properties of different benzisothiazoles have attracted the attention of many chemists. In 1979 Davis and Danylec synthesized all the possible angular benzo[*c,c'*]*bis*-isothiazoles (**135,136,137**) (Scheme 73) by repeated use of Singerman's reagent (CH_3SO_2NSO) [80JHC(17)533]. However little attention has yet been paid to the fused benzo[*d,d'*]*bis*-isothiazoles other than work by Meth-Cohn and co-workers describing the preparation of the benzo[*d,d'*]*bis*-isothiazole **139** from the dialdehyde **138** (Scheme 74) [78S58].

The research described here is in four main areas:

1. To synthesize the five possible isomers of the benzo[*d,d'*]*bis*-isothiazole system, namely benzo[1,2-*d*:3,4-*d'*]*bis*-isothiazole (**140**), benzo[1,2-*d*:4,3-*d'*]*bis*-isothiazole (**141**), benzo[1,2-*d*:4,5-*d'*]*bis*-isothiazole (**142**), benzo[1,2-*d*:5,4-*d'*]*bis*-isothiazole (**139**), and benzo[1,2-*d*:6,5-*d'*]*bis*-isothiazole (**143**) (Scheme 75), and if possible, some of the six isomers of the benzo[*c,d'*]*bis*-isothiazole system, namely benzo[1,2-*c*-:3,4-*d'*]*bis*-isothiazole (**144**), benzo[1,2-*c*:4,3-*d'*]*bis*-isothiazole (**145**), benzo[1,2-*c*:4,5-*d'*]*bis*-isothiazole (**146**) benzo[1,2-*c*:5,4-*d'*]*bis*-isothiazole (**147**), benzo[1,2-*c*:5,6-*d'*]*bis*-isothiazole (**148**) and benzo[1,2-*c*:6,5-*d'*]*bis*-isothiazole (**149**) (Scheme 76).

2. To study and determine factors affecting the electrophilic substitution on benzisothiazoles arising from Part 1.



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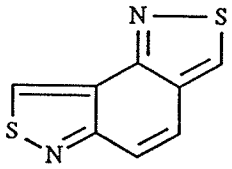

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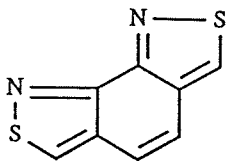
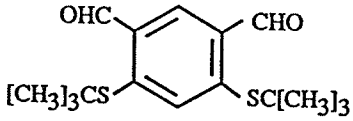


137

Scheme 73



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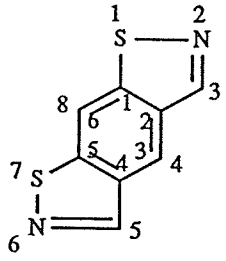
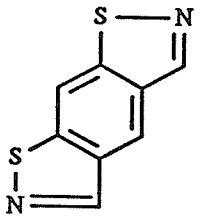


139

Scheme 74



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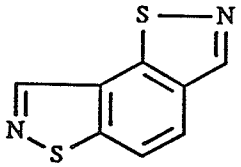

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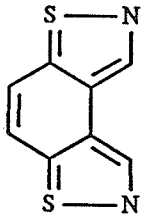

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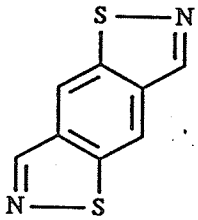

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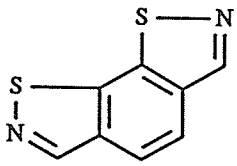
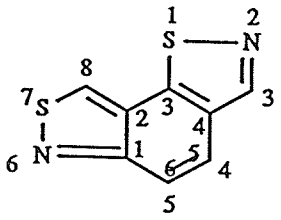


143

Scheme 75

3. To investigate possible fused systems, where the sulfur atom may form a bridge between two isothiazole rings (Scheme 77), being common to both rings simultaneously or alternatively.

4. To synthesize some of the possible isothiazole analogues of ellipticine (151) alkaloids, of which there are 4 systems, namely 5-H-isothiazolo [3,4-*c*]carbazole (152), 5-H-isothiazolo[4,3-*c*]carbazole (153), 5-H-isothiazolo[4,5-*d*]carbazole (154) and 5-H-isothiazolo [5,4-*d*]carbazole (155) (Scheme 78).



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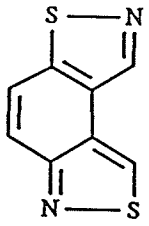

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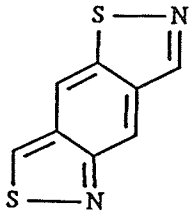

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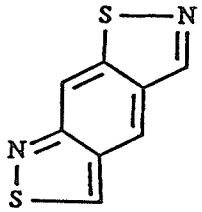

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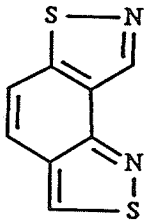

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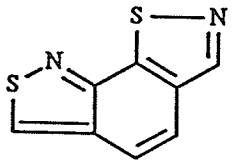
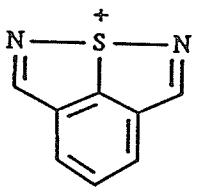
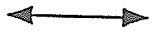


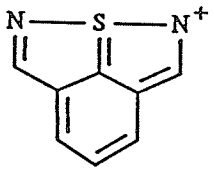
149

Scheme 76



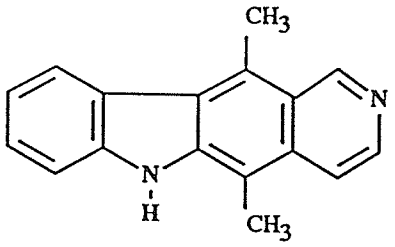
150 a





150 b

Scheme 77



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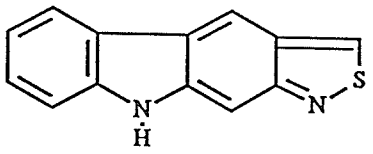

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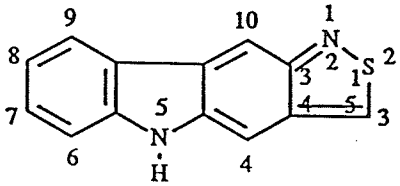

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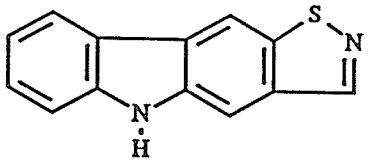

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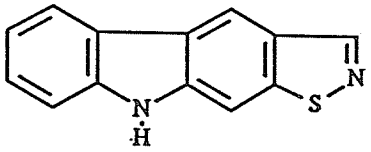


155

Scheme 78

3. DISCUSSION

3.1 Synthesis of benzo-[*d,d'*]*bis*-isothiazoles

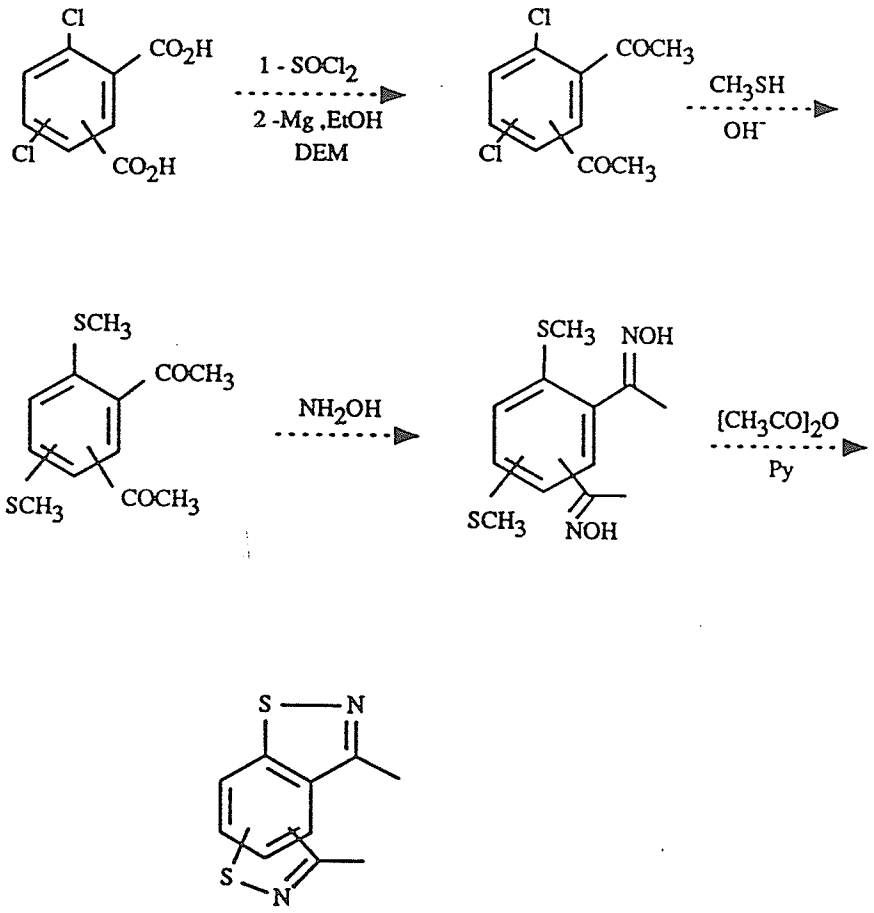
Since it has been found that the ketoxime method modification of McKinnon and Lee [88CJC(66)1405] gives good yields of 1,2-benzisothiazoles, two general procedures appeared suitable; either a) simultaneous as in Scheme 79, or b) consecutive formation of the isothiazole rings as in Scheme 80. In the latter case the precursors to the second ring would be prepared by modification of substituents on an initially formed benzisothiazole. In these syntheses we decided to use the ketone oximes (i.e. *o*-methylthiobenzoketoximes) as synthetic precursors, rather than the aldehyde derivatives as the former are likely to be more easily handled, being less prone to oxidation. It is also considered, that if necessary, the methyl groups could be removed by oxidation followed by decarboxylation as with simpler methyl benzisothiazoles to provide the unsubstituted system [72AHC(14)43]. Initially, a suitable approach appeared to be the preparation of different isomers of the *bis*-(methylthio) benzene followed by acylation.

Attempts to synthesize the *o*- and *m-bis*-(methylthio) benzenes according to Tiecco's method [79JOC(44)2642] by heating the corresponding dichlorobenzenes with sodium methanethiolate in hexamethylphosphoramide were unsuccessful. The *p-bis*-(methylthio) benzene was synthesized according to Burton's method (with some modifications) from methylthiobenzene [48JCS604] by sulfonation using chlorosulfonic acid. According to Burton, 4-methylthiobenzene sulfonyl chloride may be prepared by chlorosulfonation of methylthiobenzene with two equivalents of chlorosulfonic acid, the initially formed chlorosulfonic acid being further converted by the extra chlorosulfonic acid into the acid chloride. However, the isolation procedure described did not give any of the desired product. The sulfonic acid intermediate was therefore separated and converted into the

sulfonyl halide with phosphorus pentachloride. Reduction of the sulfonyl halide with zinc in sulfuric acid followed by methylation using dimethyl sulfate gave the *p-bis*-(methylthio)benzene (159) (Scheme 81). Sulfonation of the 1-methyl-4-(methylthio)benzene in the same manner gave an apparent sulfonic acid derivative. However, on attempted filtration this appeared to decompose. Since only starting material was recovered, possibly the reaction is reversible, or the precipitate formed is merely a complex of starting material and chlorosulfonic acid or sulfuric acid.

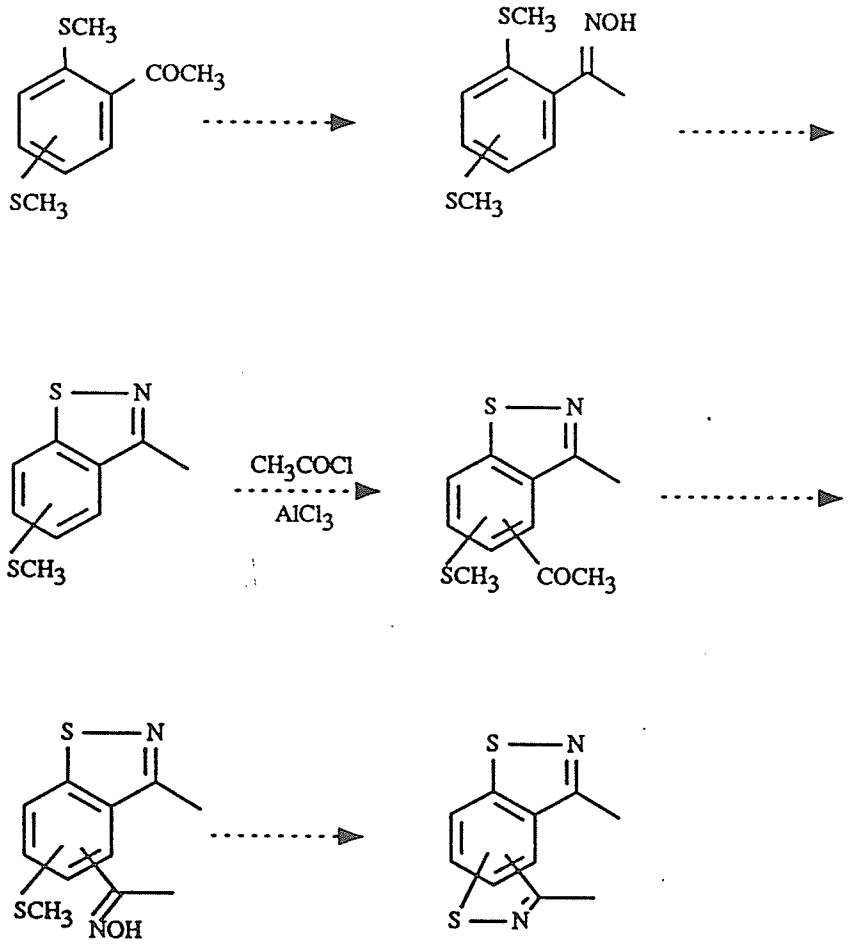
Attempts to acylate the *p-bis*-(methylthio)benzene gave only the starting material and decomposition products. This might be due to the coordination of the sulfur with the aluminum chloride allowing side reactions to proceed. Thus, the synthesis of several different *bis*-(methylthio) diacetylbenzenes was accomplished using a different route starting from different isomers of dichlorobenzene dicarboxylic acids which are available by oxidation of different dichloroxylenes. This was followed by conversion of the acids to the ketone, and nucleophilic displacement of the chlorine atoms (activated by *ortho* keto functions) with methanethiolate anion. The ketones were then converted into the oxime which subsequently allowed synthesis of the benzisothiazole rings using acetic anhydride in pyridine (Scheme 79).

The second approach is illustrated in Scheme 80. An acetyl- *bis*-(methylthio) benzene could be converted via its ketoxime into a methylthiobenzisothiazole which then is further acylated under electrophilic conditions. The resulting ketomethylthio derivative would then be converted via its ketoxime into the benzo-*bis*-isothiazole.



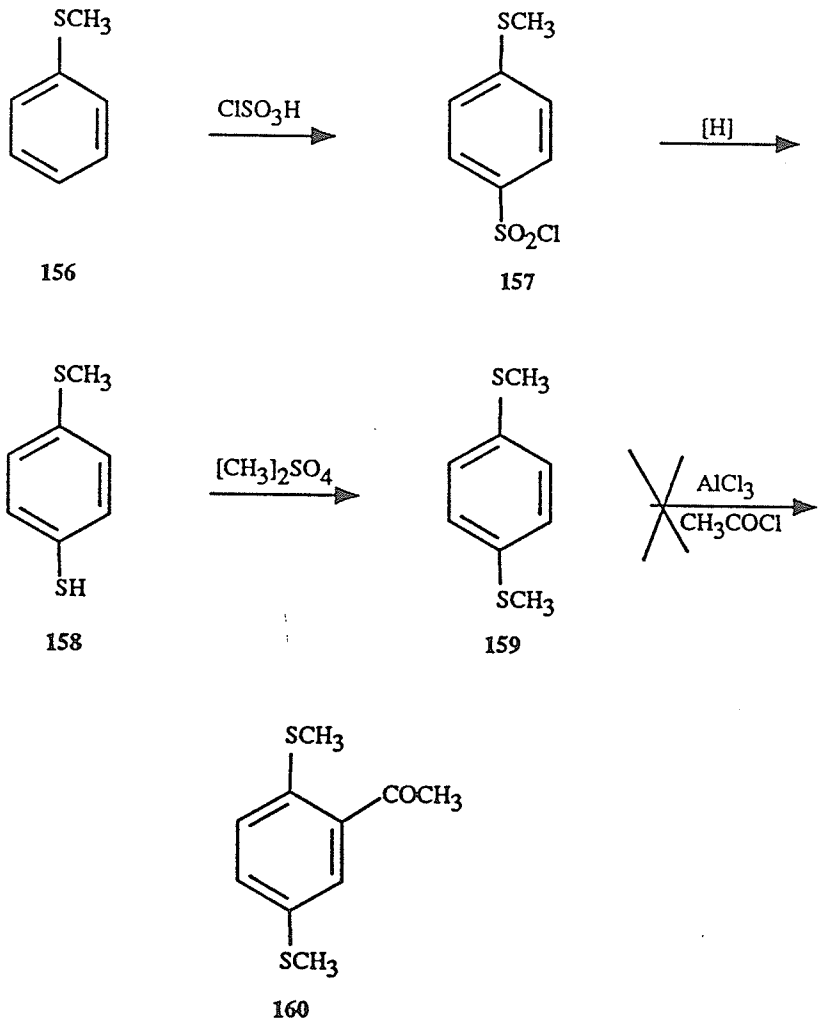
Scheme 79

(In these syntheses the methylthio and acetyl substituents on the aromatic ring must be *o*- to each other).



Scheme 80

(In these syntheses the methylthio and acetyl substituents on the aromatic ring must be *o*- to each other).

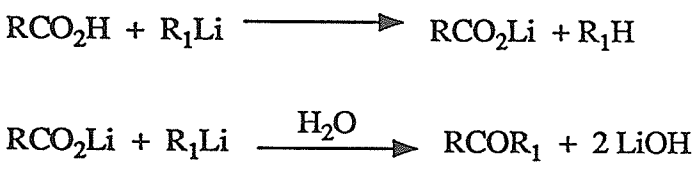

SCH3
ClSO3H
SCH3
SO2Cl
[H]
156
157
SCH3
[CH3]2SO4
SCH3
SH
SCH3
AlCl3
CH3COCl
158
159
SCH3
COCH3
SCH3
160

Scheme 81

3.1.1 Synthesis of 3,7-dimethylbenzo[1,2-*d*:4,5-*d'*]*bis*-isothiazole (167)

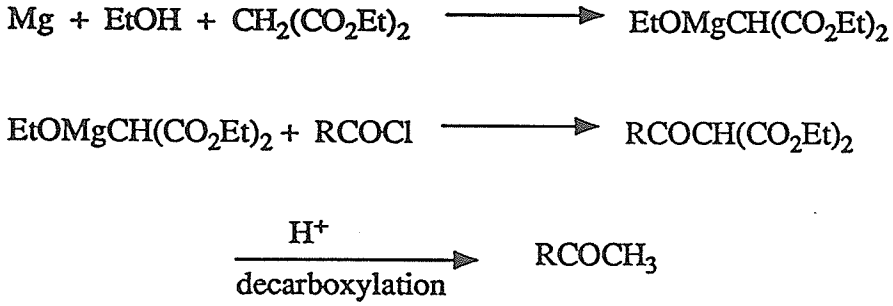
2,5-Dichlorobenzene-1,4-dicarboxylic acid (**162**) [67BSF3377] was prepared by oxidation of the commercially available 1,4-dichloro-2,5-dimethylbenzene with potassium permanganate. The required ketones could be synthesized directly from the carboxylic acids using organolithium reagents, i.e. with 2 moles of the organolithium reagent reacting with 1 mole of the carboxylic acid as shown in Scheme 82 [70OR(18)1]. Alternatively the ketones could also be synthesized from acid halides using other organometallic reagents, as in Scheme 83. Organocadmium and organomagnesium reagents have been found to be generally useful for such syntheses [54OR(8)28]. However, in our synthesis we found that the reaction of ethoxymagnesium malonic ester with the acid chloride gave better yields; the steps of this reaction are outlined in Scheme 84.

Thus the reaction of 2,5-dichlorobenzene-1,4-dicarboxylic acid (**162**) with thionyl chloride in benzene (Scheme 85) afforded the acid chloride **163**, which was then converted to the acyl malonate on treatment with ethoxymagnesium malonic ester [50JCS322, 66JOC(31)1655]. Hydrolysis of the acyl malonate afforded the 1,4-diacetyl-2,5-dichlorobenzene (**164**). This gave a pmr spectrum with the two acetyl methyl protons resonating at $\delta = 2.70$ ppm and the ring protons at $\delta = 7.62$ ppm. The infrared spectrum showed the carbonyl stretch at 1700 cm^{-1}. Nucleophilic displacement of halo and nitro groups either *ortho* or *para* to an electron withdrawing group has been well documented [40JCS1521, 67CI1525, 71CC1120, 74JOC(39)3343]. The procedure can be utilized for a variety of nucleophiles including alkoxides, thiol anions, amines, azide, chloride and hydroxide ions [57JAS(79)385]. It has been suggested that this reaction occurs via the addition - elimination mechanism of nucleophilic aromatic substitution (Scheme 86)

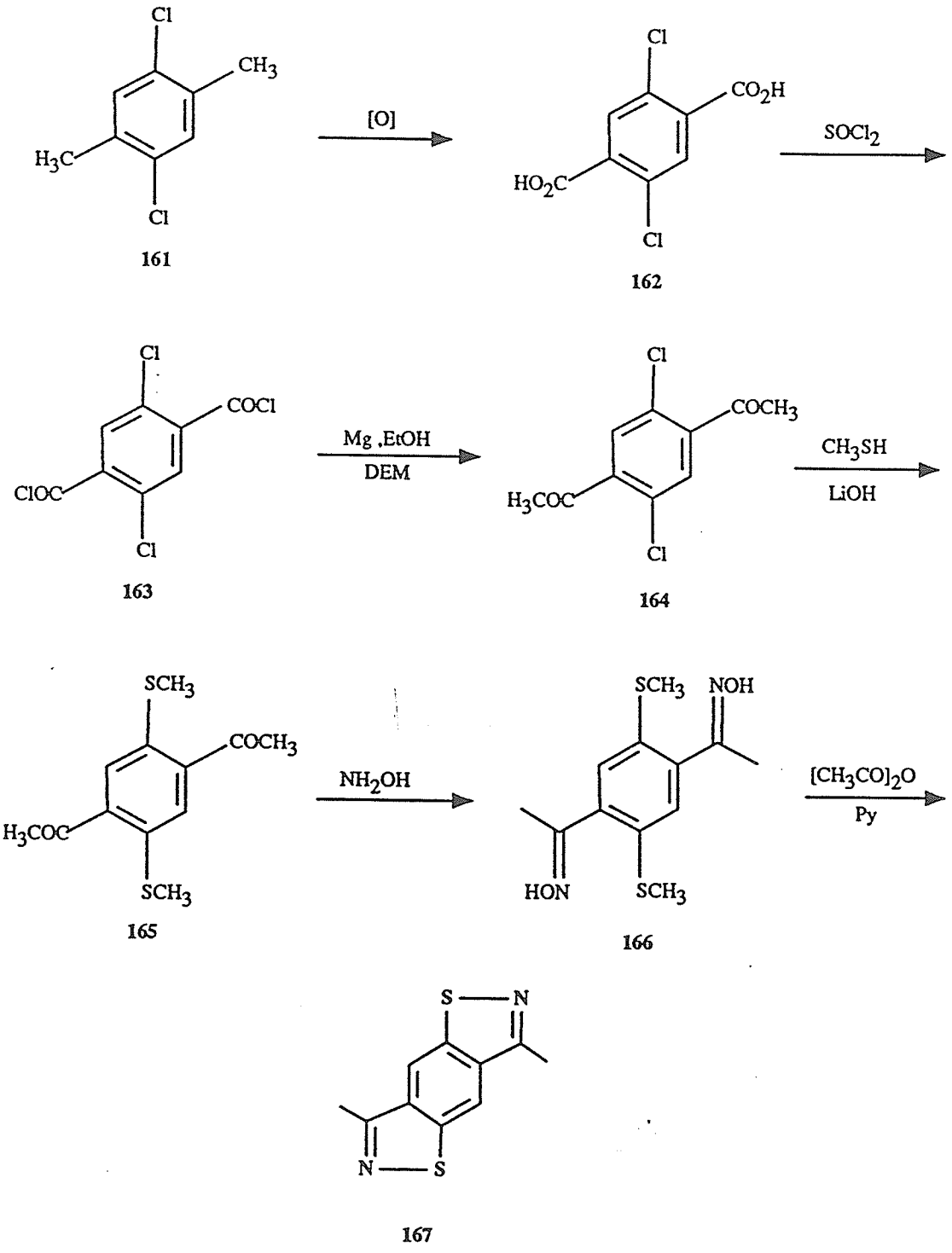


Scheme 82

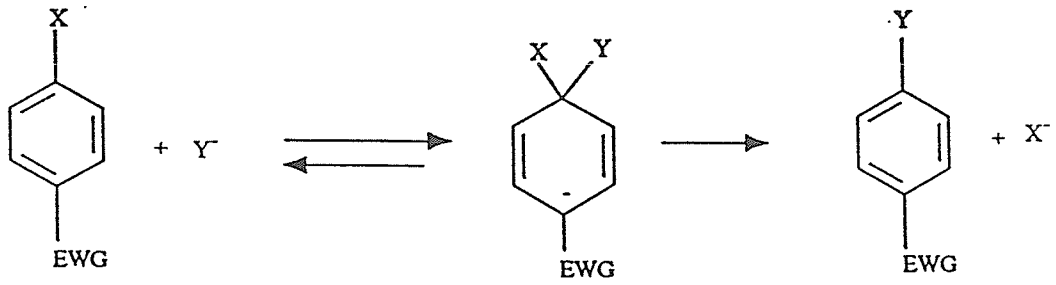
Scheme 83



Scheme 84


Cl
CH3
H3C
Cl
161
[O]
Cl
CO2H
HO2C
Cl
162
SOCl2
Cl
COCl
ClOC
Cl
163
Mg ,EtOH
DEM
Cl
COCH3
H3COC
Cl
164
CH3SH
LiOH
SCH3
COCH3
H3COC
SCH3
165
NH2OH
SCH3
NOH
HON
SCH3
166
[CH3CO]2O
Py
S
N
N
S
167

Scheme 85



Scheme 86

However in some cases, halogen or nitro groups *ortho* or *para* to an alkylthio group may be further displaced by alkanethiolate ions. The mechanism of these reactions is less clear, an elimination/addition mechanism via dehydrobenzene intermediates is unlikely as the reaction works even without hydrogens adjacent to the halogen or nitro group. Perhaps these reactions have some radical character.

This versatile reaction was used in this work for the preparation of different methylthiobenzene derivatives. 1,4-Diacetyl-2,5-*bis*-(methylthio)benzene (165) was prepared by treatment of 1,4-diacetyl-2,5-dichlorobenzene with excess methanethiolate anion (as the lithium salt) in cold dimethylformamide for 30 min. following Beck's method for nitro and chloride displacement by methanethiolate anion [78JOC(43)2052]. Examination of the pmr spectrum showed the chemical shifts of the S-methyl and acetyl methyl protons to be at $\delta = 2.50$ and 2.70 ppm respectively and the aromatic protons at 7.70 ppm. The chemical shifts of the S-methyl and the acetyl methyl protons were tentatively assigned according to comparison with the chemical shifts of the S-methyl and the acetyl methyl protons of different aromatic compounds [Sec. 3.4]. The infrared spectrum showed carbonyl stretching at 1680 cm^{-1}. The oxime 166 was prepared as crystalline pale yellow plates by reaction of the ketone 165 with hydroxylamine hydrochloride and pyridine in methanol and the reaction was refluxed until no starting

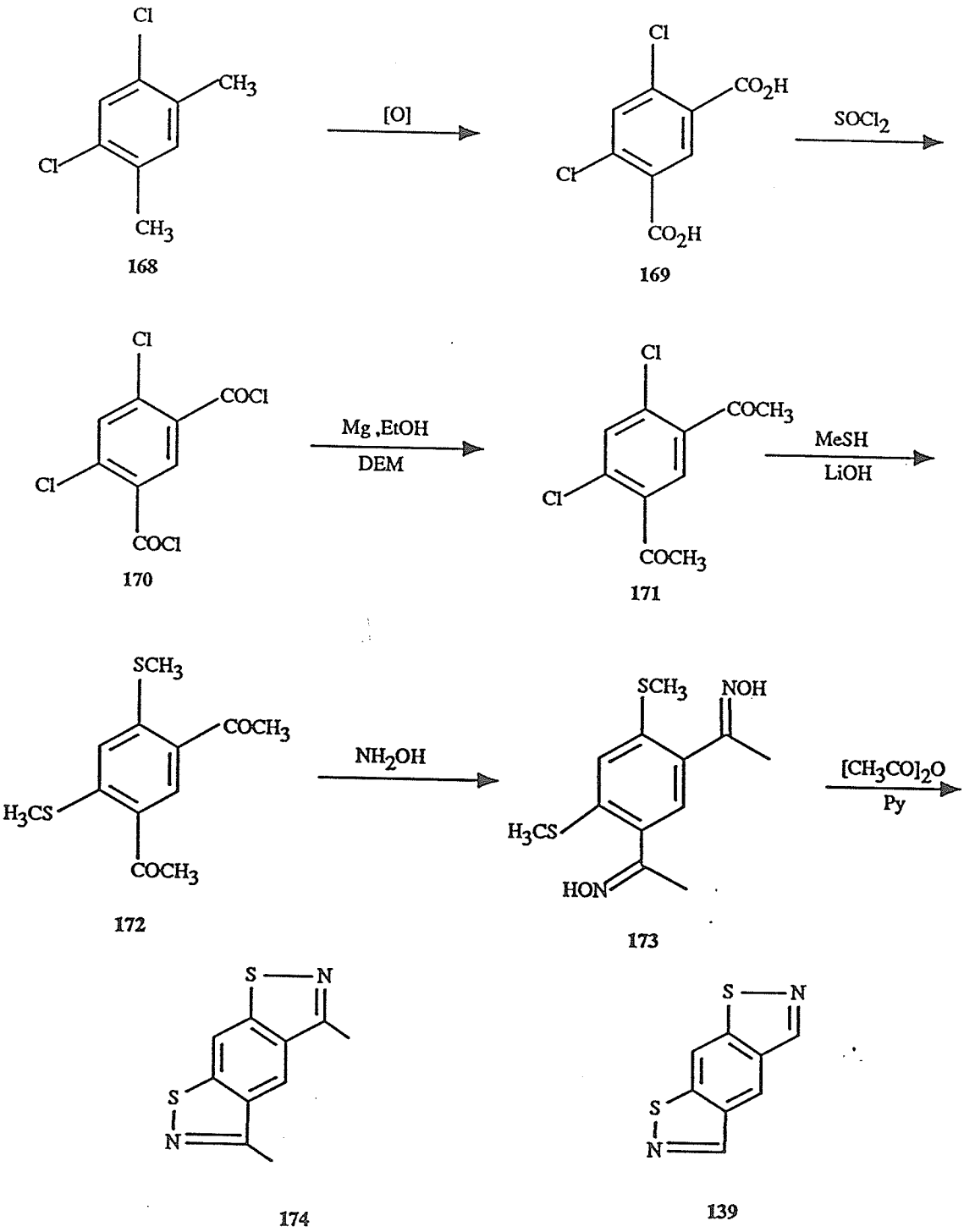
material was observed on thin layer chromatography. The crude oxime **166** was treated with acetic anhydride in pyridine and the reaction was left to reflux for 24 hours. Purification of the product with silica gel chromatography followed by recrystallization gave 3,7-dimethylbenzo[1,2-*d*:4,5-*d'*] *bis*-isothiazole (**167**) as yellow needles. The pmr spectrum showed two single peaks at $\delta = 2.85$ and 8.44 ppm corresponding to the protons of the two methyl groups and the two aromatic protons respectively, consistent with the symmetry of the compound.

3.1.2 Synthesis of 3,5-dimethylbenzo[1,2-*d*:5,4-*d'*]*bis*-isothiazole (174)

A suitable starting material for the synthesis of this benzo-*bis*-isothiazole **174** (Scheme 87) is 1,5-dichloro-2,4-dimethylbenzene (**168**) which was prepared as described [890CB(23)2318] by reaction of *m*-xylene with chlorine using a catalytic amount of iodine. The 1,5-dichloro-2,4-dimethylbenzene was then oxidized to the 4,6-dichlorobenzene-1,3-dicarboxylic acid (**169**) using potassium permanganate. Reaction of the acid with thionyl chloride in benzene afforded the acid chloride **170**, which was then converted to the acyl malonate on treatment with ethoxymagnesium malonic ester, and hydrolysis of the resulting acyl malonate afforded the 1,5-diacetyl-2,4-dichlorobenzene (**171**). The pmr spectrum of diketone **171** showed the chemical shift of the acetyl methyl protons at $\delta = 2.62$ ppm with the C-3 and C-6 aromatic protons resonating as two singlets at $\delta = 7.80$ and 8.02 ppm respectively. The C-6 proton absorbs at a higher δ value than that of the C-3 due to the deshielding effect of the 1- and 5-acetyl groups on the C-6 proton. The diketone derivative was then treated with methanethiol and lithium hydroxide in dimethylformamide to afford 1,5-diacetyl-2,4-*bis*-(methylthio) benzene (**172**). The pmr spectrum of the product showed two singlets at $\delta = 2.51$ and 2.70 ppm corresponding to the S-methyl and the acetyl methyl protons respectively (once more these protons were tentatively assigned as described

earlier Sec. 3.1.1) and two downfield doublets at 7.12 and 8.40 ppm corresponding to the C-3 and C-6 protons respectively. These chemical shifts are assigned according to the shielding effect of the S-methyl and the deshielding effect of the acetyl groups towards *ortho*-protons [63JCP(39)1722, 64JMS(12)146]. The infrared spectrum showed carbonyl stretching at 1670 cm^{-1}. This is within the range for diacetylbenzenes, since 1,4-diacetylbenzene and 1,3-diacetylbenzene exhibit carbonyl absorption at 1682 cm^{-1} and 1681 cm^{-1} respectively. While compounds **165** and **172** both have *ortho*-methylthio substituents, sulfur has only a small conjugative effect on the carbonyl group.

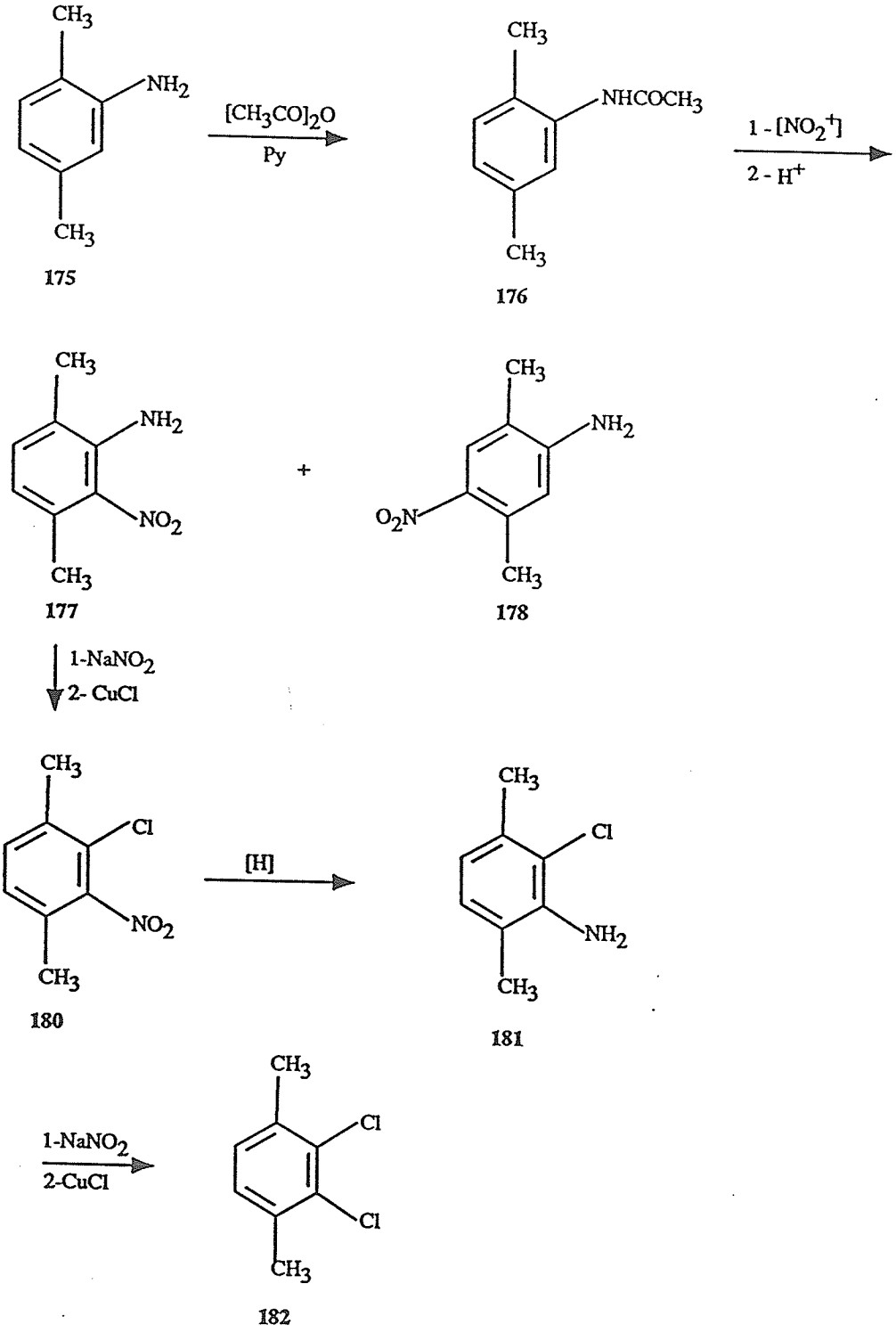
The *bis*-(methylthio)diketone (**172**) was treated with hydroxylamine hydrochloride in pyridine to give the dioxime **173**, which on treatment with acetic anhydride in pyridine gave the desired 3,5-dimethylbenzo[1,2-*d*:5,4-*d'*]*bis*-isothiazole (**174**) as yellow needles. Examination of the pmr spectrum showed the chemical shift of the 3- and 5-methyl group at $\delta = 2.86$ ppm, the C-8 proton at $\delta = 8.32$ ppm as a doublet (J=1Hz) and the C-4 proton at a lower field $\delta = 8.44$ ppm due to the higher deshielding effect of the isothiazole ring toward that proton. The pmr spectrum of benzo[1,2-*d*:5,4-*d'*] *bis*-isothiazole (**139**) [78S58] synthesized by Meth-Cohn showed a doublet at $\delta = 9.07$ ppm (J=0.8 Hz) which was assigned to the C-4 proton and a doublet of doublets at $\delta = 8.95$ ppm assigned to the C-8 proton. This was in agreement with our proton assignment of the 3,5-dimethyl derivative **174**.


Cl
CH3
Cl
CH3
168
[O]
Cl
CO2H
Cl
CO2H
169
SOCl2
Cl
COCl
Cl
COCl
170
Mg ,EtOH
DEM
Cl
COCH3
Cl
COCH3
171
MeSH
LiOH
SCH3
COCH3
H3CS
COCH3
172
NH2OH
SCH3
NOH
H3CS
HON
173
[CH3CO]2O
Py
S
N
S
N
174
S
N
S
N
139

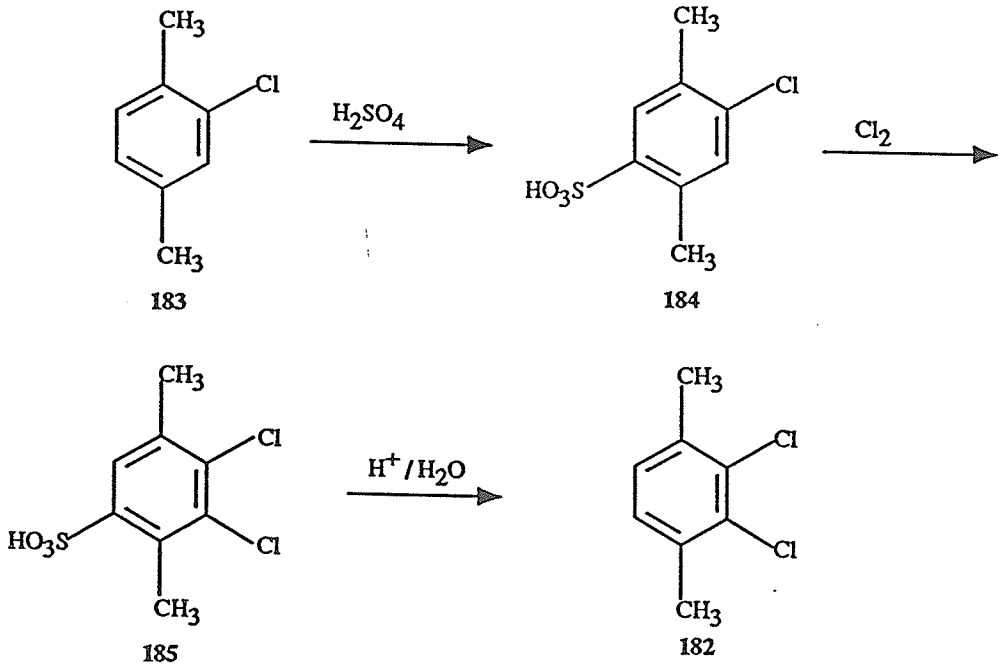
Scheme 87

3.1.3 Synthesis of 3,6-dimethylbenzo[1,2-*d*:6,5-*d'*]*bis*-isothiazole (191)

2,3-Dichloro-1,4-dimethybenzene (182) (Scheme 88) is a suitable precursor for the synthesis of the 3,6-dimethylbenzo[1,2-*d*:6,5-*d'*]*bis*-isothiazole (191). Wahl synthesized 2,3-dichloro-1,4-dimethylbenzene (182) [36AC(P)(5)5] from 2-amino-1,4-dimethyl-benzene (175) by the following method. Acylation of the xylidine 175 followed by nitration and hydrolysis gave a mixture of 2-amino-3-nitro-1,4-dimethylbenzene (177) and 2-amino-5-nitro-1, 4-dimethylbenzene (178). Steam distillation of the mixture separated the more volatile 2-amino-3-nitro-1,4-dimethylbenzene (177) from the 5-nitro isomer 178. The nitroxylidine 177 was then converted to the chloronitroxylene 180 by diazotization and treatment of the diazonium salt 179 with cuprous chloride. Reduction of the chloro-nitroxylene 180 gave the aminochloroxylene 181 which was treated with sodium nitrite hydrochloric acid and cuprous chloride to give the desired 2,3-dichloroxylene 182 (Scheme 88). However, Wahl's preparation of 2,3-dichloroxylene was unsuitable due to the very low yield of the 2-amino-3-nitroxylene intermediate 177. Therefore a new method allowing the synthesis of the 2,3-dichloro-1,4-dimethylbenzene (182) in a better yield and less tedious manner was devised (Scheme 89). The starting 2-chloro-1,4-dimethylbenzene (183) was commercially available. However, since direct chlorination of this yields the 2,5- and not the 2,3-dichloro-1,4-dimethylbenzene, our aim was to block the 5- position with a suitable group followed by chlorination and then removal of that group. The sulfonic acid group was chosen as it is easily introduced and may be removed by boiling in acid. The sulfonation of the 2-chloro-1,4-dimethylbenzene was accomplished using sulfuric acid at 100°C for one hour and crystallization of the reaction product from water gave the 4-chloro-2,5-dimethylbenzenesulfonic acid (184). This was chlorinated in sulfuric acid at 60°C. After the addition of one equivalent of chlorine, the sulfonic acid derivative (185) was hydrolysed by addition of water and on steam distillation of the reaction mixture under these conditions the desired dichloro compound distilled out of the mixture.


CH3
NH2
CH3
175
[CH3CO]2O
Py
CH3
NHCOCH3
CH3
176
1 - [NO2+]
2 - H+
CH3
NH2
NO2
CH3
177
+
CH3
NH2
O2N
CH3
178
1-NaNO2
2- CuCl
CH3
Cl
NO2
CH3
180
[H]
CH3
Cl
NH2
CH3
181
1-NaNO2
2-CuCl
CH3
Cl
Cl
CH3
182

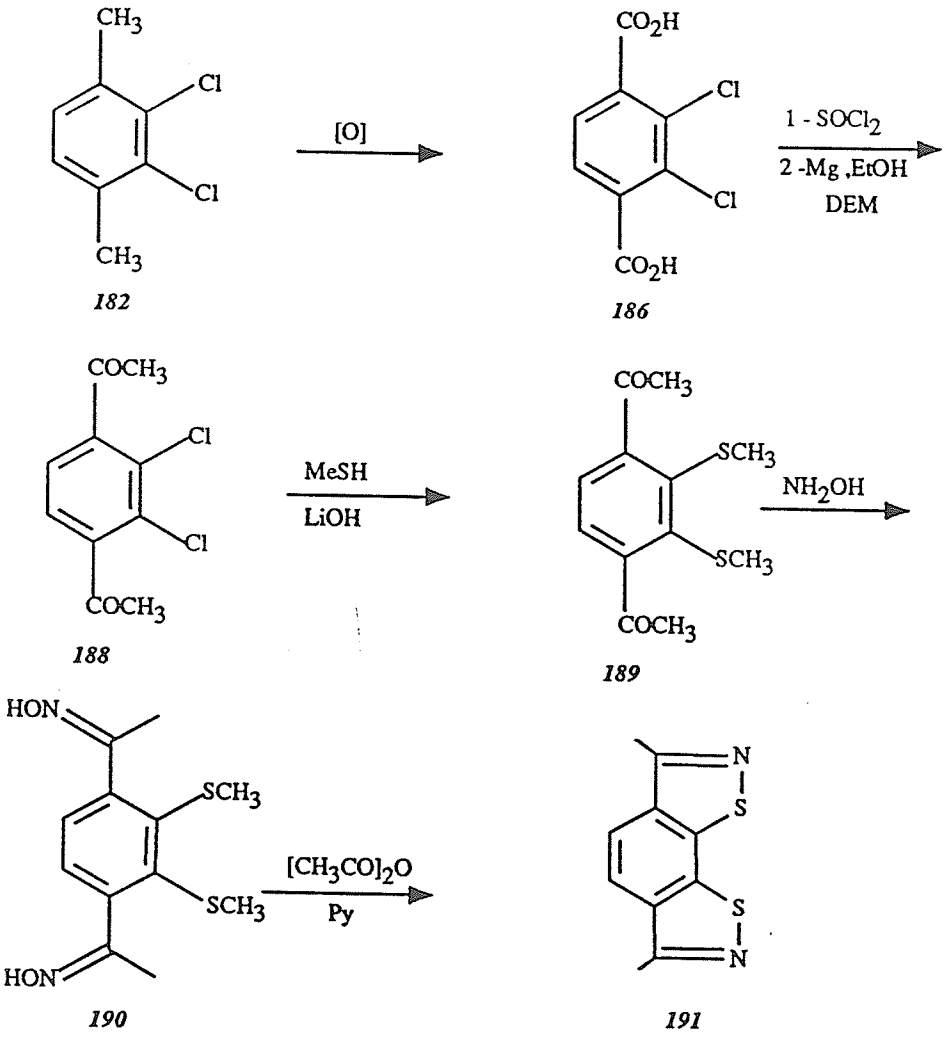
Scheme 88



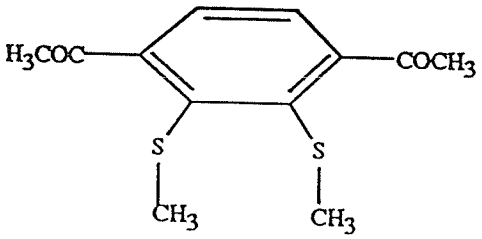
183 184 185 182

Scheme 89

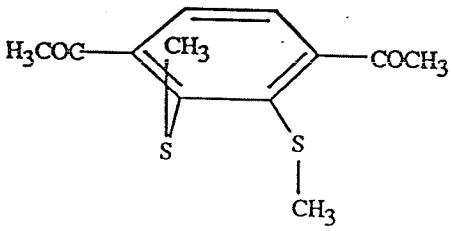
The resulting dichlorodimethylbenzene had a boiling point (230°C) and a pmr spectrum in agreement with the desired 2,3-dichloro-1,4-dimethylbenzene (**182**) (Scheme 89). This compound was converted to the 2,3-dichlorobenzene-1,4-dicarboxylic acid (**186**) (Scheme 90) by potassium permanganate, and further to the acid chloride on treatment with thionyl chloride. Reaction of the acid chloride with ethoxymagnesium diethylmalonate and hydrolysis gave 1,4-diacetyl-2,3-dichlorobenzene (**188**). The pmr spectrum of this compound showed the chemical shift of the two acetyl methyl protons at $\delta = 2.60$ ppm and that of the aromatic protons resonating as a singlet at $\delta = 7.40$ ppm. Conversion of this compound to the *bis*-(methylthio) diketone **189** was then accomplished using lithium methanethiolate in dimethylformamide. The pmr spectrum of this compound exhibited two singlets at $\delta = 1.60$ and 2.07 ppm, assigned respectively to the S-methyl and the acetyl methyl protons. While the δ value of the acetyl methyl protons ($\delta = 2.07$ ppm) is somewhat on the low side compared to acetophenone ($\delta = 2.53$ ppm), this may be the result of orientation with respect to the ring and the neighboring S-methyl group affecting electron density and magnetic field. Disentangling their relative effects could be difficult. The S-methyl protons are considerably out of their normal range. This reflects the lack of planarity of the system. While the S-methyl bond normally lies within the plane of the aromatic ring, steric hindrance with the acetyl group would make this unlikely. Thus, the sulfur orbitals no longer conjugate with the ring, and the sulfur atoms, normally slightly electron releasing, now retain electron density, thus the S-methyl protons resonate at higher field. There may also be some change in the amount of deshielding of the S-methyl groups by the aromatic ring and the carbonyl groups. If the S-methyl groups lie out of the plane of the ring, two conformers are possible, *syn* and *anti*. On steric grounds the latter (**189b**) (Scheme 91) appears more reasonable. The two aromatic protons resonate as a singlet at $\delta = 7.40$ ppm.


CH3
Cl
Cl
CH3
182
[O]
CO2H
Cl
Cl
CO2H
186
1 - SOCl2
2 -Mg ,EtOH
DEM
COCH3
Cl
Cl
COCH3
188
MeSH
LiOH
COCH3
SCH3
SCH3
COCH3
189
NH2OH
HON
SCH3
SCH3
HON
190
[CH3CO]2O
Py
N
S
S
N
191

Scheme 90



189a



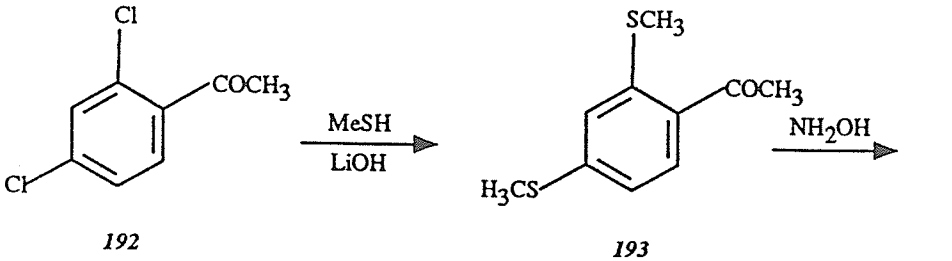
189b

Scheme 91

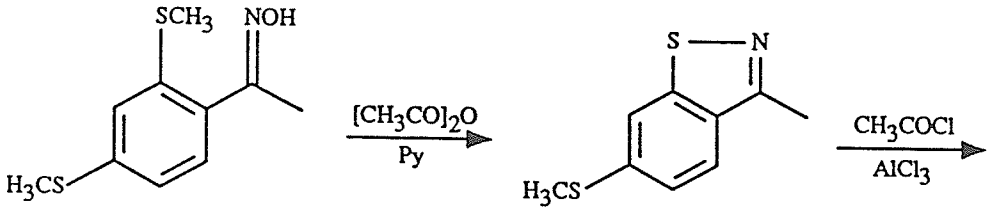
This *bis*-(methylthio)diketone derivative **189** permitted the synthesis of the 3,6-dimethylbenzo-[1,2-*d*:6,5-*d'*]*bis*-isothiazole (**191**) through the oxime **190** followed by treatment with acetic anhydride in pyridine. The compound was eventually obtained as crytalline colorless needles. The pmr spectrum of the benzo-*bis*-isothiazole **191** showed only two singlets at $\delta = 2.86$ and 7.89 ppm corresponding to the methyl and aromatic protons respectively in agreement with the expected symmetry of the molecule.

3.1.4 Synthesis of 3,6-dimethylbenzo [1,2-*d*:3,4-*d'*]*bis*-isothiazole (198)

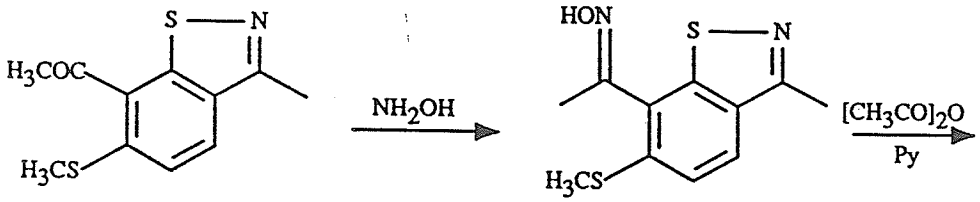
1-Acetyl-2,4-*bis*-(methylthio)benzene (**193**) (Scheme 92) was prepared by treatment of the commercially available 1-acetyl-2,4-dichlorobenzene (**192**) with excess methanethiolate anion in cold dimethylformamide. Its pmr spectrum showed chemical shifts at $\delta = 2.57$, 2.53 and 2.43 ppm corresponding to the acetyl methyl, 2- and 4-S-methyl protons respectively. These are tentatively assigned according to pmr data obtained from Sec. 3.4. The C-5 and C-6 aromatic protons resonate as two doublets at $\delta = 6.93$ and 7.68 ppm respectively and the C-3 proton as a broad singlet at 7.06 ppm (for reason of assignment see Sec. 3.1.2). The infrared spectrum showed carbonyl stretching at 1690 cm^{-1} (the significance of the different values of the carbonyl stretching frequency will be discussed in Sec. 3.4).



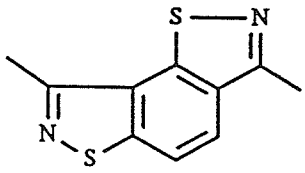
192 *193*



194 *195*



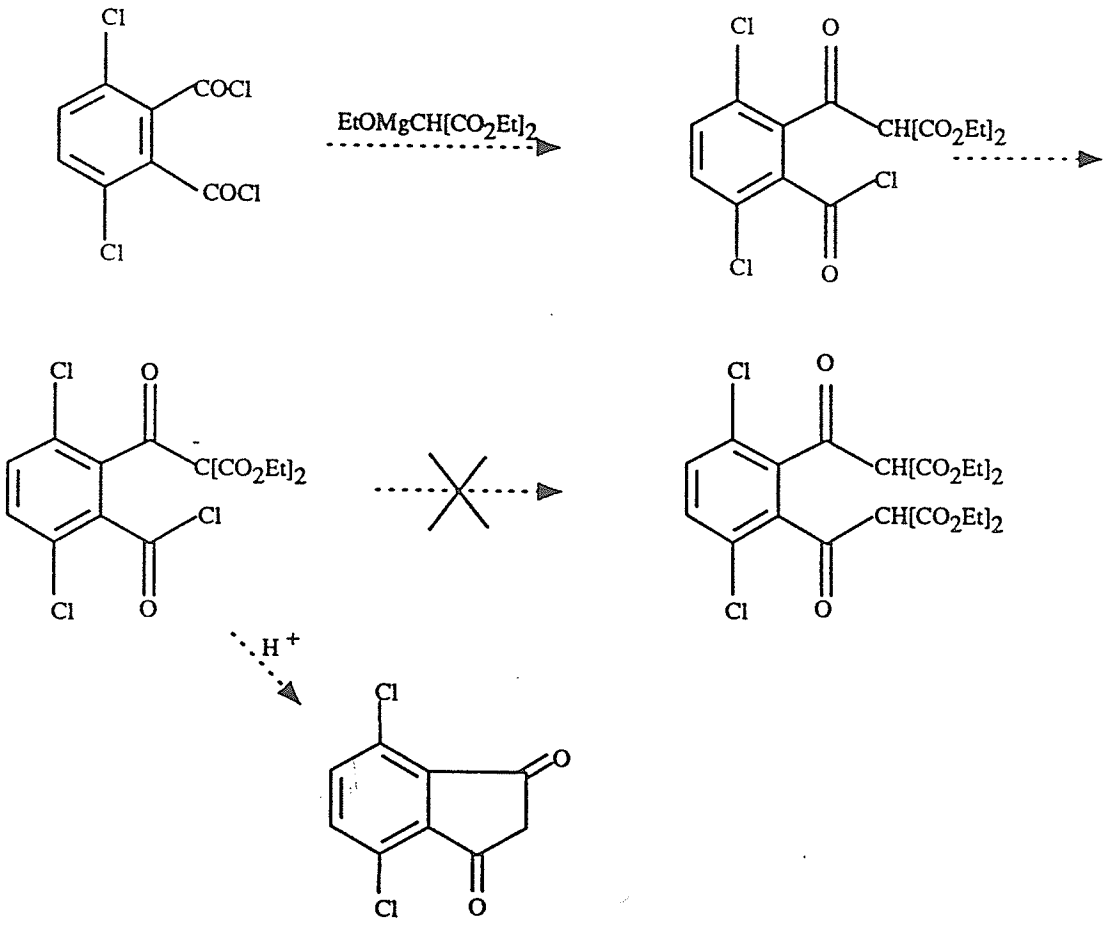
196 197



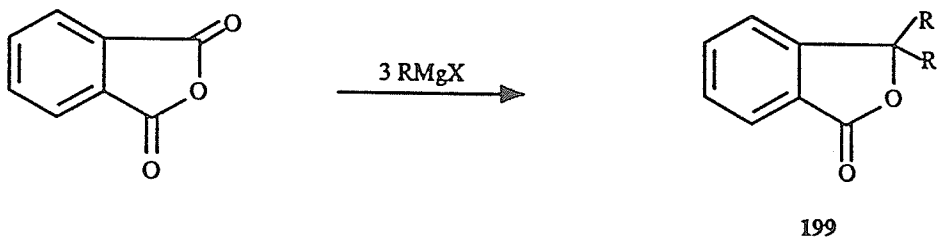
198

Scheme 92

1-Acetyl-2,4-*bis*-(methylthio)benzene (**193**) was converted to the oxime **194** on treatment with hydroxylamine hydrochloride in pyridine, and from the oxime, the 3-methyl-6-methylthio-1,2-benzisothiazole (**195**) was then prepared by refluxing with acetic anhydride in pyridine for 24 hours. The pmr spectrum showed two singlets at δ = 2.50 and 2.63 ppm corresponding to the S-methyl and the 3-methyl protons respectively. The assignment of the chemical shifts were made according to previous report of chemical shifts of the 3-methyl protons of 3-methyl and 3,6-dimethyl-1,2-benzisothiazole which were found to resonate at δ = 2.72 and 2.59 ppm respectively [88CJC(66) 1405]. The benzisothiazole derivative **195** was acylated in methylene chloride using acetyl chloride, aluminum chloride. Previous reports [80JCR(M)2845] indicated the difficulty of acylating benzisothiazoles, i.e. the benzo ring should be somewhat deactivated toward electrophilic substitution by the fused isothiazole ring. Since this reaction was successful, the ring is possibly sufficiently activated by the S-methyl substituent. The acylated compound showed a pmr spectrum with the C-4 and C-5 aromatic protons resonating as two doublets δ = 7.76 and 7.45 ppm respectively. The coupling constant of protons 4 and 5 was found to be J=9Hz, a typical *ortho*-coupling, indicating that the acylated product is the 7-acetyl-3-methyl-6-methylthio-1,2-benzisothiazole (**196**) and not the 5-isomer. No evidence of the other isomer was found. Note that the substitution occurs in the 7 position, i.e. next to the isothiazole ring sulfur, and not in the less hindered 5 position. This appears to be a general reaction and will be discussed later (Sec. 3.3). The infrared spectrum showed the carbonyl stretching frequency at 1640 cm^{-1}. The acetyl product **196** was then converted to the oxime **197** by treatment with hydroxylamine hydrochloride and pyridine, and reaction of this oxime **197** with acetic anhydride in pyridine afforded the 3,6-dimethylbenzo[1,2-*d*:3,4-*d'*]*bis*-isothiazole (**198**) as yellow prisms. The pmr spectrum showed the chemical shifts of the 3- and 6-methyl protons at δ = 2.85 and 2.94 ppm respectively.



Scheme 93



199

Scheme 94

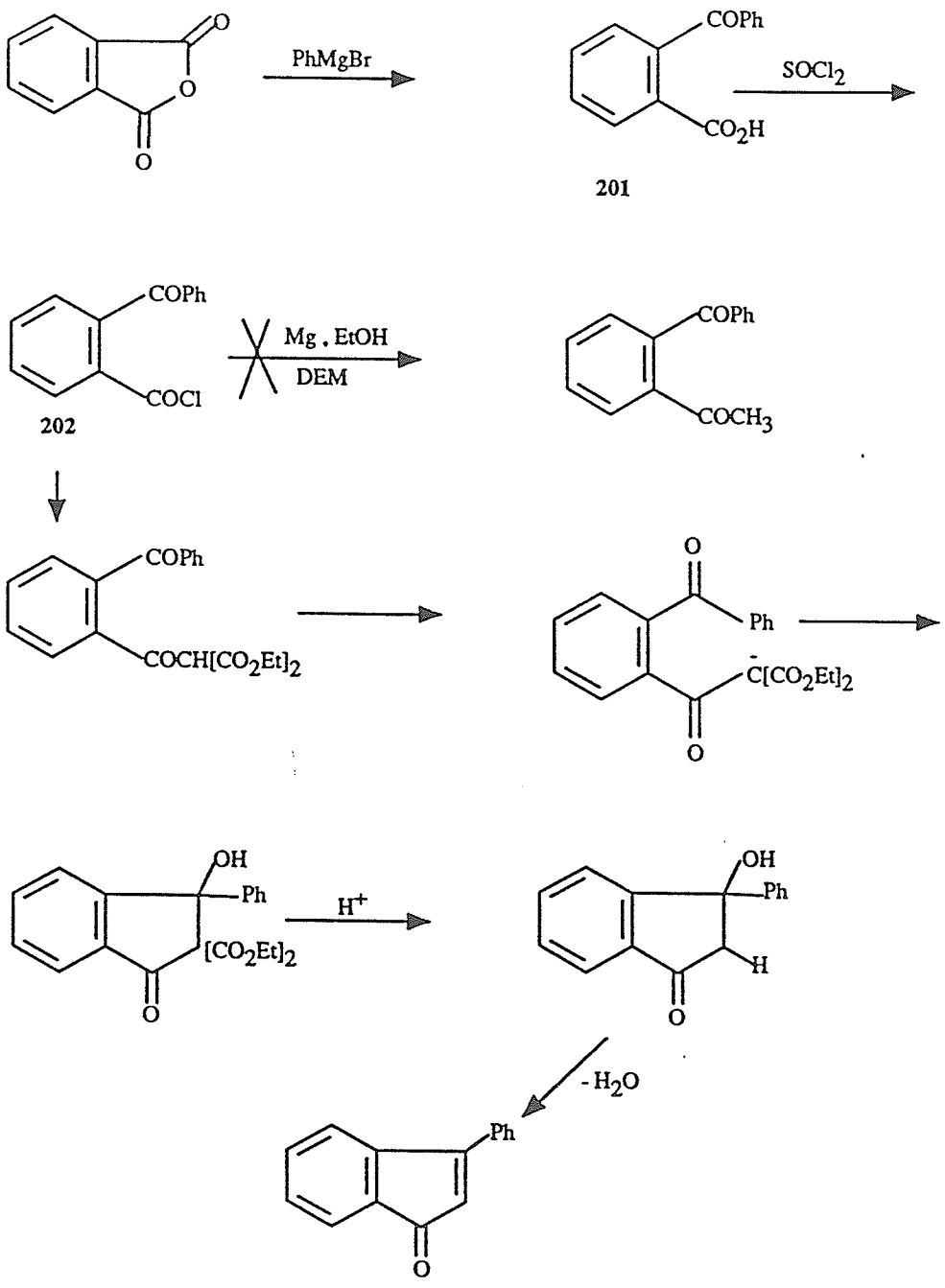
These chemical shifts were tentatively assigned considering the fact that the 3-methyl protons have two *ortho* sulfur containing substituents while the 6-methyl protons have one *ortho* and one *para* sulfur containing substituent which might have a lower shielding effect on the 6-methyl protons. The C-7 and C-8 protons were found to resonate as two doublets at $\delta = 7.97$ and 7.90 ppm respectively (J=9Hz) (for reason of assignment see Sec. 3.1.2).

3.1.5 Attempts towards the synthesis of benzo[1,2-*d*:4,3-*d'*]*bis*-isothiazole (141).

Consideration of the usual synthesis of the diketone from the dicarbonyl chloride that we have used above indicated that it could not be applied to the synthesis of the 1,4-dichloro-2,3-diacetyl benzene for the following reason. The monoacyl malonate derivative obtained from the reaction of the first equivalent of the ethoxymagnesium malonic ester with the 1,4-dichloro-2,3-benzenedicarbonyl chloride would have a more acidic proton than the ethoxymagnesium malonic ester itself, and thus might give an intramolecular reaction between the monoacyl malonate and the other carbonyl chloride function (Scheme 93) leading to an indanedione derivative. It has also been reported that the reactions of phthalic anhydride with different organometallic reagents yield the phthalide derivatives (Scheme 94) [35JCS1367, 51JCS2297]. When Wang and coworkers [47JAS (69) 1909] attempted to treat the 2-acetyl-3-nitrobenzoyl chloride (200) (Scheme 95) with dimethylcadmium, no diacetyl derivative was isolated from the reaction products.

For model studies we attempted to synthesize the 1-acetyl-2-benzoylbenzene using organometallic compounds prior to working with chlorinated precursors. We have prepared 2-benzoylbenzoic acid (Scheme 96) (**201**) from phthalic anhydride using one equivalent of phenylmagnesium bromide [35JCS1367]. (However this can be prepared easily by Friedel-Crafts acylation of benzene by phthalic anhydride). The monoketoacid **201** obtained was then converted to the acid chloride **202** using thionyl chloride, which was treated with one equivalent of ethoxymagnesium malonic ester. Hydrolysis of the resulting product gave a product whose mass spectrum corresponded to a molecular formula of $C_{15}H_{10}O$. Possibly this may be the 3-phenylindenone (**203**) produced by internal condensation. While the mass spectrum fragmentation pattern compared well to that of 9-anthracenecarboxaldehyde, the pmr spectrum results did not correspond to that aldehyde. Because the desired product was not obtained, this approach was not investigated further.

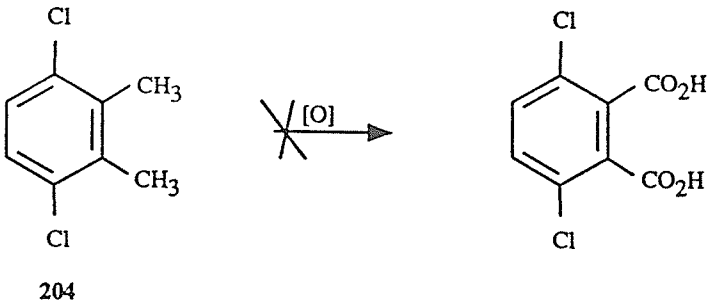
Considering these results and those previously reported, a different route for the synthesis of 2,3-diacetyl-1,4-dichlorobenzene or the corresponding dialdehyde had to be investigated. The next approach we tried toward this synthesis was to start from 1,4-dichloro-2,3-dimethylbenzene (**204**) [34JCS1946] followed by oxidation to 1,4-dichloro-2,3-benzenedicarboxylic acid and functional group interconversion to the aldehyde or the keto derivative. While 3,6-dichlorophthalic anhydride is commercially available, it is very expensive. Therefore, 1,4-dichloro-2,3-dimethylbenzene was synthesized as described by Hinkel [34JCS1946] from the 1-amino-4-chloro-2,3-dimethylbenzene by diazotization of the amino group and replacement of the diazonium group by chlorine.


PhMgBr
COPh
CO_2H
$SOCl_2$
201
COPh
COCl
202
Mg , EtOH
DEM
COPh
$COCH_3$
COPh
$COCH[CO_2Et]_2$
O
Ph
$C[CO_2Et]_2$
O
OH
Ph
$[CO_2Et]_2$
O
H^+
OH
Ph
H
O
$-H_2O$
Ph
O
203

Scheme 96

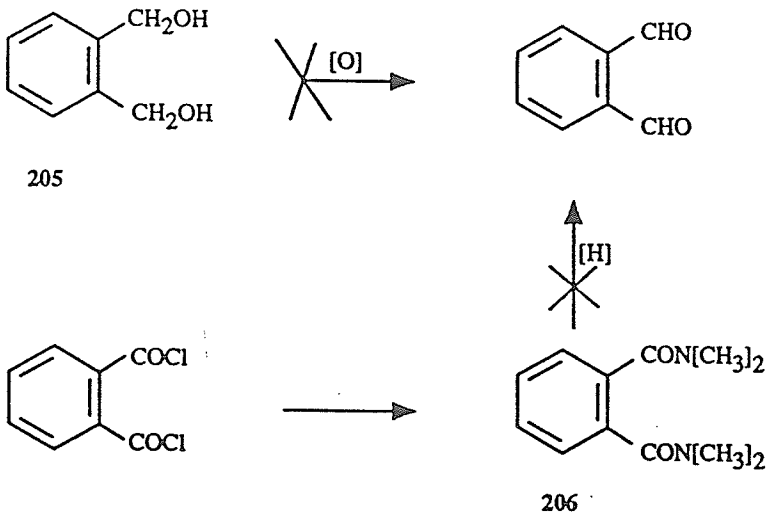
However when the dichloroxylene **204** (Scheme 97) was oxidized with either potassium permanganate or sodium dichromate, none of the desired dichlorodicarboxylic acid could be isolated, in contrast to oxidation of other dichloroxylenes. The starting material however is consumed. It may be that the initially formed acid undergoes oxidative ring fission. Likewise, attempted oxidation with nitric acid, which has been used for some phthalic acids, gave only a mixture of products, none of which corresponded to the desired diacid.

Considering the difficulties encountered in the synthesis of the 1,4-dichloro-2,3-benzenedicarboxylic acid we decided to purchase the 3,6-dichlorophthalic anhydride. The following reactions were however performed using phthalic anyhdride or phthalic acid in order hopefully to establish a successful procedure before the use of the expensive 3,6-dichlorophthalic anhydride. The first approach taken for the conversion of the phthalic acid or anhydride to the dialdehyde followed Brown's method [47JAS(69)1197] involving the reduction to the alcohol using lithium aluminum hydride followed by oxidation using potassium dichromate (Scheme 98) [63OSC(2)541]. Even though the alcohol **205** was produced in high yields, no aldehyde could be detected in the product from the oxidation reaction.



204

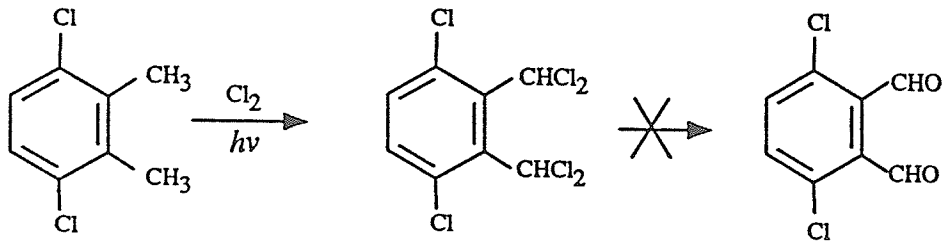
Scheme 97



205

206

Scheme 98



204

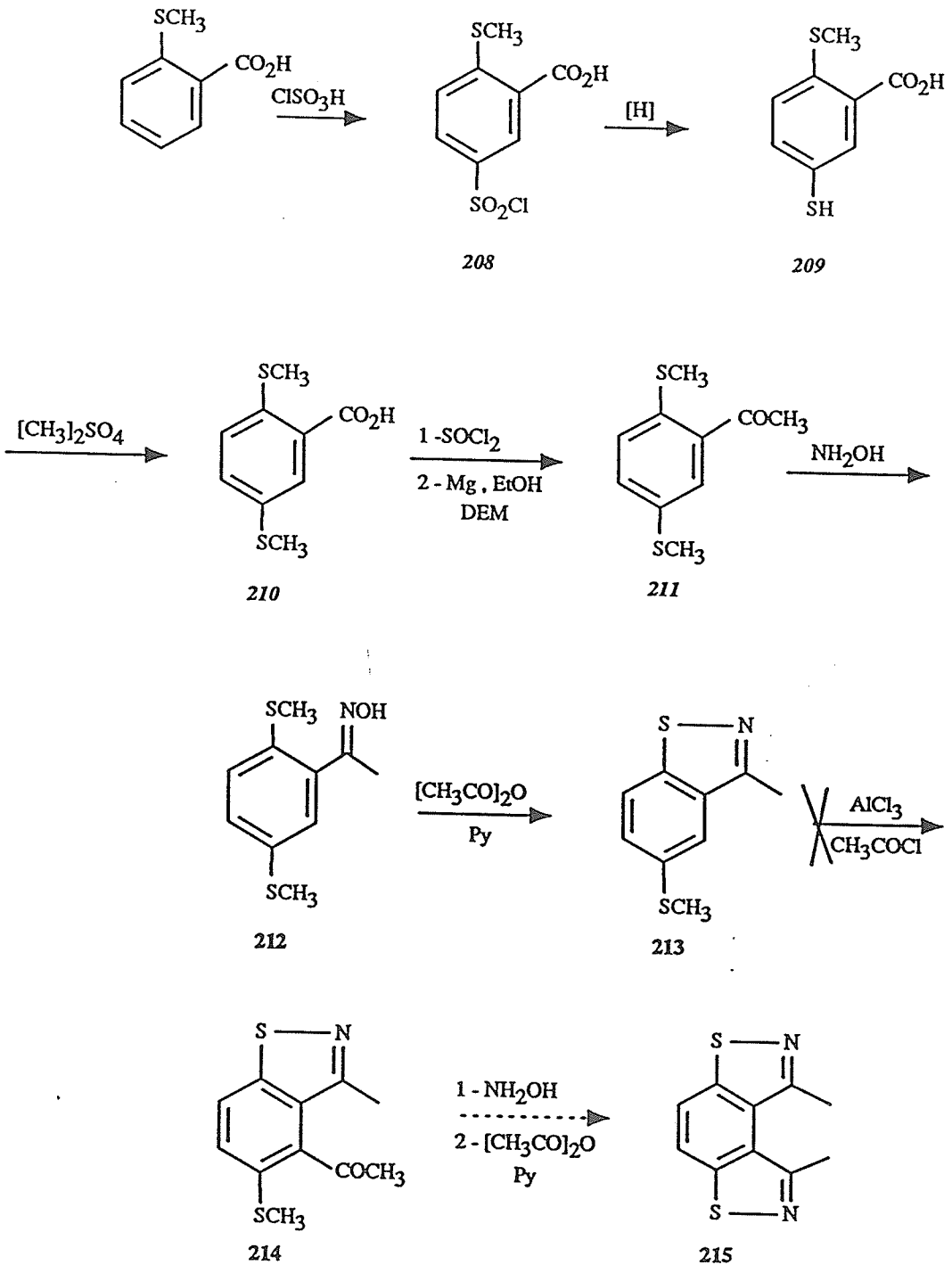
207

Scheme 99

A general method of conversion of a carboxylic acid to the corresponding aldehyde can be achieved through the corresponding amides followed by reduction using lithium aluminum hydride [51CB(84)625]. Therefore the amide was prepared from the 1,2-benzenedicarbonyl chloride by treatment with dimethylamine in benzene, but reduction of the produced amide using lithium aluminum hydride gave a mixture of the desired aldehyde and another product (Scheme 98). This method was unsatisfactory considering the low yield of the aldehyde and the cost of the dichlorophthalic anhydride, and was therefore abandoned.

Another approach attempted for the functionalization of the methyl groups is shown in Scheme 99. The methyl groups could each be disubstituted by chlorine under photochemical conditions, and hydrolysis of the resulting 1,4-dichloro-2,3-*bis*-(dichloromethyl) benzene should give dichlorophthaldehyde. This hydrolysis reaction can be effected [63OS(C)(4)807] with potassium oxalate. While the chlorination of the xylene appeared to proceed satisfactorily to form the required chloroxylene, treatment of this material with potassium oxalate afforded a mixture which appeared to contain a small amount of the dialdehyde.

Since the benzo[1,2-*d*:4,3-*d'*]*bis*-isothiazole (**141**) seemed inaccessible starting from the 1,4-dichloro-2,3-dimethylbenzene, a different route (illustrated in Scheme 100) was sought involving the synthesis of 2,5-*bis*-(methylthio)acetophenone (**211**) which can be converted through its ketoxime **212** to the 3-methyl-5-methylthio-1,2-benzisothiazole (**213**). This could possibly then be acylated followed again by ring closure through the ketoxime.


SCH3
CO2H
ClSO3H
SO2Cl
[H]
SH
208
209
[CH3]2SO4
1 -SOCl2
2 - Mg , EtOH
DEM
COCH3
NH2OH
210
211
NOH
[CH3CO]2O
Py
AlCl3
CH3COCl
212
213
1 - NH2OH
2 - [CH3CO]2O
214
215

Scheme 100

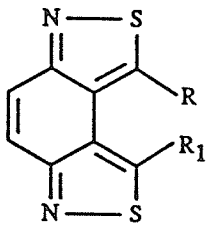
This approach was pursued through the initial synthesis of 2-methylthio-5-chlorosulfonylbenzoic acid (**208**) from 2-methylthiobenzoic acid by chlorosulfonation using chlorosulfonic acid (Scheme 100).

The sulfonylchloride derivative **208** obtained was then reduced to the mercaptan **209** using zinc in hydrochloric acid. When **209** was treated with methyl sulfate and sodium hydroxide 2,5-*bis*-(methylthio)benzoic acid (**210**) was obtained. This was converted to the acid chloride then treated with ethoxymagnesium malonic ester to give 2-5-*bis*-(methylthio)acetophenone (**211**) after hydrolysis. The pmr spectrum of the ketone **211** showed three upfield singlets at δ = 2.55, 2.46 and 2.33 ppm corresponding to the acetyl methyl, 2- and 5-methylthio protons respectively, in agreement with the desired acetophenone **211**.

Treatment of the ketone **211** with hydroxylamine hydrochloride and pyridine afforded the oxime **212**, which was then cyclized to the 3-methyl-5-methylthio-1,2-benzisothiazole (**213**) using acetic anhydride in pyridine. The pmr spectrum showed the 3-methyl and the 5-methylthio protons at δ = 2.66 and 2.54 ppm respectively. Attempts to acylate this benzisothiazole derivative **213** using aluminum chloride and acetyl chloride afforded only decomposed product and the starting isothiazole. This result is in agreement with that reported by Scrowston and coworkers [80JCR(M)2845] stating that 3-methyl-1,2-benzisothiazoles and its 5-substituted derivatives (e.g. Br, OMe) were all unreactive in attempted Friedel-Crafts acylation.

While acylation of the 3-methyl-6-methylthio-1,2-benzisothiazole (195) was successful (Sec. 3.1.4), this might be attributed to the presence of the methylthio group at the 6-position which increases the reactivity at the more reactive 5- and 7-positions. On the other hand the 5-methylthio group in the 3-methyl-5-methylthio-1,2-benzisothiazole (213) increases the reactivity in the less reactive 4- and 6- positions.

In light of the difficulties encountered in the synthesis of the benzo[1,2-*d*:4,3-*d'*]*bis*-isothiazole (141) through the more usual methods above, a less conventional approach was then considered. A synthesis through the benzo[1,2-*c*:4,3-*c'*]*bis*-isothiazole derivative 216 (Scheme 101), followed by ring modification appeared possible. 1,4-Diaminotetralin (219) could be prepared (Scheme 102) from 1-aminotetralin via acetylation followed by nitration. Subsequent hydrolysis of this product should afford the 1-amino-4-nitrotetralin (218). Reduction of the nitrotetralin derivative 218 should yield the 1,4-diaminotetralin (219) which on reaction with N-sulfinylmethane sulfonamide should give the benzisothiazole derivative 220.

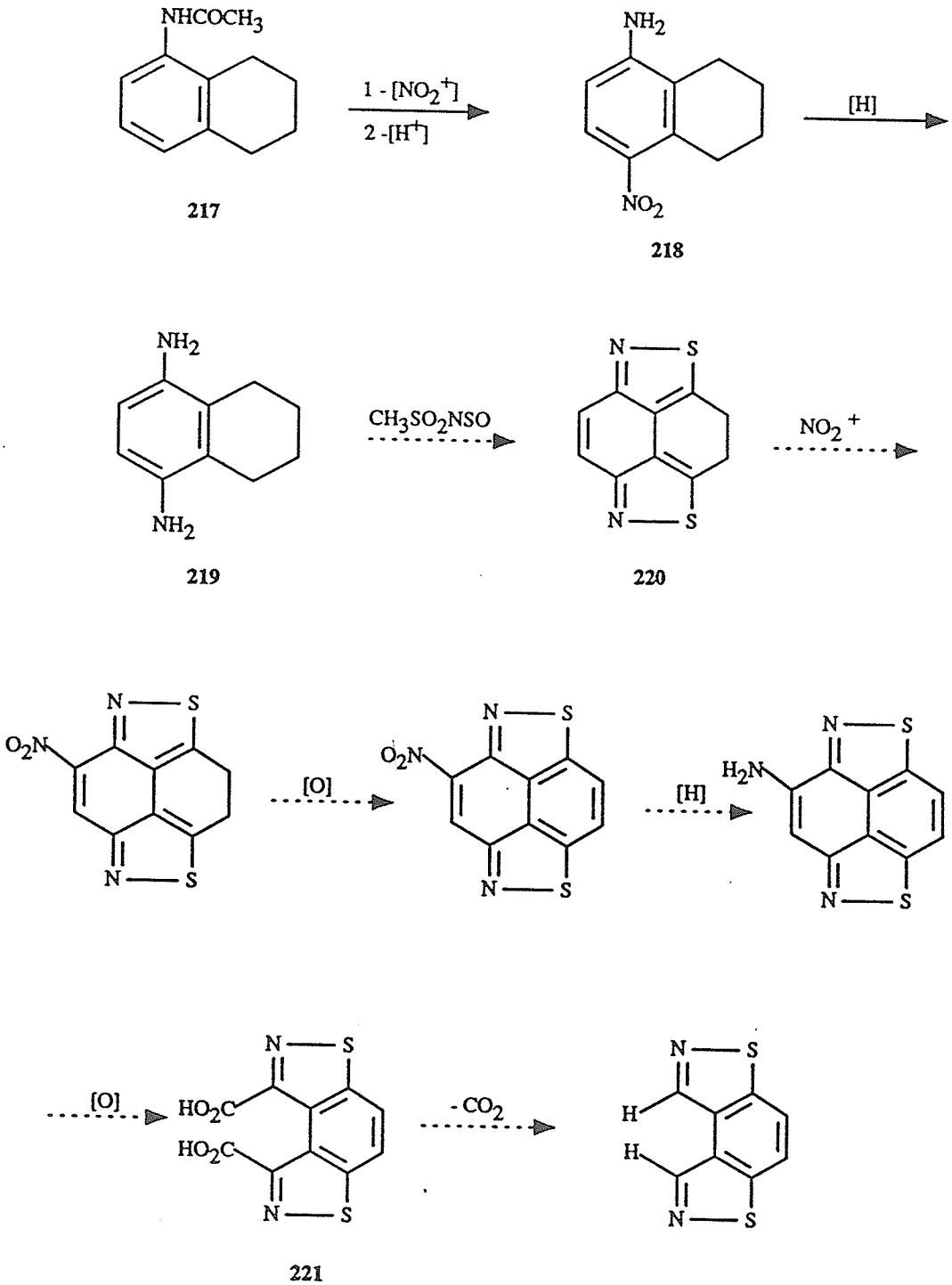


216

$R = R_1 = H$ or

$R, R_1 = CH_2 - CH_2$

Scheme 101


NHCOCH3
1 - [NO2+]
2 -[H+]
NH2
NO2
[H]
217
218
NH2
NH2
CH3SO2NSO
N — S
N — S
NO2 +
219
220
O2N
[O]
H2N
[H]
[O]
HO2C
HO2C
- CO2
H
H
221

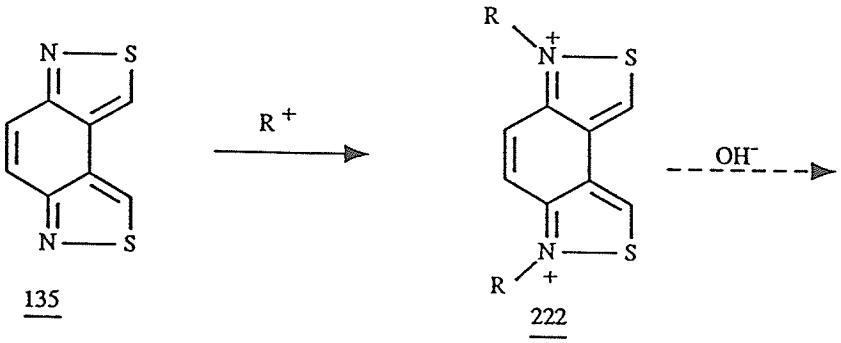
Scheme 102

Nitration, aromatization, reduction of the nitro group, then oxidation should give the diacid **221**, which should decarboxylate readily, as with isothiazole-3- or 5-carboxylic acids [84CHC(6)131] to form the unsubstituted system. It would be necessary to nitrate the aromatic ring before the stage of aromatization, as consideration of intermediate benzenonium ion structures for nitration of the highly fused system indicated substitution would be more likely to occur in the other ring, i.e. position 7 or 8. Treatment of the 1,4-diaminotetralin (**219**) with two equivalents of N-sulfinylmethanesulfonamide however yielded starting material along with some N-sulfinyl-1,4-diaminotetralin and this approach was abandoned. These results were unexpected since a 2,1-benzisothiazole derivative has been synthesized from an *ortho*-aminomethylene derivative [88JHC(25)1095]. Failure of the reaction here might be due to some steric factors affecting ring closure, but is rather puzzling since the related compound **135** below was synthesized successfully.

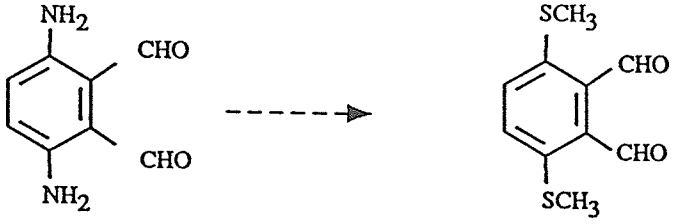
Another possible approach is shown In Scheme 103. This approach proceeds through the synthesis of benzo [1,2-*c*:4,3-*c'*]*bis*-isothiazole (**135**) followed by conversion to the quaternary salt **222** and ring decomposition to the 1,4-diamino-2,3-benzenedicarboxaldehyde (**223**).

The aldehyde **223** could then be modified to the 1,4-*bis*-(methylthio)-2,3-benzenedicarboxaldehyde through functional group interconversion.

The basis of this scheme is the report [73JCS(P1)1863] that *o*-aminobenzaldehyde is readily obtained by treatment of 2,1-benzisothiazole with ethyl chloroformate in an aqueous tetrahydrofuran medium, followed by basification and steam distillation of the intermediate *o*-ethoxycarbonylaminobenzaldehyde (Scheme 104). A plausible mechanism is shown.

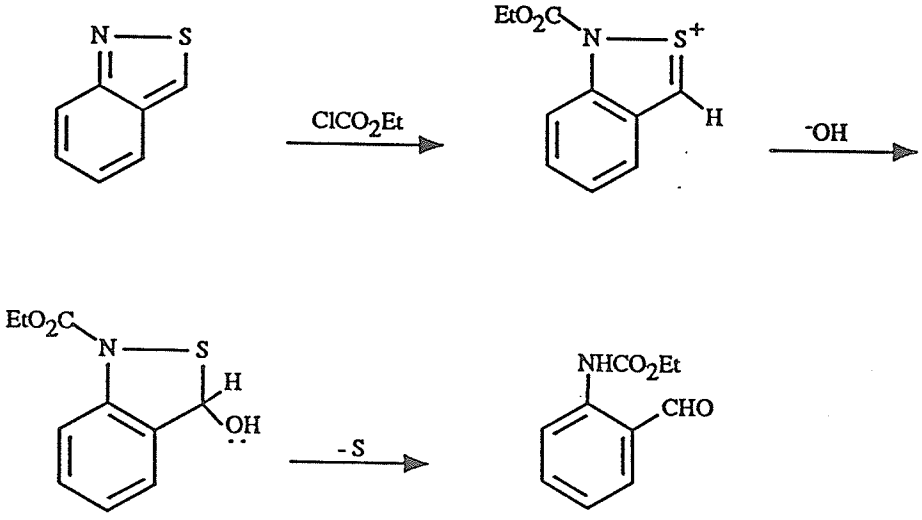


135 222



223 224

Scheme 103



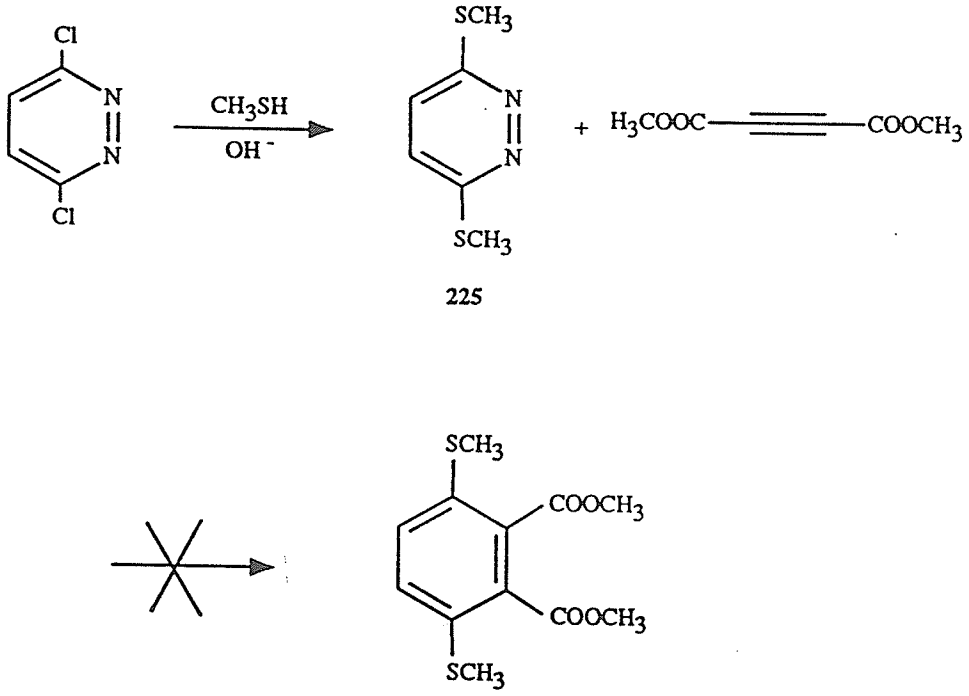
Scheme 104

The benzo[1,2-*c*:4,3-*c'*]*bis*-isothiazole (**135**) was synthesized as described by Davis [80JHC(17)533] from the 1,4-diamino-2,3-dimethylbenzene using two equivalents of N-sulfinylmethanesulfonamide. However, treatment with ethyl chloroformate followed by basification afforded no observable reaction. When the benzo-*bis*-isothiazole **135** was warmed neat with ethyl chloroformate no salt could be observed in the reaction product. The reaction failure might be due to the low nucleophilicity of the *bis*-isothiazole system leading to the inability to form a salt with the chloroformate reagent.

Diels-Alder type reactions are very useful methods for synthesizing six membered rings. This suggested the use of *bis*-alkylthio-1,2-diazines (**225**). Compounds of this type are potential dienes for Diels-Alder reactions and the intermediates could rearomatize by loss of nitrogen. A possible approach is outlined in Scheme 105.
3,6-*Bis*-(methylthio)-1,2-diazine was made by reaction of the 3,6-dichloro-1,2-diazine with lithium methanethiolate. As a trial it was allowed to react with dimethyl acetylenedicarboxylate. However, the reaction failed to work and this approach was not further investigated. As 1,2-diazines are reported to work best by reverse electron demand, i.e. dienophile needs electron releasing groups, this may be why this reaction failed. It is difficult to envisage suitable electron releasing groups that could be converted to ketones, yet that are compatible with alkylthio substituents. The difficulty here is in having a leaving group that is better than a sulfur containing substituents.

3.2 Synthesis of Benzo[*c,d'*]*bis*-isothiazoles

In this chapter we describe the synthesis and attempted synthesis of some benzo-*bis*-isothiazoles with one of the isothiazole rings "*c*" fused to the benzene ring while the other is "*d*" fused.


Cl
N
N
Cl
CH3SH
OH-
SCH3
N
N
SCH3
+ H3COOC
COOCH3
225
SCH3
COOCH3
COOCH3
SCH3

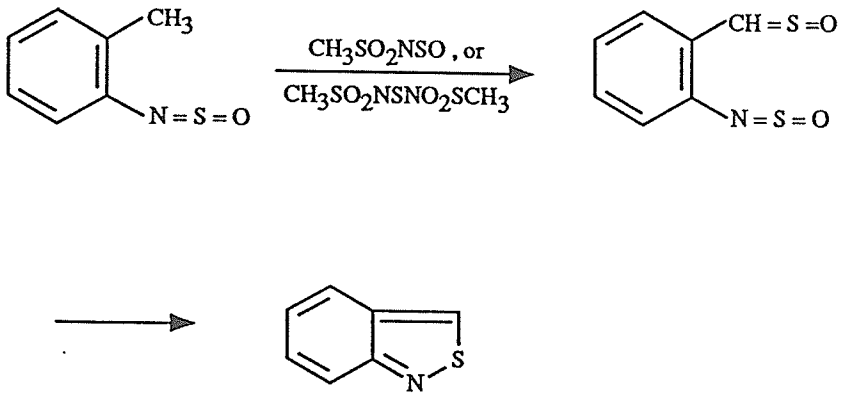
Scheme 105

In these syntheses the 1,2-benzisothiazole ring was again synthesized from the oxime using acetic anhydride in pyridine [88CJC(66)1405], while the Singerman method [75JHC(12)877] was chosen for the synthesis of the 2,1-benzisothiazole ring. This latter reaction usually gives high yields and avoids the production of chlorinated side products, which are a problem when the thionyl chloride method of Davis is used [68CC1547]. The mechanism of the reaction is unclear; two possible sequences however have been proposed by Singerman [75JHC(12)877]. The first involves the interaction between N-sulfinyl-*o*-toluidine and N-sulfinylmethanesulfonamide. The intermediate produced then cyclizes with loss of sulfur dioxide to give the 2,1-benzisothiazole (Scheme 106a). The second sequence, shown in Scheme 106b, involves the abstraction of a proton from the methyl group followed by cyclization.

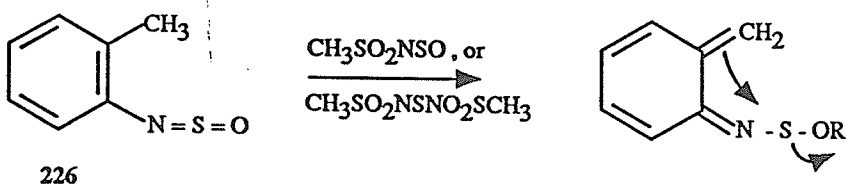
Two routes were chosen for the syntheses of different benzo [*c*,*d*']*bis*-isothiazoles, either a) conversion of substituents on an initially formed 1,2- or 2,1-benzisothiazole ring followed by closure of the second ring, or b) synthesis of a suitable precursor for the 1,2- and the 2,1-benzisothiazole rings followed by consecutive closure of each ring.

3.2.1 Synthesis of 3-methylbenzo[1,2-*c*:5,6-*d*']*bis*-isothiazole (232)

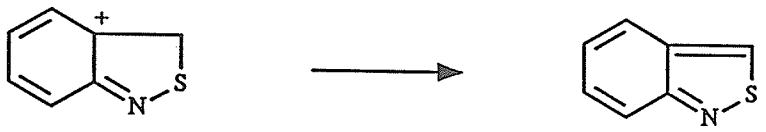
The benzo-*bis*-isothiazole **232** was prepared using the first route, i.e. 3,5-dimethyl-1,2-benzisothiazole was first synthesized followed by substitution on the aromatic ring to afford a suitable precursor for the construction of the second ring (Scheme 107).



Scheme 106 a



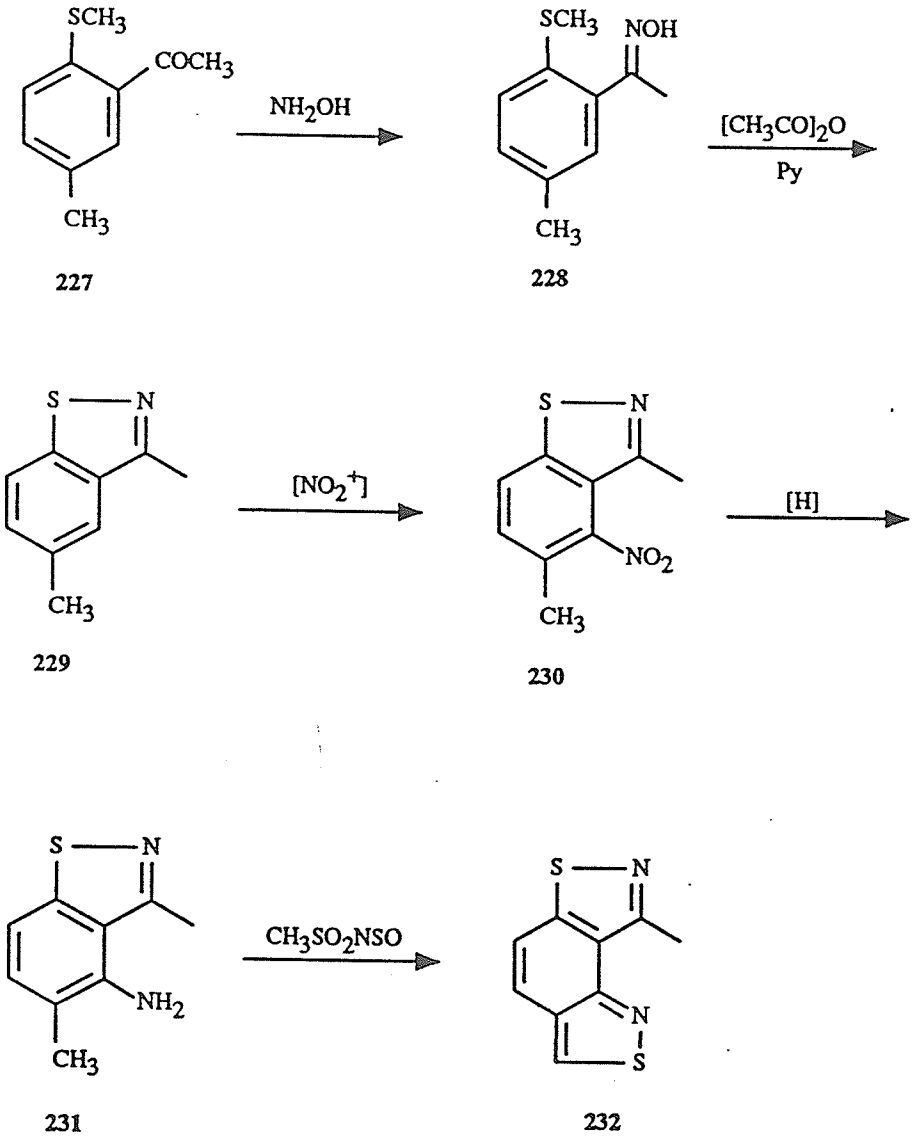
226



3

R = $SONHSO_2CH_3$, $CH_3SO_2NHS{=}NSO_2CH_3$

Scheme 106 b



227 228 229 230 231 232

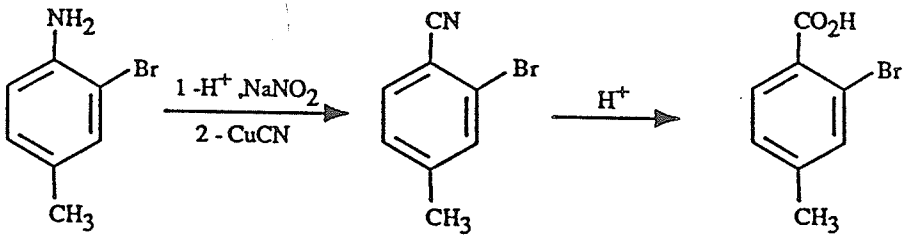
Scheme 107

5-Methyl-2-methylthioacetophenone (**227**) was prepared by acylation of 1-methyl-4-methylthiobenzene following a previously reported method [09CB(42)537]. When the ketone was treated with hydroxylamine in pyridine the reaction product was the corresponding oxime **228**, which was then cyclized in acetic anhydride and pyridine to afford the desired 3,5-dimethyl-1,2-benzisothiazole (**229**) [88CJC(66)1405]. When this benzisothiazole **229** was nitrated using a mixture of nitric and sulfuric acid only one product was observed. The pmr spectrum showed the 3- and 5-methyl peaks at $\delta = 2.61$ and 2.45 ppm respectively. The assignment of the 3- and 5-methyl protons was made considering the deshielding effect of the isothiazole ring toward the 3-methyl protons. The aromatic protons were found to resonate as two doublets at $\delta = 7.42$ and 7.89 ppm with a coupling constant J = 8 Hz corresponding to an *ortho* coupling indicating that the nitrated product was the 3,5-dimethyl-4-nitro-1,2-benzisothiazole (**230**) and not the less hindered 6- or 7-nitro derivative. No signs of other isomers were observed (this phenomenon will be discussed in Section 3.3). When the nitrobenzisothiazole derivative was reduced with iron in glacial acetic acid, pale yellow crystals were obtained corresponding to the 4-amino-3,5-dimethyl-1,2-benzisothiazole (**231**).

Cyclization of the aminomethylbenzisothiazole derivative **231** with N-sulfinyl-methanesulfonamide and pyridine gave one product, which on crystallizing from nitromethane gave colorless needles whose properties were consistent with the desired 3-methylbenzo[1,2-*c*:5,6-*d*']*bis*-isothiazole (**232**). The pmr spectrum of this material showed a singlet at $\delta = 9.26$ ppm typical for the proton at C-3 of a 2,1-benzisothiazole ring, indicating the successful formation of the second isothiazole ring. The two aromatic protons were found to resonate as two doublets at $\delta = 7.76$ and 7.67 ppm, J = 9 Hz, corresponding to an *ortho* coupling. These are assigned to the 7- and 8-aromatic protons respectively (for reason of assignment see Section 3.1.2). These results also further confirm that the nitration of the compound **229** proceeds in the 4 position.

3.2.2 Synthesis of 3-methylbenzo[1,2-*c*:6,5-*d*']*bis*-isothiazole (243)

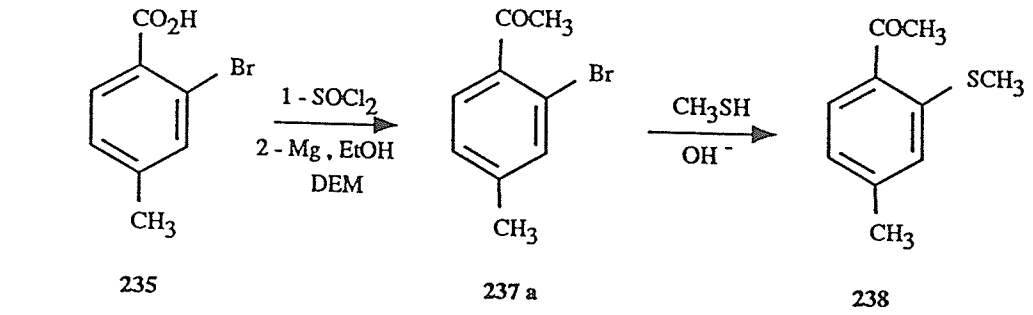
This synthesis was accomplished using the first route, in which 3,6-dimethyl-1,2-benzisothiazole was first synthesized. Nitration and reduction of the nitro group gave an *o*-toluidine derivative, a suitable precursor for cyclization of the second ring. 2-Bromo-4-methylbenzoic acid (235) (a suitable precursor for the synthesis of the 3,6-dimethyl-1,2-benzisothiazole) was synthesized using a previously reported method [28A(462)24] from the *p*-toluidine by acetylation followed by bromination. Subsequent hydrolysis afforded the 1-amino-2-bromo-4-methylbenzene (233) which was then converted via a Sandmeyer procedure (Scheme 108) using cuprous cyanide to the 2-bromo-4-methylbenzonitrile (234). Hydrolysis gave the 2-bromo-4-methylbenzoic acid (235). The acid 235 when treated with thionyl chloride formed the acid chloride 236, which was then converted to



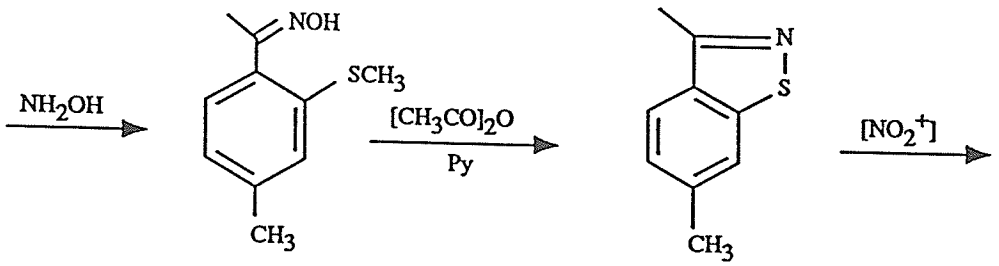
233 234 235

Scheme 108

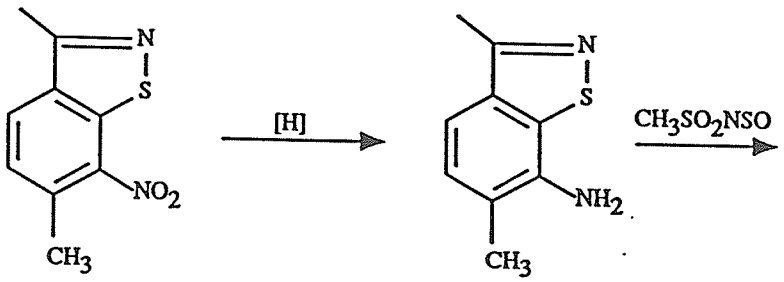
the 2-bromo-4-methylacetophenone (237a) using the ethoxymagnesium malonate method (Scheme 109). The pmr of the ketone showed two upfield single peaks at $\delta = 2.33$ and 2.58 ppm corresponding to the methyl and acetyl methyl protons respectively. The 2-bromo-4-methylacetophenone (237a) was then converted to the 4-methyl-2-methylthioacetophenone (238) using excess lithium methanethiolate in cold dimethylformamide. The pmr spectrum of the resulting product showed an overlapping peak at $\delta = 2.33$ ppm corresponding to the S-methyl and the ring methyl protons and a



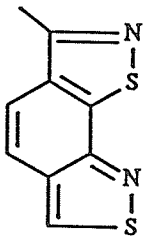
235 237 a 238



239 240



241 242



243

Scheme 109

single peak at $\delta = 2.46$ ppm corresponding to the acetyl methyl protons (for reason of assignment see Sec. 3.1.1). The C-5 and C-6 protons were found to resonate as two doublets at $\delta = 6.93, 7.70$ ppm respectively (J=9Hz) while C-3 aromatic proton resonates as a broad singlet at $\delta = 7.03$ ppm.

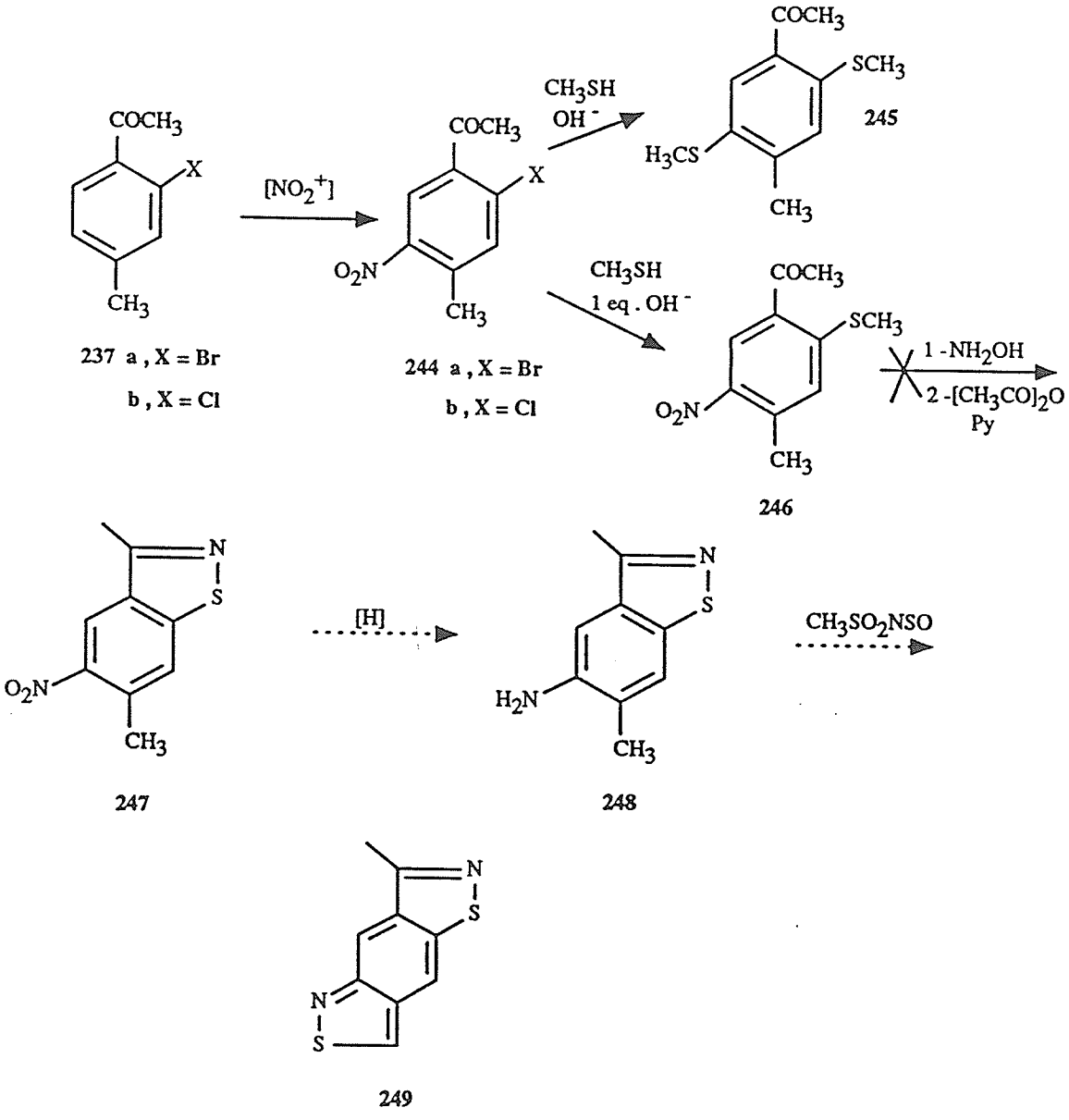
The 4-methyl-2-methylthioacetophenone was then converted to the oxime **239** using hydroxylamine hydrochloride and pyridine which was treated with acetic anhydride in pyridine without further purification. When the resulting material was purified by preparative thick layer chromatography a pale yellow liquid was obtained which showed two upfield peaks in the pmr spectrum at $\delta = 2.50$ and 2.70 ppm corresponding to the 6- and 3-methyl protons respectively (for reason of assignment see Sec. 3.2.1). No signal corresponding to an S-methyl proton was observed in agreement with the desired 3,6-dimethyl-1,2-benzisothiazole (**240**). The C-4 and C-5 aromatic protons were found to resonate as two doublets at $\delta = 7.80$ and 7.23 ppm respectively (for reason of assignment see Sec. 3.1.2). When this benzisothiazole derivative was nitrated using fuming nitric in sulfuric acid only one product was observed. Examination of the pmr spectrum showed two peaks at $\delta = 2.96$ and 2.77 ppm corresponding to the 3- and 6-methyl protons respectively. The two aromatic protons were found to resonate as two doublets with coupling constant J = 8 Hz corresponding to an *ortho*-coupling, suggesting that the resulting product is the 3,6-dimethyl-7-nitro-1,2-benzisothiazole **241** and not the less sterically hindered 5-nitro derivative. No signs of other isomers were observed (this will be discussed in Sec. 3.3). Reduction of the 7-nitrobenzisothiazole derivative using iron in glacial acetic acid gave the 7-amino-3,6-dimethyl-1,2-benzisothiazole (**242**). The pmr of the amine derivative **242** showed two singlets at $\delta = 2.72$ and 2.33 ppm corresponding to the 3- and 6-methyl protons respectively (for reason of assignment see Sec. 3.2.1), while the protons of the amino group were evident as a broad singlet at $\delta = 3.92$ ppm and the aromatic protons as two doublets at $\delta = 7.20$ and 7.31 ppm. The cyclization of the

o-toluidine derivative **242** was then effected by refluxing with N-sulfinylmethanesulfonamide and pyridine in benzene to yield the 3-methylbenzo[1,2-*c*:6,5-*d*']*bis*-isothiazole (**243**) as colorless prisms.

The pmr spectrum of the *bis*-isothiazole **243** showed two singlets at $\delta = 2.80$ and 9.27 ppm corresponding to the 3-methyl protons and the proton on the 2,1-benzisothiazole ring respectively. The downfield absorption appears to be a characteristic feature of the proton in the 3-position of the 2,1-benzisothiazoles. This absorption appears as a singlet, and its exact position depends on the substituent group attached to the benzenoid ring [75JHC(12)877]. The aromatic protons were found to resonate as two doublets (J=9Hz). A nuclear Overhauser difference spectrum from the 3-methyl and the C-4 protons suggested that the C-4 proton resonates at $\delta = 7.60$ ppm and the C-5 at $\delta = 7.68$ ppm.

3.2.3 Attempts towards the synthesis of 3-methylbenzo[1,2-*c*:4,5-*d*']*bis*-isothiazole(249)

A possible approach for the synthesis of the *bis*-isothiazole **249** is illustrated in Scheme 110. This involves the nitration of 2-bromo-4-methylacetophenone (**237a**) to the 2-bromo-4-methyl-5-nitroacetophenone (**244a**) followed by nucleophilic displacement of the bromine to obtain the 4-methyl-2-methythio-5-nitroacetophenone (**246**). This subsequently could be converted through the oxime to the 1,2-benzisothiazole derivative **247**. Reduction of the nitro group would yield an *o*-toluidine derivative **248**, which could be cyclized to the 3-methylbenzo[1,2-*c*:4,5-*d*']*bis*-isothiazole (**249**) using N-sulfinylmethanesulfonamide and pyridine. The 2-bromo-4-methylacetophene was synthesized as described in Sec. 3.2.2. Nitration of this using one equivalent of fuming nitric in sulfuric acid afforded the nitro derivative **244a**. The pmr spectrum of the nitro


COCH3
X
CH3
237 a , X = Br
b , X = Cl
[NO2+]
O2N
244 a , X = Br
b , X = Cl
CH3SH
OH -
H3CS
SCH3
245
CH3SH
1 eq . OH -
246
1 -NH2OH
2 -[CH3CO]2O
Py
N
S
247
[H]
H2N
248
CH3SO2NSO
249

Scheme 110

compound **244a** showed chemical shifts at $\delta = 2.67$ and 2.73 ppm corresponding to the 4-methyl and the acetyl methyl protons respectively. The C-3 and C-6 aromatic protons were found to resonate as two broad singlets at $\delta = 7.74$ and 8.25 ppm respectively. The lower field shift of the C-6 proton compared to the C-3 is due to the higher deshielding effect of the acetyl and the nitro groups towards the *o*-proton than the *m*-proton. Our aim was then to displace the bromine in the 2-bromo-4-methyl-5-nitroacetophenone (**244a**) with methanethiolate anion using lithium hydroxide and methanethiol in dimethylformamide. The compound obtained was however the 4-methyl-2,5-*bis*-(methythio)acetophenone (**245**) rather than the 5-nitro derivative **246**, i.e. a nitro group, as well as a bromine atom had been displaced.

The pmr spectrum showed three peaks in the upfield position, their integration corresponding to twelve protons in agreement with the displacement of the 5-nitro group with a methanethiolate anion. These results are in agreement with the reported result [78JOC(43)2049] that describes several examples of facile nitro displacement by methanethiolate anion where the activation is due to an *ortho*- or *para*-methythio function. The mass spectral data confirmed the identity of the compound by giving a parent peak at 226. Nucleophilic displacement of the bromine atom without affecting the nitro group might have been accomplished using one equivalent of potassium methanethiolate in methanol according to a previously reported method [71JCS(C)3994]. Owing to the low yield and tediousness encountered in the current synthesis of the starting 2-bromo-4-methylacetophenone (**237a**), this reaction has been reinvestigated starting from the 2-chloro-4-methylacetophenone (**237b**).

Although 2-chloro-4-methylacetophenone (**237b**) was reported [16CB(49)2222] as the sole product of the Friedel-Crafts acetylation of 3-chlorotoluene, more recent work [85CPB(33)2809] has in fact shown that there are two products of the acylation: the

compound above, and the 4-chloro-2-methyl-isomer. In the original work the structural assignment was made on the basis of the oxidation to 2-chloro-1,4-benzenedicarboxylic acid. It may be that this was the only product that was isolated from the oxidation reaction. The authors, however, reported the further isolation of 2-chloro-4-methyl-5-nitroacetophenone by nitration of the acylated product. This scheme appeared a quicker route to a suitable precursor of the benzo-*bis*-isothiazole **249**, and has been re-investigated.

The acylation reaction did indeed give a mixture of two products, as detected by pmr. The mixture was then nitrated as described, and from the crude product a reasonably pure compound, m.p. 68-70°, was isolated by fractional crystallization. Borsche [16CB(49)2222] reported that the melting point of this compound was 74-76°. Since the other product of the nitration appears to be lower in melting point, it seems reasonable that this compound is mainly the 2-chloro-4-methyl-5-nitro isomer. Treatment of this compound with one equivalent of lithium methanethiolate in dimethylformamide gave a bright yellow compound, m.p. 145°, whose pmr spectrum and other data indicated that it was pure, and was the desired 4-methyl-2-methylthio-5-nitroacetophenone. In this case the chlorine had been successfully replaced, without further replacement of the nitro group. This ketone was converted to its oxime under the usual conditions, but the oxime failed to give any isothiazole under the pyridine/acetic anhydride conditions. It appears that a nitro-group *ortho* or *para* to the methylthio-group is not compatible with the cyclisation reaction.

3.3 Studies of the Electrophilic Substitution on 1,2- and 2,1-Benzisothiazoles

Substitution reactions of 4- and 5- substituted 1,2-benzisothiazoles have been described

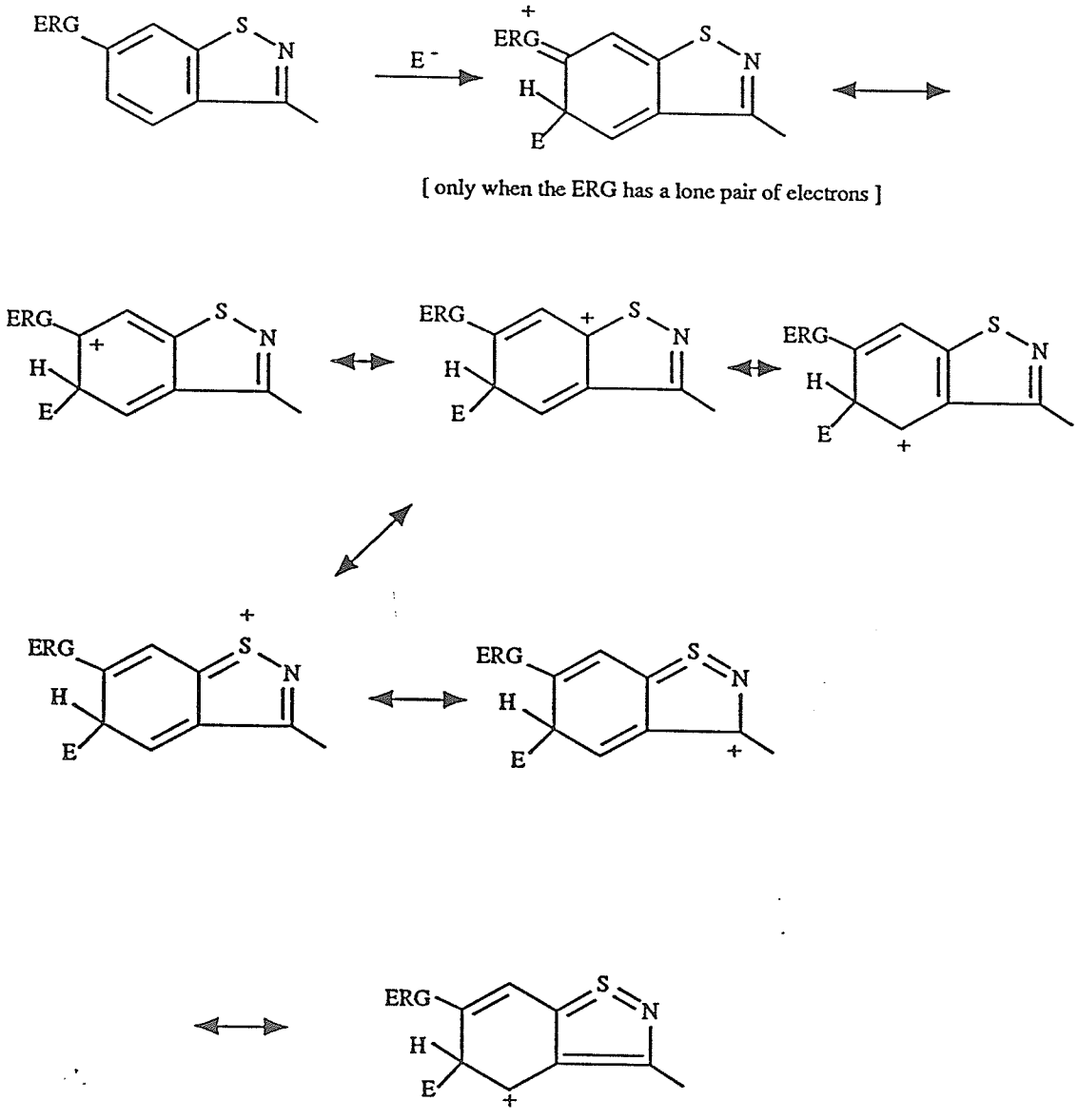
before [80JCR(M)2845]. Also nitration studies of 4-, 5- and 6-methyl-2,1-benzisothiazole have also been reported [80JHC(17)533,537], and in Sec. 3.1 and 3.2 we described the acylation of the 3-methyl-6-methylthio-1,2-benzisothiazole and the nitration of the 3,5- and the 3,6-dimethyl-1,2-benzisothiazoles. In this section we wish to discuss the preference of substitution of benzisothiazole derivatives in terms of charge distribution and resonance stabilization of the intermediates of these benzisothiazoles. Clarke and coworkers [80JCR(M)2845] have studied the electrophilic substitution of the 5-acetamido-, 5-amino-, 5-bromo-, 5-hydroxy, and 5-methoxy-1,2-benzisothiazoles involving bromination and nitration reactions. All of these reactions performed were found to yield the 4-substituted derivative exclusively, with the exception of the 5-bromo-3-methyl-1,2-benzisothiazole which gave a mixture on bromination.

In the synthesis of benzo[*c,c'*]*bis*-isothiazoles, Davis and coworkers [80JHC(17)533,537] have performed nitration reactions on 5- and 6-methyl-2,1-benzisothiazole. Nitration in these compounds was found to occur at the 4- and 7- position respectively. In our own work we found that 1,2-benzisothiazoles substituted at the 5-position with *ortho/para* directing groups undergo electrophilic reactions at the 4-position while the 6- substituted compounds undergo further substitution at the 7- position. From the previous results one can conclude that the substitution reactions on benzisothiazoles containing an *ortho/para* directing group are controlled by the substituent rather than the isothiazole ring, even with the weak electron donating methyl group. We now wish to discuss the preference for substitution of the 5- substituted benzisothiazole at the 4- position and the 6- substituted ones at the 7- position. Palmer has used the linear combination of Gaussian orbital approach to the Hatree-Fock method for the calculation of the electron densities in the 1,2- and 2,1-benzisothiazoles [78JMS(43)33,203]. While their results have been used successfully to predict the site of electrophilic substitution in 1,2-benzisothiazole (C-5 and C-7), they do not predict the site of electrophilic substitution in 2,1-benzisothiazole (C-5

and C-7), as the electron density is calculated to be highest on C-3. Electron density distribution also cannot rationalize the preference of substitution on the 4-position rather than the 6-position in the 1,2-benzisothiazoles as it is predicted that C-6 will have a higher electron density than C-4.

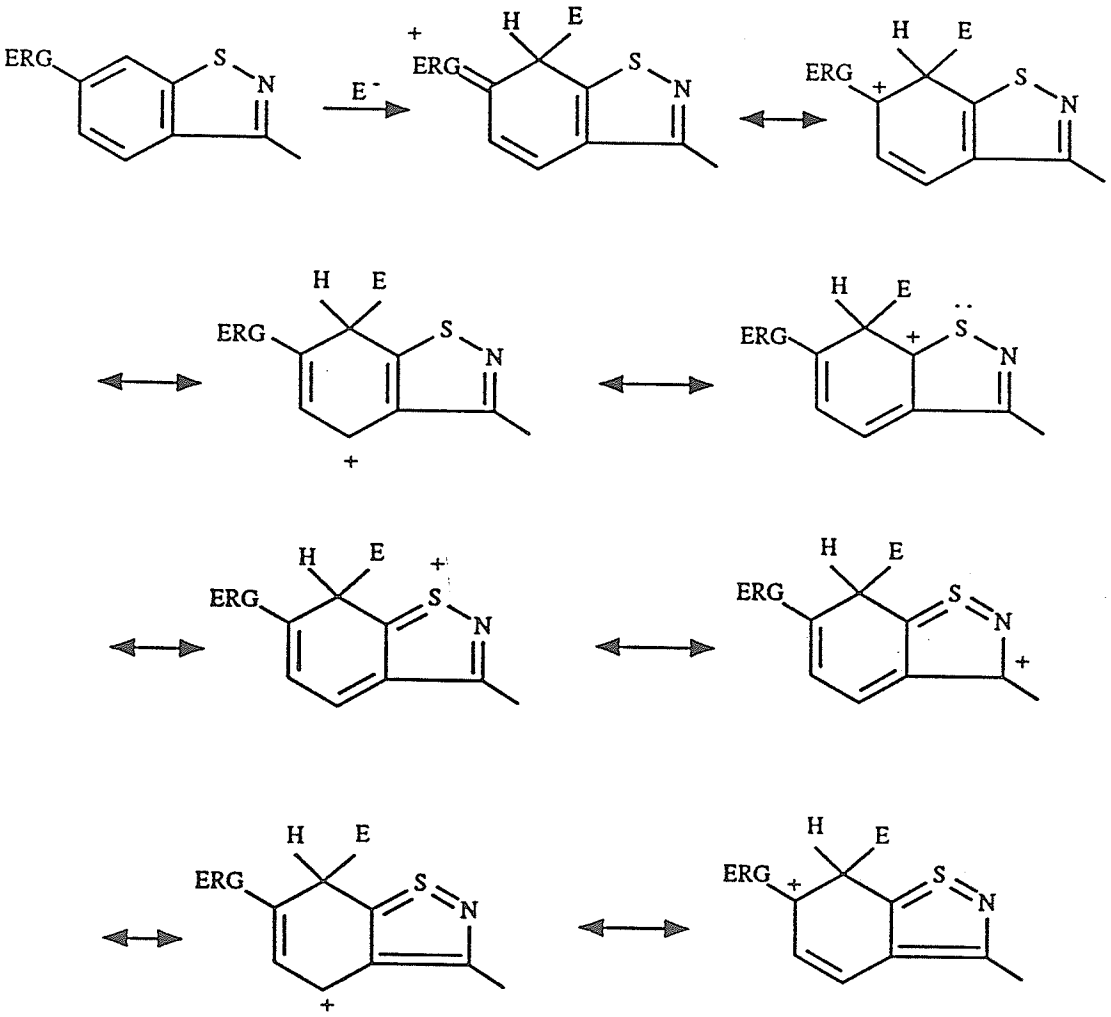
It may not be surprising to find that the site of electrophilic substitution cannot be reliably predicted from the electron density distribution since the first step of these reactions is most likely endothermic with a late transition state (Hammond postulate). For such reactions the stability of the intermediate benzenonium ion would be a better predictor of site of attack, i.e. by looking at the intermediate resonance structures for electrophilic attack in the 5- and 7- positions, (Scheme 111, 112), one can anticipate preferential 7-substitution due to the presence of eight intermediate resonance structures, with three of those intermediate structures retaining the aromatic stability of the isothiazole ring, while the 5- substitution would yield seven intermediate resonance structures, with only one intermediate retaining the aromatic stability. This rationalization is similar to that proposed by Bordwell and Stange [55JAS(77)5939] for substitution preference in the 4-position of 5-aminobenzo[*b*]thiophene derivatives. Preference of substitution in the 7-position over the 5-position in 4- substituted 1,2-benzisothiazoles can also be rationalized in the same manner, where the 7- substitution has nine intermediate resonance structures with the aromaticity of the isothiazole ring retained in three of those intermediates, while the 5- substitution has eight intermediates with the aromaticity retained in only two of those intermediates (Scheme 113, 114). The preference for 7-substitution can also be attributed to less steric hindrance in the 7- than in the 5- position.

Intermediate resonance structures for electrophilic attack:

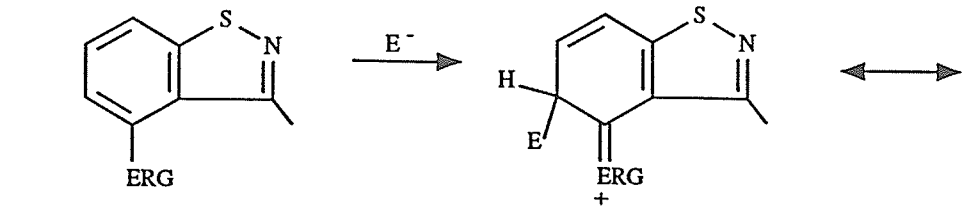


Scheme 111

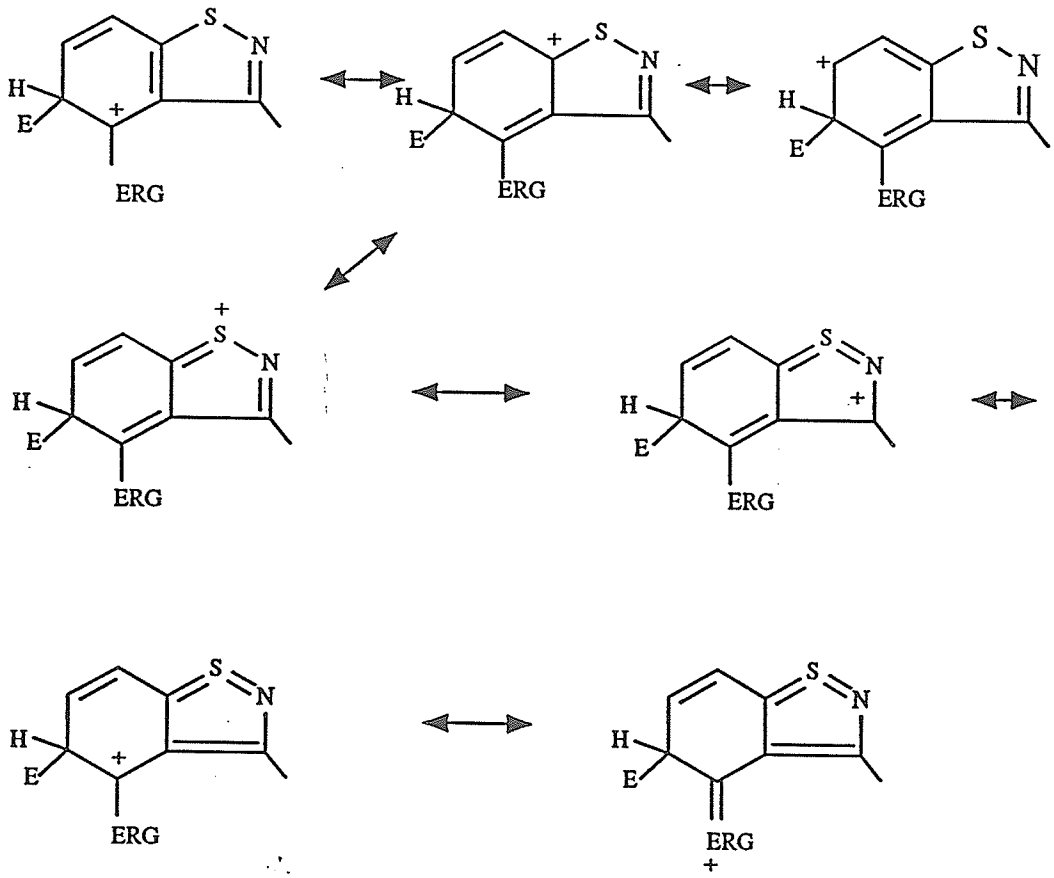
Intermediate resonance structures for electrophilic attack:



Scheme 112

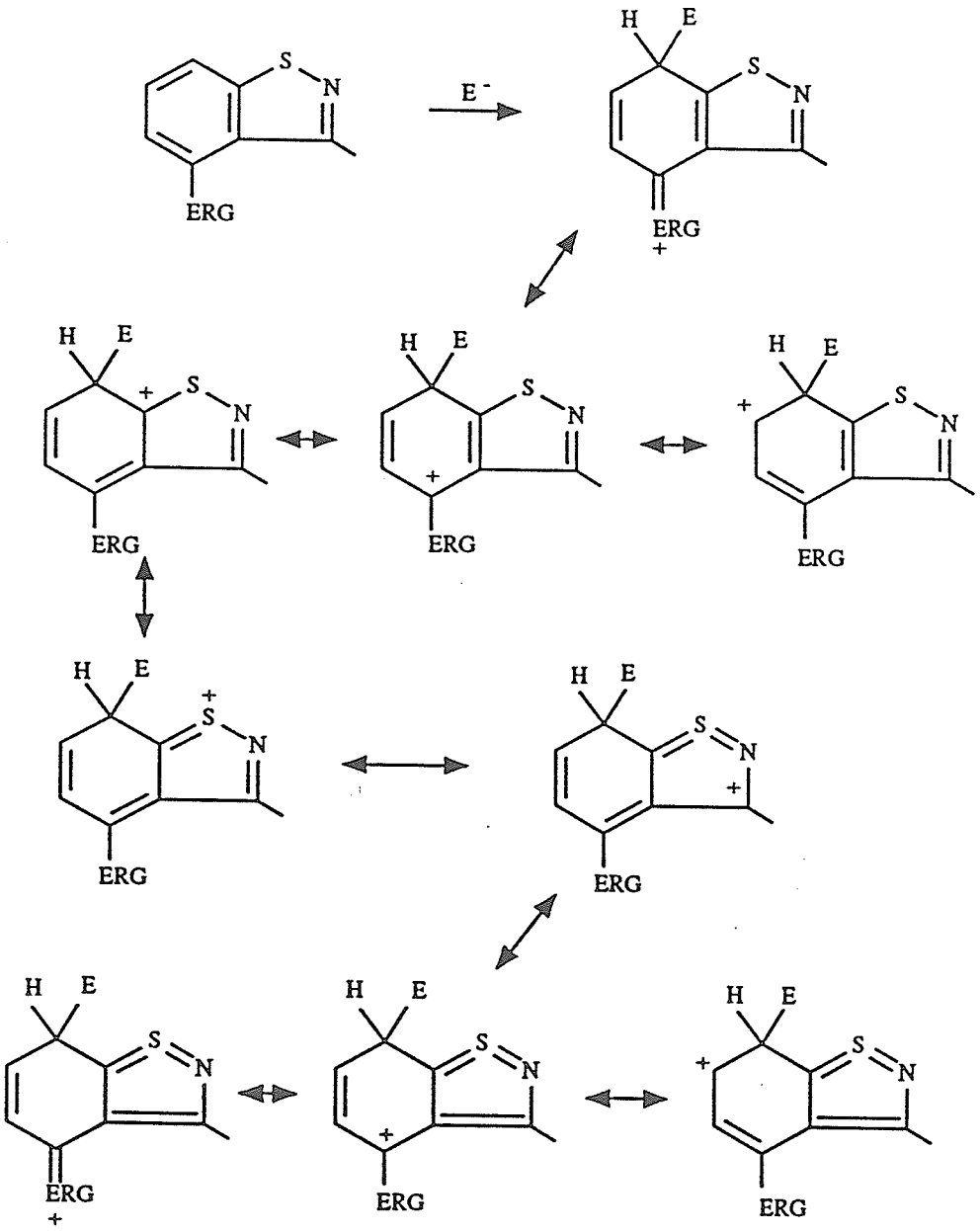


[only when the ERG has a lone pair of electrons]



Scheme 113

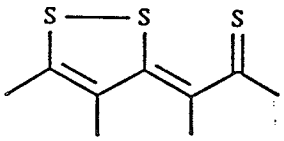
Intermediate resonance structures for electrophilic attack:



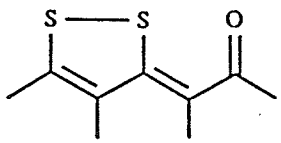
Scheme 114

3.4 Investigation of Fused Isothiazoles and Related Systems

The electronic configuration and bonding in 1,2-dithiole derivatives **250** are currently open to discussion. Classical Lewis bonding theory does not appear to explain all the properties of these compounds [71AHC(13)161]. A survey published by Johnstone and Ward gives a good summary of the problems involved [69TCA(14)420]. Whenever x-ray determinations have been made on structure **250** and **251** it has been found that the three atoms, S, S, and S or S, S and O are approximately colinear. The carbonyl stretching vibration is markedly affected in these 3-acylmethylene-1,2-dithioles. Infrared evidence shows the absence of the usual carbonyl frequencies in the 1620-1720 cm^{-1} range, with one or more strong bands in the 1500-1600 cm^{-1} range.



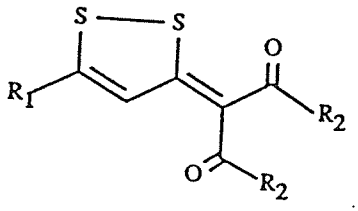
250



251

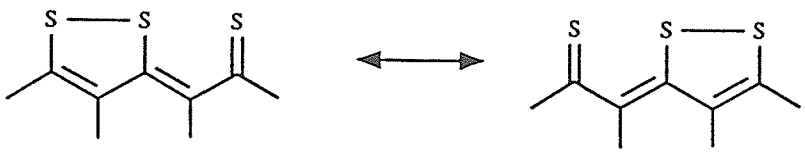
Scheme 115

The difference between the stretching vibration of the carbonyl group in the *cis*-[1530-1540 cm^{-1}] and the *trans*-[1620-1640 cm^{-1}] α-(1,2-dithiol-3-ylidine) β-diketones (**252**) indicates that there is a special effect between one sulfur atom and the neighboring carbonyl. Also the thione properties, expected for structures such as the 3-thioacylmethylene-1,2-dithioles, are in fact not observed to the same extent as for simpler thiones.



252

Thus, it appears that some effect by the rest of the molecule is exerted on the sulfur and oxygen atoms of the exocyclic function. One earlier explanation given for this behaviour of the ketone and thione groups was the rapid equilibrium between valence isomers, although no real proof of individual existence of such isomers has been found for this particular equilibrium. The unique characteristics of these compounds have also been attributed to "single bond - no bond resonance" (Scheme 116) or to the presence of tetravalent sulfur (Scheme 117). The last two proposals were generally preferred due to x-ray evidence that showed that the O-S-S atoms for the 3-acylmethylene-1,2-dithioles (254) and the S-S-S atoms for 3-acylthiomethylene-1,2-dithioles (253) are nearly aligned. There is also some shortening of the O-S distance in 254 (2.41Å) and the S-S distance in 253 (2.36Å) in comparison with the van der Waals contact distance (3.20 and 3.40Å respectively) [64JPC(68)441]. From all these considerations it has been concluded that a bonding of moderate strength exists between the dithiole ring sulfur and the exocyclic sulfur or oxygen atom. On the basis of this, it is probably more reasonable to name these compounds as 1, 6, 6aλ^4 trithiapentalenes and 1, 6, 6aλ^4 oxadithiapentalenes respectively.



250 a 250 b

Scheme 116

253 254

Scheme 117

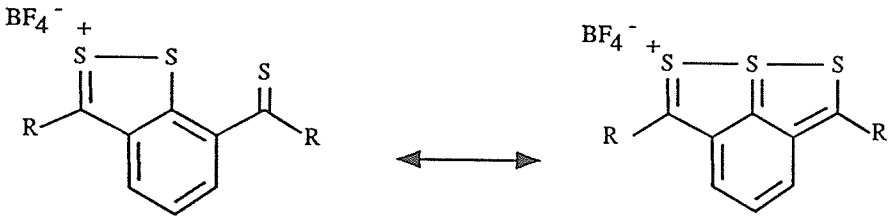
255 256

Scheme 118

The pmr spectra of the 1, 6, 6aλ^4 trithiapentalenes (253) show the magnetic symmetry of symmetrically substituted structures. While this may be the result of a rapid exchange between valence isomers, it seems more and more accepted that this is a real case of equivalence corresponding to a symmetrical pattern of bonding.

There is some possibility that compounds of the type 255 (Scheme 118), i.e. 7-acetyl-1,2-benzisothiazole, would exhibit tetravalency of the sulfur atom by utilization of sulfur d orbitals, as they have some structural resemblances to the trithiapentalenes 253. One such possible resonance contributor 256 is shown. In such a case the carbonyl absorption should be considerably altered, i.e. to lower frequency. In light of this hypothesis we have investigated the synthesis and properties of 7-acetyl-3-methyl-1,2-benzisothiazole (255).

Somewhat related to this, it has also been reported that a thioacylbenzodithiolium salts 257 (Scheme 119) demonstrate symmetry in the pmr, i.e. both aryl groups are equivalent, suggesting some ring interaction due to single-bond no-bond resonance, rapid valency tautomerism or contributions from structures of type 258 with hypervalency of the central sulfur.

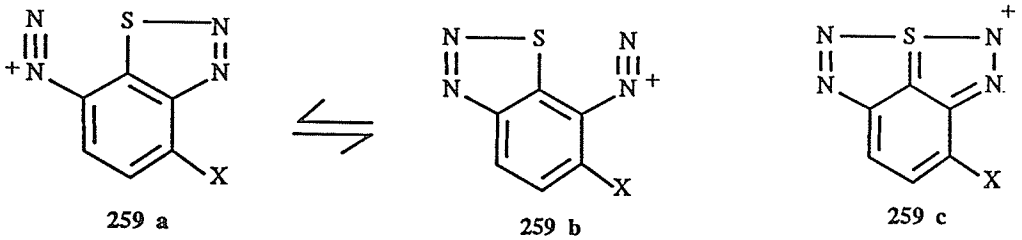


257 258

a R = Ph

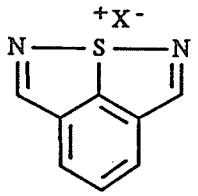
b R = p-$CH_3C_6H_4$

Scheme 119

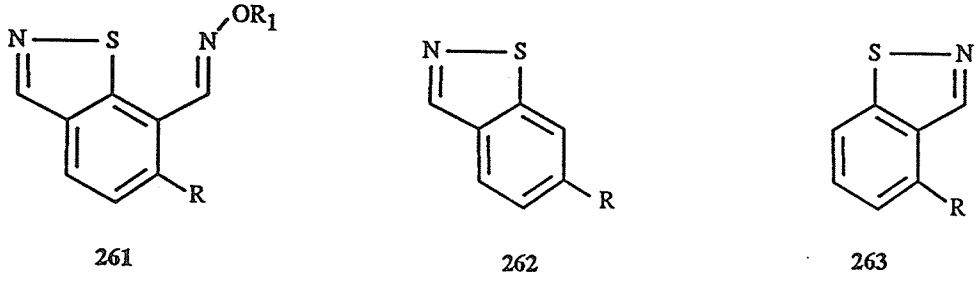


259 a 259 b 259 c

Scheme 120



260



261 262 263

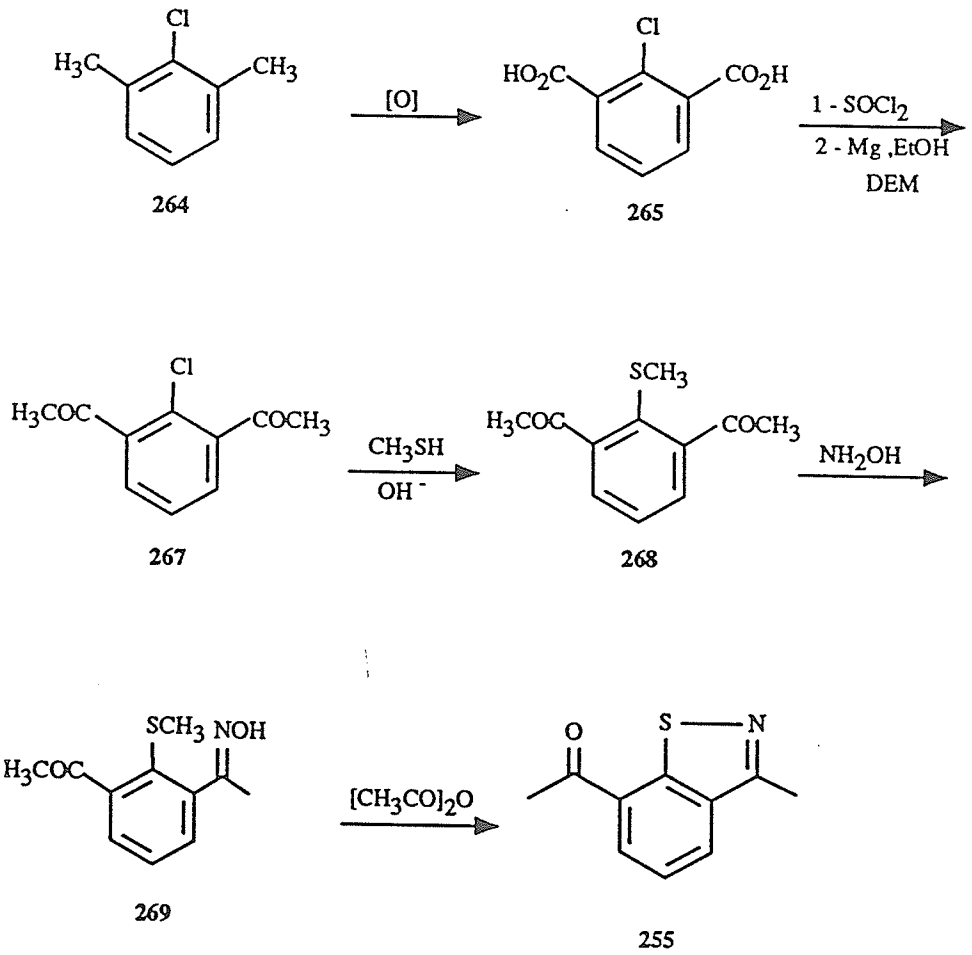
Scheme 121

In their studies of the 1,2,3-benzothiadiazole-7-diazonium salts (**259**) (Scheme 120), Kirby and coworkers [70JCS(C)2514] showed that while the thiadiazole diazonium salt can rearrange i.e. **259a** ⇌ **259b**(X=Cl), the pmr spectrum of the compound **259** (X=H), indicated no symmetrical structure of the type **259c**. Any ring structure allowing interconversion would have to be a "transition state" rather than a resonance contributor and consideration of possible hypervalent structures for **259** which might allow such resonance, shows an unfavorable type **259c** situation for the nitrogen atom. However, since some of the work described here involves compounds with acyl groups in a situation where interaction with a ring sulfur might be possible, it would be interesting to test the possibility of making the fused isothiazoloisothiazolium structure **260**, or to determine what possibility there would be for any rearrangement reactions (Scheme 121) corresponding to Scheme 120. Probably on the basis of the thiadiazoles above a symmetrical intermediate is unlikely as it would also require an unfavorable nitrogen valency if sulfur d-orbitals are to be included. However, the incorporation of an electron releasing group, e.g. dimethylamino, could lead to a very stable tetravalent sulfur form, and such a compound (or intermediate or transition state) might be more favorable and symmetry and stability would be possible.

On this basis we decided to investigate the possibility of synthesis of 7-acetyl-3-methyl-1,2-benzisothiazole (**255**) and the fused benzo-1,2-*bis*-isothiazole **260**.

3.4.1 7-Acetyl-3-methyl-1,2-benzisothiazole (255)

2-Chloro-1,3-benzenedicarboxylic acid (**265**) was obtained as previously reported [54JAA(43)193] (with some modifications) from 2-chloro-1,3-dimethylbenzene (**264**) by oxidation with potassium permanganate (Scheme 122). The diacid **265** was then converted to the acid chloride **266** using thionyl chloride in benzene. Treatment of the acid chloride with ethoxymagnesium malonic ester followed by hydrolysis in acid afforded 2-chloro-1,3-diacetylbenzene (**267**). Examination of the pmr spectrum showed a singlet at δ = 2.62 ppm corresponding to the 1- and 3-acetyl methyl protons and an unresolved multiplet at δ = 7.31-7.71 ppm corresponding to the aromatic protons. When the 2-chloro-1,3-diacetylbenzene (**267**) was treated with lithium methanethiolate in cold dimethylformamide, chlorine displacement by the methanethiolate ion gave 1,3-diacetyl-2-methylthiobenzene (**268**) which gave a pmr spectrum with the two acetyl methyl protons at δ = 2.66 ppm, the S-methyl protons at δ = 2.35 ppm. The infrared spectrum showed the carbonyl stretching at 1714 cm^{-1}. The methylthiodiketone derivative **268** was treated with one equivalent of hydroxylamine hydrochloride in pyridine to give the monoxime **269**, which on treatment with acetic anhydride in pyridine gave the desired 7-acetyl-3-methyl-1,2-benzisothiazole (**255**). The pmr spectrum showed a singlet at δ = 2.80 ppm, corresponding to the acetyl methyl and the 3-methyl protons, while the aromatic protons showed an unresolved multiplet at δ = 7.30-8.30 ppm. The infrared spectrum showed a carbonyl stretching absorption at 1660 cm^{-1}. While this observed value is rather high considering that in the 3-acylmethylene-1,2-dithioles the carbonyl stretching frequency is ~1590 cm^{-1}, there is however a difference of ~ 54 cm^{-1} frequency between the 7-acetyl-3-methyl-1,2-benzisothiazole (**255**) and the 1,3-diacetyl-2-methylthiobenzene

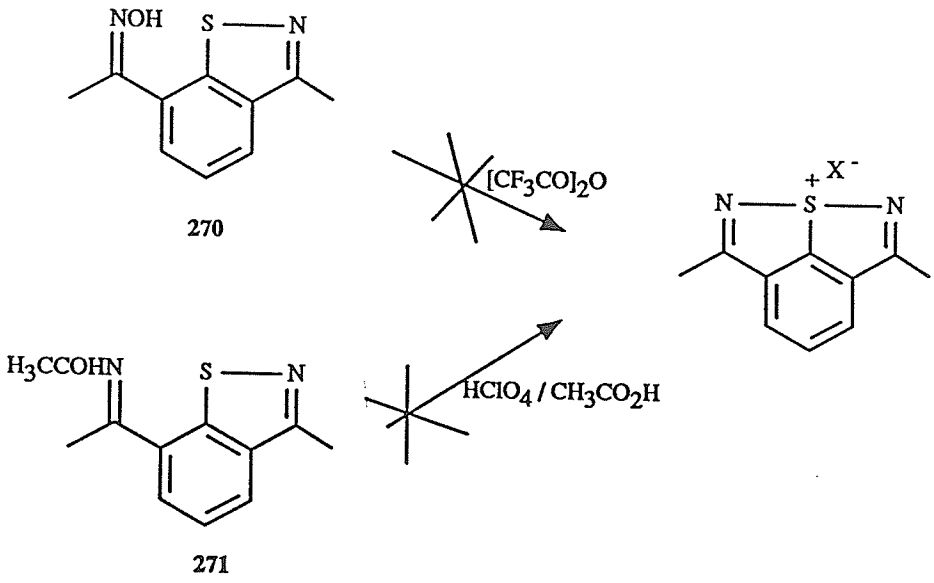

Cl
H3C
CH3
[O]
HO2C
CO2H
1 - SOCl2
2 - Mg ,EtOH
DEM
264
265
Cl
H3COC
COCH3
CH3SH
OH -
SCH3
H3COC
COCH3
NH2OH
267
268
SCH3 NOH
H3COC
[CH3CO]2O
O
S
N
269
255

Scheme 122

(268). This might be attributed to a small contribution from the tetravalent sulfur atom, i.e. by utilization of d orbitals (Scheme 118). The infrared spectrum of 7-acetyl-3-methyl-6-methylthio-1,2-benzisothiazole (**196**) (Sec. 3.2.4) showed a carbonyl stretching absorption at 1640 cm^{-1}. The 20 cm^{-1} difference between compound **255** and **196** might be due to extra congugation contributed by the 6-methythio group.

3.4.2 Investigation of the possibility of synthesis of fused benzo-1,2-*bis*-isothiazoles

The synthesis of the title compound could be approached through the oxime of the 7-acetyl-3-methyl-1,2-benzisothiazole (**255**) followed by conversion of the hydroxy group of the oxime into a suitable leaving group. Subsequent cyclization by attack of the ring sulfur, similar to the initial cyclisation might lead to a symmetrical bridged ion (Scheme 123). Treatment of the 7-acetyl-3-methyl-1,2-benzisothiazole with hydroxylamine hydrochloride and pyridine in methanol gave the oxime which on crystallization from benzene yielded pale yellow prisms. When this oxime was treated with trifluoroacetic anhydride and the reaction was left to stand for 4 days no product was observed and the starting oxime **270** was recovered. An attempt to synthesize the fused ring was then made through the acetate **271**. The oxime derivative **270** was converted to the acetate by warming the oxime in acetic anhydride and pyridine for 30 min. The acetate derivative **271** was then treated with perchloric acid in acetic acid. However, no perchlorate salt was obtained and once more the starting material was recovered.

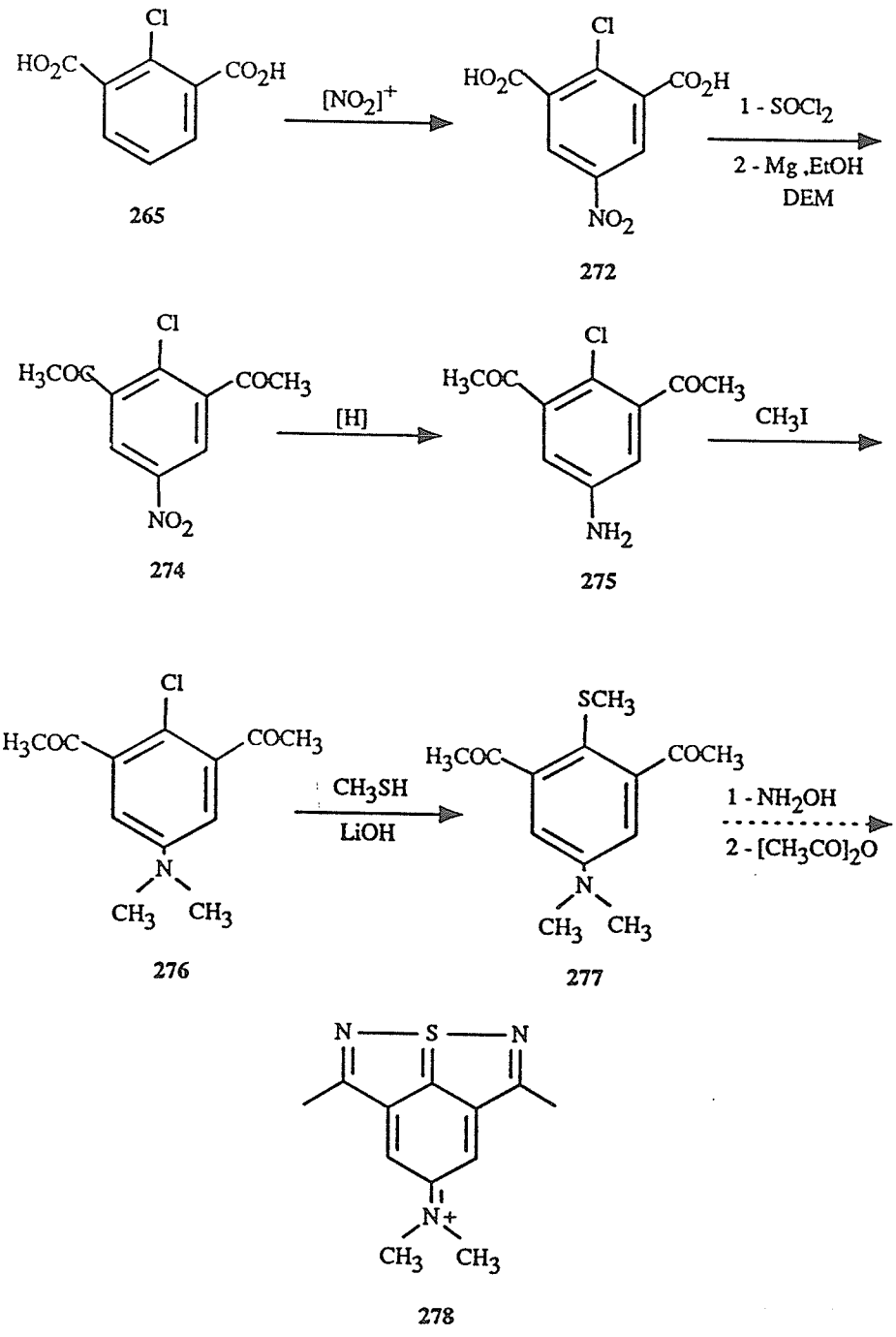


Scheme 123

These results suggest that the sulfur atom, once incorporated in the isothiazole ring, is insufficiently nucleophilic to displace acetate from the oximinoacetate to form some type of sulfonium salt and further suggests that the fused benzisothiazoloisothiazolium salt **260** cannot be made, i.e. that **260** does not represent a very stable structure.

Since this indeed might confirm our theories on stability, the next step was to try to synthesize the fused system, but with an electron releasing group, hopefully to stabilize the structure. The compound we proposed to synthesize was the fused system **278** (Scheme 124) with the dialkylamino substituent acting as an electron releasing group. A possible approach for this fused system was through nitration of the 2-chloro-1,3-benzenedicarboxylic acid (**265**), followed by conversion of the diacid to the 2-chloro-1,3-diacetyl-5-nitrobenzene (**274**). Reduction of the nitro group should then give the 5-amino-2-chloro-1,3-diacetylbenzene (**275**). This amine could then be dialkylated using two equivalents of methyl halide to give the 2-chloro-1,3-diacetyl-5-(N,N dimethyl) aminobenzene (**276**) followed by displacement of the chloride ion with a methanethiolate anion to give the 1,3-diacetyl-5-(N,N-dimethyl)amino-2-methylthiobenzene (**277**), which is a good precursor for the synthesis of the fused benzisothiazoloisothiazolium salt **278** (Scheme 124).

The 2-chloro-1,3-benzenedicarboxylic acid (**265**) was nitrated using one equivalent of fuming nitric acid in sulfuric acid following Effenberger's method [83JOC(48)4649], and the 2-chloro-5-nitro-1,3-benzenedicarboxylic acid (**272**) was then converted to the diketone through the acid chloride using ethoxymagnesium malonic ester as described in Sec. 3.1.1. The 2-chloro-1,3-diacetyl-5-nitrobenzene (**274**) showed one singlet in the pmr spectrum at $\delta = 2.73$ ppm corresponding to the two acetyl methyl protons and one at $\delta =$ 8.43 ppm corresponding to the two equivalent aromatic protons.

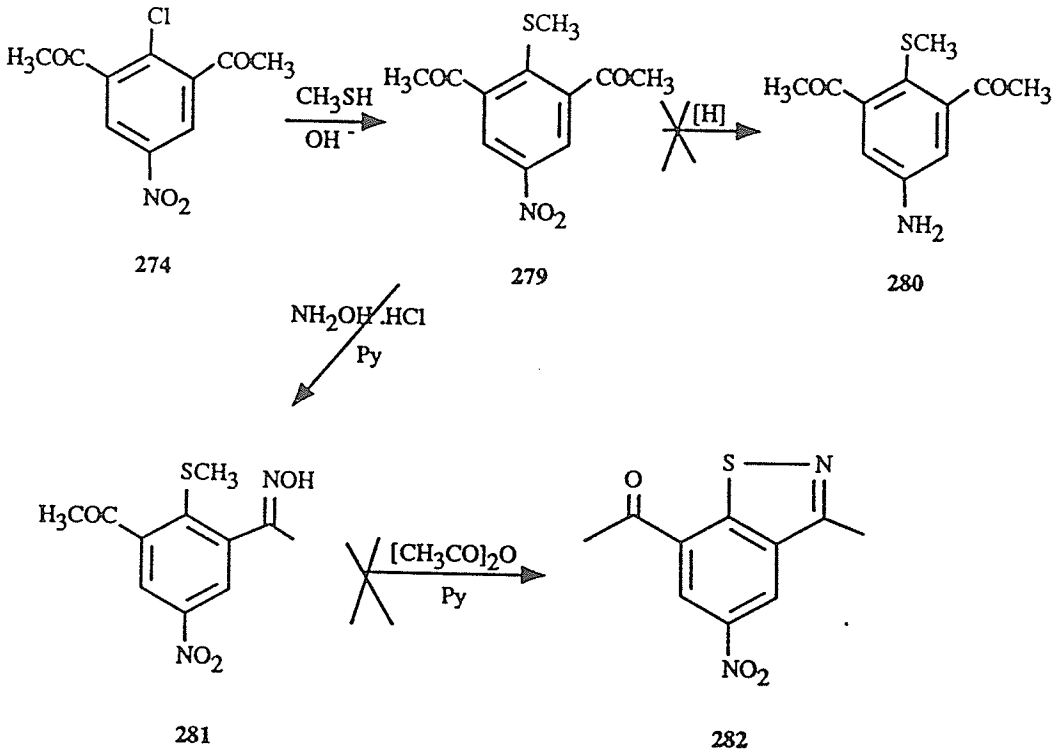

Cl
HO2C
CO2H
[NO2]+
1 - SOCl2
2 - Mg ,EtOH
DEM
NO2
265
272
H3COC
COCH3
[H]
CH3I
NH2
274
275
SCH3
CH3SH
LiOH
1 - NH2OH
2 - [CH3CO]2O
N
CH3
276
277
S
N+
278

Scheme 124

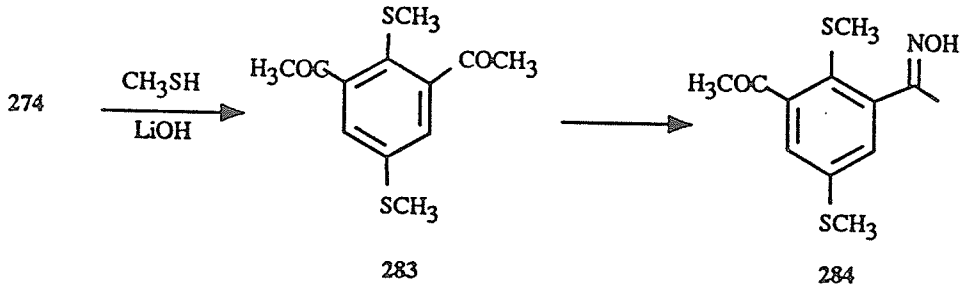
When the nitro derivative **274** was treated with tin in concentrated hydrochloric acid the 5-amino-2-chloro-1,3-diacetylbenzene (**275**) was obtained as pale yellow prisms. The pmr of the amine **275** showed a singlet at $\delta = 2.66$ ppm integrating for six protons corresponding to the two acetyl methyl protons and a singlet at $\delta = 6.90$ ppm, corresponding to the aromatic protons, the protons of the amino group resonating as a broad singlet centered at $\delta = 4.10$ ppm. The amine **275** was then dialkylated using two and one half equivalents of methyl iodide and potassium hydroxide in methanol which yielded a mixture of mono- and dialkylated product. Subsequent fractional crystallization of the mixture gave a compound whose pmr spectrum showed two singlets at $\delta = 2.66$ and 3.03 ppm corresponding to the N-methyl protons and the acetyl methyl protons. Integration showed the two signals to be equivalent in agreement with the expected analysis of the 2-chloro-1,3-diacetyl-5-(N,N-dimethyl) aminobenzene (**276**). When compound **276** was treated with excess lithium methanthiolate in tetrahydrofuran and the reaction mixture was heated to 150°C in a pressure bottle the product obtained showed a pmr spectrum with three upfield singlets at $\delta = 3.00$, 2.66 and 2.23 ppm which might be attributed to the acetyl methyls, the N,N-dimethyl and the S-methyl protons, with the integration of the S-methyl protons being half that of each the acetyl methyl and the N-methyl protons. There was also a low field singlet at 6.56 ppm attributed to the two aromatic protons. The mass spectrum, however, showed a molecular ion of 196,181 which does not correspond to the expected value of 251. The experiment was therefore repeated using one equivalent of potassium methanethiolate in methanol, but the same results were obtained.The difference in the mass value might be due to some fragmentation product in mass spectrum. The reaction product was then treated with one equivalent of hydroxylamine hydrochloride and pyridine followed by acetic anhydride in pyridine. However, no benzisothiazole derivative could be isolated.

A second approach for the synthesis of the dialkylamino fused system **278** was investigated through the displacement of the chloride with one equivalent of methanethiolate ion before the reduction of the nitro group (Scheme 125). The 1,3-diacetyl-2-methylthio-5-nitrobenzene (**279**) produced gave a pmr spectrum that showed the two acetyl methyl protons at $\delta = 2.70$ ppm, the S-methyl protons at $\delta = 2.36$ ppm with the S-methyl protons integrating as half that of the acetyl methyl protons and the aromatic protons resonating as a singlet at $\delta = 8.20$ ppm. Attempts to reduce the nitro group to the amine however gave only starting material with two minor products. Synthesis of 7-acetyl-3-methyl-5-nitro-1,2-benzisothiazole (**282**) followed by reduction was also investigated. The cyclization of the monoxime **281** to the 1,2-benzisothiazole derivative **282** was however unsuccessful, which once more might be attributed to the presence of two electron withdrawing groups (the acetyl and the nitro groups) *ortho-* and *para-* to the methylthio group.

In light of the difficulties encountered in the synthesis of the fused benzo-*bis*-isothiazole with the N,N-dimethylamino stabilizing group, a different electron releasing group was chosen to stabilize the ring, i.e. the methylthio group. The 1,3-diacetyl-2,5-*bis*-(methylthio)benzene was prepared from the 2-chloro-1,3-diacetyl-5-nitrobenzene (**274**) by using excess lithium methanethiolate in dimethylformamide (Scheme 126). The pmr spectrum showed the two acetyl methyl protons at $\delta = 2.66$ ppm and the 2- and 5-S-methyl protons at $\delta = 2.53$ and 2.33 ppm respectively. The S-methyl protons were assigned considering the higher deshielding effect of the acetyl groups toward the 2-S-methyl (*ortho*) protons than toward the 5-S-methyl (*meta*) protons. The aromatic protons were found to resonate as a singlet at $\delta = 7.31$ ppm. When this diacetyldimethylthiobenzene was treated with one equivalent of hydroxylamine hydrochloride and pyridine the monoxime **284** was obtained. This oxime



Scheme 125



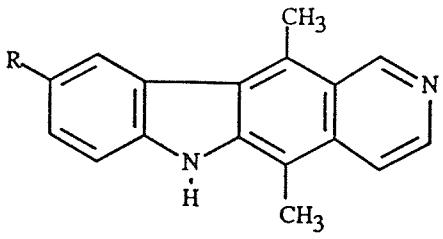
Scheme 126

however gave only decomposed products on attempted conversion to the 1,2-benzisothiazole. This is one of the few cases studied where this cyclisation fails and the reasons for this are not apparent.

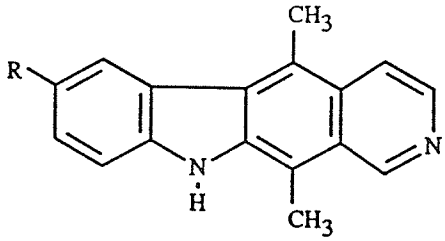
3.5 Synthesis of Isothiazolocarbazoles Analogous to Ellipticine

Ellipticine [a pyrido-carbazole derivative] and 9-methoxyellipticine (285 R=OMe) were first isolated from the plant *Ochrosia elliptica Labill* in 1959 [59JAS(81)1903]. Ellipticine and other pyrido [4,3-*b*] carbazoles [67AJC(20)2715, 66JMC(9)237] were found to have a significant anti-tumour activity. Their mode of action is by intercalation between the base pairs of DNA thus inhibiting replication [76BC(4)275]. Interest developed in the synthesis of ellipticine analogues and derivatives [77S437] and the subject has received continuous attention for many years.

It has been shown that a change from a pyrido[4,3-*b*]-carbazole (285) to a pyrido [3,4-*b*]-carbazole (286) (Scheme 127), in which the mesomerism is no longer possible between the two nitrogens, removed anti-tumour activity [67JMC(10)126]. In view of the similar chemical reactivity of isothiazoles and pyridines, e.g. basicity, alkylation and substitution reactions, one objective of this work was to synthesize isothiazolocarbazoles with (152, 155), and without, (153,154) the mesomerism between the nitrogen atoms (Scheme 78). These compounds would still have the planarity and the electronic properties of ellipticine. The 5-H-isothiazolo[4,3-*c*] carbazole (153) was synthesized. However, the attempts to prepare the [3,4-*c*] (152), the [4,5-*d*] (154) and the [5,4-*d*] (155) 5-H-isothiazolocarbazoles have not been successful.

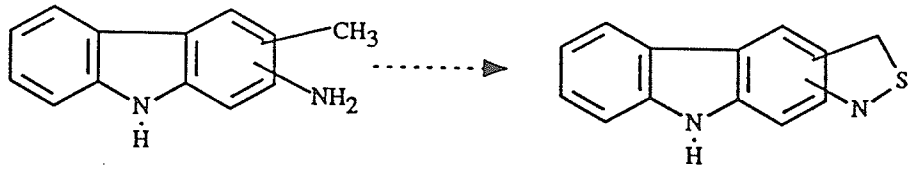


285

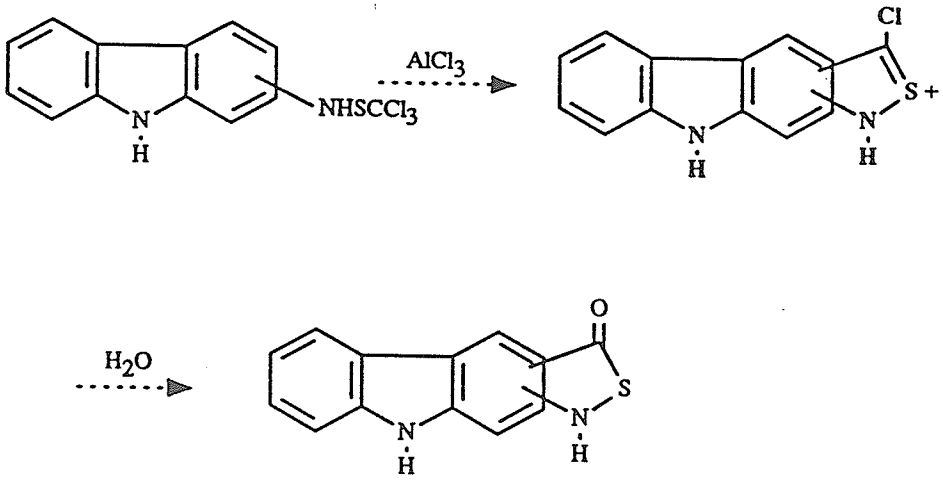


286

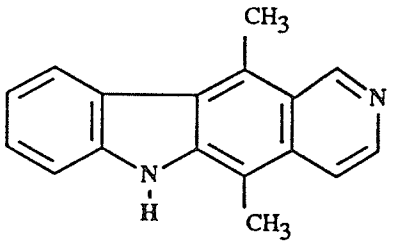
Scheme 127



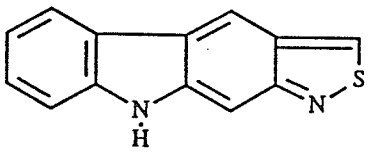
Scheme 128



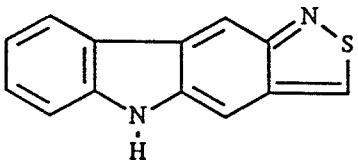
Scheme 129



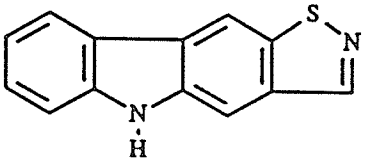
151



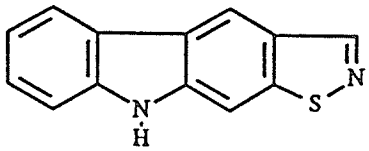
152



153



154



155

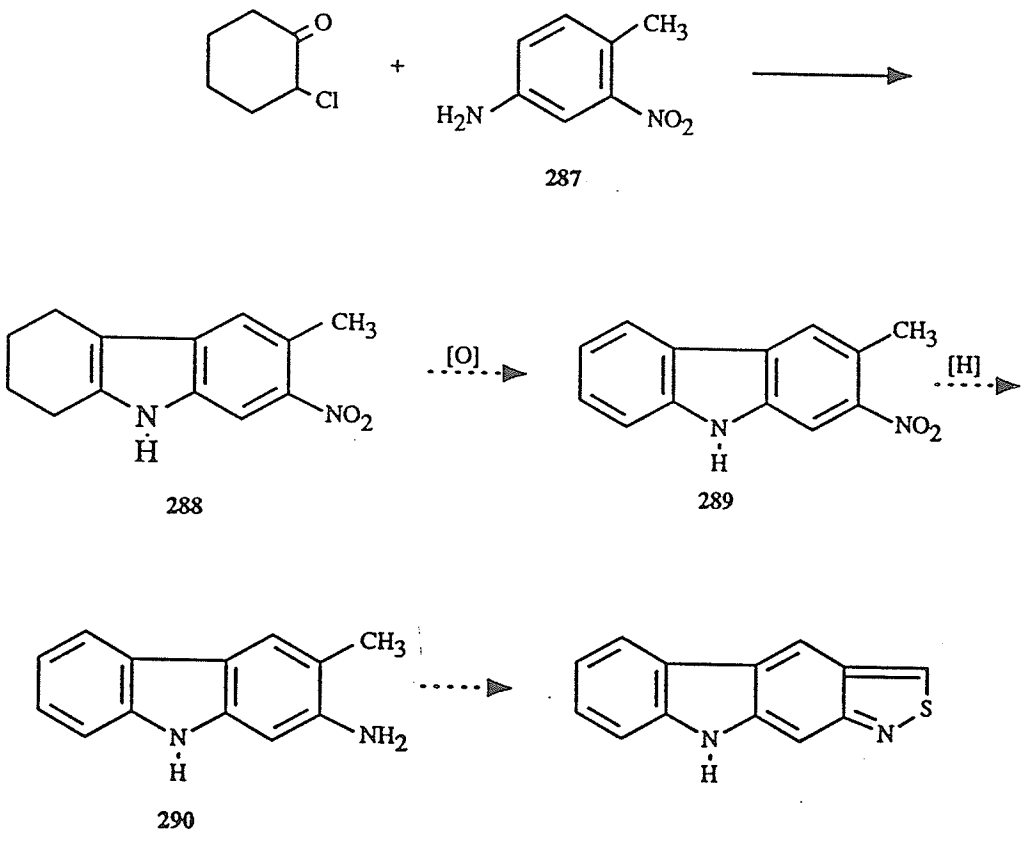
Scheme 78

3.5.1 Isothiazolo[*c*]carbazoles

There are two possible isomers in this category, namely 5-H-isothiazolo[3,4-*c*]carbazole (**152**) and 5-H-isothiazolo[4,3-*c*]carbazole (**153**). Two different routes were taken in the attempt to synthesize these compounds. The first route was to synthesize *o*-aminomethylcarbazoles followed by cyclization to the isothiazole derivative using N-sulfinylmethanesulfonamide (Scheme 128). The second route was through the synthesis of a trichloromethanesulfenamide derivative [34JCS822], followed by cyclization using aluminum chloride to form a salt which on hydrolysis should give an isothiazolone derivative (Scheme 129). This route is similar in concept to the syntheses of benzodithiolones from benzenethiols and trichloromethanesulfenylchloride [66MI257].

3.5.1.1 Attempts towards synthesis of 5-H-isothiazolo[3,4-*c*] carbazole (152)

The first approach taken in the attempt to synthesize the title isothiazolocarbazole was through the synthesis of 1,2,3,4-tetrahydro-6-methyl-7-nitrocarbazole (**288**) followed by aromatization, reduction of the nitro group and cyclization (Scheme 130). The methylnitrotetrahydrocarbazole derivative (**288**) can be prepared from the 4-methyl-3-nitroaniline (**287**) and 2-chlorocyclohexanone followed by acid treatment. The product obtained, however, was a mixture of compounds with very close R_f values. The very low yield and the problems encountered in obtaining a pure final product led us to abandon this approach.


O
Cl
+
CH3
H2N
NO2
287
CH3
NO2
N
H
[O]
288
CH3
NO2
N
H
[H]
289
CH3
NH2
N
H
290
S
N

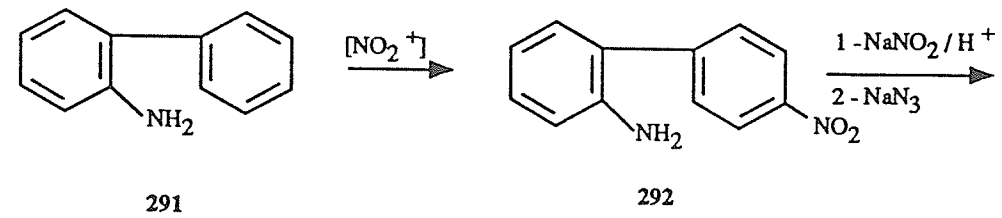
Scheme 130

Another possible approach was to treat 2-aminocarbazole (295) [54JAS(76)664] with trichloromethanesulfenylchloride to form a trichloromethanesulfenamide. Possibly this would cyclize with aluminum chloride to generate the isothiazole ring (Scheme 131).

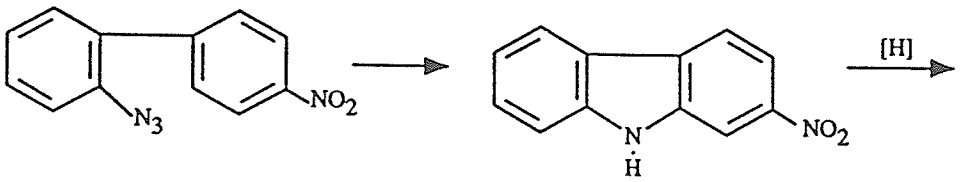
2-Aminocarbazole was prepared from the *o*-aminobiphenyl (291) following Smith and Brown's method [51JAS(73)2435], i.e. by nitration of the *o*-aminobiphenyl in sulfuric acid. This reaction yields the 2-amino-4′-nitrobiphenyl (292) (the nitration reaction occurs at this position due to the deactivation of the other ring with the ammonium salt formed in sulfuric acid). The aminonitrobiphenyl 292 was then converted to the 2-azido-4′-nitrobiphenyl (293) by treatment with nitrous acid followed by sodium azide [51JAS(73)2435]. Refluxing the azide 293 in *o*-dichlorobenzene gave the 2-nitrocarbazole (294), by an insertion reaction of an intermediate nitrene. When 294 was treated with hydrazine and Raney Nickel the reduction product was the 2-aminocarbazole.

Treatment of the 2-aminocarbazole with trichloromethanesulfenylchloride afforded a product which on treatment with aluminum chloride followed by water led mainly to the starting material and a complex mixture of products so the approach was abandoned.

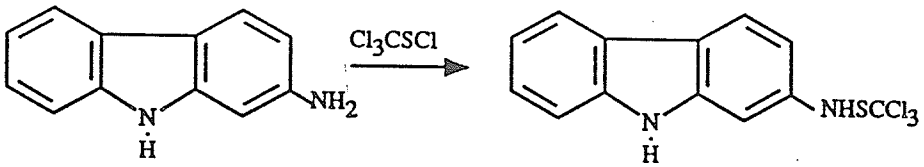
Carbazole derivatives have also been synthesized from different *o*-aminodiphenylamine by the following method. Diazotization of the amino group produces the triazole derivative. Thermal [77TL3465, 67CB(100)1646] or photochemical [69JHC(6)503, 68JAS(90)1923] elimination of nitrogen generates a species which on cyclization gives a carbazole (Scheme 132).



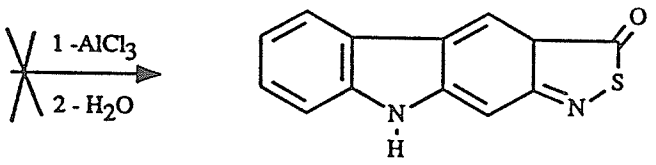
291 292



293 294

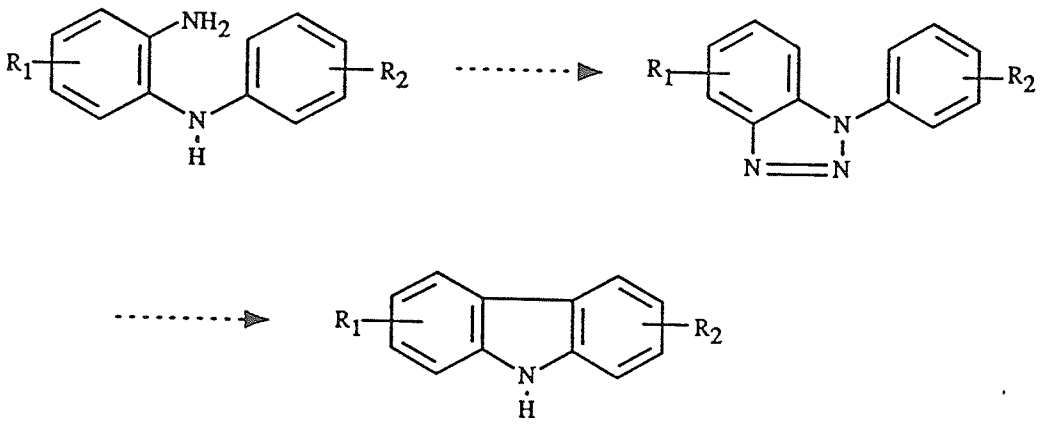


295 296

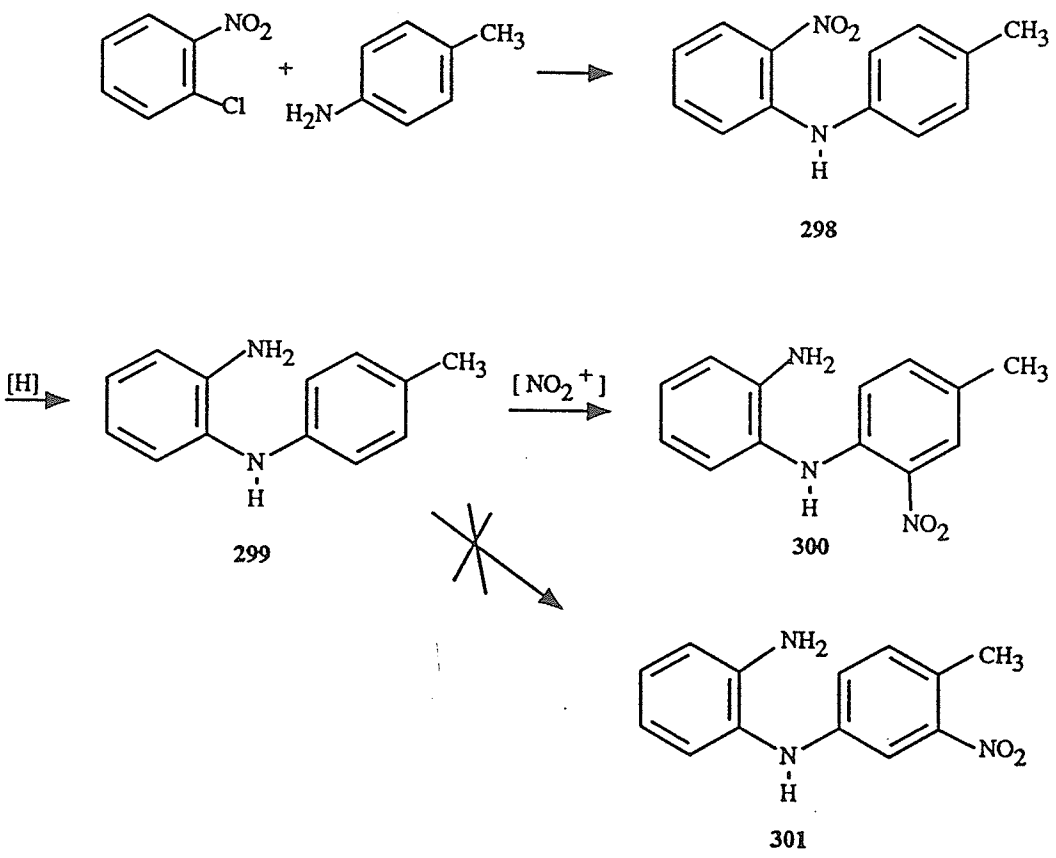


297

Scheme 131



Scheme 132


NO2
Cl
+
H2N
CH3
N
H
298
[H]
NH2
CH3
N
H
299
[NO2+]
NH2
CH3
N
H
NO2
300
NH2
CH3
N
H
NO2
301

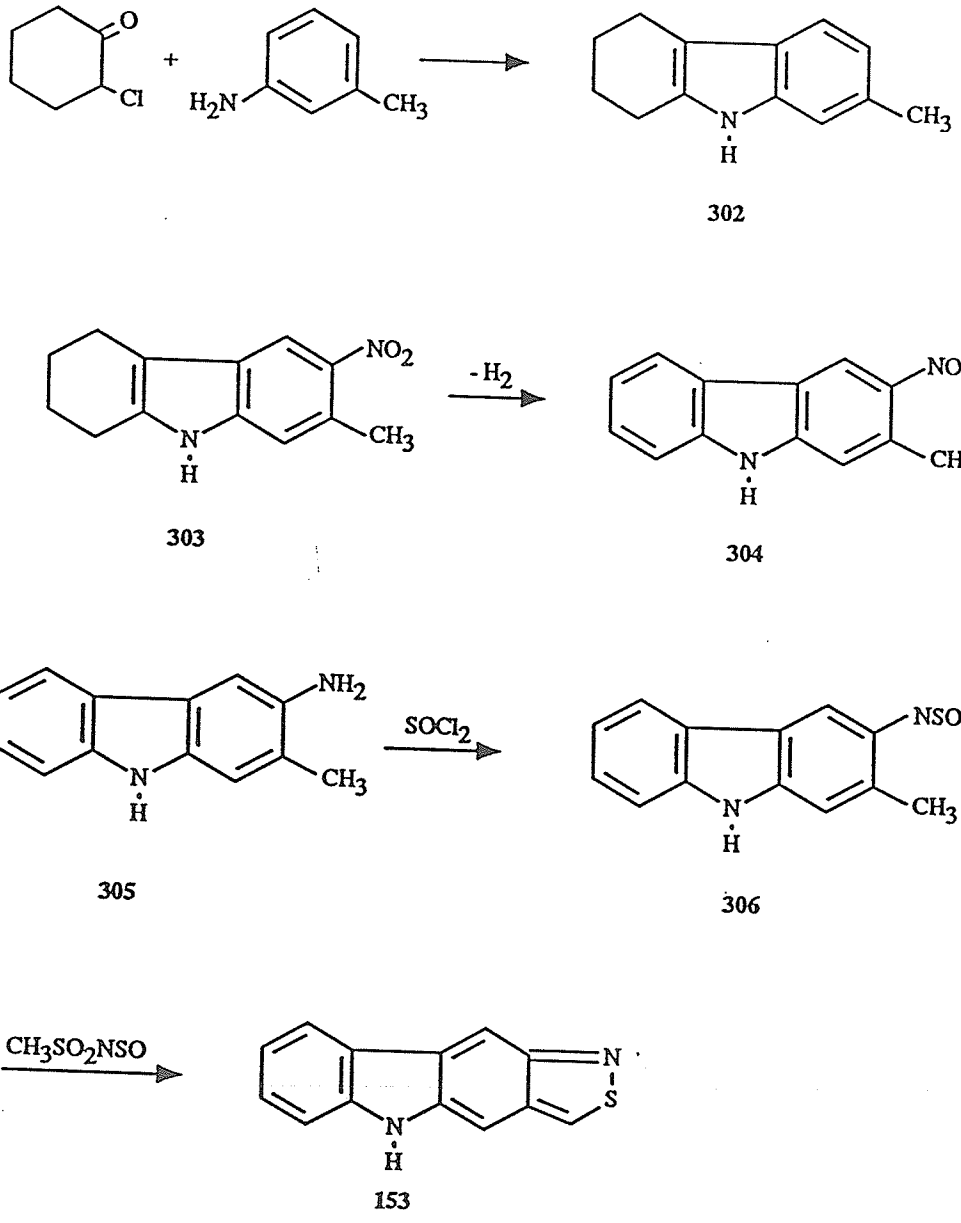
Scheme 133

This approach was used in an attempt to synthesize the 3-methyl-2-nitrocarbazole from the 2-amino-4′-methyl-3′-nitrodiphenylamine (**301**) (Scheme 133), using the following procedure. Treatment of *p*-toluidine with 1-chloro-2-nitrobenzene in pyridine yielded 2-nitro-4′-methyldiphenylamine (**298**) as an orange crystalline material. Reduction of the nitro group using Raney nickel in ethanol yielded 2-amino-4′-methyldiphenylamine (**299**). To obtain the desired substitution pattern, with a nitro group *ortho* to the methyl group, we attempted the nitration in concentrated sulfuric acid, on the following basis. If the two amino groups can be protonated, the ring bearing the two amino substituents should be deactivated towards substitution, and nitration should therefore occur in the ring with one amino substituent and at the position *meta* to the amino group, since it should now be a *meta* director.

Nitration of the diphenylamine derivative **299** using one equivalent of fuming nitric acid in sulfuric acid gave mainly one product. The pmr analysis showed three protons coupled to the methyl group, indicating that the nitration was on the ring substituted with the methyl group. A nuclear Overhauser effect from the methyl showed that the methyl group has two *ortho* protons. These spectral findings suggested that the nitration occurred *meta* to the methyl group and *ortho* to the secondary amino group giving the 2-amino-4′-methyl-2′-nitrodiphenylamine (**300**) rather than the desired 4′-methyl-3′-nitro derivative **301** and suggest the nitrating mixture was only strong enough to protonate the primary amino group but not the secondary amino group. This is much less basic owing to the extra aromatic conjugation.

3.5.1.2 Synthesis of 5-H-isothiazolo[4,3-*c*] carbazole (153)

A suitable precursor for this isothiazolocarbazole is the 9-H-3-amino-2-methylcarbazole (**305**). To prepare the aminocarbazole **305**, the previously reported method [69AJC(22)185] was followed with some modifications (Scheme 134). 1,2,3,4-Tetrahydro-7-methylcarbazole was prepared from 2-chlorocyclohexanone and *m*-toluidine by refluxing in ethanol for seven hours. The resulting product was then nitrated using one equivalent of fuming nitric acid in sulfuric acid to yield the 1,2,3,4-tetrahydro-7-methyl-6-nitrocarbazole (**303**). The very low yield achieved in the aromatization of the tetrahydrocarbazole using chloranil following Dalton's method [69AJC185] and the problems encountered in the separation of the chloranil from the final product, have led us to use a different method of aromatisation. Dehydrogenation of the tetrahydrocarbazole was achieved using 5% palladium on charcoal (Pd/C) and refluxing in xylene, the 2-methyl-3-nitrocarbazole (**304**) was obtained in 50% yield. While aromatization of 1,2,3,4-tetrahydro-7-methylcarbazole (**302**) using palladium on charcoal gave a better yield, the 2-methylcarbazole obtained was found to nitrate on both rings giving a mixture of three products. When the 2-methyl-3-nitrocarbazole was treated with Raney nickel and hydrazine hydrate in ethanol the 3-amino-2-methylcarbazole (**305**) was obtained as pale yellow crystals. However, when the aminomethylcarbazole **305** was treated with N-sulfinylmethanesulfonamide and pyridine under the usual conditions only the starting material and an N-sulfinyl derivative was observed. The reaction was then repeated using preformed N-sulfinyl-3-amino-2-methylcarbazole (**306**). Under the same conditions the desired 5-H-isothiazolo[4,3-*c*]carbazole (**153**) was obtained as pale yellow needles in 10% yield. The pmr spectrum showed a singlet at $\delta = 9.43$ ppm characteristic of the C-3 protons of 2,1-benzisothiazole derivatives, corresponding to the C-3 proton of the isothiazolocarbazole **153** and an unresolved multiplet at $\delta = 7.25$-7.96 ppm. The mass spectrum showed a molecular ion at 224 in agreement with the desired product.

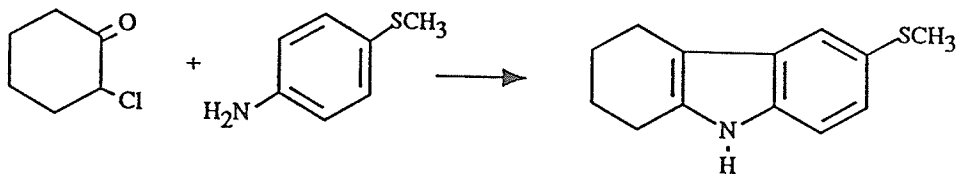

O
Cl
+
H_2N
CH_3
N
H
CH_3
302
$[NO_2^+]$
NO_2
N
H
CH_3
303
$-H_2$
NO_2
N
H
CH_3
304
[H]
NH_2
N
H
CH_3
305
$SOCl_2$
NSO
N
H
CH_3
306
CH_3SO_2NSO
N
S
N
H
153

Scheme 134

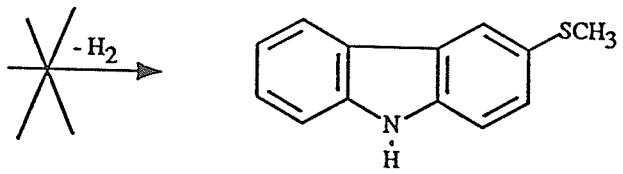
3.5.2 Isothiazolo[*d*]carbazole

It appeared that the carbazole derivatives **154** and **155** might be approached in two ways, i.e by initial synthesis of a mercaptocarbazole followed by i) Friedel-Crafts acylation and cyclization through the oxime, or ii) cyclization to the thiophenedione derivative using oxalyl chloride followed by conversion to the 1,2-benzisothiazole using ammonia and hydrogen peroxide as described in the Introduction section (Scheme 44). An attempt to synthesise the 3-methylthiocarbazole (**308**) was made through 1,2,3,4-tetrahydro-6-methythiocarbazole (**307**) which was prepared by the reaction of 2-chlorocyclohexanone with 4-methylthioaniline in ethanol. However aromatization of the product using iodine, nitrobenzene or chloranil was unsuccessful (Scheme 135).

Another possible method of introducing the thiol function to the carbazole may be effected through direct sulfonation [70KKT(13)269] or thiocyanation [72KKT(15)1678] of the carbazole followed by reduction. However the sulfonation reaction gave a low yield (4%) and thiocyanation gave a mixture of 1- and 3-thiocyanocarbazole and 1,3-dithiocyanocarbazole. Due to the problems encountered in the synthesis of the precursors for different isothiazolocarbazoles and the very low yield achieved in some of the syntheses as described above, the synthesis of the other three benzisothiazolocarbazoles **152**, **154** and **155** was abandoned.



307



308

Scheme 135

4. SUMMARY AND SUGGESTIONS FOR FURTHER RESEARCH

4.1 SUMMARY

As a result of this work, four examples of the five possible benzo[*d*,*d*']*bis*-isothiazole system have been successfully prepared i.e.
3,7-dimethylbenzo[1,2-*d*:4,5-*d*']*bis*-isothiazole (167),
3,5-dimethylbenzo[1,2-*d*:5,4-*d*']*bis*-isothiazole (174),
3,6-dimethylbenzo[1,2-*d*:6,5-*d*']*bis*-isothiazole (191) and
3,6-dimethylbenzo[1,2-*d*:3,4-*d*']*bis*-isothiazole (198). Several approaches to the synthesis of the benzo[1,2-*d*:4,3-*d*']*bis*-isothiazole system have been made, some of them involving the preparation of other isothiazoles, but because of various problems these have failed.

Two isomers of the benzo[*c*,*d*']*bis*-isothiazole have been successfully synthesized, i.e. the 3-methylbenzo[1,2-*c*:5,6-*d*']*bis*-isothiazole (232) and
3-methylbenzo[1,2-*c*:6,5-*d*']*bis*-isothiazole (243). Approaches towards the synthesis of the 3-methylbenzo[1,2-*c*:4,5-*d*']*bis*-isothiazole (249) have shown some limitations of the cyclization of *o*-methylthioketoxime, i.e the reaction is incompatible with an electron withdrawing group *ortho* or *para* to the methylthio-group.

Some of this work has involved electrophilic substitution on benzisothiazole rings, as a result, substitution patterns for benzisothiazoles have been determined. Preference for substitution in the 4-position has been observed for 3,5-dimethyl-1,2-benzisothiazole and in the 7-position for the 3,6-dimethyl- and the 6-acetyl-3-methyl-1,2-benzisothiazole. This has been rationalized [55JAS(77)5939, 80JCR(M)2845] in terms of resonance stabilization of the reaction intermediates.

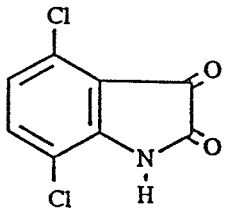
7-Acetyl-3-methyl-1,2-benzisothiazole (255) has been synthesized. This showed a carbonyl stretching frequency slightly lower than expected which might be attributed to a small contribution from the tetravalent sulfur atom. Further investigation of the possibility of synthesis of fused benzo-1,2-*bis*-isothiazoles has established that a bridged sulfonium ion type of structure 260 is not likely to be stable, agreeing with earlier work on related thiadiazoles.

One isothiazolocarbazole analogue of the ellipticine alkaloids, i.e. 5-H-isothiazolo[4,3-*c*]carbazole (153) has been synthesized. The low yield of cyclization of the N-sulfinyl-3-amino-2-methylcarbazole (306) and the problems encountered in the synthesis of the precursors for different isothiazolocarbazoles has led us to abandon the synthesis of the other three isomers (152, 154, 155).

4.2 SUGGESTIONS FOR FURTHER RESEARCH

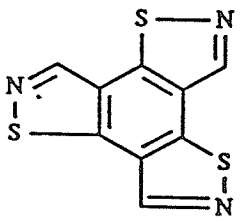
It would be useful for comparative purposes to synthesize the remaining benzo[*d*,*d*']*bis*-isothiazole, i.e. compound 141. The major problem here is achieving the desired 1,2,3,4-tetrasubstitution and with suitable substituents for further elaboration to the two isothiazole rings. Some of the difficulties are interaction of the two *o*-acetyl groups, and the incompatibility of any diazonium salts (precursors to nitriles and acids) with *ortho*-sulfur substituents, i.e. synthesis of the nitrile would have to be done before the incorporation of sulfur. One possible approach would be via the known dichloroisatin (309) (Scheme 136) which might be elaborated to the system as it has both the desired substitution pattern and suitable groups for elaboration. The other four members of the benzo[*c*,*d*']-*bis-isothiazoles* 144, 145, 146 and 147 too would be useful for comparison purposes and their syntheses should be attempted.

One at least, might be available via the 4-methyl-2-methylthio-5-nitroacetophenone (246) which is described above, although an attempt in this work to cyclize this to the benzisothiazole derivative failed; perhaps, with more work, it could be effected. To complete the series it would be appealing to synthesize the benzo-*tris*-[*d*]isothiazoles (Scheme 137) of which there are two examples **310** and **311**. Having completed the series it would be useful to do N-alkylation studies, to determine the position of alkylation, i.e, on which ring, and then compare nucleophilic attack on these with simpler 1,2- and 2,1-benzisothiazoles.

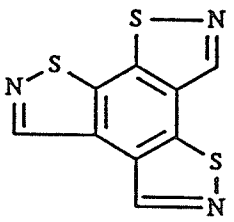


309

Scheme 136



310



311

Scheme 137

5. EXPERIMENTAL

All melting points given were determined on a Reichert hot stage melting point apparatus, and are uncorrected.

All organic solutions were dried over anhydrous magnesium sulfate.

All pmr spectra were obtained in chloroform-d solution using tetramethylsilane as an internal standard. Pmr spectrum were obtained on either a Varian model EM-360 spectrometer or a Bruker model AM-300 spectrometer. Infrared spectra were obtained on a Perkin-Elmer model 881 spectrophotometer in Nujol mulls. Mass spectra were obtained on a V.G. model 7070E mass spectrometer.

Thick layer chromatography was performed on Merck "Kieselgel 60 PF_{254}" silica gel supplied by Terochem laboratories. Silica gel used in column chromatography was supplied by Terochem laboratories, 20-45 microns. Thin layer chromatography was performed on silica gel F_{254} supplied by Whatman Ltd.. Lithium hydroxide used was the lithium hydroxide monohydrate supplied by Fisher Scientific Company.

N-Sulfinylmethanesulfonamide was made by the method of Singerman [75JHC(12)877].

Monoximes can exist in two geometrical forms, and dioximes in three forms. The products obtained from the oxime forming reactions in some cases appeared to be reasonably homogenous, and in other cases mixtures were evident by melting point and pmr spectra, no attempt was made to separate, or further purify them and materials were simply used in the form isolated for the next stage in the reaction.

5.1 SYNTHESIS OF BENZO-*d,d'BIS*-ISOTHIAZOLES

5.1.1 Approaches to 3,7-dimethylbenzo[1,2-*d*:4,5-*d'*]*bis*-isothiazole (167)

2,5-Dichlorobenzene-1,4-dicarboxylic acid (162)

1,4-Dichloro-2,5-dimethylbenzene (5g, 0.029 mol), potassium permanganate (40g) and potassium hydroxide (5g) were stirred under reflux in water (600 mL) for 24 h. It was necessary to clean sublimed material off the condenser periodically. The manganese dioxide was removed by filtration and the solution was decolorized using sodium bisulfite, filtered then the filtrate acidified with hydrochloric acid, cooled and filtered to give the acid **162** (yield = 3g = 45%), m.p. 306°C, (lit. m.p. 306°C [67BSF3377].)

2,5-Dichlorobenzene-1,4-dicarbonylchloride (163)

The 2,5-dichlorobenzene-1,4-dicarboxylic acid (**162**) (7g, 0.03 mol) was suspended in benzene (30 mL), thionyl chloride (10 mL) was added, and the mixture was heated under reflux for 18 h. (until all of the acid went into solution). The organic solvent was evaporated under reduced pressure giving the product which was used for the next reaction without further purification.

1,4-Diacetyl-2,5-dichlorobenzene (164)

In a three-necked flask equipped with magnetic stirrer and a reflux condenser, magnesium turnings (2.16 g, 0.09 g-atoms) were stirred with a mixture of anhydrous ethanol (3 mL), benzene (30 mL) and a drop of carbon tetrachloride. The mixture was warmed to initiate reaction, then a mixture of benzene (30 mL), diethyl malonate (14.4 g, 0.09 mol) and anhydrous ethanol (10 mL) was added dropwise and the reaction was stirred until all the magnesium had reacted. The condenser was removed and the reaction mixture was heated under reflux to evaporate excess ethanol. The crude acid chloride **163** (8.1 g, 0.03 mol) in benzene (20 mL) was then added dropwise with stirring and the reaction was left at room

temperature for 16 h. The reaction mixture was then stirred with 10% sulfuric acid (100 mL) for 15 min., the benzene layer separated and the aqueous layer extracted with dichloromethane. The combined organic extracts were evaporated to give an oil which was added to a mixture of glacial acetic acid (30 mL), concentrated sulfuric acid (2 mL) and water (8 mL) and heated under reflux until the evolution of carbon dioxide had stopped. The reaction mixture was then poured into ice water to precipitate the ketone which was collected. The product was washed with water and recrystallized from benzene as colorless plates (yield = 6.5 g = 94%), m.p. 99°- 102°C.

The pmr spectrum of **164** δ: 2.70 (6H, s, acetyl methyl protons), 7.62 (2H, s, the aromatic protons). The ir spectrum, 1700 cm^{-1} (C=O str). MS, m/z 230(30), 215(100), 200(10). Exact mass calcd. for $C_{10}H_8{}^{35}Cl_2O_2$: 229.9901, found: 229.9890, calcd. for $C_{10}H_8{}^{35}Cl^{37}ClO_2$:231.9871, found: 231.9850.

1,4-Diacetyl-2,5-*bis*-(methylthio)benzene (165)

To a cold solution (under nitrogen) of the diketone **164** (3.45g, 0.015 mol) and methanethiol (10 mL) in dimethylformamide (80 mL) was added portionwise lithium hydroxide (10 g). The mixture was stirred in the cold for 30 min., poured into ice water and acidified with hydrochloric acid. The solid was collected and on recrystallization from nitromethane, gave yellow needles (yield = 3.4 g = 89%) m.p. 203°C.

The pmr spectrum of **165** δ: 2.50 (6H, s, S-methyl protons), 2.70 (6H, s, acetyl methyl protons), 7.70 (2H, s, aromatic protons). The ir spectrum, 1680 cm^{-1} (C=O str). MS, m/z 254(100), 239(82), 181(30). Exact mass calcd. for $C_{12}H_{14}O_2S_2$: 254.0435, found: 254.0427.

1,4-Diacetyl-2,5-*bis*-(methylthio)benzene dioxime (166)

The diketone **165** (1.27 g, 0.005 mol) in methanol (10 mL) with pyridine (0.81 g, 0.01 mol) and hydroxylamine hydrochloride (0.7 g, 0.01 mol) was heated under reflux for 18 h. The mixture was cooled and the solid precipitate which crystallized from the solution was collected and used for the next reaction without further purification m.p. 245°-250°C. MS, m/z 284(80), 267(90), 220(100).

3,7-Dimethylbenzo[1,2-*d*:4,5-*d'*]*bis*-isothiazole (167)

The diketoxime **166** (100 mg, 0.35 mmol) in pyridine (2.00 mL) and acetic anhydride (0.5 mL) was heated under reflux for 24 h. The mixture was diluted with 5% hydrochloric acid, extracted with chloroform, washed with water, dried, and evaporated under reduced pressure. The product was purified by preparative thick layer chromatography using chloroform as an eluent. Recrystallization from dimethylformamide gave the product as yellow needles, (yield = 50 mg = 65%), m.p. 233°-235°C.

The pmr spectrum of **167** δ: 2.85 (6H, s, methyl protons), 8.44 (2H, s, aromatic protons). MS, m/z 220(20), 149(50), 69(100). Exact mass calcd. for $C_{10}H_8N_2S_2$:220.0128, found: 220.0116. Anal. calcd. for $C_{10}H_8N_2S_2$: C, 54.55%; H, 3.64%, N, 12.73%; S, 29.09%. Found :C, 54.25%; H, 3.82%; N, 12.63%; S, 29.22%.

5.1.2 Approaches to 3,5-dimethylbenzo[1,2-*d*:5,4-*d'*]*bis*-isothiazole. (174)

4,6-Dichlorobenzene-1,3-dicarboxylic acid (169)

A mixture of 1,5-dichloro-2,4-dimethylbenzene [890B2318] (5 g, 0.029 mol), potassium permanganate (40 g) and potassium hydroxide (5 g) was stirred under reflux in water (600 mL) for 24 h. Excess potassium permanganate was destroyed with sodium bisulfite and the manganese dioxide was removed by filtration. The solution was acidified with hydrochloric acid, and cooled to give the acid which was collected (yield = 3.5 g = 52%), m.p. 280°C, (lit. m.p. 280°C [76JOC(41)3580]).

4,6-Dichlorobenzene-1,3-dicarbonylchloride (170)

The diacid **169** (6 g, 0.026 mol) was suspended in benzene (30 mL). Thionyl chloride (8.5 mL) was added and the mixture was heated under reflux for 18 h. (until all the solid dissolved). The organic solvent was evaporated under reduced pressure and the brown oil produced was used for the next reaction without further purification or characterization.

1,5-Diacetyl-2,4-dichlorobenzene (171)

The acid chloride **170** (13.5 g, 0.05 mol) was treated in benzene (30 mL) with ethoxymagnesium malonate [prepared from magnesium (3.62 g, 0.15 atoms), ethanol (20 mL), and diethyl malonate (24.05 g, 0.15 mol)] as described for the preparation of compound **164**. Work-up as described in **164** gave **171**. Recrystallization from acetone gave pale yellow needles (yield = 11 g = 96%), m.p. 50 - 51°C.

The pmr spectrum of **171**, δ:262 (6H, s, acetyl methyl protons), 7.80 (1 H,s, C-3 aromatic proton) and 8.02 (1 H, s, C-6 aromatic proton). The ir spectrum 1670 cm^{-1} (C=O str). MS, m/z 230(16), 215(100), 181(20). Exact mass calcd. for $C_{10}H_8{}^{35}Cl_2O_2$: 229.9901, found 229.9898, calcd. for $C_{10}H_8{}^{35}Cl^{37}ClO_2$: 231.9871 found: 231.9867.

1,5-Diacetyl-2,4-*bis*-(methylthio)benzene (172)

To a cold solution (under nitrogen) containing the diketone 171 (3.45 g, 0.015 mol) and methanethiol (10 mL) in dimethylformamide (80 mL) was added portionwise lithium hydroxide (10 g). The mixture was stirred in the cold for 30 min., poured into ice water and acidified with hydrochloric acid. The solid was collected to give a product which recrystallized from nitromethane as yellow prisms (yield = 3.6 g = 95%), m.p. 209°-210°C.

The pmr spectrum of 172, δ:2.51 (6H, s, S-methyl protons), 2.70 (6H, s, acetyl methyl protons), 7.12 (1 H, d, J=1 Hz, C-3 aromatic proton). 8.40(1 H, d, J=1 Hz, C-6 aromatic proton). The ir spectrum, 1670 cm^{-1} (C=O str). MS, m/z 254(40), 239(100), 149(6). Exact mass calcd. for $C_{12}H_{14}O_2S_2$: 254.0435, found: 254.0450.

1,5-Diacetyl-2,4-*bis*-(methylthio)benzene dioxime 173

The diketone 172 (1.27 g 5 mmol) in methanol (10 mL) with pyridine (0.81 g, 10 mmol) and hydroxylamine hydrochloride (0.7 g, 10 mmol) was heated under reflux for 18 h. The methanol was evaporated under reduced pressure, the residue diluted with ice-cold 5% hydrochloric acid and then extracted with chloroform. The organic layer was washed with water and evaporated under reduced pressure to give pale yellow plates (yield = 1. 3 g = 91%), m.p. 150° - 155°C. The crude product was used for the next reaction without further purification.

MS, m/z 84(100).

3,5-Dimethylbenzo[1,2-*d*: 5,4-*d'*]*bis*-isothiazole (174)

The diketoxime 173 (0.4 g, 1.4 mmol) in pyridine (5 mL) and acetic anhydride (2 mL) was heated under reflux for 24 h. The mixture was diluted with 5% hydrochloric acid, extracted with chloroform, washed with water, dried, and evaporated under reduced pressure. The product was purified by a preparative scale chromatography using

chloroform as an eluent. Recrystallization from nitromethane gave the product as yellow needles, (yield = 260 mg = 84%), m. p. 246°- 248°C.

The pmr spectrum of 174 δ:2.86 (6H, s,methyl protons), 8.32 (1 H, d, J = 1 Hz, C-8 proton), 8.44 (1 H, d, J=1 Hz, C-4 proton). MS, m/z 220(100), 205(10), 190(20). Exact mass calcd. for $C_{10}H_8N_2S_2$: 220.0128, found: 220.0122. Anal. calcd. for $C_{10}H_8N_2S_2$: C, 54.55%; H, 3.64; N, 12.73%; S, 29.09%. Found: C, 54.15%; H, 3.74%; N, 12.63%; S, 28.88%.

5.1.3 Approaches to 3,6-dimethylbenzo[1,2-*d*:6,5-*d*']*bis*-isothiazole (191)

4-Chloro-2,5-dimethylbenzenesulfonic acid (184)

2-Chloro-p-xylene (50 g, 0.36 mol) was heated for 4 h. under gentle reflux in concentrated sulfuric acid (100 mL). The reaction mixture was poured into water (20 mL), filtered and the residue recrystallized from benzene to give silver plates (yield = 40 g = 50%), m.p. 90-92°C [unhydrous form].

(Too insoluble for pmr spectra in $CDCl_3$) MS, m/z 220(50), 186(30), 138(100). Exact mass calcd. for $C_8H_9{}^{35}ClO_3S$: 219.9960, found: 219.9953, calcd. for $C_8H_9{}^{37}ClO_3S$: 221.9939, found: 221.9928 [dihydrated form, m.p. 100°-102C° (36AC(P)(5)5)].

2,3-Dichloro-1,4-dimethylbenzene (182)

The sulfonic acid 184 (33.5 g, 0.15 mol) in sulfuric acid (20 mL) was warmed to 60°C and chlorine was passed into the solution until the weight of the reaction mixture increased to 38.75 g, corresponding to the addition of one equivalent of chlorine. The reaction mixture was then diluted with water (50 mL) and steam distilled to give the 2,3-dichloro-1,4-dimethylbenzene as pale yellow liquid (yield = 20 g = 77%). Upon redistillation the fraction boiling between 225°-235°C (1 atm.) was collected (lit. b.p. 230°C

[36AC(P)(5)5]).

2,3-Dichlorobenzene-1,4-dicarboxylic acid (186)

2,3-Dichloro-1,4-dimethylbenzene (5.3 g, 0.03 mol) was stirred under gentle reflux in water (1.00L). Potassium permanganate (30 g) was added over an 8 h. period. Ethanol was added slowly to the reaction mixture to destroy excess permanganate after which the mixture was filtered. Acidification of the filtrate and cooling gave white needles which were collected (yield = 4.1 g = 58%) m.p. 234°-238°C [60ARE(56)197].
MS, m/z 234(100), 217(95), 133(20).

2,3-Dichlorobenzene-1,4-dicarbonylchloride (187)

The diacid **186** (4.0 g, 0.017 mol) in benzene (30 mL) and thionyl chloride (8 mL) was heated under reflux until a clear solution was obtained (~24 h.). The organic solvent was then evaporated under reduced pressure and the product was used in the next step without further purification or characterization.

1,4-Diacetyl-2,3-dichlorobenzene (188)

The crude diacid chloride **187** (4.1 g, 0.015 mol) was treated in benzene (30 mL) with ethoxymagnesium malonate [prepared from magnesium (1.1 g, 0.45 g-atoms), ethanol (10 mL), and diethyl malonate (7.31 g, 0.045 mol) as described for the preparation of compound **164**]. Work-up as previously described gave a yellow liquid (yield =3.4 g = 99%). As this decomposed on attempted purification by distillation, the product was taken to the next step without further purification.
The pmr of **188**, δ:2.60 (6H, s, acetyl methyl protons), 7.40 (2 H, s, aromatic protons).
The ir spectrum, 1710 cm^{-1} (C=O str): MS, m/z 230(41), 215(100), 200(15).

1,4-Diacetyl-2,3-*bis*-(methylthio)benzene (189)

To a cold solution (under nitrogen) of the diketone **188** (3.4 g, 0.015 mol) and methanethiol (10 mL) in dimethylformamide (50 mL) was added portionwise lithium hydroxide (10 g). The mixture was stirred in the cold for 30 min., poured into ice water and acidified with hydrochloric acid. The acidic solution was then extracted with chloroform, and the chloroform layer washed with water, dried and evaporated under reduced pressure to give an orange liquid (yield = 3.02 g = 79%).

The pmr of **189**, δ:1.60 (6H, s, S-methyl protons), 2.07 (6H, s, acetyl methyl protons), 7.40 (2 H, s, aromatic protons). The ir spectrum, 1700 cm^{-1} (C=O str). MS, m/z 254(54), 239(100), 224(30). Exact mass calcd. for $C_{12}H_{14}O_2S_2$: 254.0435, found: 254.0426.

1,4-Diacetyl-2,3-*bis*-(methylthio)benzene dioxime (190)

The diketone **189** (1.00 g, 4 mmol) in methanol (10 mL) with pyridine (0.63 g, 8 mmol) and hydroxylamine hydrochloride (0.55 g, 8 mmol) was heated under reflux for 24 h. The methanol was evaporated under reduced pressure and the residue was diluted with ice-cold 5% hydrochloric acid, then extracted with chloroform. The organic layer was washed with water, and evaporated under reduced pressure to give a light yellow paste (yield = 1.1 g = 97%). This was used without further purification in the next stage.

MS, m/e 284(20), 267(100), 250(10).

3,6-Dimethylbenzo[1,2-*d*: 6,5-*d'*]*bis*-isothiazole (191)

The diketoxime **190** (0.80 g, 2.8 mmol) in pyridine (5 mL) and acetic anhydride (2 mL) was heated under reflux for 24 h. The mixture was diluted with 5% hydrochloric acid, extracted with chloroform, washed with water, dried, and evaporated under reduced pressure. The product was purified by preparative thick layer chromatography using chloroform as an eluent. Recrystallization from acetone gave colorless needles (yield = 150 mg = 24%), m.p. 182°-183°C.

The pmr spectrum of **191**, δ:2.86 (6 H, s, methyl protons), 7.89 (2 H, s, the aromatic protons). MS, m/z 220(100), 205(10), 192(12). Exact mass calcd. for $C_{10}H_8N_2S_2$: 220.0129, found: 220.0128. Anal. calcd. for $C_{10}H_8N_2S_2$: C, 54.55%; H, 3.64%; N, 12.73%; S, 29.09%. Found: C, 54.36%; H, 3.70%; N, 12.57%; S, 29.39%.

5.1.4 Approaches to 3,6-Dimethylbenzo[1,2-*d*-:3,4-*d*']*bis*-isothiazole (198)

2,4-*Bis*-(methylthio)acetophenone (193)

To a cold solution of the 2,4-dichloroacetophenone (7 g, 0.04 mol) and methanethiol (10 mL) in dimethylformamide (80 mL) under nitrogen was added portionwise lithium hydroxide (10 g). The mixture was stirred in the cold for 30 min. and then poured into ice water and acidified with hydrochloric acid. The product was collected and recrystallized from a benzene/cyclohexane 1:1 mixture as colorless needles (yield = 7.3 g = 93%), m.p. 83°C.

The pmr spectrum of **193**, δ:2.43 (3 H, s, 4-S-methyl protons), 2.53 (3 H, s, 2-S-methyl protons), 2.57 (3 H, s, acetyl methyl protons), 6.93 (1 H, d, J=9 Hz, C-5 aromatic proton), 7.06 (1 H, bs, C-3 aromatic proton), 7.68 (1 H, d, J = 9 Hz , C-6 aromatic proton). The ir spectrum, 1690 cm^{-1} (C=O str). MS, m/z 212(10), 185(100), 170(10).

2,4-*Bis*-(methylthio)acetophenone oxime (194)

The acetophenone **193** (2 g, 0.01 mol) in methanol (10 mL) containing pyridine (4 mL) and hydroxylamine hydrochloride (2 g, 0.029 mol) was heated under gentle reflux for 4 h. The mixture was then added to ice water (50 mL). The product was collected and recrystallized from methanol as pale yellow prisms, m.p. 112°C. This was used in the next stage without further purification.

MS, m/z 227(20), 211(100), 180(20).

3-Methyl-6-methylthio-1,2-benzisothiazole (195)

The ketoxime 194 (10 g, 0.05 mol) in pyridine (50 mL) and acetic anhydride (5 mL) was heated under reflux for 24 h. The mixture was diluted with 5% hydrochloric acid, extracted with chloroform, washed with water, dried, and evaporated under reduced pressure. The product was purified by a preparative thick layer chromatography using chloroform as an eluent. Recrystallization from benzene gave the product as buff prisms (yield = 8.2 g = 92%), m.p 58-60°C.

The pmr spectrum of 195, δ:2.50 (3 H, s, S-methyl protons), 2.63 (3 H, s, 3-methyl protons), 7.16(1 H, d, J=7.8 Hz, C-4 or C-5 aromatic proton), 7.56(1 H, bs, C-7 aromatic proton), 7.63(1 H, d, J = 7.8 Hz, C-4 or C-5 aromatic proton). MS, m/z 195(100), 180(40), 149(25). Exact mass calcd. for $C_9H_9NS_2$: 195.0176, found: 195.0172.

7-Acetyl-3-methyl-6-methylthio-1,2-benzisothiazole (196)

To a stirred solution of 3-methyl-6-methylthio-1,2-benzisothiazole (0.3 g, 1.7 mmol) methylene chloride (5 mL) and acetyl chloride (140 mg, 1.7 mmol), was added portionwise anhydrous aluminum chloride (0.5 g, 3.5 mmol). The reaction was stirred for 4 days and poured into ice water. The reaction mixture was extracted with chloroform and the organic layer separated, washed with water and evaporated under reduced pressure. The crude product was purified by column chromatography using 25% ethyl acetate in cyclohexane as an eluent to give the product, which on recrystallization from benzene gave yellow needles (yield = 150 mg = 40%), m.p. 142°-143°C.

The pmr spectrum of 196, δ:2.42 (3 H, s, S-methyl protons), 2.53 (3H, s, 3-methyl or acetyl methyl protons), 2.58(3H, s, 3-methyl or acetyl methyl protons), 7.45 (1 H, d, J=9 Hz, C-5 aromatic proton), 7.76 (1 H, d, J=9 Hz, C-4 aromatic proton). The ir spectrum 1640 cm^{-1} (C=O str). MS, m/z 237(36), 222(100), 149(20). Exact mass calcd. for $C_{11}H_{11}NOS_2$: 237.0282, found: 237.0281.

7-Acetyl-3-methyl-6-methylthio-1,2-benzisothiazole oxime (197)

The ketone **196** (50 mg, 0.23 mmol) in methanol (10 mL) with pyridine (2 mL) and hydroxylamine hydrochloride (100 mg, 1.4 mmol) was heated under reflux for 18 h. The mixture was poured into 5% hydrochloric acid (50 mL) and extracted with chloroform (3 x 30 mL). The combined extracts were washed with 5% hydrochloric acid (3 x 30 mL), water (3 x 30 mL), and evaporated under reduced pressure to give pale yellow plates (yield = 40 mg = 73%), m.p. 50°C.

3,6-Dimethylbenzo[1,2-*d*:3,4-*d'*]bis-isothiazole (198)

The ketoxime **197** (40 mg, 0.17 mmol) in pyridine (2.00 mL) and acetic anhydride (0.5 mL) was heated under reflux for 24 h. The mixture was diluted with 5% hydrochloric acid (50 mL), extracted with chloroform (3 x 50 mL), washed with water (3 x 20 mL), dried, and evaporated under reduced pressure. The product was purified by preparative thick layer chromatography using chloroform as an eluent to give a product, which on recrystallization from acetone gave yellow prisms (yield = 30 mg = 80%), m.p. 142°-143°C.

The pmr spectrum of **198**, δ:2.85 (3 H, s, 3-methyl protons), 2.94 (3 H, s, 6-methyl protons), 7.90 (1 H, d, J=9 Hz, C-8 aromatic proton), 7.97 (1 H, d, J=9 Hz, the C-7 aromatic proton). MS, m/z 220 (100), 205(10), 178(9). Exact mass calcd. for $C_{10}H_8N_2S_2$: 220.0128, found: 220.0152. Anal. calcd. for $C_{10}H_8N_2S_2$: C, 54.55%; H, 3.64%; N, 12.73%; S, 29.09%. Found: C, 54.36; H, 3.70%; N, 12.69%; S, 28.93%.

5.1.5 Attempts towards the synthesis of benzo[1,2-*d*:4,3-*d'*]*bis*-isothiazole (141)

1,4-*Bis*-(methylthio)benzene (159)

To a solution of thioanisole (5 g, 0.04 mole) in chloroform (20 mL) was added dropwise chlorosulfonic acid (25 g) at 0°-5°C. The sulfonic acid derivative was filtered off, added to a saturated solution of sodium chloride, the reaction mixture was then cooled and the sodium salt was collected. The crude sodium salt was then covered with phosphorus oxychloride and warmed. The solid dissolved eventually forming a homogenous solution. The reaction mixture was poured into ice water and stirred to hydrolyse the excess phosphorus oxychloride. The reaction mixture was cooled and the precipitate was filtered. The precipitate was recrystallized from cyclohexane to give the sulfonyl halide as colorless prisms. This was reduced with zinc in sulfuric acid followed by alkylation using dimethyl sulfate giving the product in 60% yield. m.p. 85°C (lit. m.p. 85°C [59JAS(81)4939]).

Attempted acylation of 1,4-*bis*-(methylthio)benzene

To the *bis*-(methylthio)benzene 159 (8.5 g, 0.05 mol) in methylene chloride (10 mL) was added acetyl chloride (4 g, 0.05 mol) and anhydrous aluminum chloride (7 g, 0.05 mol) portionwise. The reaction was left for 2 days, then poured into water and extracted with chloroform. When the chloroform was evaporated only starting material was recovered. The reaction was repeated under the same conditions using 3 equivalents of aluminum chloride. A mixture of the starting material, a product with acetylation on the sulfur and a trace of 2,5-*bis*-(methylthio)acetophenone was obtained.

2-Benzoylbenzoic acid (201)

Phthalic anhydride (1.48, 0.01 mol) was suspended in boiling benzene (20 mL) and the Grignard solution [prepared from magnesium (0.24, 0.01 mol), bromobenzene (1.57, 0.01

mol)] slowly added through a dropping funnel. The mixture was then boiled for 2 h., decomposed with 30% ice-cold sulfuric acid (50 mL) and extracted with chloroform. Evaporation of the chloroform layer gave the product (yield = 1.02 g, 44%) (identical to the commercial product available from Aldrich Chemical Company, Ltd.) which was taken to the next stage without further purification.

2-Benzoyl-1-benzenecarbonylchloride (202)

2-Benzoylbenzoic acid (**201**) (0.5 g, 0.002 mol) was stirred in benzene (10 mL), thionyl chloride (3 mL) was added, and the mixture was heated under reflux of 24 h. The organic solvent was evaporated under reduced pressure giving the product which was used for the next reaction without further purification or characterization.

Reaction of 2-benzoyl-1-benzenecarbonyl chloride with ethoxymagnesium malonate

The crude acid chloride **202** (0.54 g, 0.002 mol) was treated in benzene (30 mL) with ethoxymagnesium malonate [prepared from magnesium (0.048 g, 0.002 mol), ethanol (10 mL), and diethylmalonate (0.32 g, 0.002 mol) as described for the preparation of **164**]. Work-up as described gave a brown paste (yield = 0.2 g = 49%).

The pmr spectrum corresponded to that of 3-phenylindenone with ~ 20% impurities [64JOC(29)1394]. MS, m/z 206(100), 178(80), 152(20).

Reaction of 1,4-dichloro-2,3-dimethylbenzene (204) with potassium permanganate

The dichloroxylene **204** (5 g, 0.03 mol) in water (1L) was treated with potassium permanganate (30 g), the reaction was refluxed for 17 h and worked up as described for compound **162**, no precipitate was observed directly, or on concentration and cooling.

Reaction of 1,4-dichloro-2,3-dimethylbenzene (204) with sodium dichromate

The dichloroxylene 204 (4.6 g, 0.026 mol), sodium dichromate (13.6 g) and water (30 mL) was placed in a round bottom flask equipped with an efficient stirrer. Concentrated sulfuric acid (18 mL) was added dropwise during about 30 min. to the well stirred mixture and the reaction was refluxed for another 30 min. The reaction mixture was cooled and poured into ice water (70 mL), no precipitate was observed. Extraction with chloroform afforded the starting dichloroxylene (2 g, 0.01 mol).

Reaction of 1,4-dichloro-2,3-dimethylbenzene (204) with nitric acid

The dichloroxylene 204 (3.5 g, 0.02 mol) was heated under reflux with 50% nitric acid (20 mL) for 24 h. The reaction mixture was poured on ice water (50 mL) and the product was collected.

This was dissolved in 10% sodium hydroxide (50 mL) and extracted with chloroform to separate unreacted dichloroxylene. The aqueous layer was then poured slowly on concentrated hydrochloric acid cooled and the solid product collected. This showed a mixture of three products on thin layer chromatography, none of which showed an R_f that might correspond to an acid.

The pmr spectrum did not show any downfield peaks that might correspond to the diacid.

Reaction of 1,2-benzenedimethanol with potassium dichromate

The benzenedimethanol (4 g, 0.03 mol) [47JAS(69)1197] potassium dichromate (7 g) and water (30 mL) was placed in a round bottom flask equipped with an efficient stirrer. Concentrated sulfuric acid (10 mL) was added drop-wise during about 30 min. to the well stirred mixture and the reaction was warmed to 60°C for another 30 min. The reaction mixture was cooled and poured into ice-water (50 mL). No precipitate was observed.

Extraction with ethyl acetate afforded the starting benzenedimethanol (1.2 g, 0.009 mol).

1,2-Benzene-*bis*-N,N-dimethyldicarboxamide (206)

1,2-Benzenedicarbonylchloride (5 g, 0.025 mol) in benzene (20 mL) was stirred with aqueous dimethylamine (50 mL) for 1 h., the organic layer was separated and evaporated under reduced pressure and the crude product was used for the next stage without further purification or characterization.

Reaction of 1,2-benzene-*bis*-N,N-dimethyldicarboxamide with lithium aluminum hydride

Lithium aluminum hydride (0.25 g, 0.007 mol) was added to a solution of 1,2-benzene-*bis*-N,N-dimethyldicarboxamide (1 g, 0.005 mol) in dry tetrahydrofuran (20 mL) and ether (20 mL). The reaction was left at room temperature for 17 h. The reaction mixture was poured into ice cold 10% sulfuric acid, extracted with ethyl acetate and the organic layer was dried and evaporated to give 0.2 g of a mixture. The pmr spectrum showed a singlet at δ=10.06 ppm that might correspond to an aldehyde proton (10%).

1,4-Dichloro-2,3-*bis*-(dichloromethyl) benzene (207)

Chlorine was passed into a flask containing the dichloroxylene 204 (1.74 g, 0.01 mol) and exposed to a bright light source. The reaction was warmed to 60°C and the chlorine was passed until the pmr spectrum showed no upfield peaks and the only protons observed were in the aromatic region. The colorless needles were taken to the next stage without further purification.

The pmr spectrum of 207, δ:7.51 (2 H, s, methyne protons), 8.06 (2 H, s, aromatic protons).

Reaction of 1,4-dichloro-2,3-*bis*-(dichloromethyl) benzene with potassium oxalate

Potassium oxalate (5 g, 0.02 mol) was added to a solution of **207** (3.7 g, 0.012 mol) in ethanol (40 mL) and the reaction mixture was refluxed for 48 h. The ethanol was evaporated under reduced pressure. Ice-water (50 mL) and disodium monohydrogen phosphate was added to the residue. The reaction was then extracted with chloroform and the chloroform layer evaporated under reduced pressure. The pmr spectrum showed that starting material was recovered.

2,5-*Bis*-(methylthio)benzoic acid (210)

2-(Methylthio)benzoic acid (36 g, 0.2 mol) was added with stirring to chlorosulfonic acid (90 mL) keeping the temperature below 20°C. The reaction was stirred for 24 h. then poured over ice, stirred, filtered and the precipitate washed with water. The crude material was dissolved in tetrahydrofuran (50 mL) and to this was added zinc (20 g) amalgamated with mercuric chloride (2 g) and concentrated hydrochloric acid (100 mL). The reaction mixture was stirred for 4 h., at which time a yellow precipitate had formed which was collected and washed. The crude precipitate (which contains zinc) was filtered, extracted with ethyl acetate, and the organic layer was evaporated under reduced pressure to give a crude 5-mercapto-2-methythiobenzoic acid (**209**). The mercaptan was then dissolved in 20% sodium hydroxide (100 mL) and filtered. The filtrate was treated with dimethyl sulfate (10 mL) and let stand for 10 min. at room temperature. Acidification of the reaction mixture using hydrochloric acid gave a precipitate which was collected and recrystallized from 50% ethyl acetate / ethanol giving pale yellow plates. (Yield = 12 g = 30%) m.p 186-188°C.

The pmr spectrum of **210**, δ=2.43 (3 H, s, 5-S-methyl protons), 2.55 (3 H, s, 2-S-methyl protons), 7.13- 7.63 (2H, m, aromatic protons), 8.15 (1 H, d, J=6 Hz, aromatic proton). The ir spectrum 1688 cm^{-1} (C=O str). MS, m/z 214(100), 199(30), 149(50).

2,5-*Bis*-(methylthio)benzoyl chloride

2,5-*Bis*-(methylthio)benzoic acid (10 g, 0.05 mol) in benzene (30 mL) and thionyl chloride (15 mL) was stirred under reflux until all the solid went into solution (24 h.) The organic solvents were then evaporated under reduced pressure to give a brown oil which was taken to the next stage without further purification.

2,5-*Bis*-(methylthio)acetophenone (211)

The crude 2,5-*bis*-(methylthio)benzoyl chloride (2.32 g, 0.01 mol) was treated in benzene (20 mL) with ethoxymagnesium malonate [prepared from magnesium (0.48 g, 0.02 mol), ethanol (10 mL), and diethylmalonate (3.2 g, 0.02 mol)] as described for compound **164**. Work up as described gave the product which was taken to the next stage without further purification.

The pmr spectrum of **211**, δ:2.33 (3 H, s, 5-S-methyl protons), 2.46 (3 H, s, 2-S-methyl protons), 2.55 (3 H, s, acetyl methyl protons), 7.16 (1 H, bs, aromatic proton), 7.18 (1 H, d, J=2 Hz, aromatic proton), 7.53 (1 H, d, J=2 Hz, aromatic proton).

2,5-*Bis*-(methylthio)acetophenone oxime (212)

The 2,5-*bis*-(methylthio)acetophenone (1.06 g, 0.5 m mol) in methanol (10 mL), pyridine (2 mL) and hydroxylamine hydrochloride (1 g) were heated under reflux overnight (until all the starting material was consumed). The reaction mixture was diluted with water (50 mL) and the excess pyridine and methanol was evaporated under reduced pressure. The reaction mixture was diluted with ice-water (50 mL), extracted with chloroform and the chloroform layer was evaporated under reduced pressure to give a pale yellow solid which was taken to the next stage without further purification. m.p. 75-90°C.

3-Methyl-5-methylthio-1,2-benzisothiazole (213)

The oxime 212 (1.12 g, 0.005 mol) was refluxed in acetic anhydride (3 mL) and pyridine (10 mL) for 24 h. The reaction mixture was poured into ice-water (100 mL), neutralized with 10% hydrochloric acid and extracted with chloroform. The chloroform layer was washed with 5% hydrochloric acid and evaporated under reduced pressure. The product was developed on a silica gel column chromatography to give buff prisms (yield = 0.9 g = 89%), m.p. 65°C.

The pmr spectrum of 213, δ:2.54 (3 H, s, S-methyl protons), 2.66 (3 H, s, 3-methyl protons), 7.40 (1 H, d, J=7.8 Hz, C-7 aromatic proton), 7.73 (1 H, bs, J=7.8 Hz, C-4 aromatic proton), 7.80 (1 H, d, J=7.8 Hz, C-6 aromatic proton). MS, m/z 195(100), 180(60), 149(10). The exact mass calcd. for $C_9H_9NS_2$:195.0176, found: 195.0178.

Attempted Friedel-Crafts acylation of 3-methyl-5-methythio-1,2-benzisothiazole

To a stirred solution of the benzisothiazole 213 (1.95, 0.01 mol) methylene chloride (5 mL) and acetyl chloride (0.84, 0.01 mol) was added portionwise anhydrous aluminum chloride (1.33 g, 0.01 mol). The reaction was stirred for 48 h., poured into ice water and extracted with chloroform. The chloroform layer was evaporated under reduced pressure to give a dark brown solid and pmr analysis showed this to be mainly starting material.

4-Nitro-1-aminotetralin (218)

This was prepared by following a literature procedure by hydrolysis of the corresponding acetamide available from a nitration reaction on 1-acetamidotetralin [17JCS(113)959].

1,4-Diaminotetralin (219)

To a solution of 1-amino-4-nitrotetralin (1.92 g, 0.001 mol) in 95% ethanol (10 mL) was added a suspension of Raney nickel (an ethanol (5 mL) suspension containing ~ 0.75 g of

nickel), hydrazine hydrate (3 mL) and water (1 mL). The reaction mixture was refluxed for 2 h. (until it turned colorless). The reaction mixture was filtered while hot to remove Raney nickel and the filtrate concentrated by evaporation under reduced pressure poured into water and extracted with chloroform. The chloroform layer was evaporated to give the 1,4-diaminotetralin (**219**) (yield = 1.70 g = 99%), m.p. 80-82°C, (lit. m.p. 83°-85°C [21A(426)1]).

Reaction of 1,4-diaminotetralin with N-sulfinylmethanesulfonamide

Treatment of 1,4-diaminotetralin (2.62 g, 0.001 mol) in benzene (10 mL) with N-sulfinylmethanesulfonamide (2.9 g, 0.002 mol) and pyridine (1.6 g, 0.002 mol) following Singerman's method [75JHC(12)877] as described in the preparation of **232** gave only the starting material and a trace of the N-sulfinyl derivative.

Reaction of benzo[1,2-*c*:4,3-*c'*]*bis*-isothiazole (135) with ethyl chloroformate

The benzo-*bis*-isothiazole **135** [80JHC(17)533] (0.324 g, 0.0015 mol), ethyl chloroformate (1.7 g, 0.015 mol), water (2 mL) and tetrahydrofuran (10 mL) were heated together under reflux for 3 h. The reaction mixture was extracted with chloroform, and the organic layer washed with water and evaporated under reduced pressure.

The pmr of the product obtained corresponded to the starting benzo-*bis*-isothiazole **135**.

When the reaction was repeated using a neat solution of benzo-*bis*-isothiazole in ethyl chloroformate the same results were obtained.

3,6-*Bis*-methylthio-1,2-diazine (225)

To a cold solution of 3,6-dichloro-1,2-diazine (7.4 g, 0.05 mol), and methanethiol (10 mL) in dimethylformanide (80 mL) under nitrogen was added portionwise lithium hydroxide (10 g). The mixture was stirred in the cold for 30 min. and then poured into ice water and neutralized with hydrochloric acid. The solid was collected to give colorless needles (yield = 7.9 g = 92%), m.p. 125-127°C, (lit. m.p. 126°-127°C [54HCA(37)121]).

Reaction of 3,6-*bis*-methylthio-1,2-diazine with dimethyl acetylenedicarboxylate

A mixture of the diazine 225 (1.72, 0.01 mol) and the acetylenedicarboxylate (1.42, 0.01 mol) was warmed at 60°C for 17 h. while the reaction turned dark brown. The pmr spectrum and thin layer chromatography showed only the starting materials.

5.2 SYNTHESIS OF BENZO-[*c,d*]-*BIS*-ISOTHIAZOLE

5.2.1 Approaches to 3-methylbenzo[1,2-*c*:5,6-*d*]*bis*-isothiazole (232)

5-Methyl-2-(methylthio)acetophenone oxime (228)

The ketone 227 [09CB(42)537] was treated with an equal weight of hydroxylamine hydrochloride and excess pyridine in methanol. The reaction mixture was heated under reflux for 24 h. The mixture was worked up by addition to ice cold 20% hydrochloric acid as in the previously reported method [88CJC(66)1405]. This compound was used without further purification or characterization.

3,5-Dimethyl-1,2-benzisothiazole (229)

The ketoxime 228 (1 g, 5.1 mmol) in pyridine (20 mL) and acetic anhydride (2 mL) was heated under reflux for 24 h. The mixture was diluted with 20% concentrated hydrochloric acid and extracted with chloroform as previously reported [88CJC(66)1405]. Drying and evaporation gave the compound 229, b.p 262°C (1 atm) (lit. b.p 262°C [88CJC(66)1405]).

3,5-Dimethyl-4-nitro-1,2-benzisothiazole (230)

The dimethylbenzisothiazole **229** (2 g, 0.012 mol) was dissolved in sulfuric acid (10 mL) and cooled to -10°C. A solution of concentrated nitric acid (0.77 g, 0.012 mol) in sulfuric acid (1 mL) was added dropwise and the mixture kept between -5°→0°C throughout the addition. The reaction mixture was then left for 30 min., poured into ice-water and the resulting precipitate formed was collected giving the nitro compound **230**. This was recrystallized as pale yellow needles from cyclohexane (yield = 2.3 g = 91%), m.p. 94-95°C.

The pmr spectrum of **230**, δ:2.45 (3 H, s, 5-methyl protons), 2.61 (3 H, s, 3-methyl protons), 7.42 (1 H, d, J=8 Hz, C-6 aromatic proton), 7.89 (1 H, d, J=8 Hz, C-7 aromatic proton). MS, m/z 208(100), 191(95), 173(20). Exact mass calcd. for $C_9H_8N_2O_2S$: 208.0306, found: 208.0292.

4-Amino-3,5-dimethyl-1,2-benzisothiazole (231)

4-Nitro-3,5-dimethyl-1,2-benzisothiazole (0.52 g, 2.5 mmol) in glacial acetic acid (10 mL) and water (2.5 mL) was treated with iron powder (0.5 g) and the reaction mixture was heated at 100°C for 3 h. The reaction mixture was then filtered, poured on water and extracted with chloroform. Evaporation of the organic layer gave a product which on recrystallization from cyclohexane gave **231** as yellow needles (yield = 0.35 g = 82%), m.p. 120-122°C.

The pmr of **231**, δ: 2.20 (3 H, s, 5-methyl protons), 2.86 (3 H, s, 3-methyl protons), 4.30 (2 H, bs, amine protons), 7.10 (2 H, s, aromatic protons). MS, m/z 178(100), 149(20), 134(30).

3-Methylbenzo[1,2-*c*:5,6-*d*']*bis*-isothiazole (232)

To a cooled solution of 4-amino-3,5-dimethyl-1,2-benzisothiazole (0.35 g, 0.002 mol) and dry benzene (10 mL) was added a solution of N-sulfinylmethanesulfonamide (0.4 g, 0.003 mol) [75JHC(12)877] in dry benzene (1 mL). Pyridine (0.23 g, 0.003 mol) in benzene (1 mL) was added to the chilled mixture. After this addition a colorless solid precipitated from the reaction mixture. The mixture was then stirred and heated under reflux for 18h. After completion of the reflux period, the benzene and pyridine were removed from the reaction mixture by evaporation under reduced pressure. The residue was chilled in an ice bath, water (35 mL) was added. The mixture was allowed to stand at room temperature for 30 min. with occasional swirling and was then extracted with chloroform. The extract was dried and evaporated giving a crude product which was purified by a preparative thick layer chromatography using 50% chloroform/benzene as an eluent. The product **232** was obtained as colorless needles (yield = 100 mg = 26%), m.p. 142°-144°C.

The pmr spectrum of **232**, δ:3.21 (3 H, s, 3-methyl protons), 7.67 (1 H, d, J=9 Hz, C-8 aromatic proton), 7.76 (1 H, d, J=9 Hz, C-7 aromatic proton), 9.26 (1 H, s, C-6 proton). MS, m/z 206(55), 149(40), 69(100). Exact mass calcd. for $C_9H_6N_2S_2$:205.9972, found: 205.9985. Anal. calcd. for $C_9H_6N_2S_2$: C, 52.3%; H, 2.91%; N, 13.59%; S, 31.07%. Found: C, 52.71%; H, 2.98%; N, 13.38%; S, 31.03%.

5.2.2 Approaches to 3-methylbenzo[1,2-*c*:6,5-*d*']*bis*-isothiazole (243)

2-Bromo-4-methylbenzoic acid

This was prepared by hydrolysis of the corresponding nitrile, available from a Sandmeyer reaction on 2-bromo-4-methylaniline. The modified method of Lindemann [28A(462)24] was used.

2-Bromo-4-methylbenzenecarbonylchloride (236)

2-Bromo-4-methylbenzoic acid 235 (20 g, 0.09 mol) was suspended in benzene (200 mL), thionyl chloride (10 mL) was added, and the mixture was heated under reflux for 48 h. (until all the solid dissolved). The organic solvent was evaporated under reduced pressure giving the product which was used for the next reaction without further purification or characterization.

2-Bromo-4-methylacetophenone (237a)

The crude acid chloride 236 (17 g, 0.07 mol) was treated in benzene (50 mL) with ethoxymagnesium malonate [prepared from magnesium (3.85 g, 0.16 mol), ethanol (25 mL), and diethylmalonate (25.54 g, 0.16 mol) as described for compound 164]. Work up as previously described gave a yellow oil which was sufficiently pure for the next reaction. (Yield = 14 g = 94%).

The pmr spectrum of 237a, δ:2.33 (3 H, s, methyl protons), 2.58 (3 H, s, acetyl methyl protons, 7.10 (1 H, d, J=6.9 Hz, C-5 aromatic proton), 7.34 (1 H, bs, C-3 aromatic proton), 7.41, d, J=6.9 Hz, C-6 aromatic proton). MS, m/z 214,212(20), 197(100, 169(21). Exact mass calcd. for $C_9H_9{}^{79}BrO$:211.9837, found: 211.9844, calcd. for $C_9H_9{}^{81}BrO$:213.9816, found: 213.9810.

4-Methyl-2-(methylthio)acetophenone (238)

To a cold solution of 2-bromo-4-methylacetophenone (5 g, 0.023 mol), and methanethiol (5 mL) in dimethylformamide (50 mL) under nitrogen was added portionwise lithium hydroxide (5 g). The mixture was stirred in the cold for 30 min. and then poured into ice water and acidified with hydrochloric acid.

The reaction mixture was extracted with chloroform, washed with water, dried and evaporated under reduced pressure to give a product which was purified by a preparative thick layer chromatography using chloroform as an eluent to give a yellow oil. (Yield = 3.5 g = 85%).

The pmr of 238, δ:2.33 (6H, s, methyl and S-methyl protons), 2.46(3H, s, the acetyl methyl protons), 6.93 (1H, d, J=9 Hz, C-5 aromatic proton), 7.03 (1 H, bs, C-3 aromatic proton), 7.70 (1 H, d, J=9 Hz, C-6 aromatic proton).

4-Methyl-2-(methylthio)acetophenone oxime (239)

The ketone 238 (2.50 g, 0.014 mol) in methanol (10 mL) with pyridine (3 mL) and hydroxylamine hydrochloride (2.50 g, 0.035 mol) was heated under reflux for 18 h. (until all the starting material was consumed). The methanol was evaporated under reduced pressure and the residue was diluted with ice-cold 5% hydrochloric acid and extracted with chloroform. The organic layer was washed with water and evaporated under reduced pressure to give a yellow paste. This was then taken to the next stage without further purification.

MS, m/z 195(5), 178(100), 163(85).

3,6-Dimethyl-1,2-benzisothiazole (240)

The ketoxime 239 (2.7 g, 0.014 mol) in pyridine (10 mL) and acetic anhydride (4 mL) was heated under reflux for 24 h. The mixture was diluted with 5% hydrochloric acid, extracted with chloroform, washed with water, dried, and evaporated under reduced pressure. The crude product was purified by column chromatography using chloroform as an eluent to give 240 as yellow liquid (yield = 2 g = 88%).

The pmr spectrum of **240**, δ:2.50 (3 H, s, 6-methyl protons), 2.70 (3 H, s, 3-methyl protons), 7.23 (1 H, d, J=8.1 Hz, C-5 aromatic proton), 7.73 (1 H, bs, the C-7 aromatic proton) 7.80 (1 H, d, J=8.1 Hz, C-4 aromatic proton). MS, m/z 163(100), 148(10), 121(20).

3,6-Dimethyl-7-nitro-1,2-benzisothiazole (241)

To a cold solution of 3,6-dimethylbenzisothiazole (1.5 g, 0.009 mol) in sulfuric acid (10 mL) was added a mixture of sulfuric acid (2 mL) and fuming nitric acid (0.58 g, 0.009 mol) dropwise, keeping the temperature lower than 5°C. The reaction mixture was stirred at room temperature for 2 h. then poured into ice-water (100 mL). The yellow precipitate was filtered, washed with water to give a crude product, which on recrystallization from ethanol gave pale yellow needles (yield = 1.7 g = 89%), m.p. 143°C.

The pmr spectrum of **241**, δ: 2.77 (3 H, s, 6-methyl protons), 2.96 (3 H, s, 3-methyl protons), 7.47 (1 H, d, J=8 Hz, C-5 aromatic proton), 8.08 (1 H, d, J = 8 Hz, C-4 aromatic proton). MS, m/z 208(95), 191(100), 163(40). Exact mass calcd. for $C_9H_8N_2O_2S$:208.0306, found: 208.0306.

7-Amino-3,6-dimethyl-1,2-benzisothiazole (242)

3,6-Dimethyl-7-nitro-1,2-benzisothiazole (241) (0.4 g, 0.002 mol) in glacial acetic acid (10 mL) and water (2.5 mL) was treated with iron powder (0.4 g) and the reaction mixture was heated at 100° for 3 h. The reaction mixture was then filtered, poured into water and extracted with chloroform. Evaporation of the organic layer gave the desired amine 242 as pale yellow needles (yield = 0.34 g = 99%). This was taken to the next stage without further purification.

The pmr spectrum of 242, δ:2.33 (3 H, s, 6-methyl protons), 2.72 (3 H, s, 3-methyl protons), 3.92 (2 H, bs, N-protons), 7.20 (1 H, d, J=9.6 Hz, C-4 or C-5 aromatic proton), 7.31 (1 H, d, J=9.6 Hz, C-4 or C-5 aromatic proton). MS. m/z 178(100), 163(26), 131(32).

3-Methylbenzo[1,2-*c*:6,5-*d*']*bis*-isothiazole (243)

The dimethylaminobenzisothiazole 242 (0.3 g, 0.0016 mol) was treated in dry benzene (5 mL) with a solution of N-sulfinylmethanesulfonamide (0.24 g, 0.0017 mol) [75JHC(12)877] in benzene (2 mL), followed by a solution of dry pyridine (0.14 g, 0.0017 mol) in benzene (2 mL) as described in the preparation of compound 232. Work up as previously described gave colorless prisms (yield = 0.15 g = 46%), m.p. 205°-207°C.

The pmr spectrum of 243, δ:2.80 (3 H, s, 3-methyl protons), 7.60 (1 H, d, J=9 Hz, C-4 aromatic proton), 7.68 (1 H, d, J=9 Hz, C-5 aromatic proton), 9.27 (1 H, s, C-6 aromatic proton). A nuclear Overhauser difference spectrum from the protons at δ = 2.80 ppm confirmed its proximity to the proton at δ = 7.60 ppm and a nuclear Overhauser difference from the proton at δ = 9.25 ppm confirmed its proximity to the proton at δ = 7.68 ppm. MS, m/z 206(100), 191(5), 173(20). Exact mass calcd. for $C_9H_6N_2S_2$: 205.9972, found: 205.9969. Anal. calcd. for $C_9H_6N_2S_2$: C, 52.43%; H, 2.91%; N, 13.59%; S, 31.07%. Found: C, 52.35%; H, 3.04%; N, 11.53%; S, 30.85% (sample size was insufficient for reanalysis of nitrogen).

5.2.3 Attempts towards the synthesis of 3-methylbenzo[1,2-*c*:4,5-*d*']*bis*-isothiazole (249)

2-Bromo-4-methyl-5-nitroacetophenone (244a)

To a cold solution of 2-bromo-4-methylacetophenone (6.3 g, 0.03 mol) in sulfuric acid (30 mL) was added a mixture of concentrated sulfuric acid (5 mL) and fuming nitric acid (1.9

g, 0.03 mol) dropwise while keeping the temperature below 5°C. The reaction mixture was stirred at room temperature for 2 h., poured into ice water (200 mL), extracted with chloroform and the chloroform layer evaporated under reduced pressure to give a product which on development on preparative thick layer chromatography using chloroform as an eluent gave light yellow needles (yield = 7.1 g = 92%), m.p. 63°C.

The pmr spectrum of **244a**, δ: 2.67 (3 H, s, 4-methyl protons), 2.73 (3 H, s, acetyl methyl protons), 7.74 (1 H, bs, C-3 aromatic proton), 8.25 (1 H, bs, C-6 aromatic proton). MS, m/z 257(20), 242(100), 227(11). Exact mass calcd. for $C_9H_8{}^{79}BrNO_3$: 256.9687, found: 256.9683, calcd. for $C_9H_8{}^{81}BrNO_3$: 258.9666, found: 258.9662.

4-Methyl-2,5-*bis*-(methylthio)acetophenone (245)

To a cold solution of 2-bromo-4-methyl-5-nitroacetophenone (244) (7 g, 0.027 mol), and methanethiol (10 mL) in dimethylformamide (80 mL) under nitrogen was added portionwise lithium hydroxide (10 g). The mixture was stirred in the cold for 30 min. and then poured into ice water and acidified with hydrochloric acid. The reaction mixture was extracted with chloroform, washed with water, dried and evaporated under reduced pressure to give a product which on recrystallization from benzene gave yellow prisms (yield = 4.9 g = 80%), m.p. 130°-133°C.

The pmr spectrum of **245**, δ: 2.50 (3 H, s, methyl protons), 2.70 (6H, s, S-methyl protons), 2.74 (3 H, s, acetyl methyl protons), 7.20 (1 H, s, C-3 aromatic proton), 8.63 (1 H, s, C-6 aromatic proton). MS, m/z 226(70), 211(100), 196(30).

Acetylation of 3-chlorotoluene

Acetylation was done by the method of Borsche [16CB(49)2222] as described for the synthesis of 2-chloro-4-methylacetophenone (yield = 91%). This was, however, a mixture

of the 2-chloro-4-methylacetophenone and 4-chloro-2-methylacetophenone. This was taken to the next stage without further purification or characterization.

2-Chloro-4-methyl-5-nitroacetophenone (244b)

The crude mixture from above was nitrated as described [16CB(49)2222]. Fractional crystallization of the product from ethanol gave long fibrous needles (m.p. 68°-70°C) as the less soluble product, (lit. m.p. 74°-76°C [16CB(49)2222]).

The pmr spectrum indicated that this was not completely pure. It was, however, sufficiently pure for the next reaction (yield = 21%).

4-Methyl-2-methylthio-5-nitroacetophenone (246)

The crude ketone from above (2.27 g, 0.01 mol) in dimethylformamide (20 mL) containing lithium hydroxide (0.41 g, 0.01 mol) was stirred and to it added liquid methanethiol (~1 mL). The mixture slowly turned yellow and after 2 h. a precipitate formed. After 16 h. the mixture was diluted with water and the yellow precipitate collected. Fractional crystallization from ethanol gave the product as lemon yellow needles (yield = 1.37 g = 61%), m.p. 145°C.

The pmr spectrum of 246, δ: 2.55 (3 H, s, methyl or S-methyl protons), 2.70 (6 H, s, acetyl methyl, methyl or S-methyl protons), 7.39 (1 H, s, C-3 aromatic proton), 8.73 ppm (1 H, s, C-6 aromatic proton). The ir spectrum 1691 cm^{-1} (C=O str). MS, m/z 225(60), 210(40), 164(100).

4-Methyl-2-methylthio-5-nitroacetophenone oxime.

To the ketone 246 (516 mg, 0.002 mol) in ethanol (20 mL) and pyridine (2 mL) was added hydroxylamine hydrochloride (1 g) and the solution refluxed for 16 h. (until all the starting

material was consumed). The mixture was diluted with ice-water, cooled and the precipitate collected was recrystallized from ethanol as bright yellow curved needles, (yield = 490 mg = 89%), m.p. 175-180°C. This was used in the next stage without further purification.

Attempted cyclization of 4-methyl-2-methylthio-5-nitroacetophenone oxime

The oxime (258 mg, 0.001 mol) in pyridine (5 mL) and acetic anhydride (0.5 mL) was refluxed for 6 h. The mixture became dark. Workup by dilution with water, and chloroform extraction gave only ~20 mg of an amorphous material which was not characterized due to low yield.

5.3 APPROACHES TOWARDS THE SYNTHESIS OF FUSED ISOTHIAZOLE SYSTEMS

5.3.1 Approaches to 7-acetyl-3-methyl 1,2-benzisothiazole (255)

2-Chloro-1,3-benzenedicarboxylic acid (265)

2-Chloro-1,3-dimethylbenzene (20 g, 0.14 mol) in water (2 L) was stirred under gentle reflux for 16 h. with potassium permanganate (150 g). Excess potassium permanganate was destroyed by adding 95% ethanol to the still warm reaction mixture, the formed manganese dioxide removed by filtration and the reaction acidified with concentrated hydrochloric acid. The reaction mixture was cooled and the colorless needles were collected (yield = 19.3 g = 70%), m.p. 222°-227°C (lit. m.p. 223-223.5°C [54JAA193]).

2-Chlorobenzene-1,3-dicarbonylchloride (266)

The diacid 265 (20 g, 0.1 mol) suspended in benzene (50 mL) and thionyl chloride (10 mL) was heated under reflux for 24 h. (until all the acid dissolved). The organic solvent

was evaporated under reduced pressure and the brown oil produced was taken to the next step without further purification or characterization.

2-Chloro-1,3-diacetylbenzene (267)

Preparation of the ketone 267 was carried out as described for the preparation of compound 164 using the diacid chloride 266, (20.4 g, 0.1 mol) magnesium (7.2 g, 0.3mol), diethylmalonate (48 g, 0.3 mol), absolute ethanol (20 mL). The reaction was left at room temperature for 17 h. The reaction mixture was poured into ice-cold 10% sulfuric acid (500 mL), the organic layer separated and the aqueous layer extracted with chloroform. The combined organic layers were evaporated and the red oil produced treated with glacial acetic acid (60 mL), concentrated sulfuric acid (10 mL) and water (40 mL). The reaction mixture was refluxed until evolution of carbon dioxide stopped, then poured into ice-water (500 mL) and extracted with chloroform. Evaporation of the chloroform layer gave a yellow oil (yield = 16.5 g = 84%).

The pmr spectrum 267, δ:2.62 (6 H, s, acetyl methyl protons), 7.31 - 7.71 (3 H, m, aromatic protons). MS, m/z 196(20), 181(100), 125(21). Exact mass calcd. for $C_{10}H_9{}^{35}ClO_2$: 196.0290, found: 196.0283, calcd. for $C_{10}H_9{}^{37}ClO_2$: 198.0261, found: 198.0249.

1,3-Diacetyl-2-methylthiobenzene (268)

2-Chloro-1,3-diacetylbenzene (267) (6 g, 0.03 mol) in dimethylformanide (20 mL) was treated with methanethiol (10 mL) and lithium hydroxide (10 g) as described for the preparation of compound 165. The reaction mixture was acidified with ice-cold 30% hydrochloric acid, extracted with chloroform and the chloroform layer washed with water. Evaporation of the chloroform layer gave a yellow liquid (yield = 5.4 g= 87%).

The pmr spectrum of 268 δ: 2.35 (3 H, s, S-methyl protons), 2.66 (6 H, s, acetyl methyl protons), 7.43 (3 H, m, aromatic protons). The ir spectrum 1714 cm^{-1} (C=O str). MS, m/z 208(10), 193(100), 147(20). Exact mass calcd. for $C_{11}H_{12}O_2S$: 208.0557, found 208.0549.

1,3-Diacetyl-2-(methylthio)benzene monoxime (269)

To a solution of the diketone 268 (2.08 g, 0.01 mol) in methanol (10 mL) was added hydroxylamine hydrochloride (0.69 g, 0.01 mol) and pyridine (0.79 g, 0.01 mol) and the reaction was refluxed for 17 h. The methanol was evaporated under reduced pressure, the residue diluted with cold water (10 mL) and extracted with chloroform. Evaporation of the chloroform layer gave a yellow prisms. This was taken to the next stage without further purification.

MS, m/z 223(2), 206(47), 193(100).

7-Acetyl-3-methyl-1,2-benzisothiazole (255)

The crude oxime 269 (2 g, 0.009 mol) was refluxed in acetic anhydride (3 mL) and pyridine (10 mL) for 24 h. The reaction mixture was poured into ice-water (100 mL), neutralized with concentrated hydrochloric acid and extracted with chloroform. The chloroform layer was washed with water and evaporated under reduced pressure to give the a product which was purified by preparative thick layer chromatography using 25% ethyl acetate in dichloromethane as an eluent giving light yellow plates (yield = 1 g = 58%), m.p. 115 - 120°C.

The pmr spectrum of 255, δ: 2.80 (6 H, s, acetyl methyl and 3-methyl protons), 7.30 - 8.30 (3 H, m, aromatic protons). The ir spectrum 1660 cm^{-1} (C=O str.). MS, m/z 191(72), 176(100), 149(70).

5.3.2 Attempts towards the synthesis of fused benzo-1,2-*bis*-isothiazoles.

7-Acetyl-3-methyl-1,2-benzisothiazole oxime (270)

To a solution of the 7-acetyl-3-methyl-1,2-benzisothiazole (**255**) (0.8 g, 0.004 mol) in methanol (5 mL) was added hydroxylamine hydrochloride (0.3 g, 0.004 mol) and pyridine (0.32 g, 0.004 mol) and the reaction was refluxed for 17 h. (until all the starting material was consumed). The methanol was evaporated under reduced pressure, the residue diluted with cold water (10 mL) and extracted with chloroform. Evaporation of the chloroform layer gave a product which recrystallized from benzene as pale yellow prisms (yield = 0.5 g = 61%), m.p. 222-227°C.

The pmr spectrum of **270**, δ:2.21 (3 H, s, oxime methyl protons), 2.52 (3 H, s, C-3 methyl protons), 7.10 (3 H, s, aromatic protons). MS, m/z 206(100), 191(40), 176(30).

Reaction of the oxime 270 with trifluoroacetic anhydride

To a solution of the oxime **270** (8 mg, 0.04 mmol) in chloroform-d (0.5 mL) was added trifluoroacetic anhydride (2 drops) and the reaction was left at room temperature for 4 days, during which the pmr spectrum and the R_f was checked periodically. No change in the starting oxime was observed.

Synthesis of the acetate 271 from the oxime 270

The oxime **270** (10 mg., 0.05 mmol) was warmed in acetic anhydride (1 mL) and pyridine (2 mL) at 60°C for 30 min. The reaction mixture was poured into ice-water (10 mL), extracted with chloroform and the chloroform layer washed with 5% hydrochloric acid followed by water. Evaporation of the chloroform layer gave the acetate **271** as colorless plates which was taken to the next stage without further purification. m.p 160°-170°C.

The pmr spectrum of **271**, δ:2.40 (3 H, s, acetoxime methyl protons), 2.53 (3 H, s, ester methyl protons), 2.76 (3 H, s, C-3 methyl protons), 7.49 - 8.10 (3 H, m, aromatic protons).

Reaction of the acetate **271** with acetic acid and perchloric acid

The acetate **271** (10 mg, 0.04 mmol) was dissolved in acetic acid (1 mL). The addition of 1 drop of perchloric acid gave a precipitate which was collected. The pmr spectrum and the R_f of this material indicated that it was the starting acetate.

2-Chloro-5-nitro-1,3-benzenedicarbonylchloride (273)

The acid **272** (4.0 g, 0.02 mol) [83JOC(48)4649] suspended in benzene (100 mL) and thionyl chloride (10 mL) was heated under reflux for 24 h. (until all the acid dissolved). The organic solvent was evaporated under reduced pressure and the produced oil was taken to the next stage without further purification or characterization.

2-Chloro-1,3-diacetyl-5-nitrobenzene (274)

Synthesis of the ketone **274** was carried out as described for the preparation of compound **164** using the diacid chloride **273** (5 g, 0.02 mol) magnesium (1.44 g, 0.06 mol), diethylmalonate (9.6 g, 0.06 mol), absolute ethanol (20 mL). The reaction was left at room temperature for 17 h. The reaction mixture was poured into ice-cold 10% sulfuric acid (200 mL), the organic layer separated and the aqueous layer extracted with chloroform. The combined organic layer was evaporated and the ester produced was hydrolysed as previously described for compound **164**. Workup as above gave a product which on recrystallization from acetone yielded pale buff plates (yield = 4.7 g = 98%), m.p. 162°-163°C.

The pmr spectrum of **274**, δ:2.73 (6 H, s, acetyl methyl protons), 8.43 (2 H, s, aromatic protons). The ir spectrum, 1720 cm^{-1} (C=O str.). MS, m/z 241(10), 226(100), 18(26). Exact mass calcd. for $C_{10}H_8{}^{35}ClNO_4$:241.0141, found: 241.0144.

5-Amino-2-chloro-1,3-diacetylbenzene (275)

To a mixture of the diketone **274** (1.5 g, 0.006 mol) and tin (3 g) was added dropwise concentrated hydrochloric acid (30 mL) and the reaction was heated on a steam bath for 4 h. A solution of sodium hydroxide (1 g) in water (10 mL) was added, the reaction mixture extracted with chloroform, washed with water and the chloroform layer evaporated under reduced pressure. Recrystallization from benzene gave the amine **275** as pale yellow prisms (yield = 1.2 g = 95%), m.p. 96°-97°C.

The pmr spectrum of **275**, δ: 2.66 (6 H, s, acetyl methyl protons), 4.10 (2 H, bs, amino protons), 6.90 (2 H, s, aromatic protons). The ir spectrum, 1713 cm^{-1} (C=O str). MS, m/z 211(79), 196(100), 149(30). Exact mass calcd. for $C_{10}H_{10}{}^{35}ClNO_2$:211.0 399, found: 211.0398, calcd for $C_{10}H_{10}{}^{37}ClNO_2$:213.0370, found: 213.0362.

2-Chloro-1,3-diacetyl-5-(N,N-dimethyl) aminobenzene (276)

A mixture of the diketoamine **275** (7 g, 0.033 mol), methanol (20 mL), methyl iodide (11.7 g, 0.083 mol), potassium hydroxide (2 g) and water (10 mL) was heated under reflux for 17 h. The reaction mixture was poured into ice-water, extracted with chloroform and the chloroform layer evaporated under reduced pressure. Recrystallization from methanol gave yellow prisms (yield = 5.5 g = 70%), m.p. 86-87°C.

The pmr spectrum of **276**, δ:2.66 (6 H, s, N-methyl or acetyl methyl protons), 3.03 (6 H, s, N-methyl or acetyl methyl protons), 6.83 (2 H, s, aromatic protons). The ir spectrum 1685 cm^{-1} (C=O str.). MS, m/z 239(100), 224(40), 196(42). Exact mass calcd. for $C_{12}H_{14}{}^{35}ClNO_2$:239.0713, found: 239.0706, calcd. for $C_{12}H_{14}{}^{37}ClNO_2$:241.0683, found: 241.0683.

1,3-Diacetyl-5-(N,N-dimethyl)amino-2-methylthiobenzene (277)

A solution of **276** (0.28 g, 0.001 mol) in dimethylformamide (10 mL) was heated for 30 min. at 150°C in a pressure bottle with lithium hydroxide (1 g) and methanethiol (1 mL). The solution turned orange after 10 min. with the formation of a gelatinous precipitate. The reaction mixture was poured into water, neutralized with hydrochloric acid and extracted with ether. Evaporation of the ether layer under reduced pressure gave yellow needles, m.p. 75°C. This was taken to the next stage without further purification.

The pmr spectrum of **277**, δ:2.23 (3 H, s, the S-methyl protons), 2.66 (6 H, s, N-methyl or acetyl methyl protons), 3.00 (6 H, s, N-methyl or acetyl methyl protons), 6.56 (2 H, s, aromatic protons). MS, m/z 196(20), 181(100), 149(20).

1,3-Diacetyl-5-(N,N-dimethyl)amino-2-methylthiobenzene monoxime

The diketone **277** (0.7 g, 0.003 mol) in methanol (10 mL), with pyridine (0.22 g, 0.003 mol) and hydroxylamine hydrochloride (0.2 g, 0.003 mol) was heated under reflux for 18 h. The methanol was evaporated under reduced pressure and the residue diluted with ice cold 5% hydrochloric acid then extracted with chloroform. The organic layer was washed with water and evaporated under reduced pressure to give 710 mg of yellow oil. The crude product was used for the next reaction without further purification.
MS, m/z 266(5), 251(100), 236(70).

Reaction of the 1,3-Diacetyl-5-(N,N-dimethyl)amino-2-methylthiobenzene monoxime with acetic anhydride in pyridine

The crude oxime (0.4 g, 1.5 mmol) in pyridine (5 mL) and acetic anhydride (1 mL) was heated under reflux for 24 h. The mixture was diluted with 5% hydrochloric acid, extracted with chloroform, washed with water, dried, and evaporated under reduced pressure. Pmr spectrum and thin layer chromatography indicated that the starting material was recovered.

1,3-Diacetyl-2-methylthio-5-nitrobenzene (279)

The diketone **274** (1.2 g, 0.005 mol) was dissolved in hot methanol (10 mL). Methanethiol (0.24 g, 0.005 mol), potassium hydroxide (0.28 g, 0.005 mol) and methanol (10 mL) were added during 30 min. The mixture was heated under reflux for 1 h. and was then cooled and filtered to give yellow needles (yield = 1 g = 80%), m.p. 100 - 103°C.

The pmr spectrum of **279**, δ: 2.36 (3 H, s, S-methyl protons), 2.70 (6 H, s, acetyl methyl protons), 8.20 (2 H, s, aromatic protons). The ir spectrum, 1705 cm^{-1} (C=O str.) MS, m/z 253(10), 238(100), 192(50). Exact mass calcd. for $C_{11}H_{11}NO_4S$: 253.0408, found: 253.0399.

1,3-Diacetyl-2-methylthio-5-nitrobenzene monoxime (281)

The diketone **279** (0.5 g, 0.002 mol) in methanol (5 mL) with pyridine (0.16 g, 0.002 mol) and hydroxylamine hydrochloride (0.14 g, 0.002 mol) was heated under reflux for 18 h. The methanol was evaporated under reduced pressure and the residue diluted with ice-cold 5% hydrochloric acid then extracted with chloroform.

The organic layer was washed with water and evaporated under reduced pressure to give a yellow solid (0.5 g). The crude product was used for the next reaction without further purification.

MS, m/z 268(1), 238(80), 193(100).

Reaction of the monoxime 281 with acetic anhydride in pyridine

The crude oxime from above 281 (0.3 g, 0.001 mol) in pyridine (5 mL) and acetic anhydride (1 mL) was heated under reflux for 24 h. The mixture was diluted with 5% hydrochloric acid, extracted with chloroform, washed with water, dried, and evaporated under reduced pressure. Pmr spectrum and thin layer chromatography indicated that the starting material was recovered.

1,3-Diacetyl-2,5-*bis*-(methythio)benzene (283)

To a cold solution (under nitrogen) containing the diketone 274 (4.70 g, 0.02 mol) and methanethiol (10 mL) in dimethylformamide (80 mL) was added portionwise lithium hydroxide (10 g), and the reaction was stirred in the cold for 30 min. The mixture was poured into ice water, acidified with hydrochloric acid, extracted with chloroform, washed with water and evaporated under reduced pressure. The product was purified by thick layer chromatography using chloroform as an eluent to give yellow needles (yield = 4.5 g = 90%), m.p. 37°C.

The pmr spectrum of 283, δ: 2.33 (3 H, s, 5-S-methyl protons), 2.53 (3 H, s, 2-S-methyl protons), 2.66 (6 H, s, acetyl methyl protons), 7.31 (2 H, s, aromatic protons). The ir spectrum, 1715 cm^{-1} (C=O str.) MS, m/z 254(60), 239(100), 224(10). Exact mass calcd. for $C_{12}H_{14}O_2S_2$: 254.0435, found: 254.0427.

1,3-Diacetyl-2,5-*bis*-(methylthio)benzene monoxime (284)

The diketone 283 (0.5 g, 0.002 mol) in methanol (10 mL) with pyridine (0.16 g, 0.002 mol) and hydroxylamine hydrochloride (0.14 g, 0.002 mol) was heated under reflux for 18 h. The methanol was evaporated under reduced pressure and the residue diluted with ice cold 5% hydrochloric acid then extracted with chloroform. The organic layer was washed with water and evaporated under reduced pressure to give a yellow liquid (0.35 g), this was taken to the next stage without further purification.

MS, m/z 269(10), 252(50), 84(100).

Reaction of the monoxime 284 with acetic anhydride in pyridine

The crude oxime from above 284 (0.35 g, 0.001 mole) in pyridine (2 mL) and acetic anhydride (0.5 mL) was heated under reflux for 24 h. The mixture was diluted with 5% hydrochloric acid, extracted with chloroform, washed with water, dried and evaporated under reduced pressure. Pmr spectrum and thin layer chromatography indicated that the starting material was recovered, along with decomposed products.

5.4 ATTEMPTS TOWARDS THE SYNTHESIS OF ISOTHIAZOLOCARBAZOLES

5.4.1 Synthesis of 5-H-isothiazolo[*c*]carbazole

5.4.1.1 Attempts towards the synthesis of 5-H-isothiazolo[3,4-*c*]carbazole (152)

Reaction of 4-methyl-3-nitroaniline (287) with 2-chlorocyclohexanone

A mixture of 2-chlorocyclohexanone (1.32 g, 0.01 mol), 4-methyl-3-nitroaniline (1.5 g, 0.001 mol), quinoline (6.5 g, 0.05 mol), sodium carbonate (1.5 g, 0.015 mol) and methylcellosolve (5 mL) was refluxed, with stirring, for 2 h. The cooled reaction mixture was then filtered and the inorganic residue washed with methylcellosolve (5 mL). The combined filtrate, and anhydrous magnesium chloride (0.2 g, 0.002 mol) was refluxed

under nitrogen for 4 h. The cooled reaction mixture was then added dropwise to a vigorously stirred mixture of 40% hydrochloric acid (30 mL). After stirring for 17 h. the mixture was filtered, washed with 10% hydrochloric acid, water and evaporated under reduced pressure. The product was developed on preparative thick layer chromatography using 25% ethyl acetate in cyclohexane to give a material with close R_f.
The pmr spectrum indicated a mixture.

2-Aminocarbazole (295)

To a solution of 2-nitrocarbazole [51JAS(73)2435] (0.8 g, 0.004 mol) in 95% ethanol (3 mL) Raney nickel (an ethanol (2 mL) suspension containing ~ 0.3 g of nickel) water (2 mL) and hydrazine hydrate (2 mL) was added and the reaction mixture was refluxed for 3 h. (until the yellow color disappeared). The catalyst was separated, the solvent concentrated and the solid which formed was collected to give a crude product which on recrystallization from ethanol gave pale yellow needles (yield = 0.5 g = 68%), m.p. 238°C (lit m.p 238°-239°C [54JAS(76)664]).

Reaction of 2-aminocarbazole with trichloromethanesulfenylchloride and anhydrous aluminum chloride

2-Aminocarbazole (0.5 g, 0.003 mol) was slowly added to a stirred mixture of trichloromethanesulfenylchloride (1 g, 0.005 mol) in ether (60 mL) and sodium carbonate (4 g) in water (100 mL) and the reaction was stirred for 15 min. The organic layer was separated, the aqueous layer extracted with ether, and the combined extracts washed with water and evaporated under reduced pressure. The colorless needles produced were stirred in benzene (10 mL), and anhydrous aluminum chloride (0.4 g, 0.003 mol) was added portionwise.

The reaction was stirred for 24 h. and poured into ice-water. The reaction mixture was extracted with ether and the organic layer separated, washed with water and evaporated under reduced pressure. Examination of the crude product by thin layer chromatography showed a mixture of 5 products.

2-Nitro-4′-methyldiphenylamine (298)

A mixture of 1-chloro-2-nitrobenzene (16.1 g, 0.1 mol), *p*-toluidine (10.7 g, 0.12 mol), potassium carbonate (6.9 g), potassium iodide (2 g, 0.01 mol), and copper (0.1 g, 0.0016 mol) was refluxed in pyridine (10 mL) for 48 h. The inorganic residue was separated, pyridine and excess *p*-toluidine separated by steam distillation. The precipitate left in the aqueous solution was separated and purified by column chromatography using chloroform as an eluent giving the desired **298** as orange prisms, with physical properties identical to that of the literature [56AC(P)(1)115].

2-Amino-4′-methyldiphenylamine (299)

To a solution of the diphenylamine **298** (0.5 g, 0.002 mol) in 95% ethanol (3 mL), Raney nickel (an ethanol (2 mL) suspension containing ~ 0.3 g of nickel), water (2 mL) and hydrazine hydrate (2 mL) was added and the reaction mixture refluxed for 3 h. (an ethanol (2 mL) suspension containing ~ 0.3 g of nickel). The catalyst was separated, the solvent concentrated and the residue extracted with chloroform. Evaporation of the chloroform under reduced pressure gave the product as pale yellow plates which was taken to the next stage without further purification.

2-Amino-4′-methyl-2′-nitrodiphenylamine (300)

To a cold solution of the crude diphenylamine **299** (11.2 g, 0.05 mol) in sulfuric acid (15 mL) was added a mixture of sulfuric acid (2 mL) and fuming nitric acid (3.15 g, 0.05 mol) dropwise keeping the temperature lower than 5°C. The reaction mixture was stirred at

room temperature for 2 h. then poured into ice-water (100 mL). The precipitate was filtered, washed with water to give a crude product, which on recrystallization from methanol gave orange prisms (yield = 11.5 g = 95%), m.p. 90°-95°C.

The pmr spectrum of **300**, δ:2.28 (3 H, s, 4′-methyl protons), 3.80 (2 H, bs, 2-amino protons), 6.66 (1 H, d, J=8.1 Hz, 6′-aromatic proton), 7.16 (1 H, d, J=8.1 Hz, 5′-aromatic proton), 8.01 (1 H, bs, 3′-aromatic proton), 8.95 (1 H, bs, the 1-amino proton), a series of doublets at δ = 6.79, 6.84 and δ = 7.13, 7.17 were tentatively assigned to the 3,5-protons (higher field) and 4,6-protons (lower field) respectively, with J_o values of 4.5 Hz and J_m of 1 Hz. Difference double resonance from the methyl protons confirmed that the methyl protons are coupled with three protons. A nuclear Overhauser difference spectrum from the methyl protons confirmed the presence of two protons *ortho* to the methyl group.

5.4.1.2 Approaches to 5-H-isothiazolo[4,3-*c*]carbazole (153)

1,2,3,4-Tetrahydro-7-methylcarbazole (302)

This was prepared from 2-chlorocyclohexanone and m-toluidine following Dalton's method [69AJC(22)185].

1,2,3,4-Tetrahydro-7-methyl-6-nitrocarbazole (303)

To a cold solution of the tetrahydrocarbazole **302** (0.5 g, 0.003 mol) in sulfuric acid (15 mL) was added a mixture of concentrated sulfuric acid (2 mL) and fuming nitric acid (170 mg, 0.003 mol) dropwise while keeping the temperature below 5°C. The reaction mixture was stirred at room temperature for 2 h., then poured into ice water (50 mL) and neutralized with 10% sodium hydroxide. The neutral mixture was then extracted with chloroform, the chloroform layer separated, washed with water and evaporated under reduced pressure. The product was then purified by preparative thick layer

chromatography using benzene as an eluent giving yellow prisms (yield = 0.5 g = 78%), m.p. 139°-141°C (lit. m.p 140°-142°C [69AJC(22)185]).

2-Methyl-3-nitrocarbazole (304)

To a solution of the tetrahydrocarbazole 303 (0.5 g, 0.002 mol) in xylene (5 mL), 5% palladium on charcoal (1.2 g) was added and the mixture was refluxed for 48 h. The reaction mixture was then filtered while hot and the residue washed with ethyl acetate. The ethyl acetate was evaporated under reduced pressure and the product purified by column chromatography using benzene as an eluent to give light yellow prisms (yield = 0.35 g = 77%). m.p. 216°-218°C (lit. m.p 216°-218°C [69AJC(22)185]).

3-Amino-2-methylcarbazole (305)

To a solution of the nitrocarbazole 304 (0.2 g, 0.001 mol) in 95% ethanol (1 mL), Raney nickel (an ethanol (1 mL) suspension containing ~ 0.15 g of nickel), water (1 mL) and hydrazine hydrate (1 mL) was added and the reaction mixture refluxed for 3 h. (until the yellow color disappeared). The catalyst was separated, the solvent concentrated and the filtrate cooled, the precipitate separated and recrystallized from ethanol giving pale yellow needles (yield = 150 mg = 76%). m.p. 312°-315°C (lit m.p 314°-317°C [69AJC(22)185]).

N-sulfinyl-3-amino-2-methylcarbazole (306)

The 3-amino-2-methylcarbazole (1.0 g, 0.005 mol) was dissolved in benzene (10 mL), the solution cooled in an ice bath and thionyl chloride (2 mL) added dropwise. After the reaction exotherm was dissipated in the ice bath, the mixture was stirred magnetically and heated under reflux for 3 h. (until the precipitate dissolved). The organic solvent was evaporated under reduced pressure giving the product which was used for the next reaction without further purification or characterization.

5-H-Isothiazolo[4,3-*c*]carbazole (153)

The crude N-sulfinyl-3-amino-2-methylcarbazole (306) (1.0 g, 0.004 mol) was treated in dry benzene (10 mL) with a solution of N-sulfinylmethanesulfonamide (1.4 g, 0.01 mol) [75JHC(12)877] in benzene (5 mL), followed by a solution of dry pyridine (0.79 g, 0.01 mol) in benzene (5 mL) as described for the preparation of compound 232. Workup as previously described gave pale yellow needles (yield = 100 mg = 10%), m.p. 230°-234°C.

The pmr spectrum of 153, δ=7.25 - 7.96 (6 H, m, aromatic protons), 9.43 (1 H, s, C-3 isothiazolo protons). MS, m/z 224(100), 192(10), 112(12).

5.4.2. Attempts towards the synthesis of 5-H-isothiazolo[*d*]carbazole

1,2,3,4-Tetrahydro-6-methylthiocarbazole (307)

2-Chlorocyclohexanone (0.264 mg, 0.002 mol) in ethanol (2 mL) was added dropwise to a refluxing solution of 4-methylthioaniline (0.560 g, 0.004 mol) in ethanol (10 mL), and the refluxing continued for 24 h. The ethanol was evaporated under reduced pressure, and the residue dissolved in a 1:1 mixture of chloroform and water (50 mL). The separated aqueous phase was extracted with chloroform, and the combined chloroform layers washed with 5% hydrochloric acid, water, and evaporated under reduced pressure giving a clean product which was taken to the next stage without further purification.

Attempted aromatization of the tetrahydrocarbazole 307 with chloranil

Chloranil (0.5 g, 10 mmol) was added to a boiling solution of the crude tetrahydrocarbazole 307 (0.15 g, 0.7 mmol) in xylene (3 mL). The mixture was refluxed for 24 h., the liquid separated from the precipitated solid while hot, and chromatographed on preparative thick layer chromatography. The pmr spectrum and thin layer chromatography indicated that the starting material was recovered.

Attempted aromatization of the tetrahydrocarbazole 307 with nitrobenzene

A solution of the tetrahydrocarbazole **307** (0.15 g, 0.7 mmol) in nitrobenzene (2 mL) was refluxed for 17 h. The nitrobenzene was steam distilled, the reaction mixture extracted with chloroform, the chloroform layer separated and evaporated under reduced pressure. The pmr spectrum and thin layer chromatography indicated that the starting material was recovered.

Attempted aromatization of the tetrahydrocarbazole 307 with iodine

A solution of the tetrahydrocarbazole **307** (0.15 g, 0.7 m. mol) in benzene (3 mL) was refluxed with iodine (0.5 g) for 24 h. The reaction mixture was diluted with chloroform (15 mL), washed with 10% sodium bisulfite and the separated organic layer evaporated under reduced pressure. The pmr spectrum and thin layer chromatography indicated that the starting material was recovered.

Reaction of carbazole with chlorosulfonic acid

The reaction was carried out following Shishkina's method [70KKT(13)269] by heating the carbazole (4.01 g, 0.002 mol) with chlorosulfonic acid (4.6 g, 0.04 mol) at 100°-110°C for 4 h. The reaction mixture was poured into ice-water (100 mL), the precipitate separated and purified by preparative thick layer chromatography to give the carbazole -3-sulfonylchloride (yield = 250 mg = 4%).

Thiocyanation of carbazole

The reaction was done following Baranova and Shishkina's method [72KKT(15)1678] a mixture of 1- and 3-thiocyanocarbazole and 1,3-dithiocyanocarbazole was obtained. These could not be separated.

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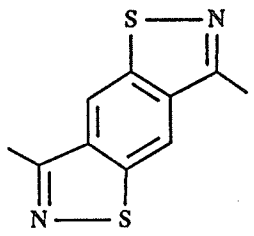

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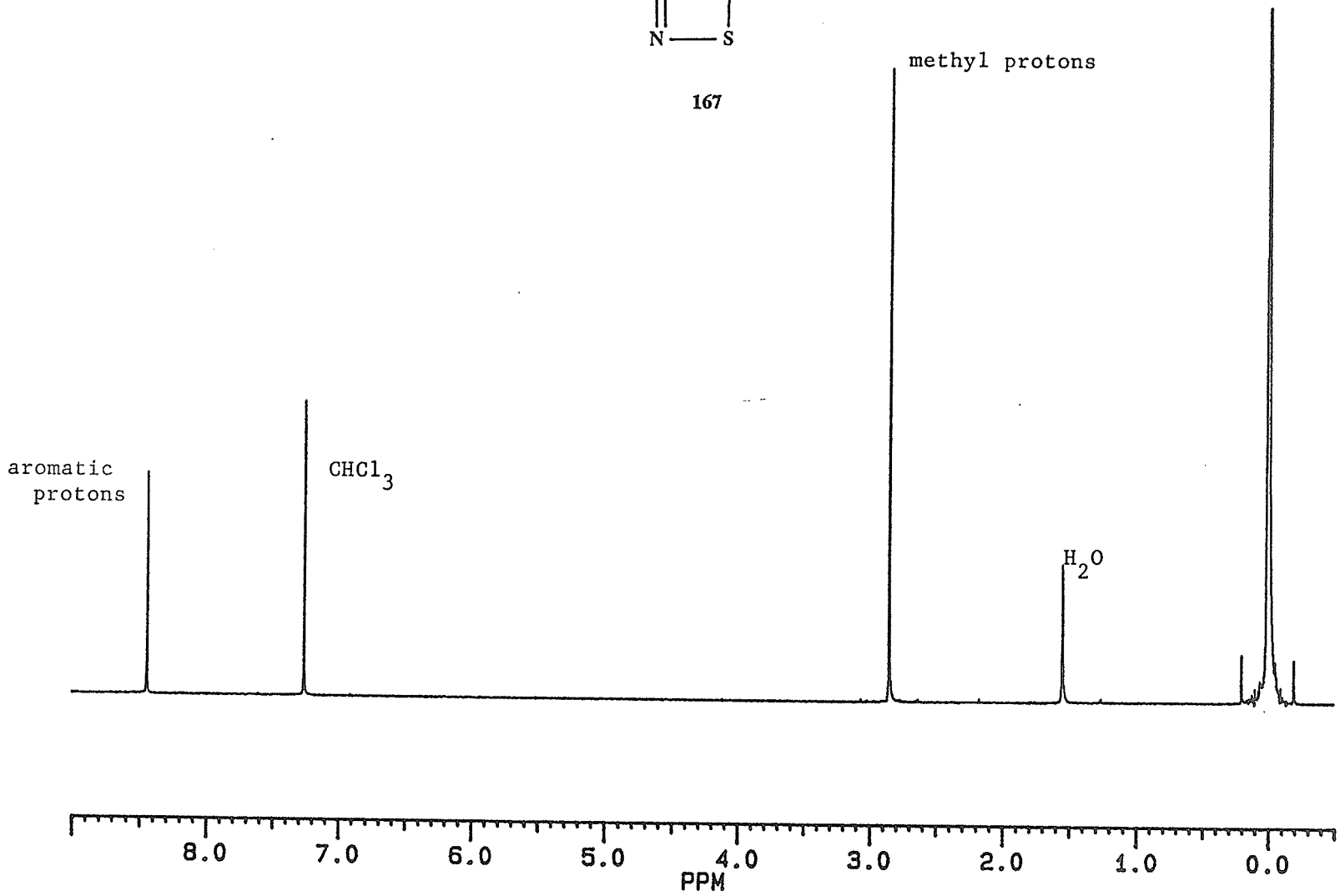

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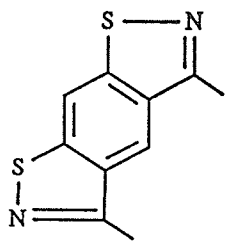

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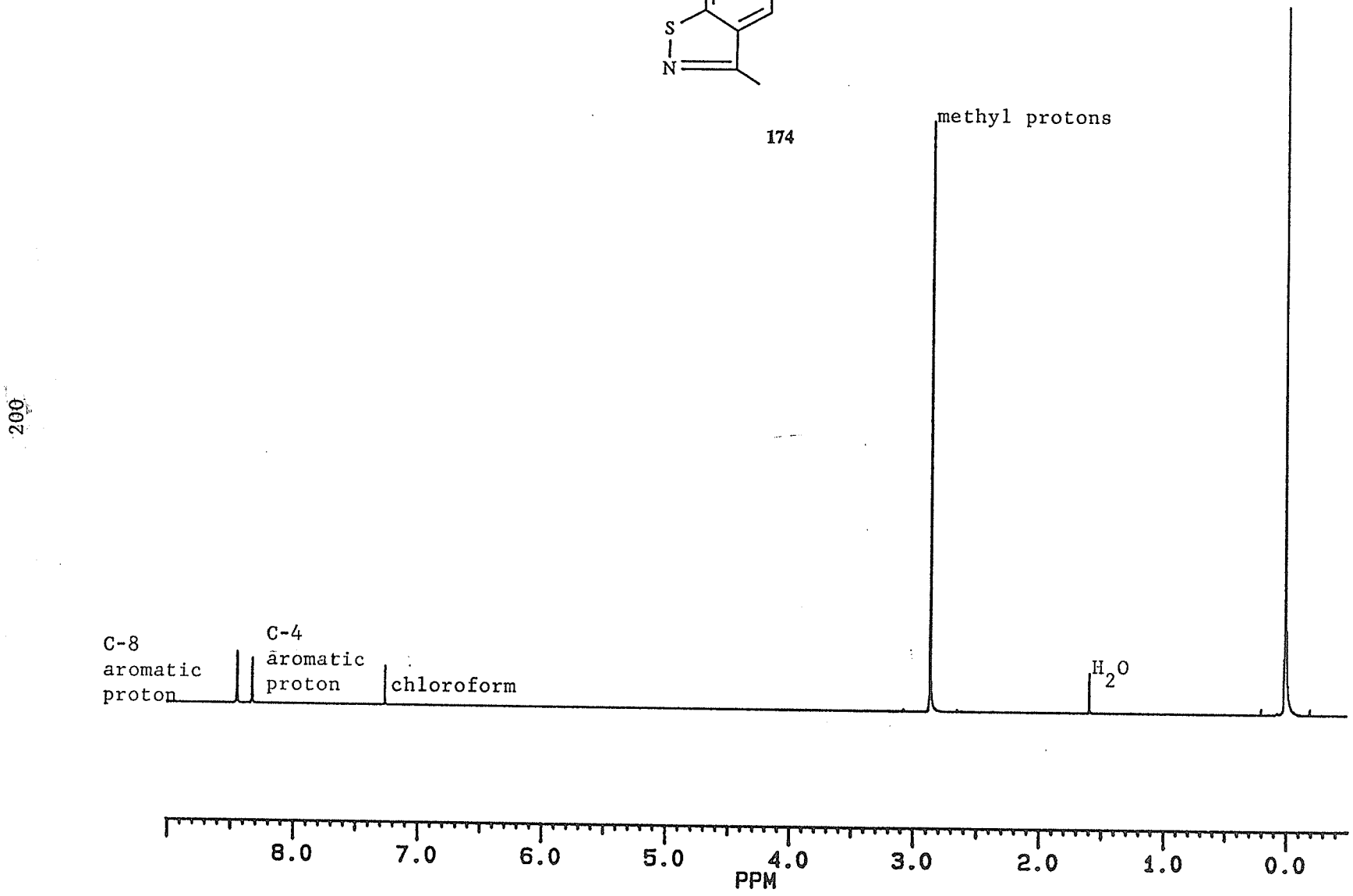

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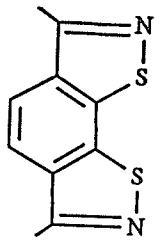

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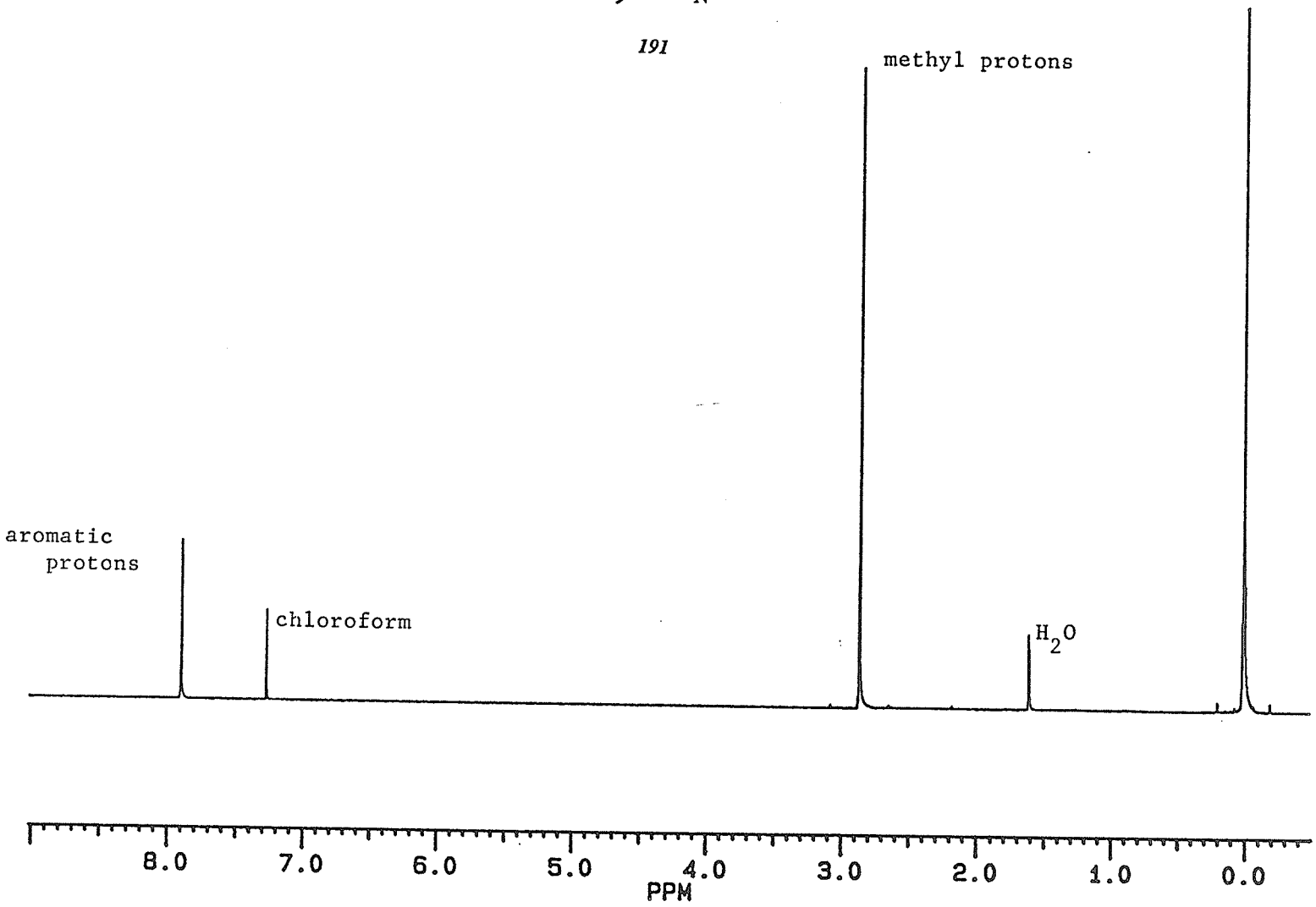

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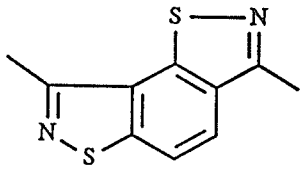

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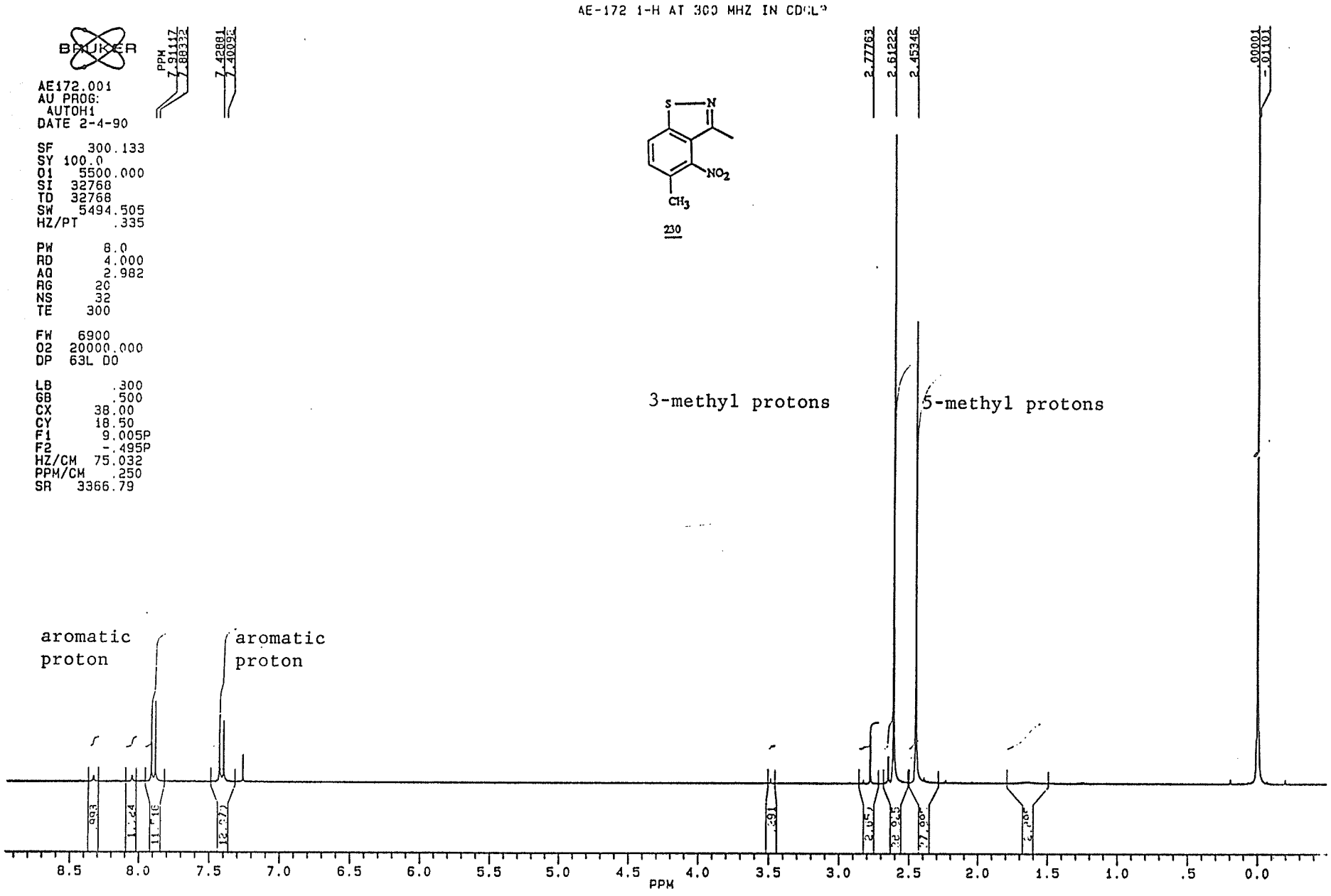

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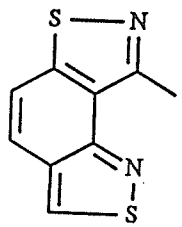

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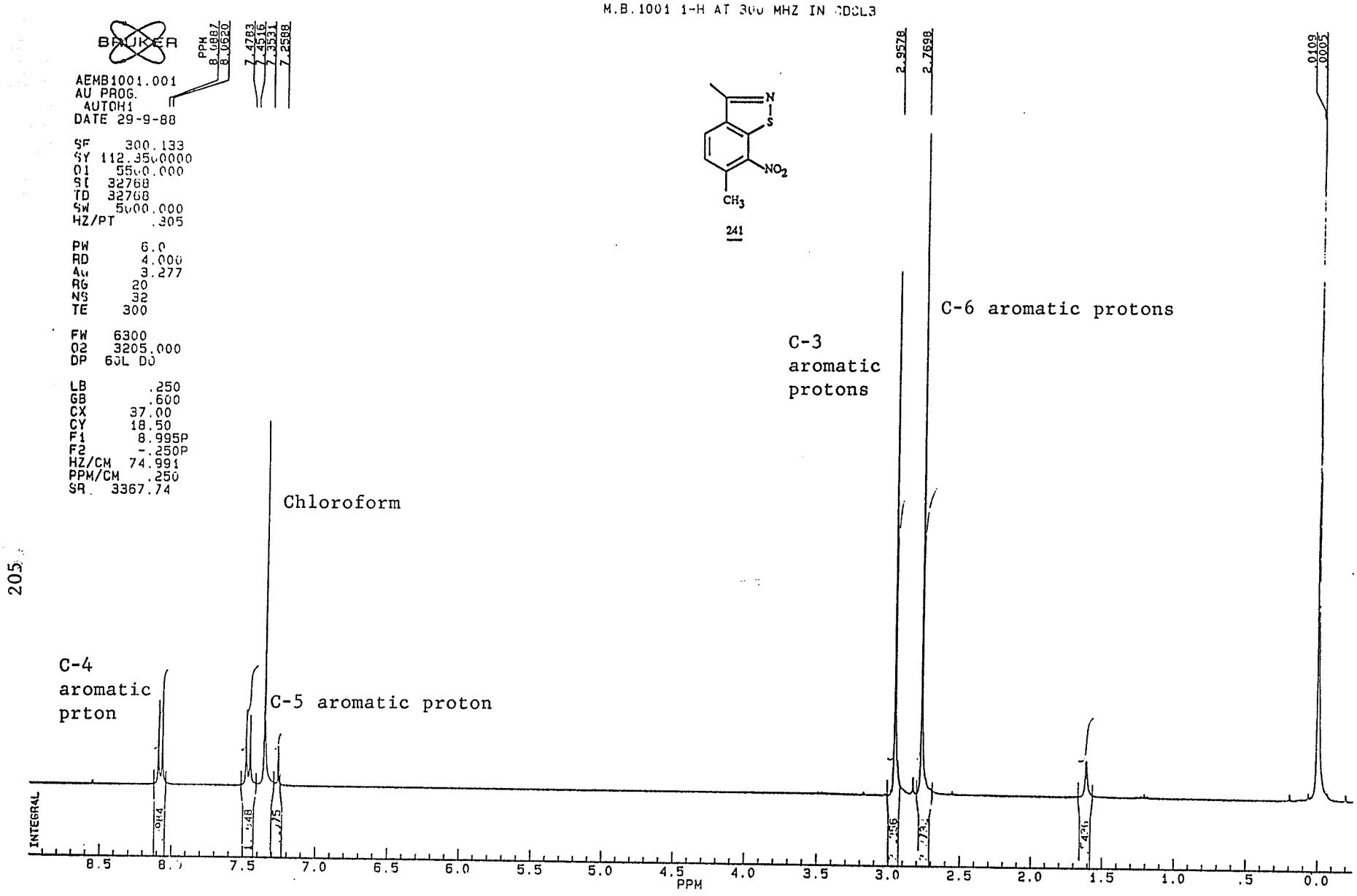

Pmr spectrum of 3,6-dimethyl-7-nitro-1,2-benziosthiazole

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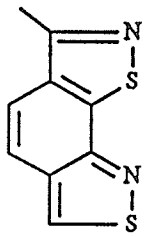

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