THE UNIVERSITY OF HULL

Some Derivatives of 1,2-Benzisothiazole

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by

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TO

CAROL AND SIMON

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INTRODUCTION

Several groups of workers[1] have synthesised the benzo[b]thiophen analogues of biologically active indole derivatives and have made detailed studies of their biological activities. The present work aims to extend the theme of isosteric relationship to the synthesis of 1,2-benzisothiazoles related to naturally occurring indole compounds in the hope that such compounds would possess useful pharmacological activity.

Some Naturally Occurring Indole Derivatives

The indole nucleus, which itself is found in many _Jasminium_ and _Citrus_ species,[2] is the main heterocyclic unit of a large number of derivatives which occur widely in the vegetable and animal kingdoms.[3] These range from the relatively simple tryptamine (I; R=H) and indole-3-acetic acid (II) to the more complex alkaloids such as rutaecarpine (III) and reserpine (IV), and consequently the following account will be limited to those derivatives which are relevant to later work and discussion.
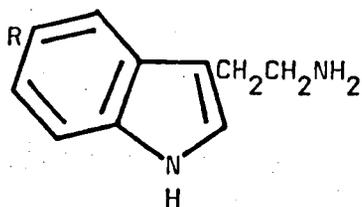
(I)
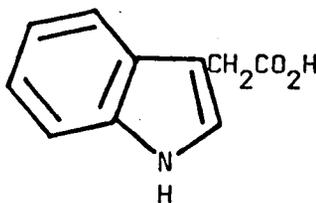
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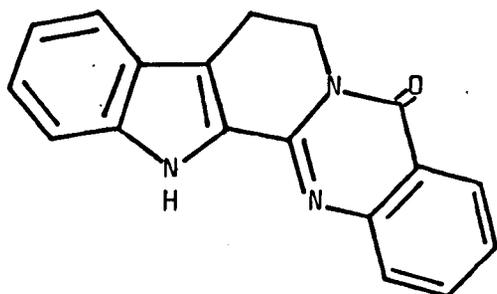
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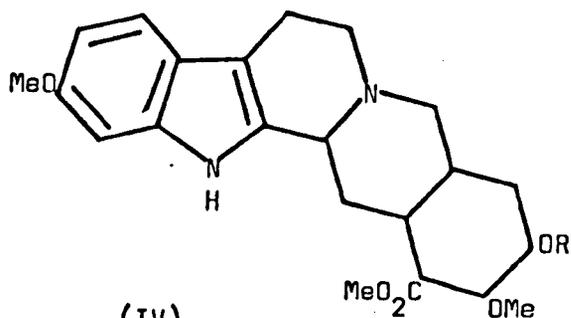
(IV)

R = 3,4,5-Trimethoxybenzoyl

Indole-3-acetic acid (II), commonly called heteroauxin, occurs extensively in the plant world where it is a growth hormone. It acts by increasing the cell size, rather than promoting the division of cells, but the precise mechanism of this cell enlargement is not known.[4]

Gramine (V), one of the simplest of the indole alkaloids, is found in

, Gramineae, including Arundo donax (Asiatic Sedge)[5] and Hordeum vulgare L. (barley).[6] It is formed from tryptophan (VI), also the precursor for other indole alkaloids, by conversion into 3-methyleneindolenine (VII), amination, and then N-methylation.
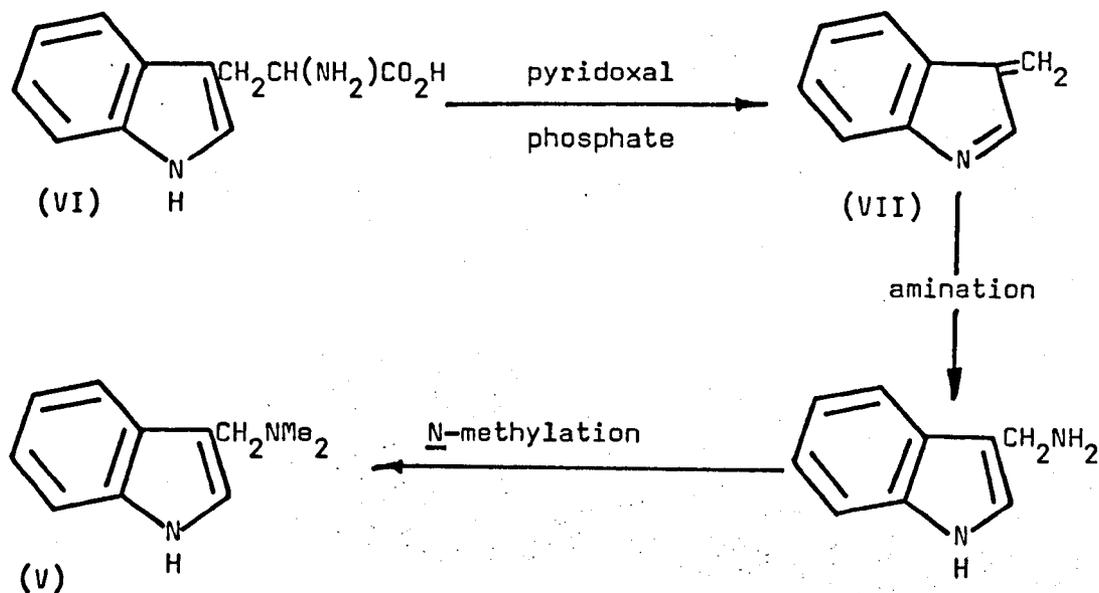
Tryptamine (I; R=H) and its N-methyl and NN-dimethyl derivatives have been found in many species in the vegetable plant kingdom. Tryptamine has been found in certain Acacia species[7], in the inkcap fungus (Coprinus micaceus)[8] and in some common fruits (including the tomato, aubergine and plum).[9] N-Methyltryptamine occurs in certain members of Asiatic Chenopodiaceae[10] (a family which includes the beetroot and spinach), whilst NN-dimethyltryptamine is more widely found[11-13] and has been shown to exhibit psychotomimetic activity.[14]

Psilocybin (VIII) and psilocin (IX) are found in several species of Mexican

fungi[15,16] and both have been extensively studied since they possess

psychotomimetic activity similar to that shown by lysergic acid diethylamide

(L.S.D.) (X) and mescaline (XI).[17,18] Hofmann has reviewed the main chemical

and pharmacological properties of psilocybin.[19]
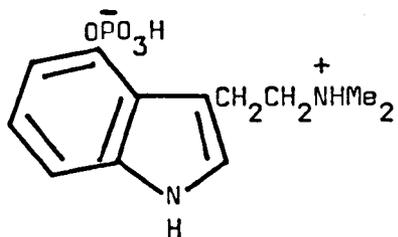
(VIII)
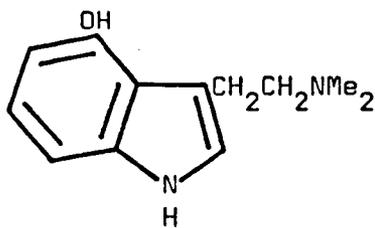
(IX)
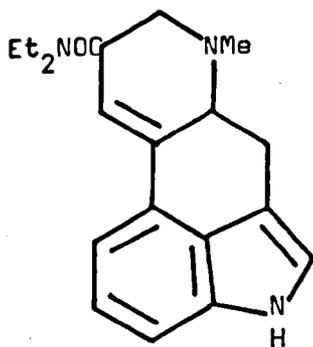
(X)
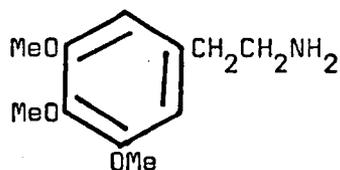
(XI)

5-Hydroxytryptamine

Commonly called serotonin, 5-hydroxytryptamine (I; R=OH) is arguably the

most important naturally occurring indole derivative and therefore it has been

extensively studied.

It is widely distributed in the plant world, being found in Urtica dioica L.

(stinging nettle),[20] Mucana pruriens DC. (cowhage),[21] several fungi (Panaeolus)[22,23] and in certain edible fruits, including the banana[9] and pineapple.[24]

5-Hydroxytryptamine is also found in many invertebrate and vertebrate

animals. In the former it is present in stings and venoms[25] and in the peripheral nervous system of molluscs and certain lower forms of animal life,[26] whilst in the latter it is found in the brain, stomach, lungs, intestines and blood.[25]

Erspamer[27] has extensively reviewed the isolation, synthesis and many varied biological activities of 5-hydroxytryptamine. The various effects of the amine are thought to be due to its muscle contracting action on susceptible smooth muscles, such as those in the stomach, bladder, uterus, intestines and blood vessels. However, 5-hydroxytryptamine does not cause most striated muscles to contract. The most frequently observed effects on the cardiovascular system in man are hypertension and increased heart rate.

The role of 5-hydroxytryptamine in controlling mental balance has been, and is still, a topic of much debate. In the early 1950's both Gaddum[28] and Woolley[29] suggested that the hallucinatory effects of L.S.D. (X), NN-dimethyl-tryptamine and 5-hydroxy-NN-dimethyltryptamine (bufotenine) might result from interference with the normal levels of 5-hydroxytryptamine in the brain. This led Woolley[30] to advance his "serotonin hypothesis" in which he suggested that an excess of 5-hydroxytryptamine in the brain caused psychotic excitement, whilst a deficiency caused depression. Support for the hypothesis came from the observations that (i) tranquillising drugs, such as reserpine (IV), depressed the level of 5-hydroxytryptamine in the brain, (ii) an increase in the level of 5-hydroxytryptamine in the brain of labile schizophrenics caused an increase in mental disorder, and (iii) various drugs , which relieve certain types of depression, caused the level of 5-hydroxytryptamine in the brain to increase. However, this relationship between hallucinations caused by L.S.D. and 5-hydroxytryptamine is now strongly doubted[31] and clearly further investigation is required.

Isosterism

The concept of isosterism has undergone many changes and elaborations since it was first introduced into inorganic chemistry by Allen[32] and later, apparently independently, by Langmuir.[33] It was an attempt to correlate the properties of isoelectronic molecules having the same number and distribution of electrons, in a manner similar to that in which the Periodic Law correlates the properties of atoms with similar outer valency shells of electrons.

In 1929, Grimm[34] extended the concept of isosterism to groups of atoms when he advanced his "hydride displacement law", which states that if an element in Group X of the first row of the periodic table is combined with one hydrogen atom, then the resulting group (called a "pseudoatom") is similar in properties to the element in Group (X+1) of the table. Thus, -CH= is "equivalent" to -N= and -NH- is "equivalent" to -S-, which forms the basis of the isosteric relationship between indole (XII) and 1,2-benzisothiazole (XIII).

(XII)   (XIII)
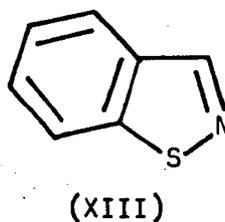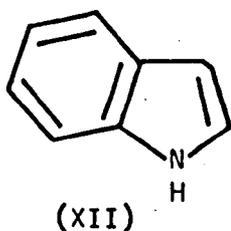
Erlenmeyer[35] further modified the concept when he defined isosteres as "atoms, ions or molecules in which the peripheral layers of electrons can be considered to be identical". He used this modification to propose[36] that the compound group -CH=CH- and the sulphur atom were isosteres, and illustrated his point by the similarity between the chemical, physical and biological properties of benzene and thiophen. Friedman[37] suggested that compounds which can be considered as isosteres and which have similar biological activity be called "bio-isosteres".

The validity of the isosteric theory as a basis for drug design is supported by the large number of bio-isosteres that exhibit similar properties, e.g., 5-hydroxytryptamine (I; R=OH) and its indazole isostere (XIV).[38]
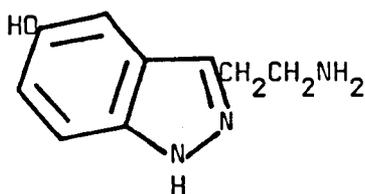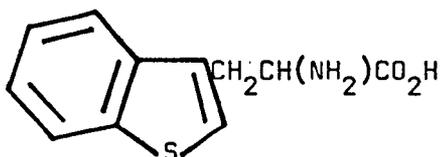
(XIV)   (XV)

Burger[39] has reviewed a number of bio-isosteres.

However, isosteric molecules do not necessarily exhibit similar biological activity, which is not surprising in view of the complexity of the simplest living system. For example, the sulphur analogue of tryptophan (XV) has been shown[40] to inhibit the growth of some micro-organisms that require tryptophan (VI) for growth.

Therefore, although the concept of isosterism has in the past promoted the synthesis of many useful compounds, a more rational approach to drug design will have to be evolved. This need has led to the development of structure-activity relationships in an attempt to correlate the structure of a compound with its biological activity.

Most quantitative studies of structure-activity relationships, notably those using free energy relationships, such as the Hansch analysis,[41] other physicochemical approaches,[42] and the molecular orbital approach,[43,44] correlate the structures of a set of derivatives with their biological activity. A severe limitation shared by these methods is their restriction to series of compounds with closely related structures. Thus they are inappropriate for (i) the correlation of the data from compounds which fall into many different structural series or into no series at all; and (ii) the prediction of activity

in compounds outside a structural class of known biological interest. A second

major limitation of these methods, is their inability to accomodate data

represented by inactive compounds and hence they are only useful for optimising

activity in a previously recognised "lead" structure; not for predicting or

classifying pharmacological activity in a group of diverse organic compounds.

Kowalski and Bender[45] proposed that the recent development of artificial

intelligence techniques, particularly the use of pattern recognition and

cluster analysis, might be applied to chemistry and used to predict the

pharmacological activity of organic compounds. The mass of data available on

the activity of organic compounds has prompted several workers[46-48] to attempt

to use these computer based techniques to develop structure-activity relation-

ships that will predict activities.

Chu,[46] using cluster analysis and pattern recognition techniques, was

able to classify a set of sixty-six widely different compounds, with respect

to their sedative or tranquilizer activity, and achieved 84-96% and 85-86%

success respectively. Both techniques require a compound to be defined in

terms of its atom-centred fragments[49] (or augmented atom fragments) which are,

"an atom and its adjacent atoms and bonds. For example, for butethal (XVI) the

fifteen atom-centred fragments are shown:

(XVI)

1. $\overset{*}{C}$——N——$\overset{*}{C}$ (cyclic)

2. N——CO——N (cyclic)

3. $\overset{*}{C}$——N——$\overset{*}{C}$ (cyclic)

4. C——CO——N (cyclic)

5. $\overset{*}{C}$——C——$\overset{*}{C}$ (cyclic)

   C   C

6. N——CO——C (cyclic)

7. C≡≡O

8. C══O

9. C══O

10. C——C——C

11. C——C——C

12. CH_3——C

13. C——C——C

14. C——C——C

15. CH_3——C

$*$ = sp^2 carbon atom

As this approach does not define spatial relationships involving two or more bonds, e.g. ring size, additional information can be added to the representation of a molecule to overcome this problem. Hence, any compound can be expressed in a form which can be processed by a computer.

A different approach by Cramer and his co-workers[47] has yielded some encouraging results. This technique also uses atom fragments (substructures) to define a compound, and is based on the assumptions that (i) the probability of a given biological activity can be usefully approximated by an analysis of the substructural contributions, ignoring their inter- and intramolecular interactions; and (ii) the contribution of a given substructure to the probability of activity can be obtained from data on previously tested compounds containing that substructure. Using available pharmacological results, Cramer computed for each substructure a "Substructural Activity Frequency" (S.A.F.), defined as the ratio of the number of active compounds containing that substructure to the total number of compounds containing that substructure. The S.A.F. represents the contribution which that substructure can make to the probability of a compound being active. Cramer then used these S.A.F. values to determine the "Mean Substructure Activity Frequency" (M.S.A.F.) for each compound in a new series of

diverse organic compounds. The M.S.A.F. is the arithmetic mean of the S.A.F. values for the substructures present in that compound; therefore, the nearer the M.S.A.F. value to unity, the greater the probability of activity. Cramer and his co-workers found that the correlation between the M.S.A.F. (calculated) and the frequency of activity (experimentally determined) was very good, considering the limitations of the data used to compute the S.A.F. values and the coarse discriminatory power of the substructural system used.

Future improvements in computational procedures should refine these methods and so rationalise drug design.

The Biological Activities of some 1,2-Benzisothiazole Derivatives

Davis[50] has reviewed the subject upto late 1970, hence the following discussion will be restricted to the work published since and will not cover the biological activity of the corresponding 1,2-benzisothiazole-1,1-dioxides, which fall outside the scope of the present investigation.

(a.) Chemosterilizing, insecticidal and bactericidal activity

Compounds of the type (XVIIa-f) have been prepared for biological evaluation. A mixture of compounds (XVIIa-b), and also compound (XVIIc), have shown[51] chemosterilizing activity on Dysdercus intermedius larvae in the penultimate laval stage; whilst both compound (XVIIc)[51] and the aziridine derivative (XVIId)[52] have shown chemosterilizing activity against Musca domestica (housefly).
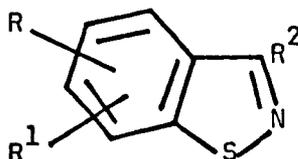
(XVII)

(a)	R = 4-Cl	,	R^1 = 7-Cl	,	R^2 = H.
(b)	4-Cl	,	5-Cl	,	H↓
(c)	4-Cl	,	H	,	H.
(d)	H	,	H	,	$N(CH_2)_2$.
(e)	H	,	H	,	$NH.SO_2 \cdot \underline{p}-C_6H_4NH_2$.
(f)	H	,	H	,	$NH.SO_2 \cdot \underline{p}-C_6H_4NHAc$.

A series of benzene-substituted 3-chloro-1,2-benzisothiazoles has been claimed[53] to show insecticidal activity; whilst a pharmaceutical mixture containing 6-chloro-1,2-benzisothiazol-3(2H)-one and 2-nitrofuryl and

2-nitrothienyl derivatives has exhibited[54] interesting synergistic bactericidal properties. Compounds (XVIIe-f) were prepared in a series of 3-sulphanilamido isothiazoles and tested against Streptococcus wacker and Klebsiella pneumoniae organisms.[55]

(b.) Phytotoxic and fungicidal activity

A number of compounds of the type (XVIIIa-o) have been prepared by Vitali and his co-workers.[56,57]
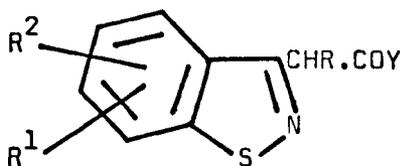
(XVIII)

(a)	R = H	,	R^1 = H	,	R^2 = H	,	Y = OH, OEt, NH_2.
(b)	H	,	H	,	4-Cl	,	OH, OEt, NH_2.
(c)	H	,	H	,	5-Cl	,	OH, OEt, NH_2.
(d)	H	,	H	,	6-Cl	,	OH, OEt, NH_2.
(e)	H	,	H	,	7-Cl	,	OH, OEt, NH_2.
(f)	H	,	H	,	5-Me	,	OH, OEt, NH_2.
(g)	H	,	H	,	5-OMe	,	OH, OEt, NH_2.
(h)	H	,	H	,	5-NO_2	,	OH, OEt, NH_2.
(i)	H	,	6-Me	,	5-Me	,	OH, OEt, NH_2.
(j)	H	,	5-Cl	,	4-Cl	,	OH.
(k)	Me	,	H	,	H	,	OH, OEt, NH_2.
(l)	Et	,	H	,	H	,	OH, OEt, NH_2.
(m)	Pr^n	,	H	,	H	,	ONa, OEt, NH_2.
(n)	allyl	,	H	,	H	,	ONa, OEt, NH_2.

(o)

$Y = OH, \quad OEt, \quad NH_2.$
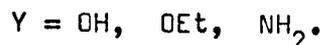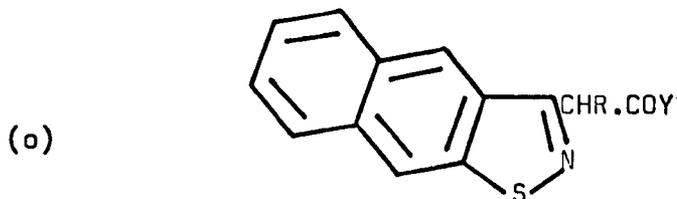
The fifteen compounds (XVIIIa-e) have been tested for phytotoxicity to common weeds and crop plants.[56] It was found that all the compounds were toxic to weeds, in both pre- and post-emergence tests, and they showed some selectivity between weeds and crop plants, unlike the indole type auxins. The results also showed that modification of the carboxylic acid function or the introduction of a chlorine atom into the 4,5 or 6-position does not effect the potency or spectrum of activity; whilst substitution at the 7-position markedly reduced the herbicidal activity. From the results[57] of similar tests on compounds (XVIIIf-o) it was deduced that, in general, phytocidal activity (i) decreases for 5-substituted derivatives in the order, $Cl > H \geqslant OMe > Me \gg NO_2$; (ii) increases on the introduction of a methyl group into the side-chain (e.g. R = Me), but then decreases progressively as the carbon chain becomes longer; and (iii) for the naptho[2,3-d]isothiazole compounds (XVIIIo) is much less than the phytocidal activity of the corresponding 1,2-benzisothiazole derivatives. These results and others[58-60] have led to the compounds being considered as a new class of potent, selective phytocides.
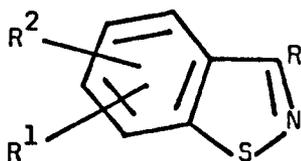
(XIX)

(a) R = H , R^1 = 7-NO₂ , R^2 = 4-Cl.

(b) NH₂ , 5-Cl , 4-Cl.

(c) H , 7-NO₂ , 4-cyclohexylamino.

(d)	H	,	7-NO$_2$	,	4-O(CH$_2$)$_3$CH$_3$.
(e)	Cl	,	5-CH$_3$	,	H.
(f)	Cl	,	7-CH$_3$	,	H.
(g)	Cl	,	5-Cl	,	H.
(h)	Cl	,	5-NO$_2$	,	H.
(i)	Cl	,	5-OMe	,	H.

Compounds (XIXa-d) have shown 90-100% phytotoxicity to weeds and good compatibility towards culture plants.[61] Compounds (XIXe-i) have been found to be plant protecting agents for several varieties of plants.[62]

3,6-Dichloro- and 3,6-dichloro-7-nitro-1,2-benzisothiazole have been claimed as fungicidal agents.[63] Since Katz and Schroeder[64] first noted the fungicidal properties of 1,2-benzisothiazol-3(2H)-one derivatives, they have been the subject of numerous publications.[50] Grivas[65] has incorporated derivatives of the type (XX) into paints, as they protect exterior painted surfaces from attack by mildew.
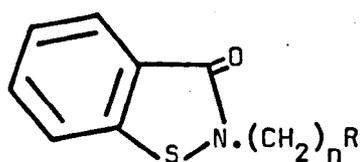
n = 1 or 2.

R = halogen, -CN or C$_6$H$_5$CO.

(XX)

A series of 1,2-benzisothiazol-3-one-2-carboxylic esters, such as 2-methoxycarbonyl-1,2-benzisothiazol-3-one, have been found[65] to be effective fungicides and bactericides when tested against Piricularia oryzae and Xanthomones citri; they also showed anthelmintic activity in domestic animals.

(c.) Auxin-like activity

Giannella and his co-workers[67] reported that (5-chloro-1,2-benzisothiazol-3-yl)acetic acid was thirty times more active than indole-3-acetic acid (I.A.A.) by the split pea curvature test. Branca,[68] using various pea bioassays, found that (1,2-benzisothiazol-3-yl)acetic acid (XXIc) had 35% of the activity of I.A.A. and that changing the carboxylic acid function progressively from the 3- acetic to the 3-butyric only decreased the auxin-like activity.[69] Tests on dormant Helianthus tuberosus (Jerusalem artichoke) tubers with (1,2-benzisothiazol-3-yl)acetic acid showed[70] a stimulation of cell growth, similar to that found using I.A.A.

These results contrast with those for benzo[b]thiophen-3-acetic acid, which has been shown[71] to have one-thirtieth the activity of I.A.A. by the split pea curvature test, and (1,2-benzisothiazol-3-yl)acetic acid, which has been found[72] to be a hundredth as active as I.A.A.

(d.) Anti-inflammatory, analgesic and anti-pyretic activity

The activity of 1,2-benzisothiazol-3(2H)-one has been evaluated by Vitali and his co-workers.[73] On oral application it was found to have a higher anti-inflammatory activity than salicyamide in rats, a higher anti-pyretic activity than paracetamol in rabbits, and to be more active than phenylbutazone when tested for analgesic activity in mice and rats. Unfortunately it had an undesirable level of toxicity.

(XXI)
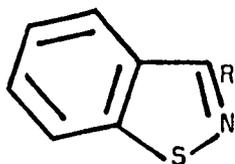
(a)   R = CO_2H.   (c)   R = CH_2CO_2H.

(b)   CONHOH.   (d) CH_2CONHOH.

Compounds (XXIa-d) were prepared and showed anti-inflammatory activity.[74]

Compounds (XXIa, b and d) reduced ovalbumin- and hyaluronidase-induced œdema

formation, while compound (XXIc) reduced dextran-induced œdema formation.[74]

Compound (XXIa), and to a lesser extent compound (XXIb), showed analgesic

activity in mice and rats. Anti-pyretic activity in the rabbit was shown by

compounds (XXIa and b) and to a lesser extent by compounds (XXIc and d).[74]

(e.) <u>Anaesthetic activity</u>

Amoretti and his co-workers[75,76] have evaluated a series of amides of

(1,2-benzisothiazol-3-yl)carboxylic acid, of the type (XXII), for their local

anaesthetic activity.
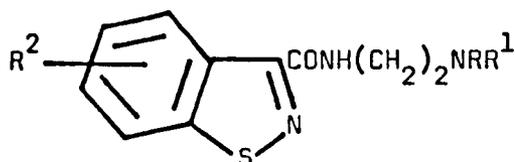
(XXII)

where,   R = H or Me.

R^1= Me or cyclohexyl.

R^2= H, Me or Cl.

All compounds showed infiltration anaesthesia in the mouse tail test and

conduction anaesthesia in the frog test, but only the amides without a

substituent in the benzene ring (R^2= H)[76] showed surface anaesthesia in the

rabbit cornea test. The anaesthetic activity of an analogous series of esters

was found to be decreased.[77]

Synthesis of 3-Substituted 1,2-Benzisothiazoles

The synthesis of 1,2-benzisothiazoles has been surveyed by Davis in his recent review,[50] therefore the following discussion will only be concerned with the subsequent developments which have proved useful to the author's present investigation.

Ricci and Martani[78,79] first published what appeared to be a versatile synthesis of 1,2-benzisothiazole derivatives, involving the cyclisation of the oxime, semicarbazone or phenylhydrazone of an o-mercaptoaldehyde or ketone (XXIII) in polyphosphoric acid (P.P.A.) at 110-140°.
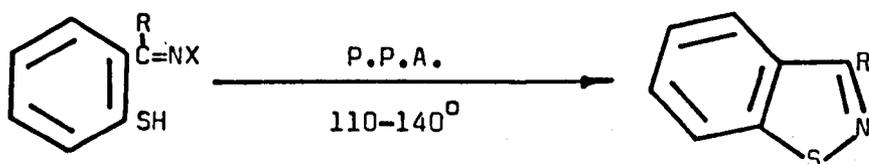
(XXIII)

X = OH, NHCONH$_2$ or NH.C$_6$H$_5$.

R = H, Me or C$_6$H$_5$.

As the Italian workers failed to give adequate experimental details, El Shanta,[80] who was studying the reactions of 3-methyl-1,2-benzisothiazole in this department, synthesised o-mercaptoacetophenone oxime (XXIV) by an alternative route and attempted a cyclisation using the conditions of Ricci and Martani. It was later shown[81,82] that the product from this cyclisation was mainly the isomeric 2-methylbenzothiazole (XXV), which was formed   by the Beckmann rearrangement of the oxime (XXIV) to the thiol (XXVI) prior to cyclisation, with a little of the required 3-methyl-1,2-benzisothiazole (XXVII). All attempted cyclisations, using a variety of conditions, gave the mixture of products.[82]

(XXIV) → Beckmann rearrangement → (XXVI)

P.P.A./110-140°

(XXV)
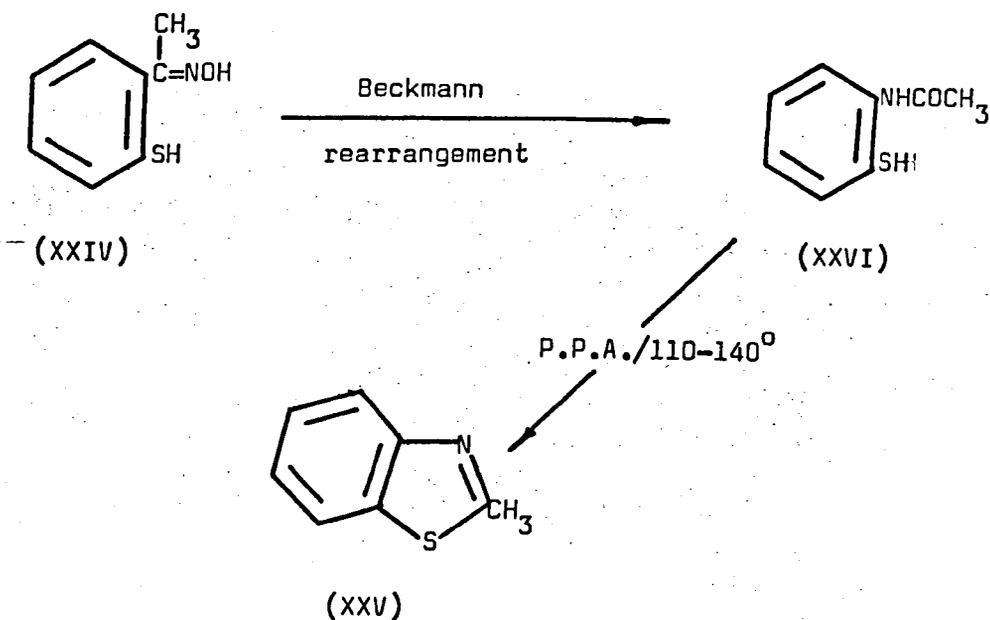
However, the physical data quoted by the Italian workers for their 3-methyl-1,2-benzisothiazole (XXVII) and for a number of substituted 3-methyl-1,2-benzisothiazoles agreed well with other independent data.[67,83-85] In view of the discrepancy between our experiments and the reported synthesis,[78,79] Hughes[82] decided to repeat the Italians synthesis, which is outlined in Scheme 1 (p. 18). Hughes found that reaction of o-thiocyanatoacetophenone (a compound the identity of which had been rigorously established) with hydroxylamine hydrochloride in aqueous ethanol in the presence of sodium acetate did not afford the expected oxime (XXVIII). Instead a product resulted which a) failed to give the oxime of o-mercaptoacetophenone (XXIV) on reduction; b) showed no characteristic SCN absorption in the i.r. spectrum; and c) failed to regenerate o-thiocyanatoaceto-phenone on attempted hydrolysis. Reaction of this unexpected product with P.P.A. afforded 3-methyl-1,2-benzisothiazole without formation of any isomeric 2-methylbenzothiazole (XXV), but with the liberation of a molar proportion of carbon dioxide (Scheme 1).

These facts are consistent with the unexpected product from the action of hydroxylamine hydrochloride on o-thiocyanatoacetophenone being 2-imino-5-methyl-3,1,4-benzoxathiazepine (XXIX). Confirmatory evidence of the structure of this compound with its novel ring system was provided by its conversion on heating in

Scheme 1

1. SOCl$_2$/benzene
2. Mg/CH$_2$(CO$_2$Et)$_2$ /EtOH
3. H$^+$/H$_2$O
4. OH$^-$

Sn/HCl

1. HCl/NaNO$_2$/0-8°
2. KSCN/CuSCN

NH$_2$OH.HCl/AcONa

Na$_2$S

(XXVIII)

(XXIV)

P.P.A./110-140°
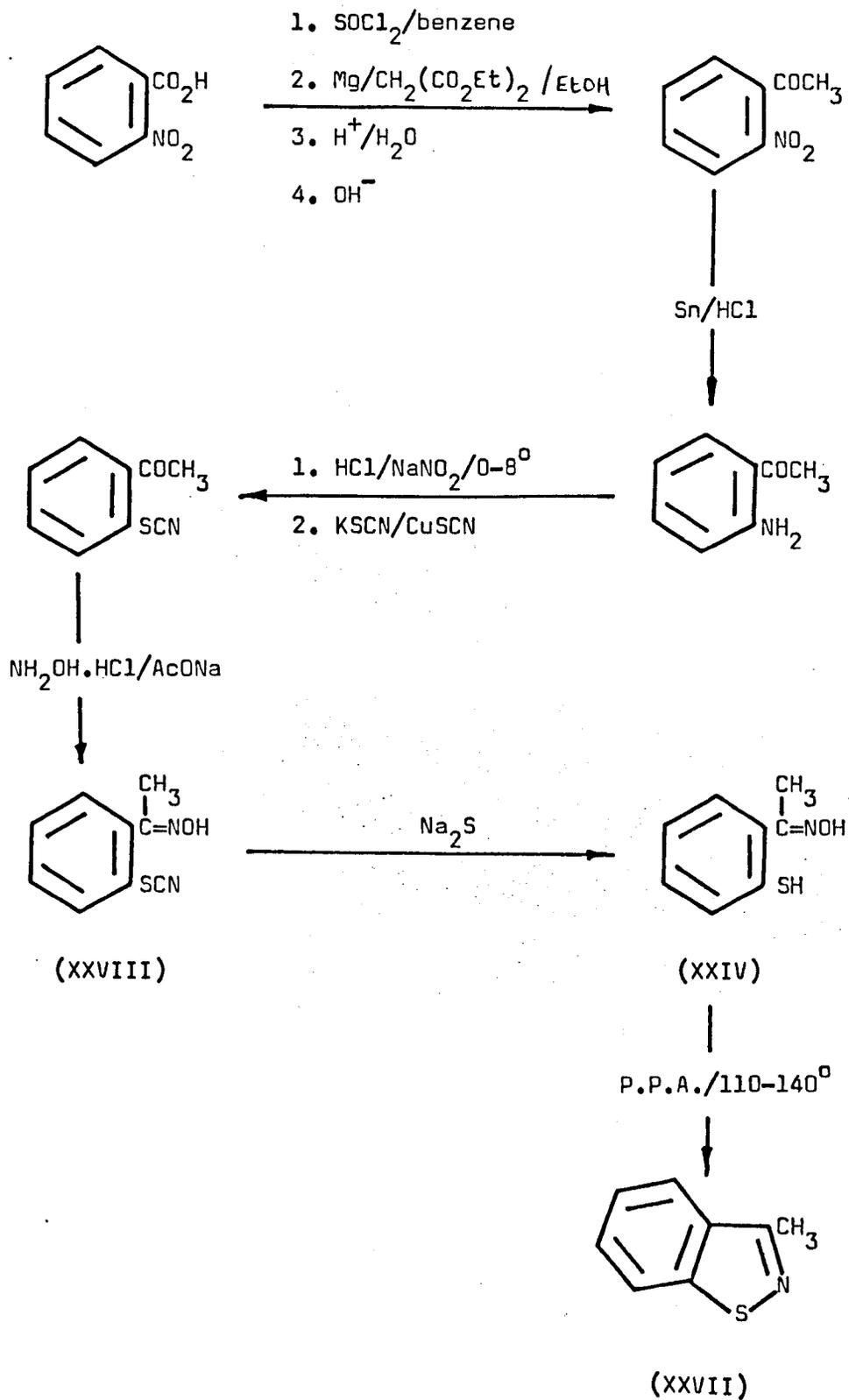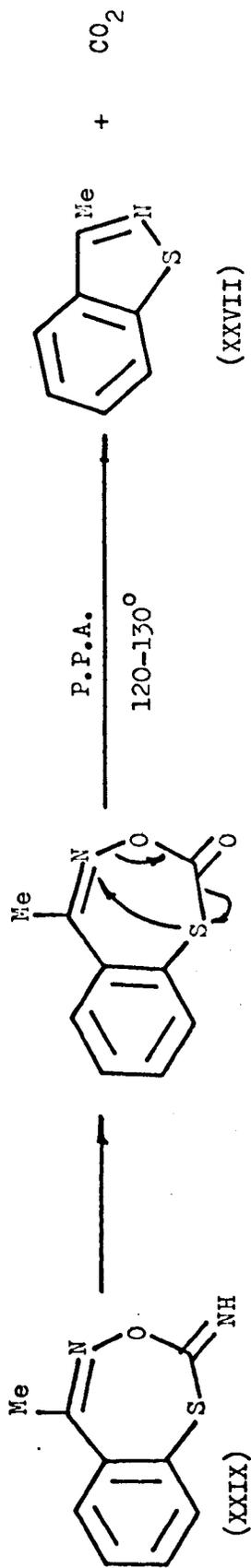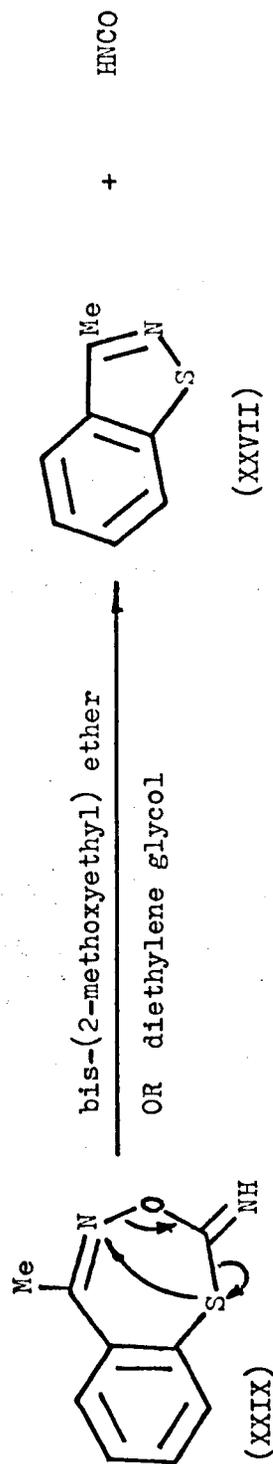
(XXVII)

Scheme 2

Scheme 3

an inert solvent into 3-methyl-1,2-benzisothiazole (XXVII) when the only other product detected was cyanic acid, which was trapped and identified as an allophanate (Scheme 2).

From investigations into the lability of the chlorine atom in 3-chloro-1,2-benzisothiazole (XXX) with various nucleophiles, Carrington et al.[86] found that ethyl cyano(sodio)acetate replaced the chlorine atom to give ethyl (1,2-benzisothiazol-3-yl)cyanoacetate (XXXI) (67%). Hydrolysis of the cyano ester (XXXI) with aqueous dimethylsulphoxide[84] at 100° gave (1,2-benzisothiazol-3-yl)-acetonitrile (XXXII) (85%), which offered promise as a useful intermediate in the preparation of the desired 3-alkylamino derivatives.
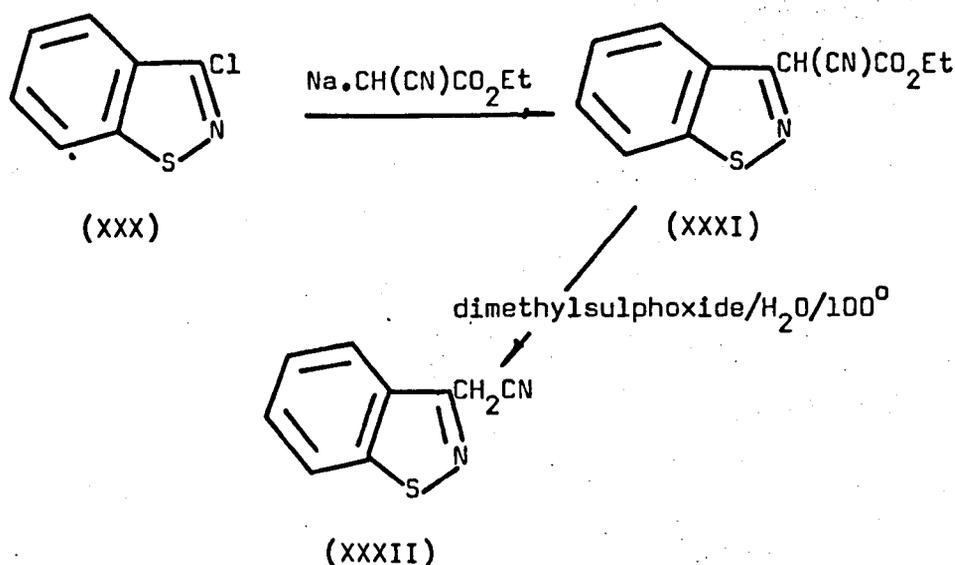
Vitali and his co-workers[56,57] have demonstrated the generality of the reaction by applying it to a number of 3-chloro-1,2-benzisothiazoles bearing substituents in the benzene ring, in order to prepare the corresponding acetic acid derivatives, by the direct alkaline hydrolysis of the cyanoacetate derivatives.

The Present Investigation

The present investigation covers two main areas. The first concerns the synthesis of a number of 3-aminomethyl- and 5-substituted 3-aminomethyl-1,2-benzisothiazoles with potential biological activity. The preparation of a number of 3-aminoethyl-1,2-benzisothiazole derivatives was planned and the difficulties encountered will be discussed.

The second main area concerns the electrophilic substitution reactions of some 5-substituted 3-methyl-1,2-benzisothiazoles, and of 4-bromo-3-methyl- and 3-methyl-1,2-benzisothiazole.

DISCUSSION OF THE EXPERIMENTAL WORK

The Synthesis of N-Methyl- and NN-Dimethyl-(1,2-benzisothiazol-3-yl)acetamide

3-Chloro-1,2-benzisothiazole was prepared by the method of Reissert,[87] in an overall yield of 50% from o-mercaptobenzoic acid. Carrington,[81] in this department, investigated the reactions of 3-chloro-1,2-benzisothiazole with various nucleophiles and found that attack could take place at either the chlorine atom, the sulphur atom or at the carbon atom in the 3-position. Some nucleophiles attacked exclusively at the carbon atom giving the expected 3-substituted 1,2-benzisothiazole (e.g., sodium ethoxide[88] and ethyl cyano(sodio)-acetate[86]), whilst other nucleophiles[88] gave products which were formed due to fission of the isothiazole ring resulting from nucleophilic attack at either the chlorine or sulphur atoms [e.g., copper (1) cyanide, sodium thiophenoxide or n-butyl lithium]. Also, with certain nucleophiles[88] (e.g., ethyl aceto(sodio)-acetate) ring fission was followed by rearrangement to a benzo[b]thiophen derivative.

As mentioned previously (p. 20), the reaction of ethyl cyano(sodio)acetate with 3-chloro-1,2-benzisothiazole[86] led to a simple preparation of (1,2-benzisothiazol-3-yl)acetonitrile (XXXII)[84] which was hydrolysed,[89] with concentrated hydrochloric acid at 45°, to give the acetic acid derivative (XXIc) in 84% yield. Treatment of the acid (XXIc) with boiling thionyl chloride gave the acid chloride (XXXIII) (82%), which on subsequent treatment with anhydrous dimethylamine in boiling dry benzene failed to give any of the expected NN-dimethyl-amide (XXXIV). Even when the acid chloride was kept at 100° for 24 h in a sealed tube with an excess of anhydrous dimethylamine only 30% of NN-dimethyl-(1,2-benzisothiazol-3-yl)acetamide was isolated.

However, ethyl (1,2-benzisothiazol-3-yl)acetate (XXXV), prepared in 84% yield from the acid (XXIc) by the usual Fischer-Speier method, gave the required N-methyl- (XXXVI) and NN-dimethyl-amide (XXXIV) in 87% and 60% yields respectively, when stirred with an aqueous ethanolic solution of the appropriated amine.

Wilson and Weingarten[90] described a general method for the direct conversion

of an acid to an amide which involved stirring the acid with a sixfold excess

of the appropriate amine in dry tetrahydrofuran under an atmosphere of dry

nitrogen using titanium ($\underline{1V}$) chloride as catalyst. The $\underline{NN}$-dimethyl- derivative

(XXXIV) was prepared (90%) in this way after stirring the mixture for 3 days at room temper-

ature.

(1,2-Benzisothiazol-3-yl)acetamidoxime

Treatment of (1,2-benzisothiazol-3-yl)acetonitrile (XXXII) with hydroxyl-

amine hydrochloride and sodium carbonate in aqueous ethanol gave the amidoxime

(XXXVII) in quantitative yield.

The foregoing reactions are outlined in Scheme 4 (p. 24).

Scheme 4
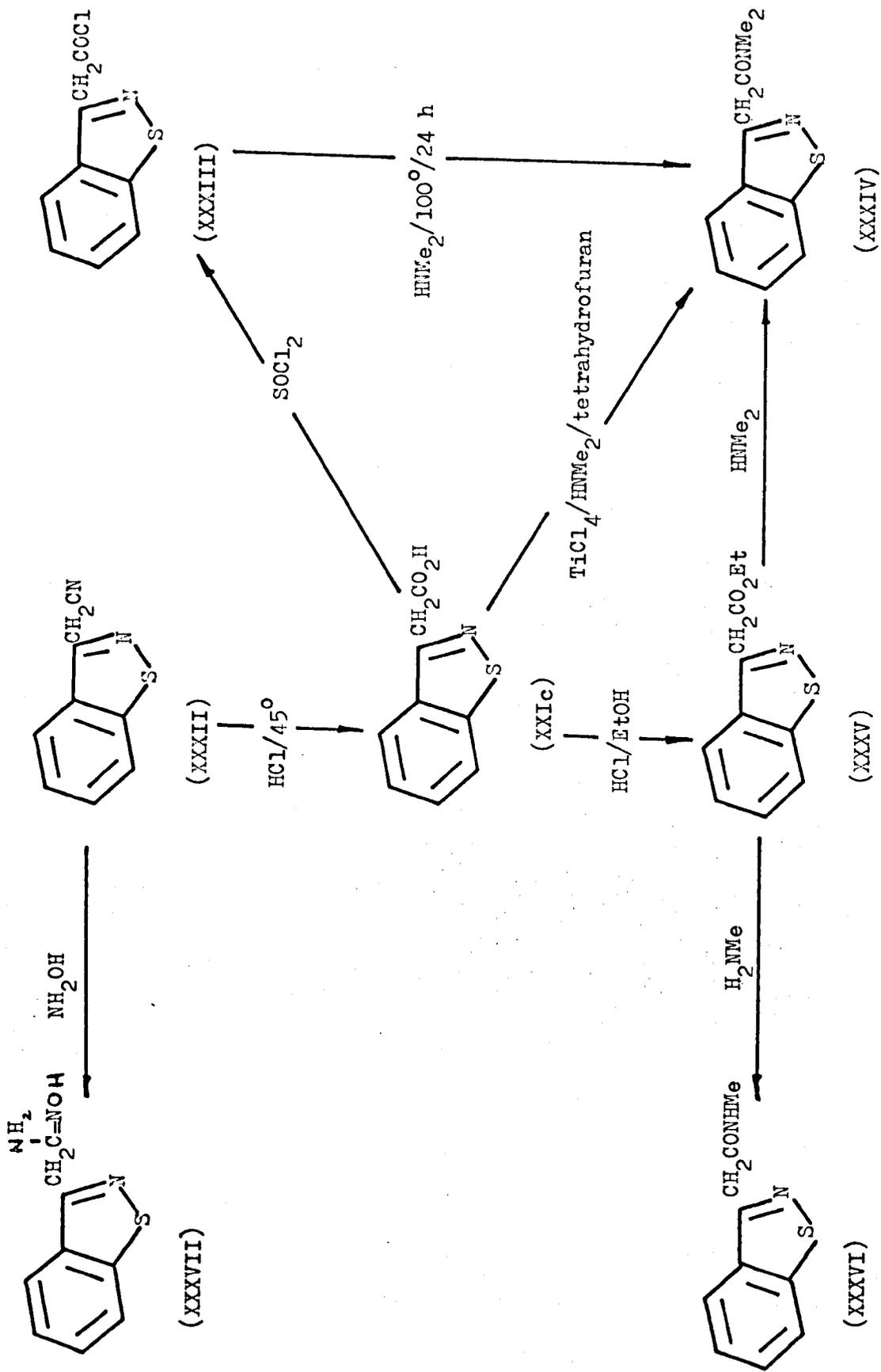
The Synthesis of 3-Methyl-1,2-benzisothiazole

As mentioned earlier (p. 18), the Ricci and Martani[78,79] route for the preparation of 3-methyl-1,2-benzisothiazole was re-examined by Hughes et al.[82] and the oxime of o-thiocyanatoacetophenone (XXVIII) was shown to have spontaneously cyclised to 2-imino-5-methyl-3,1,4-benzoxathiazepine (XXIX) which then decomposed to give the 3-methyl derivative (XXVII) by the mechanism outlined in either Scheme 2 or 3 (p. 19) depending on the solvent used.

Commercially available o-nitrobenzoic acid was converted into o-nitroacetophenone (83%) by treatment of the acid chloride with diethyl ethoxy-magnesiomalonate, followed by hydrolysis and decarboxylation of the resulting di-ester.[91] Reduction[92] of o-nitroacetophenone with tin and concentrated hydrochloric acid gave o-aminoacetophenone (97%), which was then diazotised.[93] The diazonium salt was decomposed overnight in an aqueous mixture of potassium and copper (1) thiocyanates to give o-thiocyanatoacetophenone (62%) which reacted with a solution of hydroxylamine hydrochloride and sodium acetate to give the benzoxathiazepine derivative (XXIX). Decomposition of this oxathiazepine in hot (120-130°) polyphosphoric acid gave 3-methyl-1,2-benzisothiazole in an overall yield of 33% from o-nitrobenzoic acid.

It was felt that it would be interesting to prepare the semicarbazone derivative and examine its structure and possible decomposition to 3-methyl-1,2-benzisothiazole. The semicarbazone derivative was prepared by refluxing o-thiocyanatoacetophenone with a boiling, aqueous ethanolic solution of semicarbazide hydrochloride and sodium acetate for 3 h. As it did not show the characteristic SCN absorption in the i.r. spectrum and decomposed smoothly in hot (200°) diethylene glycol to 3-methyl-1,2-benzisothiazole (XXVII) (ca. 50%) it seems probable that the semicarbazone of o-thiocyanatoacetophenone (XXXVIII) also exists as a cyclised 7-membered ring (XXXIX). The decomposition of this novel compound, in an inert solvent, should extrude compound (XL) which is a tautomeric form of cyanourea (XLI).

(XXXVIII)

(XXXIX)

diethylene glycol/200°

(XL)   HN=C=N-CONH₂

(XLI)   NC-NH-CONH₂

(XXVII)
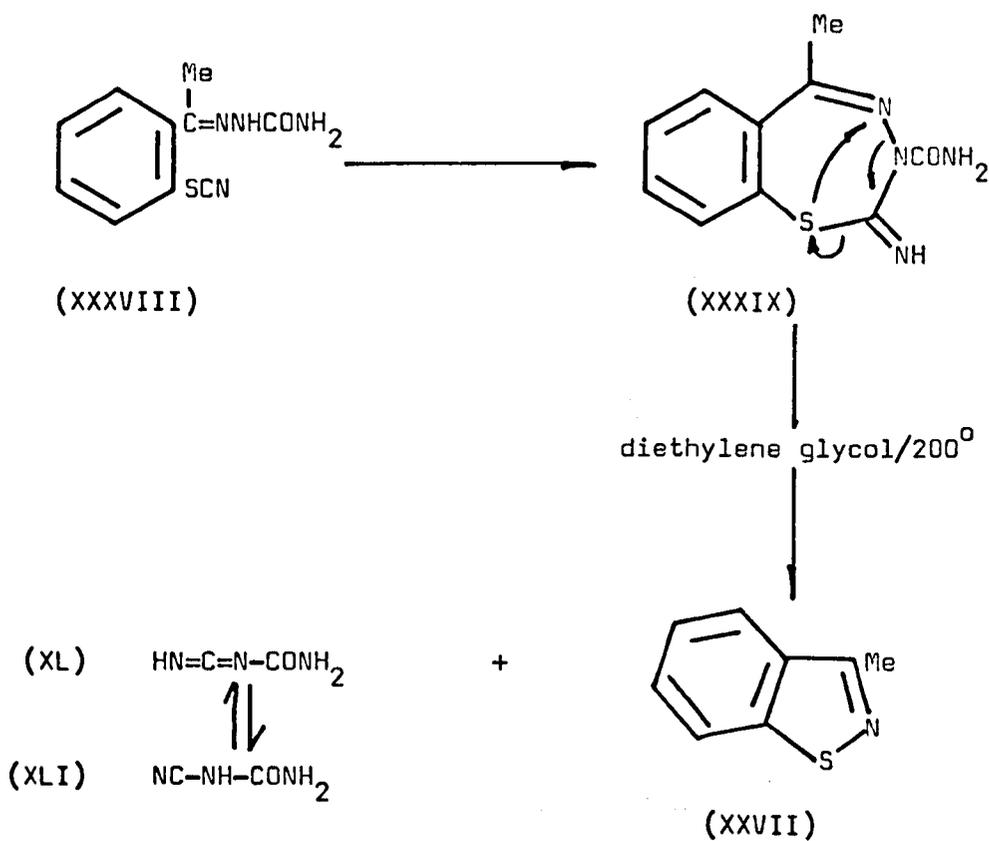
Werner[94] has suggested the participation of this imino tautomer (XL) in the covalent heavy metal salt (XLII), formed when the potassium salt of cyanourea is added to an aqueous solution of pyridine and copper sulphate.

(XLII)
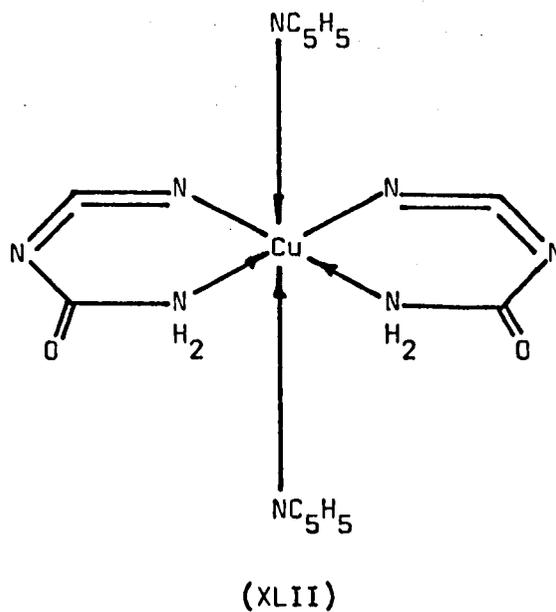
Unfortunately, attempts to prepare a pure sample of cyanourea by a known route[95] were unsuccessful and so the proposed investigation into the precise nature of the extruded compound had to be abandoned. An additional complication is that cyanourea decomposes[96] on heating to 100° and so its decomposition in diethylene glycol would have to be studied before any further work on the mechanism of the reaction could be attempted.

Some Reactions of 3-Methyl-1,2-benzisothiazole

Molecular orbital calculations[97] for the 1,2-benzisothiazole nucleus indicate that it has a low π-electron density at the carbon atom in the 3-position, due to the adjacent electonegative nitrogen atom. The calculations also show that the order of the various positions towards electrophilic attack would be expected to be 7~5>6~4. This has been verified by a nitration study[98] when the 7- and 5-isomers were isolated, with the 7-nitro isomer predominating. It would be expected therefore that 3-methyl-1,2-benzisothiazole would undergo electrophilic substitution at the 5- and 7-positions, and due to the deactivation of the system by the nitrogen atom, electrophilic substitution would require "forcing" conditions. As these "forcing" conditions normally involve the use of a strongly acidic medium, the nitrogen atom will be protonated and so cause the nucleus to be further deactivated towards electrophilic attack.

Bromination

As the bromination of 2,1-benzisothiazole using bromine and silver sulphate in concentrated sulphuric acid had been reported,[99] and gave a mixture of the 5- and 7-bromo-2,1-benzisothiazoles with small amounts of 4,7-dibromo- and 4-bromo-2,1-benzisothiazole, similar conditions were used for the bromination of 3-methyl-1,2-benzisothiazole. A four component mixture was obtained which was separated by column chromatography to give the expected 5-bromo- (XLIII) (32%) and 7-bromo-3-methyl-1,2-benzisothiazole (XLIV) (37%), identified by comparison with samples prepared by alternative routes (see pp. 43 and 34 respectively). Further confirmation of the structure of the 7-isomer (XLIV) was afforded by its n.m.r. spectrum which showed, inter alia, a methyl signal at $\delta_{p.p.m.}$ 2.7, whereas the methyl signal of the other possible isomer, 4-bromo-3-methyl-1,2-benzisothiazole (p. 69), was shifted downfield by 0.27 p.p.m. due to deshielding by the 4-bromo substituent.

Two minor dibromo components were also isolated and were identified later by comparison of the spectral and physical data with that of other dibromo-3-methyl-1,2-benzisothiazoles which were prepared during the course of the present investigation. One isomer (R_f 0.84) showed an AB quartet ($J_{5,6}$ = 8.1 Hz) in the n.m.r. and was identified as the 4,7-dibromo derivative (XLV) (2.3%), whilst the other isomer (R_f 0.76) showed two meta coupled signals ($J_{4,6}$ = 1.4 Hz) and was identified as the 5,7-dibromo derivative (XLVI) (1.7%). It can be appreciated therefore that these two minor components were probably formed by further bromination of the 5-bromo- and 7-bromo-3-methyl-1,2-benzisothiazole formed initially.

Nitration

3-Methyl-1,2-benzisothiazole underwent nitration at 0° with a solution of potassium nitrate in concentrated sulphuric acid to give a two-component mixture which was resolved by column chromatography. The major component (R_f 0.29) was the 5-nitro derivative (XLVII) (44%) and the minor component (R_f 0.13) was 3-methyl-7-nitro-1,2-benzisothiazole (XLVIII) (39%). The results are similar to those obtained by other workers.[85,100]

Oxidation

(a) The oxidation of a methyl group to a carboxylic acid function, by boiling with an excess of thionyl chloride, has previously been reported.[101] Recently[102] it has been postulated as an intermediate stage in the conversion of 2-methyl-chromone (XLIX) into 4-hydroxycoumarin (L). The reaction proceeds via the trichlorination of the methyl group, followed by alkaline hydrolysis to chromone-2-carboxylic acid[102] which then undergoes rearrangement. Another proposed mechanism is shown over the page.

(XLIX) → SOCl₂ →

OH⁻

−CCl₃ +

(L)
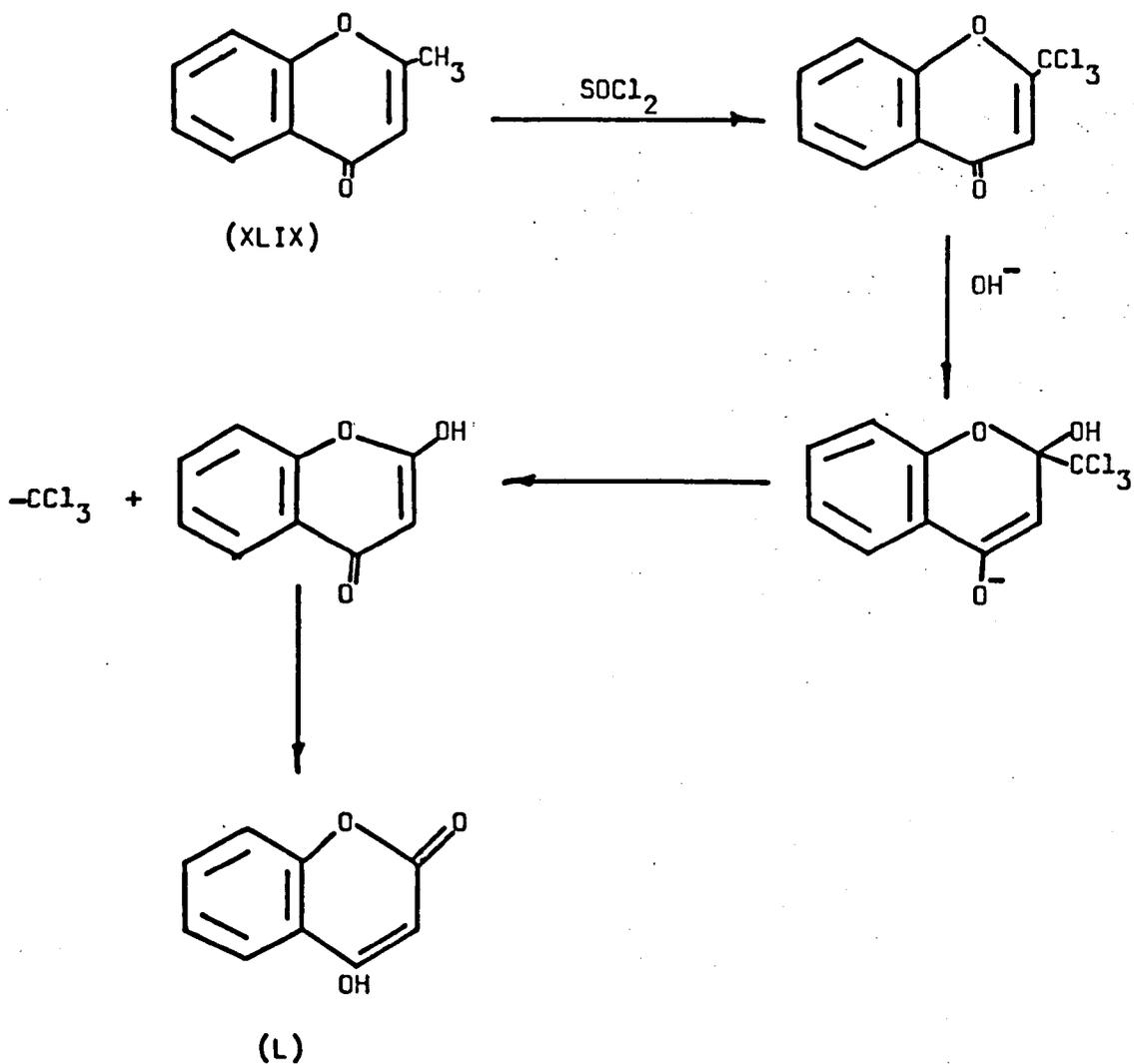
When 3-methyl-1,2-benzisothiazole was heated under reflux with thionyl
chloride in dry toluene for several days followed by treatment with dilute sodium
hydroxide a 42% yield of (1,2-benzisothiazole-3-yl)carboxylic acid (XXLa) was obtained

(b) During attempts to prepare (1,2-benzisothiazole-3-yl)carbaldehyde (LII),
Carrington[84] investigated the oxidation of 3-methyl-1,2-benzisothiazole with
selenium dioxide in toluene and with chromium trioxide in acetic anhydride in the
presence of concentrated sulphuric acid. The first procedure yielded only
starting material; whilst in the second, oxidation occurred to give a low yield
(19%) of 3-methyl-1,2-benzisothiazole-1,1-dioxide with none of the required
aldehyde (LII).

The oxidation was effected using a method reported[103] for the oxidation of

2-methylpyridine (LIII) to pyridine-2-carbaldehyde (LIV) using iodine and

dimethylsulphoxide. The mechanism for the reaction is claimed to be:[103]
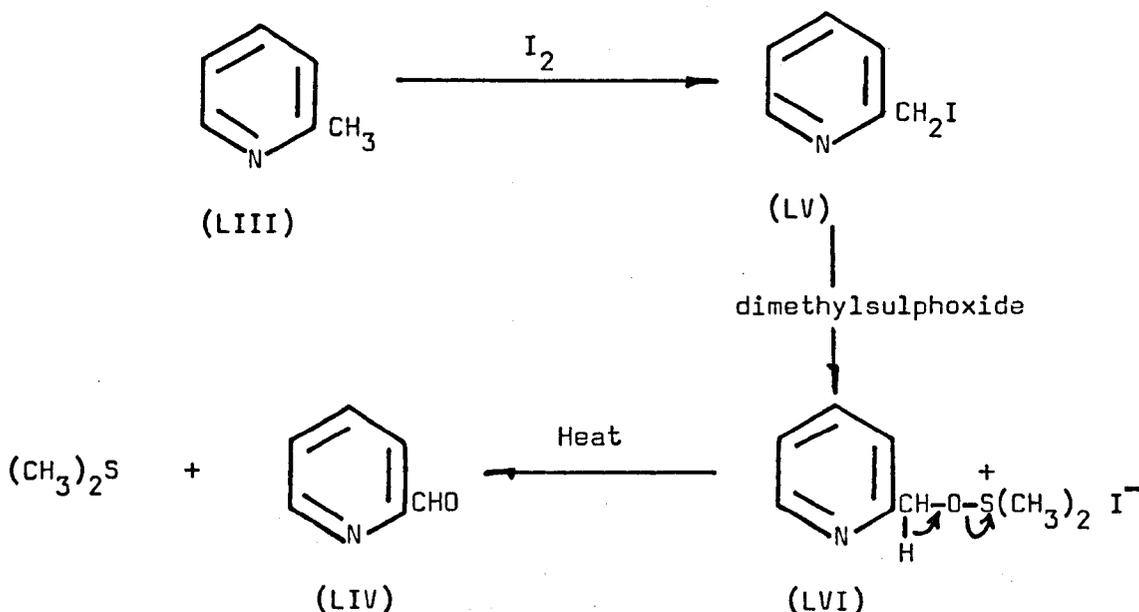
The initial formation of the transient 2-iodomethyl compound (LV) is probably

the limiting stage of the reaction as its formation is effected by simply mixing

the two chemicals at ca. 35°. Reaction of the solid complex, so formed, with

dimethylsulphoxide is claimed to result in formation of the dimethylsulphonium

iodide derivative (LVI) which then undergoes thermal decomposition to the

aldehyde (LIV), with simultaneous liberation of dimethylsulphide.

Using essentially the same conditions, 3-methyl-1,2-benzisothiazole gave a

crude reaction mixture from which 35% of (1,2-benzisothiazole-3-yl)carbaldehyde

and 54% of unchanged starting material were isolated by column chromatography.

Even 2-methylpyridine and related compounds give only ca. 50% yield of the

corresponding aldehyde and hence the relatively low yield of (1,2-benzisothiazole

3-yl)carbaldehyde (LII) is not unexpected.

The crystalline oxime formed from the aldehyde (LII) by the usual method[104]

was shown by n.m.r. to be a 1:1 mixture of the syn (LVII) and anti (LVIII) isomers.
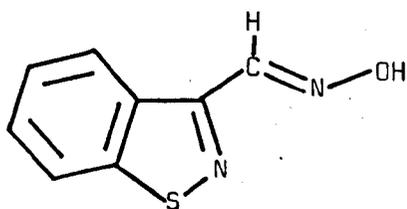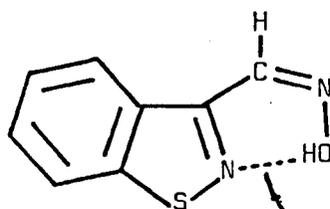
(LVII)   (LVIII)   intramolecular
                                 hydrogen bonding

The ease of ease of exchange of the hydroxyl proton with other protons in the

system caused the OH signal of the syn isomer (LVII) to appear as a broadened

singlet, whilst intramolecular hydrogen bonding in the anti isomer (LVIII) caused

a sharpening of the hydroxyl signal. Deshielding of the hydroxyl proton by the

adjacent ring nitrogen atom in the anti isomer caused the OH signal to be moved

downfield by 1.75 p.p.m. from the OH signal of the syn isomer.

Attempted Friedel-Crafts Acylation

        3-Methyl-1,2-benzisothiazole was stirred with acetyl chloride and anhydrous

aluminium chloride in dry nitrobenzene for 24 h at room temperature and was then

heated to 70-80° for 4 h. No acylated product was obtained.

        The foregoing reactions are summarised in Scheme 5 (p. 33).

Scheme 5
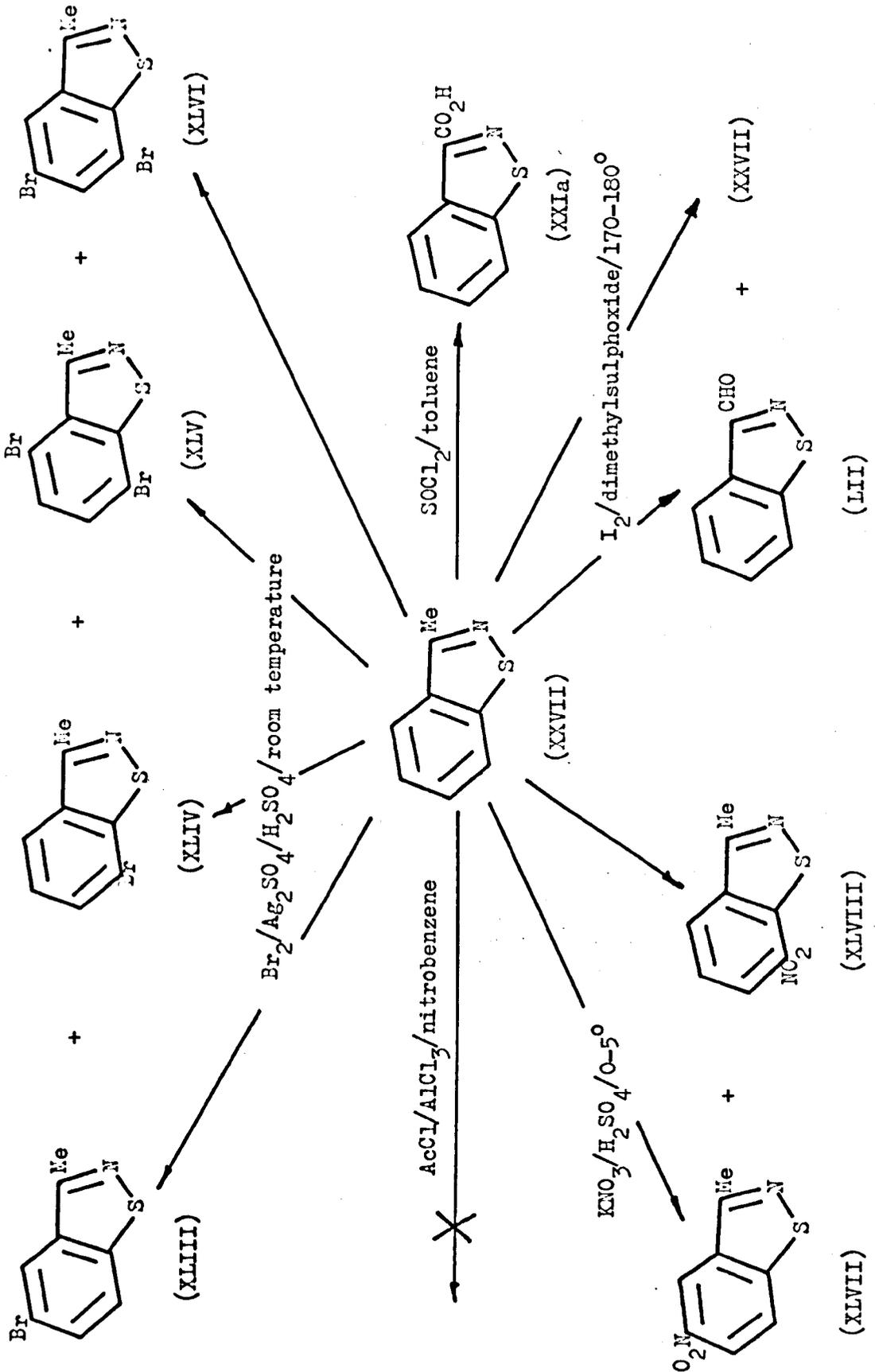
The Preparation of 7-Bromo and 7-Chloro-3-methyl-1,2-benzisothiazole

3-Methyl-7-nitro-1,2-benzisothiazole (XLVIII) was reduced with aluminium amalgam[105] to give a good yield (94%) of 7-amino-3-methyl-1,2-benzisothiazole, whereas Haddock et al.[85] only obtained a moderate yield (55%) of the amine using iron and acetic acid.

The diazotisation of various 7-amino-1,2-benzisothiazoles and the subsequent decomposition of the diazonium salt in the presence of a metal chloride and concentrated hydrochloric acid has been shown[85] to be rather complex. Depending upon the metal chloride, 4-chloro-1,2-benzisothiazole-7-diazonium salt gave the unexpected 6-chloro-1,2,3-benzothiadiazole-7-carbaldehyde (LIX; R=H; X=Cl) either as the sole product or mixed with the expected 4,7-dichloro-1,2-benzisothiazole. Some typical results are shown below.

Metal Chloride	Oxidation of metal cation	Standard Oxidation Potential at 25°	% Sandmeyer Reaction	% Rearrangement Reaction
$CrCl_2$	$Cr^{2+} \longrightarrow Cr^{3+}$	+ 0.41	-	45
$SnCl_2$	$\frac{1}{2}Sn^{2+} \longrightarrow \frac{1}{2}Sn^{4+}$	- 0.15	-	65
$CuCl$	$Cu^{+} \longrightarrow Cu^{2+}$	- 0.153	20	40
$FeCl_2$	$Fe^{2+} \longrightarrow Fe^{3+}$	- 0.771	40	15

The balance of the two reactions, i.e. Sandmeyer reaction (displacement of the diazonium group to give the 4,7-dichloro derivative) or rearrangement [to give 6-chloro-1,2,3-benzothiadiazole-7-carbaldehyde (LIX; R=H; X=Cl)], seems to be governed by the oxidation potential of the metal ion used in the reaction. This led Haddock and his co-workers[85] to suggest co-ordination of the metal salt with the benzisothiazole diazonium salt, probably by means of the sulphur atom as in the intermediate (LXI; R=H; X=Cl), with subsequent decomposition of the complex and oxidation of the metal to give the rearranged product. The proposed

mechanism is shown in Scheme 6.

(LX)

(LXI)

−2 electrons

(LIX)
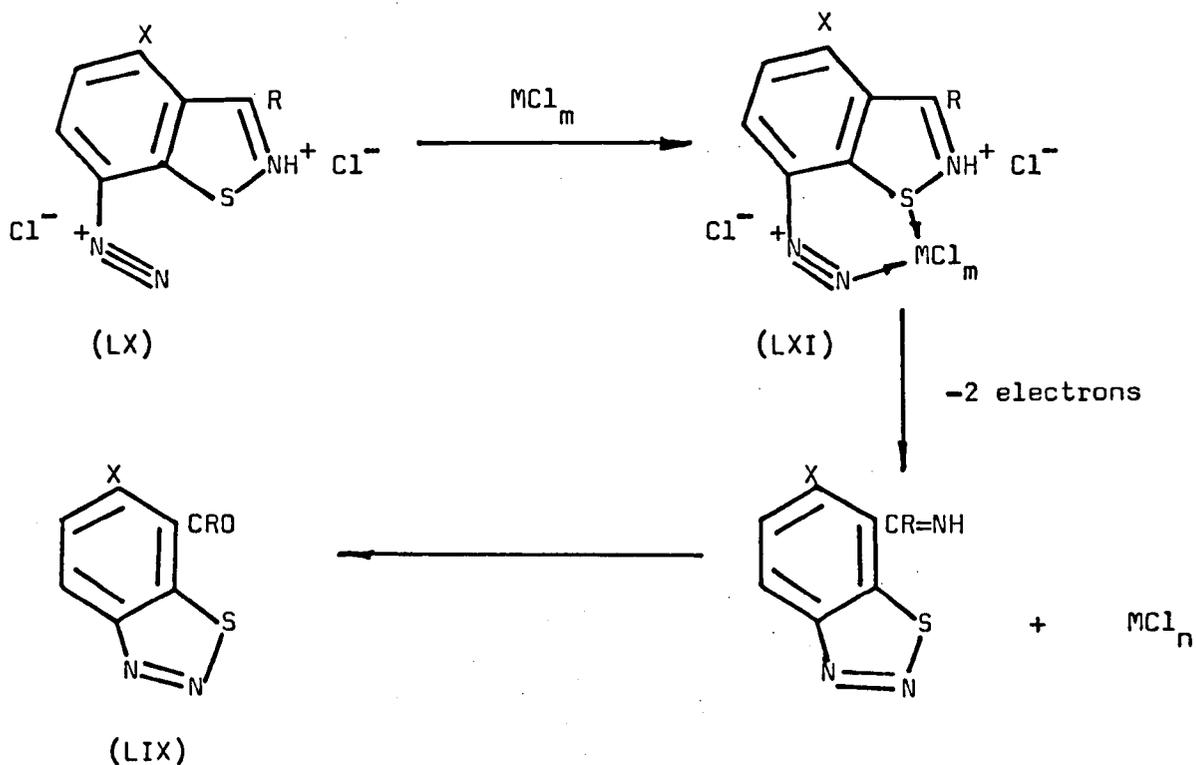
MCl_m = metal salt in lower oxidation state.

MCl_n = metal salt in higher oxidation state.

Scheme 6

Haddock et al.[85] claimed that the decomposition of the diazonium salt of

7-amino-3-methyl-1,2-benzisothiazole, in the presence of tin (11) chloride, gave

only 7-acetyl-1,2,3-benzothiadiazole (LIX; R=Me; X=H) (86%). However, the

present author found that decomposition of the diazonium salt (LX; R=Me; X=H)

with copper (1) chloride and concentrated hydrochloric acid gave a 32% yield of

7-chloro-3-methyl-1,2-benzisothiazole as well as the 7-acetyl compound (LIX; R=Me;

X=H) (51%). This result is compatible with general trends observed by Haddock.

The decomposition of the diazonium salt (LX; R=Me; X=H) with copper (1)

bromide and hydrobromic acid similarly gave 7-bromo-3-methyl-1,2-benzisothiazole

(40%) and 7-dibromoacetyl-1,2,3-benzothiadiazole (LIX; R=$CHBr_2$; X=H) (32%).

The mass spectrum of the 7-dibromoacetyl compound (LIX; R=CHBr$_2$; X=H) showed

base peaks at 306/308/310 ($\underline{M}$-N$_2$), thus following the fragmentation pattern

normally associated with benzothiadiazoles.[106]   It seems probable that 7-acetyl-

1,2,3-benzothiadiazole was formed initially and then brominated under the

conditions of the reaction.   The alternative dibromination of 3-methyl-1,2-

benzisothiazole-7-diazonium sulphate, followed by rearrangement, is unlikely owing

to the unreactivity of the methyl group in 1,2-benzisothiazoles (see later, p. 51).

The Preparation of 5-Amino-3-methyl-1,2-benzisothiazole

5-Amino-3-methyl-1,2-benzisothiazole was required (a) as a precursor for a number of 5-substituted 3-methyl-1,2-benzisothiazoles that were required for the present investigation, (b) to study its bromination and nitration and hence to prepare some 4-substituted 3-methyl-1,2-benzisothiazoles. The 4- and 5-substituted 3-methyl-1,2-benzisothiazoles so obtained are shown in Scheme 9 (p.44).

Ricci and Martani[78,79] claimed the preparation of 5-amino-3-methyl-1,2-benzisothiazole (LXII) by the cyclisation of the oxime of 4-amino-2-mercaptoacet-ophenone in hot polyphosphoric acid. Hughes[82] showed that the Italians had in fact decomposed 2-imino-5-methyl-3,1,4-benzoxathiazepine when preparing 3-methyl-1,2-benzisothiazole and it seemed probable that they had decomposed 7-amino-2-imino-5-methyl-3,1,4-benzoxathiazepine when preparing the 5-amino compound (LXII).

Acetophenone was nitrated[107] with fuming nitric acid at -15 to -8° and the resulting meta-isomer (53%) was purified by crystallisation from ethanol. Reduction[108] with iron filings in glacial acetic acid at 75° gave m-aminoacetoph-enone in 85% yield, which was then thiocyanated[109] at -10 to -2° with thiocyanogen, prepared in situ by the action of a dry methanolic solution of bromine on a suspension of anhydrous sodium thiocyanate in dry methanol. The resulting 5-amino-2-thiocyanatoacetophenone (55%) was boiled with an aqueous ethanolic solution of hydroxylamine hydrochloride and sodium acetate to give 7-amino-2-imino-5-methyl-3,1,4-benzoxathiazepine in 74% yield. Decomposition of the foregoing product in polyphosphoric acid at 120-130° gave 5-amino-3-methyl-1,2-benzisothiazole (LXII) in 88% yield. The reaction sequence is outlined in Scheme 7.

Scheme 7
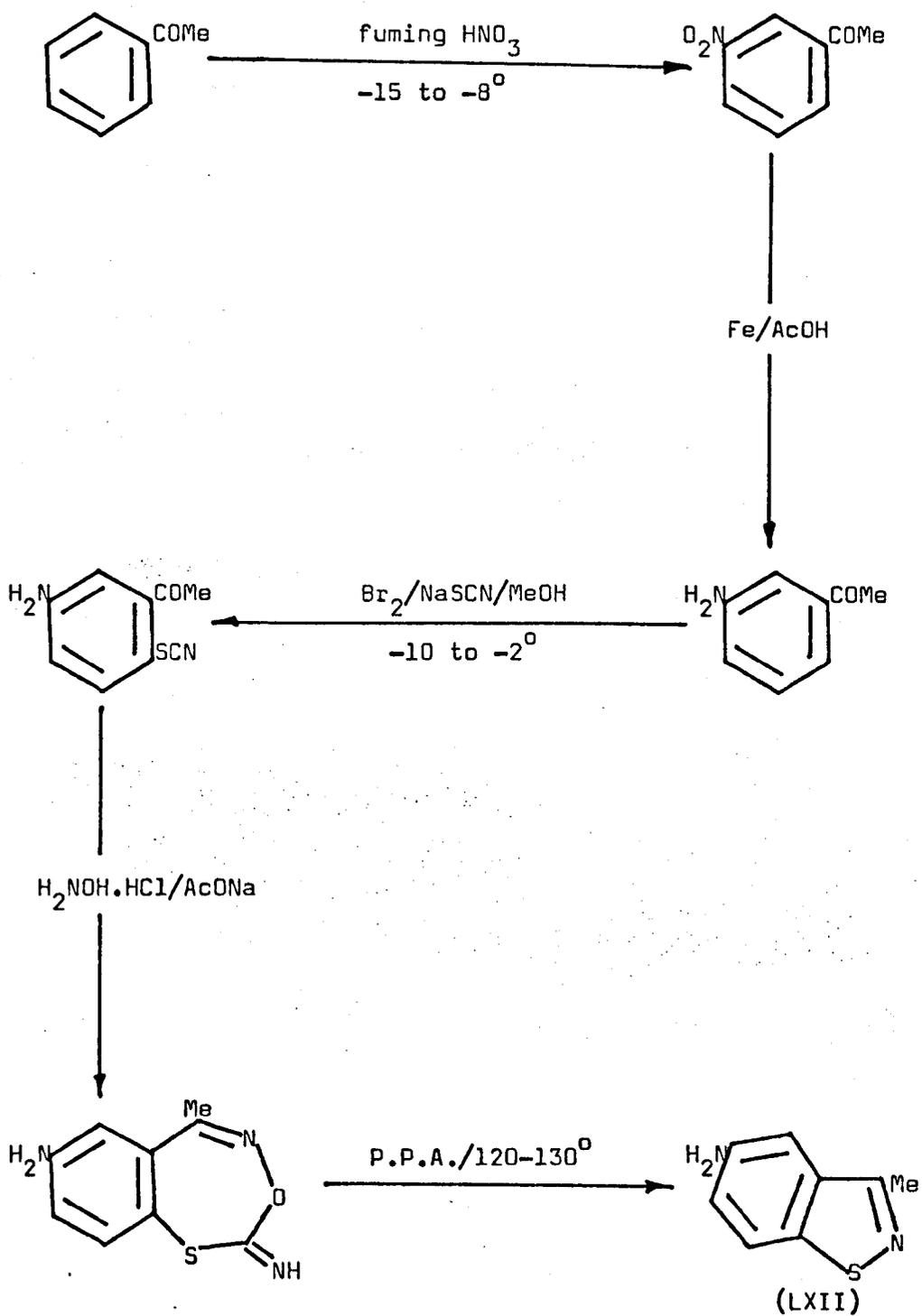
(LXII)

The Bromination of 5-Amino-3-methyl-1,2-benzisothiazole

5-Amino-3-methyl-1,2-benzisothiazole proved too reactive to nitrate directly. Only dark unresolvable mixtures were obtained and therefore the 5-acetamido derivative had to be used (see later, p. 42). But bromination of the 5-amino compound did proceed smoothly.

5-Amino-3-methyl-1,2-benzisothiazole reacted with bromine in dry chloroform at 0° to give 5-amino-4-bromo-3-methyl-1,2-benzisothiazole (LXIII) in 90% yield. The n.m.r. spectrum showed an AB quartet for the 6- and 7-protons ($\underline{J}_{6,7}$ = 8.5 Hz), with the doublet due to the 6-proton being moved upfield due to the shielding effect of the adjacent 5-amino substituent.

Bromination with bromine in glacial acetic acid at room temperature gave a three component solid which was resolved by column chromatography. The major product (70%) was identified as the 5-amino-4-bromo derivative (LXIII) and one minor product (10%) was unchanged starting material. The other minor product (10%), a dibromo derivative (mass and n.m.r. spectra), was identified as the 5-amino-4,6-dibromo compound (LXIV) by deamination of a sample by treatment of the diazonium salt with hypophosphorous acid. The resulting 4,6-dibromo-3-methyl-1,2-benzisothiazole (LXV) (80%) was identified from its n.m.r. spectrum which showed two <u>meta</u> split singlets ($\underline{J}_{4,6}$ = 1.4 Hz).

The bromination results indicated, as expected, that a strongly electron-donating 5-substituent causes the <u>ortho</u>-positions (especially the 4-position) to be activated towards electrophilic attack. A similar pattern has been observed with 5-substituted 3-methylbenzo[b]thiophens[110] and has been rationalised[111] in terms of a greater resonance stabilisation of the reaction intermediate during 4-substitution.
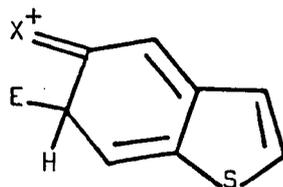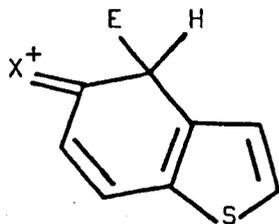
E = Electrophile.

X = Electron Donating

Substituent.

The intermediate for electrophilic attack at the 4-position has the aromaticity

of the thiophen ring preserved, whilst the intermediate for attack at the

6-position only has resonance stabilisation due to a conjugated triene system.

The foregoing reactions are summarised in Scheme 8 (p. 41).

Scheme 8
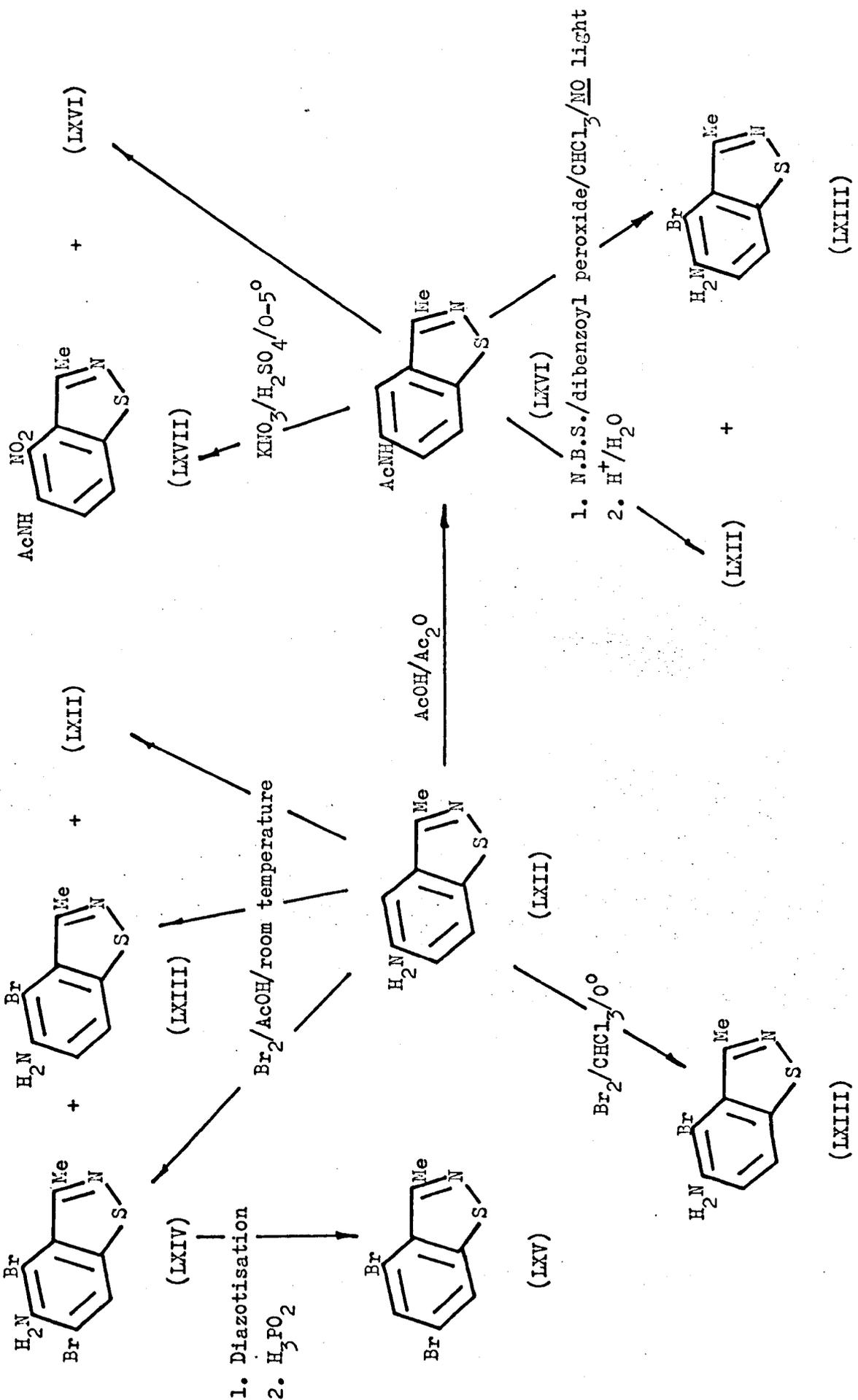
The Bromination and Nitration of 5-Acetamido-3-methyl-1,2-benzisothiazole

As mentioned previously (p. 39) the high reactivity of 5-amino-3-methyl-1,2-benzisothiazole prevented the study of its nitration. However, the 5-acetamido derivative (LXVI) might be expected to undergo nitration due to its decreased reactivity.

5-Acetamido-3-methyl-1,2-benzisothiazole was obtained in 96% yield by the treatment of 5-amino-3-methyl-1,2-benzisothiazole with acetic anhydride and glacial acetic acid.[78]

Bromination

Treatment of the acetamido compound (LXVI) with N-bromosuccinimide in boiling chloroform, containing a catalytic amount of dibenzoyl peroxide, gave a two component mixture which proved impossible to separate by column chromatography. Consequently, the mixture was hydrolysed with 40% sulphuric acid and the two amines were separated by chromatography. The major component (56%) was the 5-amino compound (LXII), whilst the minor component (34%) was identified as 5-amino-4-bromo-3-methyl-1,2-benzisothiazole (LXIII).

Nitration

The nitration of 5-acetamido-3-methyl-1,2-benzisothiazole, with potassium nitrate in concentrated sulphuric acid at 0-5° for 3 h, gave a solid product which contained two components. Column chromatography gave 5-acetamido-3-methyl-4-nitro-1,2-benzisothiazole (LXVII) as the major product (60%) and unchanged starting material (8%). Longer periods of stirring or higher temperatures only increased the percentage of tars formed.

The foregoing reactions are summarised in Scheme 8 (p. 41).

## The Preparation of 5-Bromo and 5-Chloro-3-methyl-1,2-benzisothiazole

5-Bromo-3-methyl-1,2-benzisothiazole (LXVIII) was prepared in good yield (88%) from 5-amino-3-methyl-1,2-benzisothiazole by the Sandmeyer reaction,[112] involving decomposition of the diazonium sulphate in the presence of copper ($\underline{1}$) bromide in hydrobromic acid. The n.m.r. spectrum showed an AB quartet for the 6- and 7-protons ($J_{6,7} = 8.5$ Hz). The signal due to the 6-proton was further split due to meta coupling ($J_{4,6} = 1.7$ Hz) and the 7-proton signal was finely split due to para coupling ($J_{4,7} = 0.5$ Hz) with the 4-proton, which consequently occurred as a doublet of doublets.

5-Chloro-3-methyl-1,2-benzisothiazole (LXIX) was prepared (91%) similarly from the 5-amino precursor, by treatment of the diazonium chloride with copper ($\underline{1}$) chloride in concentrated hydrochloric acid. Its n.m.r. spectrum was similar to that of the 5-bromo compound mentioned above, but the coupling constants being slightly larger ($J_{4,7} = 0.75$, $J_{4,6} = 1.95$, and $J_{6,7} = 8.6$ Hz).

The above preparations are summarised in Scheme 9 (p. 44).

Scheme 9

1. Diazotisation
2. H_2SO_4/H_2O

(LXXXIX)

1. AcOH/Ac_2O
2. KNO_3/H_2SO_4/0-5°
3. Diazotisation
4. Cu_2O/EtOH

(CXIII)

1. Diazotisation
2. CuBr/HBr

(LXVIII)

1. Br_2/$CHCl_3$/0°
2. Diazotisation
3. H_3PO_2

(LXII)

(CIV)

1. Diazotisation
2. CuCl/HCl

(LXIX)

1. N.Cl.S./dibenzoyl peroxide/$CHCl_3$
2. Diazotisation
3. H_3PO_2

(CXII)
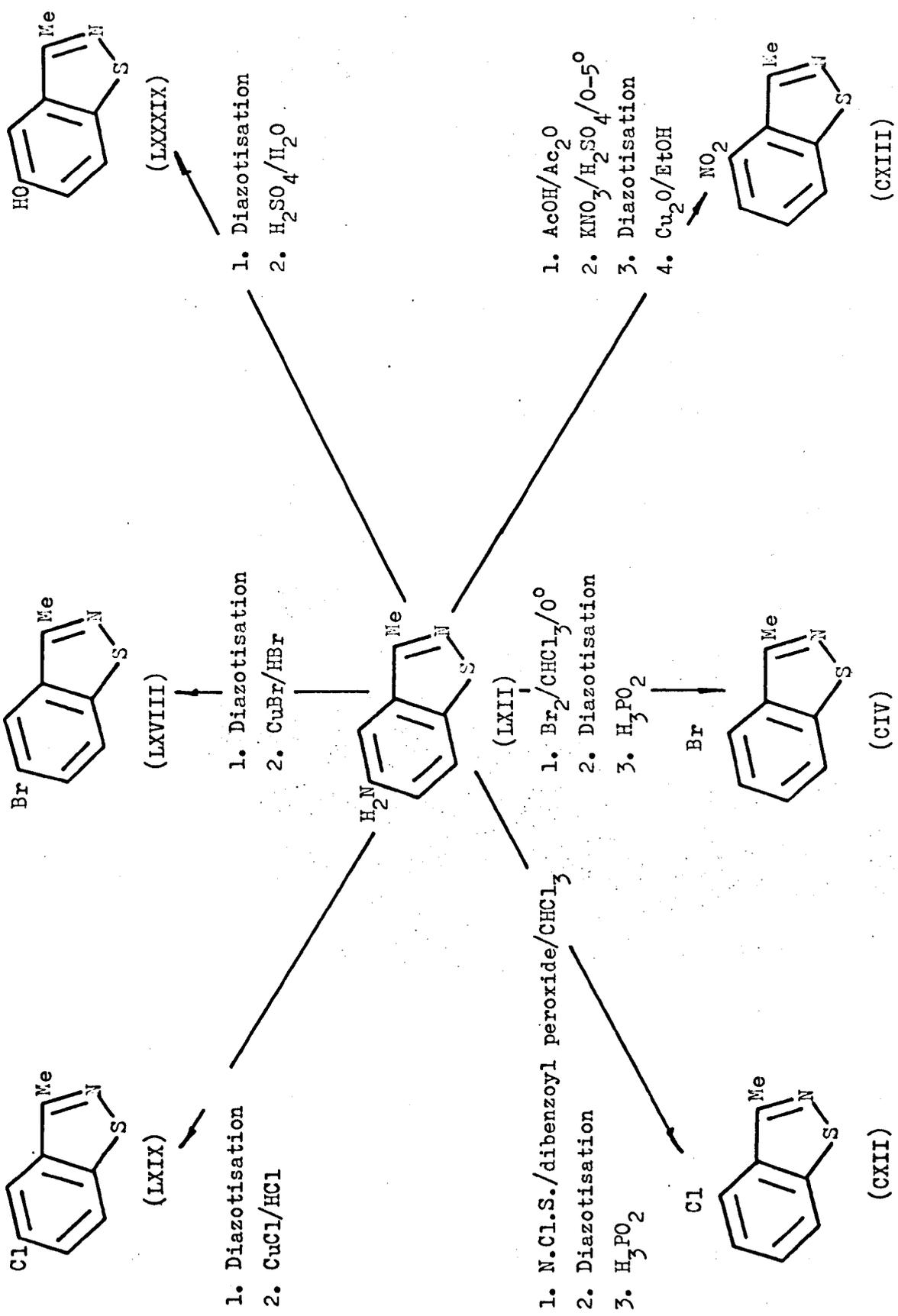
Some Electrophilic Substitution Reactions of 5-Bromo-3-methyl-1,2-benzisothiazole

The benzenoid ring of benzisothiazole will be further deactivated by the introduction of a bromo-substituent into the 5-position. It was seen, from the bromination study of 5-amino-3-methyl-1,2-benzisothiazole, that the substitution pattern is governed not by the isothiazole ring (which would promote the formation of the 7-isomer) but by the activating substituent in the 5-position. Hence, the 4-position was strongly activated and the 6-position weakly activated— there being no evidence for activation of the 7-position. Therefore, it could be argued that with a deactivating 5-substituent (i.e. bromo-group), the deactivating effect of the isothiazole ring might now become important and cause substitution also at the 7-position to some extent. Therefore, as the 4- and 7-positions of 5-bromo-3-methyl-1,2-benzisothiazole could be expected to be activated towards electrophilic attack the reactions summarised in Scheme 10 (p. 50) were carried out.

Bromination

Treatment of 5-bromo-3-methyl-1,2-benzisothiazole with bromine and silver sulphate in concentrated sulphuric acid at room temperature gave a white solid which contained four components. Separation by column chromatography gave a tribromo product, probably 3-methyl-4,5,7-tribromo-1,2-benzisothiazole (LXX), as the major component (34%). Unchanged starting material (23%) and 4,5-dibromo-3-methyl-1,2-benzisothiazole (LXXI) (24%) were also isolated. The latter had an n.m.r. spectrum, when observed in deuteriochloroform, which showed a single peak for the aromatic protons and not the expected AB quartet. However, when the spectrum was observed in hexadeuteriobenzene the chemical shift differences were of sufficient magnitude to produce a first order spectrum. This solvent effect is illustrated in Figure 1 (p. 46), and similar effects have been successfully used[113] for the analysis of complex n.m.r. spectra.

765

(a)

697   670

(b)
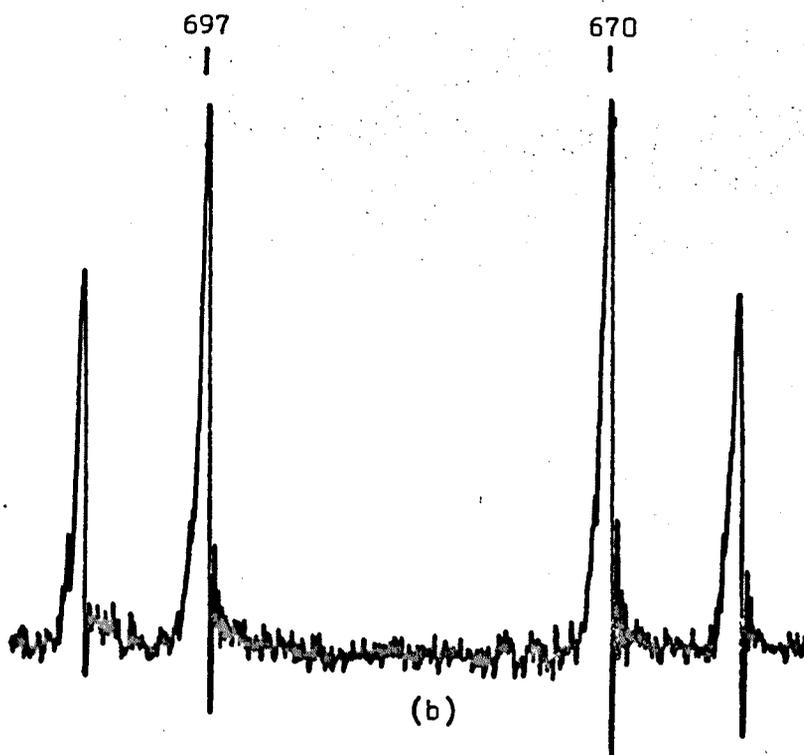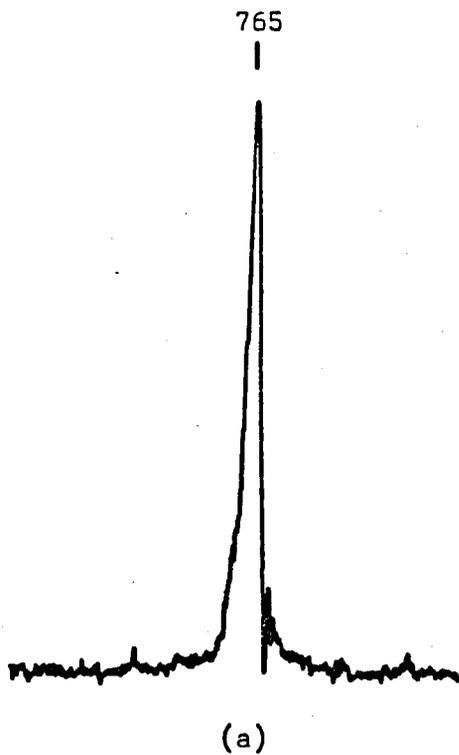
Figure 1

The expanded n.m.r. spectrum of the aromatic protons of 4,5-dibromo-

3-methyl-1,2-benzisothiazole in (a) $CDCl_3$ and (b) C_6D_6.

The identity of the 4,5-dibromo compound (LXXI) was verified by its preparation in 79% yield from 5-amino-4-bromo-3-methyl-1,2-benzisothiazole (LXIII), by treating the diazonium sulphate with copper ($\underline{1}$) bromide in hydrobromic acid. By a similar method 4-bromo-5-chloro-3-methyl-1,2-benzisothiazole (LXXII) was prepared (99%) from the 5-amino-4-bromo compound (LXIII).

The fourth component (10%) was isolated and identified as 5,7-dibromo-3-methyl-1,2-benzisothiazole (XLVI). Its n.m.r. spectrum showed two meta coupled signals ($\underline{J}_{4,7}$ = 1.4 Hz) as well as the methyl singlet. The isolation of this component shows that deactivation of the 4- and 6-positions, by the isothiazole ring, was of a sufficient magnitude so as to become important in the bromination of 5-bromo-3-methyl-1,2-benzisothiazole. The product was identical with a minor component isolated from the bromination of 3-methyl-1,2-benzisothiazole (p. 29). Repeating the reaction at 0° did not effectively change the composition of the mixture (by t.l.c.).

Nitration

Reaction of 5-bromo-3-methyl-1,2-benzisothiazole with potassium nitrate in concentrated sulphuric acid at 0-5° gave 5-bromo-3-methyl-4-nitro-1,2-benzisothiazole (LXXIII) in 81% yield. Its n.m.r. spectrum showed an AB quartet for the 6- and 7-protons ($\underline{J}_{6,7}$ = 8.7 Hz). The 7-proton signal was moved well upfield from its expected chemical shift (by ca. 0.6 p.p.m.) due to the loss of co-planarity between the nitro-group and the ring. The twisting of the nitro-group, caused by steric effects of the 5-bromo and 3-methyl group, reduced its conjugation with the ring so decreasing the deshielding experienced by the 7-proton (compare with 5-hydroxy-3-methyl-4-nitro-1,2-benzisothiazole, p. 57).

Reduction of the 4-nitro compound (LXXIII) with hydrazine hydrate and Raney nickel gave 4-amino-5-bromo-3-methyl-1,2-benzisothiazole in good yield (81%).

Formylation

Carrington et al.[84] found that treatment of 3-methyl-1,2-benzisothiazole with phosphoryl chloride and dimethylformamide gave a mixture of formamidines (LXXIV; X=H) and (LXXV). The proportion of the 2-formyl compound (LXXV) increased as the temperature of the reaction was increased.
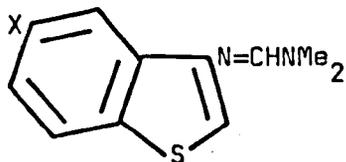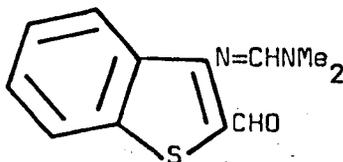
(LXXIV)   (LXXV)

It was also found[84] that the Vilsmeier-Haack formylation of 3-aminobenzo[b] thiophen gave a similar mixture, suggesting that isomerism of 3-methyl-1,2-benzisothiazole to 3-aminobenzo[b]thiophen probably occurs first. Such isomerism would involve cleavage of the sulphur-nitrogen bond and Böshagen and his co-workers have reported many examples[114,115] of such bond cleavage in benzisothiazoles. For example, an aqueous solution of 3-ethylamino-1,2-benzisothiazole hydrochloride (LXXVI) exists in equilibrium with 2-ethyl-3-imino-1,2-benzisothiazolinyl hydrochloride (LXXVII).[116,117]
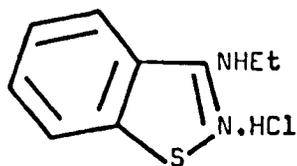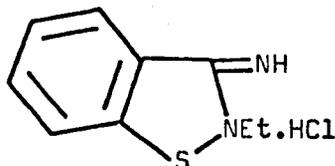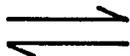
(LXXVI)   (LXXVII)

The formylation of 5-bromo-3-methyl-1,2-benzisothiazole at room temperature gave a solid which contained two components in the ratio 1:1 (by t.l.c.). The mixture proved difficult to resolve but slow elution from a silica gel column gave 5-bromo-3-formylamidobenzo[b]thiophen (LXXVIII) and $\underline{N}^2$-(5-bromo-2-formyl-3-benzo[b]thienyl)-$\underline{N}^1\underline{N}^1$-dimethylformamidine (LXXIX). The products were character-ised by n.m.r., mass, and i.r. spectra and were similar to those obtained for

3-methyl-1,2-benzisothiazole, except that the corresponding formamidine compound (LXXIV; X=Br) was not isolated presumably due to hydrolysis during the work-up to the formylamido derivative (LXXVIII).

Repeating the reaction at 110° increased the proportion (by t.l.c.) of the 2-formyl-formamidine component (LXXIX) in the mixture. These results parallel those obtained in the formylation of 3-methyl-1,2-benzisothiazole, and suggest that the formamidine (LXXIV; X=Br) was formed first and then subsequently formylated to give the 2-formyl derivative (LXXIX).

Attempted Friedel-Crafts Acylation

Attempted acylation of 5-bromo-3-methyl-1,2-benzisothiazole by the usual method,[118] using tin (1V) chloride and acetyl chloride in either nitrobenzene or dichloromethane or using aluminium chloride and acetyl chloride in nitrobenzene, failed to give any acylated product.

Scheme.10

(LXVIII)

(LXX)

(XLVI)

(LXXIII)

Raney Ni/H$_2$NNH$_2$

Me
NO$_2$
Br
S
N

Me
NH$_2$
Br
S
N

Me
Br
Br
Br
S
N

Me
Br
Br
S
N

Br$_2$/Ag$_2$SO$_4$/H$_2$SO$_4$/room temperature

KNO$_3$/H$_2$SO$_4$/0–5°

Me
Br
S
N

(LXVIII)

POCl$_3$/dimethylformamide

NHCHO
Br
S

(LXXVIII)

N=CHNMe$_2$
CHO
Br
S

(LXXIX)

Me
Br
Br
S
N

(LXXI)

1. Diazotisation
2. CuBr/HBr

Me
Br
H$_2$N
S
N

(LXIII)

1. Diazotisation
2. CuCl/HCl

Me
Br
Cl
S
N

(LXXII)
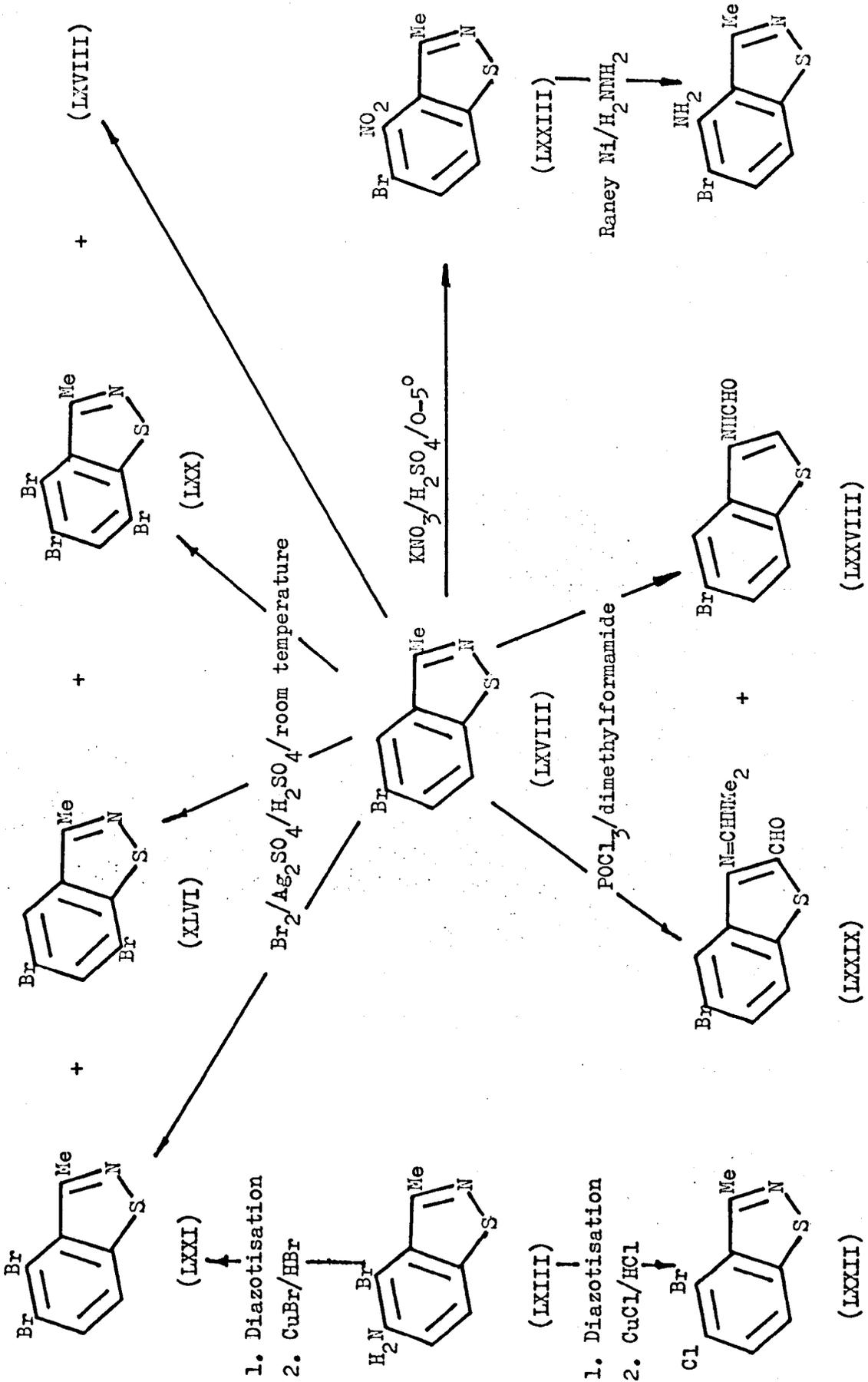
Some 3-Aminomethyl and NN-Disubstituted-3-aminomethyl-1,2-benzisothiazole

hydrochlorides

Preparation of some 3-Bromomethyl-1,2-benzisothiazoles

Preliminary work in this department[119] had indicated that the usual

conditions[120] for the bromination of the methyl group, using N-bromosuccinimide

with dibenzoyl peroxide and irradiating the reaction (200W tungsten lamp), were

unsuccessful for 3-methyl-1,2-benzisothiazole. Consequently other methods of

bromination were tried initially.

Photobromination,[121] using bromine in dry carbon tetrachloride added

dropwise (2 h) to an irradiated solution of 3-methyl-1,2-benzisothiazole in dry

carbon tetrachloride, gave a low yield (37%) of the bromomethyl component which

was isolated from the reaction mixture (several components by t.l.c.) as the

hexaminium salt.

Repetition of the reaction at 120° without a solvent also gave several

components (t.l.c.), but treatment of the mixture with dimethylamine did

give NN-dimethyl-(1,2-benzisothiazol-3-yl)methylamine, isolated as its

hydrochloride (20%).

A re-investigation of the bromination of 3-methyl-1,2-benzisothiazole with

N-bromosuccinimide,[120] using a stream of dry nitrogen to expel any hydrogen

bromide formed, showed (g.l.c.) that a reaction did occur to give a mixture

containing the 3-bromomethyl derivative (LXXX; X=H) (84%) and the 3-dibromomethyl

derivative (LXXXI; X=H) (7%). These results have been verified by Gilham,[100]

but so far details of his work are unpublished.

5-Bromo-(LXVIII) and 5-chloro-3-methyl-1,2-benzisothiazole (LXIX) underwent

a similar bromination with N-bromosuccinimide to give reaction mixtures containing

(n.m.r.) the corresponding 3-bromomethyl derivative (LXXX; X=Br, 70%; X=Cl, 70%),

3-dibromomethyl derivative (LXXXI; X=Br, 10%; X=Cl, 15%), and unchanged starting

material (20% and 15% respectively).

5-Bromo-3-bromomethyl and 3-bromomethyl-5-chloro-1,2-benzisothiazole were isolated in moderate yields (ca. 50%) from the respective bromination mixture by crystallisation with light petroleum. But attempts to isolate 3-bromomethyl-1,2-benzisothiazole (LXXX; X=H) by either crystallisation or distillation were unsuccessful.

N-Chlorosuccinimide (N.Cl.S.) has been shown[122] to be a more selective reagent than N-bromosuccinimide (N.B.S.) for halogenation of the methyl group in 3,4-dimethyl-1,2,5-thiadiazole (LXXXII).
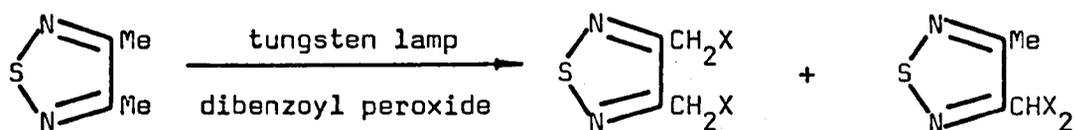
(LXXXII)

1. N.B.S./3 h	10%	38%
2. N.Cl.S./15 h	50%	10%

Using the same conditions[120] as before, the use of N-chlorosuccinimide on 5-bromo- and 5-chloro-3-methyl-1,2-benzisothiazole did not increase the proportion of monohalogenomethyl derivative and the dihalogenomethyl derivative was still formed (from n.m.r. study of the reaction mixtures). As N-chlorosuccinimide required a much longer reaction time (several days)[122] this modification was abandoned in favour of the use of N-bromosuccinimide.

Preparation of some NN-Disubstituted-3-aminomethyl-1,2-benzisothiazole hydrochlorides and 5-Halogeno derivatives

Scheme 11 outlines the route to the required NN-disubstituted-3-aminomethyl-1,2-benzisothiazole hydrochlorides (LXXXIII; X=H, Br, Cl).

(LXXX) + (LXXXI)

1. HNR$_2$

2. HCl/Et$_2$O

(LXXXIII)
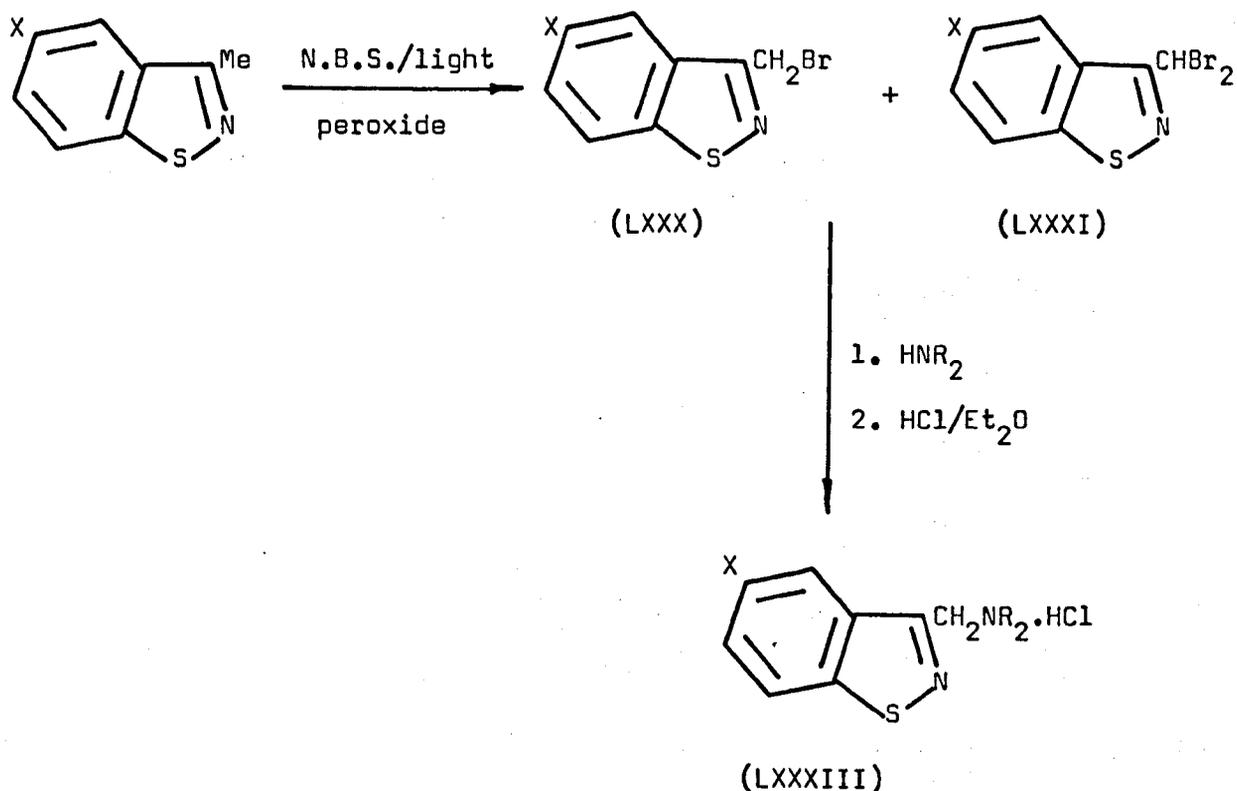
NR$_2$ = NMe$_2$, NEt(CH$_2$)$_2$OH, morpholino,

piperidino, pyrrolidino.

Scheme 11

In order to maximise the yield of the amine, the bromination mixtures were not resolved but the bromomethyl component (LXXX; X=H, Br, Cl) was treated in situ with the appropriate secondary amine. The resulting NN-disubstituted-3-amino-methyl derivative (LXXXIII; X=H, Br, Cl) was isolated in good yield (ca. 65-80%) from the reaction mixture by precipitation as the hydrochloride.

Preparation of (1,2-Benzisothiazol-3-yl)methylamine hydrochloride and related 5-Halogeno derivatives

The required amines were prepared by the Délépine reaction.[123]
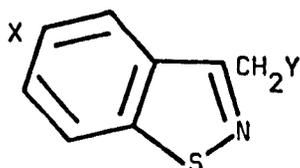
(LXXXIV; Y=N$_4$(CH$_2$)$_6$$^+$ Br$^-$)

(LXXXV; Y=NH$_2$.HCl)

As before the bromination mixture was not resolved but reacted directly with hexamethylenetetramine to give good yields of the hexaminium bromide (LXXXIV; X=H, 72%; Br, 67%; Cl, 69%). Hydrolysis of the quaternary salts, with ethanolic hydrochloric acid, gave good yields (75%; 78%; and 75% respectively) of the corresponding methylamine hydrochlorides (LXXXV; X=H, Br, Cl).

Preparation of N-2-Chloroethyl-N-ethyl-(1,2-benzisothiazol-3-yl)methylamine hydrochloride and related 5-Halogeno derivatives

The amine hydrochlorides [LXXXIII; X=H, Br, Cl; NR_2=NEt$(CH_2)_2$Cl] were prepared from the corresponding N-2-hydroxyethyl compounds [LXXXIII; X=H, Br, Cl; NR_2=NEt$(CH_2)_2$OH] by treatment with thionyl chloride in dry chloroform. The compounds were obtained in good yields (ca. 90%) and purified by crystallisation from dry ethanol or dry ethanol-ether.
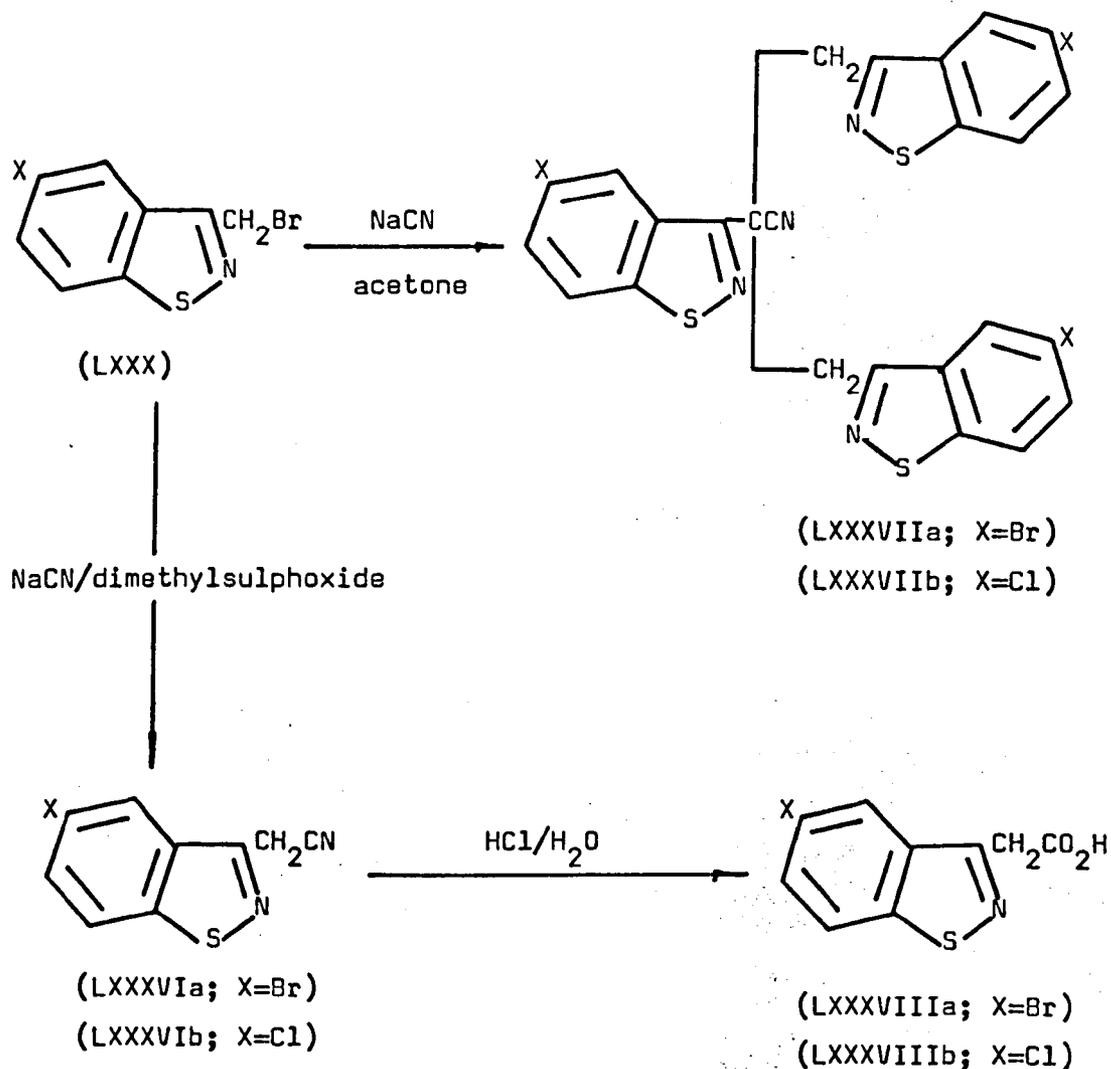
Scheme 12

A similar pattern was observed when the reactions were carried out on 5-chloro-3-methyl-1,2-benzisothiazole. Treatment of the 3-bromomethyl compound (LXXX; X=Cl) with sodium cyanide in aqueous acetone gave compound (LXXXVIIb) (95%), whereas the reaction with dry dimethylsulphoxide, as solvent, gave the required nitrile (LXXXVIb) (62%). Acidic hydrolysis of the nitrile gave (5-chloro-1,2-benzisothiazol-3-yl)acetic acid (LXXXVIIIb) in 66% yield.

As the overall yield of the 5-halogeno acetonitrile derivatives was very small (ca. 5%, starting from acetophenone), an alternative route to the nitriles was explored (see later, p. 78).

The Preparation of (5-Bromo and 5-Chloro-1,2-benzisothiazol-3-yl)acetonitrile
and the related acetic acid derivatives

It was hoped to prepare some ethylamine derivatives from 5-bromo-and
5-chloro-3-methyl-1,2-benzisothiazole and consequently the corresponding 3-
acetonitrile derivatives were required as intermediates.

Sutton,[118] when preparing 2-(4-hydroxy-3-benzo[b]thienyl)ethylamine – the
sulphur analogue of 4-hydroxytryptamine, showed that the intermediate 4-
methylsulphonyloxy-3-benzo[b]thienylacetonitrile was best prepared by treating
the 3-bromomethyl compound with a partial solution of sodium cyanide in aqueous
acetone, rather than in dimethylsulphoxide which is liable to give side reactions.
124,125

However, when 5-bromo-3-bromomethyl-1,2-benzisothiazole was treated with
sodium cyanide in aqueous acetone a product (84%) was isolated which was not the
required nitrile (LXXXVIa). Its n.m.r. spectrum showed aromatic and methylene
protons, in the ratio 9:4, while its mass spectrum, when run at low energy,
indicated the presence of three bromine atoms and a molecular weight of 702/704/
706/708. A weak CN absorption in the i.r. spectrum coupled with the microanalyt-
ical data finally identified the compound as di(5-bromo-1,2-benzisothiazol-3-ylC
methyl)-(5-bromo-1,2-benzisothiazol-3-yl)acetonitrile (LXXXVIIa). It was
probably formed by attack of the excess of bromomethyl compound at the active
methylene protons in the initially formed nitrile. In an attempt to minimise
this secondary reaction the bromomethyl compound (LXXX; X=Br) was added over
2.5 h to aqueous acetone containing a fourfold excess of sodium cyanide, but still
only compound (LXXXVIIa) was isolated (73%).

When the reaction was repeated using dry dimethylsulphoxide as solvent[124]
and the reaction product purified by elution from a column of silica gel,
(5-bromo-1,2-benzisothiazol-3-yl)acetonitrile was obtained in 60% yield.
Hydrolysis[89] of the nitrile (LXXXVIa) gave (5-bromo-1,2-benzisothiazol-3-yl)acetic
acid (LXXXVIIIa) in good yield (70%). The foregoing reactions are outlined in
Scheme 12.

Some Reactions of 5-Hydroxy-3-methyl-1,2-benzisothiazole

The reactions of 5-hydroxy-3-methyl-1,2-benzisothiazole were investigated to see if they were characteristically phenolic and if they followed the emerging pattern for 3-methyl-1,2-benzisothiazole derivatives. Scheme 13 (pp. 61, 62) summarises the reactions investigated.

5-Hydroxy-3-methyl-1,2-benzisothiazole (LXXXIX) was prepared by decomposing the diazonium sulphate from 5-amino-3-methyl-1,2-benzisothiazole in the usual manner (Scheme 9, p. 44). The moderate yield (45%) which corresponds to an overall yield of only 7% (from acetophenone) prompted the author to investigate other alternative routes (see later, p. 83).

Bromination

Unlike 5-hydroxy-3-methylbenzo[b]thiophen,[118] 5-hydroxy-3-methyl-1,2-benzisothiazole due to its comparative unreactivity proved a suitable substrate for monosubstitution. Treatment with bromine in ethyl acetate at 0° gave 4-bromo-5-hydroxy-3-methyl-1,2-benzisothiazole (XC) in high yield (95%). Its n.m.r. spectrum showed an AB quartet for the 6- and 7-protons ($J_{6,7}$ = 8.6 Hz), with the signal for the 6-proton moved upfield due to shielding by the 5-hydroxyl group.

Nitration

The nitration of 5-hydroxy-3-methyl-1,2-benzisothiazole with nitric acid in glacial acetic acid at room temperature gave 5-hydroxy-3-methyl-4-nitro-1,2-benzisothiazole (XCI) in 72% yield. The n.m.r. spectrum showed the expected AB quartet for the 6- and 7-protons. The 7-proton signal was not appreciably moved upfield from the expected chemical shift as was found for 5-bromo-3-methyl-4-nitro-1,2-benzisothiazole (p. 47). This being due to hydrogen bonding between the 5-hydroxy and 4-nitro group, so keeping the nitro group essentially co-planar

with the ring.

3-Methyl-5-methylsulphonyloxy-1,2-benzisothiazole

5-Hydroxy-3-methyl-1,2-benzisothiazole when treated with methylsulphonyl chloride in dry pyridine at $0°$ gave the methylsulphonyloxy derivative (XCII) in 76% yield. Its n.m.r. spectrum showed the expected splitting pattern for the aromatic protons, with additional fine splitting of the 4- and 7-signals due to para coupling ($J_{4,7} = 0.7$, $J_{4,6} = 2.2$, and $J_{6,7} = 8.5$ Hz).

Claisen Rearrangement of 5-Allyloxy-3-methyl-1,2-benzisothiazole

Treatment of 5-hydroxy-3-methyl-1,2-benzisothiazole with allyl bromide in boiling anhydrous butanone, with potassium carbonate as hydrogen bromide scavenger, gave the allyl ether (XCIII) in 81% yield.

The Claisen rearrangement readily occurred when 5-allyl-3-methyl-1,2-benzisothiazole was kept at the b.p. of NN-dimethylaniline[126] to give the ortho allyl phenol (XCIV) in 90% yield.

Attempted Fries Rearrangement of 5-Acetoxy-3-methyl-1,2-benzisothiazole

5-Acetoxy-3-methyl-1,2-benzisothiazole (XCV) (94%) was obtained by treating 5-hydroxy-3-methyl-1,2-benzisothiazole with acetic anhydride in boiling acetic acid. Reaction of the ester (XCV) with aluminium chloride at 180-200$°$, without a solvent, failed to cause the expected ortho-rearrangement. Only 5-hydroxy-3-methyl-1,2-benzisothiazole (88%) was isolated − the acetyl function presumably being evolved as acetyl chloride. Repeating the reaction in boiling benzene, conditions that generally favour para-rearrangement, also failed to give any rearranged product. 5-Acetyl-3-methyl-1,2-benzisothiazole has no available para-position and so one would expect no reaction or possibly ortho-rearrangement. However, 5-hydroxy-3-methyl-1,2-benzisothiazole (50%), unchanged starting material (XCV) (44%) and acetophenone were isolated. Hence the acetyl group

(formed during an intermolecular mechanism) must attack the more reactive benzene solvent in preference to the unreactive benzisothiazole system. An additional cause of the failure to undergo the Fries rearrangement could be steric blocking of the 4-position by the 3-methyl group. Chapman and his co-workers[127] found that the Fries rearrangement of 5-acetoxy-3-methylbenzo[b]thiophen gave essentially the 2-acetyl derivative, whereas 5-acetoxybenzo[b]thiophen[128] gave the expected 4-acetyl derivative. Consequently the failure of 5-acetoxy-3-methyl-1,2-benzisothiazole to undergo rearrangement is probably due to a combination of the decreased reactivity of benzisothiazoles with possible peri-interaction between the 3-methyl group and the 4-position. The Fries rearrangement of 5-acetoxy-1,2-benzisothiazole would be of considerable interest in determining the relative importance of the two effects.

Attempted Formylation and von Pechmann Reaction

The Adam's modification[129] of the Gattermann reaction, using zinc cyanide and hydrogen chloride, failed to give the required aldehyde. A solid precipitated from the reaction mixture and was identified (n.m.r. and i.r. spectra) as the hydrochloride salt of 5-hydroxy-3-methyl-1,2-benzisothiazole.

Similarly, the von Pechmann reaction[130] precipitated the hydrochloride salt after ca. 15 min.

Attempted Friedel-Crafts Acylation

Although the acylation of 5-bromo-3-methyl-1,2-benzisothiazole (p. 49) was unsuccessful, it was hoped that a more reactive substrate might undergo the Friedel-Crafts reaction.

The acylation of 5-hydroxy-3-methyl-1,2-benzisothiazole, using acetyl chloride and aluminium chloride in dry nitrobenzene, gave a solid which contained two components. Chromatography gave the 5-acetyl-3-methyl derivative (XCV) (10%) and unchanged starting material (47%). It seemed possible that the size of the

solvated aluminium chloride-acetyl chloride complex had prevented the expected

acylation at the 4-position and so the reaction was repeated using acetyl

chloride in dichloromethane with boron trifluoride as Lewis acid. A similar

mixture was obtained containing 64% and 30% respectively of the 5-acetoxy

derivative (XCV) and starting material.

The acylation of 3,5-dimethylbenzo[b]thiophen, using either aluminium

chloride or boron trifluoride as catalyst, gives the 2-acetyl derivative.[131]

Again, it is possible that peri-interaction between the 4-position and 3-methyl

group[118] prevents the formation of the 4-acetyl derivative and such factors

could explain the failure to acylate 5-substituted 3-methyl-1,2-benzisothiazoles.

However, Davis and White[99] have found that 2,1-benzisothiazole does not undergo

the Friedel-Crafts acylation and it would appear that the main cause of failure

is the fundamental unreactivity of the benzisothiazole nucleus.

Scheme 13

(XCIII)

CH₂=CH.CH₂O

$CH_2=CH.CH_2O$

$BrCH_2CH=CH_2/K_2CO_3/butanone$

1. $AcCl/AlCl_3/nitrobenzene$

2. $AcCl/BF_3/CH_2Cl_2$

$AcOH/Ac_2O$

AcO

(XCV)

Me

$Br_2/EtOAc/0°$

Br

HO

(XC)

Me

HO

Me

(LXXXIX)

$HNO_3/AcOH$

O_2N

HO

(XCI)

Me

$CH_3COCH_2CO_2Et/HCl/MeOH$

$ZnCN/HCl/Et_2O$

$MeSO_2Cl/pyridine/0°$

MeO_2SO

Me

(XCII)

Me

N.HCl

HO
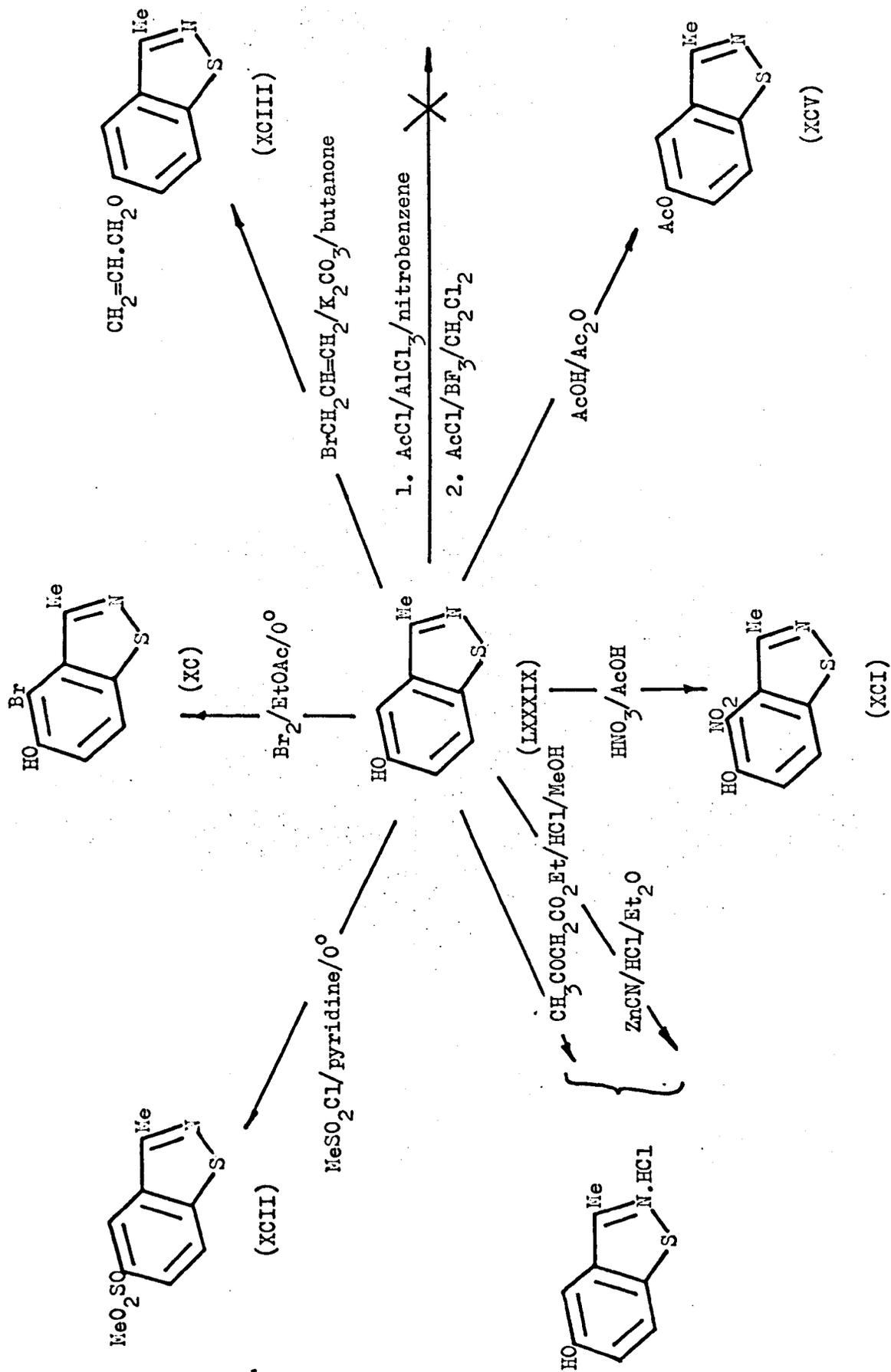
Scheme 13 (continued)
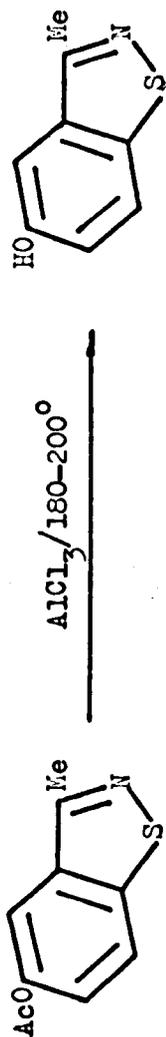
AlCl$_3$/180-200°
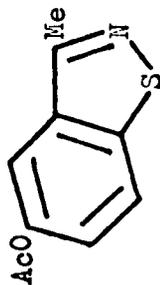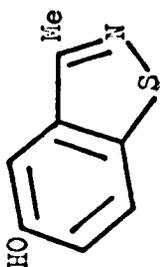
AlCl$_3$/benzene/80°
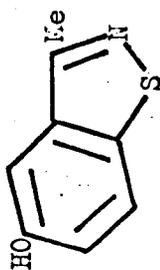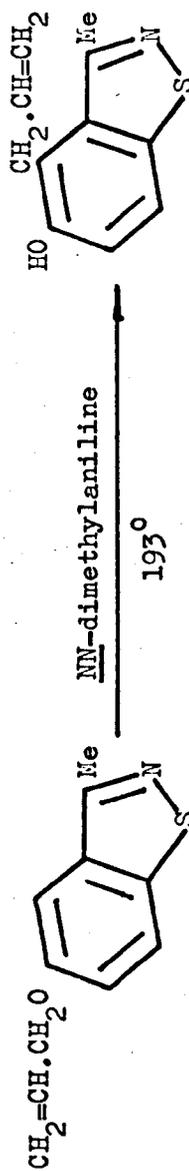
$\underline{\text{NN}}$-dimethylaniline
193°
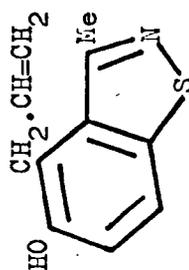
(XCV)

(LXXXIX)

(XCV)

(LXXXIX)

(XCIII)

(XCIV)

(XCV)

COMe

CH$_2$=CH.CH$_2$O

CH$_2$.CH=CH$_2$

Some Electrophilic Substitution Reactions of 5-Methoxy-3-methyl-1,2-benzisothiazole

In order to determine whether methylation of 5-hydroxy-3-methyl-1,2-benzisothiazole would modify the substitution pattern previously observed, the electrophilic substitution reactions of 5-methoxy-3-methyl-1,2-benzisothiazole were investigated. The reactivity of the methyl ether (XCVI) would be expected to be intermediate between that of 5-bromo and 5-hydroxy-3-methyl-1,2-benzisothiazole. Hence substitution should occur using milder conditions than used for the 5-bromo system.

5-Methoxy-3-methyl-1,2-benzisothiazole was obtained in 90% yield by treating 5-hydroxy-3-methyl-1,2-benzisothiazole in ethanolic potassium hydroxide with methyl iodide.

Bromination

Treatment of the ether (XCVI) with bromine in carbon tetrachloride gave a solid which contained two components. Chromatography gave starting material (50%) and 4-bromo-5-methoxy-3-methyl-1,2-benzisothiazole (XCVII) in 40% yield.

Bromination under forcing conditions, using bromine and silver sulphate in concentrated sulphuric acid at 0-5°, gave the 4-bromo derivative (XCVII) in good yield (87%). Its n.m.r. spectrum showed the aromatic protons as the expected AB quartet ($J_{6,7}$ = 8.7 Hz), with the 6-proton signal at high field due to the shielding by the adjacent methoxy group. The methyl signal occurred at δ p.p.m. 2.97, downfield by ca. 0.35 p.p.m. from the methyl signal usually found for 3-methyl-1,2-benzisothiazoles. This downfield shift is due to steric crowding of the 4-position by the 3-methyl group. As a bromo group is spherically symmetrical it cannot relieve the steric interaction and so the methyl protons come under the deshielding influence of the bromo group. Hence, the methyl signal is shifted downfield and such an effect will occur for any substituted 3-methyl-1,2-benzisothiazole with a bulky deshielding group in the 4-position

(e.g. bromo or chloro group).

N-Bromosuccinimide in refluxing carbon tetrachloride in the presence of a small amount of dibenzoyl peroxide brominated the ether (XCVI) to give a mixture containing three components in the ratio 70:15:15 (by t.l.c.). Chromatography gave 3-bromomethyl (XCVIII) (major component) and 3-dibromomethyl-5-methoxy-1,2-benzisothiazole (XCIX), as well as unchanged starting material. These conditions usually favour nuclear bromination.

Using the conditions[120] employed earlier for side-chain bromination [carefully purified N-bromosuccinimide, pumped out [132] prior to use, in redistilled carbon tetrachloride containing dibenzoyl peroxide and irradiating the reaction (200W tungsten lamp)] gave a similar mixture of the 3-bromomethyl derivative (XCVIII) and 3-dibromomethyl derivative (XCIX). The mixture was resolved by chromatography to give the components in 28% and 24% yield respectively. Isolation of the 3-bromomethyl component from the mixture by crystallisation from light petroleum , using the technique employed in previous bromination reactions, proved impossible.

Nitration

5-Methoxy-3-methyl-1,2-benzisothiazole was readily nitrated under forcing conditions, with potassium nitrate in concentrated sulphuric acid, and gave 5-methoxy-3-methyl-4-nitro-1,2-benzisothiazole in 93% yield. Its n.m.r. spectrum showed the usual AB quartet for the 6- and 7-protons ($J_{6,7}$ = 8.8 Hz), with the 6-proton signal at high field. The methyl signal appeared at $\delta_{p.p.m.}$ 2.56, which is an average shift value for a 3-methyl group in the 1,2-benzisothiazole series. The downfield shift of the methyl signal observed with the 4-bromo compound (XCVII), does not occur in the spectrum of the 4-nitro compound because the 4-nitro group can twist out of the plane of the ring and so decrease the steric crowding experienced at the 4-position due to the 3-methyl group. Thus the methyl protons do not fall within the space where the deshielding effect of the

nitro group is effective and the chemical shift of the methyl protons is not appreciably changed.

Formylation

The Vilsmeier–Haack formylation of 5-methoxy-3-methyl-1,2-benzisothiazole, using phosphoryl chloride and dimethylformamide for 4 h at room temperature, gave a mixture which contained two components in the ratio 1:1 (t.l.c.). Resolution of the mixture , by column chromatography, gave 3-formylamido-5-methoxybenzo[b]thiophen (C) (R_f 0.26) and N^2-(2-formyl-5-methoxy-3-benzo[b]thienyl)-N^1N^1-dimethylformamidine (CI) (R_f 0.45). The products compared (n.m.r. and i.r. spectra) with those from previous formylations and were as expected.

Attempted Friedel–Crafts Acylation

Treatment with acetyl chloride and anhydrous aluminium chloride in dry dichloromethane, for 22 h at room temperature and for 48 h at 40°, failed to give any product except unchanged starting material (99%).

The foregoing reactions are summarised in Scheme 14 (pp. 67, 68).

Preparation of (5-Methoxy-1,2-benzisothiazol-3-yl)acetonitrile and the acetic acid derivative

3-Bromomethyl-5-methoxy-1,2-benzisothiazole (XCVIII) was reacted with sodium cyanide in dry dimethylsulphoxide to give the required nitrile (CII) in 55% yield.

Hydrolysis[89] of the foregoing product, in hydrochloric acid at ca. 45°, gave (5-methoxy-1,2-benzisothiazol-3-yl)acetic acid (CIII) in good yield (85%). Unfortunately, lack of time prevented the preparation of further derivatives of the acid.

The above reactions are included in Scheme 14 (p. 67).
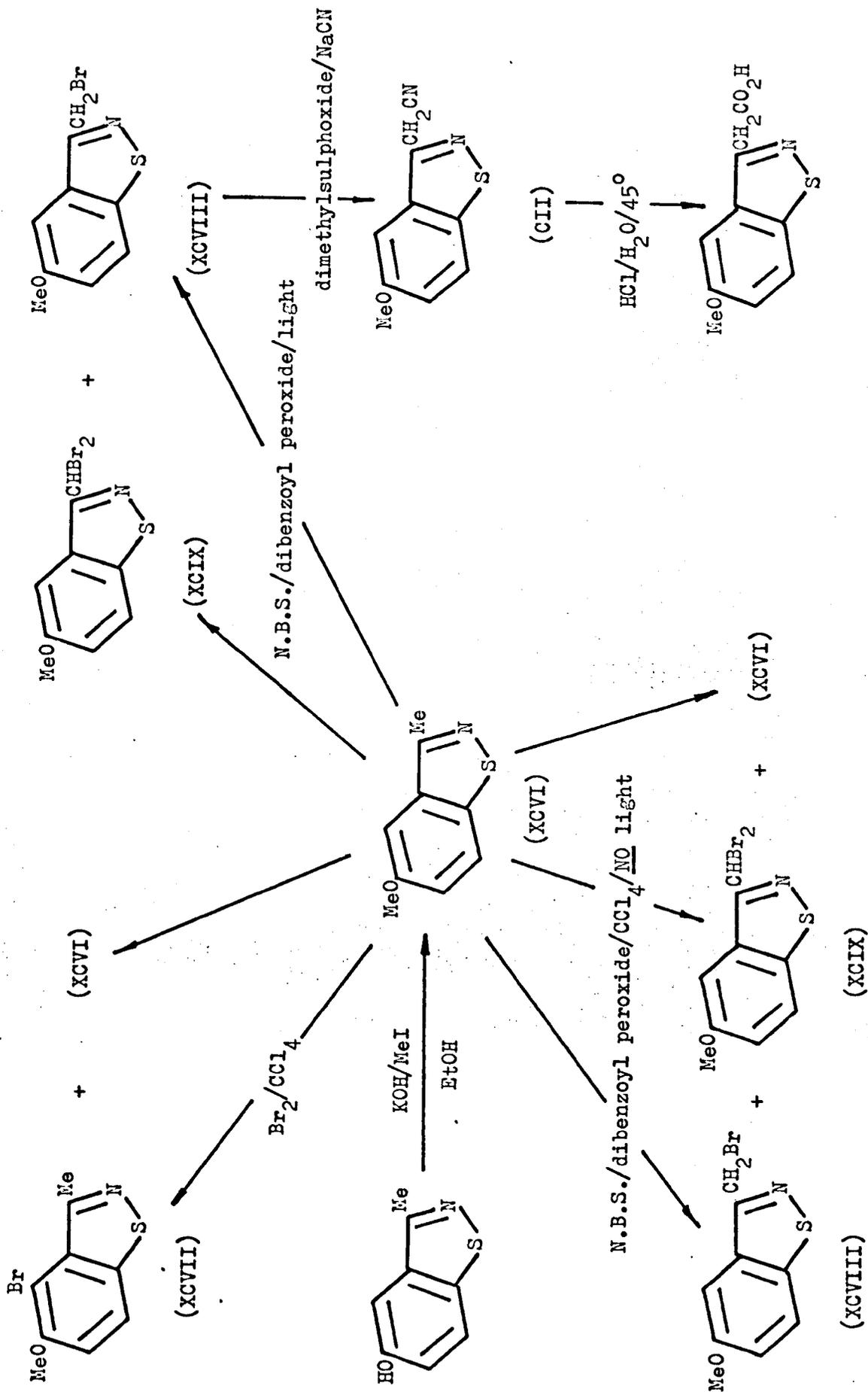
Scheme 14

Scheme 14 (continued)

(XCVII)

Br$_2$/Ag$_2$SO$_4$/H$_2$SO$_4$/0°

AcCl/AlCl$_3$/CH$_2$Cl$_2$

POCl$_3$/dimethylformamide/4 h/room temperature

KNO$_3$/H$_2$SO$_4$/0-5°

(XCVI)

(CI)

(c)
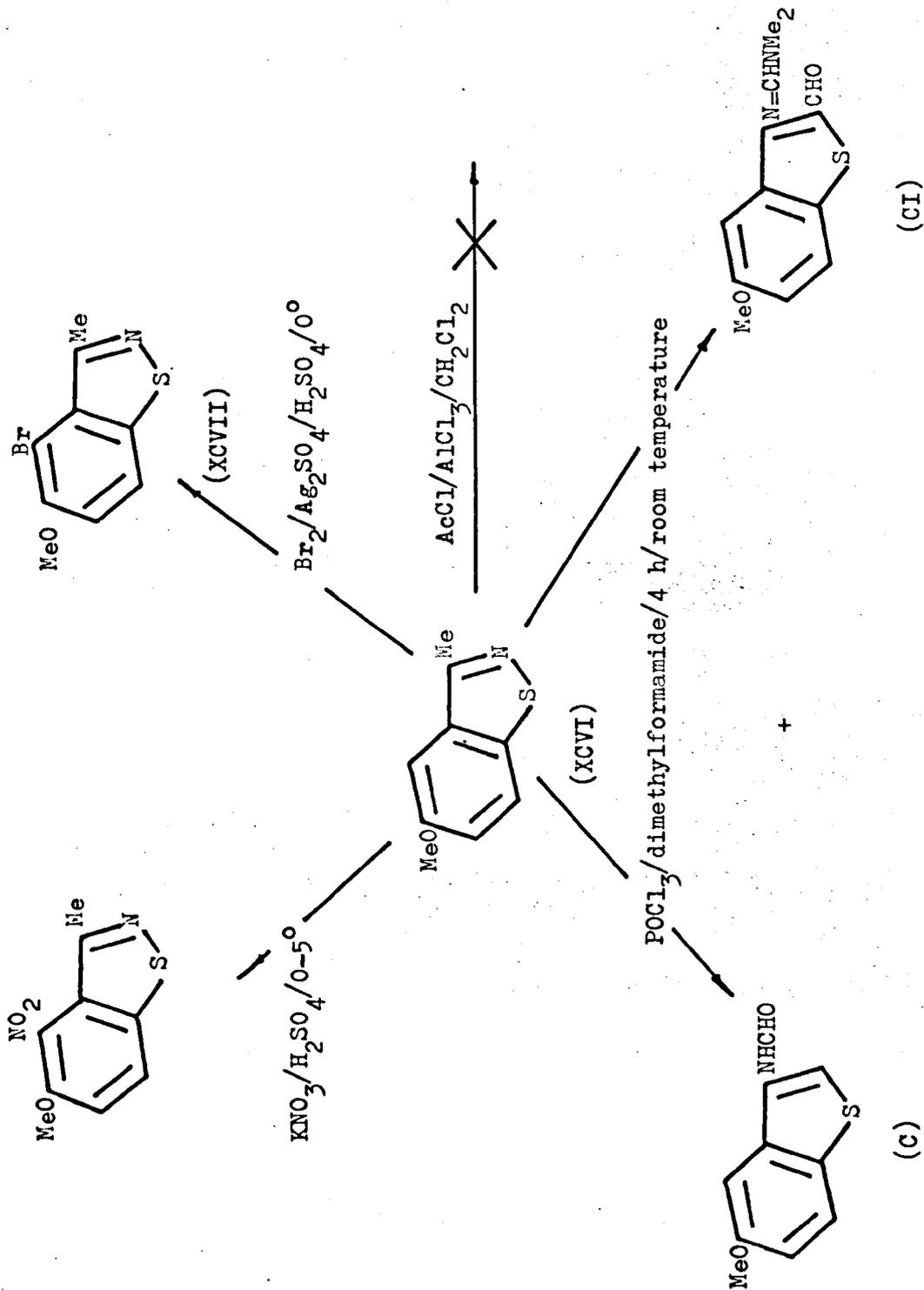
Some Electrophilic Substitution Reactions of 4-Bromo-3-methyl-1,2-benzisothiazole

4-Substituted 3-methyl-1,2-benzisothiazoles have not previously been reported and hence their preparation and properties are of some interest. Scheme 15 (p. 73) summarises some elecrophilic substitution reactions of 4-bromo-3-methyl-1,2-benzisothiazole. From theoretical considerations, substitution would be expected at both the 5- and 7-positions and would require forcing conditions due to the deactivating effect of the 4-bromo group.

4-Bromo-3-methyl-1,2-benzisothiazole (CIV) was prepared in 95% yield by the deamination of 5-amino-4-bromo-3-methyl-1,2-benzisothiazole (LXIII), using hypophosphorous acid. Its n.m.r. spectrum showed the 6-proton as a triplet ($J_{5,6} = J_{6,7} = 7.75$ Hz) and the 5- and 7-protons as a doublet of doublets ($J_{5,7} = 1$ Hz). The signal due to the methyl group was shifted downfield by ca. 0.3 p.p.m., compared with its usual position for 3-methyl-1,2-benzisothiazole derivatives, because of steric interactions, discussed previously (p. 63), between the 4-bromo substituent and the 3-methyl group. The preparative sequence is outlined in Scheme 9 (p. 44).

Bromination

Treatment with bromine and silver sulphate in concentrated sulphuric acid at 0-5° gave 4,7-dibromo-3-methyl-1,2-benzisothiazole (XLV) in 96% yield. There was no evidence (t.l.c. and n.m.r.) for the formation of any of the expected 4,5-dibromo isomer (LXXI), probably prevented due to steric factors. The 4,7-dibromo product (XLV) was identical with a minor component obtained from the bromination of 3-methyl-1,2-benzisothiazole (p. 29).

Nitration

When 4-bromo-3-methyl-1,2-benzisothiazole was treated with potassium nitrate in concentrated sulphuric acid at 0-5°, a mixture containing the 5-nitro (CV) (41%)

and 7-nitro derivative (CVI) (42%) was obtained. These isomers were separated

with difficulty by column chromatography ($\underline{R}_f$ values 0.38 and 0.45 respectively).

Their n.m.r. spectra were similar and identification was achieved by reduction

(tin and hydrochloric acid) of one of the isomers. The resulting amino compound

(15%) was identified as 7-amino-4-bromo-3-methyl-1,2-benzisothiazole (CVII) as

its spectra (n.m.r. and i.r.) and m.p. were quite different from those of the

known 5-amino-4-bromo compound (LXIII).

Formylation

The Vilsmeier-Haack formylation, with phosphoryl chloride in dimethylform-

amide at 90-100°, gave a mixture of the 2-formyl-formamidine compound (CVIII)

and 4-bromo-3-formylamidobenzo[$\underline{b}$]thiophen (CIX) in the ratio 29:66 (g.l.c.)

respectively. The mixture could not be separated by chromatography but

trituration with light petroleum extracted the minor component (CVIII) (18%).

Formylation at room temperature gave a mixture (1:1 by t.l.c.) which

chromatographed to yield the formylamido compound (CIX) (36%) and unchanged

starting material (50%).

The rearranged products were similar to those already obtained during

formylations of other 3-methyl-1,2-benzisothiazoles. It can be seen from Table 1

that only with 4-bromo-3-methyl-1,2-benzisothiazole is formylation, at room

temperature, limited to the formylamido compound (or its precursor).

1,2-Benzisothiazole substrate	Reaction Time (h)	% Formylamido Derivative[1.] in reaction mixture	% 2-Formyl Derivative in reaction mixture	
3-Me	ca. 20	60[2.]	40[2.]	(g.l.c.)
5-OMe, 3-Me	4	50	50	(t.l.c.)
5-Br, 3-Me	18	50	50	(t.l.c.)
4-Br, 3-Me	22	50	—	(t.l.c.)

1. For 3-Me substrate, corresponding formamidine compound isolated.
2. Ref. 84.

Table 1

From the length of time required to complete the reaction it would appear that an electron donating substituent enhances the initial isomerism to the corresponding 3-aminobenzo[b]thiophen (see p. 48) and a possible mechanism is shown in Scheme 16. The deactivating effect of a 5-bromo substituent may well be balanced by its increased stabilisation of the reaction intermediate (CX) and hence 3-methyl-1,2-benzisothiazole and its 5-bromo derivative appear equally reactive. When the bromo group is in the 4-position, no such mesomeric stabilisation of the intermediate (CXI) can occur and so the deactivating effect of the bromo substituent will be unchecked and the reaction will not proceed as readily.
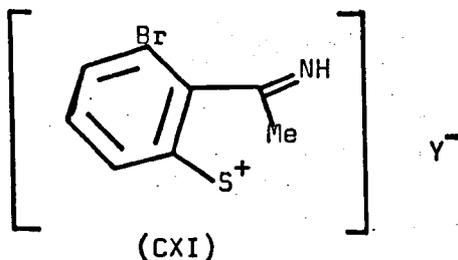
(CXI)

Attempted Friedel-Crafts Acylation

Treatment with acetyl chloride and anhydrous aluminium chloride in dry nitrobenzene at ca. 100° gave only unchanged starting material.

Scheme 16
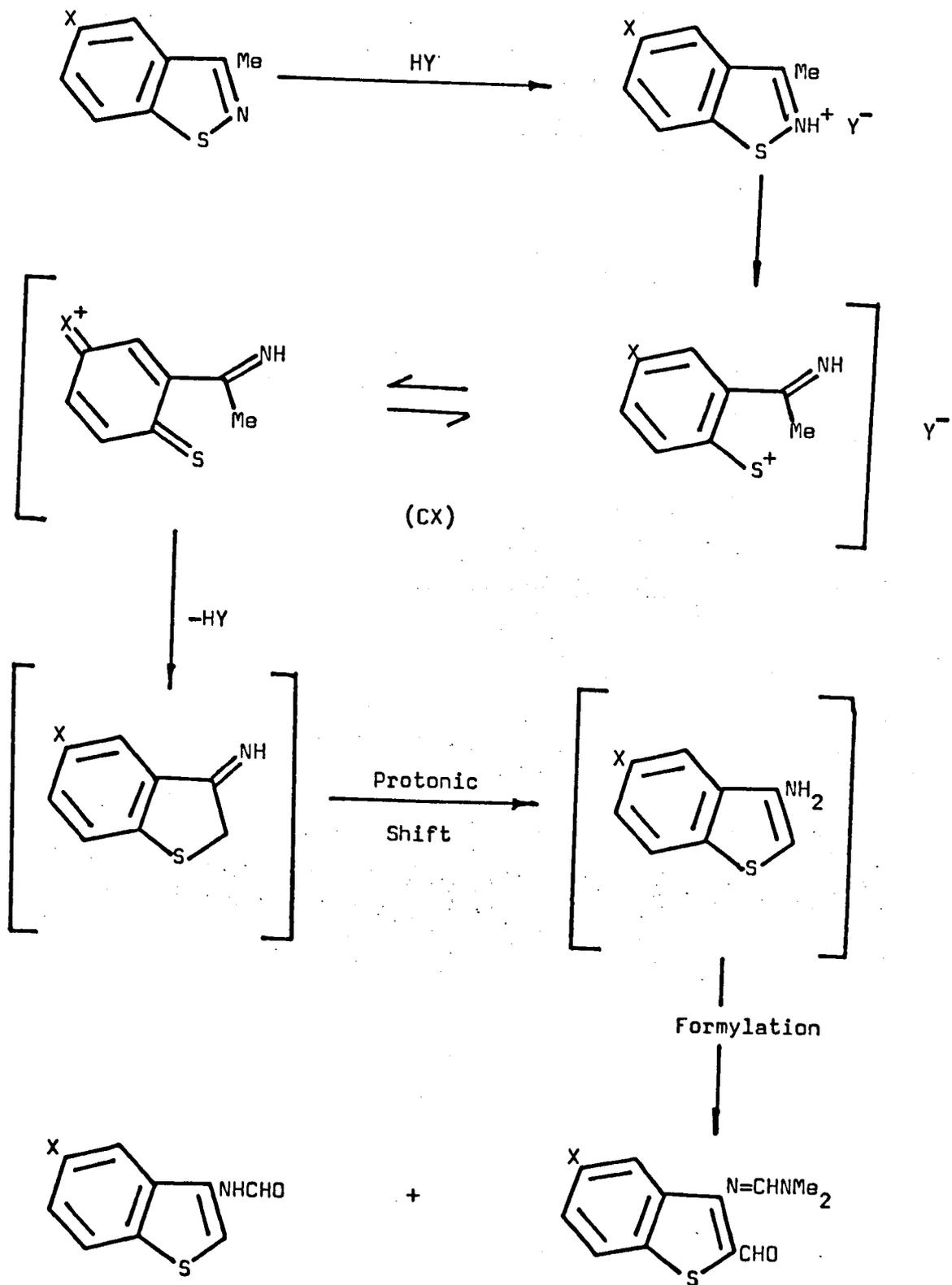
X = MeO, Br.

Y = Suitable anion.

Scheme 15

Me
Br
NO$_2$
(CVI)

Sn/HCl

Me
Br
NH$_2$
(CVII)

KNO$_3$/H$_2$SO$_4$/0-5°

+

Me
Br
O$_2$N
(CV)

Br$_2$/Ag$_2$SO$_4$/H$_2$SO$_4$/0-5°

Me
Br
Br
(XLIV)

AcCl/AlCl$_3$/nitrobenzene
90-100°/8 h

Me
Br
S
N
(CIV)

POCl$_3$/dimethylformamide/room temperature/22 h

(CIV)

+

NHCHO
Br
S
(CIX)

1 : 1 (t.l.c.)

POCl$_3$/dimethylformamide/90-100°/3 h

N=CHNMe$_2$
CHO
Br
S
(CVIII)

+

NHCHO
Br
S
(CIX)
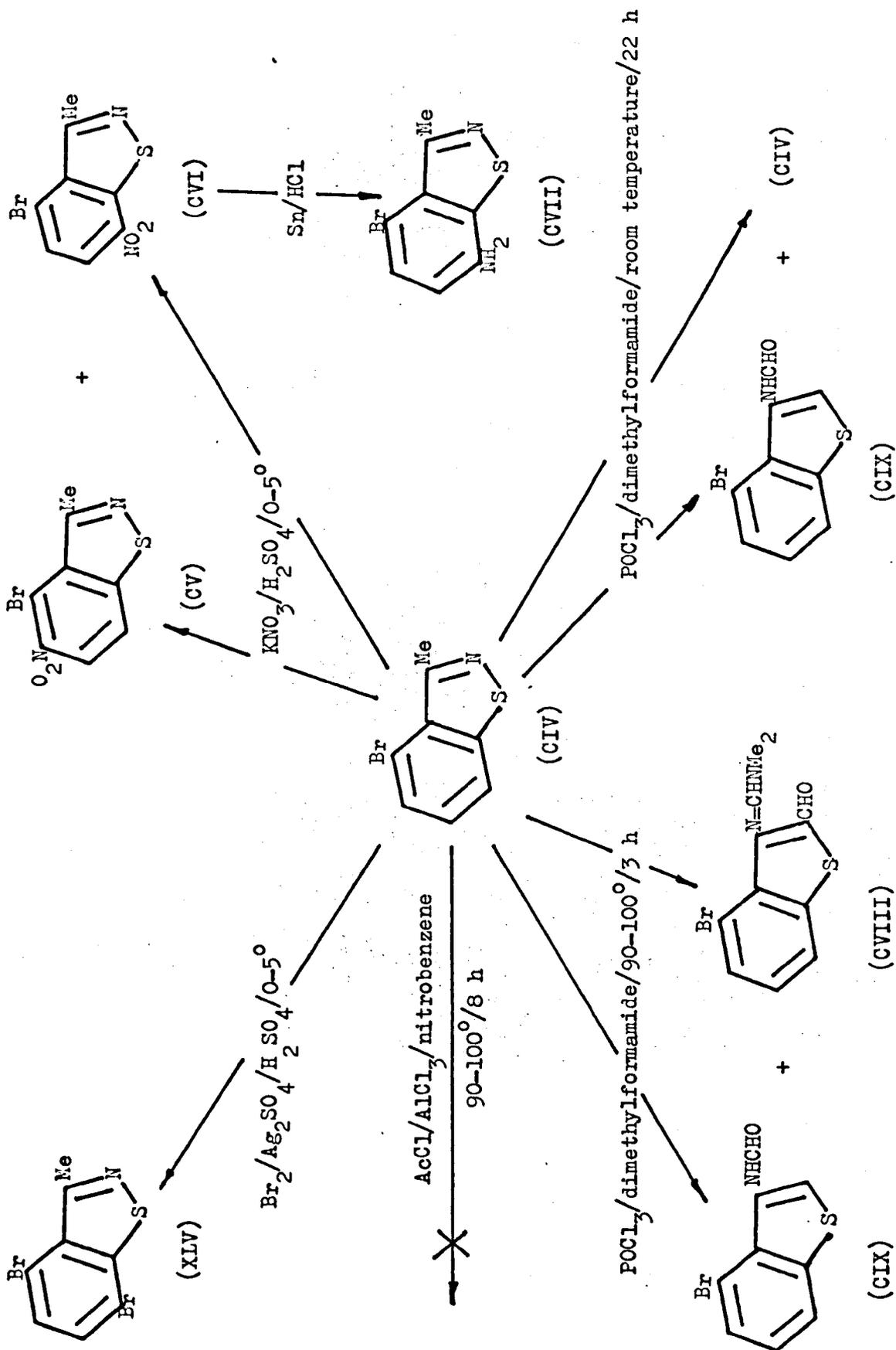
66 : 29 (g.l.c.)

The Preparation of 4-Chloro-3-methyl-1,2-benzisothiazole

The chlorination of 5-amino-3-methyl-1,2-benzisothiazole, with a solution of chlorine in dry carbon tetrachloride, gave a low yield (27%) of 5-amino-4-chloro-3-methyl-1,2-benzisothiazole which was separated from unchanged starting material (50%) by chromatography.

N-Chlorosuccinimide in boiling dry chloroform containing a catalytic amount of dibenzoyl peroxide gave 5-amino-4-chloro-3-methyl-1,2-benzisothiazole in 81% yield. Its n.m.r. spectrum showed, <u>inter alia</u>, an AB quartet for the 6- and 7-protons ($J_{6,7}$ = 8.5 Hz), with the 6-proton at high field due to shielding by the adjacent amino group.

Deamination of the foregoing product, by treatment of the diazonium sulphate with hypophosphorous acid, gave 4-chloro-3-methyl-1,2-benzisothiazole (CXII) in 76% yield. Its n.m.r. spectrum when observed in deuteriochloroform was second order because the difference in the chemical shifts of the coupled protons was equal or less than their coupling constants. As before (p. 46), a first order spectrum resulted when the spectrum was observed in hexadeuteriobenzene.

The reaction sequence is summarised in Scheme 9 (p. 44).

The Preparation of 3-Methyl-4-nitro-1,2-benzisothiazole

Hydrolysis of 5-acetamido-3-methyl-4-nitro-1,2-benzisothiazole (LXVII) with 35% sulphuric acid gave 5-amino-3-methyl-4-nitro-1,2-benzisothiazole in 95% yield. Diazotisation of the foregoing amine, in sulphuric acid with aqueous sodium nitrite at 0-8°, followed by deamination of the diazonium sulphate, in aqueous hypophosphorous acid, gave a semi-solid which contained two components. Chromatography gave 4-chloro-3-methyl-1,2-benzisothiazole (55%) which was identical with an authentic sample. The minor component (R_f 0.51) was isolated in a trace amount (< 10 mg) but n.m.r., i.r., and mass spectra confirmed it as being 3-methyl-4-nitro-1,2-benzisothiazole.

5-Amino-3-methyl-4-nitro-1,2-benzisothiazole contained no impurity (n.m.r. and t.l.c.) and so all reagents were tested for halogen. These tests showed that the aqueous hypophosphorous acid was contaminated with chloride ions. It seems probable that the 4-position is activated towards nucleophiles by the adjacent positively charged diazonium group and by the isothiazole ring. In addition the 4-nitro group is twisted (vide infra) out of the plane of the ring and its conjugation with the ring is consequently diminished. Under these circumstances the 4-nitro group is readily displaced by chloride ions and then deamination leads to the isolation of 4-chloro-3-methyl-1,2-benzisothiazole.

Diazotisation[133] of the amine in glacial acetic acid by a solution of sodium nitrite in concentrated sulphuric acid and deamination of the diazonium salt with ethanol and copper (1) oxide gave only 3-methyl-4-nitro-1,2-benzisoth iazole (CXIII) in 35% yield. The foregoing preparation is summarised in Scheme 9 (p. 44).

From a comparison of the n.m.r. spectra of 3-methyl-4-nitro-1,2-benzisoth iazole and other substituted 3-methyl-1,2-benzisothiazoles the existance of steric interactions between the 3-methyl group and the 4-position can be positively determined.

The n.m.r. spectrum of 3-methyl-4-nitro-1,2-benzisothiazole showed a triplet for the 6-proton signal at high field ($J_{5,6} = J_{6,7} = 7.75$ Hz) and the 5- and 7-protons were observed as doublet of doublets ($J_{5,7} = 1.25$ Hz). If one assumes that the substituent chemical shifts in benzo[b]thiophen are the same as those in 1,2-benzisothiazole, good correlation between the predicted and observed chemical shifts of the aromatic protons for a number of 1,2-benzisothiazole derivatives can be obtained. Using the substituent chemical shifts for the nitro group (determined for the isosteric benzo[b]thiophen[134]), the chemical shifts for the 6- and 4-proton signals of 3-methyl-7-nitro-1,2-benzisothiazole were accurately predicted.

Proton	Chemical Shift for 3-Methyl-7-nitro-1,2-benzisothiazole	
	Observed (p.p.m.)	Predicted (p.p.m.)
4	8.28	8.28
6	8.48	8.45

However, when used to predict the chemical shifts for the 5- and 7-protons in 3-methyl-4-nitro-1,2-benzisothiazole, the observed 5-proton signal was 0.68 p.p.m. upfield from its predicted position; whilst the 7-proton signal was only 0.16 p.p.m. upfield.

Proton	Chemical Shift for 3-Methyl-4-nitro-1,2-benzisothiazole	
	Observed (p.p.m.)	Predicted (p.p.m.)
5	7.77	8.45
7	8.12	8.28

Deshielding, caused mainly by electron withdrawal through overlapping p-orbitals, is greater at the ortho-position than at the para-position. The signals due to the 5- and 7-protons are therefore expected to move downfield from the positions observed with the parent system and the predicted results are shown in the table. However the observed results do not show the expected movement due

to the deshielding influence of the 4-nitro group and hence the nitro group must be twisted out of the plane of the ring thus decreasing the overlap of its p-orbitals with the π-system of the ring. This twisting takes place as a result of steric interactions between the 4-nitro group and the 3-methyl substituent.

An Alternative Preparation of (5-Chloro-1,2-benzisothiazol-3-yl)acetonitrile

As the overall yield of (5-bromo and 5-chloro-1,2-benzisothiazol-3-yl)acet○
onitrile from the 5-halogeno-3-methyl-1,2-benzisothiazole, by side-chain
bromination followed by reaction with sodium cyanide in dimethylsulphoxide, was
relatively low (p. 56) an alternative preparation was investigated.

It was hoped that a substituted 3-chloro-1,2-benzisothiazole would react
with ethyl cyano(sodio)acetate by the method of Carrington[86] (outlined on p. 20)
to give, after hydrolysis, the corresponding acetonitrile derivatives. 3-Chloro-
5-nitro-1,2-benzisothiazole was chosen for the experiment because it was
relatively easy to prepare and because we hoped to replace the nitro group in the
resulting (5-nitro-1,2-benzisothiazol-3-yl)acetonitrile by other substituents.

Bis-(o-carboxy-p-nitrophenyl) disulphide (CXIV)[135] was obtained in 75%
yield by treatment of the potassium salt of 2-chloro-5-nitrobenzoic acid with
a solution of sodium disulphide, followed by acidification. Reaction of the
foregoing product with phosphorus pentachloride in dry toluene[135] gave the
acid chloride (CXV) (76%), which was boiled with bromine in dry tetrachloroethane
then poured into cold aqueous ammonia to give 5-nitro-1,2-benzisothiazol-3(2H)-
one (CXVI)[135] in 78% yield. Reaction of the foregoing product with phosphorus
pentachloride in dry pyridine at 170-180° gave 3-chloro-5-nitro-1,2-benzisothiazole
(CXVII) (90%).[136] The foregoing reactions are summarised in Scheme 17.

Ethyl (5-nitro-1,2-benzisothiazol-3-yl)cyanoacetate (CXVIII) (78%) was
obtained after stirring 3-chloro-5-nitro-1,2-benzisothiazole with ethyl cyanoacet-
ate in the presence of sodium ethoxide for 9 days. Hydrolysis of the ~~foregoing~~
ester (CXVIII) in aqueous dimethylsulphoxide[84] gave the nitrile (CXIX) in 88%
yield. Reduction of the nitrile (CXIX) with aluminium amalgam gave a brown gum
from which (5-amino-1,2-benzisothiazol-3-yl)acetonitrile was isolated as its
hydrochloride (CXX) (56%). Using iron filings in aqueous acetic acid improved
the yield of amine hydrochloride (CXX) (75%). The reduction was complete after

Scheme 17
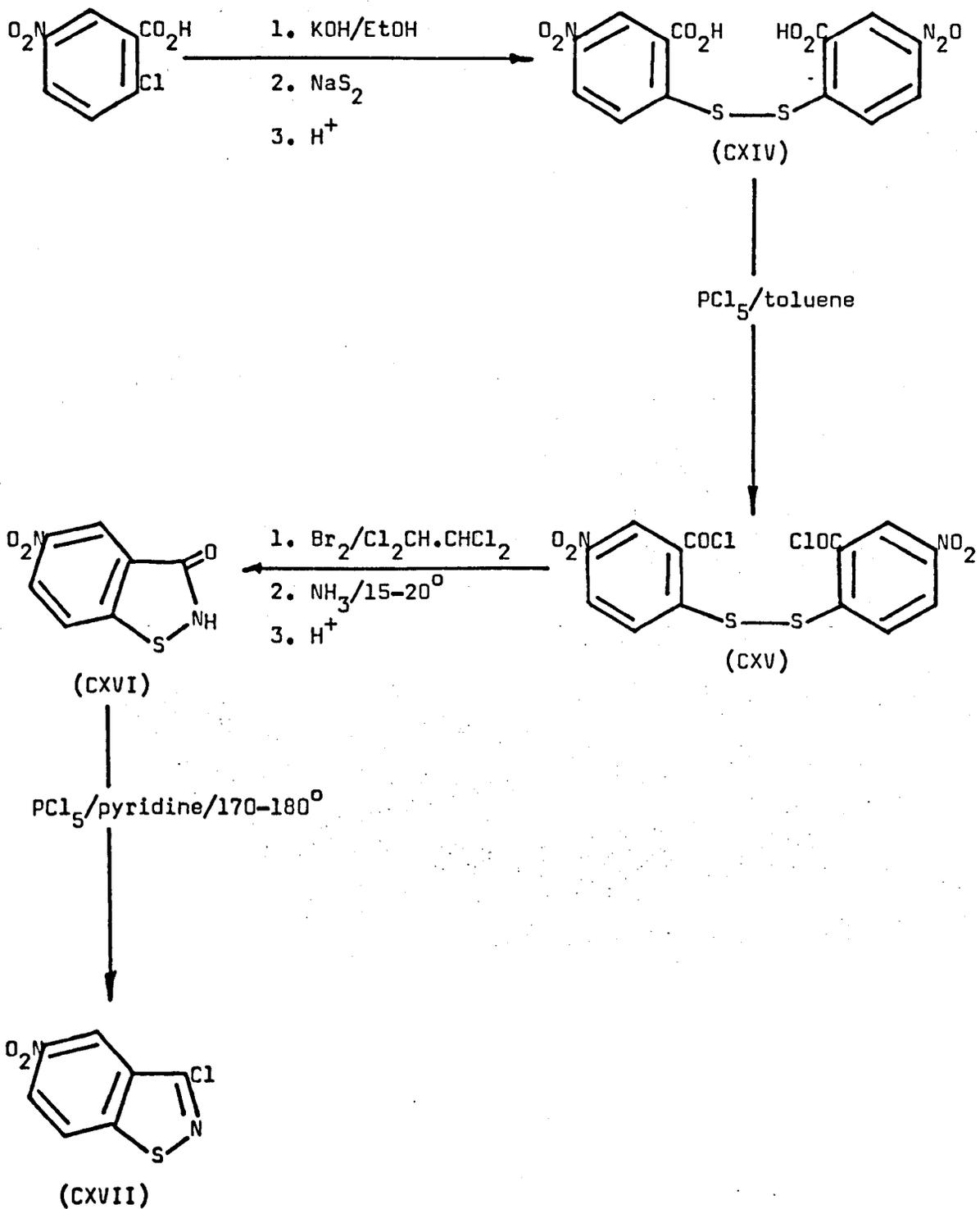
Scheme 18
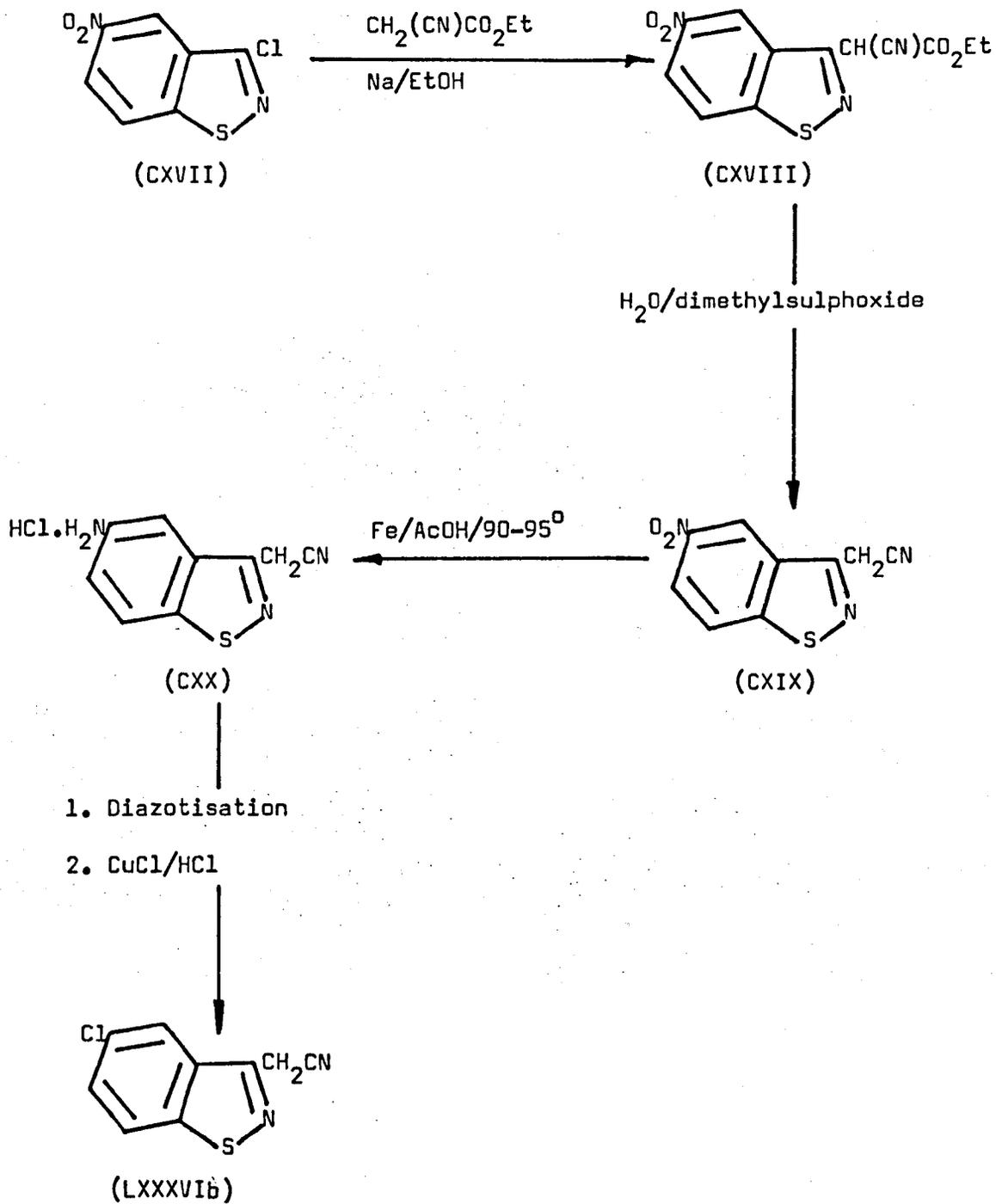
only 10 min at <u>ca.</u> 90° and longer reaction times only increased the proportion of (5-acetamido-1,2-benzisothiazol-3-yl)acetonitrile also formed. The usual Sandmeyer replacement of the amino group gave (5-chloro-1,2-benzisothiazol-3-yl)acetonitrile (LXXXVIb) in good yield (81%).

The overall yield of 26% by the eight stage synthesis, outlined in Schemes 17 and 18, is a considerable improvement on ~~compares favourably with~~ the yield of 5% obtained by the route starting from acetophenone (p. 56) which also has eight stages. Application of a similar sequence of reactions to any ~~benzene substituted~~ 3-chloro-1,2-benzisoth⊃ iazole with a substituent in the phenyl ring should provide a useful synthetic route to the corresponding 3-acetonitrile derivative and hence related compounds.

Attempted Preparation of (5-Bromo-1,2-benzisothiazol-3-yl)acetonitrile

The preparation of (5-bromo-1,2-benzisothiazol-3-yl)acetonitrile (LXXXVIa) in a manner similar to that used for the 5-chloro nitrile (LXXXVIb) was not straightforward. Decomposition of the diazonium sulphate in the presence of copper (1) bromide and hydrobromic acid gave a solid, which contained three components. Chromatography gave the required 5-bromo nitrile (LXXXVIa) (21%) and (5-bromo-1,2-benzisothiazol-3-yl)bromoacetonitrile (CXXI; X=H) (45%), which was identified from its i.r., n.m.r. and mass spectra. The third component (6%) showed only three aromatic protons in its n.m.r. spectrum and a weak CN absorption in its i.r. spectrum. Lack of time has prevented further characterisation, but the product is probably (5-bromo-1,2-benzisothiazol-3-yl)dibromoacetonitrile (CXXI; X=Br).
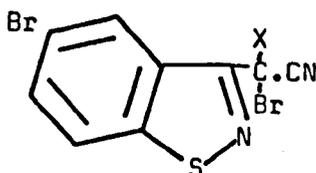
(CXXI)

The side-products were probably formed by bromination of (5-bromo-1,2-benzisothiazol-3-yl)acetonitrile initially formed due to its active methylene protons (see also pp. 55 and 56) and the presence of copper (11) bromide, a brominating agent (p. 36). Consequently the required 5-bromo nitrile (LXXXVIa) would probably be successfully prepared starting from 5-bromo-3-chloro-1,2-benzisothiazole.

Some Attempted Thiocyanations on m-Hydroxyacetophenone and related compounds

It was hoped to prepare 5-hydroxy-3-methyl-1,2-benzisothiazole by a method similar to that used previously for the preparation of 5-amino-3-methyl-1,2-benzisothiazole (Scheme 7, p. 38).

Although the thiocyanation of amines occurs readily and has received much attention, phenols have been less comprehensively studied and yields are usually lower.[137] Phenols usually undergo thiocyanation in the para-position, unless it is blocked when ortho-substitution occurs. Generally, higher yields are obtained when the thiocyanation of phenols is carried out in glacial acetic acid rather than in neutral solvents, such as methanol.[138]

Treatment of m-hydroxyacetophenone in dry methanol at ca. -5° with thiocyan-ogen, generated in situ by the action of bromine on anhydrous sodium thiocyanate, failed to give any thiocyanated product. This procedure had previously been used successfully for m-aminoacetophenone (p. 37).

Kaufmann and Küchler[139] found that freshly prepared copper (11) thiocyanate could be used to thiocyanate amines and phenols at higher temperatures (ca. 35-80°). Copper (11) thiocyanate releases thiocyanogen by the dissociation of the black copper (11) to the white copper (1) salt.

$$2Cu(SCN)_2 \longrightarrow 2CuSCN + (SCN)_2$$
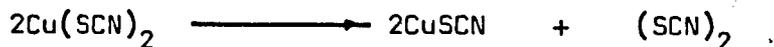
Thiocyanation of m-hydroxyacetophenone by copper (11) thiocyanate[139,140] did not give the required 5-hydroxy-2-thiocyanatoacetophenone but a product which was identified (n.m.r.) as 3-hydroxy-ω-thiocyanatoacetophenone (CXXII) (31%).

Aryl ethers, which are unreactive towards thiocyanogen, react with thiocyanogen chloride in acetic acid to give para-substituted thiocyanato derivat-ives in high yield.[141,142] Treatment of either m-hydroxyacetophenone or m-methoxyacetophenone with thiocyanogen chloride[142] in glacial acetic acid gave complex mixtures from which a major component could not be isolated. In an

attempt to minimise any thiocyanation of the methyl ketone side-chain, m-hydroxy and m-methoxyacetophenone were reduced with sodium borohydride[143] to 1-(3-hydroxyphenyl)ethanol (CXXIII) and 1-(3-methoxyphenyl)ethanol (CXXIV) respectively. Reaction of 1-(3-hydroxyphenyl)ethanol (CXXIII) failed to give a major component but 1-(3-methoxyphenyl)ethanol gave 1-(5-methoxy-2-thiocyanatophenyl)ethyl acetate (CXXV) in 62% yield. The ethyl acetate derivative was identified by its very characteristic n.m.r. spectrum and strong SCN and ester bands in the i.r. spectrum. Thiocyanogen chloride in chloroform with 1-(3-methoxyphenyl)ethanol (CXXIV) gave a mixture of several minor components. These thiocyanation studies are summarised in Scheme 19.

Consequently, hydrolysis of the ester (CXXV) followed by oxidation of the alcohol, possibly using chromium trioxide-pyridine complex[144] which gives high yields, should give 5-methoxy-2-thiocyanatoacetophenone and hence by the usual method, 5-methoxy-3-methyl-1,2-benzisothiazole. Demethylation, possibly using either pyridine hydrochloride[145] or boron trichloride,[146] should afford an alternative route to 5-hydroxy-3-methyl-1,2-benzisothiazole. Unfortunately the lack of time prevented completion of this investigation.

Scheme 19
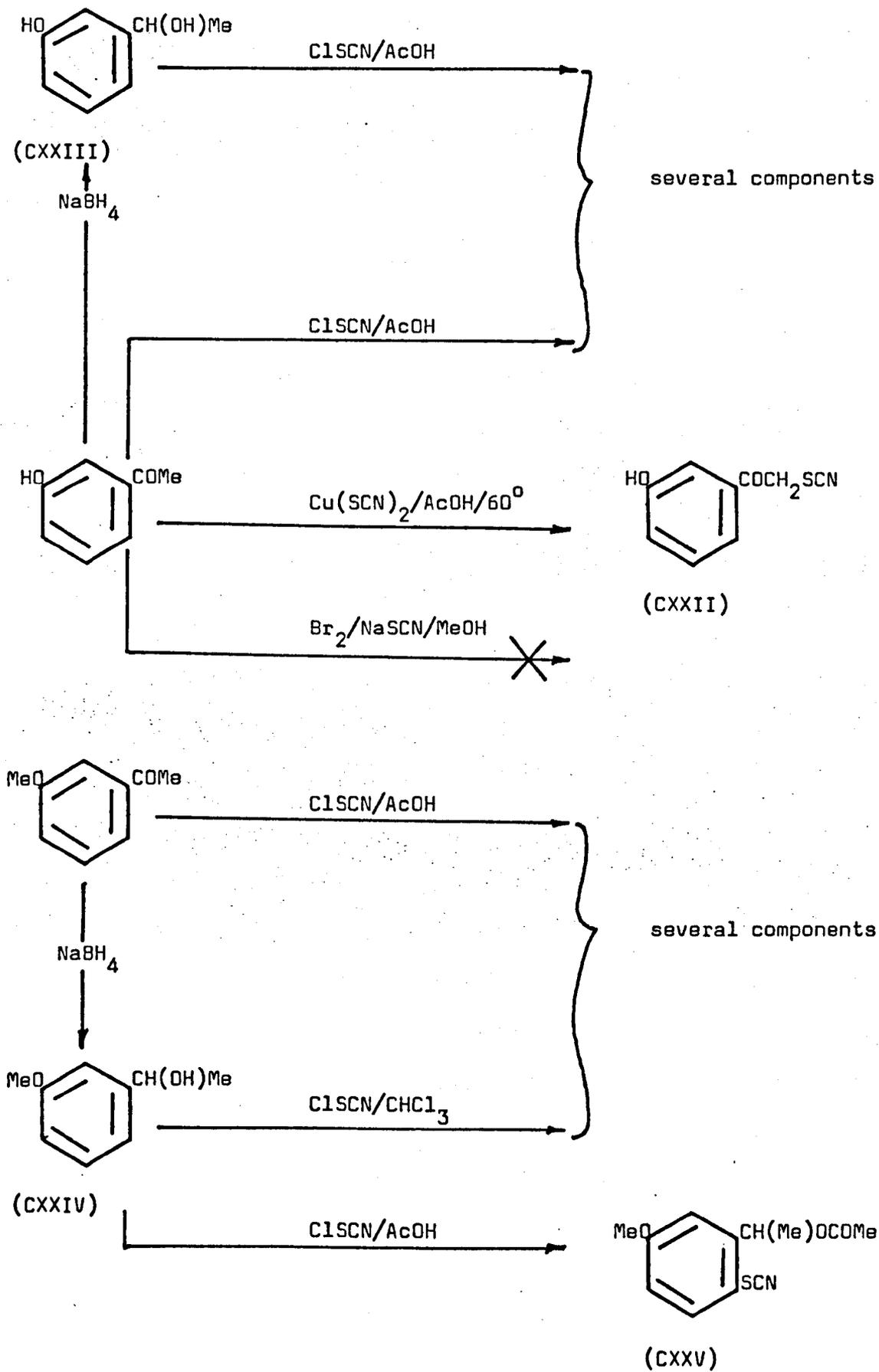
Attempted Reduction of (1,2-Benzisothiazol-3-yl)acetonitrile

In order to prepare some 3-(2-aminoethyl)-1,2-benzisothiazole derivatives
for pharmacological evaluation and comparison with tryptamine derivatives it
was hoped to carry out the reduction of (1,2-benzisothiazol-3-yl)acetonitrile
and of the N-methyl and NN-dimethyl amides derived from (1,2-benzisothiazol-3-
yl)acetic acid.

Workers in this department[118,147] and elsewhere[148] have found that in the
benzo[b]thiophen system the acetonitrile and N-substituted acetamide moieties
can be readily reduced using either lithium aluminium hydride, in the presence
of aluminium chloride, or diborane in a suitable anhydrous solvent. Consequently
it was hoped to extend this work to (1,2-benzisothiazol-3-yl)acetonitrile and
then to the required amides which were readily available.

Reduction of (1,2-benzisothiazol-3-yl)acetonitrile by the usual method[118]
with fresh lithium aluminium hydride in the presence of anhydrous aluminium
chloride using carefully dried tetrahydrofuran gave a basic orange semi-solid,
consisting of several minor components (t.l.c.), which could not be resolved by
column chromatography. It has been shown[81,149] that the benzisothiazole ring
system undergoes cleavage in the presence of nucleophiles and perhaps it is not
surprising that none of the expected product was isolated under the conditions
of the reaction.

Reduction using diborane in carefully dried tetrahydrofuran under a dry
nitrogen atmosphere proceeded smoothly to give a solution, after 15 h boiling,
which contained no starting material (t.l.c.). Destruction of the excess of
diborane with dry ethanol caused an orange solid (probably a boron complex) to
precipitate from the solution. Kornett and his co-workers[150] found that the
reduction of 1,2-dimethyl-5-ethoxycarbonyl-3-pyrazolidinone (CXXVI) to the
ester (CXXVII) with diborane proceeded via a boron complex which was destroyed

by boiling in ethanolic hydrogen chloride solution.

$$B_2H_6$$

(CXXVI)   (CXXVII)
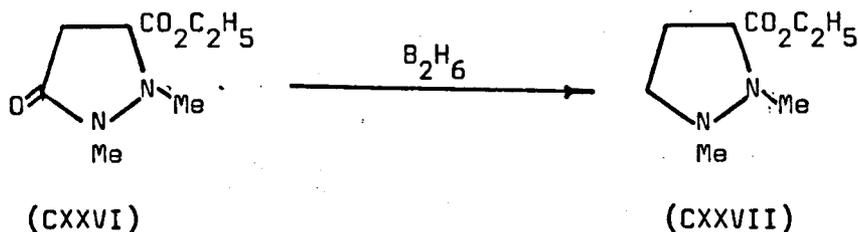
Schuetz and his co-workers[151] also found a similar occurrence when diborane was used to reduce 6-methoxy-2-benzo[b]thienylacetamide to the corresponding amine; the boron complex required 6M hydrochloric acid to decompose it.

Attempted decomposition of the benzisothiazole-boron complex by either of these two methods failed to produce any identifiable product.

Catalytic hydrogenation of (1,2-benzisothiazol-3-yl)acetonitrile at atmospheric pressure using either 10% palladium on carbon or Raney nickel failed to give any reaction. Adam's platinium catalyst at room temperature for 6 h gave a minor basic product (ca. 5% by t.l.c.) but there was insufficient material for characteration.

A possible alternative route to the 1,2-benzisothiazole analogues of tryptamine is outlined in Scheme 20. The reduction of the acetic acid (XXIc) has been reported by Carrington[81] to give 2-(1,2-benzisothiazol-3-yl)ethanol (CXXVIII) in 55% yield. Unfortunately, lack of time prevented further investigation of this route to the tryptamine analogues.
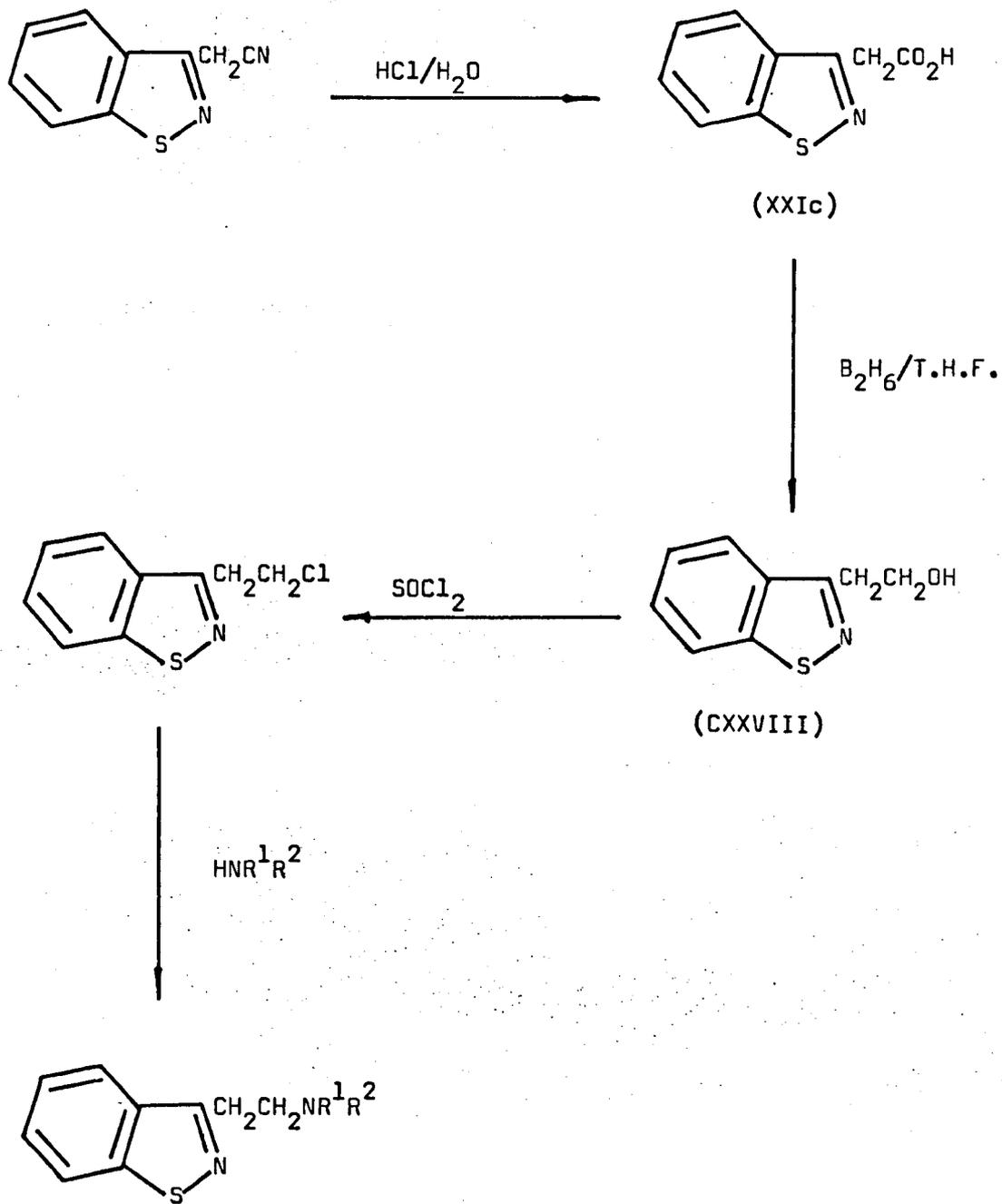
Scheme 20

EXPERIMENTAL WORK

Melting points and boiling points are uncorrected. Melting points were determined on an electrically heated metal block.

Proton magnetic resonance (n.m.r.) spectra were determined on a JEOL 4H-100 spectrometer operating at 100 MHz or a JEOL JNM-PMX60 spectrometer operating at 60 MHz. Deuteriochloroform was used as solvent (unless otherwise stated). Chemical shifts are recorded in parts per million (p.p.m.) downfield from tetramethylsilane and coupling constants are in Hz. The abbreviations used are: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, br = broad singlet, and m = unresolved multiplets. I.r. spectra of solids were recorded on a Perkin-Elmer PE 457 spectrophotometer as KCl or KBr discs unless otherwise stated. I.r. spectra of liquids were recorded as films. Molecular weights were obtained with an A.E.I. MS902 mass spectrometer. Thin layer chromatography (t.l.c.) plates were coated with Silica Gel F_{254} (Merck). Light petroleum had b.p. 60-80° (unless otherwise stated). Identity of compounds with authentic materials was established by mixed m.p. determinations, and by comparison of i.r. and n.m.r. spectra, and R_f values (t.l.c.).

The Preparation of Dry Solvents

Benzene, diethyl ether, tetrahydrofuran, light petroleum and toluene were dried over sodium wire.

Chloroform and carbon tetrachloride were dried over calcium chloride, redistilled, and stored over calcium chloride.

Acetone and butanone were dried over anhydrous potassium carbonate, redistilled, and stored over anhydrous potassium carbonate.

Diglyme and dimethylformamide were dried over molecular sieves redistilled, and stored over molecular sieves.

Superdry ethanol was prepared by the method of Smith[152] using sodium and diethyl phthalate.

Absolute methanol was prepared by the method of Lund and Bjerrum.[153]

Miscellaneous Preparations

NN-Dimethylaniline

Commercially available NN-dimethylaniline was redistilled under reduced pressure under nitrogen, and stored over sodium hydroxide pellets.

N-Bromosuccinimide

N-Bromosuccinimide was recrystallised from water[154], then allowed to stand in vacuo for 45 min prior to use.

Thionyl Chloride

Commercially available thionyl chloride was purified by distillation from quinoline followed by a second distillation from linseed oil.[155]

Bis-(o-chlorocarbonylphenyl) disulphide

Iodine (180 g, 0.7 mol) was added in portions during 30 min to a stirred solution of o-mercaptobenzoic acid (100 g, 0.65 mol) in ethanol (1300 ml). The mixture was stirred for a further 30 min, and the precipitated bis-(o-carboxyphenyl) disulphide (95 g, 95%) was filtered off and washed with ethanol (3 x 100 ml) and dried at 60°.

Thionyl chloride (200 ml) was added to a suspension of the precipitate in dry benzene (250 ml) and the mixture was boiled under reflux for 24 h. Benzene and excess of thionyl chloride were removed under reduced pressure, and the crude product was used in the next stage.

1,2-Benzisothiazol-3(2H)-one

Dry chlorine was bubbled through a stirred suspension of finely powdered bis-(o-chlorocarbonylphenyl) disulphide in dry carbon tetrachloride (800 ml) until a clear solution was formed (1-2 h). A rapid stream of dry nitrogen was used to remove any excess of chlorine from the solution, which was then added dropwise to stirred, ice-cold aqueous ammonia (d. 0.88, 1.5 l). The resulting solid (90 g) was filtered off, washed with water, and dried at 100°. A small sample was crystallised from methanol, to give 1,2-benzisothiazol-3(2H)-one, m.p. 155-156° (lit.,[156] 155-156°).

3-Chloro-1,2-benzisothiazole

A stirred mixture of 1,2-benzisothiazol-3(2H)-one (75 g, 0.5 mol), phosphorus pentachloride (105 g, 0.5 mol) and phosphoryl chloride (1 ml) was kept at 130-140° for 1 h, then cooled and poured on to crushed ice (1 Kg). The mixture was neutralised by the cautious addition of aqueous sodium hydroxide (40% w/v), and the brown oil was extracted with ether. The ethereal solution was washed with water, and dried ($MgSO_4$). Evaporation of the solvent and distillation of the residue gave 3-chloro-1,2-benzisothiazole (54 g, 50%

based on o-mercaptobenzoic acid), b.p. 111° at 3.5 mmHg, m.p. 39-40° (lit.,[157] 40°).

Ethyl (1,2-benzisothiazol-3-yl)cyanoacetate

Ethyl cyanoacetate (26.6 g, 0.235 mol) was added dropwise during 15 min to a stirred solution of sodium (5.4 g, 0.235 g atom) in dry ethanol (160 ml). Stirring was continued for a further 15 min, then powdered 3-chloro-1,2-benziso-thiazole (20 g, 0.115 mol) was added in one portion, and the mixture was stirred at 20° for 48 h, poured into water (900 ml), and shaken with ether (3 x 200 ml). The aqueous layer was acidified by the dropwise addition of concentrated hydrochloric acid. The precipitate was filtered off, washed with water, dried at 60° and crystallised from ethanol to give the product (26.7 g, 89%) as pale-yellow needles, m.p. 149-151° (decomp) [lit.,[86] 149.5-152° (decomp)].

(1,2-Benzisothiazol-3-yl)acetonitrile

A mixture of ethyl (1,2-benzisothiazol-3-yl)cyanoacetate (17.36 g, 0.72 mol), water (2.4 ml) and dimethylsulphoxide (80 ml) was kept at 100° for 24 h, then cooled and poured into ice-water (1.5 l). The precipitate (9.6 g, 84%) was filtered off, washed with water, dried in the air and crystallised from ethanol-light petroleum (b.p. 40-60°) (charcoal), to give the product as needles, m.p. 58-59° (lit.,[84] 57-59°).

(1,2-Benzisothiazol-3-yl)acetic acid

A mixture of (1,2-benzisothiazol-3-yl)acetonitrile (6 g, 0.034 mol) and concentrated hydrochloric acid (50 ml) was stirred at 60° for 2 h, then diluted with water (50 ml) and boiled for 3 h. The mixture was kept in the refigerator overnight and the product was filtered off, dried and crystallised from ethanol (charcoal) as prisms of (1,2-benzisothiazol-3-yl)acetic acid (5.5 g, 84%), m.p. 148-149° (lit.,[84] 148-149°).

Ethyl (1,2-benzisothiazol-3-yl)acetate

Ethanol (200 ml), previously saturated with hydrogen chloride, and (1,2-benzisothiazol-3-yl)acetic acid (10 g, 0.051 mol) were boiled under reflux for 3 h, then cooled, and poured into water (500 ml). The ethereal extract of the resulting oil was washed with water and dried ($MgSO_4$). Removal of the solvent and crystallisation of the residual oil from light petroleum (b.p. 40-60°) gave white needles of ethyl (1,2-benzisothiazol-3-yl)acetate (9.5 g, 84%), m.p. 47-49° (lit.,[84] 48-50°).

.)

N-Methyl-(1,2-benzisothiazol-3-yl)acetamide

A solution of ethyl (1,2-benzisothiazol-3-yl)acetate (8 g, 0.036 mol), ethanolic methylamine (48 ml, 33% w/w), and water (24 ml) was stirred at room temperature for 18 h, then poured into water (500 ml). The product was filtered off, dried at 60°, and crystallised from benzene-light petroleum (b.p. 80-100°), to give N-methyl-(1,2-benzisothiazol-3-yl)acetamide (6.5 g, 87%) as white needles, m.p. 127-128° (Found: C, 58.3; H, 4.9; N, 13.3%; M, 206. $C_{10}H_{10}N_2OS$ requires C, 58.25; H, 4.9; N, 13.6%; M, 206), $\nu_{max.}$ 3300 (N-H) and 1645 (C=O) cm^{-1}, $\delta_{p.p.m.}$ 2.8 (d, -NHMe), 4.08 (s, 3-CH$_2$CONHMe), 6.8 (br, -NHMe), 7.46 (m, 5-H and 6-H), and 7.97 (m, 4-H and 7-H).

NN-Dimethyl-(1,2-benzisothiazol-3-yl)acetamide

(a) Aqueous dimethylamine (40 ml, 26% w/w) was added to a solution of ethyl (1,2-benzisothiazol-3-yl)acetate (2 g, 0.009 mol) in the minimum amount of ethanol, and the mixture was stirred at room temperature for 4 days. The ethanol was removed and the product was extracted with chloroform. The solvent was evaporated to leave an oil (1.2 g, 60%) which slowly solidified and was crystallised from light petroleum (b.p. 80-100°) as white platelets, m.p. 138-139° (Found: C, 50.1; H, 5.25; N, 12.5%; M, 220. $C_{11}H_{12}N_2OS$ requires C, 50;

H, 5.5; N, 12.7%; $\underline{m}$, 220), $\nu_{max.}$ 1640 (C=O) cm^{-1}, $\delta_{p.p.m.}$ 3.04 (2 × s, -NMe$_2$),

6.24 (s, 3-C$\underline{H}_2$CONMe$_2$), 7.47 (m, 5-H and 6-H), 7.91 (m, 7-H), and 8.21 (m, 2-H).

(b) A solution of dimethylamine in tetrahydrofuran (64 ml, 36% w/v) was

added to a stirred solution of (1,2-benzisothiazol-3-yl)acetic acid (5 g, 0.025 mol)

in dry tetrahydrofuran (50 ml) and the mixture was cooled to -70° under an

atmosphere of dry nitrogen. Titanium ($\underline{IV}$) chloride (2.9 g, 0.0254 mol) was

added dropwise and the mixture was stirred for 15 min at -70°, and then at room

temperature for 3 days. Water (3 ml) was added to destroy the titanium complex

and the solution was filtered through 'Hyflosupercel', the filter cake being

washed successively with tetrahydrofuran (25 ml) and carbon tetrachloride (2 ×

25 ml). The filtrate was evaporated, and the residue was shaken with chloroform.

The chloroform solution was dried (MgSO$_4$) and the solvent was removed to leave

a brown solid which crystallised from light petroleum (b.p. 80-100°) to give

NN-dimethyl-(1,2-benzisothiazol-3-yl)acetamide (5 g, 90%), identical with the

foregoing sample.

(c) (1,2-Benzisothiazol-3-yl)acetic acid (2 g, 0.01 mol) and thionyl chloride

(15 ml) were boiled together under reflux for 1 h. Excess of thionyl chloride

was removed under reduced pressure and the residue was crystallised from light

petroleum (b.p. 80-100°) to give the (1,2-benzisothiazol-3-yl)acetyl chloride

(1.75 g, 82%), $\nu_{max.}$ 1754 (C=O) cm^{-1}.

The foregoing product (1 g, 0.0047 mol) and an excess of dimethylamine

were kept in a sealed tube at 100° for 24 h. The cooled reaction tube was opened

and the residue was extracted with chloroform. The extract was washed successively

with 10% hydrochloric acid, water , and saturated sodium hydrogen carbonate

solution, then dried (MgSO$_4$). The solvent was evaporated to give the product

(0.3 g, 30%) which was identical with the foregoing samples.

(1,2-Benzisothiazol-3-yl)acetamidoxime

A mixture of (1,2-benzisothiazol-3-yl)acetonitrile (2.44 g, 0.014 mol),

hydroxylamine hydrochloride (3.5 g), sodium carbonate (2.5 g) and water (38 ml)

was heated on a steam bath for 90 min with sufficient ethanol to maintain a

clear solution. The mixture was cooled and the resulting product (2.9 g, 99%)

was collected and crystallised from ethanol-light petroleum (b.p. 40-60°) to give

white <u>cubes</u>, m.p. 146-147° (Found: C, 52.1; H, 4.45; N, 20.3%; $\underline{M}$, 207. $C_9H_9N_3OS$

requires C, 52.15; H, 4.4; N, 20.3%; $\underline{M}$, 207), $\vartheta_{max.}$ 3460, 3150 (NH_2), 3260 (OH),

and 1657 (C=N) cm^{-1}, $\delta_{p.p.m.}$ [$(CD_3)_2SO$] 3.86 (s, 3-C$\underline{H}_2$.C), 5.5 (s, $-NH_2$), 7.53

(m, 5-H and 6-H), 8.16 (m, 4-H and 7-H), and 9.11 (s, -NOH).

The Preparation of 3-Methyl-1,2-benzisothiazole

o-Nitrobenzoyl chloride

A stirred mixture of o-nitrobenzoic acid (100 g, 0.6 mol) and thionyl chloride (125 g) in dry benzene (500 ml) was boiled under reflux for 1 h. Excess of thionyl chloride and benzene were removed under reduced pressure and the crude o-nitrobenzoyl chloride was used in the next stage.

(N.B. o-Nitrobenzoyl chloride is liable to explode, therefore care was taken when removing the excess of thionyl chloride and benzene).

o-Nitroacetophenone

A stirred mixture of magnesium (16.2 g, 0.66 g atom), dry ethanol (15 ml, 0.255 mol) and carbon tetrachloride (1.5 ml) was boiled under reflux for 5 min, then dry ether (450 ml) was added slowly. A solution of diethyl malonate (105.6 g, 0.66 mol), dry ethanol (60 ml, 1.02 mol) and dry ether (75 ml) was added at a rate sufficient to maintain rapid boiling, and the stirred mixture was boiled for 3 h. A solution of o-nitrobenzoyl chloride in dry ether (150 ml) was then added during 15 min, and stirring was continued until the resulting green paste became too viscous to stir. The mixture was cooled and concentrated sulphuric acid (75 g) and then water (500 ml) were cautiously added, the ether phase was separated and the aqueous phase shaken with ether (200 ml). The combined organic phases were evaporated and the residue was boiled with a mixture of glacial acetic acid (180 ml), concentrated sulphuric acid (22.8 ml), and water (120 ml) for 4 h. The cooled mixture was neutralised with 20% aqueous sodium hydroxide, and the product was extracted with ether. The solution was distilled to give pale yellow o-nitroacetophenone (88 g, 83%), b.p. 107-109° at 0.6 mmHg (lit.,[158] 80-81° at 0.5 mmHg).

o-Aminoacetophenone

Concentrated hydrochloric acid (181 ml) was added dropwise over 1 h to a mixture of o-nitroacetophenone (33.5 g, 0.203 mol) and tin (67 g, 0.56 g atom) and the mixture was heated on a steam bath for 1 h, cooled, made strongly alkaline with 20% aqueous sodium hydroxide and steam distilled. The distillate was saturated with sodium chloride and the product was extracted with ether. Distillation gave o-aminoacetophenone (26.7 g, 97%), b.p. 94-96° at 1.2 mmHg (lit.,[158] 74-77° at 0.02 mmHg).

o-Thiocyanatoacetophenone

A stirred mixture of o-aminoacetophenone (23.3 g, 0.173 mol), concentrated hydrochloric acid (44 ml) and water (44 ml) was cooled to 3° and then diazotised at between 3-10° with a solution of sodium nitrite (12.5 g, 0.18 mol) in water (60 ml). The diazotised solution was added to a stirred suspension of copper (1) thiocyanate (80 g) and potassium thiocyanate (47.5 g) in water (480 ml) and the mixture was stirred for 1 h, then left overnight at room temperature. The mixture was filtered and the organic product was extracted from the residual solid with chloroform. Evaporation of the solvent gave a solid which crystallised with difficulty from light petroleum (b.p. 40-60°) as yellow needles (19 g, 62%), m.p. 59-60° (lit.,[93] 60-61°).

2-Imino-5-methyl-3,1,4-benzoxathiazepine

o-Thiocyanatoacetophenone (10 g, 0.566 mol), hydroxylamine hydrochloride (4.8 g), sodium acetate (5.6 g), water (60 ml) and ethanol (sufficient to maintain homogeneity) were boiled together under reflux for 1 h, and the hot solution was filtered. Orange-yellow needles of 2-imino-5-methyl-3,1,4-benzoxa-thiazepine (9 g, 83%), m.p. 208-209° (decomp) (ethanol) (lit.,[82] 208-210° [decomp]), separated from the cooled filtrate.

3-Methyl-1,2-benzisothiazole

2-Imino-5-methyl-3,1,4-benzoxathiazepine (9 g, 0.047 mol) was added in portions to stirred, hot (120°) polyphosphoric acid (50 g). The temperature was maintained at 120-130° for 1 h, then the cooled mixture was poured onto crushed ice (300 g) and basified. The organic product was extracted with chloroform, the extract dried ($MgSO_4$), and distilled to give 3-methyl-1,2-benzisothiazole (80%), b.p. 74° at 0.55 mmHg (lit.,[84] b.p. 66-70° at 0.2 mmHg).

2-Imino-5-methyl-1,3,4-benzthiadiazepine-3-carboxamide

o-Thiocyanatoacetophenone (5 g, 0.0283 mol), semicarbazide hydrochloride (9 g), sodium acetate (10 g), water (45 ml) and ethanol (sufficient to maintain homogeneity) were boiled together under reflux for 3 h. On cooling the pale orange "semicarbazone" (90%) was filtered off and a sample crystallised with difficulty from methanol, $\nu_{max.}$ 3300br (NH_2) and 1690 (CO) cm^{-1} (no SCN band), $\delta_{p.p.m.}$ [$(CD_3)_2SO$] 2.25 (s, CH_3), 6.38 (s, NH_2), 7.52 (m, 4 x aromatic-H), and 9.59 (s, NH).

Cyclisation of 2-Imino-5-methyl-1,3,4-benzthiadiazepine-3-carboxamide

The "above product" (1 g) was cyclised in diethylene glycol (50 ml) in the usual manner.[82] The dark brown oil (0.62 g) was purified by elution from a column of silica gel with ether-light petroleum (1:7) to give 3-methyl-1,2-benzisothiazole (ca. 50%), identical with an authentic sample.

Some Reactions of 3-Methyl-1,2-benzisothiazole

Bromination

Bromine (0.8 g, 0.005 mol) was added to a rapidly stirred solution of 3-methyl-1,2-benzisothiazole (0.75 g, 0.005 mol) and silver sulphate (0.78 g, 0.0025 mol) in concentrated sulphuric acid (7 ml). The mixture was stirred at room temperature for 3 h, then at 60° for 30 min, cooled and poured onto ice (100 g). The solution was neutralised and shaken with ethyl acetate (2 x 50 ml), and the combined exracts were dried ($MgSO_4$). Evaporation of the solvent left an oil (1 g) which was separated into its four components by elution from a column of silica gel, with chloroform-light petroleum (1:6).

The first component (R_f 0.84, ether-light petroleum [3:1]), a white solid (0.0358 g, 2.3%), was identified as 4,7-dibromo-3-methyl-1,2-benzisothiazole by comparison with an authentic sample prepared by the bromination of 4-bromo-3-methyl-1,2-benzisothiazole (p. 139).

The second component (R_f 0.76), a pale pink solid (0.0257 g, 1.7%), was identified as 5,7-dibromo-3-methyl-1,2-benzisothiazole by comparison with an authentic sample obtained by the bromination of 5-bromo-3-methyl-1,2-benzisothiazole (p. 111).

The third component (R_f 0.68), was identified as 5-bromo-3-methyl-1,2-benzisothiazole (0.36 g, 32%) by comparison with an authentic sample prepared by the Sandmeyer reaction on 5-amino-3-methyl-1,2-benzisothiazole (p. 111).

The final component (R_f 0.59), was identified as 7-bromo-3-methyl-1,2-benzisothiazole (0.42 g, 37%) by comparison with an authentic sample isolated from the Sandmeyer reaction on 7-amino-3-methyl-1,2-benzisothiazole (p. 102).

Nitration

3-Methyl-1,2-benzisothiazole (3 g, 0.019 mol) was added dropwise during 15 min to a stirred solution of potassium nitrate (2.3 g, 0.022 mol) and concen-

trated sulphuric acid (30 ml) at 0°. The mixture was stirred at -5 to 5° for 4 h, then at room temperature for 12 h, and then poured onto ice (100 g). The yellow solid was extracted into chloroform (200 ml) and the extract was washed successively with water (100 ml) with aqueous sodium hydrogen carbonate (until neutral), again with water (100 ml) and dried ($MgSO_4$). The solvent was evaporated to leave a two component solid (4.05 g) which was eluted from a column of silica gel with ethyl acetate-light petroleum (1:10).

The major component (R_f 0.29) was crystallised from ethyl acetate to give 3-methyl-5-nitro-1,2-benzisothiazole (1.7 g, 44%), as fluffy white needles, m.p. 115-116° (lit.,[78] 95-96°; lit.,[100] 116-117°) (Found: $\underline{M}$, 194. Calculated for $C_8H_6N_2O_2S$ $\underline{M}$, 194), $\vartheta_{max.}$ 1500 and 1350 (aromatic NO_2) cm^{-1}, $\delta_{p.p.m.}$ 2.84 (s, 3-CH_3), 8.03 (dd, 7-H), 8.36 (dd, 6-H) and 8.83 (dd, 4-H), ($\underline{J}_{4,7}$ = 0.75, $\underline{J}_{4,6}$ = 1.9, $\underline{J}_{6,7}$ = 8.5 Hz).

The minor component (R_f 0.13) was crystallised from ethyl acetate to give 3-methyl-7-nitro-1,2-benzisothiazole (1.5 g, 39%), as yellow microneedles, m.p. 176-177° (lit.,[100] 177-178°) (Found: $\underline{M}$, 194. Calculated for $C_8H_6N_2O_2S$ $\underline{M}$, 194), $\vartheta_{max.}$ 1540 and 1340 (aromatic NO_2) cm^{-1}, $\delta_{p.p.m.}$ 2.78 (s, 3-CH_3), 7.64 (t, 5-H), 8.28 (dd, 4-H) and 8.48 (dd, 6-H), ($\underline{J}_{4,6}$ = 0.9, $\underline{J}_{4,5}$ = $\underline{J}_{5,6}$ = 7.8 Hz).

Oxidation

(a) A solution of 3-methyl-1,2-benzisothiazole (1 g, 0.0066 mol), thionyl chloride (60 ml), and dry toluene (10 ml) was boiled for 7 days, basified$_\wedge$ (2M NaOH) and boiled for a further 15 min. The solution was steam distilled, to remove the solvent, filtered and then acidified. Extraction with chloroform and evaporation of the extract gave (1,2-benzisothiazol-3-yl)carboxylic acid (0.5 g, 42%), which crystallised from hot water as white needles, m.p. 141-143° (lit.,[159] 143°), $\vartheta_{max.}$ 3300-2600 br (O-H), 1710 (C=O), and 1210 (C-O) cm^{-1}, $\delta_{p.p.m.}$ 7.54 (m, 5-H and 6-H), 7.95 (m, 7-H), 8.24 (m, 4-H), and 9.83 (s, 3-$CO_2\underline{H}$).

(b) A mixture of iodine (8.42 g, 0.033 mol) and 3-methyl-1,2-benzisothiazole

(5 g, 0.033 mol) was warmed at 35-40° for 15 min, and then dissolved in dry

dimethylsulphoxide (14 ml). This solution was then added dropwise to dry

dimethylsulphoxide (16 ml), preheated to 120°, and the resulting solution kept

at 170-180° for 4 h. The solution was cooled , poured into an excess of aqueous

sodium hydrogen carbonate and then was shaken with ether (2 x 100 ml). The

combined extracts were washed successively with 10% sodium thiosulphate solution

(2 x 100 ml), with water (3 x 100 ml), and dried ($MgSO_4$). The solvent was evap-

orated to leave an oil which was resolved into its two components by chromatography

on silica gel, using benzene-chloroform (4:1) to elute the column.

The minor component (R_f 0.62), after short path distillation (50° at 0.25

mmHg), gave (1,2-benzisothiazol-3-yl)carbaldehyde (1.89 g, 35%) as white fibrous

needles, m.p. 41-43° (Found: C, 58.95; H, 3.4; N, 8.7%; M, 163. C_8H_5NOS requires

C, 58.9; H, 3.1; N, 8.6%; M, 163), $\upsilon_{max.}$ (CHCl$_3$) 2930, 2840 (H-CO), and 1705 (C=O)

cm^{-1}, $\delta_{p.p.m.}$ 7.56 (m, 5-H and 6-H), 7.97 (m, 7-H), 8.78 (m, 4-H), and 10.22

(s, 3-CHO).

It formed an oxime which crystallised from aqueous ethanol as needles,

m.p. 144-145° (Found: C, 53.8; H, 3.7; N, 15.6%; M, 178. $C_8H_6N_2OS$ requires C,

53.9; H, 3.4; N, 15.7%; M, 178), $\upsilon_{max.}$ 3200-2860br (O-H) and 937 (N-O) cm^{-1},

$\delta_{p.p.m.}$ [(CD$_3$)$_2$SO] 7.62 (m, 5-H and 6-H), 8.25 (m, 7-H), 8.49 (s, 3-CH=NOH), 8.7

(m, 4-H), 10.23 (br, syn NOH), and 11.98 (s, anti NOH).

The major component (R_f 0.52) was identified as 3-methyl-1,2-benzisothiazole

(2.69 g, 54%) by comparison with an authentic sample.

Synthesis of 7-Bromo and 7-Chloro-3-methyl-1,2-benzisothiazole

7-Amino-3-methyl-1,2-benzisothiazole

Strips of aluminium foil (12 g) were washed several times with absolute ethanol, then with dry ether and dipped into 2% aqueous mercury (11) chloride for 15-20 sec, rinsed momentarily in absolute ethanol and finally submerged in dry ether, where they were cut into smaller pieces.

The aluminium amalgam (prepared above) was quickly added to a stirred solution of 3-methyl-7-nitro-1,2-benzisothiazole (1.45 g, 0.0075 mol) in a mixture of ether (600 ml), methanol (72 ml), and water (3.5 ml) which was then stirred for 24 h at room temperature. The mixture was filtered through 'Hyflosupercel', the filter pad being washed thoroughly with (1:1) ether-methanol (500 ml) and the combined filtrates were concentrated and partitioned between ether and 2% aqueous sodium hydroxide. The organic layer was dried ($MgSO_4$) and evaporated to leave the required amine (1.15 g, 94%) which sublimed (84° at 0.4 mmHg) as a pale yellow solid, m.p. 104-106° (lit.,[100] 110-111°; lit.,[85] 108-110°) (Found: $\underline{M}$, 164. Calculated for $C_8H_8N_2S$ requires $\underline{M}$, 164), $\nu_{max.}$ 3430, 3330, 3220, 1625 (NH_2), and 1300 (C-N) cm^{-1}, $\delta_{p.p.m.}$ 2.7 (s, 3-CH_3), 3.94 (br, 7-NH_2), 6.72 (dd, 6-H), and 7.29 (m, 4-H and 5-H), ($\underline{J}_{4,6}$ = 1.5 and $\underline{J}_{5,6}$ = 6.75 Hz).

7-Bromo-3-methyl-1,2-benzisothiazole

A solution of 7-amino-3-methyl-1,2-benzisothiazole (0.4 g, 0.0024 mol) in concentrated sulphuric acid (10 ml) and water (5 ml) was diazotised with a solution of sodium nitrite (0.173 g, 0.0025 mol) in water (5 ml) at 0-8°. The diazotised solution was added dropwise to an ice-cold, stirred solution of copper (1) bromide (0.4 g) in hydrobromic acid (4 ml, 48% w/w) and the solution kept at 80° for 1 h. The solution was cooled, diluted with water (100 ml) and shaken with ether (2 x 50 ml). The solvent was evaporated to leave a solid which was resolved into its two

components by elution with ethyl acetate-light petroleum (1:4) from a column of silica gel.

The major component (R_f 0.45) was sublimed (54° at 0.2 mmHg) to give 7-bromo-3-methyl-1,2-benzisothiazole (0.22 g, 40%) as translucent plates, m.p. 66-67° (Found: C, 42.3; H, 2.8; N, 6%; $\underline{M}$, 227/229. C_8H_6BrNS requires C, 42.1; H, 2.65; N, 6.15%; $\underline{M}$, 227/229), $\vartheta_{max.}$ 1065 (aromatic Br) cm^{-1}, $\delta_{p.p.m.}$ 2.7 (s, 3-CH$_3$), 7.29 (t, 5-H), 7.57 (dd, 6-H), and 7.81 (dd, 4-H), ($\underline{J}_{4,6}$ = 0.75, $\underline{J}_{4,5}$ = $\underline{J}_{5,6}$ = 7.75 Hz). The product was identical with the fourth component obtained from the bromination of 3-methyl-1,2-benzisothiazole (p. 99).

The minor component (R_f 0.195) was crystallised from benzene-light petroleum to give 7-dibromoacetyl-1,2,3-benzothiadiazole (0.24 g, 32%) as straw-coloured needles, m.p. 119-120° (Found: C, 28.85; H, 1.1; N, 8.3%; $\underline{M}$ (weak), 334/336/338; base peak ($\underline{M}$-N$_2$), 306/308/310. $C_8H_4Br_2N_2OS$ requires C, 28.6; H, 1.2; N, 8.35%; $\underline{M}$ (weak), 334/336/338; $\underline{M}$-N$_2$^{106} , 306/308/310), $\vartheta_{max.}$ 1670 (C=O), 775 and 650 (alkyl Br) cm^{-1}, $\delta_{p.p.m.}$ 6.89 (s, 3-COC$\underline{H}$Br$_2$), 7.84 (q, 5-H), 8.65 (dd, 6-H), and 8.94 (dd, 4-H), ($\underline{J}_{4,6}$ = 0.9, $\underline{J}_{5,6}$ = $\underline{J}_{5,4}$ = 7.6 Hz).

7-Chloro-3-methyl-1,2-benzisothiazole

A solution of 7-amino-3-methyl-1,2-benzisothiazole (0.4 g, 0.0024 mol) in concentrated hydrochloric acid (10 ml) and water (5 ml) was diazotised as already described (p. 102). The diazonium solution was added dropwise to an ice-cold, stirred solution of copper ($\underline{1}$) chloride (0.5 g) in concentrated hydrochloric acid (10 ml) and the solution was warmed at 60° for 1 h. The mixture was cooled, diluted with water (100 ml) and shaken with ether (2 x 50 ml). The dried extract was evaporated to give a solid which was resolved into its two components by elution with ethyl acetate-light petroleum (1:6) from a column of silica gel.

The minor component (R_f 0.45), after short path distillation (65° at 0.2 mmHg) gave 7-chloro-3-methyl-1,2-benzisothiazole (0.16 g, 32%) as a white crystalline solid, m.p. 43-44° (Found: C, 52.6; H, 3.15; N, 7.3%; $\underline{M}$, 183/185. C_8H_6ClNS require

C, 52.3; H, 3.3; N, 7.3%; $\underline{M}$, 183/185), $\vartheta_{max.}$ 1080 (aromatic Cl) cm^{-1}, $\delta_{p.p.m.}$ 2.67 (s, 3-CH$_3$), 7.28 (t, 5-H), 7.4 (dd, 6-H), and 7.72 (dd, 4-H), ($\underline{J}_{4,6}$ = 1.8, $\underline{J}_{4,5}$ = $\underline{J}_{5,6}$ = 7.4 Hz).

The major component ($\underline{R}_f$ 0.09) was crystallised from benzene-light petroleum to give 7-acetyl-1,2,3-benzothiadiazole (0.25 g, 51%) as long fibrous needles, m.p. 126° (lit.,[85] 125-127°) (Found: $\underline{M}$ (weak), 178; base peak ($\underline{M}$-N$_2$), 150. Calculated for C$_8$H$_6$N$_2$OS $\underline{M}$, 178; $\underline{M}$-N$_2$[106], 150), $\vartheta_{max.}$ 1665 (C=O) cm^{-1}, $\delta_{p.p.m.}$ 2.82 (s, 7-COCH$_3$), 7.94 (q, 5-H), 8.28 (dd, 6-H), and 8.83 (dd, 4-H), ($\underline{J}_{4,6}$ = 0.8, $\underline{J}_{4,5}$ = $\underline{J}_{5,6}$ = 8 Hz).

The Preparation of 5-Amino-3-methyl-1,2-benzisothiazole

m-Nitroacetophenone

Acetophenone (300 g, 2.5 mol) was added dropwise during 45 min to stirred fuming nitric acid (1.3 l, $\underline{d}$. 1.5) at -8 to -15°. The mixture was stirred at -10 to -15° for 1 h and then poured onto crushed ice (2 Kg). The pale yellow solid was filtered off, dried by suction at the pump and crystallised from ethanol to give $\underline{m}$-nitroacetophenone (440 g, 53%), as needles, m.p. 78-79° (lit.,[107] 78-79°).

m-Aminoacetophenone

$\underline{m}$-Nitroacetophenone (90 g, 0.55 mol) was added in portions, over 90 min, to a stirred suspension of iron filings (105 g) in glacial acetic acid (30 ml) and water (600 ml) at 75° and then the stirred mixture was boiled under reflux for a further 45 min. The hot mixture was filtered through 'Hyflosupercel' and the product collected from the cooled filtrate. Crystallisation from hot water gave $\underline{m}$-aminoacetophenone (62.6 g, 85%), as translucent plates, m.p. 97-98° (lit.,[108] 98-99°).

5-Amino-2-thiocyanatoacetophenone

A solution of bromine (76.3 g, 0.48 mol) in dry methanol (200 ml) saturated with sodium bromide was added over 30 min to a stirred suspension of anhydrous sodium thiocyanate (118 g, 1.46 mol) in a solution of $\underline{m}$-aminoacetophenone (60 g, 0.44 mol) in dry methanol (1.3 l) at -2 to -10°. The solution was stirred for 1 h at this temperature, then poured into water (5 l), filtered through 'Hyflosupercel' and neutralised by the addition of solid sodium carbonate. The pale yellow precipitate was filtered off, dried at 60° and crystallised from ethanol to give 5-amino-2-thiocyanatoacetophenone (46.5 g, 55%), m.p. 136-137° (lit.,[109] 140°), $\nu_{max.}$ 3440, 3360 (NH_2), 2150 (SCN), 1660 (C=O), and 1620 (N-H) cm^{-1}, $\delta_{p.p.m.}$ [$(CD_3)_2SO$] 2.56 (s, $COCH_3$), 5.7 (s, 5-NH_2), 6.96 (dd, 4-H), and 7.5 (m, 3-H and 6-H).

7-Amino-2-imino-5-methyl-3,1,4-benzoxathiazepine

5-Amino-2-thiocyanatoacetophenone (60 g, 0.31 mol), hydroxylamine hydrochloride (28.4 g, 0.46 mol), sodium acetate (33.2 g, 0.46 mol), water (40 ml), and ethanol (sufficient to maintain homogeneity) were boiled together under reflux for 1 h, and the hot solution filtered. Yellow microcrystals of 7-amino-2-amino-5-methyl-3,1,4-benzoxathiazepine* (47.2 g, 74%), m.p. 191-193° (Found: $\underline{M}$, 207. $C_9H_9N_3OS$ requires $\underline{M}$, 207), $\vartheta_{max.}$ 3350-2790br (NOH and NH_2), 1629 (C=N), and 1605 (N-H) cm^{-1}, $\delta_{p.p.m.}$ [$(CD_3)_2SO$] 2.57 (s, 5-CH_3), 5.33 (br, 7-NH_2), 4.85 (dd, 8-H), 3.05 (d, 9-H), 3.21 (d, 6-H), and 3.6 (br, 2 =NH).

5-Amino-3-methyl-1,2-benzisothiazole

7-Amino-2-imino-5-methyl-3,1,4-benzoxathiazepine (47 g, 0.24 mol) was added portionwise with stirring to hot (120-130°) polyphosphoric acid (700 g). The mixture was kept at this temperature for 1 h, and then was poured onto crushed ice (2 Kg) and carefully basified. The product was filtered off, and crystallised (with difficulty) from light petroleum to give 5-amino-3-methyl-1,2-benzisothiazole* (32.8 g, 88%) as needles, m.p. 122-124° (lit.,[79] 133-134°; lit.,[100] 127.5-130.5°) (Found: $\underline{M}$, 164. Calculated for $C_8H_8N_2S$ $\underline{M}$, 164), $\vartheta_{max.}$ 3400, 3325, 3210 and 1630 (NH_2) cm^{-1}, $\delta_{p.p.m.}$ 2.62 (s, 3-CH_3), 2.86 (br, 5-NH_2), 6.9 (dd, 6-H), 7.08 (d, 4-H), and 7.62 (d, 7-H), ($\underline{J}_{4,6}$ = 2.2, $\underline{J}_{6,7}$ = 8.3 Hz).

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* light sensitive.

Bromination of 5-Amino-3-methyl-1,2-benzisothiazole

(a) A solution of bromine (4.4 g, 0.058 mol) in dry chloroform (50 ml) was added

dropwise during 1 h to an ice-cold, stirred solution of 5-amino-3-methyl-1,2-

benzisothiazole (9.5 g, 0.058 mol) in dry chloroform (250 ml). The solution was

stirred for a further 30 min at 0-5°, then poured into water (500 ml). The organic

phase was separated, the aqueous phase washed with chloroform (50 ml) and the

combined chloroform extracts were washed successively with 10% aqueous sodium

hydroxide (2 x 50 ml), with water (2 x 50 ml), and were then dried ($MgSO_4$). Evap-

oration of the solvent left a pale solid which crystallised from benzene-light

petroleum (charcoal) to give 5-amino-4-bromo-3-methyl-1,2-benzisothiazole (12.7 g,

90%) as pale pink microcrystals, m.p. 148.5-149° (Found: C, 39.75; H, 2.9; N, 11.35

%; $\underline{M}$, 242/244. $C_8H_7BrN_2S$ requires C, 39.5; H, 2.9; N, 11.5%; $\underline{M}$, 242/244), $\nu_{max.}$

3420, 3300, 3190, 1625 (NH_2), and 1052 (aromatic Br) cm^{-1}, $\delta_{p.p.m.}$ 2.96 (s, 3-CH_3),

4.43 (br, 5-NH_2), 6.95 (d, 6-H), and 7.57 (d, 7-H), ($\underline{J}_{6,7}$ = 8.5 Hz).

(b) A solution of bromine (1.07 g, 0.0067 mol) in glacial acetic acid (10 ml)

was added during 30 min to a stirred solution of 5-amino-3-methyl-1,2-benzisothia-

zole (1 g, 0.006 mol) in glacial acetic acid (10 ml) at room temperature. After

being stirred for 15 min, the solution was poured into water (300 ml) and the

resulting solid resolved into its three components by elution with ethyl acetate-

light petroleum (1:4) from a silica gel column.

The third component ($\underline{R}_f$ 0.15) was identified as 5-amino-3-methyl-1,2-benziso-

thiazole (0.1 g, 10%) by comparison with an authentic sample.

The second component ($\underline{R}_f$ 0.4) was identified as 5-amino-4-bromo-3-methyl-1,2-

benzisothiazole (1.05 g, 70%) by comparison with the sample prepared above.

The first component ($\underline{R}_f$ 0.69) crystallised from light petroleum to give

5-amino-4,6-dibromo-3-methyl-1,2-benzisothiazole (0.2 g, 10%) as yellow needles,

m.p. 149-150° (Found: C, 30.2; H, 1.7; N, 8.5%; $\underline{M}$, 320/322/324. $C_8H_6Br_2N_2S$

requires C, 29.85; H, 1.9; N, 8.7%; $\underline{M}$, 320/322/324), $\nu_{max.}$ 3425, 3325, 1608 (NH_2),

and 1060 (aromatic Br) cm^{-1}, $\delta_{p.p.m.}$ 2.95 (s, 3-CH_3), 4.79 (s, 5-NH_2), and 7.89

(s, 7-H).

4,6-Dibromo-3-methyl-1,2-benzisothiazole

A solution of 5-amino-4,6-dibromo-3-methyl-1,2-benzisothiazole (0.2 g, 0.0062 mol) in concentrated sulphuric acid (4 ml) and water (4 ml) was treated with a solution of sodium nitrite (0.06 g, 0.0084 mol) in water (4 ml) at 3-8°. The diazonium salt was stirred for 15 min at this temperature and then hypophosphorous acid (20 ml, 50% w/w) was added and stirring continued at room temperature for a further 2 h. Water (150 ml) was added and the organic product was extracted with ether (2 × 50 ml). Evaporation of the solvent gave the product (0.153 g, 80%) which crystallised from light petroleum (charcoal) as fluffy white microneedles, m.p. 125-126° (Found: C, 31.5; H, 1.75; N, 4.45%; $\underline{M}$, 305/307/309. $C_8H_5Br_2NS$ requires C, 31.3; H, 1.65; N, 4.55%; $\underline{M}$, 305/307/309), $\nu_{max.}$ 1040 (aromatic Br) cm^{-1}, $\delta_{p.p.m.}$ 2.98 (s, 3-CH$_3$), 7.71 (d, 5-H), and 7.95 (d, 7-H), ($\underline{J}_{5,7}$ = 1.4 Hz).

Some Electrophilic Substitution Reactions on 5-Acetamido-3-methyl-1,2-benzisothiazole

5-Acetamido-3-methyl-1,2-benzisothiazole

5-Amino-3-methyl-1,2-benzisothiazole (5 g, 0.03 mol), acetic anhydride (5 ml) and glacial acetic acid (5 ml) were gently heated under reflux for 15 min, cooled and poured into ice-water (100 ml). The product was filtered off and crystallised from hot water to give 5-acetamido-3-methyl-1,2-benzisothiazole (6 g, 96%) as white plates, m.p. 170-171° (lit.,[79] 172-173°) (Found: $\underline{M}$, 206. Calculated for $C_{10}H_{10}N_2OS$ $\underline{M}$, 206), $\nu_{max.}$ 1660 (C=O) cm^{-1}, $\delta_{p.p.m.}$ [$(CD_3)_2SO$] 2.1 (s, 5-NHCOC$\underline{H}_3$), 2.62 (s, 3-C$\underline{H}_3$), 3.4 (br, 5-N$\underline{H}$COCH$_3$), 7.68 (dd, 6-H), 8.05 (dd, 7-H), and 8.42 (d, 4-H), ($\underline{J}_{4,7}$ = 0.5, $\underline{J}_{4,6}$ = 1.75, $\underline{J}_{6,7}$ = 8.6 Hz).

Bromination

$\underline{N}$-Bromosuccinimide (0.87 g, 0.005 mol) was added in portions during 15 min to a boiling, stirred solution of 5-acetamido-3-methyl-1,2-benzisothiazole (1 g, 0.0049 mol) in dry chloroform (70 ml), containing a catalytic amount of dibenzoyl peroxide. The mixture was boiled for 18 h, then cooled, filtered and evaporated to leave a two component mixture (ratio 2:3) which could not be separated by column chromatography on silica gel.

The mixture was boiled with 40% sulphuric acid (20 ml) for 15 min, then cooled, made alkaline with 10% sodium hydroxide solution and shaken with chloroform. The chloroform extract was dried ($MgSO_4$) and evaporated to give a mixture of amines which could be resolved by elution from a column of silica gel with ether-light petroleum (3:1).

The first component ($\underline{R}_f$ 0.62) was identified as 5-amino-4-bromo-3-methyl-1,2-benzisothiazole (0.4 g, 34%) by comparison with an authentic sample prepared by the bromination of 5-amino-3-methyl-1,2-benzisothiazole (p. 107).

The second component (R_f 0.34) was identified as 5-amino-3-methyl-1,2-benzisothiazole (0.45 g, 56%) by comparison with an authentic sample.

Nitration

5-Acetamido-3-methyl-1,2-benzisothiazole (5 g, 0.0244 mol) was added over 90 min to an ice-cold solution of potassium nitrate (2.46 g, 0.025 mol) and concentrated sulphuric acid (50 ml) and the solution stirred at 0-5° for 3 h.[*] The solution was cautiously poured into iced water and the product extracted with ethyl acetate. Concentration of the extract left a two component solid which was eluted from a column of silica gel with ethyl acetate-light petroleum (1:4).

The first component was crystallised from hot water to give 5-acetamido-3-methyl-4-nitro-1,2-benzisothiazole (3.65 g, 60%) as fluffy yellow needles, m.p. 193-194° (Found: C, 47.5; H, 3.8; N, 16.5%; M, 251. $C_{10}H_9N_3O_3S$ requires C, 47.8; H, 3.6; N, 16.7%; M, 251), $\nu_{max.}$ 3370 (NH), 1690 (C=O), 1510 and 1295 (aromatic NO_2) cm^{-1}, $\delta_{p.p.m.}$ 2.26 (s, 5-NHCOCH_3), 2.6 (s, 3-CH$_3$), 7.98 (d, 6-H or 7-H), 8.22 (br, 5-NHCOCH$_3$), and 8.33 (d, 6-H or 7-H), ($J_{6,7}$ = 8.9 Hz).

The second component was identified as 5-acetamido-3-methyl-1,2-benzisothiazole (0.4 g, 8%).

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[*] Longer periods of stirring or higher temperatures gave a decreased yield of product and increased tar formation.

Some Electrophilic Substitution Reactions of 5-Bromo-3-methyl-1,2-benzisothiazole

5-Bromo-3-methyl-1,2-benzisothiazole

5-Amino-3-methyl-1,2-benzisothiazole (20 g, 0.122 mol) was diazotised and treated with copper (I) bromide as described earlier for 7-bromo-3-methyl-1,2-benzisothiazole (p. 102). The reaction mixture was diluted and the resulting fawn solid was filtered off, neutralised in dilute aqueous ammonia and shaken with ether (4 x 100 ml). The solvent was evaporated and the orange residue, after short path distillation (97° at 1.5 mmHg), gave 5-bromo-3-methyl-1,2-benzisothiazole (24.4 g, 88%) as fluffy white needles, m.p. 53-54° (Found: C, 42.1; H, 2.8; N, 6.2%; M, 227/229. C_8H_6BrNS requires C, 42.1; H, 2.65; N, 6.3%; M, 227/229), $\nu_{max.}$ 1065 (aromatic Br) cm^{-1}, $\delta_{p.p.m.}$ 2.7 (s, 3-CH_3), 7.52 (dd, 6-H), 7.72 (dd, 7-H), and 7.8 (dd, 4-H), ($J_{4,7}$ = 0.5, $J_{4,6}$ = 1.7, $J_{6,7}$ = 8.5 Hz).

Bromination

5-Bromo-3-methyl-1,2-benzisothiazole (1.04 g, 0.005 mol) was brominated using bromine and silver sulphate in concentrated sulphuric acid as described earlier (p. 99). The mixture was stirred for 18 h at 20°, poured onto ice (100 g), neutralised and the organic product extracted with ethyl acetate. Evaporation of the extract left a white solid which was resolved into its four components by elution [with benzene-light petroleum (2:1)] from a column of silica gel.

The first component (R_f 0.65) crystallised from light petroleum to give a tribromo product (0.65 g, 34%), probably 3-methyl-4,5,7-tribromo-1,2-benzisothiazole , as white fibrous needles, m.p. 141-142° (Found: C, 24.7; H, 1.35; N, 4%; M, 383/385/387/389. $C_8H_4Br_3NS$ requires C, 24.9; H, 1.05; N, 3.65%; M, 383/385/387/389), $\nu_{max.}$ 1065 (aromatic Br) cm^{-1}, $\delta_{p.p.m.}$ 2.96 (s, 3-CH_3), and 7.47 (s, aromatic-H).

The second component (R_f 0.5) crystallised from light petroleum to give 5,7-dibromo-3-methyl-1,2-benzisothiazole (0.14 g, 10%) as pink-white needles, m.p.

84.5-85° (Found: C, 31.45; H, 1.75; N, 4.6%; $\underline{M}$, 305/307/309. $C_8H_5Br_2NS$ requires

C, 31.3; H, 1.65; N, 4.55%; $\underline{M}$, 305/307/309), $\vartheta_{max.}$ 1065 (aromatic Br) cm^{-1}, $\delta_{p.p.m.}$

2.69 (s, 3-CH_3), 7.71 (d, 6-H), and 7.96 (d, 4-H), ($\underline{J}_{4,6}$ = 1.4 Hz).

The third component ($\underline{R}_f$ 0.46) crystallised from light petroleum to give

4,5-dibromo-3-methyl-1,2-benzisothiazole (0.36 g, 24%) as white fibrous needles,

m.p. 109-110° (undepressed on admixture with an authentic sample) (Found: C, 31.8;

H, 1.8; N, 4.65%; $\underline{M}$, 305/307/309. $C_8H_5Br_2NS$ requires C, 31.3; H, 1.65; N, 4.55%;

$\underline{M}$, 305/307/309), $\vartheta_{max.}$ 1058 (aromatic Br) cm^{-1}, $\delta_{p.p.m.}$ (C_6D_6) 2.69 (s,3-CH_3),

6.66 (d, 6-H or 7-H), and 7.01 (d, 6-H or 7-H), ($\underline{J}_{6,7}$ = 0.85 Hz).

The final component crystallised from light petroleum (b.p. 40-60°) to give

white needles of 5-bromo-3-methyl-1,2-benzisothiazole (0.26 g, 23%), identified by

comparison with an authentic sample.

4,5-Dibromo-3-methyl-1,2-benzisothiazole

A solution of 5-amino-4-bromo-3-methyl-1,2-benzisothiazole (0.3 g, 0.00125

mol) in concentrated sulphuric acid (5 ml) and water (3 ml) was diazotised in the

usual manner and treated with copper ($\underline{1}$) bromide in hydrobromic acid as described

earlier (p. 102). Crystallisation of the product from light petroleum gave white

needles (0.3 g, 79%), m.p. 109-110°, $\delta_{p.p.m.}$ (C_6D_6) 2.69 (s, 3-CH_3), 6.66 (d, 6-H

or 7-H), and 7.01 (d, 6-H or 7-H), ($\underline{J}_{6,7}$ = 8.5 Hz), which was identical with the

third component isolated from the bromination of 5-bromo-3-methyl-1,2-benzisothia-

zole (p.<u>III</u>).

Nitration

5-bromo-3-methyl-1,2-benzisothiazole (1.14 g, 0.005 mol) was added in portions

during 75 min to a stirred solution of potassium nitrate (0.55 g, 0.0052 mol) in

concentrated sulphuric acid (10 ml) at 0-5°. The solution was stirred at 0-5° for

2 h then at room temperature for 18 h before being poured onto ice (100 g) and the

yellow product extracted with ethyl acetate. The dried extract was concentrated

and the product crystallised from ethyl acetate to give 5-bromo-3-methyl-4-nitro-

1,2-benzisothiazole (1.1 g, 81%) as yellow microneedles, m.p. 104-105° (Found:

C, 35.4; H, 2.05; N, 10.15%; M, 272/274. $C_8H_5BrN_2O_2S$ requires C, 35.2; H, 1.85;

N, 10.25%; M, 272/274), $\nu_{max.}$ 1535 and 1368 (NO_2) cm^{-1}, $\delta_{p.p.m.}$ 2.6 (s, 3-CH_3),

7.67 (d, 7-H), and 7.87 (d, 6-H), ($J_{6,7}$ = 8.7 Hz).

Formylation

(a) Phosphoryl chloride (1.32 g, 0.0088 mol) was added dropwise during 15 min to

ice-cold, stirred dimethylformamide (3.05 ml). 5-Bromo-3-methyl-1,2-benzisothiazole

(2 g, 0.0088 mol) was then added portionwise during 1 h at 0° and the mixture

stirred at room temperature for 18 h, poured into an excess of saturated aqueous

sodium carbonate and the product extracted with chloroform (2 x 50 ml). Evaporation

of the dried extract left a viscous orange oil, a 1:1 mixture (by t.l.c.), which

was resolved with difficulty by elution [with ether-light petroleum (1:3)] from a

column of silica gel.

The first component was crystallised (twice) from ethanol (charcoal) to give

5-bromo-3-formylamidobenzo[b]thiophen (A) as white microneedles, m.p. 223-224°

(Found: C, 42.45; H, 2.3; N, 5.5%; M, 225/227. C_9H_6BrNOS requires C, 42.2; H,

2.35; N, 5.5%; M, 225/227), $\nu_{max.}$ 3275 (N-H), 1690 (C=O), 1660 (N-H and C-N), and

1072 (aromatic Br) cm^{-1}, $\delta_{p.p.m.}$ [(CD_3)$_2$SO] 7.55 (dd, 6-H), 7.96 (d, 7-H), 8.07

(s, 2-H), 8.34 (d, 4-H), 8.44 (s, 3-NHCHO), and 10.74 (br, 3-NHCHO), ($J_{4,6}$ = 1.8,

and $J_{6,7}$ = 8.4 Hz).

The second component was crystallised from light petroleum to give N^2-(5-

bromo-2-formyl-3-benzo[b]thienyl)-N^{1}N^1-dimethylformamidine (B) as fluffy yellow

needles, m.p. 176-177° (Found: C, 46.6; H, 3.6; N, 8.8%; M, 310/312. $C_{12}H_{11}BrN_2OS$

requires C, 46.3; H, 3.55; N, 9%; M, 310/312), $\nu_{max.}$ 2920 (H-CO), 1647 (C=O), 1620

(C=N), and 1070 (aromatic Br), $\delta_{p.p.m.}$ 3.15 (d, NMe$_2$), 7.61 (m, 3 x aromatic-H),

8.03 (s, =CH), 9.81 (s, 2-CHO).

(b) The previous experiment was repeated but on addition of the 5-bromo-3-methyl-1,2-benzisothiazole the mixture was heated at 110° for 2 h, when the ratio of (A):(B) was 1:4 (by t.l.c.).

4-Amino-5-bromo-3-methyl-1,2-benzisothiazole

Hydrazine hydrate (0.6 g, 98% w/v) was added dropwise to a stirred mixture of Raney nickel (0.4 g) and 5-bromo-3-methyl-4-nitro-1,2-benzisothiazole (0.5 g, 0.00183 mol) in ethanol (10 ml). The mixture was boiled gently for 4 h, a further portion of hydrazine hydrate (0.6 g) added and the mixture boiled for a further 3 h. The Raney nickel was filtered off, and the filtrate diluted with water (100 ml), and the product extracted with ether. The extract was dried ($MgSO_4$) and evaporated to leave an oil which crystallised from light petroleum (charcoal) to give the product (0.36 g, 81%) as white fluffy microneedles, m.p. 81-82° (Found: C, 39.6; H, 2.9; N, 11.75%; $\underline{M}$, 242/244. $C_8H_7BrN_2S$ requires C, 39.5; H, 2.9; N, 11.5%; $\underline{M}$, 242/244), $\nu_{max.}$ 3460, 3375, 1610 (NH_2), and 1070 (aromatic Br) cm^{-1}, $\delta_{p.p.m.}$ 2.89 (s, 3-CH_3), 4.89 (br, 4-NH_2), 7.05 (d, 7-H), and 7.43 (d, 6-H), ($\underline{J}_{6,7}$ = 8.5 Hz).

4-Bromo-5-chloro-3-methyl-1,2-benzisothiazole

A solution of 5-amino-4-bromo-3-methyl-1,2-benzisothiazole (0.3 g, 0.00125 mol) in concentrated hydrochloric acid (5 ml) and water (3 ml) was diazotised and treated with copper ($\underline{1}$) chloride in concentrated hydrochloric acid as described earlier (p. 103). Crystallisation from light petroleum gave white microcrystals (0.32 g, 99%), m.p. 105-106° (Found: C, 36.85; H, 2.1; N, 5.3%; $\underline{M}$, 261/263/265. $C_8H_5BrClNS$ requires C, 36.6; H, 1.9; N, 5.3%; $\underline{M}$, 261/263/265), $\nu_{max.}$ 1063 (aromatic halogen) cm^{-1}, $\delta_{p.p.m.}$ (C_6D_6) 2.71 (s, 3-CH_3), 6.73 (d, 6-H or 7-H), and 6.86 (d, 6-H or 7-H), ($\underline{J}_{6,7}$ = 8.75 Hz).

The Preparation of some N-Substituted-3-aminomethyl-1,2-benzisothiazole hydrochlorides

Side-chain Bromination of 3-methyl-1,2-benzisothiazole

(a)   Bromine (1.78 g, 0.0112 mol) in dry carbon tetrachloride (10 ml) was added dropwise over 2 h to a stirred, irradiated (200 W tungsten lamp) solution of 3-methyl-1,2-benzisothiazole (1.64 g, 0.0112 mol) in boiling, dry carbon tetrachloride (20 ml).   The solution was boiled for 5 h, basified (20% aqueous sodium hydroxide) and the product extracted with chloroform.   T.l.c. showed several spots and so the reaction mixture was treated directly with hexamine.

After evaporation of the solvent, the residue was stirred and boiled for 16 h with hexamethylenetetramine (1.57 g, 0.0112 mol) in chloroform (50 ml). The mixture was cooled and the white product (1.5 g, 37%) was filtered off, washed with chloroform and dried at 60°.   A sample of the hexamine salt was crystallised from ethanol to give white microcrystals, m.p. 174-177°, $\delta_{p.p.m.}$ [$(CD_3)_2SO$] 4.58 (m, 3 × CH_2N), 4.76 (s, 3-$CH_2 \cdot C_6H_{12}BrN_4$), 5.33 (s, 3 × CH_2N), 7.65 (m, 5-H and 6-H), 8.45 (m, 7-H), and 8.55 (m, 4-H).

(b)   Bromine (1.78 g, 0.0112 mol) was added over 30 min to 3-methyl-1,2-benzisothiazole (1.64 g, 0.0112 mol) stirred at 120° and irradiated by a 200 W tungsten lamp.   The reaction mixture was kept at 120° for 6 h, then cooled and basified.   The resulting red oil was extracted with chloroform (2 × 100 ml) and washed successively with 10% aqueous sodium hydroxide (2 × 20 ml), with water (2 × 20 ml), and dried ($MgSO_4$).   Evaporation of the solvent left a red oil, which was shown by t.l.c. to be a mixture.   No attempt was made to isolate the bromo-methyl derivative, but the crude product was reacted directly with dimethylamine (p. 116) to give NN-dimethyl-(1,2-benzisothiazol-3-yl)methylamine which was isolated as the hydrochloride (0.5 g, 20%).

(c)   N-Bromosuccinimide (3 g, 0.0163 mol) was added in portions, during 20 min, to a stirred, boiling solution of 3-methyl-1,2-benzisothiazole (2.46 g, 0.0163 mol)

in dry carbon tetrachloride (200 ml) containing dibenzoyl peroxide (0.1 g). A

stream of dry nitrogen was bubbled through the solution and the mixture was

irradiated with a 200 W tungsten lamp. The mixture was stirred and boiled for

16 h, then cooled, the succinimide was filtered off, and the filtrate was evapor-

ated. G.l.c. analysis showed that the residue was a mixture of the bromomethyl

derivative (84%) and the dibromomethyl derivative (7%). The mixture was not

separated, but was used directly in the following reactions.

Some N-Substituted-3-aminomethyl-1,2-benzisothiazole hydrochlorides

A solution of 3-bromomethyl-1,2-benzisothiazole [prepared by method (c)

above] in dry benzene (60 ml) and the appropriate amine (dimethylamine,

morpholine, piperidine, pyrrolidine, and N-ethylethanolamine, 0.0337 mol) was

boiled for 4 h, then cooled and filtered. Ether (60 ml) was added to the

filtrate which was washed with water (5 x 200 ml), then dried (MgSO$_4$). The amine

was isolated as its hydrochloride by the addition of a dry ethereal solution of

hydrogen chloride. Details are in Table 2 (p. 118).

The residual solution was evaporated to give a solid (0.35 g, 7%) which

crystallised from ether as translucent cubes of 3-dibromomethyl-1,2-benzisothiazole,

m.p. 92-93° (lit.,[100] 93.5-94°) (Found: C, 31.4; H, 1.6; N, 4.6%; $\underline{M}$, 305/307/309.

Calculated for C$_8$H$_4$Br$_2$NS C, 31.3; H, 1.65; N, 4.55%; $\underline{M}$, 305/307/309), $\nu_{max.}$ 734,

655 and 595 (C-Br) cm^{-1}, $\delta_{p.p.m.}$ 7.02 (s, 3-CH), 7.5 (m, 5-H and 6-H), 7.8 (m, 7-H),

and 8.4 (m, 4-H).

(1,2-Benzisothiazol-3-yl)methylamine hydrochloride

3-Bromomethyl-1,2-benzisothiazole [prepared by method (c) above] reacted

with hexamethylenetetramine as described previously (p. 115) to form the

hexamine salt (72% based on 3-methyl-1,2-benzisothiazole). A mixture of the

hexamine salt (5 g, 0.0136 mol), ethanol (20 ml), concentrated hydrochloric

acid (15 ml) and water (5 ml) were boiled for 40 min, then cooled and basified.

The solution was shaken with ether, the ethereal solution dried ($MgSO_4$) and the

hydrochloride prepared by the addition of dry ethereal hydrogen chloride.

Details are in Table 2 (p. 118).

N-2-Chloroethyl-N-ethyl-(1,2-benzisothiazol-3-yl)methylamine hydrochloride

　　　Thionyl chloride (3.32 g, 0.026 mol) was added dropwise over 10 min to a

stirred, boiling solution of N-ethyl-N-2-hydroxyethyl-(1,2-benzisothiazol-3-yl)c

methylamine hydrochloride (3.4 g, 0.013 mol) in dry chloroform (50 ml). After

a further 45 min, the chloroform and excess of thionyl chloride were distilled

off under reduced pressure, and the residue was dissolved in the minimum

amount of dry ethanol. On addition of an excess of dry ether the product was

obtained as a white solid. Crystallisation from dry ethanol-ether gave white

microneedles (3.65 g, 95%), m.p. 122-124° (Found: C, 49.23; H, 5.57; N, 9.47%;

M (free base), 254. $C_{12}H_{16}ClN_2S$ requires C, 49.49; H, 5.54; N, 9.62%; M (free

base), 254).

Table 2

Structure: benzisothiazole with CH$_2$NX·HCl substituent

NX	m.p. (°)	Yield (%)	M	Found (%)			Formula	M	Required (%)		
				C	H	N			C	H	N
NH$_2$[a]	178[c]	75	200/202	47.5	4.7	13.6	C$_8$H$_9$ClN$_2$S	200/202	47.8	4.5	13.9
NMe$_2$[a]	205–207	81[d]	228/231	52.15	5.8	12.8	C$_{10}$H$_{13}$ClN$_2$S	228/231	52.5	5.75	12.25
N⟨pyrrolidine⟩[b]	195–197	82[d]	218[e]	56.4	5.9	10.7	C$_{12}$H$_{15}$ClN$_2$S	218[e]	56.55	5.95	11
N⟨piperidine⟩[b]	178–180	71[d]	233[e]	57.7	6.4	10.5	C$_{13}$H$_{17}$ClN$_2$S	233[e]	58.05	6.4	10.4
N⟨morpholine O⟩[a]	215–216	71[d]	234[e]	53.4	5.6	10.4	C$_{12}$H$_{15}$ClN$_2$OS	234[e]	53.25	5.6	10.35
NEt(CH$_2$)$_2$OH[b]	99–101	82[d]	236[e]	53.1	6.3	10.2	C$_{12}$H$_{17}$ClN$_2$OS	236[e]	52.85	6.3	10.3

a. Crystallisation from dry ethanol.

b. Crystallisation from dry ethanol-ether.

c. Decomposition.

d. Calculated from 3-methyl-1,2-benzisothiazole.

e. Free base.

The Preparation of some N-Substituted-3-aminomethyl-5-bromo-1,2-benzisothiazole hydrochlorides

5-Bromo-3-bromomethyl-1,2-benzisothiazole

N-Bromosuccinimide (3.12 g, 0.0176 mol) was added in portions during 1.5 h to a stirred and boiled solution of 5-bromo-3-methyl-1,2-benzisothiazole (4 g, 0.0176 mol) in dry carbon tetrachloride (200 ml) irradiated by a 200 W tungsten lamp and containing dibenzoyl peroxide (0.1 g). A stream of dry nitrogen was bubbled through the solution and the stirred mixture was boiled for a further 4 h, then cooled thoroughly and filtered. The solvent was removed under reduced pressure to leave an orange oil (5.6 g) which slowly solidified. N.m.r. spectra showed the solid to be a mixture* of monobromomethyl derivative (70%), dibromomethyl derivative (10%) and starting material (20%).

Crystallisation of the mixture from light petroleum gave 5-bromo-3-bromomethyl -1,2-benzisothiazole (2.7 g, 50%) as white needles, m.p. 99–101° (Found: C, 31.7; H, 1.6; N, 4.7%; $\underline{M}$, 305/307/309. $C_8H_5Br_2NS$ requires C, 31.3; H, 1.65; N, 4.55%; $\underline{M}$, 305/307/309), $\upsilon_{max.}$ 1059 (aromatic Br), 605 and 505 (alkyl Br) cm^{-1}, $\delta_{p.p.m.}$ 4.79 (s, 3-CH$_2$Br), 7.61 (dd, 6-H), 7.81 (d, 7-H), and 8.25 (d, 4-H), ($\underline{J}_{4,6}$ = 1.75 and $\underline{J}_{6,7}$ = 8.75 Hz).

Some N-Substituted-3-aminomethyl-5-bromo-1,2-benzisothiazole hydrochlorides

A solution of the mixture* (prepared above) in dry benzene (80 ml) was reacted with the appropriate amine (0.0342 mol) in the manner described earlier (p. 116). Details of the amine hydrchlorides prepared are in Table 3 (p. 121).

The solution remaining after removal of the amine hydrochloride was evaporated and a portion of the residue was chromatographed on a silica gel column and eluted with benzene-chloroform (2:1). The first fraction was concentrated and

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* The unresolved mixture was used in the reactions indicated.

after short path distillation (99° at 0.3 mmHg) gave a white crystalline solid,

identified as 5-bromo-3-dibromomethyl-1,2-benzisothiazole, m.p. 78-80° (Found:

C, 25.25; H, 1.25%; $\underline{M}$, 383/385/387/389. $C_8H_4Br_3NS$ requires C, 24.9; H, 1.6%; $\underline{M}$,

383/385/387/389), $\nu_{max.}$ 1065 (aromatic Br), 680, 596 and 515 (alkyl Br) cm^{-1},

$\delta_{p.p.m.}$ 6.95 (s, 3-$CHBr_2$), 7.63 (dd, 6-H), 7.78 (dd, 7-H), and 8.65 (dd, 4-H),

($\underline{J}_{4,7}$ = 0.5, $\underline{J}_{4,6}$ = 1.7, and $\underline{J}_{6,7}$ = 8.6 Hz).

(5-Bromo-1,2-benzisothiazol-3-yl)methylamine hydrochloride

A solution of the mixture[*] (prepared previously, p. 119) in dry chloroform

(100 ml) was reacted with hexamethylenetetramine (0.018 mol) in the manner

described earlier (p. 115) to give the hexamine salt (5.4 g, 67%, based on 5-bromo-

3-methyl-1,2-benzisothiazole).

The hexamine salt (5 g, 0.0112 mol) was hydrolysed in the manner previously

described (p. 117) to form the required amine hydrochloride, details of which are

given in Table 3 (p. 121).

N-2-Chloroethyl-N-ethyl-(5-bromo-1,2-benzisothiazol-3-yl)methylamine hydrochloride

$\underline{N}$-2-Hydroxyethyl-$\underline{N}$-ethyl-(5-bromo-1,2-benzisothiazol-3-yl)methylamine

hydrochloride (4.85 g, 0.0138 mol) was treated with thionyl chloride in boiling

chloroform as described earlier (p. 117) to give the required halogenoamine

hydrochloride (4.55 g, 91%). Crystallisation from dry ethanol (charcoal) gave

pale pink microcrystals, m.p. 141-143° (Found: C, 39.2; H, 4.3; N, 7.8%; $\underline{M}$ (free

base), 331/332/333/334/335/336. $C_{12}H_{15}BrCl_2N_2S$ requires C, 38.95; H, 4.1; N, 7.6%,

$\underline{M}$(free base), 331/332/333/334/335/336).

Table 3

Structure: benzisothiazole (Br-substituted) with CH$_2$NX.HCl substituent

NX	m.p. (°)	Yield (%)	Found (%) C	H	N	$\underline{M}$	Formula	Required (%) C	H	N	$\underline{M}$
NH$_2$[a]	250–253	78	34.5	2.9	9.6	242/244[e]	C$_8$H$_8$BrClN$_2$S	34.4	2.9	10	242/244[e]
NMe$_2$[a]	220–222	64[d]	39.3	4.15	8.95	270/272[e]	C$_{10}$H$_{12}$BrClN$_2$S	39.05	3.95	9.1	270/272[e]
(pyrrolidine N)[b]	250[c]	64[d]	43.45	4.45	8.2	296/298[e]	C$_{12}$H$_{14}$BrClN$_2$S	43.2	4.25	8.4	296/298[e]
(piperidine N)[a]	220–223	68[d]	45.3	4.85	8.1	309/311[e]	C$_{13}$H$_{16}$BrClN$_2$S	44.9	4.65	8.05	~~309/311~~[e] 310/312
(morpholine N–O)[b]	248–251	67[d]	41.6	4.25	8.05	312/314[e]	C$_{12}$H$_{14}$BrClN$_2$OS	41.2	4.05	8.05	312/314[e]
NEt(CH$_2$)$_2$OH[a]	157–159	69[d]	41.1	4.9	8.05	285[f]	C$_{12}$H$_{16}$BrClN$_2$OS	41	4.6	7.95	285[f]

a. Crystallised from dry ethanol–ether.

b. Crystallised from dry ethanol.

c. Decomposition.

d. Calculated from 5-bromo-3-methyl-1,2-benzisothiazole.

e. Free base.

f. $\underline{M}$-CH$_2$OH.HCl.

The Preparation of some N-Substituted-3-aminomethyl-5-chloro-1,2-benzisothiazole hydrochlorides

5-Chloro-3-methyl-1,2-benzisothiazole

5-Amino-3-methyl-1,2-benzisothiazole (20 g, 0.122 mol) was diazotised and treated with copper ($\underline{1}$) chloride in hydrochloric acid as described earlier (p. 103) and gave the product (20.4 g, 91%), which was purified by short path distillation (61° at 0.3 mmHg) as white needles, m.p. 49-50° (lit.,[78] 52.5^{o}) (Found: $\underline{M}$, 183/185. Calculated for C_8H_6ClNS $\underline{M}$, 183/185), $\nu_{max.}$ 1075 (aromatic Cl) cm^{-1}, $\delta_{p.p.m.}$ 2.68 (s, 3-CH_3), 7.42 (dd, 6-H), 7.79 (dd, 7-H), and 7.85 (dd, 4-H), ($\underline{J}_{4,7}$ = 0.75, $\underline{J}_{4,6}$ = 1.95, and $\underline{J}_{6,7}$ = 8.6 Hz).

3-Bromomethyl-5-chloro-1,2-benzisothiazole

5-Chloro-3-methyl-1,2-benzisothiazole (3 g, 0.0154 mol) was brominated with N-bromosuccinimide (2.93 g, 0.0168 mol) as described earlier (p. 119). The n.m.r. spectrum showed the product to be a mixture* of the monobromomethyl derivative (70%), dibromomethyl derivative (15%), and starting material (15%).

Crystallisation of the mixture from light petroleum (b.p. 40-60°) gave 3-bromomethyl-5-chloro-1,2-benzisothiazole (2 g, 50%) as white rosettes, m.p. 73-75° (Found: C, 36.85; H, 1.95; N, 5.25%; $\underline{M}$, 261/263/265. $C_8H_5BrClNS$ requires C, 36.6; H, 1.9; N, 5.3%; $\underline{M}$, 261/263/265), $\nu_{max.}$ 1074 (aromatic Cl), 611 and 535 (alkyl Br) cm^{-1}, $\delta_{p.p.m.}$ 4.78 (s, 3-CH_2Br), 7.46 (dd, 6-H), 7.82 (dd, 7-H), and 8.05 (dd, 4-H), ($\underline{J}_{4,7}$ = 0.75, $\underline{J}_{4,6}$ = 1.6, and $\underline{J}_{6,7}$ = 8.5 Hz).

Some N-Substituted-3-aminomethyl-5-chloro-1,2-benzisothiazole hydrochlorides

A solution of the foregoing mixture* in dry benzene (80 ml) was reacted with the appropriate amine (0.031 mol) as described earlier (p. 116). Details of the

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* The unresolved mixture was used in the reactions indicated.

amine hydrochlorides prepared are in Table 4 (p. 124).

(5-Chloro-1,2-benzisothiazol-3-yl)methylamine hydrochloride

The crude bromination mixture (p. 122) was reacted with hexamethylenetetramine (0.0155 mol) in boiling chloroform as described earlier (p. 115) to give the hexamine salt (4.3 g, 69%, based on 5-chloro-3-methyl-1,2-benzisothiazole).

The hexamine salt (4 g, 0.01 mol) was hydrolysed in the manner previously described (p. 116) to give the required amine hydrochloride, details of which are given in Table 4 (p. 124).

N-2-Chloroethyl-N-ethyl-(5-chloro-1,2-benzisothiazol-3-yl)methylamine hydrochloride

N-2-Hydroxyethyl-N-ethyl-(5-chloro-1,2-benzisothiazol-3-yl)methylamine hydrochloride (3.7 g, 0.012 mol) was used to prepare the product (3.5 g, 90%) by the method described earlier (p. 117). Crystallisation from dry ethanol-ether (charcoal) gave fawn microcrystals, m.p. 132-134° (Found: C, 44.5; H, 4.85; N, 8.45% ; $\underline{M}$ (free base), 288/290/292. $C_{12}H_{15}Cl_3N_2S$ requires C, 44.25; H, 4.65; N, 8.6%; $\underline{M}$ (free base), 288/290/292).

Table 4

CH₂NX.HCl attached to Cl-substituted 1,2-benzisothiazole ring system

NX	m.p. (°)	Yield (%)	Found (%) C	H	N	M	Formula	Required (%) C	H	N	M
NH_2[a]	244–246	75	41	3.65	11.85	264/266/268	$C_8H_8Cl_2N_2S$	40.85	3.45	11.9	264/266/268
NMe_2[a]	229–230	68[c]	45.75	4.45	11.1	226/228[d]	$C_{10}H_{12}Cl_2N_2S$	45.65	4.6	10.65	226/228[d]
⟨N⟩[a]	243–245	68[c]	49.85	5	9.55	182/184[e]	$C_{12}H_{14}Cl_2N_2S$	49.85	4.9	9.7	182/184[e]
⟨N⟩[a]	216–218	67[c]	51	5.3	9.5	266/268[d]	$C_{13}H_{16}Cl_2N_2S$	51.4	5.3	9.3	266/268[d]
⟨N⟩O[b]	228–230	67[c]	47.4	4.8	8.8	182/184[e]	$C_{12}H_{14}Cl_2N_2OS$	47.2	4.6	8.4	182/184[e]
$NEt(CH_2)_2OH$[a]	139–141	66[c]	46.95	5.35	9.5	270/272[d]	$C_{12}H_{16}Cl_2N_2OS$	46.9	5.25	9.15	270/272[d]

a. Crystallised from dry ethanol.

b. Crystallised from dry methanol.

c. Calculated from 5-chloro-3-methyl-1,2-benzisothiazole.

d. Free base.

e. M−NX.HCl.

(5-Bromo-1,2-benzisothiazol-3-yl)acetonitrile

(a) A solution of 5-bromo-3-bromomethyl-1,2-benzisothiazole (1 g, 0.00326 mol) in dry acetone (10 ml) was added dropwise during 15 min to a stirred suspension of sodium cyanide (0.17 g, 0.0033 mol) in acetone (20 ml) and water (4 ml). The solution was stirred for 3 h at room temperature, poured into water (200 ml) and the product extracted with ethyl acetate (2 × 100 ml). The dried extract was concentrated to leave a solid which crystallised from ethyl acetate-light petroleum to give di(5-bromo-1,2-benzisothiazol-3-ylmethyl)-(5-bromo-1,2-benzisothiazol-3-yl)acetonitrile (0.65 g, 84%) as white microcrystals, m.p. 219-221° (Found: C, 42.9; H, 2.05; N, 8%; $\underline{M}$ (low energy scan), 702/704/706/708. $C_{25}H_{13}Br_3N_4S_3$ requires C, 42.6; H, 1.85; N, 7.95%; $\underline{M}$, 702/704/706/708), $\nu_{max.}$ 2235 (CN) and 1064 (aromatic Br) cm^{-1}, $\delta_{p.p.m.}$ [(CD$_3$)$_2$SO] 4.42 (s, 2 × CH$_2$), and 7.52-8.14 (m, 9 × aromatic-H).

(b) The preceding experiment was repeated using a four-fold excess of sodium cyanide and an addition time of 2.5 h, but only di(5-bromo-1,2-benzisothiazol-3-ylmethyl)-(5-bromo-1,2-benzisothiazol-3-yl)acetonitrile (73%) was obtained.

(c) A solution of 5-bromo-3-bromomethyl-1,2-benzisothiazole (0.9 g, 0.0029 mol) in dry dimethylsulphoxide (10 ml) was added dropwise during 2.5 h to a stirred solution of sodium cyanide (0.17 g, 0.0033 mol) in dry dimethylsulphoxide (20 ml) at room temperature. The solution was stirred for a further 60 min at room temperature, heated at 80° for 2 h then cooled and poured into water (300 ml). The product was extracted with ethyl acetate and the dried extract concentrated. Purification of the product by column chromatography on silica gel and eluting with chloroform gave (5-bromo-1,2-benzisothiazol-3-yl)acetonitrile (0.44 g, 60%) which crystallised from benzene-light petroleum (b.p. 40-60°) (charcoal) as white needles, m.p. 119-120° (Found: C, 43.1; H, 2.1%; $\underline{M}$, 252/254. $C_9H_5BrN_2S$ requires C, 42.7; H, 2.6%; $\underline{M}$, 252/254), $\nu_{max.}$ 2258 (CN), and 1066 (aromatic Br) cm^{-1}, $\delta_{p.p.m.}$ 4.17 (s, 3-CH$_2$CN), 7.66 (dd, 6-H), 7.84 (dd, 7-H), and 8.17 (dd, 4-H), ($\underline{J}_{4,7}$ = 0.5,

$\underline{J}_{4,6} = 1.7$, and $\underline{J}_{6,7} = 9$ Hz).

(5-Bromo-1,2-benzisothiazol-3-yl)acetic acid

(5-Bromo-1,2-benzisothiazol-3-yl)acetonitrile (0.4 g, 0.00158 mol) was hydrolysed in the manner described earlier (p. 92). Crystallisation from ethyl acetate gave the product (0.3 g, 70%) as white microcrystals, m.p. 153-154° (decomp) (Found: C, 39.9; H, 2.45; N, 5.15%; $\underline{M}$, 271/273. $C_9H_6BrNO_2S$ requires C, 39.7; H, 2.2; N, 5.05%; $\underline{M}$, 271/273), $\vartheta_{max.}$ 3000-2400br (OH), and 1720 (C=O) cm^{-1}, $\delta_{p.p.m.}$ [$(CD_3)_2SO$] 4.19 (s, 3-C$\underline{H}_2$CO$_2$H), 4.46 (br, 3-CH$_2$CO$_2\underline{H}$), 7.72 (dd, 6-H), 8.15 (dd, 7-H), and 8.38 (dd, 4-H), ($\underline{J}_{4,7} = 0.7$, $\underline{J}_{4,6} = 1.75$, and $\underline{J}_{6,7} = 8.75$ Hz).

(5-Chloro-1,2-benzisothiazol-3-yl)acetonitrile

(a) A solution of 3-bromomethyl-5-chloro-1,2-benzisothiazole (1.3 g, 0.0049 mol) in dry acetone (10 ml) was reacted as described earlier [method (a), p. 125] and the mixture was stirred for 6 h at room temperature. Crystallisation from benzene-light petroleum gave di(5-chloro-1,2-benzisothiazol-3-ylmethyl)-(5-chloro-1,2-benzisothiazol-3-yl)acetonitrile (0.9 g, 95%) as white microneedles, m.p. 202-203° (Found: C, 52.7; H, 2.35; N, 9.8%; $\underline{M}$ (low energy scan), 570/572/574/576. $C_{25}H_{13}Cl_3N_4S_3$ requires C, 52.5; H, 2.3; N, 9.8%; $\underline{M}$, 570/572/574/576), $\vartheta_{max.}$ 2240 (CN), and 1076 (aromatic Cl) cm^{-1}, $\delta_{p.p.m.}$ [(CD$_3$)$_2$SO] 4.43 (s, 2 x CH$_2$), and 7.12-8.12 (m, 9 x aromatic-H).

(b) 3-Bromomethyl-5-chloro-1,2-benzisothiazole (1 g, 0.0038 mol) was treated with sodium cyanide in dimethylsulphoxide as described earlier [method (c), p. 125] and the mixture was stirred for 21 h at room temperature. Crystallisation from benzene-light petroleum gave (5-chloro-1,2-benzisothiazol-3-yl)acetonitrile (0.49 g, 62%) as white microcrystals. After short path distillation (120° at 0.1 mmHg), a sample gave a fluffy solid, m.p. 105-106° (Found: C, 51.9; H, 2.55; N, 13.15%; $\underline{M}$, 208/210. $C_9H_5ClN_2S$ requires C, 51.8; H, 2.4; N, 13.45%; $\underline{M}$, 208/210), $\vartheta_{max.}$ 2260 (CN), and 1079 (aromatic Cl) cm^{-1}, $\delta_{p.p.m.}$ 4.18 (s, 3-CH$_2$CN), 7.53 (dd, 6-H), 7.89 (dd, 4-H), and 8.01 (dd, 7-H), ($\underline{J}_{4,7}$ = 0.75, $\underline{J}_{4,6}$ = 1.75, and $\underline{J}_{6,7}$ = 8.5 Hz).

(5-Chloro-1,2-benzisothiazol-3-yl)acetic acid

(5-Chloro-1,2-benzisothiazol-3-yl)acetonitrile (0.7 g, 0.00335 mol) was hydrolysed as before (p. 92). Crystallisation from ethyl acetate-light petroleum (charcoal) gave orange microcrystals (0.5 g, 66%), m.p. 143-145° (decomp) (lit.,[56] 159-160°) (Found: C, 47.7; H, 2.65; N, 6.15%; $\underline{M}$, 227/229. Calculated for $C_9H_6ClNO_2S$ C, 47.2; H, 2.75; N, 6.25%; $\underline{M}$, 227/229), $\vartheta_{max.}$ 2900-2500br (OH), 1720 (C=O), and 1080 (aromatic Cl) cm^{-1}, $\delta_{p.p.m.}$ 4.2 (s, 3-CH$_2$CO$_2$H), 5.22 (br, 3-CH$_2$CO$_2$H), 7.64 (dd, 6-H), 8.23 (d, 7-H), and 8.26 (d, 4-H), ($\underline{J}_{4,6}$ = 1.75, and $\underline{J}_{6,7}$ = 8 Hz).

The Bromination and Nitration of 5-Hydroxy-3-methyl-1,2-benzisothiazole

5-Hydroxy-3-methyl-1,2-benzisothiazole

A solution of 5-amino-3-methyl-1,2-benzisothiazole (10 g, 0.061 mol) in concentrated sulphuric acid (20 ml) and water (40 ml) was cooled to 0° and diazo-tised with an aqueous solution of sodium nitrite (4.5 g, 0.065 mol) at 3-8°. The diazonium solution was stirred at room temperature for 15 min, at 50° for 2 h and then at 100° until the evolution of nitrogen ceased. The hot solution was filtered and cooled to give the phenol which was crystallised from hot water (charcoal) as white needles (4.5 g, 45%), m.p. 196-198° (Found: C, 57.9; H, 4.5; N, 8.3%; $\underline{M}$, 165. C_8H_7NOS requires C, 58.15; H, 4.3; N, 8.5%; $\underline{M}$, 165), $\upsilon_{max.}$ 3120br (OH), and 1335, 1220 (C-O and OH) cm^{-1}, $\delta_{p.p.m.}$ [$(CD_3)_2SO$] 2.61 (s, 3-CH$_3$), 7.17 (dd, 4-H), 7.34 (dd, 6-H), 7.92 (dd, 7-H), and 9.77 (br, 5-OH), ($\underline{J}_{4,7}$ = 0.5, $\underline{J}_{4,6}$ = 2.4, and $\underline{J}_{6,7}$ = 8.8 Hz).

Bromination

A solution of bromine (0.96 g, 0.006 mol) in ethyl acetate (10 ml) was added during 1 h to a stirred, ice-cold solution of 5-hydroxy-3-methyl-1,2-benzisothiazole (1 g, 0.006 mol). After a further 1 h at 0°, the mixture was poured into water (150 ml) and the product was extracted with ether (3 x 50 ml). The ether extract was washed with water (3 x 50 ml), dried (MgSO$_4$) and evaporated. Crystallisation of the residue from ethyl acetate (charcoal) gave 4-bromo-5-hydroxy-3-methyl-1,2-benzisothiazole (1.4 g, 95%) as orange needles, m.p. 165-166° (Found: C, 39.25; H, 2.5; N, 5.85%; $\underline{M}$, 243/245. C_8H_6BrNOS requires C, 39.35; H, 2.5; N, 5.75%; $\underline{M}$, 243/245), $\upsilon_{max.}$ 3200br (OH), 1335, 1170 (C-O and OH), and 1064 (aromatic Br) cm^{-1}, $\delta_{p.p.m.}$ 2.96 (s, 3-CH$_3$), 5.94 (s, 5-OH), 7.23 (d, 6-H), and 7.69 (d, 7-H), ($\underline{J}_{6,7}$ = 8.6 Hz).

Nitration

A solution of concentrated nitric acid (0.38 g, 0.006 mol, d. 1.5) in glacial

acetic acid (10 ml) was added dropwise during 2.5 h to a stirred solution of 5-

hydroxy-3-methyl-1,2-benzisothiazole (1 g, 0.006 mol) in glacial acetic acid (50 ml)

at room temperature. The solution was stirred for a further 3 h, poured into water

(500 ml) and the precipitate filtered off. Crystallisation from ethyl acetate

(charcoal) gave 5-hydroxy-3-methyl-4-nitro-1,2-benzisothiazole (0.9 g, 72%) as

yellow plates, m.p. 222° (decomp) (Found: C, 45.75; H, 3; N, 13.2%; $\underline{M}$, 210.

$C_8H_6N_2O_3S$ requires C, 45.7; H, 2.9; N, 13.35%; $\underline{M}$, 210), $\nu_{max.}$ 3000br (OH), and 1530,

1320 (NO_2) cm^{-1}, $\delta_{p.p.m.}$ 2.73 (s, 3-CH_3), 4 (s, 5-OH), 7.3 (d, 6-H), and 8.1 (d,

7-H), $\delta_{p.p.m.}$ [$(CD_3)_2SO$] 2.48 (s, 3-CH_3), 3.45 (br, 5-OH), 7.42 (d, 6-H), and

8.22 (d, 7-H), ($\underline{J}_{6,7}$ = 9 Hz).

Some Further Derivatives of 5-Hydroxy-3-methyl-1,2-benzisothiazole

3-Methyl-5-methylsulphonyloxy-1,2-benzisothiazole

Methylsulphonyl chloride (4.5 ml) was added dropwise during 20 min to a

stirred solution of 5-hydroxy-3-methyl-1,2-benzisothiazole (1 g, 0.006 mol) in dry

pyridine (30 ml) at 0°. The mixture was then stirred for a further 1 h at 0° and

poured into ice-water (100 ml). The precipitate was filtered off and washed well

with ice-cold aqueous 10% hydrochloric acid and with cold water. Crystallisation

from benzene-light petroleum (charcoal) gave translucent prisms (1.1 g, 76%), m.p.

115-116° (Found: C, 44.5; H, 4.09; N, 5.55%; $\underline{M}$, 243. $C_9H_9NO_3S_2$ requires C, 44.45;

H, 3.75; N, 5.75%; $\underline{M}$, 243), $\nu_{max.}$ 1355 and 1185 (S=O) cm^{-1}, $\delta_{p.p.m.}$ 2.71 (s, 3-CH_3),

3.18 (s, SCH_3), 7.43 (dd, 6-H), 7.83 (dd, 4-H), and 7.92 (dd, 7-H), ($\underline{J}_{4,7}$ = 0.7,

$\underline{J}_{4,6}$ = 2.2, and $\underline{J}_{6,7}$ = 8.5 Hz).

5-Allyloxy-3-methyl-1,2-benzisothiazole

A mixture of 5-hydroxy-3-methyl-1,2-benzisothiazole (1.5 g, 0.009 mol),

allyl bromide (2.25 ml, 0.015 mol), anhydrous potassium carbonate (4.5 g), and anhydrous butanone (60 ml) were boiled and stirred for 2 h, then cooled, and filtered. Evaporation of the solvent left a pale brown oil, which was distilled under nitrogen to give a pale yellow oil (1.5 g, 81%), b.p. 108-110° at 0.2 mmHg (Found: C, 64.3; H, 5.5; N, 6.3%; M, 205. $C_{11}H_{11}NOS$ requires C, 64.35; H, 5.4; N, 6.8%; M, 205), $\nu_{max.}$ 3080 (=CH), 1600 (C=C), and 1220 (C-O) cm^{-1}, $\delta_{p.p.m.}$ 2.7 (s, 3-CH$_3$), 4.52 (d, -OCH$_2$-), 5.3 (t, CH$_2$=CH), 5.9 (m, CH$_2$=CH), 7.18 (dd, 6-H), 7.27 (dd, 4-H), and 7.75 (dd, 7-H), ($J_{4,7}$ = 0.9, $J_{4,6}$ = 2.4, and $J_{6,7}$ = 8.4 Hz).

4-Allyl-5-hydroxy-3-methyl-1,2-benzisothiazole

5-Allyloxy-3-methyl-1,2-benzisothiazole (1 g, 0.005 mol) was boiled with freshly distilled NN-dimethylaniline (40 ml) for 3 h. and the mixture was cooled, poured into ice-cold aqueous 10% hydrochloric acid (60 ml) and shaken with ether (3 x 30 ml). Phenolic material was extracted from the ethereal solution with aqueous 10% sodium hydroxide (3 x 30 ml) and the combined alkaline extracts were acidified with cold aqueous 10% hydrochloric acid. The product was extracted with ether (3 x 30 ml), the combined ether layers were washed with aqueous 5% sodium hydrogen carbonate (3 x 20 ml), with water (2 x 20 ml), then dried (MgSO$_4$), and evaporated to leave a white solid which crystallised from ethyl acetate as white needles (0.9 g, 90%), m.p. 150° (Found: C, 64.7; H, 5.35; N, 6.7%; M, 205. $C_{11}H_{11}NOS$ requires C, 64.35; H, 5.4; N, 6.8%; M, 205), $\nu_{max.}$ 3200-2900br (OH), 1633 (CH$_2$=CHR), and 1305, 1265 (C-O and OH) cm^{-1}, $\delta_{p.p.m.}$ [(CD$_3$)$_2$SO] 2.79 (s, 3-CH$_3$), 3.82 (d, CH$_2$-CH), 4.83 (q, CH$_2$=CH), 6.05 (m, CH$_2$-CH=CH$_2$), 7.21 (d, 6-H), and 7.78 (d, 7-H), ($J_{6,7}$ = 8.7 Hz).

5-Acetoxy-3-methyl-1,2-benzisothiazole

5-Hydroxy-3-methyl-1,2-benzisothiazole (3 g, 0.0182 mol) was boiled under reflux in acetic anhydride (14 ml) and glacial acetic acid (6 ml) for 30 min,

cooled and poured into ice-water (200 ml). The product was extracted with ether

(3 x 60 ml) and the combined extracts were washed with a saturated solution of

sodium hydrogen carbonate (until neutral). Evaporation of the solvent left an oil

which, after short path distillation (88° at 0.25 mmHg), gave white <u>needles</u> (3.54

g, 94%), m.p. 53-54° (Found: C, 57.8; H, 4.3; N, 6.7%; <u>M</u>, 207. $C_{10}H_9NO_2S$ requires

C, 57.95; H, 4.4; N, 6.75%; <u>M</u>, 207), $\nu_{max.}$ 1760 (C=O), and 1210 (C-O) cm^{-1},

$\delta_{p.p.m.}$ 2.28 (s, 5-O-OCCH$_3$), 2.63 (s, 3-CH$_3$), 7.26 (dd, 6-H), 7.65 (dd, 4-H), and

7.88 (dd, 7-H), ($\underline{J}_{4,7}$ = 0.7, $\underline{J}_{4,6}$ = 2.2, and $\underline{J}_{6,7}$ = 8.5 Hz).

<u>Attempted Fries Rearrangement of 5-Acetoxy-3-methyl-1,2-benzisothiazole</u>

(a) A mixture of 5-acetoxy-3-methyl-1,2-benzisothiazole (1.5 g, 0.00724 mol)

and anhydrous aluminium chloride (2.24 g, 0.0145 mol) in dry benzene (80 ml) was

stirred at room temperature for 16 h and then boiled for 24 h. Aqueous 10%

hydrochloric acid (30 ml) was added, the organic layer was separated and the

aqueous phase was shaken with ether (3 x 50 ml). The combined organic extracts

were shaken with aqueous 5% sodium hydroxide solution (3 x 50 ml) and with water

(20 ml), and then were concentrated to leave a two component oil which was resolved

by elution [with ether-light petroleum (1:2)] from a column of silica gel. The

first component was identified as acetophenone (0.4 g) by comparison with an

authentic sample. The second component (0.66 g, 44%) was identified as 5-acetoxy-

3-methyl-1,2-benzisothiazole.

The combined aqueous washings were acidified and shaken with ether (3 x 50 ml).

The ether extract was washed with saturated sodium hydrogen carbonate solution

(2 x 10 ml), with water (10 ml), and dried (MgSO$_4$). Evaporation of the solvent

left a solid (0.6 g, 50%) which was identified as 5-hydroxy-3-methyl-1,2-benziso-

thiazole.

(b) A stirred mixture of 5-acetoxy-3-methyl-1,2-benzisothiazole (0.5 g, 0.0024

mol) and freshly powdered anhydrous aluminium chloride was immersed in a preheated

oil bath at 90° and then kept at 180-200° for 45 min. The solid was cooled,
acidified and the product extracted with ether. The ethereal extract was shaken
with aqueous 5% sodium hydroxide (3 x 50 ml) and with water (50 ml). The combined
aqueous washings were acidified, shaken with ether (3 x 50 ml) and the ethereal
extract washed with saturated sodium hydrogen carbonate solution (2 x 20 ml), with
water (20 ml), and dried ($MgSO_4$). Evaporation of the solvent left 5-hydroxy-3-
methyl-1,2-benzisothiazole (0.35 g, 88%), identified by comparison with an authen-
tic sample.

Attempted Friedel-Crafts Acylation of 5-Hydroxy-3-methyl-1,2-benzisothiazole

(a) A solution of acetyl chloride (0.45 g, 0.006 mol) in dry nitrobenzene (5 ml)
was added dropwise during 20 min to a stirred mixture of 5-hydroxy-3-methyl-1,2-
benzisothiazole (1 g, 0.006 mol) and powdered anhydrous aluminium chloride (0.64 g,
0.006 mol) in dry nitrobenzene (20 ml) at room temperature. The mixture was
stirred at room temperature for 69 h, then heated to 100° for 24 h, cooled, poured
into aqueous 10% hydrochloric acid (20 ml), and the layers separated. The aqueous
phase was shaken with ethyl acetate (20 ml) and the combined organic layers were
washed with water (2 x 100 ml), then dried ($MgSO_4$). Evaporation of the solvent
under reduced pressure left a solid which was resolved into its two components by
elution with ethyl acetate-light petroleum (1:4) from a column of silica gel.

The first component (0.12 g, 10%) was 5-acetoxy-3-methyl-1,2-benzisothiazole
and the second component (0.47 g, 47%) proved to be starting material.

(b) A mixture of 5-hydroxy-3-methyl-1,2-benzisothiazole (1 g, 0.006 mol),
acetyl chloride (0.45 g, 0.006 mol), and boron trifluoride etherate (0.87 g, 0.006
mol, 48%) in dry dichloromethane (40 ml) was stirred at room temperature for 2 h
and was then boiled under reflux for 43 h. The cooled solution was poured into
aqueous 10% hydrochloric acid (100 ml) and the layers separated. The aqueous layer
was shaken with ether (50 ml) and the combined organic layers were washed with

5% sodium hydroxide (2 x 20 ml), and with water (2 x 25 ml), then dried ($MgSO_4$).

Evaporation of the ether left 5-acetoxy-3-methyl-1,2-benzisothiazole (0.4 g, 64%).

The combined alkaline washings were acidified and the organic material was extracted with ethyl acetate (2 x 50 ml). Concentration of the solvent gave unchanged 5-hydroxy-3-methyl-1,2-benzisothiazole (0.3 g, 30%).

Some Electrophilic Substitution of 5-Methoxy-3-methyl-1,2-benzisothiazole

5-Methoxy-3-methyl-1,2-benzisothiazole

Methyl iodide (19 g, 0.133 mol) was added dropwise to a stirred solution of 5-hydroxy-3-methyl-1,2-benzisothiazole (11 g, 0.066 mol) and potassium hydroxide (4.52 g, 0.066 mol) in dry ethanol (200 ml) and the solution was boiled for 2 h. The solution was cooled, poured into water (400 ml), and the product extracted with ether (3 x 100 ml). The combined ether extracts were washed with aqueous 10% sodium hydroxide (3 x 50 ml), with water (3 x 50 ml), and dried ($MgSO_4$). The solvent was evaporated and short path distillation (72° at 0.9 mmHg) of the residue gave white needles (10.6 g, 90%), m.p. $55-57^o$ (lit.,[100] $57-57.5^o$) (Found: C, 60.5; H, 5.05; N, 8%; $\underline{M}$, 179. Calculated for C_9H_9NOS C, 60.3; H, 5.05; N, 7.95%; $\underline{M}$, 179), $\nu_{max.}$ 1230 (C-O) cm^{-1}, $\delta_{p.p.m.}$ 2.64 (s, 3-CH_3), 3.86 (s, 5-OMe), 7.15 (dd, 6-H), 7.24 (dd, 4-H), and 7.74 (dd, 7-H), ($\underline{J}_{4,7} = 0.5$, $\underline{J}_{4,6} = 2.25$, and $\underline{J}_{6,7} = 8.3$ Hz).

Bromination

(a) A solution of bromine (0.63 g, 0.004 mol) in dry carbon tetrachloride (10 ml) was added dropwise during 2 h to an ice-cold solution of 5-methoxy-3-methyl-1,2-benzisothiazole (0.7 g, 0.004 mol) in dry carbon tetrachloride. The mixture was stirred at 0° for 1 h, at room temperature for 18 h, and was then boiled for 2 h. The cooled solution was poured into water (200 ml) and shaken with chloroform (2 x 50 ml). The extract was dried ($MgSO_4$) and evaporated to give an oil (0.9 g), which consisted of two components in the ratio 1:1 (t.l.c.). The mixture was chromatographed on a silica gel column, and elution with chloroform -light petroleum (1:1) gave the first component which crystallised from light petroleum (charcoal) as white needles of 4-bromo-5-methoxy-3-methyl-1,2-benzisothiazole (0.4 g, 40%) m.p. $87-89^o$ (Found: C, 41.6; H, 3.3; N, 5.6%; $\underline{M}$,

257/259. C_9H_8BrNOS requires C, 41.85; H, 3.1; N, 5.45%; $\underline{m}$, 257/259), $\vartheta_{max.}$ 1295 (C-O), and 1070 (aromatic Br) cm^{-1}, $\delta_{p.p.m.}$ 2.97 (s, 3-CH_3), 3.93 (s, 5-OMe), 7.16 (d, 6-H), and 7.73 (d, 7-H), ($\underline{J}_{6,7}$ = 8.7 Hz).

The second component (0.35 g, 50%) was identified as starting material.

(b) 5-Methoxy-3-methyl-1,2-benzisothiazole (1 g, 0.0056 mol) was treated with bromine and silver sulphate in concentrated sulphuric acid at 0° as described earlier (p. 99) (On addition, the solution was stirred for 3 h at 0-5°, then for 4 h at room temperature). The product was identified as 4-bromo-5-methoxy-3-methyl-1,2-benzisothiazole (1.25 g, 87%) identical with that obtained in (a).

(c) $\underline{N}$-Bromosuccinimide (0.92 g, 0.0057 mol) was added in portions during 15 min to a boiled, stirred solution of 5-methoxy-3-methyl-1,2-benzisothiazole (1 g, 0.0056 mol) in dry carbon tetrachloride (40 ml), containing a catalytic amount of dibenzoyl peroxide. The mixture was boiled for 18 h, then further $\underline{N}$-bromo-succinimide (0.4 g) was added and boiling was continued for a further 2 h. The cooled mixture was filtered and the solvent evaporated to leave an oil, which consisted of three components in the ratio 15:70:15 (by t.l.c.). The oil was resolved by chromatography on a column of silica gel and elution with benzene-light petroleum (1:4).

The first component ($\underline{R}_f$ 0.35) crystallised from benzene-light petroleum to give 3-dibromomethyl-5-methoxy-1,2-benzisothiazole as white flakes, m.p. 109.5-112° (lit.,[100] 109-112°) (Found: C, 32.3; H, 2; N, 4.1%; $\underline{m}$, 335/337/339. Calculated for $C_9H_7Br_2NOS$ C, 32.05; H, 2.1; N, 4.2%; $\underline{m}$, 335/337/339), $\vartheta_{max.}$ 1230 (C-O) cm^{-1}, $\delta_{p.p.m.}$ 3.95 (s, 5-OMe), 7.01 (s, 3-$CHBr_2$), 7.18 (dd, 6-H), 7.68-7.80 (m, 4-H and 7-H), ($\underline{J}_{4,6}$ = 2.3, and $\underline{J}_{6,7}$ = 8.9 Hz).

The second component ($\underline{R}_f$ 0.146) crystallised from light petroleum to give 3-bromomethyl-5-methoxy-1,2-benzisothiazole as white needles, m.p. 84-85° (lit., [100] 84-86.5^o) (Found: C, 42; H, 3.15%; $\underline{m}$, 257/259. Calculated for C_9H_8BrNOS C, 41.9; H, 3.1%; $\underline{m}$, 257/259), $\vartheta_{max.}$ 1230 (C-O), and 600 (alkyl-Br) cm^{-1}, $\delta_{p.p.m.}$ 3.9 (s, 5-OMe), 4.82 (s, 3-CH_2Br), 7.19 (dd, 6-H), 7.42 (d, 4-H), and 7.77 (dd,

7-H), ($\underline{J}_{4,7}$ = 0.7, $\underline{J}_{4,6}$ = 2.5, and $\underline{J}_{6,7}$ = 8.8 Hz).

The third component ($\underline{R}_f$ 0.09) was identified as 5-methoxy-3-methyl-1,2-benzisothiazole.

(d) 5-Methoxy-3-methyl-1,2-benzisothiazole (2 g, 0.0112 mol) was side-chain brominated using $\underline{N}$-bromosuccinimide as described earlier (p. 119). The product consisted of two components in the ratio 43:57 (by n.m.r.) and was resolved by column chromatography as described in (c) to give 3-dibromomethyl (0.9 g, 24%) and 3-bromomethyl-5-methoxy-1,2-benzisothiazole (0.8 g, 28%).

Nitration

5-Methoxy-3-methyl-1,2-benzisothiazole (1 g, 0.0056 mol) was nitrated in concentrated sulphuric acid with potassium nitrate as described earlier (p. 99). When the addition was complete the mixture was stirred at 0-5° for 1 h, poured onto ice-water (100 ml), and the yellow precipitate filtered off. Crystallisation from benzene-light petroleum (b.p. 80-100°) gave 5-methoxy-3-methyl-4-nitro-1,2-benzisothiazole (1.16 g, 93%) as yellow platelets, m.p. 130.5-131.5° (Found: C, 42.5; H, 3.8; N, 12.3%; $\underline{M}$, 224. $C_9H_8N_2O_3S$ requires C, 48.2; H, 3.6; N, 12.5%; $\underline{M}$, 224), $\vartheta_{max.}$ 1528 and 1370 (NO_2) cm^{-1}, $\delta_{p.p.m.}$ 2.56 (s, 3-CH_3), 3.96 (s, 5-OMe), 7.32 (d, 6-H), and 7.92 (d, 7-H), ($\underline{J}_{6,7}$ = 8.8 Hz).

Formylation

5-Methoxy-3-methyl-1,2-benzisothiazole (1 g, 0.0056 mol) was formylated with phosphoryl chloride and dimethylformamide as described earlier for the formylation of 5-bromo-3-methyl-1,2-benzisothiazole (p. 113). The addition required 30 min, and the solution was then stirred for 4 h at room temperature. The semi-solid product (1.25 g) consisted of two components in the ratio 1:1 (t.l.c.), and was resolved with difficulty by chromatography on a column of silica gel by elution with chloroform-light petroleum (b.p. 40-60°)-methanol (8:8:1).

The first component (R_f 0.45) crystallised from light petroleum to give N^2-(2-formyl-5-methoxy-3-benzo[b]thienyl)-N^1N^1-dimethylformamidine as fluffy yellow needles, m.p. 154-156° (Found: C, 59.5; H, 5.4; N, 10.3%; $\underline{M}$, 262. $C_{13}H_{14}N_2O_2S$ requires C, 59.5; H, 5.4; N, 10.65%; $\underline{M}$, 262), $\nu_{max.}$ 2920 (H-CO), 1645 (C=O), and 1615 (C=N) cm^{-1}, $\delta_{p.p.m.}$ 3.13 (m, NMe$_2$), 3.87 (s, 5-OMe), 7.12 (dd, 6-H), 7.33 (d, 4-H), 7.61 (d, 7-H), 7.65 (s, CH), and 9.79 (s, 2-CHO), ($\underline{J}_{4,6}$ = 2.5, and $\underline{J}_{6,7}$ = 9 Hz).

The second component (R_f 0.26) crystallised from benzene to give 3-formylamido-5-methoxybenzo[b]thiophen as fawn microneedles, m.p. 142-143° (Found: C, 57.75; H, 4.5; N, 6.75%; $\underline{M}$, 207. $C_{10}H_9NO_2S$ requires C, 57.95; H, 4.4; N, 6.75%; $\underline{M}$, 207), $\nu_{max.}$ 3290 (N-H), 1685 (C=O), and 1660 (N-H and C-N) cm^{-1}, $\delta_{p.p.m.}$ [(CD$_3$)$_2$SO] 3.85 (s, 5-OMe), 7.06 (dd, 6-H), 7.66 (d, 4-H), 7.82 (d, 7-H), 8 (s, 2-H), 8.45 (s, 3-NHCHO), and 10.58 (br, 3-NHCHO), ($\underline{J}_{4,6}$ = 2.25 and $\underline{J}_{6,7}$ = 8.8 Hz).

(5-Methoxy-1,2-benzisothiazol-3-yl)acetonitrile

3-Bromomethyl-5-methoxy-1,2-benzisothiazole (0.65 g, 0.0025 mol) was reacted with sodium cyanide in dimethylsulphoxide as described earlier (p. 125). Stirring was continued for 9 h at room temperature. Crystallisation from benzene gave the product (0.29 g, 56%) as yellow microcubes, m.p. 154-156° (Found: C, 58.85; H, 4.25; N, 13.7%; $\underline{M}$, 204. $C_{10}H_8N_2S$ requires C, 58.8; H, 3.95; N, 13.7%; $\underline{M}$, 204), $\nu_{max.}$ 2250 (CN), and 1245 (C-O) cm^{-1}, $\delta_{p.p.m.}$ 3.87 (s, 5-OMe), 4.12 (s, 3-CH$_2$CN), 7.24 (dd, 6-H), 7.34 (d, 4-H), and 7.82 (d, 7-H), ($\underline{J}_{4,6}$ = 2.3 and $\underline{J}_{6,7}$ = 8.7 Hz).

(5-Methoxy-1,2-benzisothiazol-3-yl)acetic acid

The foregoing product (0.147 g, 0.0007 mol) was hydrolysed by the method described earlier (p. 92). The white solid (0.137 g, 85%) was filtered off, dried and had m.p. 149-150° (Found: C, 53.6; H, 4.35; N, 6.3%; $\underline{M}$, 223. $C_{10}H_9NO_3S$ requires C, 53.8; H, 4.05; N, 6.3%; $\underline{M}$, 223), $\nu_{max.}$ 3000-2500br (OH), 1720 (C=O),

and 1230 (C-O) cm^{-1}, $\delta_{\text{p.p.m.}}$ [(CD$_3$)$_2$SO] 3.37 (br, 3-CH$_2$CO$_2\underline{H}$), 3.87 (s, 5-OMe), 4.13 (s, 3-C$\underline{H}_2$CO$_2$H), 7.23 (dd, 6-H), 7.56 (d, 4-H), and 8.03 (d, 7-H), ($\underline{J}_{4,6}$ = 2.2 and $\underline{J}_{6,7}$ = 8.8 Hz).

Some Electrophilic Substitution Reactions of 4-Bromo-3-methyl-1,2-benzisothiazole

4-Bromo-3-methyl-1,2-benzisothiazole

5-Amino-4-bromo-3-methyl-1,2-benzisothiazole (8.75 g, 0.036 mol) was deaminated by diazotisation and treatment with hypophosphorous acid as described previously (p. 108). The residue was sublimed (89° at 0.3 mmHg) to give a white crystalline solid (7.8 g, 95%), m.p. 89–91° (Found: C, 41.9; H, 2.7; N, 6%; $\underline{M}$, 227/229. C_8H_6BrNS requires C, 42.1; H, 2.65; N, 6.15%; $\underline{M}$, 227/229), $\nu_{max.}$ 1070 (aromatic Br) cm^{-1}, $\delta_{p.p.m.}$ 2.97 (s, 3-CH$_3$), 7.25 (t, 6-H), 7.56 (dd, 5-H), and 7.78 (dd, 7-H), ($\underline{J}_{5,7}$ = 1, $\underline{J}_{5,6}$ = $\underline{J}_{6,7}$ = 7.75 Hz).

Bromination

4-Bromo-3-methyl-1,2-benzisothiazole (1.04 g, 0.005 mol) was brominated at 0° with bromine and silver sulphate in concentrated sulphuric acid as described earlier (p. 99). Stirring was maintained for 1 h at 0–5°, then for 2 h at room temperature. The product was sublimed (84° at 0.3 mmHg) to give 4,7-dibromo-3-methyl-1,2-benzisothiazole (1.48 g, 96%), m.p. 97–99° (Found: C, 31.1; H, 1.65; N, 4.35%; $\underline{M}$, 305/307/309. $C_8H_5Br_2NS$ requires C, 31.5; H, 1.65; N, 4.55%; $\underline{M}$, 305/307/309), $\nu_{max.}$ 1062 (aromatic Br) cm^{-1}, $\delta_{p.p.m.}$ (C_6D_6) 2.64 (s, 3-CH$_3$), 6.65 (d, 5-H or 6-H), and 6.82 (d, 5-H or 6-H), ($\underline{J}_{5,6}$ = 8.1 Hz).

Nitration

4-Bromo-3-methyl-1,2-benzisothiazole (1 g, 0.004 mol) was nitrated with potassium nitrate in concentrated sulphuric acid as described earlier (p. 99) and stirring was continued at 0–5° for 30 min. The pale yellow product was resolved into its two components by chromatography on a column of silica gel and elution with benzene-light petroleum (2:1).

The first component [A] ($\underline{R}_f$ 0.42) crystallised from light petroleum to give

4-bromo-3-methyl-7-nitro-1,2-benzisothiazole (0.5 g, 42%) as pale yellow micro-crystals, m.p. 122-123.5° (Found: C, 35.6; H, 1.9; N, 10.3%; $\underline{M}$, 272/274. $C_8H_5BrN_2O_2S$ requires C, 35.2; H, 1.85; N, 10.25%; $\underline{M}$, 272/274), $\nu_{max.}$ 1518 and 1334 (NO_2) cm^{-1}, $\delta_{p.p.m.}$ 3.03 (s, 3-CH$_3$), 7.8 (d, 5-H), and 8.24 (d, 6-H), ($\underline{J}_{5,6}$ = 8.1 Hz).

The second component [B] ($\underline{R}_f$ 0.38) crystallised from light petroleum to give 4-bromo-3-methyl-5-nitro-1,2-benzisothiazole (0.49 g, 41%) as white microcrystals, m.p. 114-115° (Found: C, 35; H, 1.9; N, 10.4%; $\underline{M}$, 272/274. $C_8H_5BrN_2O_2S$ requires C, 35.2; H, 1.85; N, 10.25%; $\underline{M}$, 272/274), $\nu_{max.}$ 1550, 1350 (NO_2), and 1070 (aromatic Br) cm^{-1}, $\delta_{p.p.m.}$ 3.04 (s, 3-CH$_3$), 7.7 (d, 6-H or 7-H), and 7.93 (d, 6-H or 7-H), ($\underline{J}_{6,7}$ = 8.2 Hz).

Identification of component [A]

Concentrated hydrochloric acid (8 ml) was added dropwise to a stirred mixture of the foregoing component [A] (0.45 g, 0.00165 mol) and tin (0.4 g, 0.0032 g atom) and the mixture was heated at 100° for 1 h. The cooled mixture was diluted with water (20 ml), basified and filtered, the filter pad being washed with ethyl acetate (3 x 50 ml). The layers were separated and the aqueous phase extracted with ethyl acetate (2 x 50 ml) and the combined ethyl acetate layers were dried $(MgSO_4)$ and then concentrated. The residue was purified by chromatography on a column of silica gel and elution with ethyl acetate-light petroleum (4:1). A white solid ($\underline{R}_f$ 0.35) was isolated which sublimed (95° at 0.2 mmHg) to give the amine (15%), m.p. 126-130° (Found: $\underline{M}$, 242/244. $C_8H_7BrN_2S$ requires $\underline{M}$, 242/244), $\nu_{max.}$ 3350br, 3200, and 1640 (NH_2) cm^{-1}, $\delta_{p.p.m.}$ 2.97 (s, 3-CH$_3$), 3.89 (br, 7-NH$_2$), 6.63 (d, 6-H), and 7.2 (d, 5-H), ($\underline{J}_{5,6}$ = 8 Hz). The product was identified as 7-amino-4-bromo-3-methyl-1,2-benzisothiazole as the spectroscopic data did not agree with those for 5-amino-4-bromo-3-methyl-1,2-benzisothiazole (p. 107).

Consequently components [A] and [B] were assigned.

Formylation

(a) 4-Bromo-3-methyl-1,2-benzisothiazole (1 g, 0.0044 mol) was added in portions during 30 min to an ice-cold, stirred mixture of phosphoryl chloride (0.76 g, 0.0044 mol) and dry dimethylformamide (0.64 g, 0.0088 mol). The mixture was stirred at room temperature for 6 h and at 90-100° for 3 h, and then was worked up as described earlier (p. 113). The resulting orange oil (1.3 g), which slowly solidified, contained two components in the ratio 66:29 (by g.l.c.). Trituration with light petroleum left N^2-(4-bromo-2-formyl-3-benzo[b]thienyl)-N^1N^1-dimethylformamidine (0.25 g, 18%) as fluffy yellow needles, m.p. 134-136° (Found: C, 46.4; H, 4; N, 8.8%; $\underline{M}$, 310/312. $C_{12}H_{11}BrN_2OS$ requires C, 46.3; H, 3.6; N, 9%; $\underline{M}$, 310/312), $\nu_{max.}$ 2920 (H-CO), 1650 (C=O), 1628 (C=N), and 1090 (aromatic Br) cm^{-1}, $\delta_{p.p.m.}$ 3.15 (d, NMe$_2$), 7.22 (t, 6-H), 7.49 (s, CH), 7.54 (dd, 5-H), 7.68 (dd, 7-H), and 9.78 (s, 2-CHO), ($\underline{J}_{5,7}$ = 1, $\underline{J}_{5,6}$ = $\underline{J}_{6,7}$ = 7.9 Hz).

The mother liquors were concentrated but all attempts to obtain a pure sample of the major component by column chromatography were unsuccessful.

(b) The experiment was repeated, but the mixture was stirred at room temperature for 22 h. The product (1.1 g) was a 1:1 mixture (t.l.c.) of starting material and the major component in the previous experiment. Chromatography on silica gel and elution with ether-light petroleum (1:1) gave firstly unchanged 4-bromo-3-methyl-1,2-benzisothiazole (0.5 g, 50%) and then 4-bromo-3-formylamidobenzo[b] thiophen (0.3 g, 36%) as the second component, which crystallised from ethyl acetate as white needles, m.p. 142-143° (Found: C, 42.4; H, 2.45; N, 5.4%; $\underline{M}$, 255/257. C_9H_6BrNOS requires C, 42.2; H, 2.35; N, 5.45%; $\underline{M}$, 255/257), $\nu_{max.}$ 3300 (NH), 1695 (C=O), 1660 (N-H and C-N), and 1060 (aromatic Br) cm^{-1}, $\delta_{p.p.m.}$ 7.17 (t, 6-H), 7.54 (dd, 5-H), 7.79 (dd, 7-H), 8.37 (s, 2-H), 8.52 (br, 3-NHC$\underline{H}$O), and 9.31 (br, 3-N$\underline{H}$CHO), ($\underline{J}_{5,7}$ = 1, and $\underline{J}_{5,6}$ = $\underline{J}_{6,7}$ = 8 Hz).

The Preparation of 4-Chloro-3-methyl-1,2-benzisothiazole

5-Amino-4-chloro-3-methyl-1,2-benzisothiazole

(a) A solution of chlorine in dry carbon tetrachloride (6.25 ml, d. 0.0697, 0.0061 mol) was added dropwise during 30 min to a stirred solution of 5-amino-3-methyl-1,2-benzisothiazole (1 g, 0.0061 mol) in dry chloroform (50 ml) at 0°. After stirring for 15 h at room temperature the solution was poured into water, basified, the layers separated, and the aqueous layer extracted with chloroform (2 x 50 ml). The combined chloroform extracts were dried (MgSO$_4$), evaporated and the residue resolved into its two components by chromatography on a column of silica gel and elution with ethyl acetate-light petroleum (4:1).

The minor component (27%) was 5-amino-4-chloro-3-methyl-1,2-benzisothiazole and the major component (50%) was unchanged starting material.

(b) N-Chlorosuccinimide (5.85 g, 0.041 mol) was added portionwise during 30 min to a boiled, stirred solution of 5-amino-3-methyl-1,2-benzisothiazole (6.75 g, 0.041 mol) in dry chloroform (200 ml), containing a catalytic amount of dibenzoyl peroxide. The solution was boiled for 5 h, then cooled and filtered to remove succinimide. Evaporation of the solvent left a dark red residue which was purified by short path distillation (140° at 0.3 mmHg) and crystallised from ethyl acetate (charcoal) to give pale yellow microneedles, (6.6 g, 81%), m.p. 137-139° (Found: C, 48.25; H, 3.65; N, 14.3%; M, 198/200. C$_8$H$_7$ClN$_2$S requires C, 48.35; H, 3.55; N, 14%; M, 198/200), $\nu_{max.}$ 3420, 3300, 3190, 1640 (NH$_2$), and 1064 (aromatic Cl) cm^{-1}, $\delta_{p.p.m.}$ 2.93 (s, 3-CH$_3$), 4.21 (br, 5-NH$_2$), 6.96 (d, 6-H), and 7.53 (d, 7-H), ($J_{6,7}$ = 8.5 Hz).

4-Chloro-3-methyl-1,2-benzisothiazole

5-Amino-4-chloro-3-methyl-1,2-benzisothiazole (1 g, 0.005 mol) was deaminated by the method described earlier (p. 108). The product (0.7 g, 76%)

was sublimed (80° at 0.3 mmHg) to give a white crystalline <u>solid</u>, m.p. 83–85°

(Found: C, 52.15; H, 3.4; N, 7.5%; <u>m</u>, 183/185. C_8H_6ClNS requires C, 52.3; H,

3.3; N, 7.3%; <u>m</u>, 183/185), $\vartheta_{max.}$ 1076 (aromatic Cl) cm^{-1}, $\delta_{p.p.m.}$ 2.96

(s, $3-CH_3$), 7.34 (m, 5-H and 6-H), and 7.75 (m, 7-H), $\delta_{p.p.m.}$ (C_6D_6) 2.76

(s, $3-CH_3$), 6.64 (t, 6-H), 6.93 (dd, 5-H or 7-H), and 7.04 (dd, 5-H or 7-H),

($\underline{J}_{5,7}$ = 1 and $\underline{J}_{5,6}$ = $\underline{J}_{6,7}$ = 8.1 Hz).

The Preparation of 3-methyl-4-nitro-1,2-benzisothiazole

5-Amino-3-methyl-4-nitro-1,2-benzisothiazole

A solution of 5-acetamido-3-methyl-4-nitro-1,2-benzisothiazole (3.4 g, 0.0136 mol) in 35% sulphuric acid (100 ml) was gently boiled for 15 min, cooled, and then poured into ice-water (500 ml). The yellow solid was filtered off and crystallised from ethyl acetate (charcoal) as orange needles (2.7 g, 95%), m.p. 174-175° (Found: C, 45.65; H, 3.5; N, 20.05%; $\underline{M}$, 209. $C_8H_7N_3O_2S$ requires C, 45.9; H, 3.35; N, 20.1%; $\underline{M}$, 209), $\upsilon_{max.}$ 3445, 3295, 3180, 1620 (NH_2), and 1504, 1288 (NO_2) cm^{-1}, $\delta_{p.p.m.}$ [$(CD_3)_2SO$] 2.53 (s, 3-CH_3), 6.5 (br, 5-NH_2), 7.3 (d, 6-H), and 8.02 (d, 7-H), ($\underline{J}_{6,7}$ = 9 Hz).

3-Methyl-4-nitro-1,2-benzisothiazole

(a) 5-Amino-3-methyl-4-nitro-1,2-benzisothiazole (0.42 g, 0.00187 mol) was deaminated in the manner described earlier (p. 108) to give a brown semi-solid (0.25 g) which was resolved into its two components by chromatography on a column of silica gel and elution with ethyl acetate-light petroleum (1:4).

The major component ($\underline{R}_f$ 0.8) was identified as 4-chloro-3-methyl-1,2-benzisothiazole (0.18 g, 55%) by comparison with a sample prepared previously (p. 142)

A trace of the minor component ($\underline{R}_f$ 0.51) was isolated but was insufficient (<10 mg) to allow complete characterisation, although mass spectra (Found: $\underline{M}$, 194. $C_8H_6N_2O_2S$ requires $\underline{M}$, 194), n.m.r. and an i.r. solution spectra indicated that it was the required product.

(b) A solution of 5-amino-3-methyl-4-nitro-1,2-benzisothiazole (0.5 g, 0.0022 mol) in glacial acetic acid (4 ml) was diazotised at 10-15° by a solution of sodium nitrite (0.16 g, 0.0023 mol) in concentrated sulphuric acid (2 ml) and the resulting diazonium solution was stirred at room temperature for 15 min. A slurry

of freshly prepared* copper (1) oxide (0.7 g) in absolute ethanol (6 ml) was added, when the reaction temperatre rose to ca. 45°. The mixture was then stirred until the reaction temperature fell to ca. 23°, then an excess of water was added, and the organic product was extracted with ethyl acetate (3 x 40 ml). Evaporation of the dried extract gave a solid (0.5 g) which was purified by chromatography. Elution with ethyl acetate-light petroleum (1:4) gave 3-methyl-4-nitro-1,2-benzisothiazole (0.15 g, 35%) (R_f 0.51) which crystallised from light petroleum (charcoal) as pale yellow microneedles, m.p. 132-133° (Found: C, 49.8; H, 3.6; N, 14.25%; $\underline{M}$, 194. $C_8H_6N_2O_2S$ requires C, 49.45; H, 3.1; N, 14.45%; $\underline{M}$, 194), $\vartheta_{max.}$ 1525 and 1350 (NO_2) cm^{-1}, $\delta_{p.p.m.}$ 2.74 (s, 3-CH_3), 7.58 (t, 6-H), 7.77 (dd, 5-H), and 8.12 (dd, 7-H), ($\underline{J}_{5,7}$ = 1.25 and $\underline{J}_{5,6}$ = $\underline{J}_{6,7}$ = 7.75 Hz).

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*   Prepared by basifying a solution of copper (1) chloride in concentrated hydrochloric acid, filtering off the product and then washing it successively with distilled water (until free from chloride ions), with ethanol, with ether, and finally drying under vacuum.

The Preparation of 3-Chloro-5-nitro-1,2-benzisothiazole

Bis-(o-carboxy-p-nitrophenyl) disulphide [135]

A solution of potassium hydroxide (22.6 g, 0.4 mol) in ethanol (250 ml) was added dropwise to a stirred solution of 2-chloro-5-nitrobenzoic acid (81 g, 0.4 mol) in ethanol (300 ml). The potassium salt (88.5 g, 99%) was filtered off and dried at 100°.

A solution of sodium disulphide, prepared by dissolving sulphur (6.4 g, 0.2 g atom) in a hot solution of crystalline sodium sulphide (48 g, 0.2 mol) in ethanol (200 ml), was added dropwise during 90 min to a stirred suspension of the foregoing potassium salt in ethanol (800 ml). The stirred mixture was boiled on a steam bath for 90 min, cooled, and the yellow solid filtered off and dried at 60°. The yellow salts were dissolved in water (5 l) and acidified to give the free acid as a white solid (60 g, 75%) which was filtered off and dried at 60°. The product was used in the next stage without further purification.

Bis-(o-chlorocarbonyl-p-nitrophenyl) disulphide [135]

A mixture of the foregoing product (60 g, 0.152 mol), phosphorus penta-chloride (42 g, 0.194 mol) and dry toluene (700 ml) was stirred and boiled for 4.5 h. Light petroleum (b.p. $40-60^{\circ}$) (700 ml) was added to the cooled mixture and the product (50 g, 76%) was filtered off and dried in vacuo ($CaCl_2$). The product was used in the next stage without further purification.

5-Nitro-1,2-benzisothiazol-3(2H)-one [135]

A stirred mixture of the foregoing product (50 g, 0.116 mol) and bromine (40 ml) in dry tetrachloroethane (990 ml) was boiled for 90 min, cooled, and the excess of bromine and solvent (500 ml) removed under reduced pressure. Dry carbon tetrachloride (800 ml) was added and the total volume was reduced (by ca. 700 ml).

This mixture was stirred at room temperature for 2 h and the product was filtered off, washed with light petroleum (b.p. 40-60°), dried (under suction), and then dissolved in water (ca. 6 l). Acidification (pH 5-6) with glacial acetic acid gave a pale yellow precipitate (35 g, 78%) which was dried at 60°.

3-Chloro-5-nitro-1,2-benzisothiazole

A stirred mixture of 5-nitro-1,2-benzisothiazol-3(2H)-one (35 g, 0.179 mol), phosphorus pentachloride (56 g, 0.27 mol) and dry pyridine (11.6 g) was heated at 170-180° for 7 h, cooled, and poured onto crushed ice (1 Kg). The resulting solid was collected and dried in vacuo (CaCl$_2$) and then crystallised from ethanol as off-white plates (34.8 g, 90%), m.p. 130-131° (lit.,[136] 130-132°) (Found: M, 214/216. Calculated for C$_7$H$_3$ClN$_2$O$_2$S M, 214/216), $\upsilon_{max.}$ 1519, 1341 (NO$_2$), and 1073 (aromatic Cl) cm^{-1}, $\delta_{p.p.m.}$ 8.08 (dd, 7-H), 8.46 (dd, 6-H), and 8.9 (dd, 4-H), ($J_{4,7}$ = 0.7, $J_{4,6}$ = 2.2, and $J_{6,7}$ = 9.1 Hz).

Alternative Preparation of (5-Chloro-1,2-benzisothiazol-3-yl)acetonitrile

Ethyl (5-nitro-1,2-benzisothiazol-3-yl)cyanoacetate

3-Chloro-5-nitro-1,2-benzisothiazole (19.9 g, 0.094 mol) was treated with ethyl cyanoacetate and sodium ethoxide as described earlier (p. 92) but stirring was continued for 9 days. Crystallisation of the yellow solid (21 g, 78%) from acetone gave yellow microcrystals, m.p. 196-199° (decomp) (Found: C, 49.6; H, 2.9; N, 14.3%; $\underline{M}$, 291. $C_{12}H_9N_3O_4S$ requires C, 49.5; H, 3.1; N, 14.45%; $\underline{M}$, 291), $\nu_{max.}$ 3100 (NH), 2190 (CN), 1640 (C=O), and 1515, 1342 (NO$_2$) cm^{-1}, $\delta_{p.p.m.}$ [(CD$_3$)$_2$SO] 1.27 (t, -CH$_2$CH$_3$), 4.29 (q, -CH$_2$CH$_3$), 8.49 (s, 3 x aromatic-H), and 9.19 (br, -CH).

(5-Nitro-1,2-benzisothiazol-3-yl)acetonitrile

The above ester (14.6 g, 0.05 mol) was hydrolysed with dimethylsulphoxide and water as described earlier (p. 92) but heating for 4 h at 100°. Crystallisation from acetone (charcoal) gave pale yellow needles (9.7 g, 88%), m.p. 191-194° (Found: C, 49.15; H, 2.2; N, 19.15%; $\underline{M}$, 219. $C_9H_5N_3O_2S$ requires C, 49.3; H, 2.3; N, 19.15%; $\underline{M}$, 219), $\nu_{max.}$ 2250 (CN), and 1514, 1340 (NO$_2$) cm^{-1}, $\delta_{p.p.m.}$ [(CD$_3$)$_2$SO] 4.84 (s, 3-CH$_2$CN), 8.44 (dd, 6-H), 8.56 (d, 7-H), and 9.14 (d, 4-H).

(5-Amino-1,2-benzisothiazol-3-yl)acetonitrile hydrochloride

(a) (5-Nitro-1,2-benzisothiazol-3-yl)acetonitrile (1.1 g, 0.005 mol) was reduced with aluminium amalgam as described earlier (p. 102) to give a brown gum which, on treatment with an ethereal solution of hydrogen chloride, gave the required hydrochloride. Crystallisation from methanol (charcoal) gave fawn microcrystals (0.66 g, 56%), m.p. 210-215° (decomp) (Found: C, 48.05; H, 3.65; N, 19.05%; $\underline{M}$ (free base), 189. $C_9H_8ClN_3S$ requires C, 47.9; H, 3.55; N, 18.6%; $\underline{M}$ (free base), 189), $\nu_{max.}$ 2860-2500 (NH$_3^+$) and 2250 (CN) cm^{-1}, $\delta_{p.p.m.}$ [(CD$_3$)$_2$SO] 4.77 (s, 3-CH$_2$CN), 7.35 (br, NH$_3^+$), 7.71 (dd, 6-H), 8.13 (d, 4-H), and 8.37 (d, 7-H), ($\underline{J}_{4,6}$ = 1.6 and $\underline{J}_{6,7}$ = 8.5 Hz).

(b)   Iron dust (14 g) was added to a stirred solution of (5-nitro-1,2-benzisothiazol-3-yl)acetonitrile (7 g, 0.031 mol) in glacial acetic acid (240 ml) and water (38.5 ml) at 90°, and the mixture was stirred at 90-95° for 10 min, then filtered.   The cooled filtrate was diluted with water (400 ml), neutralised, and shaken with ethyl acetate.   Treatment of the dried extract with an ethereal solution of hydrogen chloride gave (5-amino-1,2-benzisothiazol-3-yl)acetonitrile hydrochloride (5.6 g, 75%), identical with the foregoing sample.

Concentration of the ethyl acetate mother liquors gave a solid which crystallised from ethyl acetate (charcoal) to give (5-acetamido-1,2-benzisothiazol-3-yl)acetonitrile (0.5 g, 7%) as white rosettes, m.p. 187.5-189° (Found: C, 57.1; H, 3.8; N, 17.8%; $\underline{M}$, 231. $C_{11}H_9N_3OS$ requires C, 57.15; H, 3.9; N, 18.15%; $\underline{M}$, 231), $\nu_{max.}$ 3375 (NH), 2240 (CN), 1690 (C=O), and 1660 (N-H and C-N) cm^{-1}, $\delta_{p.p.m.}$ [$(CD_3)_2SO$] 2.31 (s, 5-NHCOC$\underline{H}_3$), 4.59 (s, 3-CH$_2$CN), 7.7 (dd, 6-H), 8.12 (d, 7-H), 8.44 (d, 4-H), and 10.23 (s, 5-N$\underline{H}$COCH$_3$), ($\underline{J}_{4,6}$ = 1.6 and $\underline{J}_{6,7}$ = 8.8 Hz).

NOTE   A longer heating time increased the % of acetamido derivative.   When the reaction was heated for 3 h, 55% of amine hydrochloride and 22% of acetamido derivative were isolated.

(5-Chloro-1,2-benzisothiazol-3-yl)acetonitrile

(5-Amino-1,2-benzisothiazol-3-yl)acetonitrile hydrochloride (1 g, 0.0044 mol) was diazotised and treated with copper ($\underline{1}$) chloride and concentrated hydrochloric acid as described previously (p. 103) to give the required product (0.75 g, 81%), which was identical with the sample prepared previously (p. 127) by an alternative route.

Attempted Preparation of (5-Bromo-1,2-benzisothiazol-3-yl)acetonitrile

The free base was liberated from an aqueous solution of (5-amino-1,2-benzisothiazol-3-yl)acetonitrile hydrochloride (1 g, 0.0044 mol) and the isolated amine was diazotised in sulphuric acid then treated with copper (1) bromide and hydrobromic acid as described previously (p. 102). The residual solid, which consisted of three components, was resolved by chromatography on a column of silica gel and elution with ethyl acetate-light petroleum (1:6).

The first component (R_f 0.44) crystallised from benzene (charcoal) to give (5-bromo-1,2-benzisothiazol-3-yl)bromoacetonitrile (0.65 g, 45%) as white microcrystals, m.p. 128-130° (Found: C, 32.55; H, 1.2; N, 8.45%; $\underline{M}$, 330/332/334. $C_9H_4Br_2N_2S$ requires C, 32.4; H, 1.5; N, 8.7%; $\underline{M}$, 330/332/334), $\nu_{max.}$ 2250 (CN), and 660, 515 (alkyl Br) cm^{-1}, $\delta_{p.p.m.}$ (C_6D_6) 4.87 (s, 3-CHBrCN), 6.69 (d, 7-H), 7.05 (dd, 6-H), and 7.95 (d, 4-H), ($\underline{J}_{4,6}$ = 1.6 and $\underline{J}_{6,7}$ = 8.8 Hz).

The second component (R_f 0.35) was identified as (5-bromo-1,2-benzisothiazol-3-yl)acetonitrile (0.23 g, 21%) by comparison with a sample prepared earlier (p. 125).

The third component (R_f 0.22) a fawn solid (0.09 g, 6%), m.p. 189-190°, was probably (5-bromo-1,2-benzisothiazol-3-yl)dibromoacetonitrile , $\nu_{max.}$ 2230 (CN) and 1075 (aromatic Br) cm^{-1}, $\delta_{p.p.m.}$ [(CD$_3$)$_2$CO] 7.75 (dd, 6-H), 8.19 (d, 7-H), and 8.72 (d, 4-H), ($\underline{J}_{4,6}$ = 1.8 and $\underline{J}_{6,7}$ = 9 Hz). The lack of time prevented complete characterisation of the product.

Some Attempted Thiocyanations on m-Hydroxyacetophenone and related compounds

(a) m-Hydroxyacetophenone with Copper (ll) Thiocyanate

A stirred mixture of m-hydroxyacetophenone (3.37 g, 0.022 mol) and freshly prepared[139] copper (ll) thiocyanate (15 g) in dry glacial acetic acid (100 ml) was kept at 60° for 24 h then filtered, and diluted with water (300 ml). The product was extracted with ether and the extract was washed with saturated aqueous sodium hydrogen carbonate (until neutral) and dried ($MgSO_4$). Evaporation of the solvent left a two component solid, which was resolved by Soxhlet extraction with light petroleum (b.p. 60-80°). The solvent was concentrated to give unchanged starting material (1.45 g, 43%) whilst the residual solid (1.3 g, 31%) was crystallised from benzene-light petroleum to give 3-hydroxy-ω-thiocyanatoacetophenone as microcrystals, m.p. 123-125° (Found: $\underline{M}$, 193. $C_9H_7NSO_2$ requires $\underline{M}$, 193), $\nu_{max.}$ 3390 (OH), 2165 (CN), and 1690 (C=O) cm^{-1}, $\delta_{p.p.m.}$ [$(CD_3)_2SO$] 5.03 (s, -COCH$_2$SCN), 7.05-7.49 (m, 4 x aromatic-H), and 9.89 (s, 3-OH).

(b) m-Hydroxyacetophenone with Thiocyanogen

Attempted thiocyanation in the manner described earlier for the preparation of 5-amino-2-thiocyanatoacetophenone (p. 105) failed to give any product showing a SCN absorption in the i.r. spectrum.

(c) m-Hydroxyacetophenone with Thiocyanogen Chloride

A solution of thiocyanogen chloride (0.033 mol) in dry glacial acetic acid was prepared from lead thiocyanate by the method of Bacon and Guy.[142] m-Hydroxy-acetophenone (4.07 g, 0.033 mol) was then added and the mixture was stirred at room temperature for 18 h, filtered, and diluted with water (1000 ml). The filtrate was shaken with ethyl acetate and the extract dried ($MgSO_4$). Evaporation of the solvent gave a semi-solid which showed two strong SCN absorptions in its i.r. spectrum but which could not be resolved.

(d) 1-(3-Hydroxyphenyl)ethanol with Thiocyanogen Chloride

m-Hydroxyacetophenone was reduced to the alcohol with sodium borohydride at room temperature in the usual manner[143] to give 1-(3-hydroxyphenyl)ethanol (63%) which crystallised from benzene as white microcrystals, m.p. 86-88°, $\vartheta_{max.}$ 3390 and 3200-2900br (OH) cm^{-1}, $\delta_{p.p.m.}$ [(CD$_3$)$_2$SO] 1.28 (d, CH.C$\underline{H}_3$), 4.63 (q, C$\underline{H}$.CH$_3$), 5.07 (s, OH), and 6.55-7.2 (m, 4 × aromatic-H).

The foregoing product (4.54 g, 0.033 mol) was thiocyanated in the manner outlined in method (c) above. An oil was isolated, but it consisted of several minor components.

(e) m-Methoxyacetophenone with Thiocyanogen Chloride

m-Methoxyacetophenone (4.4 g, 0.27 mol) was thiocyanated in the manner outlined in method (c) above. A semi-solid was isolated, but it consisted of six minor components.

(f) 1-(3-Methoxyphenyl)ethanol with Thiocyanogen Chloride

m-Methoxyacetophenone was reduced to the alcohol by the usual method[143] to give 1-(3-methoxyphenyl)ethanol (97%), b.p. 142° at 20 mmHg, $\delta_{p.p.m.}$ 1.3 (d, CH.C$\underline{H}_3$) 3.6 (s, OMe), 3.85 (s, OH), 4.65 (q, C$\underline{H}$.CH$_3$), and 6.6-7.2 (m, 4 × aromatic-H).

(i) The foregoing product (5 g, 0.033 mol) was thiocyanated in the manner outlined in method (c) above. The product distilled,$_{\text{b.p.}}$166° at 0.2 mmHg, to give 1-(5-methoxy-2-thiocyanatophenyl)ethyl acetate (5.1 g, 62%), m.p. 57-59° (Found: $\underline{M}$, 251. C$_{12}$H$_{13}$NO$_3$S requires $\underline{M}$, 251), $\vartheta_{max.}$ 2150 (CN), 1738 (C=O), and 1240 (C-O) cm^{-1}, $\delta_{p.p.m.}$ 1.57 (d, CH.C$\underline{H}_3$), 2.03 (s, COCH$_3$), 3.83 (s, OMe), 6.26 (q, C$\underline{H}$.CH$_3$), 6.87 (dd, 4-H), 7.05 (d, 6-H), and 7.6 (d, 3-H), ($\underline{J}_{4,6}$ = 2.9, and $\underline{J}_{3,4}$ = 8.8 Hz).

(ii) 1-(3-Methoxyphenyl)ethanol (5 g, 0.033 mol) was thiocyanated by a solution of thiocyanogen chloride (0.033 mol) in dry chloroform[142] by the procedure outlined in method (c) above. A semi-solid was isolated, but it consisted of three

components in the ratio 1:1:1 (t.l.c.).

Unfortunately, lack of time has prevented further investigation into this route to 5-hydroxy-3-methyl-1,2-benzisothiazole.

Attempted Reduction of (1,2-Benzisothiazol-3-yl)acetonitrile

(a) With Lithium Aluminium Hydride

A solution of aluminium chloride (2.3 g, 0.017 mol) in dry tetrahydrofuran (50 ml) was added during 15 min to a stirred suspension of lithium aluminium hydride (0.7 g, 0.02 mol) in dry tetrahydrofuran (100 ml), under dry nitrogen. A solution of (1,2-benzisothiazol-3-yl)acetonitrile (3 g, 0.017 mol) in dry tetrahydrofuran (50 ml) was added dropwise during 15 min and the mixture was then boiled and stirred for 3 h. The excess of reducing agent was destroyed by the cautious, dropwise addition of water (10 ml) followed by aqueous 10% sodium hydroxide (50 ml). The layers were separated and the aqueous phase was shaken with ether (2 x 100 ml). Any basic material was extracted from the combined organic layers with aqueous 20% hydrochloric acid (2 x 100 ml) and these aqueous extracts were basified, and shaken with ether (3 x 100 ml). Evaporation of the ether gave an orange semi-solid (1.35 g), which consisted of several minor components (t.l.c.) that could not be separated by chromatography.

(b) With Diborane

A solution of (1,2-benzisothiazol-3-yl)acetonitrile (3 g, 0.017 mol) in dry tetrahydrofuran (100 ml) was added dropwise during 30 min to a stirred solution of diborane [prepared by the dropwise addition of sodium borohydride (2.6 g), in dry diglyme (100 ml), to boron trifluoride etherate (9.65 g), in dry ether (50 ml),] in dry tetrahydrofuran (100 ml) at 0°, under dry nitrogen. The mixture was then stirred and boiled for 15 h, cooled and treated with dry ethanol (5 ml). After about 5 min, an orange precipitate formed and was filtered off. Attempts to decompose this boron complex, by either boiling with aqueous 20% hydrochloric acid or boiling with a saturated ethanolic hydrogen chloride solution[150], failed to yield any of the required product.

(c) <u>Catalytic Hydrogenation</u>

(i) <u>Using 10% Palladium on Carbon as catalyst</u>

A rapidly stirred mixture of (1,2-benzisothiazol-3-yl)acetonitrile (1 g) and

palladium on carbon (0.5 g, 10%) in glacial acetic acid (25 ml) was kept under

hydrogen (1 atmos) at room temperature for 1 h, then at 60-70° for 1.5 h. After

an initial uptake of hydrogen (<u>ca.</u> 30 ml) no significant volume change was noted,

and only unchanged starting material (0.97 g) was recovered.

(ii) <u>Using Raney Nickel as catalyst</u>

The above procedure was repeated using Raney nickel catalyst (0.5 g) with

stirring for 18 h at room temperature, but again only unchanged starting material

(0.95 g) was recovered from the reaction.

(iii) <u>Using Adam's Platinium catalyst</u>

A rapidly stirred mixture of (1,2-benzisothiazol-3-yl)acetonitrile (1 g) and

hydrated platinium oxide (1 g) in ethanol was kept under hydrogen (1 atmos) for

6 h. The catalyst was filtered off and the solution concentrated. The residue

was mainly starting material (90-95%), but a trace of a basic component (5-10%),

which gave a hydrochloride on addition of ethereal hydrogen chloride, was present.

An insufficient amount of this minor component precluded any further investigation.

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SUMMARY

Summary of Thesis submitted for Ph.D. Degree

by

Brian Gleadhill

on

Some Derivatives of 1,2-Benzisothiazole

derivatives

The biological properties of some important indole and 1,2-benzisothiazole ∧
are reviewed and the concept of isosterism, in the light of modern theories of
drug design, is discussed briefly. Methods used to obtain some 3-substituted
derivatives of 1,2-benzisothiazole are also outlined.

Starting from the known 3-methyl- and 5-amino-3-methyl-1,2-benzisothiazole
a number of derivatives have been prepared. These include 4-bromo, 4-chloro,
4-nitro, 5-bromo, 5-chloro, 5-hydroxy, 5-methoxy, 5-nitro, 7-amino, 7-bromo,
7-chloro and 7-nitro-3-methyl-1,2-benzisothiazole. In order to prepare 5-hydroxy-
3-methyl-1,2-benzisothiazole, by a method similar to that for 5-amino-3-methyl-
1,2-benzisothiazole, the thiocyanation of m-hydroxyacetophenone and related

has
/ compounds have been investigated.

Some electrophilic substitution reactions have been carried out on 4-bromo,
5-acetamido, 5-amino, 5-bromo, 5-hydroxy and 5-methoxy-3-methyl-1,2-benzisothiazole
and the results are generally as would be predicted. The bromination, nitration
and oxidation of 3-methyl-1,2-benzisothiazole have also been completed.

The side-chain bromination of 3-methyl and 5-bromo, 5-chloro and 5-methoxy-
has
3-methyl-1,2-benzisothiazole have been acheived and the difficulties encountered
described. The aminomethyl and various NN-disubstituted aminomethyl groups have
been introduced into the 3-position of 3-methyl-1,2-benzisothiazole and its
5-halogeno derivatives. Difficulties were encountered in the preparation of
(5-bromo and 5-chloro-1,2-benzisothiazol-3-yl)acetonitrile by the usual treatment
of the 5-halogeno-3-bromomethyl derivative with sodium cyanide in aqueous acetone.

Although the required nitriles were obtained by the use of dimethylsulphoxide as solvent, due to the low overall yield, an alternative preparation is described. The corresponding acetic acid derivatives have been prepared but the lack of time prevented the preparation of other related compounds. A number of reductions of (1,2-benzisothiazol-3-yl)acetonitrile have been attempted but these unfortunately failed and the lack of time has prevented investigation of alternative routes.