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SOME INVESTIGATIONS ON BRIDGED AND POTENTIALLY BRIDGED ISOTHIAZOLES

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This review deals with some investigations on isothiazoles and benzisothiazoles, where there is potential or actual bonding of the ring sulfur or nitrogen atom to an exocyclic atom, to form an extra ring. The possibility of interactions due to hypervalent sulfur or polarizability effects is discussed.

Key words: Benzisothiazole, isothiazole, non-bonded interactions, sulfur bonding, sulfur polarizability, tautomerism.

CONTENTS

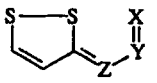
1. INTRODUCTION

In a number of investigations I have attempted to use the isothiazole system, either as the monocyclic ring, or as the benzo derivative, or incorporated into other systems, to test the interaction and bonding possibilities of exocyclic atoms

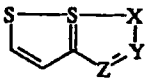
or groups to the sulfur or the nitrogen atom on the ring. This includes the construction of new rings on the existing system, but also possible new ring formation by tautomerism, hypervalent interactions, or even non-bonded interactions.

2. BONDING DESCRIPTIONS

Various types of bonding and ranges of the interatomic distances of other atoms to sulfur, in many cyclic systems, as determined by crystallographic methods, have been discussed.[1] These types included, in increasing bond length, covalent bonds, what are described as hypervalent interactions, and non-bonded interactions. Valence bond and molecular orbital methods have been used to rationalise these.[2] The authors[1] suggested general ranges of types of bonds or interactions, but since there are wide variations in the S—X bond distances in e.g. 1,2-dithioles of type **1**, it is reasonable that there is a wide variation in the actual structures of the compounds, and indeed in how they should be represented. In resonance terminology, there is a wide variation in the amount of contributions of structures of type **2**, between S—X distances of approximately 2 Å, which is the range for a normal chemical bond, to 3.25 Å, the range of the sum of the van der Waals radii, where there must be virtually zero interaction.



1



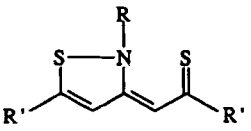
2

However, the bonding in molecules described as having hypervalent atoms may be better interpreted in terms of ionic bonding and negative hyperconjugation, where d orbitals serve to polarise σ^* orbitals.[3] Results from conformational studies by nmr of some *o*-substituted benzenethiols and sulfides also favour electrostatic interactions.[4,5] Thus the sulfur atom is relatively easily polarized by e.g. a carbonyl group. Such interactions must be weak, as it is found that the preferred conformations of 2-(methylthio)benzaldehyde and 2-(4-chlorophenylthio)benzaldehyde in solution do not allow interaction.[4,5,6] In some other cases, for nitro groups interacting with a ring sulfur,[7] as determined by ^{13}C and ^{1}H nmr, conformations are solvent dependent. The interaction appears to be stronger than for a carbonyl group, which is in accord with a polarization model, and even in this case a proper alignment is necessary. Thus *O-syn* conformations, i.e. those in which interactions are possible, are affected by the orientation of the sulfur 3p orbital. Even if the sulfur atom is not part of a ring, many examples exist for the weaker interaction mentioned above,[1] and this is now recognised as a common phenomenon. These interactions, most effective for 1,5 or 1,6 situations, affect the conformations of groups on sulfur and their reactivity.[8] Studies on 2-(diphenylphosphino)benzaldehyde by nmr methods indicate that for inter-

actions with a different second row element the conformations are consistent with a polarization model.[9]

3. STUDIES ON COMPOUNDS WITH POTENTIAL TAUTOMERIC INTERACTION AT NITROGEN

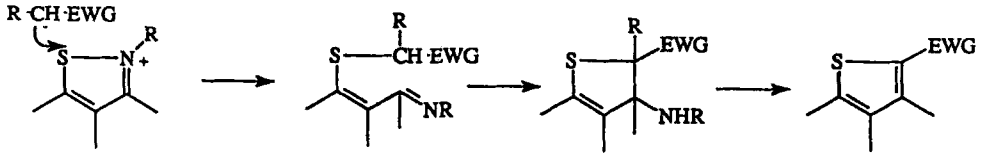
3.1. *3-(Thioacylmethylene)isothiazoles*



3

My original interest in isothiazoles was sparked by attempts to synthesize 3-(thioacylmethylene)isothiazoles (**3**), to determine how their properties might compare to those of 1,2-dithiolo[1,5-*b*]-1,2-dithioles, also known as 1,6,6aλ⁴-trithiapentalenes (**2**, X = S, Y = Z = CR). For these compounds, the structure **2** has been the most generally favoured,[10–15] but can also be interpreted on a polarization model.[16] This model would favour describing these as 3-(thioacylmethylene-1,2-dithioles. (Thus even the nomenclature gives a bias to the perceived structure). *Ab initio* methods with the 3-21G* basis set have shown that the inclusion of d polarisation functions on the sulfur atom is important in the bonding. This model implies that the properties of trithiapentalenes are best described in terms of rapid valence tautomerism, i.e. equilibration of type **1** structures. Earlier suggestions for a "single-bond–no-bond" resonance model or for a valency tautomerism description,[17] in which forms like **2** might represent a transition state between two valency tautomers rather than a resonance contributor, led to an investigation of the properties of the isothiazoles type **3**, where d-orbital participation, i.e. hypervalency of the central atom is impossible. Although compounds of the types **1** and **2** were accessible by elaboration of 3-alkylthio-1,2-dithiolium salts,[18] this was not the case for the analogous 3-(alkylthio)isothiazolium salts, or 1,2-benzisothiazolium salts. In fact, attempted attack on these of stabilized carbanions, hopefully to give products suitable for further elaboration, led to ring opening by attack on ring sulfur, instead of at C-3, as is the case with 1,2-dithiolium salts. Thus nucelophilic attack on isothiazolium salts appears to have more similarities to that on uncharged isothiazoles[19] rather than the isoelectronic 1,2-dithiolium salts. The investigation of this reaction and its scope in synthesis has formed the basis of subsequent investigations.[20–22] In these reactions a common pathway is initial formation of an acyclic intermediate which, under the conditions of the reaction, recyclises to a thiophene (Scheme 1). Occasionally other products are obtained. The actual product type, **6** or **7**, depends on the nature of the substituent groups on the attacking reagent and the isothiazolium salt.

Scheme 1

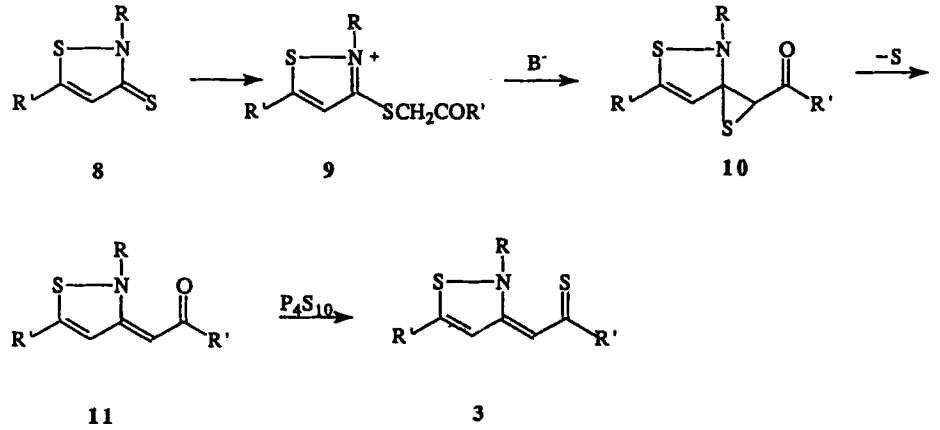


4 5 6 7

By contrast, 2,1-benzisothiazolium salts react at C-3,[23] perhaps explained by hard/soft acid/base principles, but it should be noted that in the case of the 1,2-system, the initial product by nucleophilic attack on sulfur would retain the aromaticity of the carbocyclic ring, whereas for the 2,1-system that aromaticity would be lost.

Some compounds of type **3** (R′ = *p*-Tol, R = CH_3) were eventually made[24] from isothiazoline-3-thiones **8** by the following procedure (Scheme 2). The thiones of type **8** were alkylated by α-halo ketones to form the salts **9**. In base, the carbanions derived from **9** formed the episulfides **10**, which extruded sulfur to form the ketones **11**. These were thionated to form the thiones **3**. While the reaction involves a nucleophilic attack on an intermediate isothiazolium salt, it is by an internal nucleophile, and steric factors preclude attack at the ring sulfur atom.

Scheme 2



8 9 10 11 3

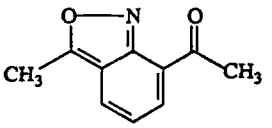
This approach, based on that initially used for elaboration of some benzothiazole-2-thiones,[25] had also been successfully used[18] for the conversion of 1,2-dithiole-3-thiones to 1,6,6aλ^4-trithiapentalenes.

For the di-*p*-tolyl compound **3a** (R′ = *p*-Tol, R = CH_3), dissolved in 1,2,4-trichlorobenzene, the two 4-methyl peaks were magnetically non-equivalent at 40 °C, being separated by 0.9 δ. At 190 °C, complete coalescence of peaks was not observed, although there was some approach of δ values to 0.3 δ. Thus the

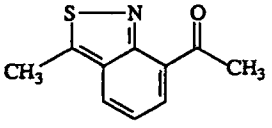
compound had a rather high energy barrier to interconversion of the valency tautomers. Probably steric hindrance of the *N*-methyl group is a major factor. In any case the properties of these compounds are distinctly different from those of the 1,6,6aλ⁴-trithiapentalenes **2**, (X = S, Z = Y = CR).

3.2. *7-Thioacyl-2,1-benzisothiazoles*

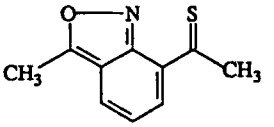
Valency tautomerism has been shown[26] for 7-acetyl-3-methyl-2,1-benzisoxazole (**12**), although a suitable high temperature and a specific solvent are necessary (compare other work[27]). Valency tautomerism may also explain the formation of 7-acetyl-3-methyl-2,1-benzisothiazole (**13**) by reaction of the isoxazole **12** with phosphorus pentasulfide. Possibly a thione **14** is initially formed which tautomerises to **13**. Direct conversion of **12** to **13**, i.e. by replacement of the ring sulfur atom, cannot be excluded, but under the same conditions, 2,1-benzisoxazole failed to form 2,1-benzisothiazole. These reactions have many similarities to furoxan rearrangements, e.g. the Katritzky-Boulton rearrangement and related reactions.[28,29]



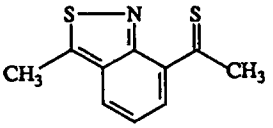
12



13

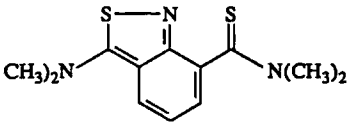


14

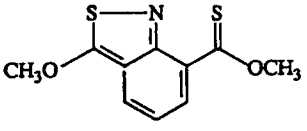


15

While a comparison of the properties of **12** with those of a thioacetyl-2,1-benzisothiazole **15** would be more useful, it would be difficult to accomplish in view of the instability of thioacyl functions. As thionoesters and thioamides are more stable we investigated the properties of *N,N*-dimethyl-3-(dimethylamino)-2,1-benzisothiazole-7-thiocarboxamide (**16**) and *O*-methyl 3-methoxy-2,1-benzisothiazole-7-thiocarboxylate (**17**).



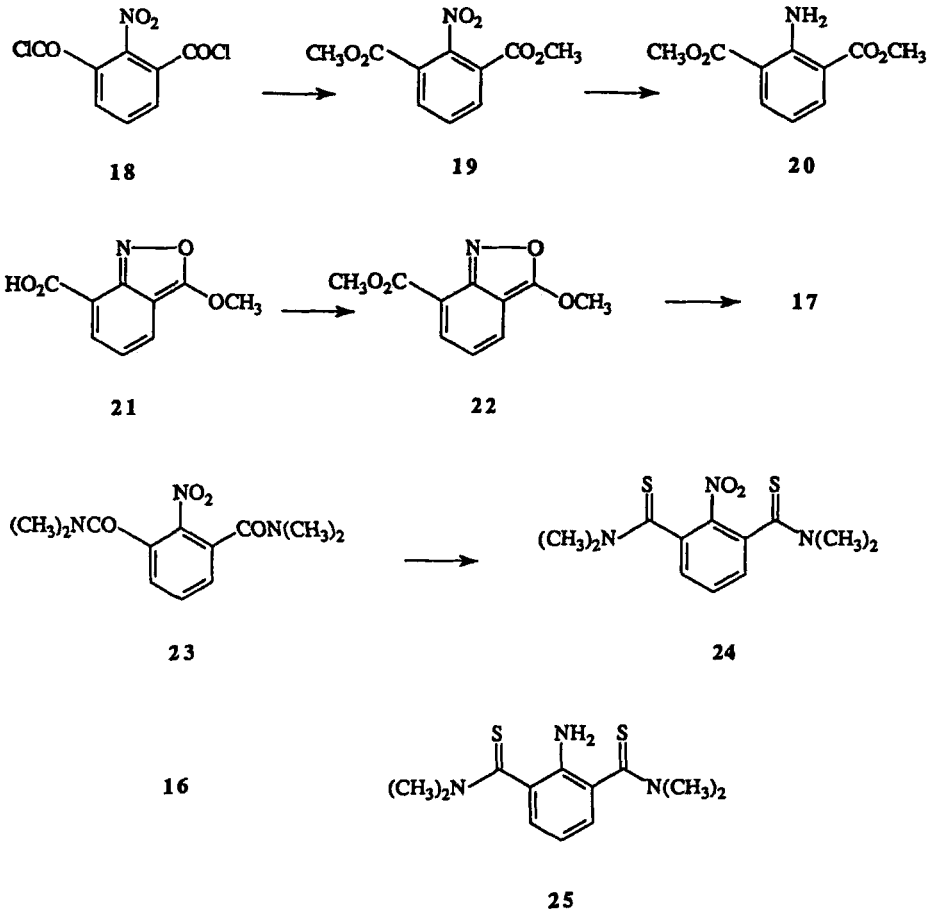
16



17

These were synthesised[30] from 2-nitroisophthaloyl chloride (**18**) as follows (Scheme 3).

Scheme 3



18 **19** **20**

21 **22** **17**

23 **24**

16 **25**

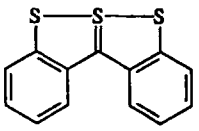
The acid chloride **18** was converted to the nitro diester **19** which was reduced with tin(II) chloride to the amino diester **20**. With persulfuric acid oxidation took place, but with simultaneous hydrolysis of the ester function, to 3-methoxy-2,1-benzisothiazole-7-carboxylic acid (**21**). This was reesterified with diazomethane, and treatment of the ester **22** with phosphorus pentasulfide gave the thionoester **17**. This conversion of an isoxazole to an isothiazole ring may also involve valency tautomerism, as with the conversion of **12** to **13**. Compound **18** was also converted into the diamide **23**, which on thionation with phosphorus pentasulfide formed the thioamide **24**. This was reduced with tin(II) chloride to the isothiazole **16**, along with the amine **25**, which could be reoxidized to **16** with peracetic acid.

Although the nmr spectrum of the methoxy-2,1-benzisothiazole ester **22** showed no equivalence of the methyl protons at 200 °C, those of the methoxy-2,1-benzisothiazole thionoester **17** were equivalent at 200 °C. This enhancement of tautomerism, on replacement of oxygen by sulfur, is consistent with the generally lower free energy of activation for reactions at sulfur atoms.[31] By comparison, the thioamide **16** showed no equivalence of the dimethylamino groups at 200 °C.

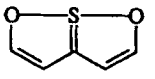
4. COMPOUNDS WITH INTERACTION AT A SULFUR ATOM

4.1. *2,1-Benzisothiazolo[2,3-b]-2,1-benzisothiazoles*

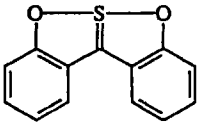
Although many examples of 1,6,6aλ^4-trithiapentalenes are known,[10,11] as well as "monobenzo" analogues,[32] the simple "dibenzo" analogue **26** is unknown, and has resisted synthesis.[33] However, the 1,2-oxathiolo[1,5-*e*]-1,2-oxathiole (**27**) system is known, as the parent heterocycle, simple derivatives, and as benzo and dibenzo analogues.[38-39] In compounds such as **26**, the S—S bond distance, being longer than the S—O or S—N bond distances in **27b** or **28a** respectively, might cause interference of the interior hydrogens, leading to distortion of the system from planarity, and hence to instability. However, the synthetic approaches may have been inappropriate, as some linked dibenzo derivatives[34-37] are known. It therefore seemed useful to prepare[40] an example of the 2,1-benzisothiazolo[2,3-*b*]-2,1-benzisothiazole system **28a** for comparative purposes. In terms of valency tautomerism, this system would be described as the *o*-quinonimine **28b**.



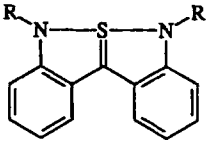
26



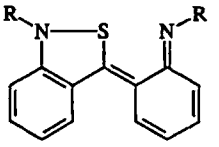
27a



27b



28a

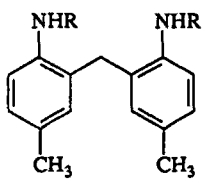


28b

As 2,1-benzisothiazoles can be made[41] from *o*-toluidines by treatment with *N*-sulfinylmethanesulfonamide (NSMSA), one approach to system **28** was by reaction of 2,2'-diaminodiphenylmethane with NSMSA.[42]

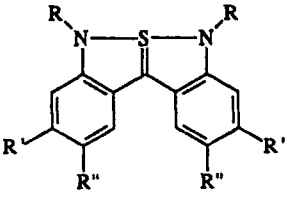
The amine **29a**, made by coupling of *p*-toluidine with formaldehyde, reacted

with NSMSA to give a reddish oil whose nmr spectrum had two equivalent methyl signals, consistent with the compound **30a**, but over several days this crystallised to a yellow material with magnetically non-equivalent methyl groups. This is likely due to tautomerism with the unsymmetrical 3-(2-amino-5-methylphenyl)-5-methyl-2,1-benzisothiazole (**31**), comparable to phenomena recognised for thiadiazoles, isothiazoles and related compounds.[43–48] *Ab initio* calculations, with 3-21G(*) and 6-31G(*) basis sets[49] on isothiazolo[2,3-*b*]isothiazole **32**, which can undergo protropic tautomerism, suggest that it is less stable than the monocyclic isothiazole tautomer **33**. The tautomerism should be blocked by methylation, and treatment of the yellow solid with iodomethane gave monomethyl and dimethyl derivatives. While the first is assigned the non-fused structure **34**, the second, a deep red solid, had two magnetically equivalent *N*-methyl- and two equivalent *C*-methyl groups, consistent with the fused symmetrical structure **30b**. Direct treatment of the amine **29b** with NSMSA failed to give **30b**, in accord with the suggestion[41] that primary amines (substituted *o*-toluidines) are needed for successful conversion to 2,1-benzisothiazoles.



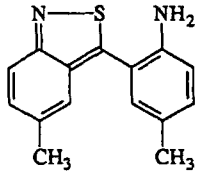
29

a R = H
b R = CH_3

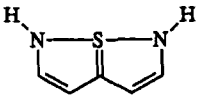


30

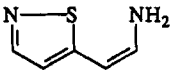
a R = R' = H, R' = H
b R = R" = CH_3, R' = H
c R = CH_3, R' = R" = H
d R = CH_3, R' = Br, R" = H



31



32



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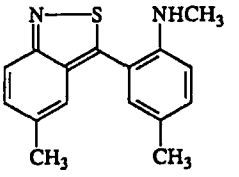
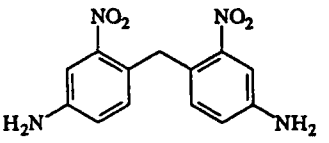


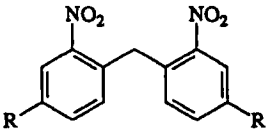
34

Some other members **30c,d** of the system were made[50] by modification of 4,4′-diamino-2,2′-dinitrodiphenylmethane (**35**), and reductive de-diazotisation with

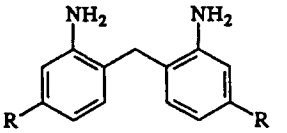
acetic acid and copper(I) oxide gave **36a**. Likewise **35** was converted to **36b** by a Sandmeyer reaction. Both of these were reduced to the diamines **37a,b**, which on treatment with NSMSA and iodomethane gave the compounds **30c,d**, respectively, whose spectra were also consistent with the symmetrical structures. These cases may be regarded as involving bonding to a hypervalent sulfur atom, or as extreme cases of interaction to a ring sulfur by an exocyclic atom. Mono"benzo" analogues suitable for comparison with trithiapentalenes and dioxathiapentalenes are so far unavailable for comparison, and some synthetic approaches were unsuccessful.[51]



35



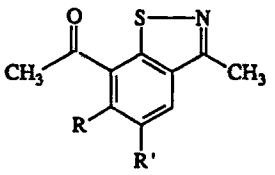
36
a R = H
b R = Br



37
a R = H
b R = Br

4.2. *7-Acyl-1,2-benzisothiazoles and related compounds*

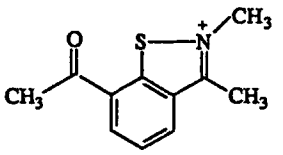
During investigations on the synthesis of some benzodiisothiazoles,[52,53] we observed that the infrared carbonyl absorptions of 7-acetyl-1,2-benzisothiazoles **38** were of similar range to those in 7-acetylbenzo[*b*]thiophenes, but lower by approximately 15 cm^{-1} than in the corresponding benzo[*b*]furans. This is inconsistent with simple conjugative effects, as sulfur has a lower mesomeric effect than oxygen. Also, quaternization of **38a** gave the salt **39**, whose infrared carbonyl absorption was even lower, by 10 cm^{-1}, than that of the original ketone **38**. Inductively, a charge on the heterocyclic ring should have increased the frequency of the carbonyl absorption. The lower frequency is consistent with enhanced non-bonded or hypervalent interaction of the carbonyl group with the ring sulfur, the more electronegative substituent (i.e. the quaternised nitrogen) on the sulfur atom, or with a polarisation model. Compound **38a** was prepared by cyclisation in acetic anhydride and pyridine of the monooxime of 2-methylthio-1,3-diacetylbenzene. Likewise the oximes **41a,b** of the 2-methylthioacetophenones **40a,b**, respectively, cyclised to the isothiazoles **42a,b**, respectively.



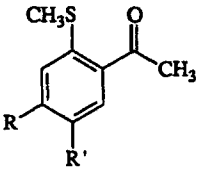
38

a R = R' = H

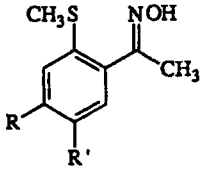
b R = SCH_3, R' = H



39



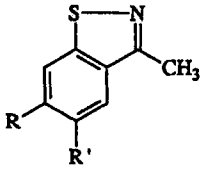
40



41

a R = SCH_3, R' = H

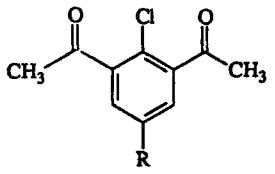
b R = H, R' = SCH_3



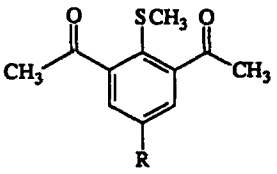
42

This method is a convenient and efficient modification of oxime based 1,2-benzisothiazole syntheses, of which there are many variations.[52,54–56] The acetylation of the 1,2-benzisothiazole **42a** to from **38a** is unusual, as 1,2-benzisothiazoles are rather resistant to Friedel-Crafts type acylations.[57] It appears that the extra methylthio substituent sufficiently activates the ring to substitution. However the substituent pattern must be important as, by contrast, 5-methylthio-3-methyl-1,2-benzisothiazole (**42b**) could not be acylated.[52] In general, electrophilic substitution at the 5- and 7-positions is favoured,[58] confirming theoretical predictions,[59] but 3,5-dimethyl-2,1-benzisothiazole underwent electrophilic substitution in the 4-position. Thus, even a weak electron releasing group, rather than the heterocyclic ring, determines the position of ring substitution.[60]

For the other examples, the chloro compounds **43a,b,c** gave, by nucleophilic displacement with methanethiolate ion,[61] the 2-methylthio-1,3-diacetylbenzenes **44a,b,c**, whose oximes gave the 1,2-benzisothiazoles **45a,b,c**, respectively.



43

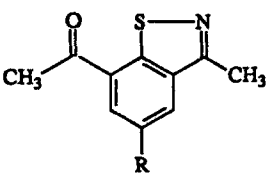


44

a R = H

b R = SCH_3

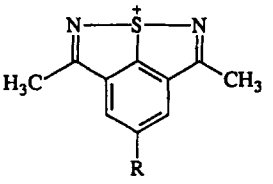
c R = $N(CH_3)_2$



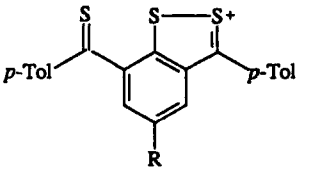
45

4.3. *Possibly bridged sulfonium ions*

We have also used these ketones **45a,b,c** to investigate the possibility of forming bridged sulfonium ions of type **46** based on isothiazoles. Our work[61] was stimulated by the reported[62] nmr symmetry of a 7-thioacylbenzo-1,2-dithiolium salt (**47**, R = *p*-Tol)), and reports[56,63–65] that diazonium groups in the 7-position of benziothiazoles, 1,2-benzisothiazoles and 1,2,3-thiadiazoles all interact with ring sulfur atoms, leading to rearranged products. However, an attempt to demonstrate a stable bridged sulfonium ion intermediate in these reactions by nmr failed. Because of our interest in isothiazoles we investigated whether the oximes of the ketones **45,a,b,c** might be able to form detectable bridged ions. However, treatment with either hydrobromic acid, perchloric acid or trifluoroacetic anhydride failed to give any evidence of bridged products, and the *p*-situated electron-donating groups (SCH_3 $N(CH_3)_2$), which possibly could have stabilized cationic intermediates by resonance forms involving hypervalent sulfur, had no effect.

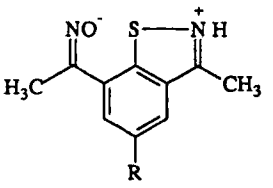


46

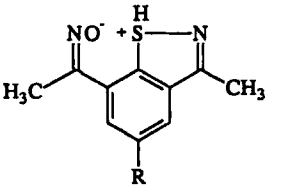


47

The starting oximes were recovered by dilution with water, and no products of Beckmann type rearrangements were observed. The mass spectra of these compounds showed ions at M-16 mass units, but not at M-17, i.e. the ions were formed by loss of an oxygen atom, confirmed by accurate mass determination. This implies some transfer in the molecular ion, possibly due to protonation on the heterocyclic ring, as in structures **48** or **49**.



48



49

However, it should be noted that transition metals may be important in the rearrangements of the diazonium salts, and there are likely to be geometrical

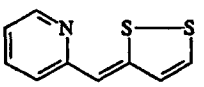
constraints on the efficiency of the reaction, depending on the actual nature of the species attacking ring sulfur. E.g. electrophiles and nucleophiles attack sulfur atoms at different orientations.[66,67] The former attack at sulfur at an angle of approximately 70° to the plane of the sulfur atom and its two substituents, while the latter attack is at approximately 180° to the nucleofuge. These data have been rationalised by means of the electrostatic model.[68,69] Because of the relatively large energy difference between 3s and 3p orbitals, the former tend to remain filled in bond formation. Thus electrophilic attack is at the 3p orbital, and thus preferably at 90° to the R′—S—R bonds, while nucleophilic attack is within the plane of the bonds. Whereas most non-bonding cases can be considered as a type of nucleophilic attack at sulfur, the diazonium group is an electrophile. The function of the transition metal may be to modify the nature of the attacking species. An "abnormal" coordination of the metal ion with the diazonium group and the sulfur atom has been suggested.[64]

However, our results are also reminiscent of the failure of benzo-1,2,3-triazole-7-diazonium salts to undergo rearrangement.[70] I.e., they do not form bridged ions either as intermediates or transition states. That is in itself curious in view of the ready formation of 1,2,3-thiadiazoles from 2-(alkylthio)diazonium salts,[71] external nucleophilic attack on the ring nitrogen atom of 1,2-benzisoxazoles,[72] and the ready interconversion of some furoxans, i.e. the Katritzky-Boulton rearrangement.[28,29]

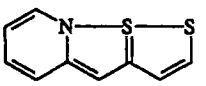
5. NITROGEN BRIDGED COMPOUNDS

5.1. *Possible interactions in pyridine dithiole compounds*

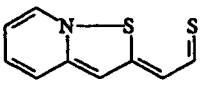
5.1.1. *1,2-Dithiol-3-ylidenepyridylmethanes.* We also sought to determine what interactions should exist in some 1,2-dithiol-3-ylidene-2-pyridylmethanes (**50a**). If possible resonance structures (**50a,b,c**) are considered, these should have isothiazole contributors. In terms of a polarisation model, a form similar to **50b** would be a transition state between **50a** and **50c**.



50a



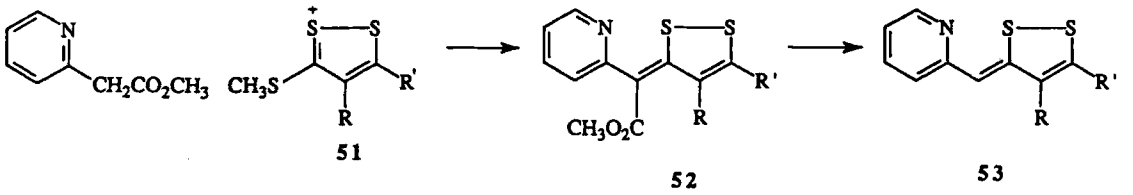
50b



50c

Compounds of type **52** were readily accessible[42] by pyridine-2-acetic ester condensations with some 3-alkylthio-1,2-dithiolium salts **51** (Scheme 4).

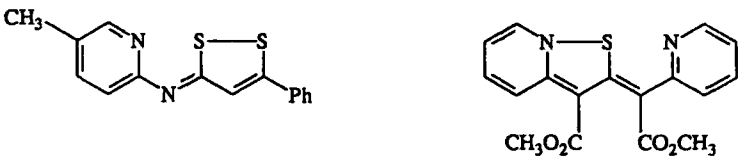
Scheme 4



51 52 53

a R' = Ph, R = H
b R = R' = Ph
c R,R' = $(CH{=}CH)_2$

These on hydrolysis and decarboxylation gave the compounds **53d,e,f**. On the basis of ^{13}C nmr studies, we concluded that the hypervalent structures of type **50b** were unimportant. A number of compounds, for which hypervalent structures have been proposed, exhibited ^{13}C resonances around 170–180 ppm for the carbon attached to the hypervalent sulfur atom,[10] and these were absent in **53**. Recent crystallographic studies[73] on these types of compounds (made by an alternative synthesis) showed sulfur-to-nitrogen bond distances of the order of 2.4 Å, i.e. within the range described[1] for "non-bonded" interactions. However, these workers concluded that the true structures were best described by a combination of the 1,2-dithiole-3-ylidene structure **50a** and the hypervalent structure **50b**. In this case *ab initio* calculations were deemed to be unsuitable for describing the system, at least when a single determinant was used. Crystallographic studies[74] on the related 3-methyl-6-(5-phenyl-1,2-dithiole-3-ylideneamino)pyridine (**54**) indicated a sulfur-to-nitrogen bond distance of 2.282 Å, attributed to a slight interaction.



54 55

Nevertheless the interaction between the sulfur and nitrogen atoms in pyridines and pyrimidines with the sulfur atom in a thiadiazole ring appears stronger.[75,76] The magnitude of these non-bonded interactions thus appears to depend on the system into which they are incorporated. It should be noted too that the examples described above[75,76] have symmetrical contributors or transition states. Also, as conformations in the crystal form appear to be biased towards those that exhibit or suggest interaction, crystal packing must be a factor. As noted[77] for 1,6,6aλ^4-trithiapentalenes, ^{13}C resonance methods appear to be unsatisfactory for

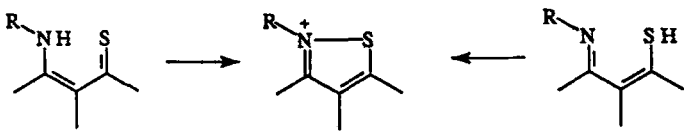
determining hypervalent or other interactions where the system under study is asymmetrical, at least until more data are available.

5.1.2. *Isothiazolo[2,3-a]pyridin-3-ylidenepyridylmethanes.* The ester **55** was prepared[78] by reaction of methyl pyridine-2-acetate with trichloromethanesulfenyl chloride. Although close in structure to the above mentioned pyridine and pyrimidine compounds[75,76] which demonstrated nmr symmetry, this showed non-equivalence of the ester methyl protons, i.e., interaction of the exocyclic atom with the ring sulfur is not significant. This may be due to a steric interference, or perhaps an electronic effect of the two ester functions. X-Ray diffraction studies should be done to determine the extent of the interactions.

5.2. *Bridged ammonium ions*

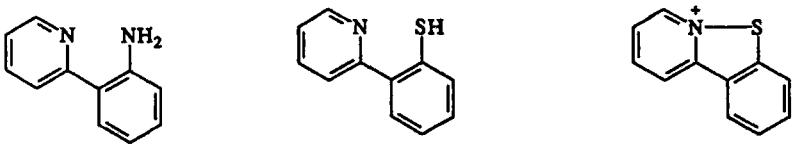
A major synthetic approach[19] to the isothiazole ring (**56**) is the oxidative cyclisation of 3-aminopropenethiones (**57**) as well as of derivatives or tautomers (**58**) (Scheme 5).

Scheme 5



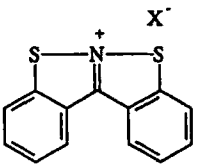
57 **56** **58**

This has also been applied[79] to the formation of isothiazolium salts, and to an example with a bridgehead nitrogen, the isothiazolo[2,3-*a*]pyridinium system.[80] Likewise we have prepared[42] the 1,2-benzisothiazolo[2,3-*a*]pyridinium system (**61**) by oxidation of 2-(2-mercaptophenyl)pyridine (**60**), prepared from 2-(2-aminophenyl)pyridine (**59**) by diazotisation, conversion to the xanthate, and hydrolysis.

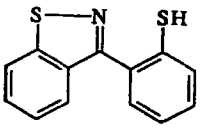


59 **60** **61**

Hoping to extend this, we attempted[81] the synthesis of the 1,2-benzisothiazolo[2,3-*b*]-1,2-benzisothiazolium system (**62**), by oxidation of 3-(2-mercaptophenyl)-1,2-benzisothiazole (**63**).



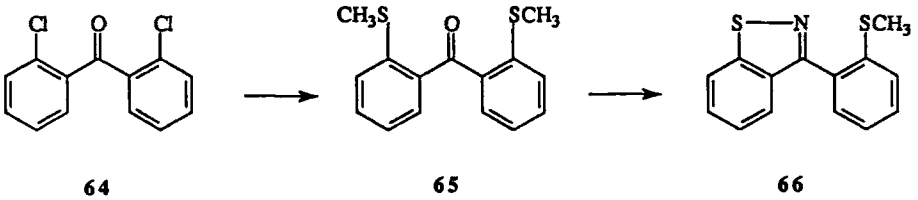
62



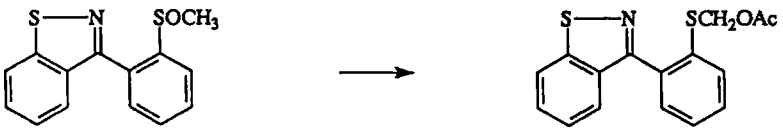
63

2,2'-Dichlorobenzophenone (**64**) reacted with sodium methanethiolate (Scheme 6) to form the keto sulfide **65**, whose oxime gave the benzisothiazole **66** on treatment with acetic anhydride in pyridine. Because a normal reductive cleavage of the methylthio group in **66** to the thiol **63** with sodium was unsuitable due to the presence of the reducible isothiazole ring, the dealkylation was effected *via* a Pummerer rearrangement. Thus the sulfide **66** was oxidized to the sulfoxide **67** which rearranged to the sulfide **68** on treatment with acid in acetic anhydride. Acid hydrolysis of **68** gave the thiol **63**.

Scheme 6



64 65 66



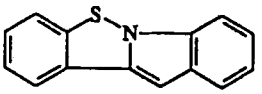
67 68

Treatment of the thiol **63** with iodine gave a dark red salt-like material, whose mass spectrum and analysis were consistent with the bridged ion **62** (X = I_3), but whose ^1H nmr spectrum showed an asymmetrical structure. Thus the exact nature of the material is in doubt.

5.3. *Bridged isothiazolopyrroles*

As mentioned above, isothiazoles are readily made by oxidation of aminopropenethiones or their tautomers. As fully unsaturated pyrrolo[1,2-*b*]isothiazoles are rather rare, only one example being recently reported,[81] we attempted[82] to

use the method for a related system, the indolo[1,2-*b*]-1,2-benzisothiazole system (**69**). Indolization of the phenylhydrazones of the ketones **70a,b** gave the sulfides **71a,b**, respectively. Reductive cleavage of **71a,b** with sodium in liquid ammonia gave the thiols **72a,b**, respectively, but these failed to give any isothiazole products on oxidation. Instead benzo[*b*]thieno[3,2-*b*]indoles **73a,b** were formed, consistent with substitution on a carbon atom of the indole ring. Even when the 3-position of the indole was blocked by alkylation no isothiazole product was obtained. These reactions thus correspond to sulfenylation reactions on indoles.[83] Indoles are attacked by radicals both in the 1- and 3-position, whereas attack by electrophiles is at the 3-position. The attacking species thus appears to be electrophilic.



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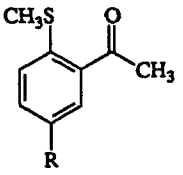
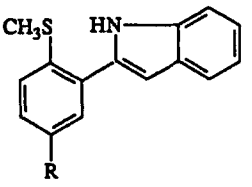
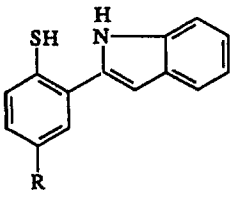
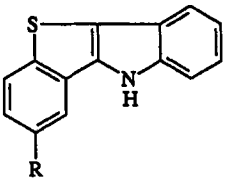






70 **71** **72**

a R = H
b R = CH_3



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