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Advances in the Chemistry of 1,2,5-Thiadiazoles and 1,2,5-Selenadiazoles

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Published information on 1,2,5-thiadiazoles, 1,2,5-selenadiazoles, their derivatives, and fused systems formed by these heterocycles is summarised. A list of 322 references is included.

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I. INTRODUCTION

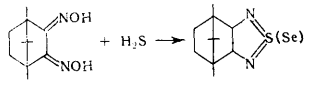
Although benzo- and naphtho-1,2,5-thia- and -selena-diazoles were described by Hinsberg in 1889,[1-4] no interest was taken in this group of compounds for more than sixty years. In 1950 the Reviewer and his coworkers began systematic investigations in this field[5]. Papers by other workers soon appeared, mainly devoted to the study of fused 1,2,5-thia- and -selena-diazole ring systems. Research in this field has been stimulated also by the discovery, among 1,2,5-thia- and -selena-diazole derivatives, of compounds which show promise of practical application in various fields. Research on monocyclic derivatives of these heterocycles began only in 1958.

Although an imense amount of information has now been accumulated on the chemistry of 1,2,5-thia- and -selena-diazoles, it has not been examined systematically or critically, apart from a short review of two or three pages[6]. The present survey covers the literature to 1968 inclusive.

II. MONOCYCLIC 1,2,5-THIADIAZOLES AND 1,2,5-SELENADIAZOLES

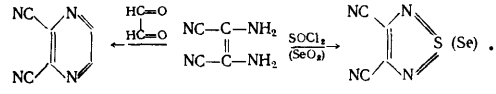
1. Synthesis

Until quite recently it proved impossible to synthesise monocyclic 1,2,5-thia- or -selena-diazoles from aliphatic compounds. The preparation of bornylene-1,2,5-thiadiazole by treating β-camphorquinone dioxime with hydrogen sulphide[7]

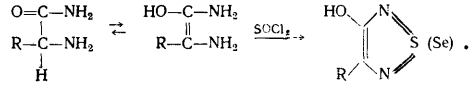


suggested that monocyclic 1,2,5-thiadiazoles might be obtained from aliphatic dioximes. However, neither dimethylglyoxime[8] nor cyclohexane-1,2-dione dioxime[9] reacts with hydrogen sulphide under similar conditions. Yet phosphorus pentasulphide or boiling sodium sulphide solution dehydrates the dioximes to the corresponding oxadiazoles. Only dimethylglyoxime has been isolated from the action of potassium sulphide on diacetyldimethylglyoxime in boiling alcohol[10].

It seemed obvious that difficultly accessible alkenediamines would be necessary for the synthesis of monocyclic 1,2,5-thiadiazoles by treatment with thionyl chloride. This was confirmed by the synthesis of the 3,4-dicyanothiadiazole from thionyl chloride and the tetramer of hydrogen cyanide[10]†, and of the selenium analogue by conducting the reaction with selenium dioxide[10]:



Drawing a further analogy with the synthesis of pyrazine derivatives, Collins and other workers[12-15] obtained hydroxy-derivatives of 1,2,5-thiadiazole from amides of α-amino-acids or their nitriles‡:

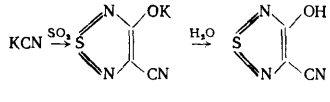


The cyclising agents used were thionyl chloride[14], sulphinylaniline[15], and sulphur monochloride[17]. Use of the *NN*-diphenylamide of sulphurous acid in a nitrogen atmosphere has been claimed[14] instead of thionyl chloride. Weinstock and his coworkers have established[16,17] that 1,2,5-thiadiazole and its derivatives are easily formed by reaction between sulphur monochloride and aliphatic compounds containing an N–C–C–N chain. Sulphur dichloride has also been employed in this reaction[18-20]. Sulphur dibromide yields bromo-derivatives of thiadiazole[18].

Thiadiazole derivatives have been obtained also by the action of sulphur dichloride on diethyloxalimide[21] or cyanogen[22].

The synthesis from sulphur nitride S_4N_4 and aliphatic compounds is of theoretical interest[23,24].

A fundamentally different method is the reaction between potassium cyanide and sulphur dioxide[19,25-28]:

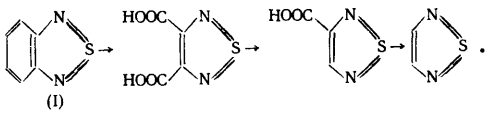


†Replacement of thionyl chloride by glyoxal yielded 2,3-dicyanopyrazine[11].

‡Replacement of thionyl chloride by a 1,2-diketone gave hydroxypyrazines[16].

1,2,5-Selenadiazole, unknown until recently, has been obtained by the reaction between ethylenediamine and selenium monochloride [29,30,32]. Higher yields of this compound and its mono- and di-methylated derivatives have been synthesised from ethylenediamine (or propylenediamine), dimethylglyoxime, and selenium dioxide [30-32].

A method of obtaining monocyclic 1,2,5-thiadiazoles and 1,2,5-selenadiazoles which is of practical importance is the degradation of fused ring systems incorporating these heterocycles. In benzo-1,2,5-thiadiazole (I) the benzene ring is less resistant than the thiadiazole ring to the action of oxidants. This permits the oxidative cleavage of (I) to 1,2,5-thiadiazole-3,4-dicarboxylic acid, which is converted by successive decarboxylation into the monocarboxy-acid and then into unsubstituted 1,2,5-thiadiazole [9,10,33-40]:



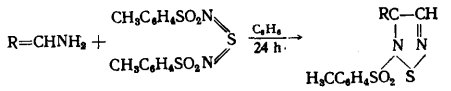
(I)

The pyrimidine ring in pyrimido-1,2,5-thia(and selena)-diazoles is readily cleaved by basic or acidic reagents under mild conditions [41-46], with the formation of various derivatives of 4-amino-1,2,5-thia(or selena)diazole-3-carboxylic acid.

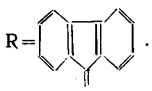
Hydrogenated 1,2,5-thiadiazoles. Michaelis[47] and more recently Shew[10] made unsuccessful attempts to obtain di- and tetra-hydro-1,2,5-thiadiazoles by treating ethylenediamine and its *NN'*-diethoxycarbonyl derivative with thionyl chloride; indeterminate results were obtained by the action of thionyl chloride on *NN'*-diethoxycarbonyl- and -dibenzoyl-vinylenediamines under various conditions [10].

1,2,5-Thiadiazolidines are obtained by treating ethylenediamines with sulphur dichloride [48]. According to Peyron [49] such thiadiazolidines and also benzothiadiazolines can be obtained by the successive action of chlorine and sodium sulphide on *NN'*-diacylethylenediamines or *NN'*-diacyl-*o*-phenylenediamines. Attempts to reproduce this synthesis and also to obtain similar heterocycles by treating dipotassium ethylenediamine-*NN'*-ditoluene-*p*-sulphonate with sulphur monochloride, sulphur dichloride, or thionyl chloride were also unsuccessful [9].

A synthesis of 1,2,5-thiadiazolines by the cycloaddition of alkeneamines to "sulphodi-imides" has been described recently [50]: e.g.

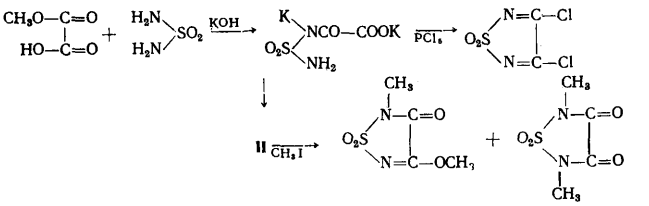


where



1,2,5-Thiadiazolidine 1,1-dioxide ("ethylenesulphamide") has been synthesised in good yield from ethylenediamine and sulphuric diamide under various conditions [51,52]. Dehydro-derivatives of this compound have been obtained by the reaction of sulphuric diamide with α-dicarbonyl compounds [53-57].

Wen [21], studying the structure of a product of the oxidation of benzo-1,2,5-thiadiazole by potassium permanganate, obtained the dipotassium salt of *N*-sulphamoyloxamic acid by the reaction of sulphuric diamide with methyl oxalate in the presence of caustic potash, and from it the disilver salt (II). He obtained two isomeric thiadiazolidine dioxides by the action of methyl iodide on this latter salt. With phosphorus pentachloride the dipotassium salt gave 3,4-dichloro-1,2,5-thiadiazole 1,1-dioxide, in which the chlorine atoms were so labile that they could easily be replaced by amino- and alkoxy-groups by known methods.



2. Properties

1,2,5-Thiadiazole (m.p. −50.1°, b.p. 94°C) is distinguished by great thermal stability (it remains unchanged when heated to 360°C [1,19]), and resists the action of acids, alkalis, and oxidants, but not reductants. It is an extremely weak base, its salts being easily hydrolysed by water [35]. The hydrochloride, nitrate, and picrate cannot be prepared; the sulphate and chlorate are extremely unstable [35]. It forms complex compounds with mercury chloride and silver nitrate [35] (analogy with pyrazine) [58].

1,2,5-Thiadiazole is extremely inert to electrophilic substitution and addition. It does not react with bromine either on irradiation or in the presence of iron(III) bromide [9,10]. It does not undergo the Friedel-Crafts reaction§.

Deuterium exchange takes place only in the presence of heavy-metal salts, but the ring then undergoes reductive cleavage with the evolution of hydrogen sulphide. Deuteration has been achieved by means of orthophosphoric acid under extremely severe conditions (in sealed tubes at 250°C for 37 h [35]). Deuteration has been effected also by decarboxylating mono- and di-carboxylic acids of 1,2,5-thiadiazole in which the carboxy-groups has previously been deuterated.

Nucleophilic substitution, on the other hand, takes place quite easily. For example, 1,2,5-thiadiazole itself is immediately aminated by sodamide. 3-Amino-1,2,5-thiadiazole has been obtained also by a different method [13,59].

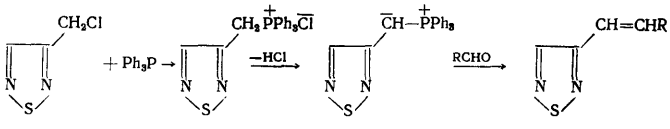
The above results indicate the electron-acceptor character of the heterocycle, which is confirmed by various reactions of 1,2,5-thiadiazole derivatives. For example, the 3-methyl compound reacts similarly to 2-methyl- and 2,5-dimethyl-pyrazines with *p*-dimethylaminobenzaldehyde [60]. A 3-chloro-substituent is highly labile, and has enabled 3-sulphanilamido-derivatives to be prepared [18,61,62]. A 3-hydroxy-group has a well developed phenolic character [15], and 3-cyano-4-hydroxy-1,2,5-thiadiazole is a stronger acid than acetic [19]. They form salts with lithium, copper, and silver. These compounds are not acylated by acetic anhydride, benzoyl chloride, or toluene-*p*-sulphonyl chloride; nor can the hydroxyl be replaced by a mercapto-group or chlorine [15,19].

The electron-acceptor influence of the thiadiazole ring is especially clearly developed in the inertness of chlorine

§However, 3-amino-1,2,5-thiadiazole undergoes halogenation in acetic acid at 20°C.[278] (Note added in proof.)

in chloromethyl and 1'-chloroethyl derivatives. These compounds do not react with aqueous silver nitrate even on boiling. On the other hand, 3-α-chlorobenzyl-1,2,5-thiadiazole yields a precipitate of silver chloride and the corresponding carbinol even when shaken in the cold [60]. In this case the intermediate carbonium cation is probably stabilised by interaction with the π-electron cloud of the benzene ring. This effect is prevented in the first two cases by the acceptor influence of the heterocycle.

It has recently proved possible [63] to detach chlorine from chloromethylthiadiazole by the action of a stronger nucleophilic reagent—triphenylphosphine:



where R = Ar, Het.

Many papers have been published on reactions, in which the ring is preserved, of 1,2,5-thia- and -selena-diazole derivatives containing various substituents in the side-chain [10,13,19,21,25,26,35-39,42,43,59-66]. In fused benzo-systems the thiadiazole ring is stable to the action of oxidising agents [9,10,21,33,34,36-40,67], but the heterocyclic ring may, depending on the conditions, be cleaved on oxidation with permanganate [9,10,19,21,25,33-40]. One of the products of the oxidation of benzo-1,2,5-thiadiazole with permanganate has a cyclic structure according to Shew [10], whereas Wen [21] has attributed the acyclic structure KOOC.CO.NK.SO_2NH_2 to the same compound. Ross [19] assumes that both compounds are formed by permanganate oxidation.

The thiadiazole ring is not stable towards reducing agents. Either reductive cleavage occurs or else the ring is not affected at all depending on the derivatives, the reductant, and the conditions. For example, 1,2,5-thiadiazole-3,4-dicarboxylic acid remains unchanged on hydrogenation (with palladium–carbon) [37]; 3-hydroxy-1,2,5-thiadiazole, when boiled with 50% alcohol in the presence of Raney nickel, undergoes fission with the formation of diethylaminoacetamide [19]. 3-Cyano-4-hydroxy-1,2,5-thiadiazole is only partly cleaved by sodium in alcohol (hydrogen sulphide is evolved), and is unaffected by sodium tetrahydroborate [19]. Other examples are known in which the thiadiazole ring is stable towards reduction by metal hydrides [60]. The thiadiazole ring is cleaved by sodium hydrogen sulphite, which readily attacks electron-deficient carbon atoms [25].

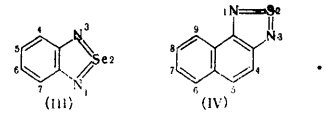
1,2,5-Selenadiazole and its methyl derivatives are cleaved by hydrogen sulphide [30,31], being reduced to the corresponding alkylenediamines and elementary selenium. 1,2,5-Selenadiazole is unaffected by treatment either with 14% NaOD in D_2O (at 60°C for 5 days) or 15% D_2SO_4 in D_2O (at 50°C for 40 min). Alkaline or ammoniacal hydrogen sulphide solution converts 3,4-dimethylselenadiazole into tetramethylpyrazine. 3,4-Diphenylselenadiazole is stable to the action of hydrogen sulphide; with sodium in alcohol it undergoes reductive cleavage to form 1,2-diphenylethylenediamine [32].

III. BENZO-1,2,5-THIADIAZOLES AND BENZO-1,2,5-SELENADIAZOLES

Many systems are now known in which these heterocycles are fused to other rings. The benzo-ring systems have been most thoroughly investigated, and the pyrimido- and naphtho-derivatives to a less extent.

1. Synthesis

The main method for synthesising benzo-1,2,5-thiadiazole (I) and benzo-1,2,5-selenadiazole (III) derivatives is the cyclisation of *o*-diamines. It was in this way that Hinsberg [1-4] first obtained (I), (III), and naphtho[1,2-*c*]-[1,2,5]-thiadiazole (IV) by treating *o*-phenylenediamines and 1,2-naphthylenediamines with concentrated sulphurous acid or with sodium hydrogen sulphite (in sealed tubes at 180–200°C for 8 h). Study of Hinsberg's reaction has shown that it can be conducted under milder conditions: several derivatives of (I) have been obtained in yields up to 40% by passing sulphur dioxide into solutions of *o*-diamines in dimethylformamide [68].



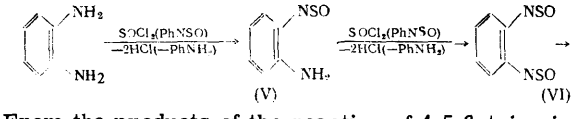
Weinstock [9] synthesised (I) in ~60% yield by heating *o*-phenylenediamine with sodium metabisulphite in ethylene glycol at 140°C for 6 h. It has been shown recently [69,70] that benzo- and naphtho-1,2,5-thiadiazoles are formed in almost theoretical yields when sulphur dioxide is passed into solutions of *o*-diamines in dichloromethane with triethylamine as catalyst.

Michaelis and his coworkers [71,72] used thionyl chloride as cyclising agent. When pyridine or triethylamine is present to combine with the hydrogen chloride formed, the reaction takes place rapidly (within a few minutes instead of many hours) and with almost quantitative yields [73-75].

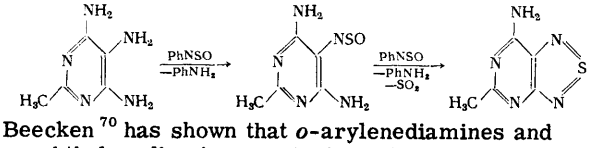
These results disprove the statement [76,77] that 4-nitro-1,2-phenylenediamine is less active than the 3-nitro-isomer in forming a thiadiazole ring.

Since thionyl chloride cannot be used for the cyclisation of *o*-diamines in which the benzene ring is substituted by hydroxyl, carboxyl, sulpho, and other groups, a study has been made of the reaction of diamines with sulphinylaniline [73-75,78,79], which Michaelis [71] had used for the preparation of (I). This reaction takes place exceptionally easily with various aromatic and heterocyclic diamines and their salts, in almost theoretical yield.

With both thionyl chloride and sulphinylaniline the reaction involves the intermediate formation of *o*-sulphinylaminoaniline (V) and *NN'*-disulphinyl-*o*-phenylenediamine (VI): [9,80]

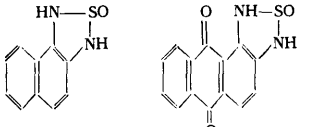


From the products of the reaction of 4,5,6-triamino-2-methylpyrimidine with sulphinylaniline Shealy and Clyton [81] isolated 4,6-diamino-2-methyl-5-sulphinylaminopyrimidine, which is converted by sulphinylaniline into 7-amino-5-methylpyrimidothiadiazole:



Beecken [70] has shown that *o*-arylenediamines and 1,2-naphthylenediamine react with sulphinylaniline to give high yields of the corresponding *o*-disulphinylamines.

The use of *p*-sulphinyltoluenesulphonamide instead of sulphinylaniline produces a similar effect [82].

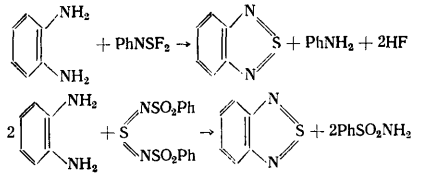


(VII) (VIII)

Dietz [83] isolated the sulphurous diamide (VII) from the products obtained by the reaction of 1,2-naphthylenediamine with sulphinylaniline. It has recently been shown [84] that the action of alkali on 6,11-dihydro-6,11-dioxoanthra[1,2-*c*]-[1,2,5]-thiadiazole at 20°C yields the analogous diamide (VIII), which, depending on the experimental conditions, can be converted into the original thiadiazole, into the *o*-diamine, or into a mixture of the two.

Thus the mechanism of the formation of (I) from *o*-arylenediamines and thionyl chloride involves the intermediate formation of an *o*-sulphinylaminoarylamine, an *o*-disulphinylaminoarene, and a cyclic sulphurous diamide.

Benzothiadiazole (I) is formed also by the use of "sulphinylaniline difluoride" [85] or *NN'*-diphenylsulphonyl-"sulphur di-imide": [86]



Derivatives of (I) are obtained by the action of sulphur monochloride on *o*-phenylenediamines or *o*-nitroanilines [87].

Schrage and Hitchings [88] obtained 7-amino-5-chloropyrimido[4,5-*c*]-[1,2,5]-thiadiazole by the action of sulphuryl chloride on 4,5,6-triamino-2-methylthiopyrimidine, but the reaction was complicated by several side-reactions. A method consisting in fusing 4-amino-5-nitrosopyrimidines with thiourea, which yields pyrimido-1,2,5-thiadiazoles, is of theoretical interest [89]. These compounds can also be synthesised [90-92] from *o*-aminonitrosopyrimidines and sodium thiosulphate.

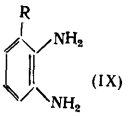
A fundamentally new method was proposed by Weinstock [9]: he synthesised naphtho-1,2,5-thiadiazole by the action of sulphur nitride S_4N_4 on 1- or 2-naphthylamine. 1,8-Naphthylenediamine yields 9-aminonaphthothiadiazole. Attempts to extend this method to aniline and other amines were unsuccessful.

Benzo-1,2,5-thiadiazole oxide was presumably obtained by the action of sulphur dichloride on *o*-benzoquinone dioxime [93]; however, it could not be obtained by treating the latter or benzofuroxan with hydrogen sulphide, sulphinylaniline, or phosphorus pentasulphide [8,93]. Unsuccessful attempts have been made [3,8,93] to replace oxygen in benzo- and naphtho-furazans by sulphur by means of various sulphurising agents.

A general method for obtaining the selenium analogues is to treat *o*-diamines with selenium dioxide [1,4,94-99]. Since this reaction takes place readily and also gives high yields, it can be used for the identification of *o*-diamines [94,99].

2. Properties

Synthesis of the polycyclic derivatives (I) and (III) from *o*-diamines is restricted by the relative inaccessibility of the latter. The preparation of many of them, in particular 1,2,3-derivatives of the type



(IX)

presents considerable difficulties. Therefore substitution in (I) and (III) is of considerable interest for preparation purposes.

(*a*) Electrophilic Substitution

Nitration. Benzothiadiazole can be nitrated as readily as can benzene (with nitric acid of density 1.35 at 0°C) to give a 95% yield of 4-nitrobenzothiadiazole [75,100,101].

The fact that the nitro-group enters the 4-position shows that the greatest electron density is located on carbon atom 4(7) and that the electron cloud is drawn towards the heterocycle. However, the acceptor effect of the latter is relatively small, since it hardly impedes the reaction at all, and is shown only in the orientation of the nitro-group [position 5(6) is less reactive]. But even this effect is considerably weakened or completely absent in the nitration of derivatives of (I) containing donor substituents (methyl, methoxy, hydroxy) at position 4.

The nitration of 5-methylbenzothiadiazole gives 94% yield of the 4-nitro-derivative. Under similar conditions 4-methylbenzothiadiazole yields a mixture of the 5- and 7-nitro-derivatives in the proportions 35 : 65, [98,102] which indicates that the influence of the methyl group predominates over that of the heterocycle. Similar proportions of *ortho* and *para* substitutions (but with the *ortho*-isomer predominating) are observed in the nitration of toluene.

The presence of two methyl groups—at positions 5 and 6—has little effect on the direction of nitration by a nitrating mixture: the 4-nitro-derivative is formed exclusively, and is converted into the 4,7-dinitro-compound on further nitration with a mixture of sodium nitrate and sulphuric acid. It is also formed in 96% yield directly from 5,6-dimethylbenzothiadiazole [103,104].

4-Acetamidobenzothiadiazole, as well as its 5(6)-mono- and 5,6-di-methyl derivatives, is easily nitrated at position 7; 5-acetamidobenzothiadiazole is readily nitrated at position 4. [105]

Stronger electron donors, such as alkoxyl and hydroxyl, weaken the influence of the heterocycle on the orientation of nitration [102,106]. Thus 4-ethoxybenzothiadiazole yields equal quantities of the 5- and 7-nitro-derivatives, which indicates that in this case these positions in the benzene ring have closely similar electron densities. On nitration with excess of nitric acid the reaction product is the 4-ethoxy-5,7-dinitro-derivative (in almost quantitative yield).

Under these conditions 4-hydroxybenzothiadiazole gives only the 5-nitro-derivative (in 95% yield), which on subsequent nitration is converted into the 5,7-dinitro-compound. Hence a 4-hydroxy-group completely suppresses the electron-acceptor effect of the thiadiazole ring and produces maximum electron density at position 5.

The nitration of 5-hydroxy- and 5-ethoxy-benzothiadiazole gives almost quantitative yields of the corresponding 4-nitro-derivatives [106,107]. In the case of the 4-hydroxy-5-methyl compound nitration yields the 7-nitro-derivative exclusively [108].

Bromomethyl derivatives of (I) are more difficult to nitrate [109]. Under the usual conditions for the nitration

of aromatic compounds 5-bromomethylbenzothiadiazole gives a 58% yield of the 4-nitro-compound; a quantitative yield of this compound can be obtained by using fuming nitric acid. Under these conditions the 4-bromomethyl derivative is nitrated at position 7 in almost quantitative yield. A 4-cyanomethyl group exerts an analogous orientating effect[109]. The presence of chlorine atoms in the side-chain of toluene has a similar retarding influence on nitration.

In the nitration of a 4-halogenobenzothiadiazole the nitro-group goes mainly to position 7. Only the use of more severe conditions (a mixture of sodium nitrate and sulphuric acid at 100°C) makes it possible to obtain the 5,7-dinitro-derivatives[104,110]. The 5-halogeno-derivatives are nitrated at position 4, and the 4,6-dihalogeno-compounds at position 7. Both mononitro-products undergo further nitration by a mixture of sodium nitrate and sulphuric acid to the 4,7- and 5,7-dinitro-compounds respectively. The 7-nitro-derivative is obtained from a 4-halogeno-5-methyl compound[104,111].

The accumulation of halogen substituents in the benzene ring of (I) strongly deactivates it to attack by the nitronium cation. The 4,5- and 4,7-dihalogeno-compounds are nitrated at positions 7 and 5 respectively with comparative difficulty, especially in the latter case. When the 4,5,7-trihalogeno-compounds are nitrated under similar conditions, the nitro-group enters the vacant 6-position. Depending on the nitrating agent the 5,6-dihalogeno-compounds yield either 4-mono- or 4,7-di-nitro-derivatives[103,104,112,113]. Two nitro-groups can be introduced into the *ortho* (5,6) positions by the action of sodium nitrate in sulphuric acid on 4-halogeno-7-methyl compounds. Under similar conditions 4- and 5-nitrobenzothiadiazoles are converted into the same 4,6-dinitro-derivative.

Both 5-methyl-4-nitro- and 5-methyl-6-nitro-derivatives are nitrated to the 4,6-dinitro-compound. The 4-methyl-5-nitro- and 4-methyl-7-nitro-isomers are likewise nitrated to the 5,7-dinitro-product[98,102].

Benzo-1,2,5-selenadiazole (III) and its many derivatives are easily nitrated under the usual conditions for aromatic compounds, the yields being high and often close to theoretical[97,98,102,114-120]. Substitution is oriented in the same way as in the corresponding thia-analogues. Nitration of unsubstituted (III) gives a 98% yield of the 4-nitro-derivative[115]. A 97% yield of a mixture of the isomeric 5- and 7-nitro-derivatives in the proportions 45 : 55 is formed from the 4-methyl compound. With identical substituents in positions 5 and 6, a mixture of sodium nitrate and sulphuric acid, depending on the nature of the substituents, either gives mono- or di-nitrobenzoselenadiazole or does not nitrate the compound at all (as e.g. in the case of the 5,6-dinitro-compound).[120]

All the nitrobenzothiadiazoles and nitrobenzoselenadiazoles obtained can be reduced to the corresponding amines, which appear in high yields in the former case[98,103,104,106,110,111,121], but in considerably lower yields in the latter case[98,115,122], owing to the lower resistance of the selenadiazole ring to the action of reducing agents (e.g. degradation under the influence of hydriodic acid[123]).

Sawicki and Carr[114] showed that the nitro-group in 5-methyl-4-nitrobenzoselendaiazole activates the adjacent methyl group, which is evident in the condensation of the latter with benzaldehydes.

Nitrosation. Like 1- and 2-naphthols, 4- and 5-hydroxybenzothiazoles are easily nitrosated, the nitroso-group entering positions 5 and 4 respectively[106,107]. The 4-hydroxy-5-methyl compound is nitrosated at position 7. Thus the nitrosation of hydroxy-derivatives of (I) proceeds similarly to their nitration[106]. From a study of the nitrosation of 5-hydroxybenzothiazole Efros and his coworkers concluded[96] that the nitroso-group in the 5-hydroxy-4-nitroso-derivative possesses no hydroxy-imino-function. This conclusion is inconsistent with the behaviour of the 4-hydroxy-5-nitroso- and 5-hydroxy-4-nitroso-derivatives under the conditions of the Bucherer reaction[124], which indicates that these compounds can exist in the tautomeric quinone oxime form. The hydroxy-nitroso-derivatives of (I) are easily reduced to the amines[107,124].

Azo-coupling. The 4- and 5-amino- and 4- and 5-hydroxy-derivatives of benzothiazole are readily coupled with diazonium salts to form the 7- and 4-azo-derivatives respectively[90,105,122,125-127]. If position 7 in the 4-hydroxy-derivative is occupied by methyl or methoxyl, the azo-group enters position 5.[127,128] This is the way in which azo-coupling occurs in the naphthalene series.

Halogenation. Chlorination and bromination in the benzothiadiazole series do not always take place in the same way, which can be explained only by the difference in the nature of the halogens. The catalytic effect of heterolysis of the interatomic bond in the molecule is less necessary for bromine than for chlorine. This is evident in the fact that, in the bromination of benzothiadiazole, electrophilic substitution takes place equally readily in the presence and in the absence of a catalyst. Bromine differs from chlorine in showing no tendency to add to benzothiadiazoles [except in the bromination of (I) itself].

Catalysed chlorination of benzo-1,2,5-thiadiazoles[110,111,131-135]. The chlorination of (I) was first studied by Efros and his coworkers[76], who concluded that this compound was incapable of addition and that no reaction took place in the absence of a catalyst. They reported also that benzothiadiazole is chlorinated in the presence of iron to the 4,7-dichloro-derivative having m.p. 57.5°C. These data were later found to be incorrect[129,130], when a 91% yield of this compound was obtained with m.p. 182°C. Further rise in temperature to 190–200°C yields successively 4,5,7-trichloro- and 4,5,6,7-tetrachloro-benzothiadiazole. Under similar conditions the 4,7-dibromo-compound is chlorinated to the 4,7-dibromo-5,6-dichloro-derivative[112].

Methyl group present at positions 4 and 5 have hardly any effect on the direction of the chlorination of melts in the presence of iron, when di- and tri-chlorinated derivatives are mainly formed. Only from the 4-methyl compound is it possible to isolate the 7-monochloro-derivative. The coincident orientating effects of heterocycle and substituents in 5,6-dimethylbenzothiadiazole result in the occurrence of chlorination under milder conditions (not only in the melt but also in acetic acid), with the formation mainly of the 4,7-dichloro-derivative. In acetic acid 4,5,6,7-tetrachlorotetrahydrobenzothiadiazole has also been isolated.

If an electron-withdrawing substituent (nitro, sulpho) is present at position 4 in benzothiadiazole, its strong deactivation of the benzene ring probably results initially in its displacement by chlorine, after which catalytic chlorination takes place in the usual way[134]. These substituents are also readily replaced by chlorine under similar conditions in nitro- and sulpho-derivatives of naphthalene and benzene.

5-Nitrobenzothiadiazole is catalytically chlorinated at position 7, as a consequence of concerted orientation by the heterocycle and by the nitro-group [134].

Uncatalysed chlorination of benzo-1,2,5-thiadiazoles. Like naphthalene, benzo-1,2,5-thiadiazole is chlorinated exothermically in chloroform, carbon tetrachloride, or dichloroethane at 60°C or in the melt at 80–90°C, four chlorine atoms being added. Alcoholic alkali eliminates two molecules of hydrogen chloride from the adduct with the formation of 4,7-dichlorobenzothiadiazole [112,129,130]. In acetic acid, chlorination gives a mixture of the tetrachloro-adduct and the substituted 4,7-dichloro-derivative. The latter is the sole product if chlorination is conducted in formic acid [133].

Neither a 4- or 5-methyl group, a 4-ethyl group, nor a 5-methoxy-group prevents the addition of four chlorine atoms under the conditions given above for (I). Alcoholic alkali splits off hydrogen chloride from the tetrachloro-adducts, converting them respectively into 4,6-dichloro-7-methyl (or ethyl)- and 4,7-dichloro-5-methyl (or methoxy)-benzothiadiazole [98,112,113]. The chlorination of 4- and 5-methylbenzothiazole in acetic acid yields in both cases a mixture of the tetrachloro-adduct and a monosubstituted product (at positions 7 and 4 respectively). Only monosubstitution takes place in formic acid.

The action of excess of sulphuryl chloride on 4- and 5-methylbenzothiadiazole yields only the corresponding 7- and 4-monochlorinated compounds. Nor do two methyl groups at positions 5 and 6 have any significant effect on the direction of chlorination [133], which occurs similarly to that of monomethyl derivatives. In the melt four chlorine atoms are added, but in acetic acid a mixture of this adduct and the dichlorinated dimethyl compound is formed.

The presence of amino, hydroxyl, and alkoxycarbonyl groups activates (I) towards chlorinating agents [78,79,111,136,137], and the reactions occur under milder conditions. The action of chloramine or sulphuryl chloride in chloroform or in acetic acid on 5-hydroxy- or 5-amino-benzothiadiazole results in the entry of chlorine at position 4. Chlorination of 4-amino-, 4-hydroxy-, and 4-methoxycarbonyl-benzothiadiazole under the same conditions yields 5,7-dichlorobenzothiadiazole: it proves impossible to limit the process to monochlorination.

Thus the heterocycle does not influence the direction of the chlorination of (I), substituents in the benzene ring being of decisive importance. The activating effect of substituents on position 5 falls in conformity with the decrease in nucleophilic character in the sequence $NH_2 > OH \gg CH_3$.

Bromination of benzo-1,2,5-thiadiazoles. Bromination results *only* in substitution, independently of the presence or the absence of a catalyst (contrast to chlorination). This can be explained by the different characters of these halogens.

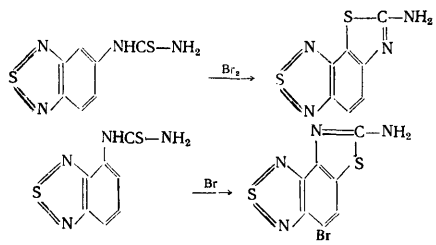
The action of excess of bromine on molten benzothiadiazole in the presence of reduced iron yields almost exclusively the 4,7-dibromo-derivative. With an equimolecular quantity of bromine under the same conditions about half the initial compound remains unchanged, and the above dibromo-derivative is accompanied by a minute amount of 4-bromobenzothiadiazole [131]. As with chlorination, the process cannot in practice be limited to monosubstitution.

In the absence of a catalyst four bromine atoms are added [112,129,130]. Subsequent treatment with alcoholic alkali yields 4,7-dibromobenzothiadiazole.

Bromination is considerably facilitated by the presence of methyl, hydroxyl, or an amino-group. The 4- and 5-methyl derivatives are brominated in the melt: the former at position 7 and in the side-chain (homolytically), and the latter to 4,7-dibromobenzothiadiazole [98]. When the reaction is conducted in the presence of reduced iron, only substitution in the benzene ring takes place, with the formation respectively of the 7-bromo- and the 4,7-dibromo derivatives [131–133].

Molten 5,6-dimethylbenzothiadiazole is brominated quantitatively to the 4,7-dibromo-derivative. In acetic-acid solution either the same product or the 4-monobromo-derivative is obtained depending on the quantity of bromine [133]. The latter product is formed also by replacing the amino-group in the 4-amino-5,6-dimethyl derivative by means of the Sandmeyer reaction. Amino-, hydroxy-, and methoxycarbonyl-benzothiadiazoles are brominated with the same orientation as in chlorination [78,78,111,136,137]. The thiocyanation of 4- and 5-amino-derivatives occurs similarly [78,79,131].

Acylated amines of (I) are brominated similarly to the amino-derivatives. The bromination of 5-thioureido-benzothiadiazole in chloroform yields 7-aminothiazolo-[5,4-*d*]benzothiadiazole; however, bromination of the isomeric 4-thioureido-compound under similar conditions results in cyclisation accompanied by the entry of bromine into the benzene ring [78,79,131].



5-Bromo- and 4,6-dibromo-benzothiadiazoles are brominated to the 4,5,7-tribromo-derivative [132]. 4- and 5-Nitrobenzothiadiazoles do not react with boiling bromine in the presence of iron.

Halogenation of benzo-1,2,5-selenadiazoles. Substitution alone occurs in the chlorination of benzo-1,2,5-selenadiazole, with formation of the 4,5,6,7-tetrachloro-derivative [98]. The 4-methyl compound, molten or dissolved in carbon tetrachloride, dichloroethane, or acetic acid, is chlorinated at position 7; in formic acid the 5,7-dichloro-derivative is also obtained. The 5-methyl compound is converted into the 4-chloro-, 4,7-dichloro-, and 4,6,7-trichloro-derivatives respectively in carbon tetrachloride, dichloroethane, or acetic acid, in the melt, and in formic acid. Sulphuryl chloride in carbon tetrachloride converts the 4- and 5-methyl compounds into the 7- and 4-chloro-derivatives respectively. The chlorination of benzoselenadiazole in the presence of silver sulphate in concentrated sulphuric acid yields a mixture of the 4-chloro- and 4,7-dichloro-derivatives [119]. The latter compound is formed also from the 4-chloro-derivative under similar conditions; 5-chlorobenzoselenadiazole gives the 4,5-dichloro-derivative [119].

Thus, in contrast to the thia-analogues, benzoselenadiazole is unable to add chlorine. In its derivatives, also, the reactivities of positions 4–7 are more alike than in the thia-analogues, in which substitution takes place preferentially at positions 4 and 7. All this provides evidence of the more aromatic character of (III) compared with (I),

probably resulting from the better ability of selenium than of sulphur to transmit conjugation.

As with chlorination, bromination produces only substitution in the benzene ring of (III).[98,119] In the presence of silver sulphate in concentrated sulphuric acid the 4,7-dibromo-derivative is formed[119]. The action of bromine on the molten 4- and 5-methyl compounds produces resinification[98]. In acetic acid the 4-bromo-7-methyl and the 4-bromo-5-methyl and 4,7-dibromo-5-methyl derivatives are formed respectively[98].

In the presence of silver sulphate in concentrated sulphuric acid, crystalline iodine acts on benzoselenadiazole to give a low yield of a mixture of the 4-iodo- and 4,7-di-iodo-derivatives[119].

Sulphonation. Benzo-1,2,5-thiadiazoles are more difficult than naphthalenes to sulphonate. Under sufficiently severe conditions (17% oleum at 150°C for 1 h) a 78% yield of the 4-sulphonic acid is obtained from (I).[76,138,139] The use of 22% oleum raises the yield to 90%, when a minute amount of the 4,7-disulphonic acid also separates[140]. Under similar conditions benzo-1,2,5-selenadiazole gives an 83% yield of its 4-sulphonic acid[119] (or a 71.5%[141]). The isomeric 5-sulphonic acid of (III) is obtained[140] by the Hinsberg reaction[4].

4- and 5-Methylbenzothiadiazoles are sulphonated more easily (with 20% oleum at 110°C for 2 h), high yields of the 7- and 4-sulphonic acids respectively being obtained[142]. The use of chlorosulphuric acid instead of oleum gives the corresponding sulphonyl chlorides. The 4-sulphonyl chloride can also be obtained directly from benzothiadiazole and chlorosulphuric acid (in the presence of thionyl chloride[143]) or by the action of phosphoryl chloride on the corresponding sulphonic acid[135,136].

Hydroxy- and amino-benzothiadiazoles are sulphonated under milder conditions. Only the 5,7-disulphonic acids are formed by the 4-hydroxy- and 4-amino-derivatives[138,139].

Thus in the presence of an active electron donor position 5 readily undergoes electrophilic attack, as is observed in halogenation and nitration. No influence of the heterocycle is apparent.

On chlorination sulpho-groups in benzothiadiazoles are replaced by chlorine. Bromination of 5-hydroxybenzothiadiazole-4-sulphonic acid yields the 4-bromo-5-hydroxy-derivative. Benzothiadiazole-4-sulphonic acid can also be converted into the 4-chloro-derivative under similar conditions, but the yield does not exceed 5–8% owing to oxidative degradation[141]. In this respect the properties of naphthalenesulphonic acids are repeated by sulphonic acids both of benzothiadiazoles and of benzoselenadiazoles.

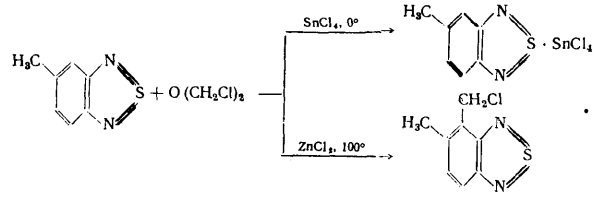
(*b*) Alkylation and Acylation at Carbon and Nitrogen

Chloromethylation. Conditions usual in the aromatic series have been applied to study the chloromethylation of benzothiadiazole and its derivatives. Attempts to chloromethylate (I) itself by the combined action of hydrogen chloride, paraformaldehyde, and zinc chloride were unsuccessful[144,145]. Negative results were obtained also when bischloromethyl ether was used in the presence of zinc chloride hydrate[146]. Only by the action of bischloromethyl ether in the presence of aluminium chloride[147,148] has it been possible to obtain 4,7-bischloromethylbenzothiadiazole (in 76% yield). The process cannot be restricted to monosubstitution even when a double excess of benzothiadiazole is used[147,148].

Chloromethylation does not take place with bischloromethyl ether in the presence of electron-donor compounds, e.g. in dimethylformamide or with a considerable excess of paraformaldehyde or hexamethylenetetramine. In the presence of a minute amount of paraformaldehyde¶ the main product is 4,7-bischloromethylbenzothiadiazole. If bischloromethyl ether prepared as in Ref. 150† is used, a mixture of the 4-chloromethyl and 4,7-bischloromethyl derivatives is formed, the ratio of which cannot be controlled[147,148,151,152].

The above results suggest that chloromethylation, in both benzothiadiazoles and aromatic compounds, is especially sensitive to the slightest changes in the reaction conditions, which cannot always be rationally taken into account.

Chloromethylation is facilitated by the introduction of an electron-donor substituent into the benzothiadiazole molecule. Thus 4- and 5-methyl compounds and the corresponding methoxy-derivatives react readily with paraformaldehyde and hydrogen chloride in the presence of zinc chloride as catalyst if the reaction is conducted in acetic acid[144]. With bischloromethyl ether the process depends[145] on the nature of the catalyst and on the temperature:



The 4-chloromethyl-5-methyl derivative is formed also with chlorosulphuric acid (at 100°C for 9 h) or aluminium chloride (at 65°C for 2 h) as catalyst, the yield being ~60%.

4-Methylbenzothiadiazole is chloromethylated at position 7 in the presence of chlorosulphuric acid, or with formation of the 5,7-disubstituted product in the presence of aluminium chloride[151]. The 5-methyl compound is chloromethylated under more severe conditions and with a lower yield than in the case of the 4-methyl compound.

Entry of a chloromethyl group is still more facilitated by the presence of a second methyl group in the benzene ring. The 4,5-dimethyl compound is chloromethylated at position 7, and the 5,6-isomer forms the 4,7-disubstituted product exclusively[135,151].

4- and 5-Chlorobenzothiadiazoles are not chloromethylated by bischloromethyl ether in the presence of chlorosulphuric acid. By using a more vigorous catalyst—aluminium chloride—it has proved possible[148] to introduce a chloromethyl group at positions 7 and 4 respectively. Nitrobenzothiadiazoles are not chloromethylated even in the presence of active catalysts under severe conditions.

When heated above 70°C with bischloromethyl ether in the presence of chlorosulphuric acid, unsubstituted benzo-1,2,5-selenadiazole is decomposed with the separation of selenium[153]. Aluminium chloride as catalyst forms a complex after 5 min, but on prolonged heating a 85–90°C small yields can be isolated of either the 4-mono- or the 4,7-bis-chloromethyl derivative depending on the extent of contamination of the initial bischloromethyl ether with paraformaldehyde[149,150].

¶Present in bischloromethyl ether prepared as in Ref. 149.

†Contaminated with a considerable quantity of paraformaldehyde.

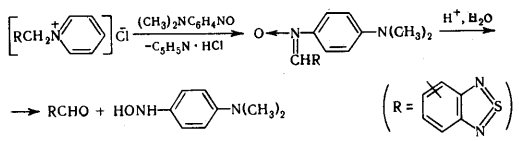
The methyl derivatives are more easily chloromethylated[153]. With bischloromethyl ether slightly contaminated with paraformaldehyde[149] 5-methylbenzoselenadiazole forms in the presence of chlorosulphuric acid the 4-chloromethyl-5-methyl compound. Under similar conditions bischloromethyl ether containing a considerable amount of paraformaldehyde gives a mixture of all three possible isomers—the 4-, 6-, and 7-chloromethyl-5-methyl derivatives (Ref. 150). The 4-methyl compound gives predominantly the 4-chloromethyl-7-methyl derivative, independently of the paraformaldehyde content of the bischloromethyl ether.

The 4- and 5-chloro-derivatives of benzoselenadiazole are more difficult to chloromethylate than are their thia-analogues under the same conditions. Processes involving degradation of the heterocycle predominate.

The chlorine in chloromethyl derivatives of benzothiadiazole and benzoselenadiazole is readily replaced by hydroxyl, alkoxyl, cyano, thiocyano, and amino: *o*- and *p*-methyl groups in chloromethylated benzothiadiazole facilitate, whereas chlorine impedes, nucleophilic substitution of the chloromethyl chlorine[140,144,145]. This shows an analogy with the behaviour of nuclear-substituted benzyl chlorides. However, the acceptor character of the heterocycle has hardly any effect.

The behaviour of chloromethylbenzothiadiazole has been studied under the conditions of the Sommelet reaction, which is employed for the synthesis of aldehydes. The acceptor influence of the heterocycle is not apparent in the preparation of the hexamethylenetetramine salt from the 4-chloromethyl-7-methyl compound. However, hydrolysis of the salt results in a low yield of the aldehyde. Similarly, the 4-formyl-5-methyl compound has been obtained in insignificant yield[144] by decomposition of the corresponding hexamethylenetetramine salt with very dilute hydrochloric acid.

Under the conditions of the Krönhke reaction[113,147,148,154] chloromethylbenzothiadiazoles are converted fairly smoothly into aldehydes. This reaction, unlike the Sommelet reaction, is favoured by electron-accepting substituents. *p*-Nitrosodimethylaniline reacts with 1-benzothiadiazol-4′-ylmethylpyridinium chloride or the corresponding 4′,7′-dipyridinium salt in the presence of piperidine or a solution of caustic soda as catalyst to form the corresponding nitrones, acid hydrolysis of which gives high yields of 4-formyl- and 4,7-diformyl-benzothiadiazoles respectively[113,147,148]:



The resulting formyl derivatives were converted into the corresponding acids by means of hydrogen peroxide or silver oxide.

The mobility of the chlorine in a chloromethylated benzothiadiazole is unaffected by a *para*-methyl group, whereas the yield of aldehyde obtained by the Krönhke reaction is considerably diminished by an *ortho*-methyl group, apparently because of steric hindrance. With *N*-methylformamide and phosphoryl chloride 4- and 5-methoxybenzothiadiazoles give the 4-formyl-7-methoxy- and 4-formyl-5-methoxy-derivatives respectively[144].

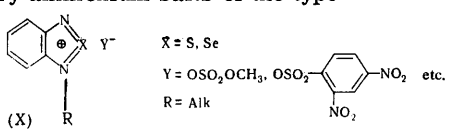
Friedel—Crafts reaction. This accompanies chloromethylation conducted in the presence of aluminium chloride, but it often plays the main part. Chloromethyl derivatives of benzothiadiazole and benzoselenadiazole do not under the Friedel–Crafts reaction with the initial heterocycles. Unsubstituted 1,2,5-thiadiazole behaves similarly in the presence of aluminium chloride[60]. This is consistent with the fact that methyl- and acetamidobenzothiadiazoles do not undergo the Friedel–Crafts reaction[151]. The probable reason is the electron-acceptor influence of the heterocycle.

Raising the temperature in the reaction of benzothiadiazole with alkyl bromides and iodides merely results in decomposition of the alkyl halides.

A relatively smooth reaction is obtained with acetic anhydride, whose interaction with aluminium chloride is not so exothermic as that of alkyl and acyl halides. This enables the process to be conducted at 130–140°C without resinification. However, the Friedel–Crafts reaction is then extremely slow[151].

Benzothiadiazole derivatives are themselves able to act as electrophilic reagents in the Friedel–Crafts reaction: e.g. benzothiadiazole-4-carbonyl chloride reacts with benzene in the presence of aluminium chloride to give an almost quantitative yield of the 4-benzoyl derivative[151].

N-Alkylation. Hinsberg[1,4] did not succeed in obtaining quaternary salts of benzothiadiazole and benzoselenadiazole, nor their 5-methyl derivatives, even by heating them with alkyl iodides at 160°C. Recently Nunn and Ralph[155] have accomplished alkylation of the unsubstituted benzo-compounds in high yields by means of dialkyl sulphates and substituted benzenesulphonates. They established that the products consisted only of monoquaternary ammonium salts of the type



The selenadiazole ring is more easily quaternised, and the resulting adduct is more stable (e.g. to hydrolysis), than with the thia-analogue.

All the quaternary salts obtained can be converted into halides, thiocyanates, perchlorates, and other salts by double decomposition.

Quaternary salts are obtained also by the reaction between *o*-aminodiphenylamine hydrochloride and selenous acid[156].

Alkylation and acylation of amino- and hydroxy-derivatives. Hydroxylated benzothiadiazoles and benzoselenadiazoles are stronger acids than the corresponding phenols and naphthols; the amines are weaker bases than the corresponding anilines and naphthylamines. Thus the pK_a of 4- and 5-hydroxybenzothiadiazoles are 7.86 and 8.16 respectively (the corresponding value for phenol is 9.99, and those for the naphthols 9.83 and 9.91); values of pK_b for 4- and 5-aminobenzothiadiazoles and aniline are respectively 11.3 and 9.4.[76,157,158] However, this has little effect on the reactivities of the hydroxy- and amino-derivatives of benzothiadiazole and benzoselenadiazole, which are close to those of naphthols and naphthylamines‡. They undergo all the reactions characteristic of the latter, in particular diazotisation, azo-coupling, alkylation, etc.

A detailed study of the hydroxyethylation of aminobenzothiadiazoles has been made in connection with the synthesis of compounds of presumed cytotoxic activity.

‡Polymorphism is observed in hydroxylated benzothiadiazoles[159].

Since the mechanism of the hydroxyethylation of amines involves addition of the amine to a carbonium ion, the basic strength of the amine plays an important part in the reaction. This is less vigorous with the 4- and 5-amines than with aniline, since they are less basic, as mentioned above [76,157,158]. On treatment with oxiran in acetic acid they form only the monohydroxyethylamino-derivatives [118].

Methyl substituents *ortho* and *para* to the amino-group promote high yields of the bishydroxyethylamino-derivatives. Interchanging methyl and amino between positions 4 and 5 has no significant influence on the reaction. With the 7-methyl-4-amine, on the other hand, bishydroxyethylation can be effected only in a considerable excess of methanol, owing to the stronger interaction of the substituents [118].

4-Amino-5-methylbenzoselenadiazole undergoes this reaction under the same conditions as its thia-analogue, with the formation of bishydroxyethylated products.

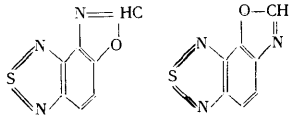
Hydroxyethylated benzothiadiazoles and benzoselenadiazoles can be converted by known methods into the corresponding chloroethylamino-derivatives. An interesting synthesis [160] is that of the thiadiazole analogue of the well known antitumorigenic preparations—*o*- and *p*-sarcolysin.

Alkylation of 4- and 5-aminobenzothiadiazoles with chloroacetic acid [161] yields the corresponding carboxymethylamino-derivatives.

On alkylation with alcohols in the presence of sulphuric acid, hydroxylated benzothiadiazoles behave like naphthols (phenols do not undergo this reaction), being converted into the corresponding alkoxy-derivatives [107], which are obtained also by alkylation with alkyl halides in the presence of alkoxides. Chloroacetic acid in the presence of alkali yields an *O*-carboxymethylated derivative. The alkylation of halogenated 4-hydroxy-derivatives with chloroacetic and with bromoacetic esters in the presence of sodium ethoxide gives 4-ethoxycarbonylmethoxy-derivatives containing halogen in the benzene ring [113,136,137].

Many studies have been made (e.g. Refs. 75, 76, 78, 79, 97, 98, 100, 101, 103, 105, 107, 108, 110, 115, 122, 134, and 162–164) of the acylation of amino- and hydroxybenzothia- and -selena-diazoles. The reactions are conducted under the usual conditions for aromatic amines and phenols, the heterocycles having no appreciable effect.

4-Amino-5-hydroxy- and 5-amino-4-hydroxy-benzothiadiazoles, like *o*-aminophenols, react with orthoformic ester to give oxazole derivatives [106,107]



Aminobenzothiazoles react with thiocyanic acid and with aryl isothiocyanates to form the corresponding thiourea derivatives [5,78,79,131].

Thus the substituent preferentially enters position 4(7) in electrophilic substitution of benzothiadiazoles and benzoselenadiazoles, as in the naphthalene series. The activating effect of substituents on the reactivity of position 5(6) increases regularly in the sequence— $CH_3 \ll OCH_3 < OH \leqslant NH_2$. [5] The influence of substituents on the reactivity of the benzene ring is qualitatively similar to analogous effects in the benzene series [5].

(*c*) Homolytic Substitution

Among homolytic substitutions in the benzo-1,2,5-thiadiazoles a detailed study has been made of bromination with *N*-bromosuccinimide. The latter does not act on (I) in boiling carbon tetrachloride, in dimethylformamide, or in the melt at 95–100°C. [5,161] Only aluminium chloride or 50% sulphuric acid catalyses this reaction, when the 4,7-dibromo-derivative is the main product [5,161]. On chlorination with chlorosuccinimide under similar conditions the process can be restricted to monosubstitution by using a threefold excess of benzothiadiazole (yield up to 20% [112]).

Benzene, too, is brominated by *N*-bromosuccinimide only in the presence of a Lewis acid. On the other hand, naphthalene, anthracene, and phenanthrene are brominated in carbon-tetrachloride solution in the absence of a catalyst. These comparisons indicate that benzothiadiazole is strongly aromatic in comparison with, for example, naphthalene. The isomeric 4- and 5-methylbenzothiadiazoles, like 1- and 2-methylnaphthalenes, are brominated by *N*-bromosuccinimide (in carbon tetrachloride, without a catalyst) in the side-chain [109,113,165]. Toluene is not brominated under these conditions. Chlorine in the benzene ring of (I) has no significant effect on the reaction. Under similar conditions to the above, 4,6-dichloro-7-methylbenzothiadiazole gives after 24 h 85% of the 7-bromomethylated compound [113].

The presence of a nitro-group in the benzene ring prevents homolytic bromination, which in the case of e.g. the 4-methyl-7-nitro-compound occurs only in the presence of benzoyl peroxide and under ultraviolet irradiation [109]. The isomeric 5-methyl-4-nitro-derivative is difficult to brominate under the same conditions; the presence of a brominated product has been detected only by thin-layer chromatography [166].

N-Bromosuccinimide (in carbon tetrachloride with benzoyl peroxide) smoothly brominates 4- and 5-carboxyethylbenzothiadiazoles [166] in the β-position with respect to the carboxyl, the yields being respectively 94% and 79%. The 4-chloromethyl-5-methyl compound is brominated under the same conditions as the corresponding carboxyethyl derivative, bromine entering the unsubstituted methyl group [145,151].

Bromine present in alkyl derivatives of benzothiadiazole readily undergoes nucleophilic substitution, which enables various derivatives to be obtained which are of interest for biological testing, in particular amino-acids and their *NN*-bis-2-chloroethyl derivatives [109,113,160,165,167–169].

(*d*) Nucleophilic Substitution

The thiadiazole ring, which has a weakly electron-acceptor character, favours nucleophilic substitution in a benzene ring fused to it. Nitro-derivatives of benzo-1,2,5-thiadiazole containing *ortho*- and *para*-halogen are easily substituted on treatment with nucleophilic reagents (alkoxides, amines, etc. [108,113,116,168–170]).

It is noteworthy that *o*- and *p*-halogenonitrobenzenes and 2,4-dibromonitrobenzene do not react with potassium thiocyanate under analogous conditions. This confirms the activating effect of the heterocycle in (I). The reactions of benzothiadiazole derivatives with other weak nucleophiles—ammonia, diethyl thiophosphate salts—reveal similar effects of the heterocycle [171,172].

An apparent anomaly is evident in the reaction of 4,6-dichloro-7-nitrobenzothiadiazole with ammonia in boiling ethylene glycol or in molten phenol, when only one chlorine atom is replaced by an amino-group (at position 6, *ortho* to the nitro-group). This shows the relatively weak influence of the heterocycle, which is insufficient to

activate two positions in the benzene ring. For this purpose, however, it is sufficient to introduce a second nitro-group: the action of ammonia on the 4,6-dichloro-5,7-dinitro-compound yields the 4,6-diamino-derivative.

As is to be expected, the nature of the halogen which is replaced has no significant influence on the course of nucleophilic substitution in the benzo-1,2,5-thiadiazoles. No departures from the above rules are observed in the reactions of the halogeno-nitro-derivatives with other amines and hydrazines [118].

The activating effect of the heterocycle on the mobility of chlorine atoms is clearly revealed [173] by the example of 4- and 5-chlorobenzo-oxa(thia, selena)diazoles, which react with sodium methoxide in methanol at 130°C with quantitative formation of the corresponding methoxy-derivatives. The nucleophilic substitution of chlorine is a second-order reaction, the rate for the 5-chloro-derivatives increasing in the sequence—O ≫ Se > S—and for the 4-chloro-derivatives in the sequence—O > Se ≫ S. [173]

The thia- and selena-diazole rings have an activating influence and make the halogen mobile also in the fused pyrimido-systems [174]. Shealy and his coworkers [42-45,81] report enhanced mobility of substituents in position 7 of pyrimidothiadiazoles. An unsuccessful attempt has been reported [175] to prepare hydroxybenzothiadiazoles by alkaline fusion.

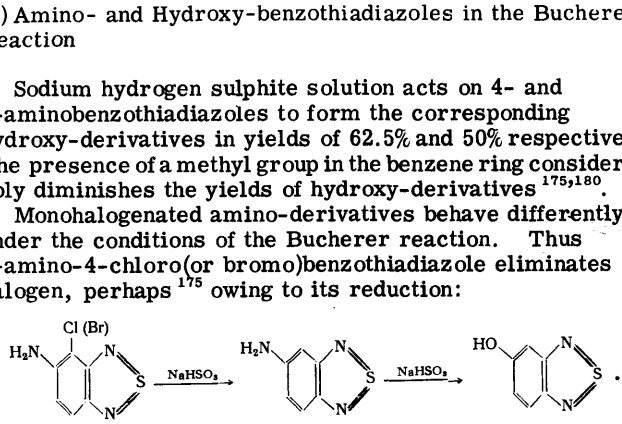
The similarity of benzothiadiazole and benzoselenadiazole to naphthalene, which is evident in several reactions, is clearly shown in the direct amination of the nitro-derivatives by hydroxylamine in alkaline medium [116,176,177]. Nitronaphthalenes undergo a similar reaction. 4- and 5-Nitrobenzo-thiadiazoles and -selenadiazoles yield the 5-amino-4-nitro- and 4-amino-5-nitro-derivatives respectively. Nitrobenzene is not aminated under these conditions, which clearly indicates the electron-acceptor character of the heterocycle. Dinitrobenzothiadiazole and also the isomeric methyl-nitro-compounds in which the position *ortho* to the nitro-group is unsubstituted undergo this reaction, but unsubstituted benzothiadiazole and benzoselenadiazole do not. The latter two compounds can be directly aminated by hydroxylamine sulphate in concentrated sulphuric acid [178].

Wen [179] found that 5-formylbenzothiadiazole reacts with nitromethane (in alkaline–alcoholic medium with subsequent acidification) to produce the 5-(1-hydroxy-2-nitro)-ethyl derivative.

(*e*) Amino- and Hydroxy-benzothiadiazoles in the Bucherer Reaction

Sodium hydrogen sulphite solution acts on 4- and 5-aminobenzothiadiazoles to form the corresponding hydroxy-derivatives in yields of 62.5% and 50% respectively. The presence of a methyl group in the benzene ring considerably diminishes the yields of hydroxy-derivatives [175,180].

Monohalogenated amino-derivatives behave differently under the conditions of the Bucherer reaction. Thus 5-amino-4-chloro(or bromo)benzothiadiazole eliminates halogen, perhaps [175] owing to its reduction:



The reverse conversion of hydroxy- into amino-compounds has been accomplished in the case of the 4- and 5-hydroxy-derivatives [124,127].

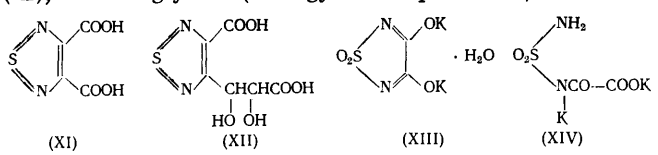
A mechanism has been suggested for the Bucherer reaction in the benzo-1,2,5-thiadiazoles which is analogous to that for naphthalene derivatives. It has been confirmed by the isolation, from the products of the reaction of isomeric hydroxy-nitroso-derivatives with sodium hydrogen sulphite, of the corresponding tetrahydro-oxonaphthalenesulphonic acids [124]. It has been stated [96] that 5-hydroxy-4-nitrosobenzothiadiazole does not react with sodium hydrogen sulphite, and hence does not undergo the Bucherer reaction.

(*f*) Oxidation of Benzothiadiazoles and Benzoselenadiazoles

Hinsberg [1] observed that benzothiadiazole is slowly oxidised by acid potassium permanganate, but he did not isolate the oxidation products. Later he noted [67] that this heterocycle is not oxidised by 30% hydrogen peroxide in acetic acid at 100°C. It has been shown recently [113] that under these conditions the 4,6-dichloro-7-ethylthio- and -7-*p*-chlorophenylthio-derivatives are converted into 27% yields of the corresponding sulphones, the heterocycle being unaffected. Nor is benzoselenadiazole oxidised by 30% hydrogen peroxide [97] under the above [67] conditions.

Perbenzoic acid in chloroform does not oxidise benzothiadiazole. Peracetic acid completely decomposes the organic part of the molecule. This occurs also in the oxidation of the 5-methyl-, 5-chloro-, and 4,7-dichloro-derivatives, ammonium sulphate and glycollaldehyde being detected among the reaction products [33,34]. Ammonium sulphate has been isolated also from the action of hydrogen peroxide on 1,2,5-thiadiazole [9].

Ozonisation of benzothiadiazole yields the dialdehyde of thiadiazole, 1,2,5-thiadiazole-3,4-dicarboxylic acid (XI), [33,34] and glyoxal (analogy with naphthalene).



(XI) (XII) (XIII) (XIV)

Among the products isolated from the oxidation of benzothiadiazole by aqueous potassium permanganate at 50–60°C were the acids (XI) and (XII) and also a compound of the presumed structure (XIII). [10,36] According to Wen [21] this compound (XIII) has the structure (XIV). His arguments suggest that this is probably closer to the truth. However, the experimental (synthetic) and spectral data which he cites are not inconsistent with the structure (XIII). The acid (XI) has been obtained also by the oxidation of 5-methyl- [37] and 4-nitro-benzothiadiazole [9] by aqueous potassium permanganate. The 4,7-dichloro-derivative is quite stable under these conditions, but is oxidised by alkaline potassium permanganate [33,34].

Benzothiadiazole and benzoselenadiazole are unaffected by a chromic mixture at 100°C. Resistance to oxidation is weakened by the presence of donor substituents in the ring. Under certain conditions it is possible to oxidise several benzothiadiazole derivatives and preserve the structure of the heterocycle. For example, the 4-amino-7-hydroxy-6-methyl and 4,7-diamino-5-methyl compounds are oxidised by a chromic mixture to the 5-methyl-4,7-dioxo-derivative of benzothiadiazole [108], which is a heterocyclic analogue of vitamin K_3.

The dibasic acid (XI) can be obtained in good yield by heating benzothiadiazole with chromium trioxide in sulphuric acid; under the same conditions benzoselenadiazole is completely decomposed [38-40]. A lower yield of

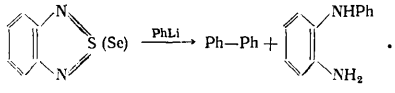
(XI) is formed by the oxidation of mono- and di-methyl derivatives of (I) under the same conditions. The oxidation of 5-bromobenzothiadiazole gives the 4,5-dibromo-derivative as well as the acid (XI). The 5-chloro-, 4,7-dichloro-, 4,7-dibromo-, 4-nitro-, and 5-nitro-derivatives are almost completely resistant to oxidation under these conditions.

The stability towards oxidising agents of benzothiadiazoles containing electron-acceptor substituents has enabled several carboxylated derivatives to be obtained [142].

Comparison of the behaviour of benzo-1,2,5-thiadiazoles and naphthalene on oxidation by chromic acid indicates that the benzene ring in the former is more stable than one of the naphthalene rings, whereas the tendency of derivatives of the latter to be oxidised to quinones is not so characteristic of compounds of the benzothiadiazole series.

(*g*) Reduction

The thiadiazole ring is extremely unstable towards reducing agents. Lane and Williams [181,182] established that phenyl-lithium reduces benzothiadiazole and benzoselenadiazole with fission of the heterocycle:



Several workers have shown [10,19,23,25,26,60] that the stability of the thiadiazole ring to the action of sodium in alcohol and also of various metal hydrides depends on the nature of the substituents in the ring. Shealy and his coworkers [42-45,81] studied the reactions of pyrimido-1,2,5-thiadiazoles, and found that both lithium tetrahydroaluminate and hydrogen sulphide reduce the heterocycle with the formation of *o*-diamines of the pyrimidine series.

The reductive cleavage of the thiadiazole ring by the action of zinc or tin in acids with the formation of aromatic or heterocyclic *o*-diamines provides a convenient method for preparing many of them, including those which are difficultly accessible by other methods [183-188].

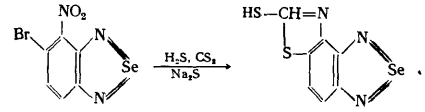
It has been established also that, in the reductive cleavage of fused thiadiazoles, the stability of the heterocycle is increased by the accumulation of chlorine atoms in the benzene ring [189]: 5 chloro- and 4,7-dichloro-benzothiadiazoles are quite stable towards sodium in boiling alcohol, whereas the unsubstituted compound and its methyl derivatives are cleaved under the same conditions [190]. Other workers have also reported that the behaviour of the heterocycle under these conditions depends on the nature of substituents in the benzene ring [19,23,25,26].

The thiadiazole ring in benzothiadiazol-5-ylacetic acid and its phenylisopropylamide [161,188] and also in chloromethylbenzothiadiazole [144] is stable to the action of sodium in alcohol and to Raney nickel.

The great stability of the thiadiazole ring to reducing conditions—in the presence of iron in 2% acetic acid, sodium dithionite, sodium hydrogen sulphide, sodium sulphide or disulphide, sodium sulphite, zinc in calcium chloride solution, ammoniacal hydrogen sulphide, hydrogen sulphide dissolved in sodium sulphide solution, alkaline iron(II) sulphate solution— has made it possible to reduce nitro-, nitroso-, and azo-derivatives of benzothiadiazole to the corresponding amino-compounds, and also to study the effects of other substituents and of the position of the reducible group on the reduction of the above derivatives [98,100,101,105,106,108,111,125,171,190,191].

The selenadiazole ring is still less resistant to reduction. Benzoselenadiazole derivatives are converted into *o*-diamines even by hydriodic acid or by sodium dithionite [10,123,192], which makes it possible to prepare many compounds of interest in connection with their biological activity, in particular derivatives of β-phenyl-α-alanine [193]. According to Elvidge et al. [123] the reduction of 4-nitro- and 4,6-dinitro-benzoselenadiazoles with hydriodic acid involves degradation of the heterocycle while the nitro-groups remain in the resulting phenylenediamines.

As with the thia-analogue, the sensitivity of the selenadiazole ring to reduction depends on the nature of substituents in the benzene ring. Thus hydrogen sulphide cleaves 4-amino-5-nitrobenzoselenadiazole to 1,2,3-triamino-4-nitrobenzene [116], whereas the 5-bromo-4-nitro-derivative in converted, without any destruction of the heterocycle, into selenadiazolobenzothiazole [194]:



The isomeric 4- and 5-nitrobenzoselenadiazoles behave differently towards iron in 2% acetic acid: the former is reduced to the 4-amino-derivative in 50% yield, whereas the 5-nitro-compound resinifies [115]. Under the same conditions 5-nitrobenzothiadiazole is reduced to the 5-amine [78]. This is evidence of the enhanced stability of benzoselenadiazole to reductive cleavage when a 4-nitro-group is present in the benzene ring.

Benzothiadiazoles and benzoselenadiazoles can be reduced either with potassium or cathodically to form radical-anions. These can be obtained also by reaction of the initial compounds with the dipotassium salt of the dianion of cyclo-octatetraene [195] or with the anions of propiophenone and 9,10-dihydroanthracene [196]. Electron transfer from the dipotassium salt is incomplete, the process being reversible [195]. Under similar conditions the reaction with 4- and 5-nitrobenzothiadiazole gives a quantitative yield of cyclo-octatetraene: electron transfer is complete, and no equilibrium is observed [197]. Thus the reduction of benzothiadiazole and benzoselenadiazole either with potassium or cathodically resembles that of naphthalene.

The ease of polarographic reduction increases from benzothiadiazole to benzoselenadiazole in conformity with the fall in electronegativity of the key heteroatoms and with the decrease in the dipole moment of the diazole. The final reduction product is *o*-phenylenediamine, which requires six electrons [198]. The overall process is irreversible and is regarded [199] as involving the intermediate formation of *o*-benzoquinonedi-imine.

In aprotic solvents the reduction of these compounds involves a reversible intermediate one-electron transfer with formation of the corresponding radical-anions [199-201]. The latter are stable at 20°C, and in the absence of oxygen are capable of one-electron oxidation to the original substances [196,199]. They are π-electron radicals.

(*h*) Complex formation

Several investigations have revealed the ability of benzothiadiazoles and benzoselenadiazoles to form complexes. Lane and Williams showed [202] that they are able to form molecular compounds with tetrahydroquinoxaline derivatives.

Bertini[30] noted that 1,2,5-selenadiazole and its methyl derivatives are able to form complexes with cadmium chloride. Benzoselenadiazole forms a 1 : 1 compound with palladium chloride, whose use has been suggested for the detection of palladium in the presence of platinum(IV), cobalt, nickel, and lead[203]. With a methanolic solution of benzoselenadiazole aqueous solutions of cadmium salts form insoluble complexes $Cd(III)_2X_2$, where X = Cl, Br, I, SCN, SeCN, NCO, N_3. On thermal decomposition these complexes split off one or two molecules of (III) in stages[204].

Benzothiadiazole and its 5-methyl derivative form 1 : 1 complexes with tin(IV) chloride[145,148,153]. A similar complex is formed with mercury(II) chloride under similar conditions[35]. Benzoselenadiazole derivatives under the same conditions form 2 : 1 complexes with aluminium chloride[153].

Apparently the formation of high yields of hydroxylated benzothiadiazoles and benzoselenadiazoles when the corresponding alkoxy-derivatives are heated with anhydrous aluminium chloride is also preceded by intermediate complex formation[158,164,173,205]. σ-Complexes of benzothiadiazole and its chloromethyl derivatives with aluminium chloride have been isolated in the presence of hydrogen chloride, and examined spectroscopically[5,151].

3. Relation between Structure and Reactivity of Benzothiadiazoles and Benzoselenadiazoles

There is no generally accepted structure for benzothiadiazole and benzoselenadiazole. On the one hand it has been shown[5,206] that these heterocyclic systems reproduce the most important properties of naphthalene, being fully comparable in aromatic character, and in this sense are its heterocyclic analogues. Examination of chemical, spectroscopic, and structural results for 1,2,5-thiadiazole, benzothiadiazole, benzoselenadiazole, and their derivatives indicates that the quinoid structure reported[76,96,115,122,126,207,208] for these systems is incorrect. On the contrary, all the experimental results indicate that the actual state of the benzothiadiazole and benzoselenadiazole molecules corresponds to a structure containing quadrivalent sulphur (or selenium), which forms two π-bonds by means of *pd*-hybrid orbitals.

From the similarity in the properties of 1,2,5-thiadiazole and pyrazine, and of benzothiadiazole and quinoxaline, an analogy was noticed[5,206] between the syntheses of benzothiadiazole and quinoxaline. A similar analogy has been shown[10,11,16,30-32] in the formation of derivatives of 1,2,5-thia(and selena)diazole and pyrazine. The ready conversion of aliphatic compounds into 1,2,5-thia(selena)-diazoles[10,12-32] also indicates the aromatic structure of benzothiadiazole and benzoselenadiazole.

Recently published spectroscopic and physicochemical investigations are also consistent with the above view. Strom and Russell[196] studied the electron spin resonance spectra of radical-anions of benzothiadiazole and benzoselenadiazole, and found that the acceptance of unpaired electrons by the key heteroatoms increases from sulphur to selenium. They calculated the distribution of spin density in the anion of benzothiadiazole by the LCAO-MO method to the Hückel approximation for a *d*-model (taking into account the *d*-orbitals of sulphur) and for a *p*-model. They obtained identical results in good agreement with the experimental data. A similar result has been obtained by other workers[209].

The e.s.r. spectra of the radical-anions from benzothiadiazole, benzoselenadiazole, naphtho[1,2-*c*]-[1,2,5]-thiadiazole, naphtho[2,3-*c*]-[1,2,5]-thiadiazole, and naphtho[1,8-*cd*]-[1,2,6]-thiadiazine have been interpreted[201] by the LCAO-MO method to the Hückel approximation. The experimental results agree satisfactorily with the *p*-orbital model, which also correlates adequately with the polarographic reduction of these compounds. However, the authors note that the e.s.r. spectra of the radical-anions containing conjugated sulphur are insufficient by themselves to decide the character of the nitrogen–sulphur bond in these compounds, which requires more extensive experimental data covering many other properties.

Solodovnikov and Todres[209] compared an analysis of the e.s.r. spectra of radical-anions from benzothiadiazole and benzoselenadiazole with calculations of the distribution of spin density in these anions. They concluded that the key heteroatoms in the molecules are in some way involved in conjugation. They based this conclusion also on an analysis of the electronic absorption spectra. Other workers[210] have reached the same conclusion. Comparison of the e.s.r. spectra of radical-anions of benzothiadiazole, benzoselenadiazole, and their 4- and 5-chloro-derivatives shows that the maximum density of the unpaired electron in the radical-anion of (I) is located on the α-carbon atom. Similar results have been obtained by other workers[196,211]. Thus the radical-anions of benzothiadiazole and of naphthalene are characterised by spin density distributions of the same type.

The unpaired electron densities on the $C_{(4)}$ and $C_{(5)}$ atoms are different in the anions from benzoxadiazole and from benzothiadiazole but the same in the anion from benzoselenadiazole[209]. The proton hyperfine splitting constants at positions 4 and 5 are equal in the radical-anion from benzoselenadiazole, but different in those from benzoxadiazole and benzothiadiazole[210]. These results agree well with those of chemical investigations[5,206].

Delocalisation of electrons in the benzothiadiazole and benzoselenadiazole molecules is confirmed also by the proton magnetic resonance spectra of these systems, which closely resemble one another and that of naphthalene: the heterocyclic compounds exhibit "naphthalenelike" spectra[212]. All three systems possess similar spin–spin splitting constants. The effects of substituents in the benzene ring of (I) and (III) (nitro, chloro, methyl, and amino in positions 4 and 5) on the chemical shifts are qualitatively identical with (and quantitatively closely similar to) analogous effects in the benzene series[212-214].

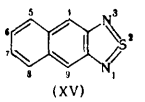
"Aromaticity" in the sense of the intensity of the ring current increases from sulphur to selenium[212].

These conclusions coincide with results of chemical experiments on the reactivity of benzothiadiazole and benzoselenadiazole[5,206]. Direct measurements of the magnetic susceptibility of these heterocyclic systems have confirmed the considerable levelling out of bonds in the heterocycle, i.e. the participation of the key atoms—sulphur and selenium—in forming the ring system of delocalised electrons[212].

It is interesting that the proton chemical shifts τ of 1,2,5-selenadiazole and 1,2,5-thiadiazole increase[32,212] from selenium (0.76) to sulphur (1.43),[29] i.e. in the opposite sequence to that following from the electronegativities of the key atoms. According to these results the selenadiazole is the most electrophilic.

Brown and Bladon[215] regard their results for the proton magnetic resonance spectra of benzothiadiazole and benzoselenadiazole as indicating that the six-membered rings are in some measure quinoid.

Ray and Narasimhan[211] have used the LCAO-MO method to calculate bond orders and lengths for 1,2,5-thiadiazole, benzothiadiazole, and naphtho[2,3-*c*]-[1,2,5]-thiadiazole (XV)



(XV)

They also calculated the π-electron density, the frontier electron density, and the localisation energy of the cation for positions 4 and 5 in (I) and positions 4–6 in (XV). Values of the spin density were computed for the radical-anion from (XV) as respectively 0.1130, 0.0413, and 0.0253 for positions 4–6 (experimental values not obtained). These workers[211] regard the calculated values as showing good agreement with corresponding experimental data where available, and also with experimental results for the reactivities and stabilities of these compounds.

The order of the N–S bond and the length of the C–N bond increase in the sequence—1,2,5-thiadiazole < (I) < (XV)—while the length of the N–S bond decreases in this sequence. These results are consistent with Cava and Schlessinger's view[216] that in the compound (XV) the sulphur is present in the quadrivalent state.

On the assumption that the sulphur is conjugated by means of *p*-orbitals Markov and Skancke[217] used the Pariser–Parr–Pople SCF MO method to calculate for the isomeric 1,2,5- and 1,3,4-thiadiazoles bond orders and lengths and π-electron charges on the sulphur, nitrogen, and carbon atoms. These workers[217] regard the calculated values as agreeing satisfactorily with certain experimental results. It must be noted that interatomic distances were not calculated for N–S, while the calculated C–C bond length diverges considerably from the observed values. Satisfactory agreement is found only for the C–N bond.

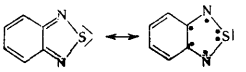
Soptrajanov[218] has shown that the enthalpy, entropy, and heat capacity increase in the sequence—1,3,4-thiadiazole, 1,2,5-thiadiazole, its deutero-analogue, and thiophen.

Calculated and experimental data relating to a quantitative estimate of the electronic structure of certain thiazoles and isomeric 1,2,5- and 1,3,4-oxa- and -thia-diazoles have been given[219], but no definite conclusions on the structure of the thiadiazoles.

Zahradnik and Koutecky[220] applied the LCAO-MO method to a comparative study of four isomeric thiadiazoles using the Longuet-Higgins model and a model which disregarded the participation of *d*-orbitals. They concluded that the limited experimental data can be interpreted better by the Longuet-Higgins model.

Kataev and Plemenkov[221] used the LCAO-MO method to the Hückel approximation to calculate the benzothiadiazole and benzoselenadiazole molecules, both with and without taking *pd*-hybridisation into account. They calculated the ionisation potentials, the $\pi-\pi^*$ transition energies, the π-moments of the molecules, the bond lengths, and the reactivity indices for both models. Comparison of calculated with experimental results showed that the actual state of these molecules corresponds to models involving *pd*-hybridisation.

The clearly defined aromaticity of (I) and (III) and the inability of their key atoms to increase their valency (to be oxidised) are consistent with another structure on the assumption that the sulphur (selenium) is involved in conjugation by the lone pair of electrons:



In this case aromaticity is achieved by the formation of a closed πp-electron system. In the benzenoid structure the closed system of electrons has the character $\pi(p-pd)$.[5,221]

With regard to which of these two structures represents the actual state of the molecule, the similarity of the chemical properties of benzothiadiazole and benzoselenadiazole to those of naphthalene, the similarity in the electronic spectra of benzothiadiazole and its derivatives to the typical spectra of fused aromatic compounds, the clearly defined aromatic character of benzothiadiazole and its derivatives revealed by their infrared spectra, the similarity of the proton magnetic resonance spectra of benzothiadiazole and of naphthalene, and the similarity in method of synthesis and in ultraviolet spectra between benzothiadiazole and quinoxaline, thiadiazole and pyrazine, and the similarity in the e.s.r. spectra of radical-anions from benzothiadiazole and from naphthalene—all these facts agree well with an aromatic, benzenoid structure for benzo-1,2,5-thiadiazole and benzo-1,2,5-selenadiazole.

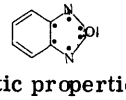
This conclusion is further confirmed by comparing benzothiadiazole and benzoselenadiazole with their oxygen analogue—the little studied benzofurazan. On nitration the nitro-group enters position 4, but the reaction occurs with considerably greater difficulty than in the (I) and (III) series. Benzofurazan readily adds four bromine atoms under normal conditions, is considerably less stable to oxidants, acids, and alkalis, and is more stable to reduction than are the thia- and selena-analogues. The reductive cleavage of benzofurazan by phenyl-lithium also takes place differently from that of (I) and (III).[181,182]

The ultraviolet spectrum of benzofurazan differs markedly from that of benzothiadiazole § and is displaced 30 nm to shorter wavelengths[10]. The dipole moments increase in conformity with the electronegativity of the key atoms in the sequence[223]

	O	>	S	>	Se
D	4.37		1.73		0.94 .

The few experimental data give no adequate concept of the reactivity of benzofurazan. However, comparison of the properties which have been described with the corresponding properties of benzothiadiazole indicates that benzofurazan is weakly aromatic. On the whole the properties of the benzochalcogenadiazoles indicate that the sequence of increasing aromaticity (and hence diminishing "unsaturation") is—oxa < thia < selena.

Oxygen, in contrast to sulphur, is unable to expand its valency shell to ten electrons by means of *d*-orbitals. The weak aromatic properties of benzofurazan can be explained by the possibility of formation, in the planar[223–225] furazan ring, of a closed πp-system comprising six electrons. The structure of benzofurazan can therefore be represented by the formula



which reflects its aromatic properties.

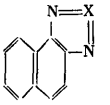
Hence the difference in reactivity between benzofurazan and benzothiadiazole is explained by the different structures of these compounds. Since the above structure for benzofurazan is unique, it must be assumed that in benzothiadiazole and benzoselenadiazole the key heteroatom forms with the nitrogen atoms two π-bonds involving *pd*-hybrid orbitals[5,206,221].

§The ultraviolet spectrumof furazan[222] also differs markedly from that of 1,2,5-thiadiazole.

IV. OTHER FUSED 1,2,5-THIADIAZOLES AND 1,2,5-SELENADIAZOLES

Naphtho[1,2-*c*]-[1,2,5]-thiadiazole (IV) and the corresponding napthoselenadiazole (XVI)

(IV, X=S)
(XVI, X=Se)



which were first obtained by Hinsberg[1,4], had not been investigated until recent years. These systems are stable towards acids, alkalis, oxidants, and heat, but are unstable towards reducing agents, which cleave the heterocycle.

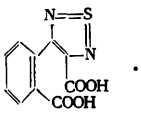
Naphthothiadiazole is nitrated as readily as is benzothiadiazole, forming predominantly the two isomeric 6- and 9-nitro-products[226,227], which can be reduced to the amino-derivatives by the action of iron in 2% acetic acid. The amines form readily hydrolysable salts, are acylated, are converted by means of the diazo-reaction into halogeno- and hydroxy-derivatives, and undergo the Bucherer reaction[226,227].

When naphthothiadiazole is chlorinated in acetic acid, either a dichloro-derivative or predominantly the 5-chloro-compound is formed, depending on the experimental conditions. The latter is obtained also by the action of sulphuryl chloride on the naphthothiadiazole. In formic acid or in the melt (in the presence of iron) chlorination occurs at position 5, and also a trichloro-derivative is formed identical with that obtained by chlorinating the 5-chloro-compound. Chlorination of molten naphthothiadiazole in the absence of iron yields an adduct—the 4,5-dichloro-4,5-dihydro-derivative[228].

Bromine acts on molten naphthothiadiazole to yield mainly the dibromo-derivative, whether in the absence or in the presence of iron[226,228]. In acetic acid the main product is the 4-bromo-compound.

Depending on the conditions and the concentration of oleum, sulphonation gives either the 4-sulphonic acid or (mainly) the corresponding disulphonic acid. Similarly, chlorosulphonation with chlorosulphuric acid gives either the 4-sulphonyl chloride or mainly the disulphonyl chloride, depending on the conditions[226,227].

The thiadiazole ring in the naphtho-compound resists oxidation by a chromic mixture: fission occurs at the $C_{(4)}-C_{(5)}$ bond, with formation of the dicarboxylic acid



The presence of electron-acceptor substituents, e.g. the nitro-group, enhances the stability of the system to oxidation. A chromic mixture or chromium trioxide in concentrated sulphuric acid produces no appreciable change in 6-nitronaphthothiadiazole: this compound is cleaved oxidatively only by an alkaline solution of potassium permanganate[226,227].

The spectrum of the radical-anion of the naphthothiadiazole has been studied[201].

Sulpho-derivatives of naphthoselenadiazole, obtained by Hinsberg's reaction, have been described[229-231].

Naphthoselenadiazole itself can, like naphthalene, be reduced by potassium or cathodically to form a radical-anion[209]. The latter is obtained also by reaction with the dipotassium salt of the dianion of cyclo-octatetraene[195] (difference from naphthalene—evidence of the electron-acceptor character of the heterocycle).

Comparison of the e.s.r. spectra of the anions of naphthoselenadiazole and benzoselenadiazole led to the conclusion that the distribution of spin density in the heterocycle probably changes little from benzologues to naphthologues[209].

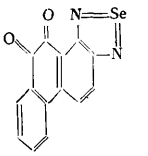
The linear naphtho[2,3-*c*]-[1,2,5]-thiadiazole (XV), which is isomeric with the above angular system (IV), was first obtained by Cava and Schlessinger[216], who showed that this compound undergoes diene synthesis with maleic anhydride and phenylmaleimide to form the corresponding adducts.

Oxidation of the linear naphthothiadiazole (XV) with potassium dichromate in acetic acid yields a heterocyclic analogue of anthraquinone, which can be reduced to a quinol of the linear naphthothiadiazole. The quinone is obtained also by cyclisation of 2,3-diamino-1,4-naphthaquinone with thionyl chloride[232,233].

Quantum-mechanical investigations of the linear naphthothiadiazole and its radical-anion have been reported[201,211].

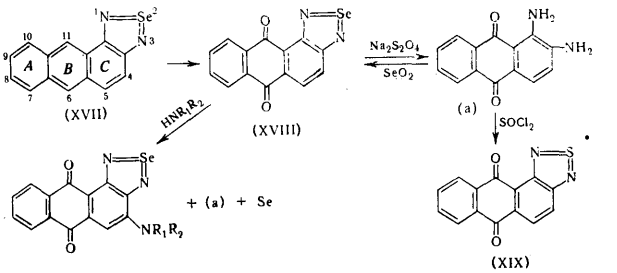
Depending on the conditions, chlorine and bromine act on the linear naphthothiadiazole to form either the 4,9-dihalogeno- or the 4,9-dihalogeno-4,9-dihydro-derivative. Chlorination with sulphuryl chloride gives a 41% yield of the 4,9-dichloro-derivative[234].

Among derivatives of phenanthrene only 10,11-dihydro-10,11-dioxophenanthro[1,2-*c*]-[1,2,5]-selenadiazole



obtained by Hinsberg's reaction, is known[235].

The same method has been used to obtain anthraselenadiazole and anthrathiadiazole, which have been subjected to several reactions[192,236-239]. Anthraselenadiazole (XVII) is oxidised by chromic acid to a quinone, which is reduced with the separation of selenium and the formation of 1,2-diaminoanthraquinone (a);[192] the latter can be converted either back into the quinone (XVIII) or into its thia-analogue (XIX):



Amines act on (XVIII) to produce partial amination of the benzene ring fused to the selenadiazole ring, the reaction being accompanied by formation of an *o*-diamine and separation of selenium[236,238].

Hydrogen or chlorine at position 4 in (XVIII) and (XIX) can be replaced by amino[237,238,240], arylthio, alkylthio, arylsulphonyl, and sulpho[239,241]. If chlorine is present at position 5, hydrogen at position 4 can also be replaced.

Chlorine at position 5 cannot undergo similar substitution. Several other reactions have been studied [241].

The above reductive opening of the selenadiazole ring has been considered [238] to involve initial addition of the amine at positions 4 and 5 of the dihydrodioxoanthraselenadiazole, after which the adduct is oxidised by the initial quinone, which is thus reduced mainly to 1,2-diaminoanthraquinone and selenium.

Nitration of the quinone (XIX) with a nitrating mixture at 50°C gives an 85% yield of a mixture of the 7- and 10-mononitro-derivatives in the proportions 1.5 : 1, which can be reduced with sodium hydrogen sulphide to the corresponding amines. Caustic soda acts on the nitro-derivatives to open the thiadiazole ring; the resulting 1,2-diaminoanthraquinones can be reduced to 1,2,5- and 1,2,8-triaminoanthraquinones [239].

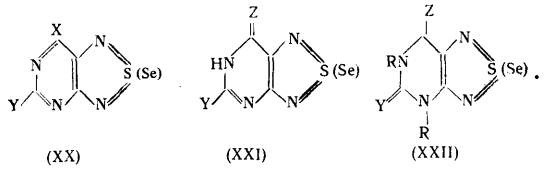
The fact that the nitro-groups enter the "outer" benzene ring A—not ring C—is explained [239] by deactivation of the latter by the thiadiazole ring, which is protonated in sulphuric acid.

A sulphurous diamide can be isolated [84] from the products of the action of alkali on the quinone (XIX) at 20°C. Both dihydrodioxoanthraselenadiazole (XVIII) and dihydrodioxophenanthroselenadiazole are equally readily cleaved by alkali to form the corresponding *o*-diamines. Fission of the selena- and thia-diazole rings by the action of alkalis on the quinone-diazoles is a convenient method for obtaining difficultly accessible derivatives of 1,2-diaminoanthraquinone [242,243].

6,11-Dihydro-6,11-dioxoanthra[1,2-*c*]-[1,2,5]-thia(and selena)diazoles are chlorinated in acetic acid at position 4, but in sulphuric acid or oleum at positions 7 and 10, with the formation of 7,10-dichloro-derivatives [244].

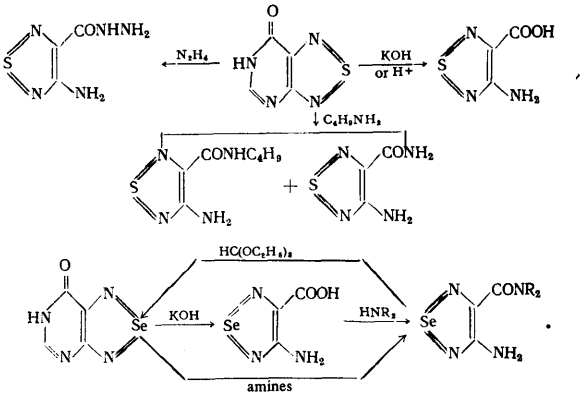
Products in which the 1,2,5-thiadiazole and 1,2,5-selenadiazole rings have been fused with many cyclic systems—carbazoles, dibenzothiophens, dibenzoselenoles, benzothiazoles, benzoxazoles, quinoxalines, benzimidazoles, quinoline (by the Skraup synthesis from aminobenzothiadiazole)¶, pyridines, pyrimidines, pyridazine, benzo-1,2,5-thiadiazoles, and benzo-1,2,5-selenadiazoles—have now been investigated [41-45,78,79,81,88,106-108,131,174,176,245-260]. These complicated heterocyclic systems have been obtained mainly by reaction of the corresponding *o*-diamines with thionyl chloride, sulphinylaniline, or selenium dioxide. Systems containing a selenadiazole ring have been obtained also from amino- or acylamino-benzothiadiazoles and -benzoselenadiazoles by known methods [249,257,259].

Especial interest attaches to investigations by Shealy and his coworkers [41-45,81] of several reactions of the pyrimidothiadiazole and pyrimidoselenadiazole derivatives



(XX) (XXI) (XXII)

The substituents X = Cl, SH, $SCH_2C_6H_5$ in the compound (XX : Y = H) are shown to be highly mobile, and readily undergo substitution on reaction with aniline. The thiadiazole ring in (XX) is cleaved by lithium tetrahydroaluminate or by hydrogen sulphide to the corresponding *o*-diamines. Basic and acidic reagents under mild conditions open the pyrimidine ring:



V. SPECTROSCOPIC PROPERTIES OF 1,2,5-THIADIAZOLES AND 1,2,5-SELENADIAZOLES

Many workers have studied the spectroscopic characteristics of 1,2,5-thiadiazoles, 1,2,5-selenadiazoles, and their fused systems in both the ultraviolet and the infrared for the purposes both of identification and of comparison with the corresponding data for typical aromatic and heteroaromatic compounds [5,9,12,21,24,32,35,59,96,97,102,114-116,122,126,144,151,157,205,207,216,234,245-248,260-273]. The Raman spectra of the monocyclic and fused heterocycles have also been studied [264,267-269,271,272].

The ultraviolet spectra revealed a constant bathochromic shift in the absorption maximum on passing from thiadiazole and benzothiadiazole derivatives to their selenium analogues. Similarity in the character of the absorption and in the distribution of the maxima was observed in the ultraviolet spectra of benzothiadiazole and quinoxaline, and of 1,2,5-thiadiazoles and pyrazines [5,9,206]. Sawicki [248] explains the similarity of the ultraviolet spectra of several benzothiadiazole and benzoselenadiazole derivatives to those of the corresponding *o*-aminonitrobenzenes—the initial compounds for the synthesis of these heterocycles—by regarding the heterocyclic derivatives as *ortho*-substituted.

Bird and Cheeseman [270] compared the infrared spectra of benzoselenadiazole and twenty-five of its mono- and di-substituted derivatives with those of di-, tri-, and tetra-substituted benzenes. They felt that the results did not permit any conclusions to be drawn on the distribution of electron density or the fine structure of the benzoselenadiazole derivatives.

Soptrajanov and Ewing [267] made a comprehensive investigation of the vibrational spectra of 1,2,5-thiadiazole and its dideuterated derivative [267]. They gave a complete interpretation of the infrared spectra of liquid and gaseous specimens and of the Raman spectra of liquid 1,2,5-thiadiazole.

Benedetti and Bertini [271] studied the infrared spectrum over the range 4000–400 cm^{-1} of 1,2,5-selenadiazole in solid, liquid, and gaseous states and dissolved in carbon disulphide. The Raman spectrum was recorded for liquid selenadiazole. The molecule of this compound was shown to be planar, the key atoms—sulphur and selenium—being conjugated.

A satisfactory correlation has been demonstrated [200,273] between the positions of the maxima in the ultraviolet

¶4- and 5-Aminobenzothiadiazoles also undergo the Herz reaction [252], as well as with aryl isothiocyanates [261].

absorption spectra of 4- and 5-substituted benzoselenadiazoles and benzothiadiazoles and the Hammett σ_m and σ_p constants.

A study has been made of the infrared, ultraviolet, and proton magnetic resonance spectra of two isomeric pyrido-1,2,5-selenadiazoles [260]. The proton magnetic resonance spectra were regarded [260] as indicating considerable fixation of C–C bonds in the pyridine ring.

Study of the mass spectra of benzoselenadiazole, its 5-methyl and 4,5,6-trimethyl derivatives, and phenanthro-[1,2-*c*]-[1,2,5]-selenadiazole showed [274] that, in spite of the great stability of their molecular ions M^+, the two carbon–nitrogen bonds undergo rupture on electron bombardment with the formation of ions of dehydrobenzene or its analogues. It has also been shown [275] that benzoselenadiazole is less stable to electron bombardment than is phenazine or the above phenanthraselenadiazole (it splits off hydrogen cyanide more easily).

The mass spectra of 1,2,5-thia- and -selena-diazoles have been studied also by Marquardt [35] and Weinstock et al. [29] The stability of these heterocycles towards electron bombardment is evidence of their aromatic character.

From investigation of the infrared and ultraviolet spectra of benzothiadiazole and some of its derivatives the conclusion is drawn that it represents a typical heteroaromatic system [5,206,262–265] and there are no grounds for supposing that benzothiadiazole and benzoselenadiazole have a quinoid structure.

VI. APPLICATION OF DERIVATIVES OF 1,2,5-THIADIAZOLES AND 1,2,5-SELENADIAZOLES

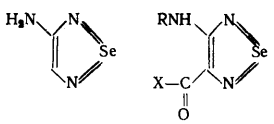
1,2,5-Thiadiazole and its benzo- and pyrimido-systems are in their way analogues respectively of pyrazine, quinoxaline, and pteridine, present in many biologically active compounds. There are indications that several derivatives of benzothiadiazole possess low toxicity [8].

The biological properties of acid derivatives of 1,2,5-thiadiazole have been investigated in detail. Hydrazides of the 3-carboxylic acid are active against *Escherichia coli*, [9] and also inhibit the action of monoamino-oxidase [276]. The *N*-phenylisopropylammonium salt of this acid has a strong stimulating action on the central nervous system and on respiration [277]. Sulphanilamides of the thiadiazole and selenadiazole series possess bactericidal activity [59,61,278–280]: thus 3-sulphanilamido-1,2,5-thiadiazole has been recommended [61,62,280] for the treatment of coccidiosis in poultry.

Several halogenated and hydroxylated 1,2,5-thiadiazoles have been found to have a bactericidal effect [12,14]. Among the above heterocyclic compounds substances have also been detected which possess insecticidal [162,163], fungicidal, herbicidal [55,56,64,65,280], antihelminthic [281–283], nematocidal [64,65], and diuretic [143] action.

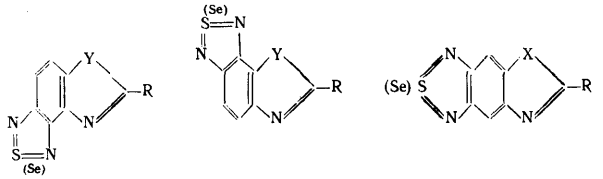
Daams, Koopman, and their coworkers have recently compared [112,113,283–285] the structure with the herbicidal and fungicidal action of chlorinated benzothiadiazoles. According to their observations the strongest herbicide is the 4,5,7-trichloro-derivative, and also the 5,7-dichloro-4-methyl compound. The latter, as well as several dichloronitrobenzothiadiazoles, exhibits high fungicidal activity. 4,5,7-Trichlorobenzothiadiazole has been proposed [286] in particular for the fight against harmful members of the fish fauna.

Several thia- and selena-diazole derivatives possess antitumorigenic activity. Shealy and his coworkers have reported [41,287] a new class of cytotoxic agents, the selenadiazoles, among which the most effective have been found to be



where R = H, Alk and X = OH, N<. Such activity is possessed also by several pyrimido-1,2,5-selenadiazoles [255,256] and their thia-analogues [249,288–290] containing hydroxy- and amino-groups in the pyrimidine ring. *NN*-Bischloroethylamino-derivatives of benzothiadiazole [5,160], including analogues of *o*- and *p*-sarcolysin, are of interest in this connection.

As mentioned above, fused thia- and selena-diazoles can be coupled with diazonium salts to form azo-dyes. Several of them show promise for industrial synthesis [205,291]. Cyanine dyes containing thia- and selena-diazole rings have been synthesised by Soviet [246,247] and Italian [245,292] chemists on the basis of the systems



(where X = S, NR; Y = O, S, Se, CH:CH, NR; and R = H, CH_3) and other fused heterocycles containing reactive methyl groups.

3-Chloro-1,2,5-thiadiazole has been claimed to possess good solvent power for certain polymers [18,61]. It is said [52] to be possible to obtain synthetic condensation resins from 1,2,5-thiadiazoline 1,1-dioxide and dialdehydes [52].

The analytical usefulness of the ability of thia- and selena-diazole derivatives to form complexes can be judged in particular from the possibility of detecting palladium in the presence of platinum(IV), nickel, cobalt, and lead by means of benzoselenadiazole [203]. It has been suggested that the ability of coloured solutions of certain derivatives of this compound, e.g. 5-(3,4-diaminophenyl)-benzoselenazole, to absorb in a certain range of the ultraviolet spectrum, should be used for analytical purposes [291,293,294]. This will permit a quantitative determination of the selenium content of benzoselenadiazole derivatives

The formation of certain derivatives—e.g. 4,5-dichlorobenzoselenadiazole, 5,5′-bibenzoselenadiazolyl—from the corresponding *o*-diamines can be used for the spectrophotometric determination of Se^{IV}. [273,295]

Dihydrodioxoanthra-thia- and -selena-diazoles can be used to obtain daylight-fluorescent colorants which show promise for practical application [296].

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