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REVIEW

SULFUR CHEMISTRY IN CROP PROTECTION

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This review aims to give an overview of the significance of sulfur-containing compounds in chemical crop protection. The main sulfur-organic agrochemical compound classes are presented, and sulfur-containing natural products which exhibit pesticidal properties are also described. The special role of sulfur in propesticide action is explained. The certain advantages of replacing an isocyclic or *N*-heterocyclic ring by a sulfur heterocycle are demonstrated by means of different isosteric relationships. Some special contributions of Syngenta and its legacy companies to crop protection-related sulfur chemistry are shown.

Keywords: Sulfur; Sulfur-organic compounds; Crop protection; Agrochemicals; Herbicides; Fungicides; Insecticides

INTRODUCTION

The history of crop protection is closely linked to elemental sulfur, which is undoubtedly the oldest of all pesticides [1]. Its fungicidal properties were already known by the ancient Greeks, when nearly thirty centuries ago Homer referred to 'pest-averting sulfur' [2]. Most of the knowledge was lost until Forsyth rediscovered sulfur for the control of plant diseases in 1802 [3]. His recommendation for the control of powdery mildew on fruit trees was a concoction of quicklime, sulfur, elderberry bud and tobacco. Since 1824 powdered sulfur was widely applied against fruit and grape diseases, *e.g.* peach powdery mildew [4], until the second half of the 19th century saw the introduction of three further pioneering sulfur-containing fungicides: Eau Grison (calcium polysulfide, $CaS \cdot S_x$) in 1852 [5], Bordeaux mixture [$CuSO_4 + Ca(OH)_2$] in 1885 [6] and Burgundy mixture ($CuSO_4 + Na_2CO_3$) in 1887 [7]. These inorganic sulfur derivatives are still in operation, but today's typical agrochemicals are definitely organic compounds. Because of the significance of sulfur in modern organic chemistry and the specific properties of these resulting compounds in biology, approximately one-third of all registered pesticides contain at least one sulfur atom [8]. This review will highlight the structural diversity of sulfur-containing crop protection chemicals and the special features of their sulfur moiety, which makes them so unique.

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MAIN STRUCTURAL CLASSES

Herbicides

Sulfonylurea herbicides [9, 10] inhibit *acetolactate synthase* (ALS), an enzyme involved in the early stage of the biosynthesis of branched-chain amino acids, resulting in a rapid cessation of plant cell division and growth [11]. The three branched-chain amino acids valine, leucine and isoleucine are called 'essential' because mammals lack biosynthetic pathways to produce them and therefore must obtain them from their diet. This selectivity towards plants undoubtedly contributes to the favorable environmental and toxicology profile of sulfonyl ureas. Other features such as high efficacy and thus extremely low use rates as well as excellent crop selectivity meant that the discovery of sulfonyl ureas in the mid 1970s by DuPont rang in the beginning of a completely new era in chemical weed control [12]. The subsequent tremendous worldwide research and development effort has led to the commercialisation of, so far, 28 different active compounds from this chemical class for selective weed control in over a dozen major crops [13], some of which are shown in Figure 1. The structure-activity requirements are relatively clear: linked to the amine end of the sulfonylurea bridge is always a pyrimidine or triazine moiety bearing two alkyl and/or alkoxy substituents. The sulfonyl moiety is usually connected to a phenyl ring or an aromatic heterocycle with an additional *ortho*-substituent. Surprisingly, the shortening of the sulfonylurea bridge to a sulfide with the retention of the other typical structural elements of sulfonylurea herbicides also leads to very active ALS inhibitors, for example pyrithiobac-sodium (**4**) [14].

Triazolopyrimidine sulfonanilide herbicides [15, 16] possess the same mode of action as sulfonylureas (ALS inhibition) [17]. This class of compounds, discovered in the mid-1980s at Dow, is also structurally closely related to sulfonylureas, having some parts of the sulfonylurea bridge inverted and other parts of it incorporated into a five-membered ring, which is annelated to the sulfonylurea pyrimidine. They are very effective in controlling various broadleaf and grass weed species at low dosages while maintaining high levels of selectivity to agronomically important crop species such as corn, soybean and wheat. Some examples of these sulfonylurea analogs are displayed in Figure 2.

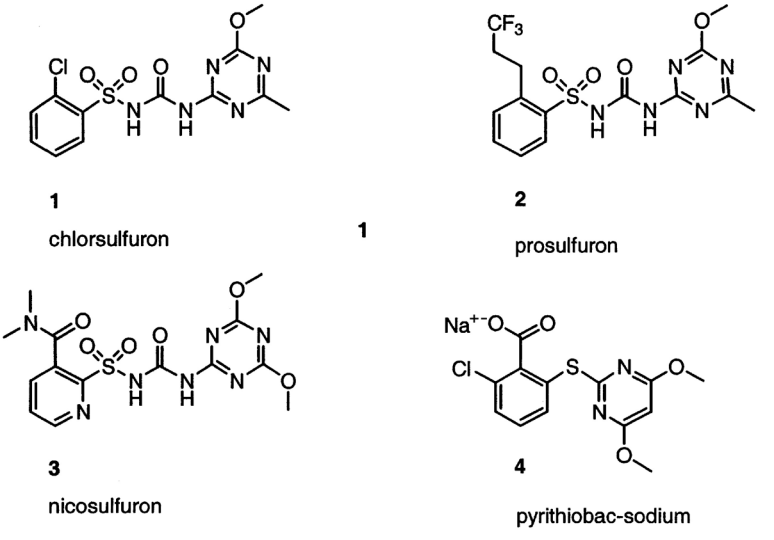


FIGURE 1 Sulfonylurea herbicides.

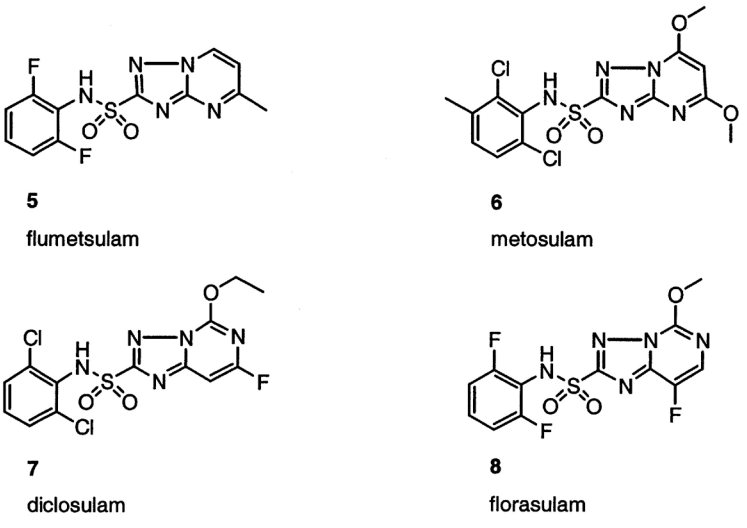


FIGURE 2 Triazolopyrimidine sulfonanilide herbicides.

The thiocarbamates are a group of pre-emergent soil herbicides, of which the first derivatives were introduced by Stauffer (now Syngenta) in the mid-1950s [18]. Also here, a sulfur atom plays an important role in the main functional group of the molecule (Figure 3).

There are several derivatives of the triazine herbicides in which the chlorine substituent in the 2-position of such landmark weed control agents as atrazine and simazine is replaced by a thiomethyl group [19, 20]. The triazine herbicides were discovered by Geigy (now Syngenta) in the early 1950s. They are powerful photosynthesis inhibitors, interrupting the light-driven flow of electrons in chloroplasts from water to nicotinamide adenine dinucleotide phosphate (NADP). A thiomethyl substituent in place of the typical chlorine offers the specific advantage that the residual activity is much shorter than of the corresponding chlorine derivatives, allowing weed control in crops, which are replaced by other, more sensitive crops after a short time-interval, as it is often the case for legumes and small grains [19]. Figure 4 shows some examples of these herbicides.

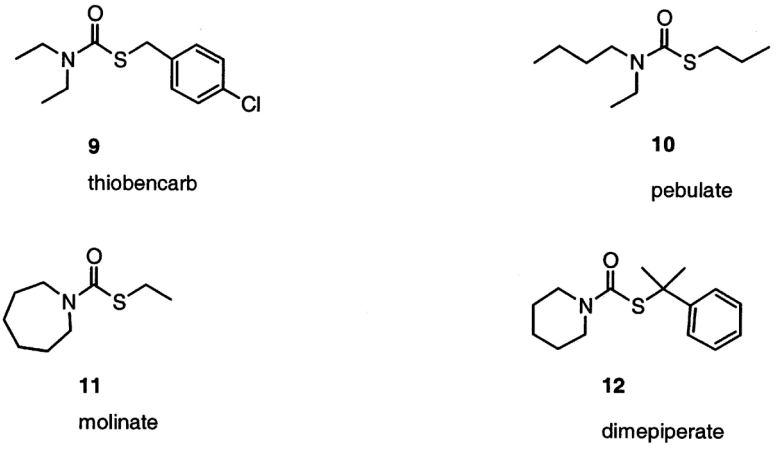


FIGURE 3 Thiocarbamate herbicides.

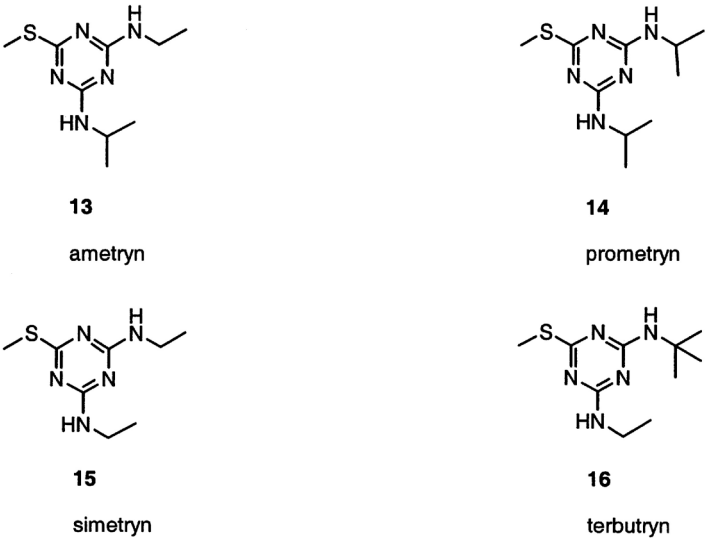


FIGURE 4 Triazine herbicides.

A special sulfur-containing substituent also seems to be important in triketone herbicides [21, 22], but here it is not the thiomethyl but rather the methylsulfonyl group. Such a methylsulfone unit in the *ortho* or *para* position of an aromatic ketone is a common motif in the most prominent derivatives of this class of herbicides, which was discovered by Stauffer (now Syngenta) in the early 1980s (Figure 5). Triketone herbicides are inhibitors of *p*-hydroxyphenylpyruvate dioxygenase (HPPD), which in plants is part of the biosynthetic pathway to plastoquinone, an important cofactor for phytoene desaturase [23]. The depletion of plastoquinone results in a reduction of the carotenoid level, leading to bleaching symptoms. The electron-withdrawing capability of an *ortho*- or *para*-methylsulfonyl group leads to increased acidity of the molecule and therefore favours the enolisation of the keto functions, which enhances transport as well as binding affinity to HPPD [21]. Isoxaflutole (**19**), itself not active on HPPD, is a special case in this class of compounds, because its isoxazole ring is

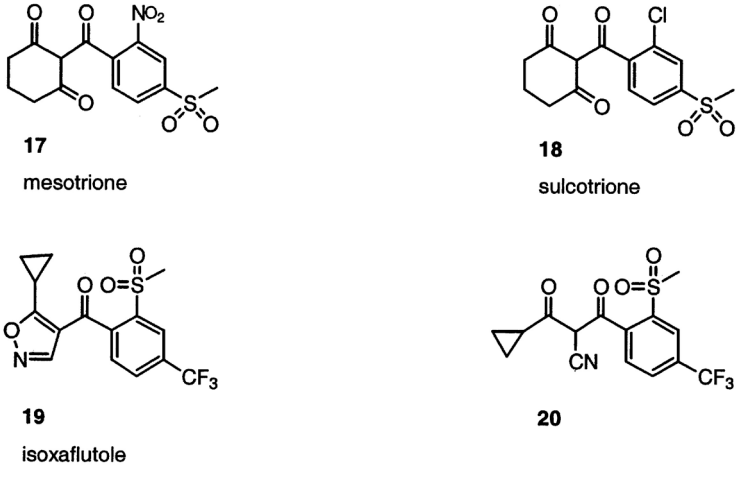


FIGURE 5 Triketone herbicides.

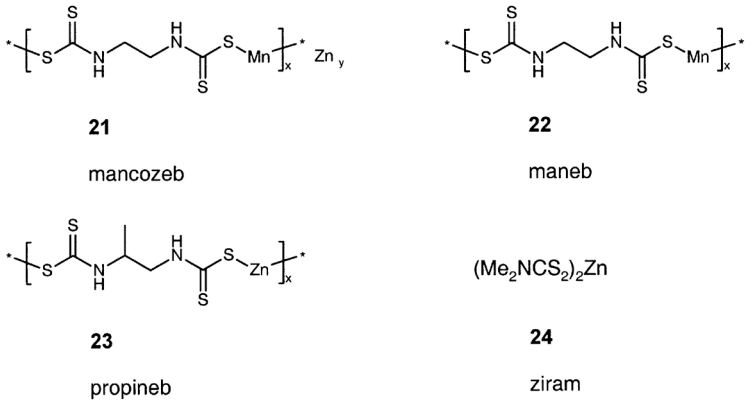


FIGURE 6 Dithiocarbamate fungicides.

metabolically opened in plants and soil to the 2-cyano-1,3-diketone **20**, which is a potent HPPD inhibitor [24, 25].

Several other special sulfur-containing classes of compounds, such as sultamsulfonamides [26] or sulfamoylnucleosides [27], were also found to possess distinct herbicidal activity.

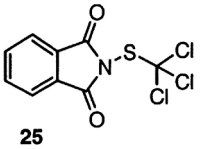
Fungicides

The discovery of dithiocarbamate fungicides in 1934 at DuPont for the first time introduced synthetic organic chemistry as well as a formerly unknown level of activity to agrochemical disease control [2]. Since then they have been widely applied to treat soil, seed, foliar and postharvest diseases because of their advantages compared to the formerly used inorganic compounds. They are multi-site inhibitors, which block several essential metal-containing enzymes, especially oxidases and dehydrogenases. Dithiocarbamate fungicides probably also interfere with some specific respiration sites, *e.g.* by inhibiting the pyruvate oxidation in the ADP–ATP cycle. Figure 6 depicts some important members of this class of compounds.

Ziram (**24**), originally developed as a vulcanisation accelerator for India rubber, is not only an efficient fungicide, it was recently also used as unique additive, suppressing undesired side reactions in the stereoselective cyclisation of 1,3-diols to oxetanes under Mitsunobu conditions [28, 29].

The *N*-trihaloalkylthioimide fungicides, found in the 1950s at Standard Oil, are also multisite inhibitors [30, 31]. They act for instance by transformation with enzymatic thiol groups, whereby thiophosgene and hydrogen disulfide are formed. The highly reactive thiophosgene reacts further with two other enzymatic thiol functions to form trithiocarbonates. Another feature which *N*-trihaloalkylthioimides have in common with the dithiocarbamates is the unfavourable toxicological/ecotoxicological profile of these fungicides, which results in a lot of pressure from environmentalists and registration agencies on these classes of compounds and stimulates the search for long-term replacements (Figure 7).

Several further organosulfur compounds, especially with sulfur-heterocycles such as thiophene carbamates [32] and thiazole carboxamides [33, 34] display interesting fungicidal activity.



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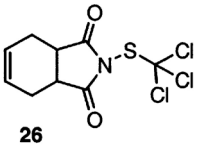
folpet



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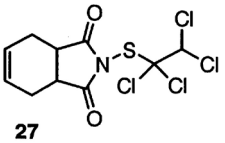

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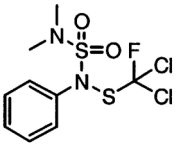


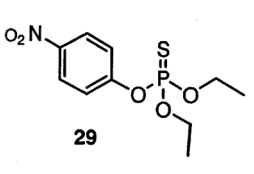
28

dichlofluanid

FIGURE 7 *N*-Trihaloalkylthioimide fungicides.

Insecticides

Few agrochemical compound classes have had such a positive impact on securing sufficient food for a steadily growing population as the phosphorothionates [35, 36]. Their insecticidal activity was discovered in the 1930s at Bayer. These compounds, of which only a few important examples are displayed in Figure 8, exert their toxic effects in insects and mammals by blocking *acetylcholinesterase* (AChE). This enzyme plays a central role in the transport of nerve impulses and its inhibition results in a steady excitement with lethal results. Most phosphorothionate insecticides are relative poor intrinsic inhibitors of this target, but are converted by the cytochrome P-450-containing monooxygenase systems into the corresponding phosphates, which are potent AChE-inhibitors. Phosphorothionate insecticides are therefore prominent examples for the unique role of sulfur in propesticide action, which will be dealt with below. Interestingly, the two isomers of the phosphorothiolate profenofos (**32**), resulting



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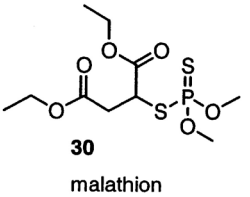
parathion



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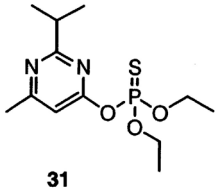
malathion



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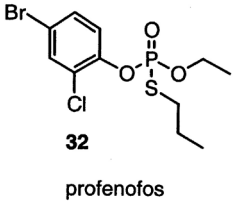
diazinon



32

profenofos

FIGURE 8 Phosphorothionate insecticides.

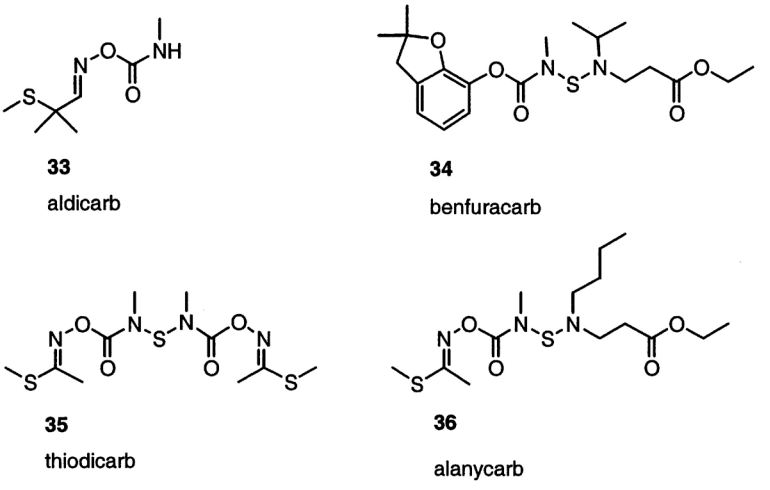


FIGURE 9 Methylcarbamate insecticides.

from its chiral phosphorus atom, are both active insecticides, but with different modes of action. The (+)-isomer acts as a typical phosphate, the (−)-isomer is stereospecifically bioactivated by oxidases to the corresponding sulfoxide, which is a 34-fold better AChE inhibitor and also efficient against resistant insects due to their increased enzyme activity [37].

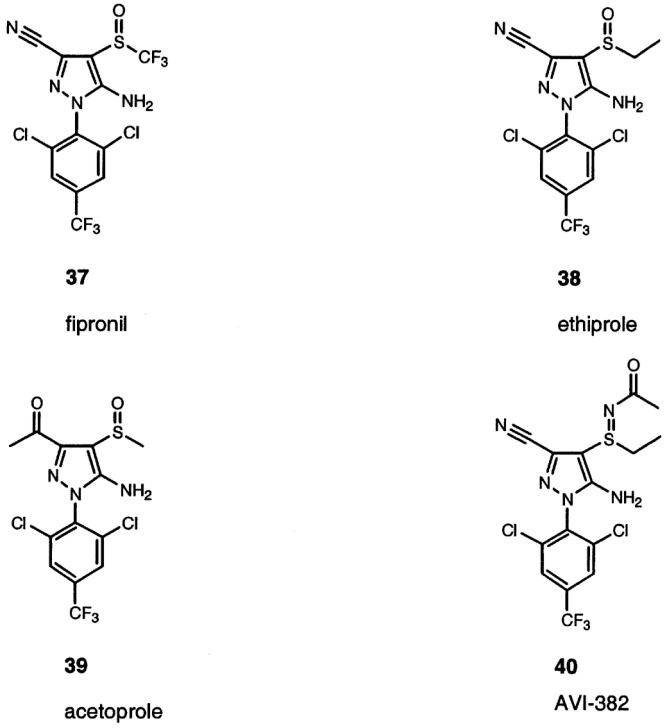


FIGURE 10 4-Alkylsulfinylpyrazole insecticides.

The introduction of sulfur atoms into the scaffold of methylcarbamate insecticides proved to be important for different reasons [38, 39]. It seems that the introduction of thioalkyl groups at the oxime carbon atom of carbomyloximes (as in **33**, **35** and **36**) contributes to high insecticidal activity, whereas the *N*-sulfenylation of the carbamoyl nitrogen (as in **34**, **35** and **36**) is responsible for low mammalian toxicity (Figure 9). This means that different sulfur functions can create the optimum balance between insecticidal efficacy and human safety. The carbamate insecticides are, as with phosphorothionate insecticides, acetylcholinesterase inhibitors. They were discovered in the 1940s at Geigy (now Syngenta).

The 4-alkylsulfinylpyrazoles constitute a very modern group of highly efficient insecticides (Figure 10). They act by blocking the GABA-regulated chloride channel [40]. Fipronil (**37**), the first derivative of this class was discovered at Rhone-Poulenc (now Bayer) [41]. The sulfoxide function at the pyrazole ring of these compounds seems to be important for optimum biological activity.

SULFUR-CONTAINING NATURAL PRODUCTS WITH PESTICIDAL PROPERTIES

The observation that feeding on diseased marine annelid worms *Lumbriconereis heteropoda* is lethal to flies led to the isolation and identification of nereistoxin (**41**) [42, 43]. Subsequently, the natural product itself and a large number of analogs were prepared and tested for insecticidal activity [44, 45]. Only those compounds which could revert to the natural product **41** after uptake by insects were active. Three such compounds were introduced to the market as broad-spectrum insecticides, namely cartap (**43**), bensultap (**44**) and thiosultap-sodium (**45**) (Figure 11). The mammalian toxicity of these prodrugs is lower than that of the natural product nereistoxin (**41**), which acts on neuronal nicotinic acetylcholinesterase receptors [46]. The synthetic analog thiacyclam (**42**) which is in comparison to the 1,2-dithiolane nereistoxin ring enlarged by one additional sulfur atom was also developed as a broad-spectrum insecticide [47].

Other 1,2-dithiolanes with insecticidal activity are the guinesines A, B and C (**46**–**48**), which were isolated from the bark of the Brazilian tree *Cassipourea guianensis* [48] (Figure 12). Their stereoselective synthesis has also been described [49]. Synthetic modifications on the guinesine scaffold led for instance to 3-dimethylaminomethyl-1,2-dithiolane (**49**), which is comparable in efficacy to nereistoxin (**41**) [50].

Asparagusic acid (**50**) and some related derivatives are effective plant growth inhibitors [51, 52]. **50** is also active against several species of plant pathogenic nematodes and, because of its presence to the extent of about 35 ppm in the roots of asparagus (*Asparagus officinalis*), is considered to be a major factor in the natural resistance of asparagus against nematodes [53]. Also α-terthienyl (**51**), found in marigold and other members of the *Compositae* plant family [54], and 2-phenyl-5-(1′-propynyl)thiophene (**52**) from *Coleopsis lanceolata* and *Cirsium japonicum* [55] display nematicidal activities (Figure 13). The antibiotic holomycin (**53**) was isolated from *Streptomyces griseus* [56], whereas its *N*-methyl derivative thiolutin (**54**) was found in *Streptomyces albus* [57]. They both exhibit broad fungicidal activity [58].

Four total syntheses of thiolutin (**54**) have since been published [58–61]; one approach is especially intriguing [58] (Scheme 1). The synthesis starts from 1,3-dichloroacetone (**55**), which is transformed by thioalkylation and amination into the imine **57** and its enamine tautomer. The imine **57** reacts with oxalyl chloride and triethylamine to give the pyrrolinone **59** as single *Z*-isomer. The enol function of **59** was transformed into an enamine by fusing it together with ammonium acetate for several hours at $>200°C$. Subsequent acetylation afforded the acetamide **60**. Deprotection of the thiol functions to **61** and oxidation leads directly to thiolutin (**54**).

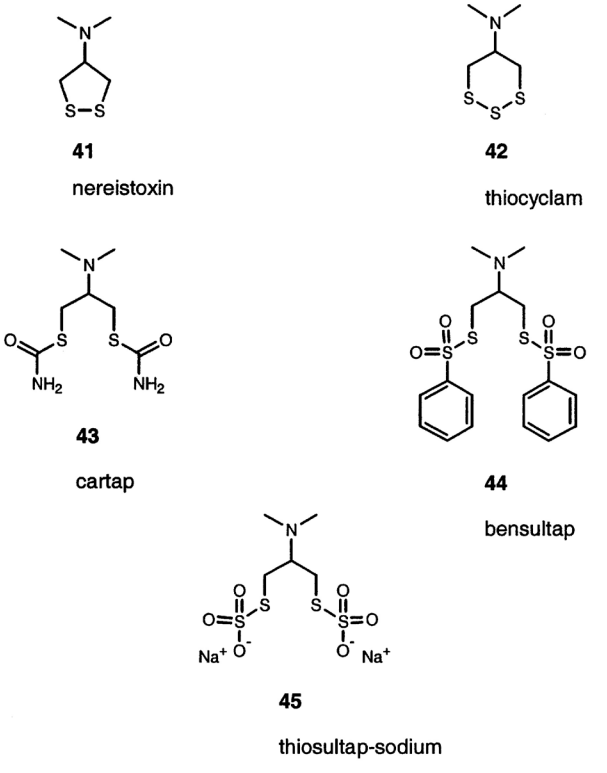


FIGURE 11 Nereistoxin (**41**) and its synthetic analogs.

Two more complex natural products with pesticidal properties are thiangazole (**62**) and myxothiazole A (**63**), discovered by the group of Höfle and Reichenbach (Figure 14). Interestingly, both were isolated from different species of gliding bacteria and both inhibit the respiratory chain by interrupting the electron transport in mitochondria, but on different sites. The tris(thiazoline) antibiotic thiangazole (**62**) was isolated from a strain of *Polyangium* sp. and shows interesting insecticidal and acaricidal effects [62, 63]. It inhibits NADH:ubiquinone oxidoreductase (complex I) [64]. The total synthesis of thiangazole has since been reported by

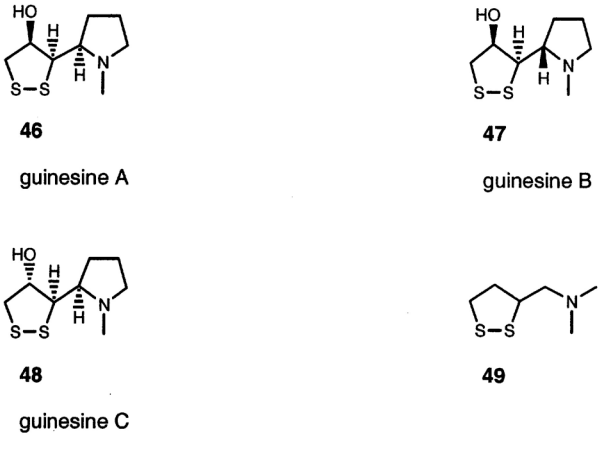


FIGURE 12 Guinesine derivatives.

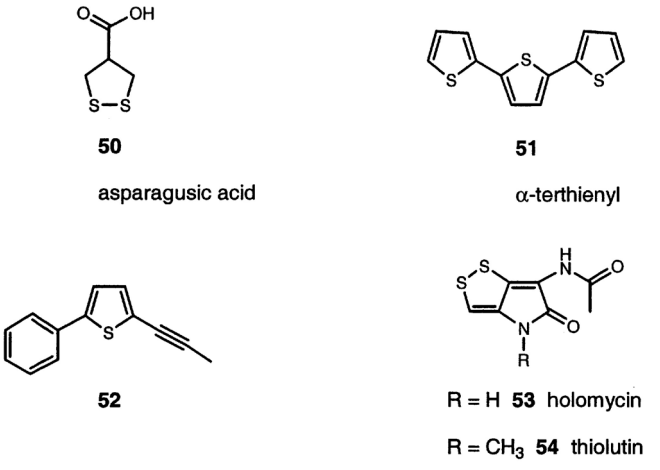
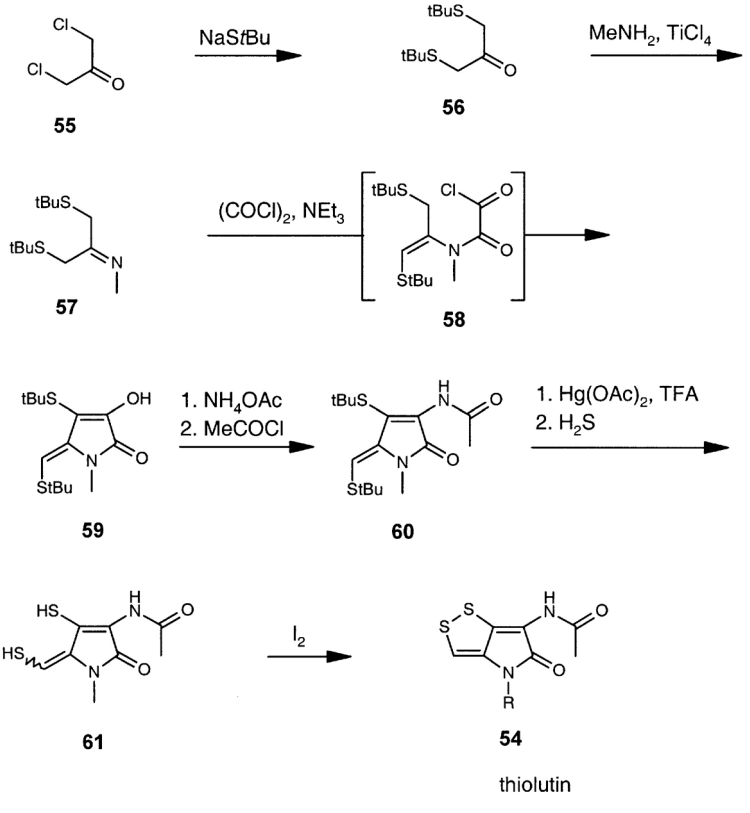
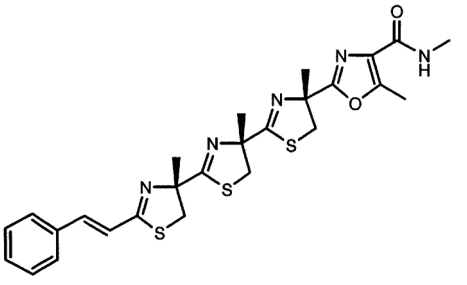


FIGURE 13 Different naturally occuring sulfur heterocycles.

Pattenden [65, 66], Heathcock [67], Wipf [68, 69], Kiso [70] and an industrial team [71, 72]. The β-methoxyacrylate myxothiazole (**63**) was isolated from *Myxococcus fulvus* and is a powerful fungicide [73, 74]. It acts like the related strobilurins by inhibition of the cytochrome bc_1 complex (complex III) [75]. So far, only one total synthesis of myxothiazole has been described [76].



SCHEME 1



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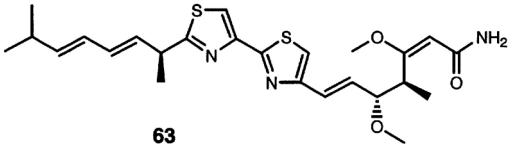
thiangazole



63

myxothiazole A

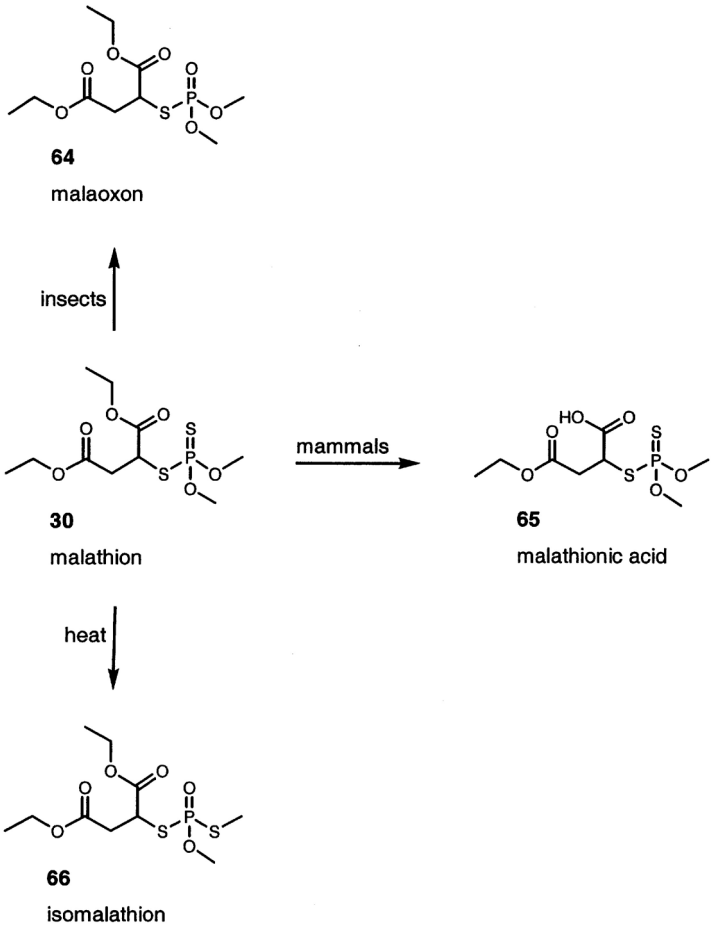
FIGURE 14 Thiangazole (**62**) and myxothiazole A (**63**).

THE ROLE OF SULFUR IN PROPESTICIDE ACTION

The special involvement of sulfur compounds in propesticide action has been mentioned above and is partially due to the proneness of sulfur to elimination and rearrangement reactions. A propesticide is a compound which in its original form is often not intrinsically active but which is transformed by UV light, heat, moisture or enzymes into an active state [77, 78]. In most cases, the target organism which is being affected unwittingly carries out a self-inflicting lethal synthesis by biochemically converting an inactive compound into an active drug. Propesticides often demonstrate favourable toxicological or physicochemical properties, *e.g.* the acute mammalian toxicity is reduced, the uptake and/or translocation in the plant is enhanced, the decomposition of the compound is delayed *etc*.

Scheme 2 demonstrates three different pathways for the transformation of the widely applied organophosphorus insecticide malathion (**30**), which is virtually nontoxic and possesses a chiral center in its succinyl moiety. In insects, oxidative desulfurisation of **30** by a monooxygenase leads to the highly potent acetylcholinesterase inhibitor malaoxon (**64**), the active principle of malathion [79]. In mammals, malathion is, rather, metabolised by carboxylesterases to malathionic acid (**65**) [79]. Malathion can also be thermally isomerised to isomalathion (**66**), which has an additional stereogenic center at the phosphorus atom and therefore consists of four stereoisomers [80]. Because isomalathion, like malaoxon, is a very efficient blocker of AChE and therefore quite toxic, its formation at elevated temperatures causes problems in the application of malathion in tropical countries.

As already mentioned, *N*-sulfenylation has a positive influence on methyl carbamates. *N*-arylsulfenyl groups especially, which can be considered to be carbamate proinsecticides, have a remarkable selectivity [81]. Aldicarb (**33**), which with a LD_{50} of 0.3–0.5 mg kg^{-1} in mice was for quite a long time one of the most toxic crop protection agents applied, is safened by introduction of a thio(4-*tert*-butyl)phenyl group. The arylsulfenyl group on the carbamate

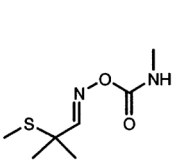


SCHEME 2

moiety allows the mammal to carry out metabolic reactions leading to less toxic products, while the toxic parent methyl carbamate is formed in insects. Arylsulfenylated methyl carbamates also develop other interesting types of selectivity, for instance to beneficial insects. Whereas propoxur (**68**) is highly toxic to the honey bee, the *N*-sulfenylated derivative **69** is virtually nontoxic to honey bees but fully maintains its efficacy against the house fly (Figure 15) [81].

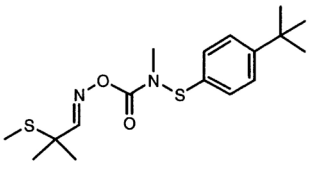
A further proinsecticide from a different class of compounds is diafenthiuron (**70**) [82]. The desulfurisation of the thiourea function, brought about either by UV light and singlet oxygen or by cytochrome P450 enzymes, leads to the formation of the carbodiimide **71**, which blocks the mitochondrial ATPase (Scheme 3) [83, 84]. The thiourea precursor **70** is less volatile than the carbodiimide **71**; it therefore acts as a molecular slow-release formulation which allows the important vapour-phase activity to be maintained for an extended period in the field. The synthesis and biological activity [85] as well as the quantitative structure-activity relationship and chemodynamic behaviour [86] of *N*-pyridylthiourea analogs of diafenthiuron have also been described. A considerable part of the biological activity of prothioconazole (**72**) can be attributed to its metabolic desulfurisation to **73**, which acts as a standard triazole fungicide by inhibiting the C14 demethylation step during the fungal ergosterol biosynthesis [87].

The cyclic dithiocarbamate dazomet (**74**) is a soil fumigant which readily decomposes, yielding methyl isothiocyanate (**75**) as principal toxicant (Scheme 3) [88]. This degradation



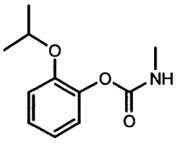
33

aldicarb



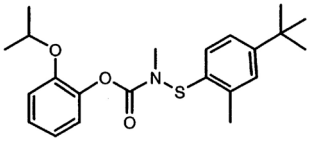
67

	mouse (mg/kg)	house fly (μg/g)	mouse (mg/kg)	house fly (μg/g)
LD_{50}	0.3 - 0.5	5.5	10	7.5



68

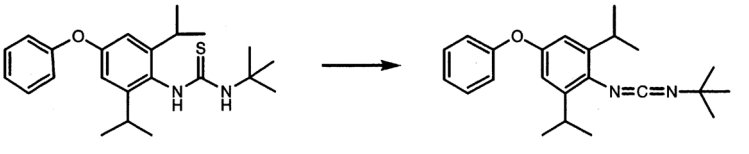
propoxur



69

	honey bee (μg/g)	house fly (μg/g)	honey bee (μg/g)	house fly (μg/g)
LD_{50}	4.5	24	>800	24.5

FIGURE 15 Toxicology profiles of methylcarbamate insecticides.

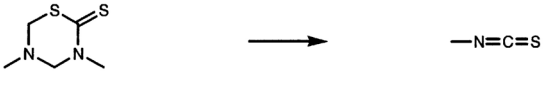


70 **71**

diafenthiuron

72 **73**

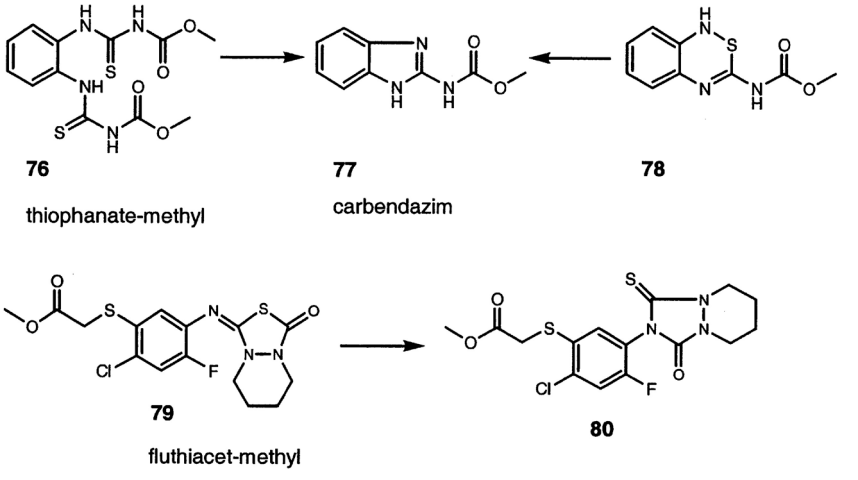
prothioconazole



74 **75**

dazomet

SCHEME 3



SCHEME 4

is favoured by increasing moisture and high temperatures; there seems to be no evidence for microbial involvement.

The fungicidal activity of both thiophanate-methyl (**76**) [89, 90] and of the benzothiadiazine derivative **78** [91] originates from their ability to be converted by cyclisation or by sulfur extrusion in aqueous solutions and in plants into the benzimidazole fungicide carbendazim (**77**) (Scheme 4).

The *in vivo* isomerisation of fluthiacet-methyl (**79**) by glutathione-*S*-transferase leads to the urazole derivative **80**, which is entirely responsible for the strong herbicidal activity (Scheme 4) [92].

BIOLOGICAL ADVANTAGES OF SULFUR-CONTAINING HETEROCYCLES

Phenyl–Thienyl Replacement

A phenyl ring in biologically active compounds can often be replaced by a thiophene without loss of activity [93, 94]. For instance in dimethenamid (**81**), the replacement of the o, o'-alkylated phenyl in the chloroacetamide herbicide metolachlor (**82**) by a 2,4-dimethylthiophene results in comparable biological activity [95]. Another thiophene-derivative of metolachlor (**82**) is thenylchlor (**83**), which employs the thiophene as a cyclic mimic of the methoxypropyl side-chain (Figure 16).

Also within the area of sulfonylurea herbicides, a phenyl ring could be successfully replaced by a thiophene, which led from metsulfuron-methyl (**85**) to thifensulfuron-methyl (**84**) (Figure 16) [96].

Three further examples demonstrate that the phenyl–thienyl exchange is also valid for insecticides and fungicides (Figure 17). The 5-methylthienopyrimidine analog **86** of the quinazoline derivative **87** exhibits a higher contact activity against the two-spotted spider mite (*Tetranychus urticae*) [97]. Also the efficacy of the thiophene analog **88** against different lepidoptera species is better compared to its benzophenone hydrazone parent **89** [98]. Finally, the thienopyrimidinone **90** is also, at low doses, at least as active against powdery mildew diseases on cereals (*Erysiphe graminis*) and grape (*Uncinula necator*) as the quinazolinone derivative proquinazid (**91**) [99].

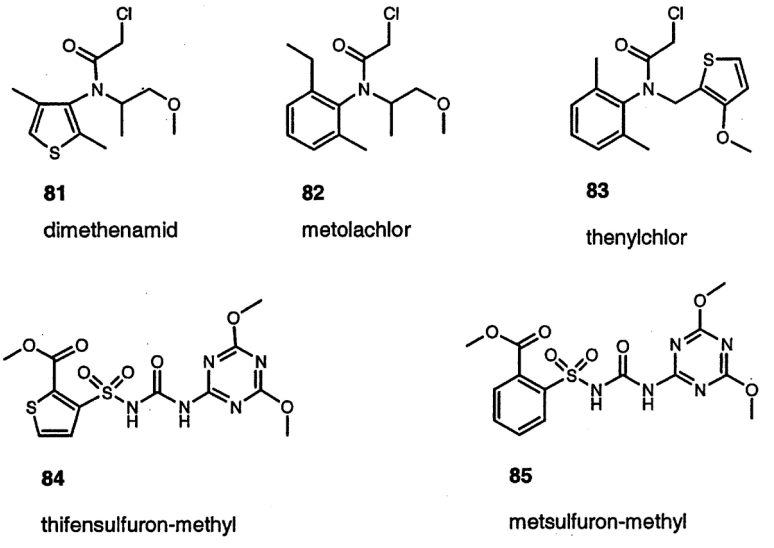


FIGURE 16 Phenyl-thienyl comparisons.

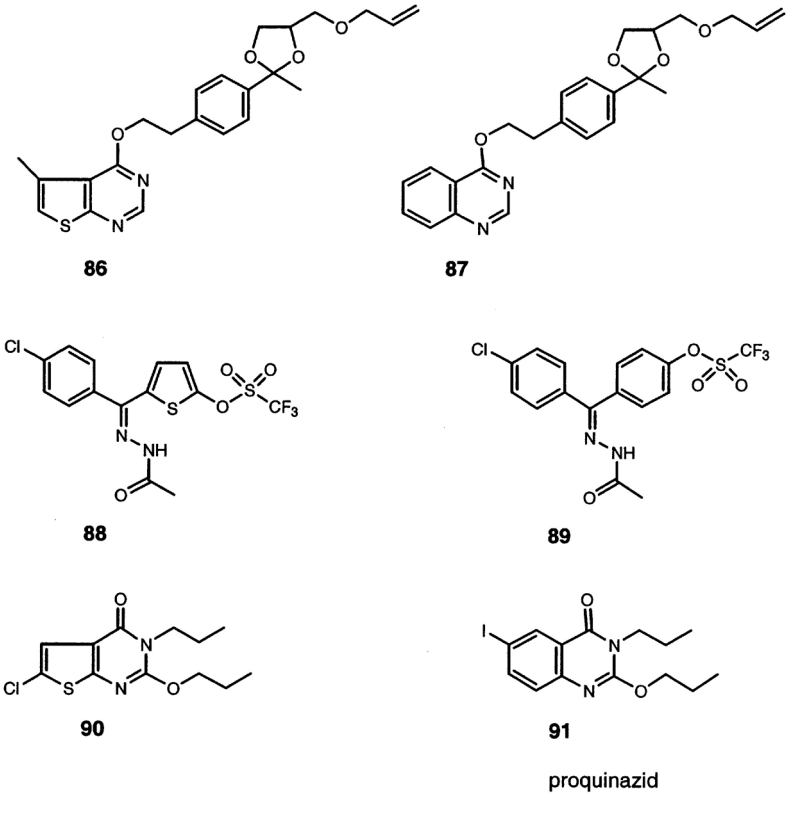


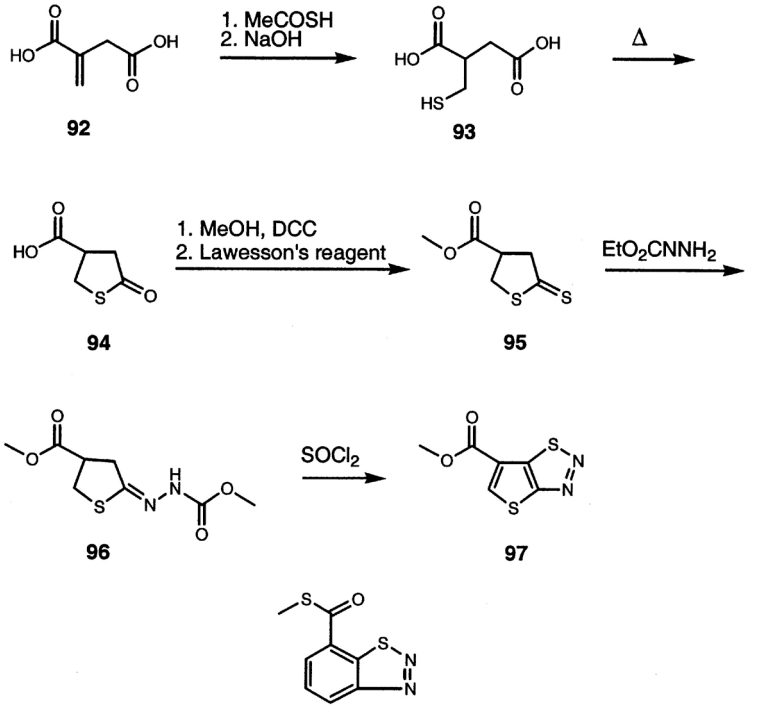
FIGURE 17 Phenyl-thienyl comparisons.

Acibenzolar-*S*-methyl (**98**) was developed as a plant activator, stimulating the plant's inherent defence mechanisms by triggering a systemic acquired resistance [100]. Its interesting thieno-analog **97** could be prepared starting from methylenebutanedionic acid (**92**) (Scheme 5). 1,4-Addition of thiolacetic acid and subsequent hydrolysis of the acetylthio group gave **93**, which could be thermally cyclized to the thiolactone **94**. Esterification of the acid function and selective thionation with Lawesson's reagent led to the dithiolactone **95**, which could be condensed with ethyl carbazate to the carbazonate **96**. The key step of the synthesis is the intramolecular Hurd–Mori cyclisation of **96** with thionyl chloride to the desired thieno[2,3-*d*][1,2,3]thiadiazole **97** [101, 102]. The Hurd–Mori reaction [103, 104] could also be successfully applied to the synthesis of related thieno[3,2-*d*][1,2,3]thiadiazoles [105].

Pyridyl–Thiazolyl Replacement

If thiophene is a good substitute for phenyl, then the thiazole ring should be appropriate to replace pyridine. This hypothesis could be proven in the group of neonicotinoid insecticides, which inhibit the nicotinic acetylcholine receptors. Imidacloprid (**99**) is the first example from this class of compounds to be commercialised [106]. Figure 18 shows that the replacement of the pyridine as well as the imidazolidine rings of imidacloprid by sulfur-heterocycles leads to the advanced second-generation products thiamethoxam (**101**) [107, 108] and thiacloprid (**100**) [109], which have reached the market recently.

The high insecticidal activity of thiamethoxam (**101**) can be partially attributed to the 2-chlorothiazole ring, which is also found in the developmental product clothianidin (**102**) [110].



92 93 94 95 96 97 98

acibenzolar-S-methyl

SCHEME 5

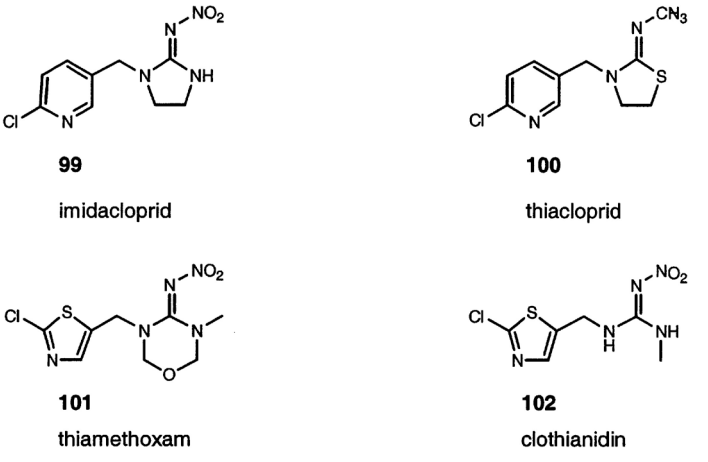
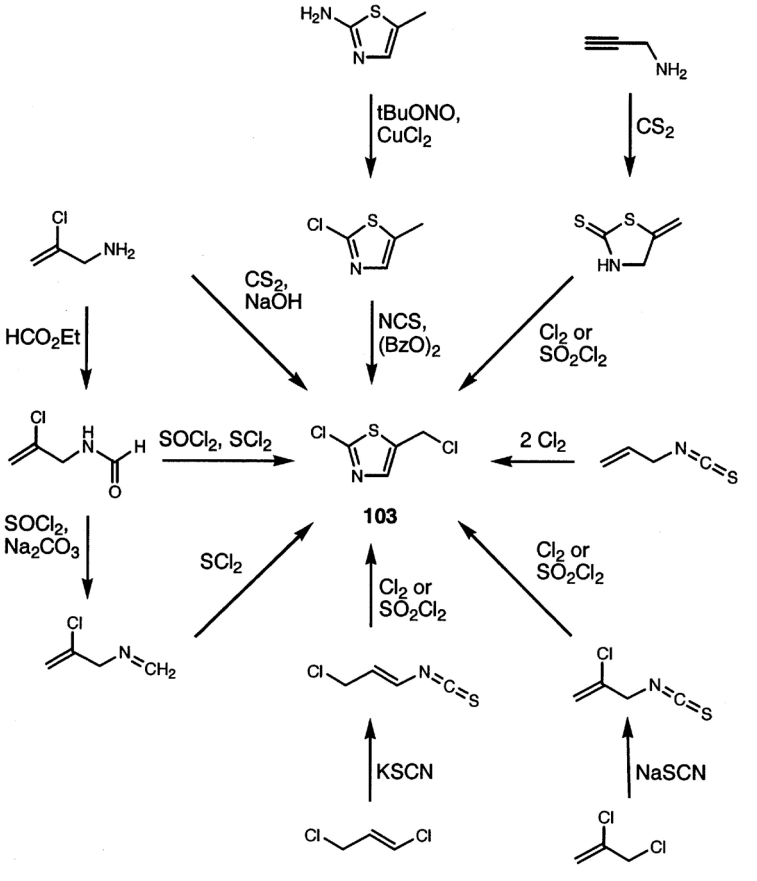
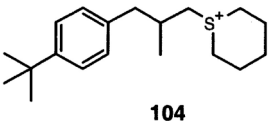


FIGURE 18 Pyridyl-thiazolyl comparisons.

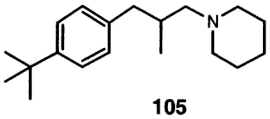
2-Chloro-5-methylthiazole (**103**) is the important building block required for the synthesis of both thiamethoxam and clothianidin. Scheme 6 shows the diverse possibilities of how it may be approached [111].



SCHEME 6



104



105

fenpropidin

FIGURE 19 Piperidinyl-thianyl comparison.

Piperidinyl–Thianyl Replacement

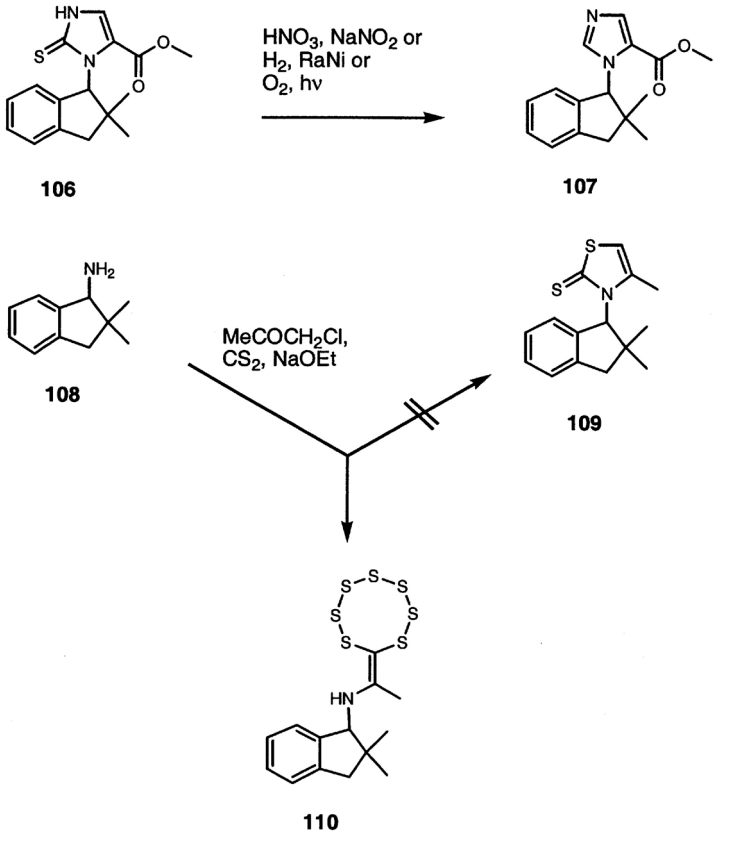
One example has also been described where a piperidine ring of a crop protection agent has been successfully replaced by a thiane [112]. Tertiary amines such as fenpropidin (**105**) are very efficient fungicides. They block the biosynthesis of ergosterol, an essential component of the cell membranes of several phytopathogenic fungi, by inhibition of the enzymes sterol Δ^8-Δ^7-isomerase and sterol Δ^{14}-reductase. There is evidence that the protonated form of **105** is the inhibitory species *in vivo*, because ammonium salts of this type may act as transition state analogs of sterol carbenium ion intermediates involved in transformations of these enzymes. The sulfonium salt **104**, mimicking the protonated fenpropidin, is quite active against some wheat diseases such as powdery mildew (*Erysiphe graminis*) and leaf rust (*Puccinia recondita*) (Figure 19).

SOME CONTRIBUTIONS OF SYNGENTA TO SULFUR-CONTAINING AGROCHEMISTRY

During a research project it was found that methyl imidazole-5-carboxylates of type **107** are highly active herbicides. Usually they have been obtained from 2-thiono-imidazole precursors such as **106** [113]. In an attempt to prepare its thiazoline-2-thione derivative **109** by reaction of 2,2-dimethyl-1-indanylamine (**108**) with carbon disulfide to the corresponding dithiocarbamate and further transformation with chloroacetone, surprisingly, the main product was the unusual heptathiocane **110** (Scheme 7) [114]. Only a few examples of this special eight-membered ring-system have been described.

The naturally occurring spironucleoside hydantocidin (**115**), isolated from the fermentation broth of *Streptomyces hygroscopicus* gives powerful herbicidal activity against a broad spectrum of mono- and dicotyledonous annual and perennial weeds, while having no toxicity to microorganisms and animals [72]. Its 1-thia-derivative **114** could be prepared starting from the readily available 2,5-anhydro-allononitrile **111**. Photobromination gives a 1:1 mixture of the two 1-bromo ribosyl cyanides **112** and **113**, which can be separated by silica gel chromatography (Scheme 8). Condensation of the α-epimer **112** with thiourea can be understood as a tandem nucleophilic transformation. First the bromine is substituted by the sulfur atom of thiourea, then the amino group of the intermediate thiocarbamate adds to the cyano triple bond under ring closure to give a thiazolidindiimine. Acidic hydrolysis of the imino functions is accompanied by deprotection of the hydroxy groups to obtain the desired 1-thia-hydantocidin (**114**) [115].

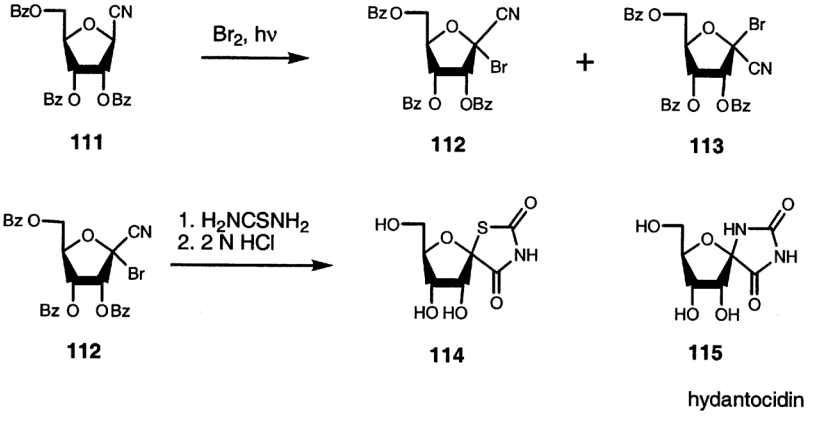
Trisubstituted thiatriazines such as **120** were found to be very efficient herbicides with predominantly pre-emergent activity. A versatile starting material for their synthesis is 1,3,5-trichloro-1λ^4,2,4,6-thiatriazine (**117**), which can be easily obtained from sodium dicyanamide (**116**) and thionyl chloride [116]. The synthetic potential of this compound is huge as its heterocyclic nucleus carries three chlorine atoms, which act as leaving groups in



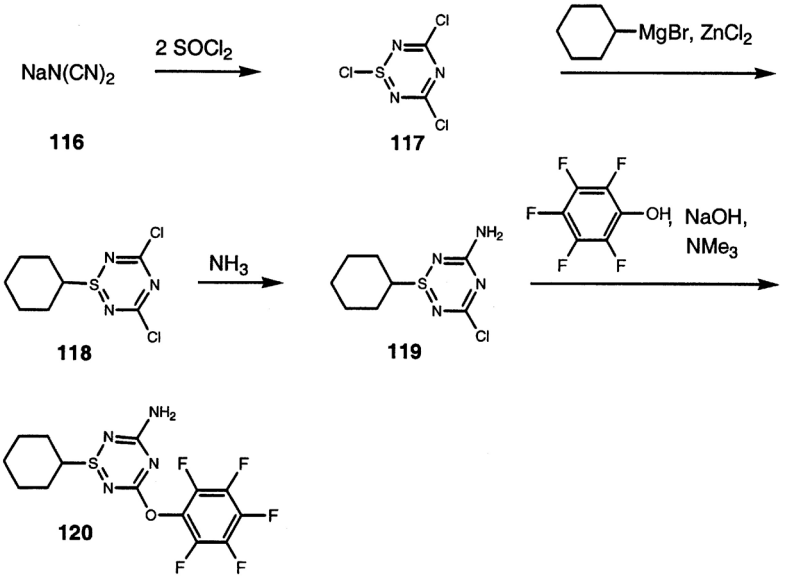
SCHEME 7

nucleophilic substitutions. Moreover the 1-position of the heterocycle is much more activated than the 3- and 5-positions, so that regioselectivity in the replacement of the chlorine atoms is attainable, as in the consecutive transformation of **117** into **120** (Scheme 9) [117, 118].

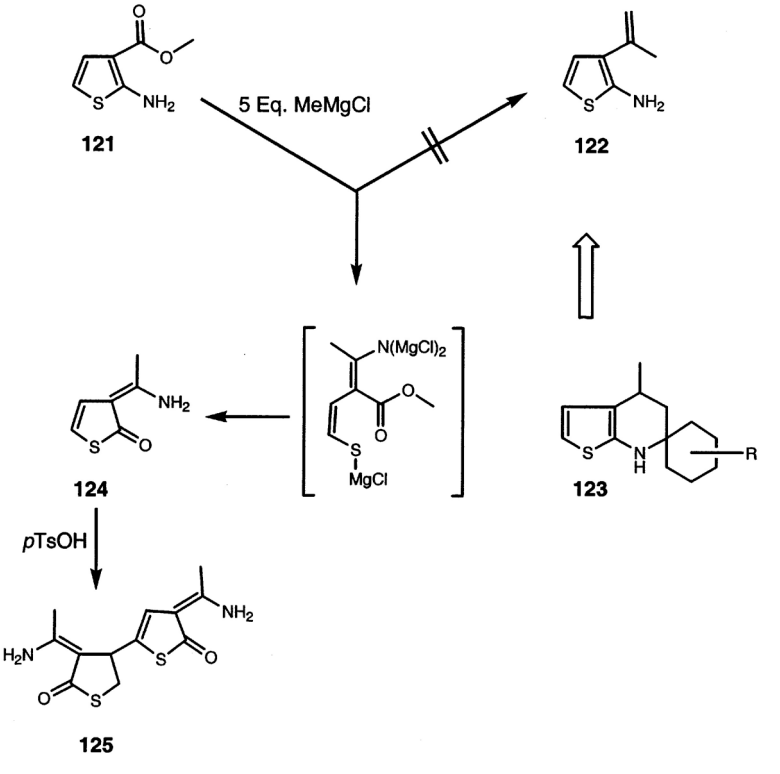
2-Amino-3-isopropenylthiophene (**122**) seemed to be a useful intermediate for the synthesis of more complex thieno-annelated heterocycles of type **123** with potential fungicidal activity



SCHEME 8



SCHEME 9



SCHEME 10

(Scheme 10). It was planned to obtain **122** by reaction of an excess; methylmagnesium chloride with 2-amino-3-carbomethoxythiophene (**121**), followed by acid-catalyzed dehydration of the intermediate tertiary alcohol. Surprisingly, only the thiophen-2-one **124** was isolated as sole product, resulting from a thiophene ring opening by the Grignard reagent. By heating with a catalytic amount of *p*-toluenesulfonic acid, **124** undergoes a unique electrophilic-induced dimerisation reaction to **125** [119].

CONCLUSION

Many sulfur-containing compounds play important roles in the control of weeds, insects and plant diseases. The wide range of different modes of action of these agrochemicals is impressive as well as the diverse functions that the sulfur groups have to fulfil. In some of these compounds, the sulfur atom plays an important role in the transformation of propesticides into active substances. Also, several natural products bearing sulfur atoms display distinctive pesticidal properties. Especially, 1,2-dithiolanes seem to be very successful in this direction. The replacement of an isocyclic group by a sulfur heterocycle often results in a certain biological advantage. All these features contribute to the fact that approximately 30% of all pesticides are sulfur compounds [8].

Acknowledgement

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