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Novel insecticides and acaricides

A F Grapov

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Abstract. This review outlines the major achievements in design of novel chemical insecticides and acaricides, especially those with non-standard mechanisms of action, *viz*., neonicotinoids and oxidative phosphorylation decouplers. The bibliography includes 119 references.

I. Introduction

The assortment of modern commercially available insecticides and acaricides is rather wide and permits solution of virtually any problem associated with protection of plants against insects and mites. Nevertheless, studies aimed at improving the preparation forms and the methods of their application do not stop. The need in the search for new highly effective groups of compounds with unusual mechanisms of action and the development of novel insectoacaricides is dictated by both economical considerations and the more rigorous requirements of the health and ecological characteristics of chemicals from the aspect of pesticide industry controlling institutions. Novel, highly effective and selective pesticides with usage rates of about 10 – 100 g ha^{-1} not only cut the finance, energy and labour expenditures per unit area treated but also decrease the impact of chemicals on the environment and enhance the safety of their application. Unfortunately, the high cost of the development and marketing of new pesticides ($US 100 – 200 million per a product) has led to a decrease in the number of companies specialising in this problem.

Since the development of every novel pesticide represents a complex and multifactor problem, its successful solution can only be attained based on joint achievements in fundamental and applied sciences of different profiles. In the design of novel pesticides, one should pursue not only high efficacy of a novel product against pests but also its compatibility with other insectoacaricides in multicomponent systems used in integrated plant protection against insects and mites, especially against pesticide resistant populations. Thus, nowadays there are populations of more than 500 species of arthropod, which are resistant to organophosphorus, carbamate and halogen-containing insectoacaricides, including pyrethroids. In order to overcome this resistance or, in the other words, to develop systems of pesticide alternation preventing the appearance of resistant populations in insects and mites, one should have at one's disposal pesticides with different mechanisms of action.

The nerve pulse, hormonal status of the insect and mite moulting process and metamorphosis, and oxidative phosphorylation may be distinguished as three vitally important functions disbalancing of which is currently used to suppress the mite and insect populations. Among these three, the nervous system is the most vulnerable and it is no surprise that the majority of insectoacaricides (more than 90%) block the conductivity of nerve fibres. Thus pyrethroids act on the neuronal sodium channels, carbamates and organophosphorus compounds (OPC) suppress the activity of acetylcholinesterase, whereas nereistoxin analogues block the acetylcholine receptors. A group of insectoacaricides that disturb the hormonal regulation of the moulting process and metamorphosis or block chitin biosynthesis is also used in the pest control programmes. So far, only the first steps have been made in the development of insecticides which decouple mitochondrial oxidative phosphorylation.

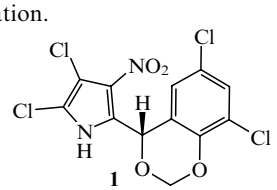
The present review is mostly devoted to novel insectoacaricides with unusual mechanisms of biological action.

II. Heterocyclic derivatives

The most impressive results and those interesting from the practical point of view, giving birth to new promising directions in the research and development of insectoacaricides, have been obtained for heterocyclic compounds belonging to derivatives of the pyrrole, pyridine, pyrazole and imidazole series.

1. Pyrrole derivatives

Pyrrole derivatives such as synthetic analogues of the antibiotic dioxapyrrolomycin (**1**) are of considerable interest as insecticides. This antibiotic has been isolated from *Streptomyces* and exhibited moderate toxicity against insects and mites. The mechanism of biological action of compound (**1**) consists in inhibition of electron transport during the mitochondrial oxidative phosphorylation.



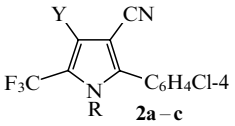
1

It was shown [1 – 4] that certain derivatives of compound **1**, first of all, such as 2- and 3-arylpyrroles, bearing electron-withdrawing substituents in positions 3,4 or 2,4 of the benzene ring, possess

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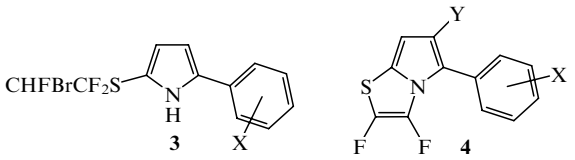
enhanced insecticidal activity. The fairly high efficacy against various insect species has been found for 2-(4-chlorophenyl)-3-cyano-4-halogeno-5-trifluoromethylpyrroles **2a–c**, 3-aryl-4-halogeno-5-trifluoromethyl-2-trifluoromethylsulfenyl(sulfinyl, sulfonyl)pyrroles, 2-aryl-4-halogeno-5-trifluoromethyl-3-trifluoromethylsulfonylpyrroles and 2-(4-chlorophenyl)-3,4,5-tris(trifluoromethyl)pyrrole.[5,6] Compound **2a** (AC-303630) is the most potent insecticide in this series. At doses of about 125–250 g ha^{-1} this compound is effective against 35 insect species from 16 families and 5 orders;[2,3,7] its LD_{50} for rats is 223–459 mg kg^{-1}.



2a–c

R = CH_2OEt, Y = Br (**a**), F (**b**); R = H, Y = Br (**c**).

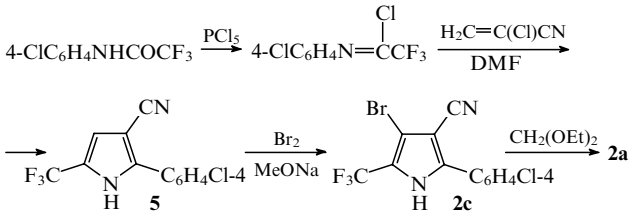
The insectoacaricidal activity of compound **2b**, 5-aryl-2-(2-bromo-1,1,2-trifluoroethylthio)pyrroles **3** and the products of intramolecular cyclisation of the latter, *viz*., pyrrolo[2,1-*b*]thiazoles **4**, is comparable with that of compound **2a**.[8]



3 **4**

X, Y are electron-withdrawing groups.

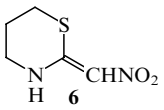
The most convenient method for the preparation of pyrrole **2a** consists in the treatment of *N*-(4-chlorophenyl)trifluoroacetamide with phosphorus pentachloride and subsequent cyclocondensation of the resulting imidoyl chloride with 2-chloroacrylonitrile in DMF. 5-(4-Chlorophenyl)-5-cyano-2-trifluoromethylpyrrole **5** thus obtained is brominated in the presence of sodium methoxide, and pyrrole **2c**, in turn, is alkylated with diethoxymethane.[9,10]



Studies on the mechanism of action of compound **2a** showed that in the insect organism this compound is activated through the oxidative dealkylation producing derivative **2c**, which acts as an inhibitor of oxidative phosphorylation blocking electron transport during ATP synthesis in the mitochondrial chain.[11,12] As has already been mentioned, this mechanism of action is rather untypical for pesticides. Such a mechanism explains fairly well the absence of cross-resistance to compound **2a** among those insect populations which are resistant to the action of OPC, carbamates and pyrethroids.

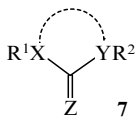
2. Pyridine derivatives (neonicotinoids)

The group of compounds under consideration can be referred to as pyridine derivatives rather arbitrarily. The history of the development of these insecticides is quite interesting. In 1978, at the 4th International Congress on Pesticide Chemistry, Soloway *et al.*[13] presented a report on the study of insecticidal activity of nitromethylidenepyridines, monocyclic and bicyclic nitromethylidenepiperidines and other five- and six-membered heterocycles and acyclic nitromethylidene derivatives. It was shown that 3-nitromethylidenetetrahydrothiazine (**6**) is several times more active against larvae of *Lepidoptera* than parathion.



6

This finding has stimulated studies on insecticidal properties of numerous acyclic, carbo- and heterocyclic compounds containing the nitromethylidene, cyanomethylidene, nitroimino and cyanoimino fragments of the general formula **7**.

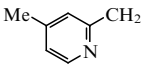
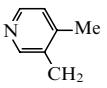
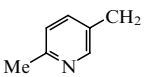
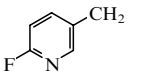
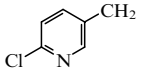
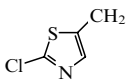


7

R^1 = H, Alk, Ar, Bn, HetAr, $HetArCH_2$;
R^2 = Alk; X, Y = N, S, CH;
Z = $CHNO_2$, CHCN, YNO_2, NCN.

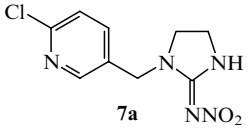
In the beginning, these investigations were unsuccessful and only when 6-chloro-3-pyridylmethyl substituents were introduced did the results obtained surpass all expectations! It is for this reason that this group of compounds is referred to as pyridine derivatives. Selected data on the activity of *N*-nitroimino- and nitroiminomethylideneimidazolidines and -thiazolidines are listed in Table 1. Overall, several thousand compounds of the general formula **7** have been synthesised and assayed.

Table 1. Insecticidal activity of some neonicotinoids of the general formula **7** (X = N) against rice green leaf hopper.[14,15]

R^1	Z	Y	R^2	LC_{90} /mg $litre^{-1}$	Relative activity [a]
$PhCH_2$	$CHNO_2$	N	H	200	0.0016
4-$ClC_6H_4CH_2$	$CHNO_2$	N	H	40	0.008
	$CHNO_2$	N	H	200	0.0016
	$CHNO_2$	N	H	8	0.04
	$CHNO_2$	N	H	1.6	0.2
	$CHNO_2$	N	H	0.32	1
	$CHNO_2$	N	H	0.32	1
	NNO_2	N	H	0.32	1
	NNO_2	N	Me	1.6	0.2
	$CHNO_2$	S		0.32	1
	NNO_2	S		1.6	0.2
	$CHNO_2$	N	H	0.32	1
	$CHNO_2$	N	H	200	0.016

[a] Relative activity was determined as a ratio of the LC_{90} value for imidacloprid to that for the specified compound.

A new systemic insecticide 1-(6-chloro-3-pyridylmethyl)-2-nitroiminoimidazolidine (**7a**, imidacloprid), is widely used for seed dressing and treatment of soil and green plants.



7a

Imidacloprid (**7a**) is employed against aphids, whiteflies, sawflies, flies, moths, leaf hoppers and noctuids at the usage rates of 30–100 g ha^{-1} (see Refs 14–18). This is one of the most effective insecticides, which is not inferior to pyrethroids and surpasses OPC and carbamates in activity. The scale of its application is rapidly growing and presumably in the beginning of the XXIst century this will achieve the scale of application of pyrethroids. This is a very promising agent for preventing the appearance of resistant aphid populations. If pesticides are alternated in the series: compound **7a** → bifenthrin → chlorpyrifos → amitraze, a resistance of aphids to these preparations is not developed.

Imidacloprid (**7a**), being an agonist of nicotinic acetylcholine postsynaptic receptors, suppresses the activity of acetylcholinesterase and induces hyperpolarisation of a nerve fiber membrane in insects. The complex mechanism of its action is reduced to the prolonged opening of the sodium channels.[19–21] The mode of action of compound **7a** and of its analogues resembles that of nicotine, and therefore this group of compounds has been named neonicotinoids. Imidacloprid (**7a**) is bound fairly well to the cerebral membrane of cockroaches, flies, bees and other insects, but very poorly to the cerebral membrane of vertebrates. This probably is the basic reason for its selective toxicity. In cockroaches, the main site of the action of compound **7a** is the synapse of the sixth ganglion.[22,23]

According to the X-ray data of the molecule of compound **7a**, the $C=NNO_2$ fragment and the imidazolidine ring are coplanar, the C–N bonds are shortened and the C=N bond is prolonged. Based on these data, two possible alternative schemes for the binding of compounds **7** to receptors have been suggested (*a* or *b*, Fig. 1).

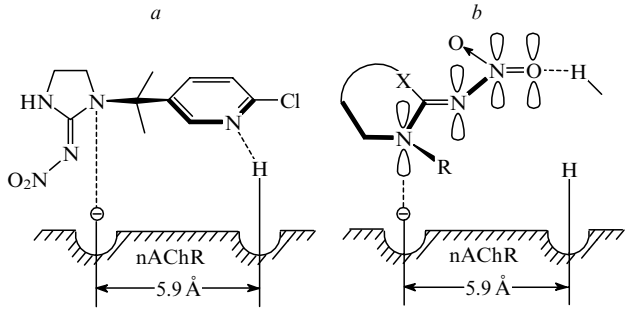
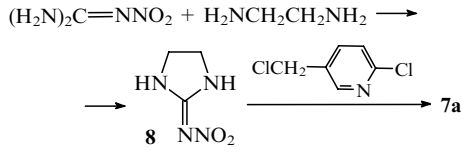


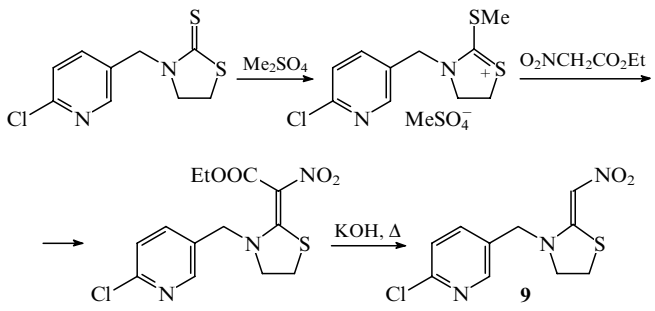
Figure 1. Schemes of interaction of imidacloprid (**7a**) with nicotinic acetylcholine receptors (nAChR).

The assumption of the existence of two distinct mechanisms for the binding permits one to rationalise both the high efficacy of compound **7a** and the lack of the cross-resistance to this agent.[24]

Imidacloprid (**7a**) is obtained by the reaction of nitroguanidine with ethylenediamine followed by alkylation of 2-nitroiminoimidazolidine (**8**) with 2-chloro-5-chloromethylpyridine.[25]

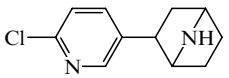


Compound **7a** is insufficiently effective against *Lepidoptera*. Its thiazolidine analogue **9**, obtained according to the scheme shown below,[23] can be successfully employed against insects which are relatively resistant to the action of imidacloprid (**7a**).



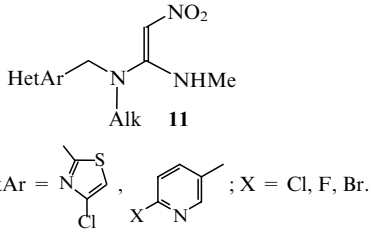
For example, the LC_{90} values for compounds **7a** and **9** against rice green leaf hopper, cabbage looper *Trichoplusia ni*, cabbage moths and leaf roller *Cnaphalocrosis medinalis* are equal to 0.32 and 0.32, 40 and 1.6, 200 and 1.6, 200 and 8 mg $litre^{-1}$, respectively.[23]

After discovery of the insecticidal properties of imidacloprid (**7a**) and its analogues, the antibiotic epibatidine (**10**), containing the 6-chloro-3-pyridyl fragment and possessing anti-cholinesterase and high analgesic activities, was isolated from the skin of the poisonous frog *Epipedobatis tricolor*. This antibiotic is highly toxic against aphids and spider mite *Tetranychus telarius* (LD_{50} 0.5 and 6 mg $litre^{-1}$, respectively).[26,27]

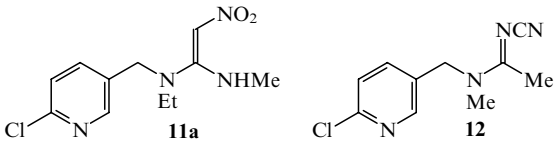


10

1-(*N*-Alkyl-*N*-hetarylmethyl)amino-1-methylamino-2-nitroethylenes **11** also possess high insecticidal activity. At a dose of 0.8 mg $litre^{-1}$ these compounds cause 100% death for cicada *Nilaparvata lugens*. Different modifications of the molecule **11** (replacement of the chlorine atom in the pyridine ring by the methyl or methoxy group, elimination of the methylene group or its replacement by the double or triple bond) do not lead to the enhancement of the biological activity.[25]



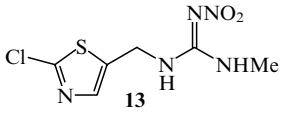
The most effective insecticide in this group of compounds is 1-[*N*-(6-chloro-3-pyridylmethyl)-*N*-ethylamino]-1-methylamino-2-nitroethylene (**11a**, nitenpyram), which is currently undergoing field testing as an aphicide.



The replacement of the nitromethylidene group by the cyanoimino group resulted in 1-(6-chloro-3-pyridylmethyl)-1,3-dimethyl-2-cyanoguanidine (**12**, acetamiprid). This compound, having the contact and systemic mode of action, is highly toxic against aphids, cabbage fly, army worms *Spodoptera litura* and *Mamestra brassicae*, whitefly and tobacco thrips in concentrations of 0.056–13.4 mg $litre^{-1}$.[28] In protecting the leaves against tobacco whitefly and cotton aphids, compound **12** considerably surpasses imidacloprid (**7a**).

3. Derivatives of heterocycles with several heteroatoms in the ring

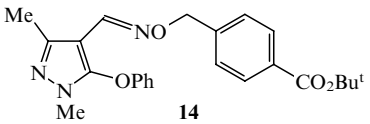
In some cases, the 2-chloro-5-thiazolyl moiety can successfully mimic the 6-chloro-3-pyridyl fragment in compounds of the nitromethylidene and nitroguanidine series, and the corresponding compounds manifest the neonicotinoid type of insecticidal activity. (*E*)-1-(2-Chlorothiazol-5-ylmethyl)-3-methyl-2-nitroguanidine (**13**, TI-435) in small doses kills sucking and chewing insects.[28]



13

Pyrazole and pyrazoline derivatives constitute one of the basic groups of compounds which were employed in the search for novel insectoacaricides over the last 15 years. The activities of such compounds as substituted anilides of 1-alkyl- and 1-arylpyrazole-5-carboxylic acids, 1-arylpyrazole-3-carboxylic acids, 1,5-diphenylpyrazoline-3-carboxylic acids, 1-arylpyrazoline-3-carboxylic acids, 3,4-disubstituted 1-alkyl- and 1-aryl-5-aminopyrazoles, substituted oximes of pyrazole-4-carbaldehydes have been studied in detail.[29]

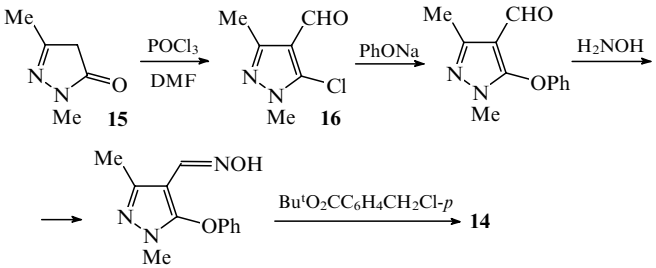
One of the most original preparations of this group of compounds is *O*-4-*tert*-butoxycarbonylbenzyl-1,3-dimethyl-5-phenoxypyrazole-4-carbaldoxime (**14**, fenpyroximate), which is a 10–100-fold more effective acaricide against mites *Tetranychidae*, *Tarsonemidae* and *Eryophydae* than dicofol and cyhexatin. This compound not only gives rapid knockdown in mobile stages but also suppresses the moulting process in larval stages of mites.[30,31]



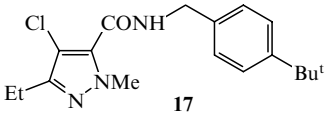
14

Fenpyroximate **14** acts as an inhibitor of the NADH-coenzyme Q-reductase, which is responsible for the electron transport in the process of mitochondrial oxidative phosphorylation.[32]

The starting compound in the synthesis of fenpyroximate **14** is 1,3-dimethylpyrazolin-5-one (**15**), which is simultaneously formylated and chlorinated at the 5-position by the reaction with a mixture of $POCl_3$ and DMF. Successive treatment of the aldehyde **16** with sodium phenoxide, hydroxylamine and 4-(*tert*-butoxycarbonyl)benzyl chloride gives compound **14** in high yield.[33]

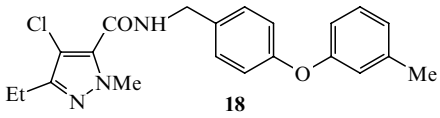


A novel acaricide, *viz*., *N*-(4-*tert*-butylbenzyl)-4-chloro-3-ethyl-1-methylpyrazole-5-carboxamide (**17**, tebufenpyrad), has been synthesised based on pyrazole-5-carboxylic acid derivatives.



17

At concentrations of 50–200 mg litre^{-1} this agent is acute against mites *Tetranyhus sp*., *Panonychus sp*., *Orygonychus sp*. and *Eotetranychus sp*. in all stages of their development, including even those populations, which are resistant to the action of dicofol, fenbutatin and hexythiazox.[34–38] Compound **17** acts as a systemic and translaminar acaricide. Its mechanism of action resembles that of compound **14** and involves the decoupling of the oxidative phosphorylation process.[10] A detailed study of the chemical structure–biological activity relationships for analogues of **17**, using the QSAR programme, has led to the design of a novel insecticide, *viz*., *N*-[4-(3-methylphenoxy)benzyl]-4-chloro-3-ethyl-1-methylpyrazole-5-carboxamide (**18**, OMI-88), having a broad range of action.[39,40]

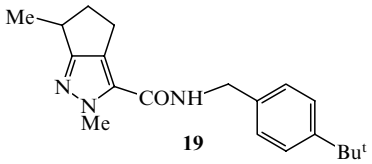


18

This agent is highly effective against cabbage moth, aphids, whitefly, leaf hoppers and thrips in concentrations of 75–150 mg litre^{-1} without inducing cross-resistance to pyrethroids, OPC and phenylbenzoylureas in insects.[41]

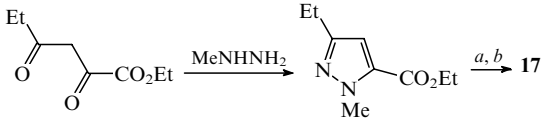
Analogues of **17** and **18** containing 3-pyridylmethyl fragments instead of the benzyl one are less effective against spider mites.[42]

Bicyclic pyrazole derivative **19** is not inferior in activity to compound **18**. According to the data of X-ray analysis, both compounds have similar crystal structures.[43]



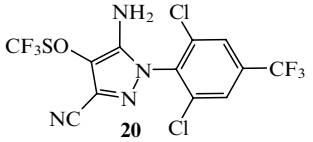
19

Compound **18** and its analogues were synthesised by cyclisation of alkyl α,γ-dioxocarboxylates with methylhydrazine followed by the chlorination and aminolysis.[44]



(*a*) Cl_2; (*b*) $H_2NCH_2C_6H_4Bu^t$-*p*.

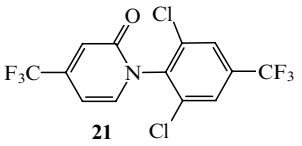
Further variation of the structure by introduction of polar and non-polar substituents in the pyrazole ring has led to the design of a fine soil and seed treating insecticide, *viz*., 5-amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-trifluoromethylsulfinylpyrazole (**20**, fipronil). This agent is employed against soil insects at doses less than 100 g ha^{-1}. Compound **20** is effective not only against susceptible insect populations but also against those resistant to dieldrine, cypermethrin and carbaryl.[45–48]



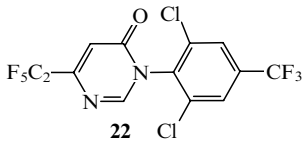
20

Insecticidal aminopyrazoles of the fipronil group (derivatives of compound **20**) are antagonists of the GABA-receptors. They block the GABA-regulated chloride channels in a membrane of the nerve fibres of insects. For the aminopyrazole **20**, the degree of blocking of the chloride channels in a membrane of the nerve cells of flies is much higher than that in a membrane of the nerve cells of rats.[48]

A study of the chemical structure–biological activity relationships for compounds of the type **20** has shown that introduction of a 2,6-dichloro-4-trifluoromethylphenyl substituent at the nitrogen atom of heterocycles enhances the insecticidal properties. According to the data of quantum-mechanical calculations, compound **20** and its pyridone (**21**) and pyrimidone (**22**) analogues have very similar electrostatic surfaces.[47,49] All of them are potent insecticides.

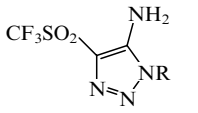


21

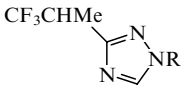


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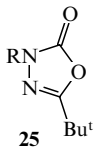
The insecticidal activities of 1-(2,6-dichloro-4-trifluoromethylphenyl)-1,2,3- (**23**) and -1,2,4-triazoles **24** as well as of 5-*tert*-butyl-4-(2,6-dichloro-4-trifluoromethylphenyl)-1,3,4-oxadiazolin-2-one (**25**) are substantially lower than that of compound **20**.[50–52] Most likely, aminopyrazole **20** and compounds **23**–**25** have different electrostatic surfaces.



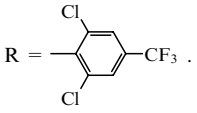
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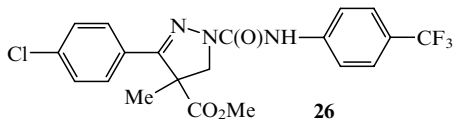
24



25

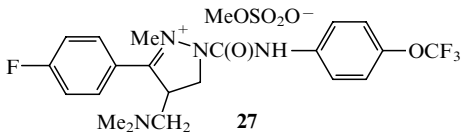


In comparison with the pyrazole derivatives, their pyrazoline analogues are less potent insectoacaricides. However, a novel insecticide, 4-methoxycarbonyl-3-(3-chlorophenyl)-4-methyl-1-[*N*-(4-trifluromethylphenyl)carbamoyl]-4,5-dihydro-5*H*-pyrazole (**26**, RH-341), has also been found in this group of compounds. Compound **26** acts as an inhibitor of the conductivity of sodium channels, which are blocked, as a rule, by veratridin, batrachotoxin and pumylotoxin B. It is important to note that compound **26** is bound to the sodium channels at the sites different from those for alkylamides, pyrethroids and DDT analogues.[53, 54]



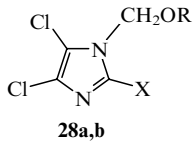
26

Compound **27** of the similar structure is effective against various species of noctuids. Methods of optimisation of the biological properties using correlation analysis have been applied in the design of this agent, in which the primary attention has been focused on the increase in lipophilic characteristics of the molecule.[55]



27

The trihalogenoimidazole derivatives represent another example of insecticides of non-standard mechanisms of biological action. They can be employed against insect populations resistant to other insecticides. The most active agent in this series of compounds is 2-bromo-1-methoxymethyl-4,5-dichloroimidazole (**28a**), which is highly effective against cockroaches.[56]



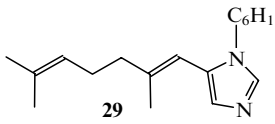
28a,b

R = Me, X = Br (**a**); R = $(CH_2)_4Cl$, X = Cl (**b**).

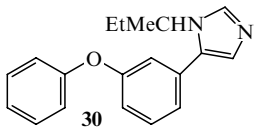
The mode of action of trihaloimidazoles has been studied in detail using 1-(4-chlorobutoxymethyl)-2,4,5-trichloroimidazole (**28b**, S-377) as a model compound. Like pyrethroids, this agent inhibits the inactivation system of the sodium channels in a membrane of nerve cells thus inducing huge excitation potentials. However, the binding sites of trihaloimidazoles and pyrethroids to the sodium channels have been found to be different.[57]

Insecticides of the class of 1,5-disubstituted imidazoles suppress the activity of insect juvenile hormones disturbing the growth, development and diapause of insects. The mechanisms of their activities are highly diverse and depend substantially on the substituents in the imidazole ring.

Thus 1-cyclohexyl-5-(2,6-dimethylhepta-1,5-dienyl)imidazole (**29**, KK-85) and particularly 1-*sec*-butyl-5-(3-phenoxyphenyl)imidazole (**30**, KK-98) at concentrations of 10^{-7}–10^{-8} mol litre^{-1} not only selectively inhibit the farnesoate epoxidases, but also suppress the activity of *O*-methyl farnesoate transferase.[58, 59]

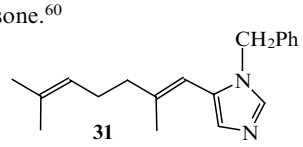


29



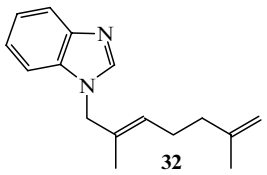
30

Compound **31**, 1-benzyl-5-(2,6-dimethylhepta-1,5-dienyl)-imidazole (KK-42), which is structurally close to imidazole **29**, suppresses *in vitro* at low concentrations the biosynthesis of ecdisteroids in protoracal glands of silkworm and reduces the ecdisteroidal titre in hemolymph of silkworm larvae and pupae. This compound induces premature metamorphosis of silkworm larvae, which is eliminated by methoprene and 20-hydroxyecdisone.[60]

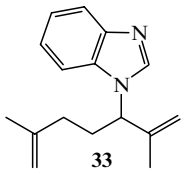


31

Terpenoids having the 2,7-dimethyloctane skeleton and a benzimidazolyl substituent, (**32**, **33**) were obtained by catalytic alkylation of benzimidazole. They possess growth regulating properties toward mealworms *Tenebrio molitor*.[61]

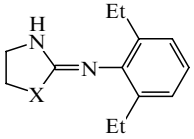


32



33

A rather unexpected mechanism of action has been found for such acaricides as *N*-substituted iminoimidazolidines and thiazolidines **34a**,**b**.

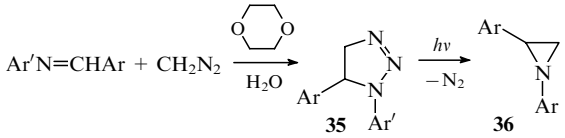


34a,b

X = NH (**a**), S (**b**).

These compounds suppress the octopamine-sensitive adenylatecyclase.[62, 63]

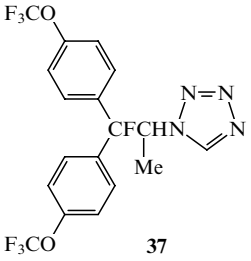
The products of 1,3-dipolar cycloaddition of diazomethane to Schiff bases, such as 1,5-diaryl-4,5-dihydro-1*H*-1,2,3-triazoles **35**, exhibit the aphicidal properties. The detailed study of the mode of their action has shown that compounds **35** are in fact proinsecticides. Upon UV irradiation, they are converted to 1,2-diarylaziridines **36**, which exhibit the aphicidal properties.



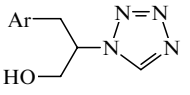
35 **36**

Model experiments have shown[64] that specially synthesised aziridines of the general formula **36** indeed manifest the same or higher activities against aphids.

1-Fluoro-1,1-bis(4-trifluoromethoxyphenyl)-2-(*N*-tetrazolyl)-propane **37** is comparable with pyrethroids in the level and the range of insecticidal activity. The mechanism of its action consists in the blockage of the axonal calcium-dependent potassium channels.[65]



37



38

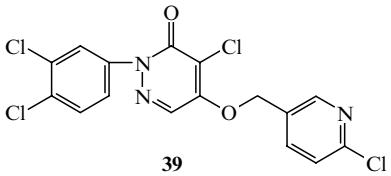
3-Aryl-2-(*N*-tetrazolyl)propanols **38** possess a good larvicidal activity against mosquito larvae and prevent the development of army worms *Spodoptera litura*.[66]

Some groups of derivatives of six-membered heterocycles with two heteroatoms in the ring also exhibit high insectoacaricidal activity.

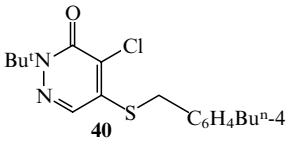
Each certain group has its own, specific mode of action. Thus 5-chloropyridazin-6-one derivatives are agonists of juvenile hormone and stimulate the biosynthesis of this hormone by activating the productivity of prothoracal glands *corpora allata*. This group of compounds not only suppresses the metamorphosis of insects, but also disturbs many other vitally important processes such as pigment biosynthesis, embryogenesis and diapause.

5-Chloro-4-(6-chloro-3-pyridylmethoxy)-1-(3,4-dichlorophenyl)pyridazin-6(2*H*)-one (**39**, NC-170) is employed as an experimental insecticide against leaf hoppers.[67–69]

Another compound of this group, *viz*., 1-*tert*-butyl-4-(4-n-butylbenzylthio)-5-chloropyridazin-6(2*H*)-one (**40**, pyridaben, NC-129), is effective against whitefly, aphids and thrips in all stages of their development. This is a tenfold more effective acaricide against mites of the orders *Tetranychus* and *Panonychus* than cyhexatin.[70,71]

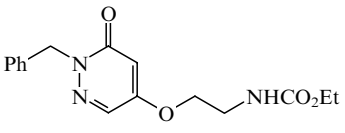


39



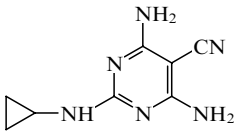
40

Being genetically associated with the group of juvenile hormone mimetics, 1-benzyl-4-(2-ethoxycarbonylamino)ethoxypyridazin-6(2*H*)-one (**41**) is of certain interest. This compound is more effective against rice green leaf hopper than fenoxycarb. It has systemic type of activity and can be applied in granulated form against soil pests at a usage rate of 200 g ha^{-1}.[72]



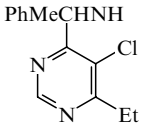
41

In the series of substituted pyrimidines, 4,6-diamino-5-cyano-2-cyclopropylaminopyrimidine (**42**, CGA-193893) is the most interesting experimental insecticide with the hormonal mode of action. This compound is tenfold more effective against aphids, pupae and imago of flies, mosquitoes and lice than cyromazine.[73]



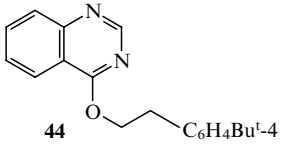
42

N-Substituted 6-alkyl-4-amino-5-chloro- and 6-alkyl-4-amino-5-cyanopyrimidines, *e.g*., compound **43**, are active against both phytophagous mites and noctuids.[74]



43

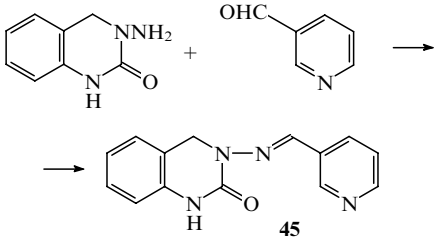
Among quinazoline derivatives, 4-[2-(4-*tert*-butylphenyl)-ethoxy]quinazoline (**44**, fenazaquin) can be distinguished as an interesting acaricide with ovicidal and larvicidal types of activity and with good ecological characteristics. Its usage rates are only 1–15 g ha^{-1}, and 85% of the preparation is decomposed after 7 days. As regards the mechanism of its action, fenazaquin is assigned to a new group of insecticides, *viz*., the mitochondrial oxidative phosphorylation decouplers.[75–78]



44

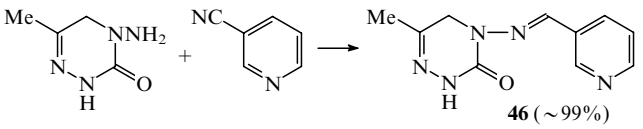
Analogues of compound **44** containing the pyridopyrimidine, thienopyrimidine, pteridine, pyrazolopyrimidine, purine, isoxazolopyrimidine and isothiazolopyrimidine fragments instead of the quinazoline moiety also possess acaricidal activity.[78]

3-(3-Pyridylmethylideneamino)-3,4-dihydroquinazolin-2-one (**45**) was obtained from 1-aminoquinazolin-2-one and nicotinaldehyde.[79]At usage rates of 75–150 g ha^{-1} this compound is effective against aphids resistant to pyrethroids, OPC and carbamates but does not affect useful insects.



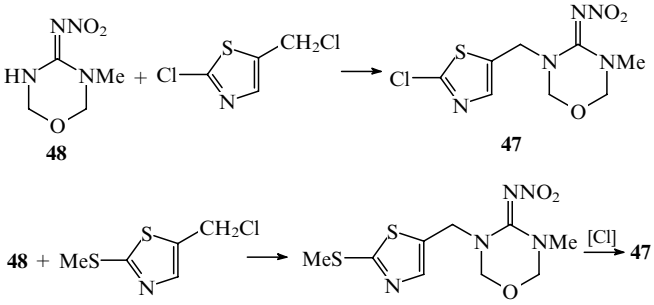
45

An analogous derivative of an asymmetrical triazine, *viz*., 2,5-dihydro-6-methyl-4-(3-pyridylmethylideneamino)-1,2,4-triazin-3-one (**46**, pymetrozine, CGA-215944), is also considered as a promising insectoacaricide. This agent with contact and ingested modes of action is effective against both susceptible and resistant populations of aphids, noctuids and whiteflies at low usage rates and can be applied for protection of vegetables in field and greenhouse plantations. This compound exhibits the antifeedant activity thus violating the insect behavioural instincts. The convenient method of its industrial preparation is based on the reduction of a mixture of commercially available 4-amino-6-methyl-1,2,4-triazin-3-one and nicotinonitrile with hydrogen over Raney Ni.[80–82]



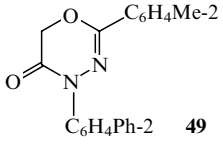
46 (~99%)

A high insecticidal activity against a large variety of insects has been found for 3-(2-chloro-5-thiazolylmethyl)-4-nitroimino-5-methyl-2,3,5,6(2*H*,5*H*)-tetrahydro-1,3,5-oxadiazine (**47**, experimental insecticide CGA-293343). This agent possesses long-lasting residual activity. The mechanism of biological action of compound **47** resembles that of neonicotinoids.[83] The method of preparation of this compound involves the alkylation of 3-methyl-4-nitroiminotetrahydro-1,3,5-oxadiazine (**48**) with either 2-chloro-5-chloromethylthiazole or 5-chloromethyl-2-methylthiothiazole followed by the replacement of the methylthio group by chlorine.[84]



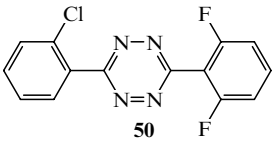
48 **47**

2,4-Diaryl-1,3,4-oxadiazin-5-ones manifest high insectoacaricidal activity. The study of the chemical structure–biological activity relationship using the QSAR programme has shown that in a series of substituted oxadiazines the maximum biocidal activity falls on 4-(2-biphenylyl)-2-(2-tolyl)-1,3,4-(4*H*,6*H*)-oxadiazin-5-one (**49**); its LC_{50} against mite *Tetranichus telarius* is equal to 25 mg litre^{-1}.[85]



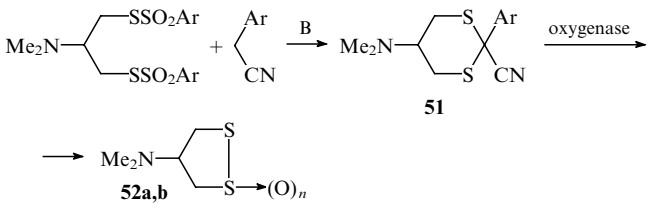
49

Among derivatives of tetrazine, one can mention 3-(2-chlorophenyl)-6-(2,6-difluorophenyl)-1,2,4,5-tetrazine (**50**, SZI-121) as an analogue of clofentezine. This compound at usage rates less than 80 g ha^{-1} is effective for protection of fruit and citrus trees, vines and vegetables against fruit tree red spider mite *Panonichus ulmi* and spider mite *Tetranichus sp*. in their ovopositional and mobile stages of development. Compound **50** has translaminar and fumigated mode of action and long-lasting residual toxicity.[86,87]



50

The most detailed study in a series of five- and six-membered sulfur-containing heterocycles has been accomplished for derivatives of substituted 1,2-dithiolanes and 1,3-dithianes. 2-Aryl-2-cyano-5-dimethylamino-1,3-dithianes **51** were synthesised by the reaction of 1,3-bis(arylsulfonylthio)-2-dimethylaminopropanes with CH-acids. These compounds possess high insecticidal activity against rice green leaf hopper and spider mites.[88]

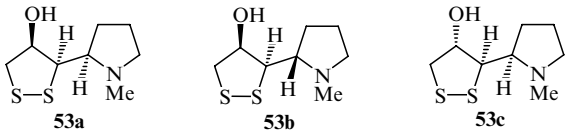


51 **52a,b**

n = 0 (**a**), 1 (**b**).

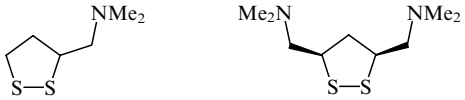
Dithianes **51** are converted into nereistoxin (**52a**) and its *S*-oxide **52b** under the action of liver microsomal oxygenases and therefore they may be considered as propesticides. The nature of the aryl substituent in the 2-position strongly affects the capability of these compounds to penetrate through the covering tissues of insects.[88]

At the end of the 80's, guinesines A, B and C (**53a–c**, respectively) were isolated from a Brazilian tree *Cassiopourea guianensis*, which showed fairly strong insecticidal properties.[89]



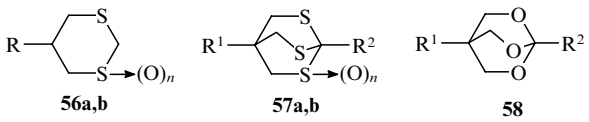
53a **53b** **53c**

Modification of the molecules of guinesines resulted in a series of dialkylaminomethyl-1,2-dithiolanes, -1,2,3-trithianes and 2,2-disubstituted 4-dialkylaminomethyl-1,3-dithiane derivatives. Among these compounds, the activity of 3-dimethylaminomethyl-1,2-dithiolane (**54**) and *cis*-3,5-bis(dimethylaminomethyl)-1,2-dithiolane (**55**) was almost the same as that of nereistoxin (**52a**).[88,90,91]



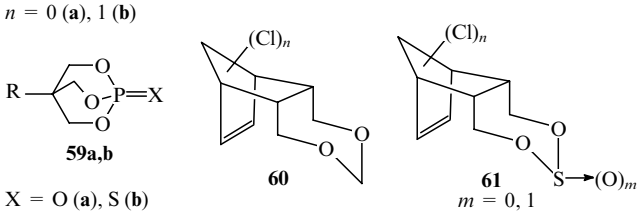
54 **55**

5-Substituted 1,3-dithiane derivatives and their *S*-oxides **56a,b**, 1,4-disubstituted 2,6,7-trithiabicyclo[2.2.2]octanes and their 2-oxides **57a,b**, 1,4-disubstituted 2,6,7-trioxabicyclo[2.2.2]-octanes **58**, 4-substituted 2,6,7-trioxa-1-phosphabicyclo-[2.2.2]octane 1-oxides and 1-sulfides **59a,b**, chlorinated 2,3:8,7-*endo*-4,6-dioxatricyclo[7.2.1.0^{2,8}]dodec-10-enes **60** and 2,3:8,7-*endo*-4,6-dioxa-5-thiatricyclo[7.2.1.0^{2,8}]dodec-10-ene oxides **61** are competitive inhibitors of the GABA-controlled chloride channels in a nerve cell membrane and show insectoacaricidal activity.[92–97]



56a,b **57a,b** **58**

n = 0 (**a**), 1 (**b**)



59a,b **60** **61**

X = O (**a**), S (**b**)

m = 0, 1

Substituents in the 5-position of compounds **56** and in the 4-position of compounds **57–59** not only substantially determine the neurotoxicity of these substances, but are also essential for their biodegradability under the action of various oxygenases.

Unfortunately, so far no commercial products among compounds **56–61** have been developed.

III. Natural compounds

Considerable qualitative changes over the last decade have taken place in the use of insectoacaricides of the natural origin.

Insecticides prepared on the basis of pyrethrum and derris-alkaloids have been employed on a small scale for certain purposes for already many decades. The same is true for the products obtained from the spore bacterium *Bacillus thuringiensis*, which are used against many types of leaf-eating insects and, primarily of all, against gypsy moth *Lymantria dispar*. All these preparations refer to the class of bioinsecticides, the total cost of their sales is estimated around $US 100 million.

The use of the methods of molecular biology and of protein and peptide chemistry in the elucidation of the nature of the toxicity of these compounds has led to impressive results over the last decade. Here, only work directly related to the problem of plant protection against insects will be considered.

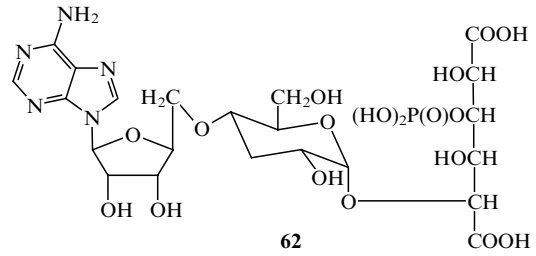
The insecticidal action of biopreparations is based on the biocidal properties of α-, β-, γ- and δ-endotoxins of protein nature. All of them contain an active trypsin-resistant active center of molecular mass 65 kDa. The highest efficacy against insects was shown by δ-endotoxin preparations of molecular mass 133 kDa. Different segments of this endotoxin are associated with its specific activities against different species of insects: the amino acid sequence 335–450 is responsible for the activity against cabbage looper *Trichoplusia ni*, and the amino acid sequence 335–615 is active against tobacco budworm *Heliothis virescens*. A chimerical toxin containing the amino acid sequence 450–612 is 30 times more active against budworm *H. Virescens* than the natural δ-endotoxin itself.[98, 99]

Selection of *Bacillus thuringiensis* has been carried out to manufacture standardised insecticidal preparations by microbiological methods. This was aimed at isolating clones that are highly productive with respect to the δ-endotoxin. Fairly simple methods for the isolation of crystalline peptide and physicochemical procedures for the control of its quality have been developed. Based on crystalline δ-endotoxin, the preparations 'agree' and 'novodor' are nowadays commercially available.

To increase economic efficiency in manufacturing the preparations based on δ-endotoxin the latest achievements of genetic engineering have been successfully employed. The gene Cryl IA, which is responsible for production of δ-endotoxin in *Bacillus thuringiensis*, was introduced into the gene of the bacterium *Escherichia coli*, which can be fairly easily cultivated. A mutant strain of *E. coli* has produced δ-endotoxin for over 500 generations without tearing away the gene implanted. δ-Endotoxin obtained by the methods of genetic engineering is approved for use as a pesticide in the US forestry industry and for control of gypsy moth *Lymantria dispar*.[100]

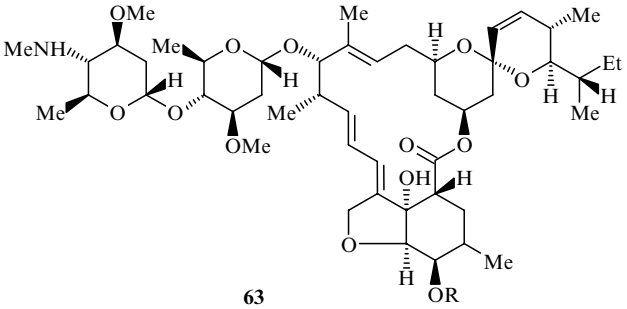
Yet another approach to the protection of plants using the biocidal properties of endotoxins is based on the creation of transgenic plants which can produce endotoxins by themselves and, as a result, are resistant to pests. The implantation of the gene Cryl IA into gene apparatus of many crops, *e.g.*, rice, tobacco, tomatoes and maize, enhances more than 100-fold their resistance. In the author's opinion, the most urgent task in this field of the research is the development of transgenic strains of potatoes resistant to Colorado beetle.[101–103]

Nucleotide **62** (dibetha, turingiensin), which is a metabolite isolated from *Bacillus thuringiensis*, possesses high insecticidal activity. At usage rates of about 40–60 g ha^{-1}, this is effective against Colorado beetle, ligus bud and phytophagous mites on cotton, potatoes and other crops.[104]



62

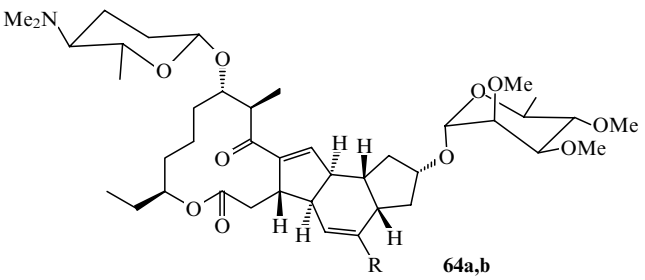
Preparations based on macrolide antibiotics avermectin and ivermectin are mainly employed in livestock farming for control of endo- and exo-pests. Modification of avermectins or structurally similar milbemectins does not usually enhance the activity.[105, 106] The only exception was the introduction of the methylamino group in the terminal oleandrosyl residue, which increased the insecticidal and acaricidal activities of semi-synthetic compound **63** more than by an order of the magnitude in comparison with the starting abamectin.[107]



63

The mode of action of avermectins and the products of their modification is based on the inhibition of the GABA-receptors.

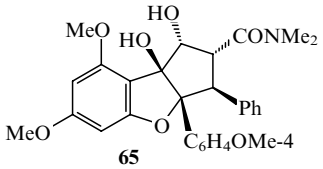
Macrolides of the spinosine group, *viz.*, spinosine A and D (**64a** and **64b**, respectively), which were isolated from the micro-organism *Saccharopolyspora spinosa*, are of considerable interest. They manifest high insecticidal activity against many widespread pests and possess contact and ingested mode of action. The preparation 'tracer' based on spinosines has good ecological and toxicological characteristics and is employed for protection of cotton.[108]



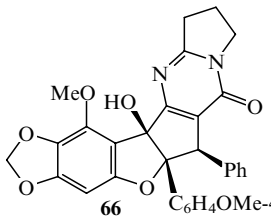
64a,b

R = H (**a**), Me (**b**).

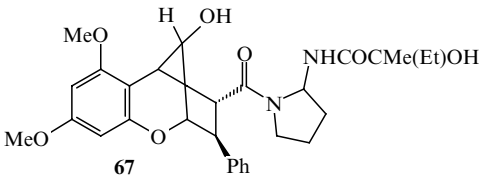
Promising results have been also obtained in the studies of insecticidal and acaricidal activities of roxaglamide and some of its analogues **65**–**67**, which were isolated from stems of the plant *Aglaja roxburgiana*.[109, 110]



65

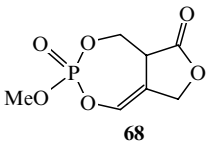


66



67

Interestingly, the first analogue of organophosphorus insecticides has been recently found among natural compounds. Antibiotic NK-901093 (**68**), which is an enol cyclophospate, was isolated from *Streptomyces sp*. At a concentration of 0.1 mg litre^{-1}, this compound causes 100% mortality in mosquitoes and suppresses the activity of cholinesterase at concentrations four orders lower than that of malaoxon.[111]

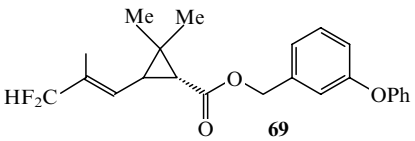


68

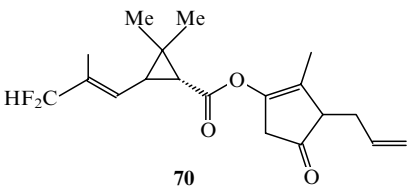
IV. Pyrethroids and other compounds

Recent years have been marked by the rapid rise in manufacture of pyrethroids, and the value of their sales has taken the first place among all types of insectoacaricides. Although it is worth mentioning that the real pyrethroid boom had already virtually abated in the 80's. In the 90's, the main emphasis in the research and manufacture of pyrethroids is made on the development of new technologies including the isolation of pure diastereomers and enantiomers for reduction of the usage rates of these compounds and minimisation of their impact on the environment. Apart from that, much attention is paid to the development of numerous multicomponent preparation forms, including mixtures, for their usage not only in farming but in the household, public health and industry.

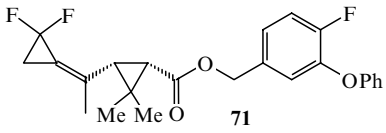
The scope of the synthetic works on pyrethroids over recent years was not so large. The most interesting result in this field was the synthesis of fluorine- and silicon-containing derivatives of previously known synthetic pyrethroids. In the case of the synthesis of fluorinated pyrethroids, the fluorine atoms and fluorine-containing groups were introduced in both the acidic part of the molecule and the aromatic ring to make these compounds more stable toward hydrolysis and the action of oxygenases. Among these compounds, phenothrin (**69**) and bioallethrin (**70**) analogues containing the difluoroisobutenyl group [112] and an analogue of cyfluthrin (**71**) bearing a difluorocyclopropylidene moiety are worth mentioning.[113]



69



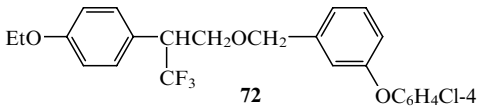
70



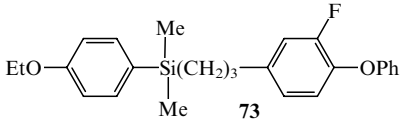
71

Compound **71** causes 100% mortality in *Spodoptera eridania*, *Aphis gossipii* and *Diabrotica undecimpunctata* at concentrations of 0.6, 2.5 and 2.5 mg litre^{-1}, respectively.

However, only two analogues of pyrethroids devoid of the ester group, *viz*., experimental insecticides flufenprox (**72**) and silafluofen (**73**), are of certain practical interest.[114, 115]



72

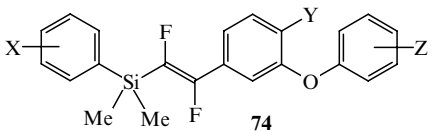


73

Flufenprox (**72**) has good economical and ecological characteristics, high insecticidal activity in doses of 75–300 g ha^{-1} against a broad range of pests, and is harmless for warm-blooded animals and bees.

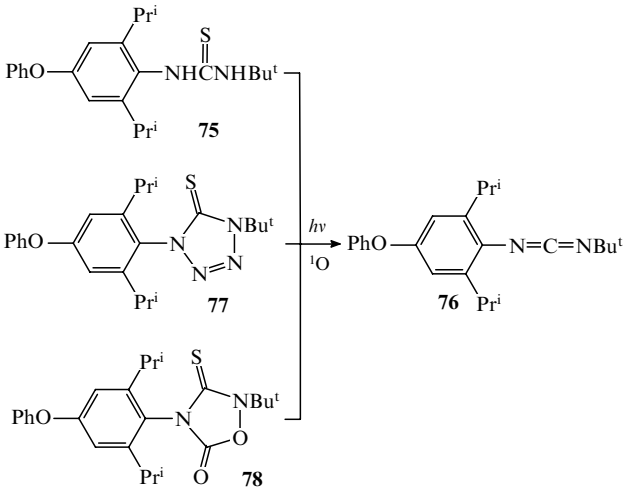
Silafluofen (**73**), which belongs to the group of silaneofans, is used against lepidopterans, dipterans, coleopterans, hemipterans, homopterans, *etc*., but is ineffective against aphids and whiteflies.

Analogues of silafluofen (**74**) containing the difluorinated double bond possess the high insecticidal activity.[116]



74

From the other groups of insectoacaricides, it is worth mentioning thiourea derivatives. Studies of the biological properties of several hundreds of di-, tri- and tetra-substituted thioureas has led to the preparation diafenthiuron, 1-*tert*-butyl-3-(2,6-diisopropyl-4-phenoxyphenyl)thiourea **75**. This is effective against sucking pests such as mites, aphids and whiteflies on cotton and vegetables. Upon UV irradiation or *in vivo*, compound **75** is converted into the corresponding carbodiimide **76**.[117, 118] It is the latter that acts as an insecticide. This intermediate blocks the activity of mitochondrial ATPase and therefore is classified as an oxidative phosphorylation decoupler.[118]



75 **77** **76** **78**

A number of other compounds were also synthesised, which are converted after elimination of a part of the molecule into carbodiimide **76**. These are, for example, 1,4-disubstituted tetra-

zoline-5-thione (**77**) and 3-thioxo-1,2,4-oxadiazol-5-one (**78**). Field tests for these compounds have also given good results.[119]

In the author's opinion, all these studies represent a fine illustration of a propesticidal approach to the development of novel insectoacaricides.

In conclusion, some general tendencies in the manufacture and application of insectoacaricides should be noted. In 1996, the production of active principles of this group of insecticidal preparations had reached 680 000 tons with a total value of $US 8.7 billion. According to the forecast, in 2001 the value of the insecticide sales will reach 10.5 – 10.7 billion dollars.

These figures show that in the beginning of the XXIst century (the author assumes that in the near future) the programmes for control of harmful insect and phytophagous mites will be based on the use of the chemical preparations despite certain recent achievements in the development of biological methods for plant protection, first of all, in the selection of transgenetic plants resistant to pests. The portion of traditional preparations such as organophosphorus compounds, carbamates and pyrethroids will constitute not less than 80% – 85% of all manufactured insectoacaricides. At the same time, the proportion of preparations with new modes of action will be gradually increased.

The wide assortment of preparations makes possible the successful application of technologies of integrated plant protection, which ensure the minimal impact of chemicals on the environment and prevent the development of resistant populations of arthropods.

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