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Contemporary trends in development of active substances possessing the pesticidal properties: neonicotinoid insecticides

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Abstract: A new group of insecticides, widely introduced to the agriculture practice since the 90-ies of XX century - neonicotinoides, is discussed. The history of its arise, and insecticidal properties, mode of action, and short characteristics of some of its representatives is presented.

Keywords: nicotine, nicotinoid insecticides, nicotinic acetylcholine receptors, agonistic activity, neonicotinoids, nitroguanidine derivatives, 2-nitroethane derivatives

INTRODUCTION

There are three important functions (of insects organisms), which interfering is the main target of insecticides mode of action (in other words: which interference determines the insecticides activity):

- nervous pulse,
- hormonal moult and metamorphosis,
- oxidative phosphorylation.

For the class of insecticides affecting the energy of oxidative phosphorylation in mitochondria, so far the first steps are done. For a long time are already used the insectoacaricides influencing the hormonal process of moulting and metamorphosis or inhibiting the chitin synthesis.

The most succeptible to the arthropods is the first function - nervous pulse. Hence, the unquestionable majority of applied insecticides acts, in different

mechanism mode, by interference in the conductivity of nervous fibres of insect organism:

- pyrethroids influence the neuron sodium channels,
- carbamates and organophosphates inhibit the acetylcholinesterase activity,
- nicotinoid insecticides bind to acetylcholinesterase receptors,
- avermectines or phenylpyrazoles block the sodium channels bonded with GABA receptors.

The world market of insecticides is still dominated by carbamates and organophosphates, but it is evidently decreasing tendency: in 1987 the AchE inhibitors made up 71% of overall insecticides market turnover, in 1999 – 52% [1], whereas in 2003 – 35.2%, giving together with pyrethroids 54.7% of overall world sale of insectoacaricides [2]. However, still growing importance is noticed in the case of insecticides targeting on acetylcholinic receptors, as nicotinoides, detaily – neonicotinoid insecticides, for which world insecticides market turnover in 2003 made up 15.7% [2].

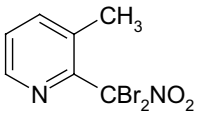
Insects acetylcholinic receptors, similarly to those present in mammals, fall into two main groups: nicotinic and muscarinic [3], where the concentration of nicotinic one is considerable higher. The central insects nervous tissues are the reachest sources of these receptors in the all animal world.

Some words about the beginning of neonicotinoid insecticides

The history of nicotinoid insecticides can be divided into three parts of development. First concerns the naturally occuring nicotin. Tobbacco was introduced to England in 1585 and starting from about 1700 its aqueous extract, consisting nicotin, was used to protect gardens from aphids. Nicotin is a chiral compound. The differences between toxicity of its enantiomers were established in 1904 (Mayor) [4]. From 1910 the nicotin sulfate was present on the market as the most popular insecticide.

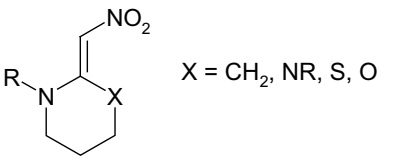
Development of synthetic insecticides in the 40-ies (DDT) and 50-ies (organophosphates and carbamates) of XXth century, being more effective and, in many cases, possessing the systemic activity, caused the diminishing of nicotin importance. Also synthetic programs based on the nicotin as prototype were not successful in elaborating the structures which could compete with other synthetic insecticides.

Second stage of the story of nicotinoid insecticides concerns the research on, so called, nitromethylenic insecticides, in Shell company. Within the investigation of new leading structures, the company obtained from Prof. Henry Feuer (Purdue University) [5] 2-dibromonitromethyl-3-methylpyridin **(I):**



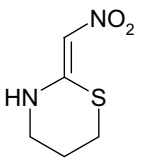
(I)

Screening tests (housefly, garden aphid) showed the weak insecticidal activity of this compound, however it was considered as the leading structure. The further research works resulted in heterocyclic derivatives of nitroethene **(II):**



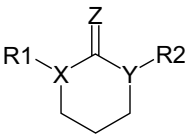
(II)

They were presented at the IUPAC conference held in Zurich in 1978 [6]. However, the selected nithiazine **(III)** was not commercialized as the plant protection agent.



(III)

The possible reason consisted in its low effectiveness in the field trials, caused by photoliability, although as well nithiazine as all the tested nitroethene derivatives induced strong systemic insecticidal activity and selectivity [7]. This group of compounds aroused great interests in many companies (Bayer, Takeda, Nippon Soda, Agro Kanesho, Mitsui Tonatsu, Ciba), and was considered as a potential promising direction in the field of new insecticides research. The subject of this investigation were structures with general formula **(IV):**



(IV)

R1 = H, alkyl, aryl, heteroaryl, heteroaryloCH$_2$;
R2 = H, alkyl, X, Y = N, S, CH; Z = CHNO$_2$, CHCN, NNO$_2$, NCN

And it was the third stage of nicotinoid insecticides history, finalized by practical application of many active substances defined as neonicotinoid insecticides (the name proposed by Yamamoto in 1996 [8]). Expression – "neonicotinoids" underlines their relation to nicotin, having yet better properties.

It is interesting, that "neonicotin" was the name used first in 1931 for the plant origin insecticide – anabazine [3-(pyperidyl-2)pyridine]. Other names of neonicotinoid insecticides present in the literature base on the names of given molecule structure fragments: e.g. chloronicotinyls, chloropyridyls, thianicotinyls, nitromethylenes, nitroguanidines, cyanoguanidines, etc.

For the development of nicotinoid insecticides the crucial turning-point (the third stage of evolution) was done by scientists from Nihon Tokushu Noyaku Seizo KK. and Nippon Bayer (Japan, 1984). By introducing to heterocyclic ring **(IV)** pyridyl-3-methyl groups, and particularly 6-chloropyridyl-3-methyl one, they achieved an essential improvement of insecticidal activity. In that way imidacloprid was invented [9], becoming the first neonicotinoid insecticide introduced to the market in 1991 by Bayer A.G. , Nihon Tokushu Noyaku Seizo KK. Starting from that time, next nicotinoids appeared: acetamiprid (Nippon Soda Co.), dinotefuran (Mitsui Chemicals Inc.), clothianidin, TJ-435 (Takeda Chemical Industries Ltd., in collaboration with Bayer A.G.), nitenpyram (Takeda Chemical Industries Ltd.), thiamethoxam (Syngenta A. G.), thiacloprid (Bayer A.G., Nihon Bayer Agrochem.).

Commercialization of imidacloprid was a great success. In 1995, with the total sale value of 360 billions dollars, this insecticide became one of the best selling insecticides, leaving behind organophosphoric chlorpyrifos [8]. Sale of imidacloprid in 1997 reached 562 billions dollars [*ibid*.].

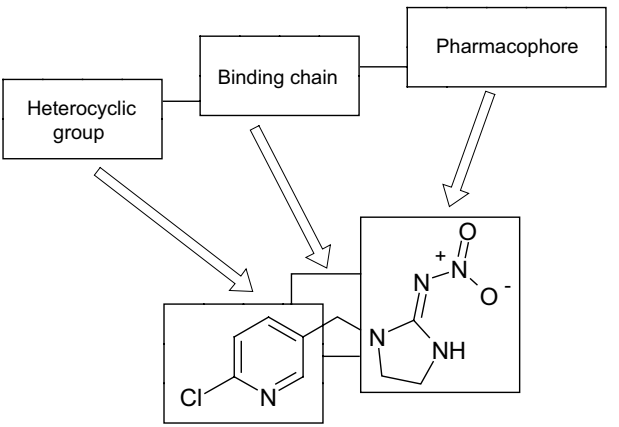
Neonicotinoids became the most important, or one of the most important, groups of insecticides.

Insecticidal properties. Mechanism of action

The significant market success of imidacloprid and other neonicotinoids can be explained by their properties. They demonstrate the outstanding insecticidal activity, particularly against Homoptera, moths, also against sucking insects as aphids, leafhoppers and beetles [8]. Having the low partition coefficient and a good solubility in water, neonicotinoids characterize the high systemicity and can be used to seed seasoning.

All neonicotinoids are structure related to nicotin, but the acute toxicity (LD_{50}, mice) e.g. for imidacloprid and thiacloprid is, respectively, 168 and 147 mg/kg, which is several fold lower than acute toxicity of natural nicotin (7 mg/kg), whereas their insecticidal activity is two magnitude orders higher [8].

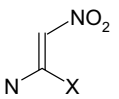
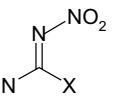
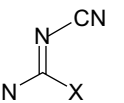
In general, the molecule of neonicotinoid insecticide is built from three parts: pharmacophore, bridging chain, and heterocyclic group - as it was illustrated on the imidacloprid example **(V)** [8]:



(V)

The pharmacophore can be represented by structure: N-C(X)-Y, where Y is electrowithdrawing group, and X is nitrogen, carbon, oxygen or sulfur atom, and is crucial for compound insecticidal activity. For instance, in the range of imidacloprid analogs, this activity tested against green leafhopper decreased as follows: Y = CH-NO_2, N-NO_2 > N-CN > $C(CN)_2$ >> CHCN, O, NH. The highest activity was observed when pharmacophore consists of nitroenamine, nitroamidine or cyanoamidine group (Table 1).

Table 1. Types of pharmacophores (X = N, C, O, or S)

Nitroenamin pharmacophore	Nitroamidin pharmacophore	Cyanoamidin pharmacophore
 (nitenpyram)	 (imidacloprid, thiametoxam, chlorthiamidine)	 (acetamiprid)

Beside of influence on the insecticidal activity of compound, pharmacophore is also responsible for some its specific properties, as photolytic activity, rate of degradation in soil, metabolism in plants and toxicity to honeybees and other beneficial insects.

As the chain bridge usually is used methylene group. Others, as for instance ethylene or substituted methylene ones, decrease the biological (insecticidal) activity.

The important effect on the biological properties of neonicotinoides plays the heterocyclic group. The highest activity is observed in compounds having 6-chloropyridyl -3 or 2-chlorothiazolyl-5 group. Others, with substituents as pyridyl-3 or thiazolyl-5 group, where chlorine atom is changed by hydrogen, fluor or bromine atom, by methyl or trifluoromethyl group, also exhibit interesting biological properties. It is worth to mention that for another neonitotinoid - dinothefurane (nitroamidine pharmacophore), the heterocyclic group is tetrahydrofuranyl-3 one.

All neonicotinoids act as agonists of insect acetylcholine nicotinic receptors, causing the hyperpolarity of nervous fibre membrane. Complex mechanism of their action induces prolonged opening of sodium channels [10, 11]. The neonicotinoids activity to postsynaptic acetylcholine nicotinic receptors was proved during the research work on the electrophysiological and radioligand bonds [12].

Imidacloprid binds very well with the brain membrane of cocroaches, flies, bees and other insects, but very weakly with membrane of mammals brain. This is a possible reason of its selective toxicity [6].

Crystallographic analysis of imidacloprid showed the coplanarity of C=N-NO_2 group with imidazolyl ring, shortening C-N bonds and increasing the lenght of C=N bond. These data allowed to present a conception, that binding between compounds of type (**IV)** with nicotinic receptors of acetylcholine, proceeds in two alternative pathways [6]. It can explain the high efficacy of imidacloprid and luck of cross resistance phenomenon to it (as for the other neonicotinoids of this type) [13].

Table 2. Dosable and toxicological characteristics of some neonicotinoids

Compound	Dosage applied (on leaf) [g/ha]	Acute toxicity (LD50, rat p.o.) [mg/kg]
Imidacloprid	25-100	> 400
Acetamiprid	75-300	> 140
Nithenpyram	15-100	> 1500
Dinothefuran	100-200	> 2000
Thiacloprid	40-216	> 400

The absence of cross resistance to imidacloprid and insecticides with different mechanisms of action can be used to create systems of integrated control of

harmful insects and programs for resistance overcoming [14].

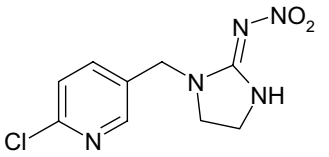
In the end of this short description of properties and mechanism of action of neonicotinoid insecticides, the limits of application dosages and toxicological characteristisctics of some of their representatives is presented in Table 2.

Characteristics of chosen neonicotinoid insecticides

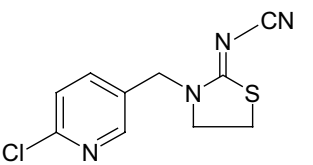
From the chemical point of view, the known neonicotinoids can be divided into two groups:

- guanidine derivatives (mainly nitroguanidines, but also cyanoguanidines), i.e. possessing nitroamidine (cyanoamidine) pharmacophore;
- 2-nitroethene derivatives (nitromethylenes), i.e. possessing nitroenamine pharmacophore.

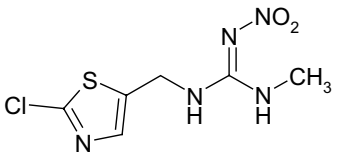
Definitely the first group predominates. Belongs to it such compounds as imidacloprid (V), thiacloprid (VI), clothianidin (VII), thiamethoxam (VIII), dinothefuran (IX) and acetamipryd (X):



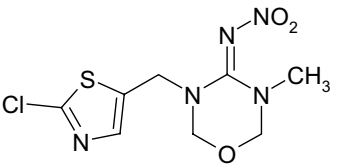
(V)



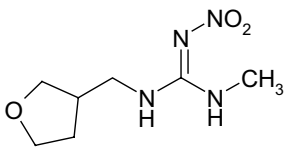
(VI)



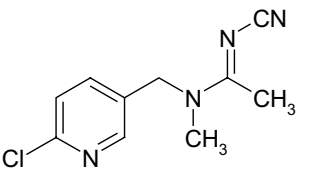
(VII)



(VIII)



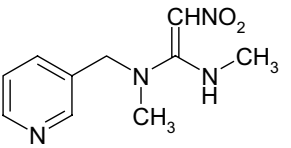
(IX)



(X)

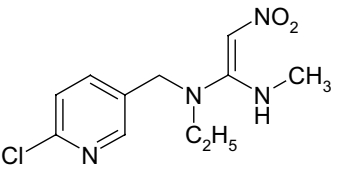
As regards the second group (nitroethene derivatives) the initial works were done in 70-ies of previous century in Shell company (second stage of

development of nicotinoid insecticides). Within these investigations, as is well known, nithiazine (III) was selected, however it was not commercialized (because of photoliability). As it was already mentioned, a group of nitromethylene structures, represented by nithiazine, aroused a great interests in many companies producing agrochemicals, among the others Takeda Chemical Industries Ltd. In this firm laboratories was synthesized a range of 2-nitroethene derivatives, with pyridyl-3-methylamine and alkylamine ligands [15-18]. For the leading structure compound (XI) was chosen, because of its greatest activity:



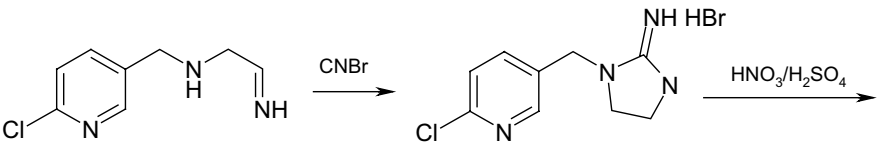
(XI)

Its further modification resulted in nithenpyram (XII), which was introduced to agricultural practice:

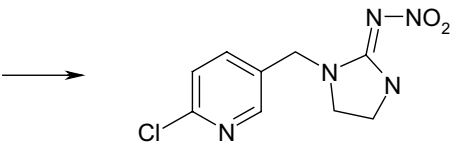


(XII)

I m i d a c l o p r i d **(V)**, 1-[(6-chloro-3-pyridynyl)methyl]-N-nitro-2-imidazolidinoamine (according to C. A. nomenclature), till 2000 was already admitted to application in over 100 countries for protection at least 65 crops [19]. It was first synthesized by coupling of diamine (XIII) with bromocyan , which resulted in iminoimidazoline (XIV); the nitration of the last with the mixture of nitric and sulfuric acids, led with low yield to imidacloprid (V):

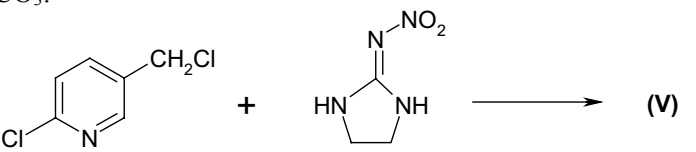


(XIII) **(XIV)**



(V)

According to patents data [21, 22], imidacloprid was also obtained with capacity of 80-90% by condensation of 2-chloro-5-chloromethylpyridine (XV) with 2-nitroiminoimidazolidine (XVI), in acetonitrile, with presence of K_2CO_3:



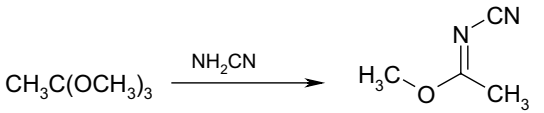
(XV) **(XVI)**

In its pure form imidacloprid has the shape of colorless crystals melting in 144 °C. It is one of the most effective insecticides, not yields to pyrethroids, in efficacy exceeds organophosphorous insecticides and carbamates [23]. Imidacloprid acts as systemic insecticide with contact and stomach activity.

Between the others, commercial formulations based on imidacloprid are Admire, Confidor, Gaucho, Merit, Premier, Premice, Provado.

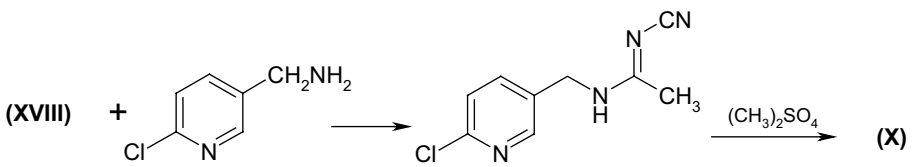
A c e t a m i p r i d **(X)**, (E)-N^1-(6-chloro-3-pyridyl)methyl-N^2-cyano-N^1-methylacetamidine (according to IUPAC nomenclature), first was registered in Japan in 1995, and commercialized by Nippon Soda Co. Its synthesis described in [24], is depicted on the figures below.

Reaction of methyl orthoacetate (XVII) with cyanamide gives with high yields compound (XVIII):



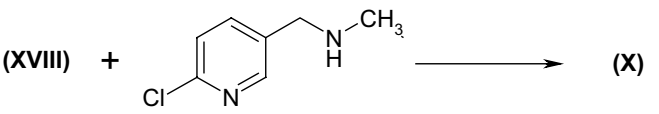
(XVII) **(XVIII)**

Condensation of the last with 2-chloro-5-aminomethylpyridine (XIX) quantitatively leads to (XX), which after methylation of the secondary amine group with dimethyl sulfate yielded in acetamiprid (X):



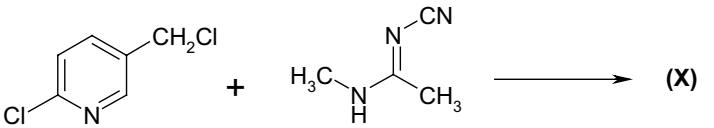
(XIX) **(XX)**

The discussed compound can be also obtained in one step by condensation of (XVIII) with 2-chloro-5-methylaminopyridin (XXI):



(XXI)

In the work [25] was presented additional option of acetamiprid preparation, namely by the reaction of 2-chloro-5-chloromethylpyridin (XV) with N-cyano-N^1-methylacetamidine (XXII):



(XV) **(XXII)**

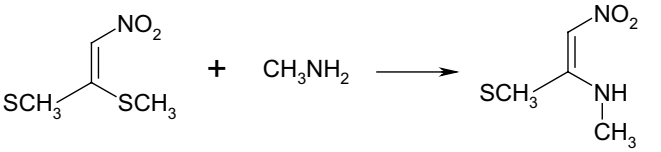
As a pure substance, acetamiprid has the shape of colorless crystals melting in 98.9 °C.

It is in (E) geometrical form, which is more stable than isomer (Z), and appears as two conformers [26].

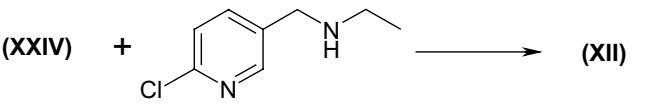
Acetamiprid is a systemic insecticide with contact and stomach activity, applied mainly against the pests of vegetables, fruits and tea trees. As an examples

of formulations based on acetamiprid can be mentioned Mospilan, Vapcomore, Adjust, Epik, Pristine.

N i t e n p y r a m **(XII)**, (E)-N-(6-chloro-3-pirydylmethyl)-N-ethyl-N^1-methyl-2-nitrovinylidene -diamine (according to IUPAC nomenclature) was first registered in 1995. For its obtaining several synthetic pathways was elaborated [15, 16, 25]. In one of them, methylamine was undertaken the reaction with 1,1-bis(thiomethyl)-2-nitroethylene (XXIII) to give 1-thiomethyl-1-methylamino-2-nitroethylene (XXIV), which next was amonolyzed with amine (XXV) to nitenpyram (XII):

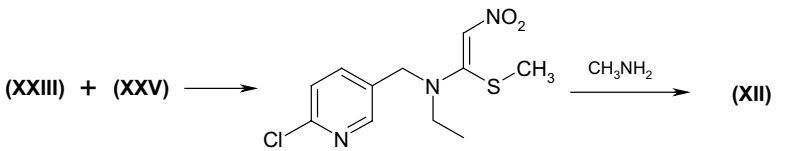


(XXIII) **(XXIV)**



(XXV)

Another variant relied on amonolysis of nitroethylene (XXIII) with amine (XXV) resulted in tertiary amine (XXVI); subsequent amonolysis of the last gave nitenpyram:

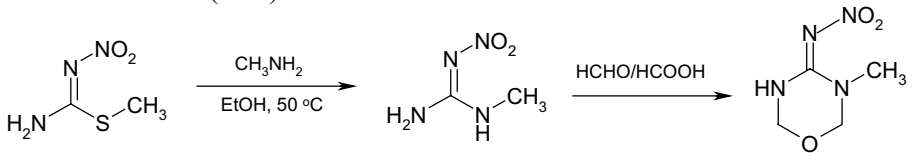


(XXVI)

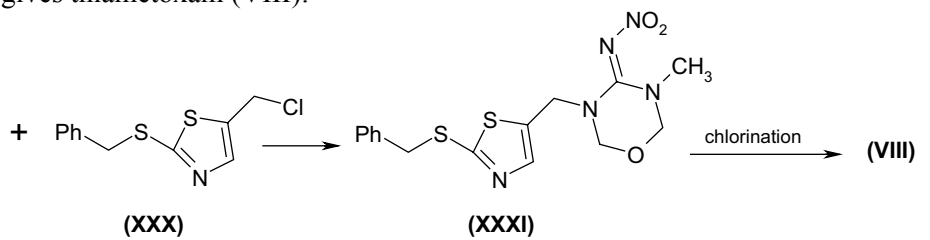
Nitenpyram forms slightly yellow crystals melting at 83-84 °C. It is a systemic insecticide with contact and stomach action. Some of chosen nitenpyram based formulations: Capstar, Bestguard, Programe, Takestar.

T h i a m e t o x a m **(VIII)**, 3-[(2-chloro-5-thiazolyl)methyl]tetrahydro-5-methyl-N-nitro-4H-1,3,5-oxadiazino-4-imine (according to C. A. nomenclature) [8, 27-29] was invented and tested by Ciba Crop Protection (since 1996 – Novartis Protection, since 2000 – Syngenta Crop Protection). On the market was introduced in 1998 under the commercial name of Actara - for on leaf and to soil application, and under the commercial name of Cruiser – for seeds treatment.

Thiametoxam was first synthesized in 1991 [30]. However, it was not accessible any practical method for preparation of 4-nitroimino-1,3,5-oxadiazinanes that time. Looking for the new solutions to overcome this problem, a new and efficient procedure was elaborated, giving with high yields 3,5-disubstituted 4-imino-1,3,5-oxadiazinanes. So, treating the easily accessible S-methyl-N-nitro-isothiourea (XXVII) with methylamine, in ethanol at 50 °C, the respective monosubstituted guanidine derivative (XXVIII) was obtained with a high 94% yield. Heating this compound at 90 °C in water solution of formaldehyde and formic acid (1:1) led to 4-nitroimino-1,3,5-diazinane (XXIX) with 71% of yield. When undertaken the alkylation with 2-chlorothiazolyl-5-methyl chloride in DMF, and with presence of potassium carbonate, it was efficiently rearranged into thiametoxam (VIII):



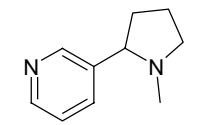
Alternatively, oxadiazinane (XXIX) can be transformed into compound (XXXI) by coupling with benzylmercaptan (XXX). Chlorination of (XXXI) gives thiametoxam (VIII):



Thiametoxam forms crystalline powder melting at 139.1 °C. It is a systemic insecticide with contact and stomach action. Besides earlier mentioned (Actara

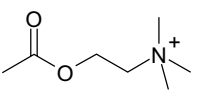
and Cruiser) thiametoxam is accessible in the following formulations: Agita (for animals protection and sanitary hygiene), Adage, Centric, Meridian, etc.

D i n o t e f u r a n **(IX)**, (R,S)-1-methyl-2-nitro-3-(tetrahydro-3-furylmethyl)-guanidine (according to IUPAC nomenclature) was invented in Life Science Laboratory of Mitsui Chemicals. In 1993, at this laboratory started research works targeted on finding a novel structure of neonicotinoid type insecticide, where pyridine part would be significantly different [31-34]. As a leading model was chosen acetylcholine (XXXII), which acts on the same receptor as nicotin (XXXIII), but doesn't have a pirydine ring:



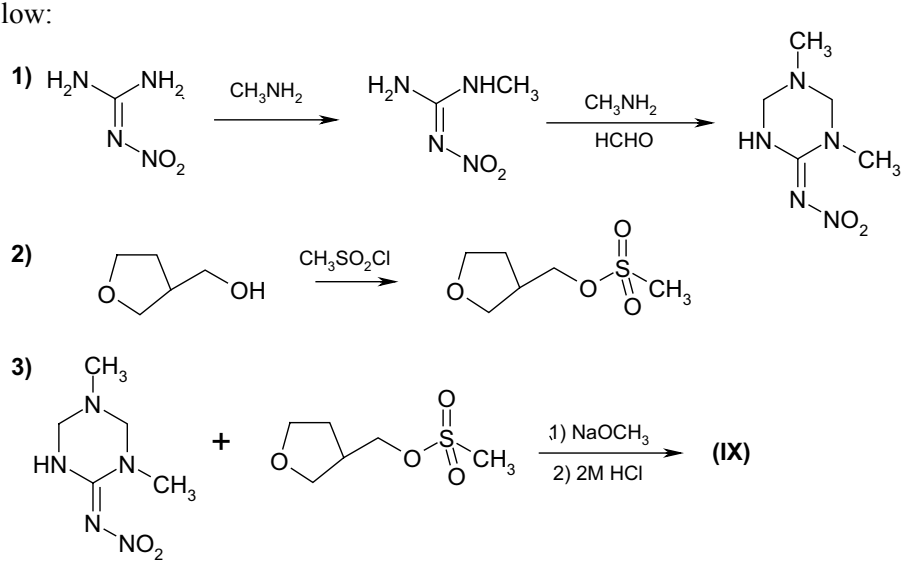
(XXXIII)

5.9 A



(XXXII)

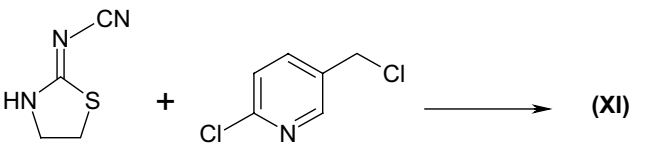
Consequently, these investigations resulted in invention of dinetefuran. Synthesis of this compound is passing through the following scheme, presented below:



Dinotefuran is a solid crystalline state, melting between 94.5-101.5 °C. As other neonicotinoides, it is characterized by a high insecticidal activity with a broad spectrum of action (contact and stomach). First it was introduced to Japan market in 2002, in the formulations under common names Starkle and Alburin, with target to protect rice, fruits and vegetables. In USA it was registered in 2004, and commercialized at this market as preparates Safari and Venon.

T h i a c l o p r i d **(VI)**, (Z)-[3-[(6-chloro-3-pyridyl)methyl]-2-thiazolidinyl dieno]cyanamide (according to C. A. nomenclature) occurs in a shape of white to beige coloured powder, melting at 136 °C. As insecticide it was presented first time by A. Elbert et al. from Crop Protection, Bayer A. G., at conference in Brighton in 2000 [35]. Synthetic methods of this compound preparation are described in patent data [36, 37].

Thiacloprid can be obtained in the reaction of 2-(cyanoimino)thiazolidine (XXXIV) with 2-chloro-5-(chloromethyl)pyridine (XV), in butyl alcohol, with presence of potassium carbonate (at 50 °C):



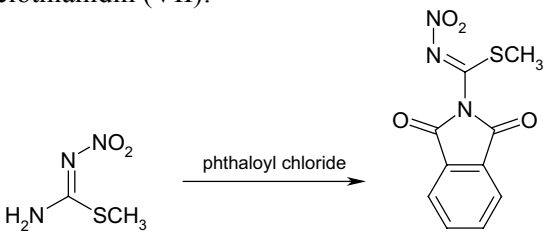
(XXXIV) **(XXXV)**

Thiacloprid is a systemic insecticide with strong contact and stomach activity. First it was introduced to the market in Switzerland, in 2000, as a formulate Alanto. Its first registration in EU took place in Great Britain in 2001. The well known preparation based on thiacloprid is Calypso, in different formulate options [38].

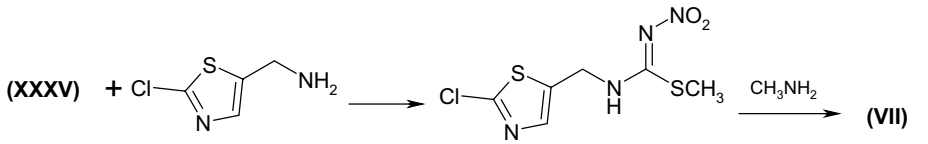
C l o t h i a n i d i n **(VII)**, (E)-N-[(2-chloro-5-thiazolyl)methyl]-N^1-methyl-N^2-nitroguanidine (according to C.A. nomenclature) occurs in a form of colorless, odourless powder, melting at 176.8 °C [39]. First it was presented at the annual conference in Brighton, in 2002 [35]. Clothianidin is produced by Bayer CropScience and Sumitomo Chemical Takeda (previously Takeda Chemical Industries).

The rules of synthesis of clothianidin are described in some published works [40-43]. One of the synthetic ways relies on the acylation of S-methyl-N-nitrozothiurea (XXVII) by phtaloyl chloride. The obtained structure (XXXV) is next condensed with 2-chloro-5-aminomethylthioazol (XXXVI), followed by

the reaction of synthesized thiazol (XXXVI) with methylamine to form expected clothianidin (VII):



(XXVII) **(XXXV)**



(XXXVI) **(XXXVII)**

Clothianidin is a systemic insecticide (presenting contact and stomach action) with a broad spectrum of activity. It is developed by Bayer company as a formulation for seeds dressing (formulation Poncho in different commercial versions), by Sumitomo Takeda (also by Bayer's) - as on leaf and in soil preparations to protect vegetables, fruits, crops, and flowers (Formulations Dantotsu, Dantotsu Dust DL). Introduction of clothianidin at the US market was ceded to Arwesta Corporation - and was done as Clutch formulation [44, 45]. Introduction of clothianidin to agricultural practice occured in 2003-2004, both in Europe and USA.

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