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Chemistry of Clothianidin and Related Compounds

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ABSTRACT: Clothianidin, a neonicotinoid insecticide, has been found by former Agro Division, Takeda Chemical Industries, Ltd. (Sumitomo Chemical Co., Ltd., at present) and codeveloped with Bayer CropScience. During the studies on neonicotinoid insecticides, nitenpyram (an open-chain nitromethylene derivative) was prepared first, showing a potent activity against Hemiptera and Thysanoptera pests, and its modification led to clothianidin (a nitroguanidine derivative). Clothianidin exhibits excellent control efficacies in small amounts for a wide variety of insect pests such as Hemiptera, Thysanoptera, Coleoptera, Lepidoptera, and Diptera for the long term, with excellent systemic action and by a variety of application methods. The structural features of clothianidin are a thiazole ring and an open-chain guanidine skeleton. The structure−activity relationships of guanidine derivatives and the synthetic studies of clothianidin are also discussed.

KEYWORDS: neonicotinoid, insecticide, clothianidin, nitenpyram, biological activity, structure−activity relationships, synthesis

INTRODUCTION

Imidacloprid,[1] discovered by Prof. Kagabu, is the first commercialized neonicotinoid insecticide and is even now most widely used in the world. At present, seven neonicotinoids in total are commercially available (Figure 1).[2]

As common superior characteristics, they show a potent insecticidal activity against sucking pests such as Hemiptera and Thysanoptera and a good systemic action, each having its own strong point. Clothianidin[3] has been found by former Agro Division, Takeda Chemical Industries, Co., Ltd. (currently Sumitomo Chemical Co., Ltd.) and codeveloped with Bayer CropScience. The structural features of clothianidin are an open-chain nitroguanidine skeleton and a thiazole ring. As its biological advantages, potent activity against Diptera, Coleoptera, and Lepidoptera pests in addition to Hemiptera and Thysanoptera, long-term control effect, excellent systemic action, and a wide variety of treatment methods can be pointed out. This paper mainly describes the details of development, biological properties, and synthetic studies of clothianidin together with the development of nitenpyram, which was commercialized before clothianidin.

HISTORY OF DEVELOPMENT

Invention of Nitenpyram. The most common crop in Japan is rice; thus, it is very important for Japanese agrochemical companies to have insecticides that cover major rice pests such as rice stem borer and rice leafroller (Lepidoptera), rice water weevil and rice leaf beetle (Coleoptera), and brown rice planthopper (Hemiptera). Takeda Chemical Industries had commercialized the insecticide cartap hydrochloride, product name, Padan (Figure 2).[4]

This compound can control the Lepidoptera and Coleoptera pests described above, but its efficacy against planthoppers such as brown rice planthopper is not adequate. A project to find a Hemiptera insecticide was then started in the company.

Just before the project was begun, it was fortuitously found that acyclic nitromethylene compounds **1a** and **1b** were moderately active against brown rice planthopper from random screening tests (Figure 3).

At almost the same time, a number of patent applications regarding heterocyclic compounds having a nitromethylene group were published by Prof. Kagabu and his co-workers in the former Nihon Tokushu Noyaku Seizo K.K. (currently Bayer CropScience).[5−7] Their structures are indicated by formula **2** in Figure 4. The example compounds in the patents, for instance, compound **2a** were prepared, and their high activity against planthoppers was confirmed.

From the structure similarity between **1a** and **1b** and **2**, it was speculated that the cyclic skeleton in **2** was not necessarily required to show an insecticidal activity. As illustrated in Figure 5, an open-chain-type compound **3** was prepared, and it was revealed that compound **3** exhibited a good activity against Hemiptera pests such as brown rice planthopper as expected. Optimization of compound **3** afforded nitenpyram (code no., TI-304; product name, Bestguard).[8] The main target pests of nitenpyram are Hemiptera and Thysanoptera.

Discovery of Clothianidin. Nitenpyram has several excellent features such as high activity against Hemiptera, low toxicity for nontarget species, systemic action, and no cross-resistance with conventional insecticides. However, the width of its insecticidal spectrum was not always satisfactory; thus, further research was continued.

Among several studies after the discovery of nitenpyram, the most successful experiment was to replace the nitromethylene group of nitenpyram with a nitroimino group (Figure 6). The

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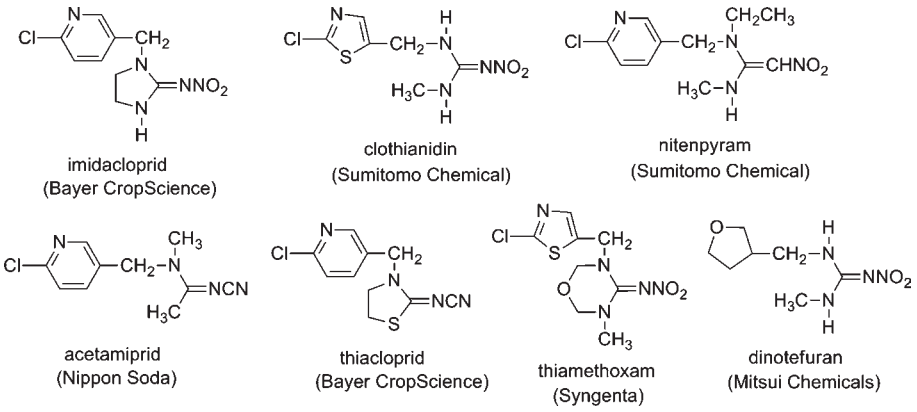

Figure 1. Neonicotinoid insecticides that are commercially available at present.

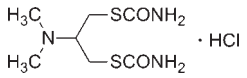

Figure 2. Structure of cartap hydrochloride.

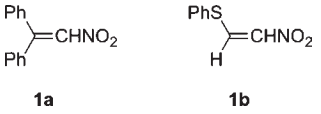

Figure 3. Initial acyclic nitromethylene compounds that showed moderate activity against planthoppers.

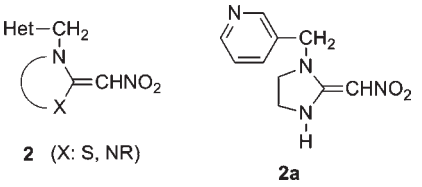

Figure 4. General structure (**2**) and a specific compound (**2a**) of cyclic patent compounds.

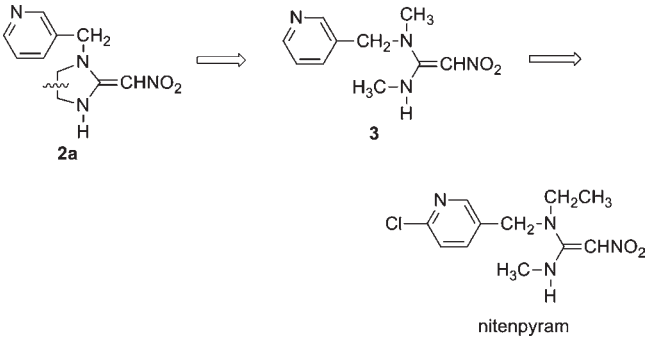

Figure 5. Optimization from the cyclic compound **2a** to nitenpyram.

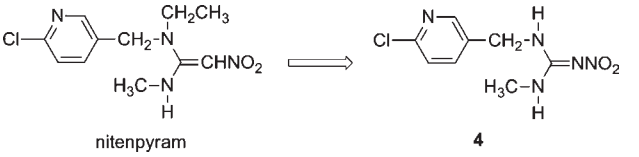

Figure 6. Nitenpyram and the lead compound **4** for nitroguanidine derivatives.

resulting nitroguanidine derivative **4** exhibited good activity on some Lepidoptera pests, maintaining the potency for Hemiptera, so compound **4** was optimized as the lead compound.

The rough structure−activity relationships of the main substituents are demonstrated in Figure 7.

As the group X, an electron-withdrawing group was essential, a nitro group being the best. A number of heterocyclic moieties such as the group Het contributed to show an activity, and among them, 2-chloro-5-thiazolyl seemed to be most preferable and next 6-chloro-3-pyridyl. Then the substituent at the 2-position of the 5-thiazole ring was modified; however, a chlorine atom, the first choice, was the most superior and a bromine atom was slightly inferior to chlorine, the order of other groups being shown in the figure. As the groups R^1, R^2, and R^3, hydrogen, methyl, and hydrogen were selected, respectively. The structure of the most potent compound, clothianidin, is demonstrated in Figure 8.

On the basis of activity on various pests, the results of field trials, and safety test data, clothianidin was selected as the candidate compound.[9] Takeda Chemical Industries and Sumitomo Chemical have been developing this compound jointly with Bayer CropScience. In Japan, clothianidin was registered in December 2001 for lawn grass and in April 2002 for crops. At present, clothianidin is registered in more than 40 countries over the world by both companies and is contributing to crop production by protecting against damage caused by a great number of insect pests.

PROPERTIES

Physical and Chemical Properties. The physical and chemical properties of clothianidin are indicated in Table 1. At present, clothianidin is commercialized under many product names depending on target fields, application methods, selling countries, developing companies, and so on, and only the major ones are listed in the table. Dantotsu is used for crops mainly in Japan; Belay and Clutch are used for crops by Valent, which is a family company of Sumitomo Chemical in the United States; and Poncho is used for seed treatment by Bayer CropScience.

Biological Properties. Examples of target pest insects recommended mainly in Japan are shown in Table 2. Clothianidin exhibits excellent control efficacies in small amounts against a large number of pest species in Homoptera, Heteroptera,

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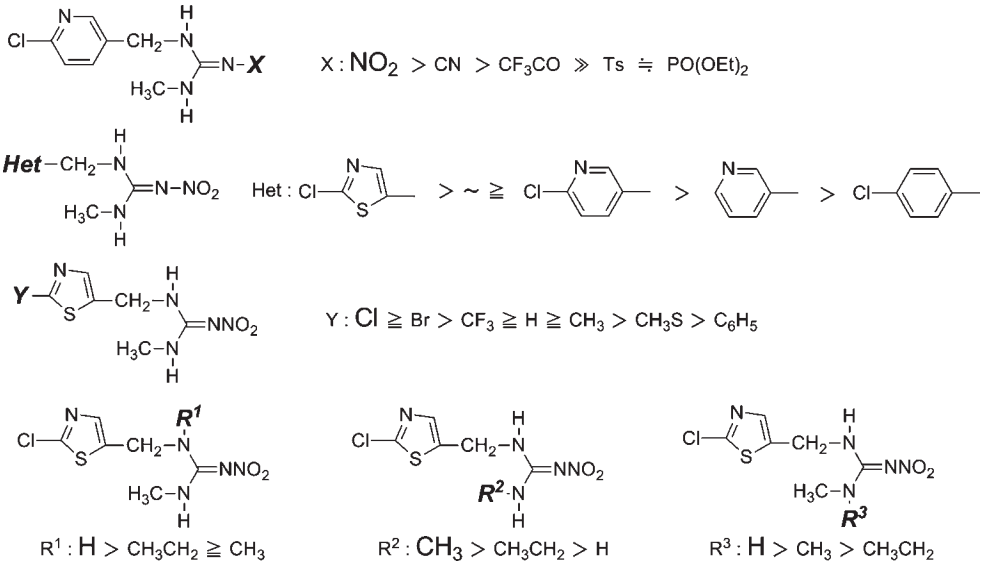
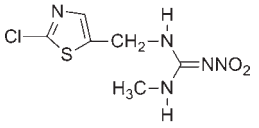


Figure 7. Structure−activity relationships of guanidine derivatives.



clothianidin

Figure 8. Structure of the most potent compound after optimization (clothianidin).

Table 1. Physical and Chemical Properties of Clothianidin

ISO name	clothianidin
chemical name (IUPAC)	(*E*)-1-(2-chloro-1,3-thiazol-5-ylmethyl)-3-methyl-2-nitroguanidine
major product name	Dantotsu (for crops, Japan); Belay (for crops, USA); Clutch (for crops, USA); Poncho (seed treatment, USA)
molecular formula	$C_6H_8ClN_5O_2S$
density	1.61 g/mL (20 °C)
melting point	176.8 °C
vapor pressure	1.3×10^{-10} Pa (extrapolated, 25 °C)
solubility (water)	0.327 g/L (20 °C)
dissociation constant (pK_a)	11.09 (20 °C)
partition coefficient (log P_{OW})	0.7 (25 °C)

Thysanoptera, Diptera, Coleoptera, Lepidoptera, Orthoptera, and Isoptera families. As a summary of the biological properties of clothianidin,[10] the following advantages can be pointed out: wide insecticidal spectrum; potent activity at low dosage; long-term control effect; excellent systemic action; wide variety of application methods; and high crop safety. Clothianidin binds in high affinity to the insect nicotinic receptors.[11] Interestingly, clothianidin shows an enhanced agonist efficacy relative to that of imidacloprid at the cholinergic neurons cultured from the central nervous system of third-instar *Drosophila* larvae.[12]

Toxicological Properties. Mammalian and environmental toxicities are listed in Tables 3 and 4, respectively. Clothianidin

Table 2. Examples of Target Pest Insects Recommended of Clothianidin

family	insect pest
Homoptera	aphid, leafhopper, planthopper, mealy bug, whitefly, scale, lace bug
Heteroptera	stink bug
Thysanoptera	thrips
Diptera	leaf miner, seedcorn maggot, house fly, cherry drosophila
Coleoptera	corn root worm, chafer, leaf beetle, longhorn beetle, weevil, billbug, wireworm, ladybird, sap beetle
Lepidoptera	noctuid moth, leaf miner, pyralid moth, fruit moth, papilionidae, diamondback moth, soybean pod borer, tea leaf roller, pieridae
Orthoptera	grasshopper, mole cricket
Isoptera	termite

Table 3. Mammalian Toxicity of Clothianidin

study	species	result[a]
acute, oral	rat	>5000 mg/kg (M, F; LD_{50})
eye and skin irritation	rabbit	not irritant
skin sensitization	guinea pig	none
chronic NOAEL	rat	M, 82.0; F, 32.5 mg/kg/day
carcinogenicity	rat, mouse	none
development	rat, rabbit	no teratogenicity
reproductive	rat	
	parental systemic NOAEL	M, 31.2; F, 36.8 mg/kg/day
	offspring systemic NOAEL	M, 9.8; F, 11.5 mg/kg/day
	reproductive NOAEL	M, 31.2; F, 188.8 mg/kg/day
mutagenicity		negative

[a] M, male; F, female.

has a low toxicity toward mammals, birds, and aquatic organisms. Clothianidin and the principal metabolites are almost inactive to the vertebrate neuronal nicotinic receptor subtypes,[13] and clothianidin can be primarily detoxified by mammalian aldehyde oxidase.[14]

Table 4. Environmental Toxicity (Acute) of Clothianidin

species	result
bobwhite quail	LD_{50} > 2000 mg/kg
rainbow trout	LC_{50} > 105.8 mg/L (96 h)

SYNTHETIC STUDIES

When clothianidin was first prepared, there were no efficient routes for either the thiazole part or the guanidine skeleton.[9] Accordingly, substantial improvement for both synthetic pathways was necessary for its industrial production. Several good methods have been reported for each of the routes by Takeda and other companies in patent applications. Their outlines are described below.

Thiazole Ring. 2-Chloro-5-chloromethylthiazole (CCT) is not only a key intermediate for clothianidin, but it seems to be also important for the production of thiamethoxam in Figure 1, and several patents for preparing CCT have been published from

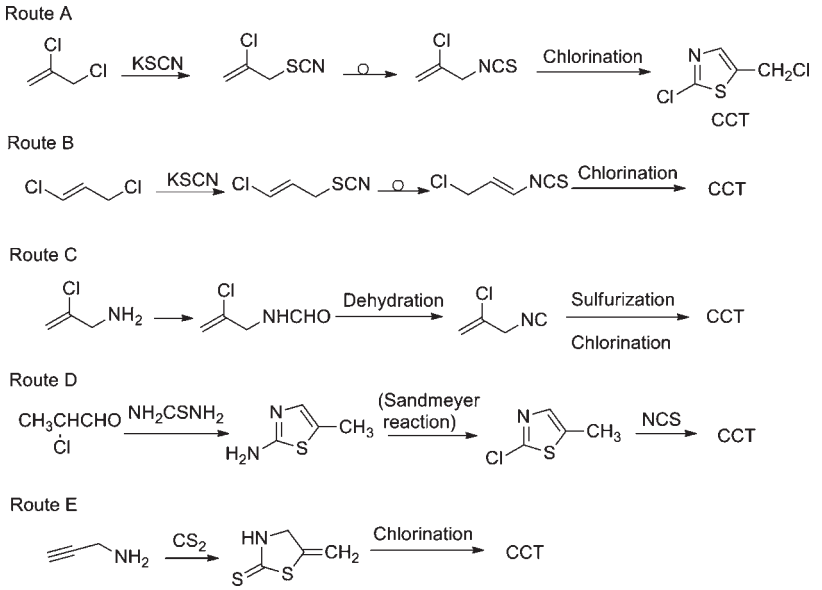


Figure 9. Synthetic routes for key intermediate CCT of clothianidin (routes A−E).

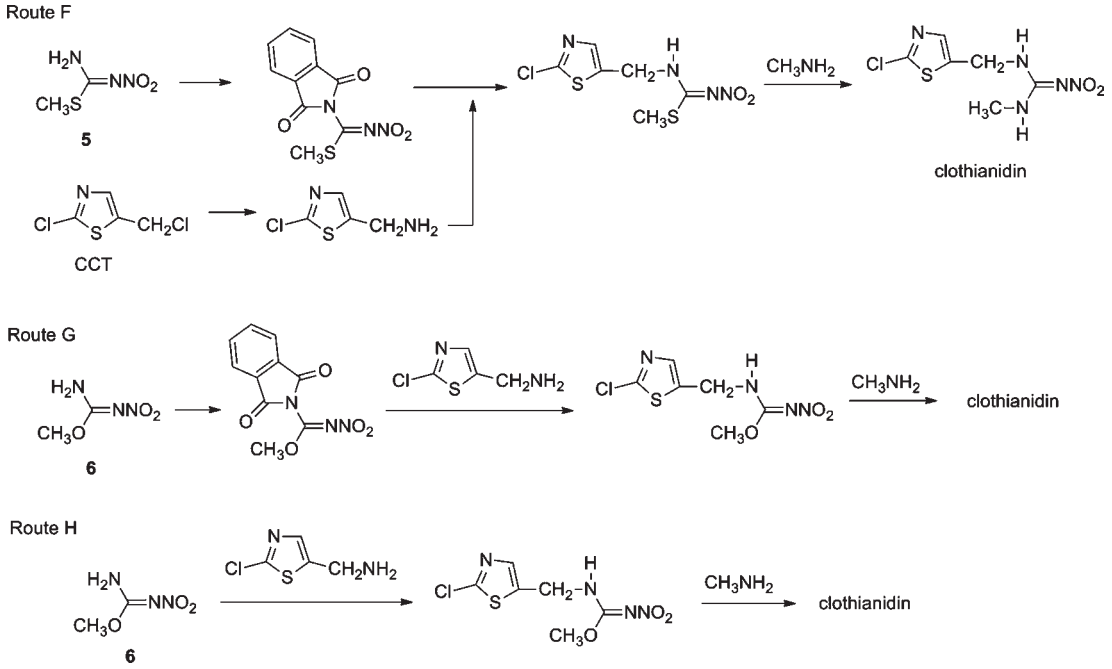


Figure 10. Processes for the nitroguanidine skeleton of clothianidin discovered by Takeda (routes F−H).

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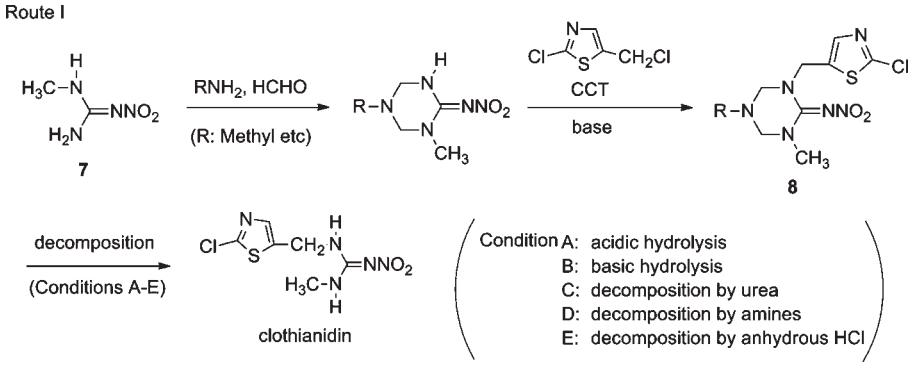

Figure 11. Processes for the nitroguanidine skeleton of clothianidin reported by companies other than Takeda (route I, conditions A−E).

multiple companies, the main ones being shown in Figure 9. Takeda has found a novel route from 2,3-dichloro-1-propene (route A).[15,16] Routes B[17−19] and C[20] have been developed by other companies and are understood to proceed by a manner similar to that of route A. In route D, CCT is obtained via conventional thiazole synthesis followed by the side-chain chlorination.[21] A method using propargylamine was also reported (route E).[22,23]

Guanidine Skeleton. As shown in Figure 10, three processes starting from *S*-methyl-*N*-nitroisothiourea (**5**) (route F)[24,25] and *O*-methyl-*N*-nitroisourea (**6**) (routes G[26] and H[26,27]) have been discovered by Takeda.

On the other hand, a completely different route has been published in patents (route I, Figure 11). Mannich-type cyclization of *N*-methyl-*N*′-nitroguanidine (**7**) followed by reaction with CCT gave a hexahydrotriazine derivative **8**. Then compound **8** was decomposed to clothianidin by several conditions, for example, conditions A,[28,29] B,[30] C,[31] D,[32] and E.[33]

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ABBREVIATIONS USED

CCT, 2-chloro-5-chloromethylthiazole; NCS, *N*-chlorosuccinimide.

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