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НОВИ НАФТОПИРАНДИОНОВИ ПРОИЗВОДНИ С ЦИКЛОАЛКАНСПИРОХИДАНТОИНИ: СИНТЕЗ, ОХАРАКТЕРИЗИРАНЕ И ФУНГИЦИДНА АКТИВНОСТ СПРЯМО *MONILIA FRUCTIGENA*

NEW NAPHTHOPYRANDIONE DERIVATIVES WITH CYCLOALKANESPIROHYDANTOINS: SYNTHESIS, CHARACTERIZATION AND FUNGICIDAL ACTIVITY TOWARDS *MONILIA FRUCTIGENA*

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Abstract

This article presents a synthesis of new naphthopyrandione derivatives with cycloalkanespirohydantoins. The target compounds were obtained by reaction of 4-bromo-1,8-naphthalic anhydride /6-bromo-1*H*,3*H*-naphtho[1,8-*cd*]pyran-1,3-dione/ with cyclopentanespiro-5-hydantoin /1,3-diazaspiro[4.4]nonane-2,4-dione/ and cyclohexanespiro-5-hydantoin /1,3-diazaspiro[4.5]decane-2,4-dione/. As a result of this interaction the following products were prepared: 3-(1,3-dioxo-1*H*,3*H*-naphtho[1,8-*cd*]pyran-6-yl)-1,3-diazaspiro[4.4]nonane-2,4-dione and 3-(1,3-dioxo-1*H*,3*H*-naphtho[1,8-*cd*]pyran-6-yl)-1,3-diazaspiro[4.5]decane-2,4-dione. The newly synthesized compounds were characterized by physicochemical parameters, elemental analysis and IR spectral data.

The fungicidal activity of the products cited above was investigated towards *Monilia fructigena* (brown rot). It was found that both compounds were able to completely inhibit the germination of the *Monilia fructigena* conidia.

Keywords: naphthopyrandione derivatives, cycloalkanespirohydantoins, 4-bromo-1,8-naphthalic anhydride, *Monilia fructigena*.

INTRODUCTION

The fungicidal activity of cyclopentanespiro-5-hydantoin (Fig. 1a), cyclopentanespiro-5-(2,4-dithiohydantoin) (Fig. 1b) and 1-aminocyclopentane-1-carboxylic acid (Fig. 1c) towards *Blumeria graminis* f. sp. *tritici* (wheat powdery mildew) has been investigated in a previous work of ours (Marinov et al., 2013).

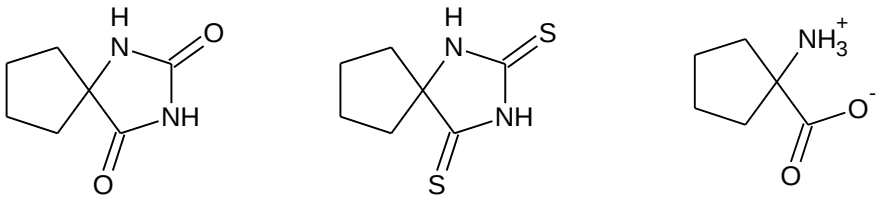


Fig. 1. *Structural formulas of cyclopentanespiro-5-hydantoin /1,3-diazaspiro[4.4]nonane-2,4-dione/ (**a**), cyclopentanespiro-5-(2,4-dithiohydantoin) /1,3-diazaspiro[4.4]nonane-2,4-dithione/ (**b**) and 1-aminocyclopentane-1-carboxylic acid (**c**)*

It has been found that all compounds were able to completely inhibit the tested phytopathogen. Furthermore, no visual phytotoxic manifestations on wheat leaves have not been observed. At the same time, these products have not been effective against *Alternaria solani* (Ganchev et al., 2013).

In the current research, we present a method for the synthesis of new organic compounds, namely naphthopyrandione derivatives with cycloalkanespirohydantoins. An investigation of their fungicidal activity towards *Monilia fructigena* (brown rot) has also been performed.

MATERIALS AND METHODS

Synthetic compounds

All chemicals used were purchased from Merck and Sigma-Aldrich. The melting points were determined with a SMP-10 digital melting point apparatus. The elemental analysis data were obtained with an automatic analyzer Carlo Erba 1106. The purity of the compounds was checked by thin layer chromatography on Kieselgel 60 F_{254}, 0.2 mm Merck plates, eluent systems (vol. ratio): benzene: ethanol = 5 : 1 and ethyl acetate : petroleum ether = 1 : 2. The IR spectra were registered in KBr pellets on a VERTEX 70 FT-IR spectrometer (Bruker Optics) from 4000 cm^{-1} to 400 cm^{-1} at resolution 2 cm^{-1} with 25 scans.

The cycloalkanespiro-5-hydantoins (**2a** and **2b**, Scheme 1) were obtained by the Bucherer-Lieb method (Bucherer and Lieb, 1934).

The 4-bromo-1,8-naphthalic anhydride /6-bromo-1*H*,3*H*-naphtho[1,8-*cd*]pyran-1,3-dione/ (**4**, Scheme 2) was synthesized in accordance with Grayshan et al. (Grayshan et al., 1974).

Synthesis of naphthopyrandione derivatives with cycloalkanespiro-5-hydantoins (5a and 5b) (Scheme 3)

A mixture of 2.77 g (0.01 mol) of 4-bromo-1,8-naphthalic anhydride (**4**) and 0.01 mol of the corresponding cycloalkanespiro-5-hydantoin (**2a** and **2b**) was refluxed for six hours in 30 ml of *N,N*-dimethylformamide (DMF). After cooling down to room temperature, the resulting solution was poured into 100 ml of cold water and was left overnight. The crystalline products obtained (**5a** and **5b**) were filtered off and recrystallized from glacial acetic acid.

***In vitro* fungicidal activity tests**

Ten different flowable concentrates in dimethylsulfoxide/water solution with compounds **5a** and **5b** were prepapred and used for the fungicidal activity tests. Phytopathogen cultures of *Monilia fructigena* were isolated from infected quince fruits (*Cydonia vulgaris*). Germ tube inhibition tests were conducted in order to be determined a possible protective activity of the synthesized products. Plant parts fresh infected with the phytopathogen were collected and incubated in a humid chamber. Conidial suspensions were prepared with 3*104 spores/ml density. Microscopic slides kind “handing drop” were sprayed with solutions of compounds **5a** and **5b** and after drying, 20 µl of conidial suspension was applied.

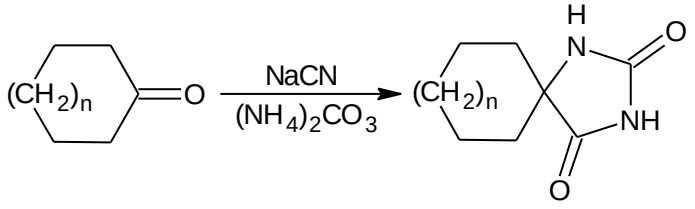
The slides were incubated in a humid chamber in thermostat and after 24-48 h the number of germinated conidia was counted with a light microscope (Nikolov and Ganchev, 2011). The pictures presented below were taken with Boeco BIB-100 light inverter microscope (400 x magnification). The effectiveness of the tested products towards *Monilia fructigena* was determined with the Abbott’s formula (Abbott, 1925).

RESULTS AND DISCUSSION

The spirohydantoins (**2a** and **2b**) used for the synthesis of the titled compounds were prepared from the corresponding cyclic ketones (cyclopentanone, **1a** and cyclohexanone, **1b**) by the Bucherer-Lieb method (Bucherer and Lieb, 1934) in accordance with Sheme 1. The bromination of 1,8-naphthalic anhydride /1*H*,3*H*-naphtho[1,8-*cd*]pyran-1,3-dione/ (**3**) led to 4-bromo-1,8-naphthalic anhydride /6-bromo-1*H*,3*H*-naphtho[1,8-*cd*]pyran-1,3-dione/ (**4**, Scheme 2) formation (Grayshan et al., 1974).

The new naphthopyrandione derivatives (**5a** and **5b**) were synthesized by the interaction between the 4-bromo-1,8-naphthalic anhydride (**4**) and the spirohydantoins (1,3-diazaspiro[4.4]nonane-2,4-dione, **2a** and 1,3-diazaspiro[4.5]decane-2,4-dione, **2b**) following scheme 3.

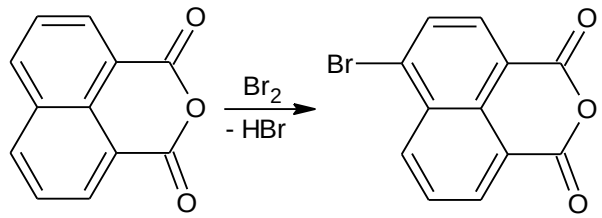
The products prepared (**5a** and **5b**) were characterized by physicochemical parameters, elemental analysis and IR spectral data. The results obtained from these analyses are presented in tables 1–3.



1 **2**

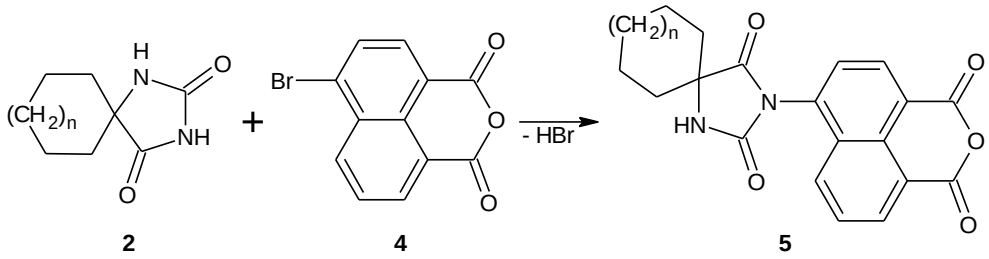
a) n = 0; **b)** n = 1

Scheme 1. *Synthesis of cycloalkanespiro-5-hydantoins (**2a** and **2b**)*



3 **4**

Scheme 2. *Synthesis of 4-bromo-1,8-naphthalic anhydride /6-bromo-1H,3H-naphtho[1,8-cd]pyran-1,3-dione/ (**4**)*

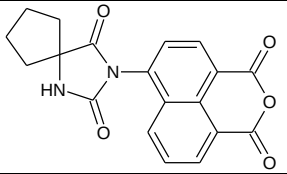
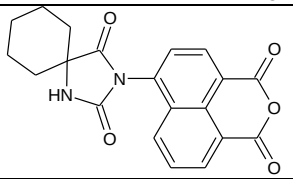


2 **4** **5**

a) n = 0; **b)** n = 1

Scheme 3. *Synthesis of naphthopyrandione derivatives with cycloalkanespirohydantoins (**5a** and **5b**)*

Table 1. Structures, systematic names, yields and melting points of compounds **5a** and **5b** shown in scheme 3*

№	Structure	Systematic name	Yield, %	M. p., C
5a		3-(1,3-dioxo-1*H*,3*H*-naphtho[1,8-*cd*]pyran-6-yl)-1,3-diazaspiro[4.4]nonane-2,4-dione	62	143-144
5b		3-(1,3-dioxo-1*H*,3*H*-naphtho[1,8-*cd*]pyran-6-yl)-1,3-diazaspiro[4.5]decane-2,4-dione	66	123-124

The purity of compounds **5a and **5b** was checked by thin layer chromatography on Kieselgel 60 F_{254}, 0.2 mm Merck plates. It was found that both products are homogeneous in two eluent systems (vol. ratio): benzene : ethanol = 5 : 1 and ethyl acetate : petroleum ether = 1 : 2.*

Table 2. Elemental analysis data of compounds **5a** and **5b**

№	Molecular formula	Formula weight	Calculated, %			Found, %		
			C	H	N	C	H	N
5a	$C_{19}H_{14}N_2O_5$	350.32	65.14	4.03	8.00	64.98	3.91	7.89
5b	$C_{20}H_{16}N_2O_5$	364.35	65.93	4.43	7.69	65.67	4.32	7.53

Table 3. IR spectral data (ν_{max}, KBr, cm^{-1}) of compounds **5a** and **5b**

№	OH	NH	Arom.	Aliph.		C=O (hydant. ring)	C=O (naphth. ring)	C-N
				as	**s**			
5a	3475	3312	3091	2945	2848	1783, 1734	1654	1459, 1385
5b	3448	3341	3091	2976	2840	1783, 1735	1655	1460, 1384

The fungicidal activity of products **5a** and **5b** was investigated towards *Monilia fructigena* (see the “Materials and methods” part). The test pictures, taken with Boeco BIB-100 light inverter microscope (400 x magnification) are presented in figures 2–4.

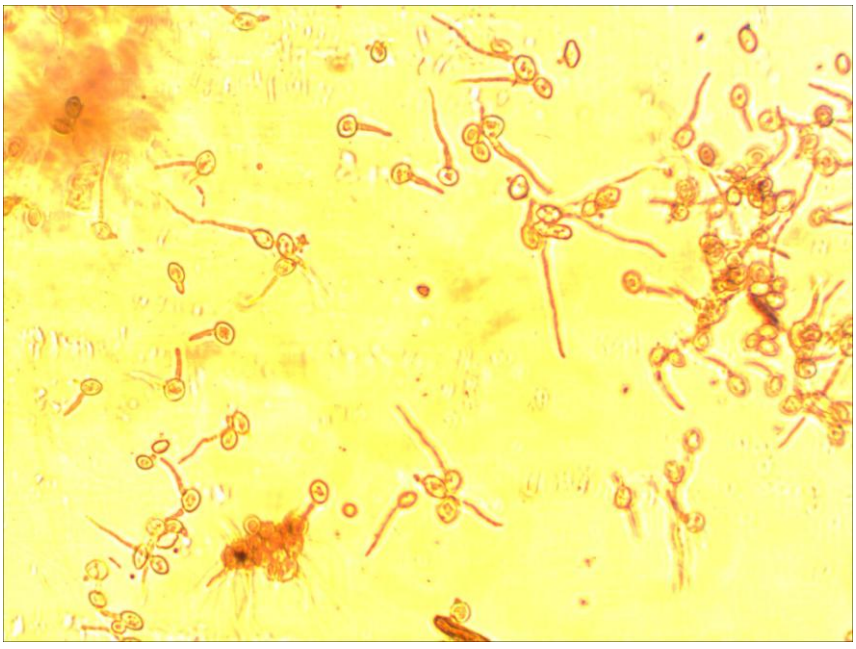


Fig. 2. *Monilia fructigena/Control variant – 1% (v/v) aqueous dimethylsulfoxide solution*

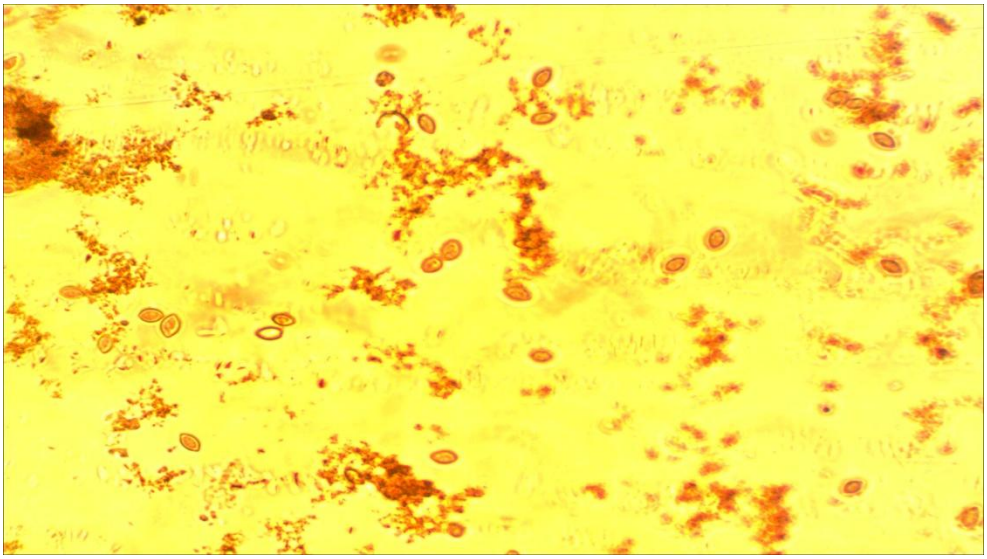


Fig. 3. *Monilia fructigena/Compound* ***5a*** *treated variant (1% (v/v) flowable dimethylsulfoxide/water concentrate, containing 0.1% (m/v) of the active substance)*

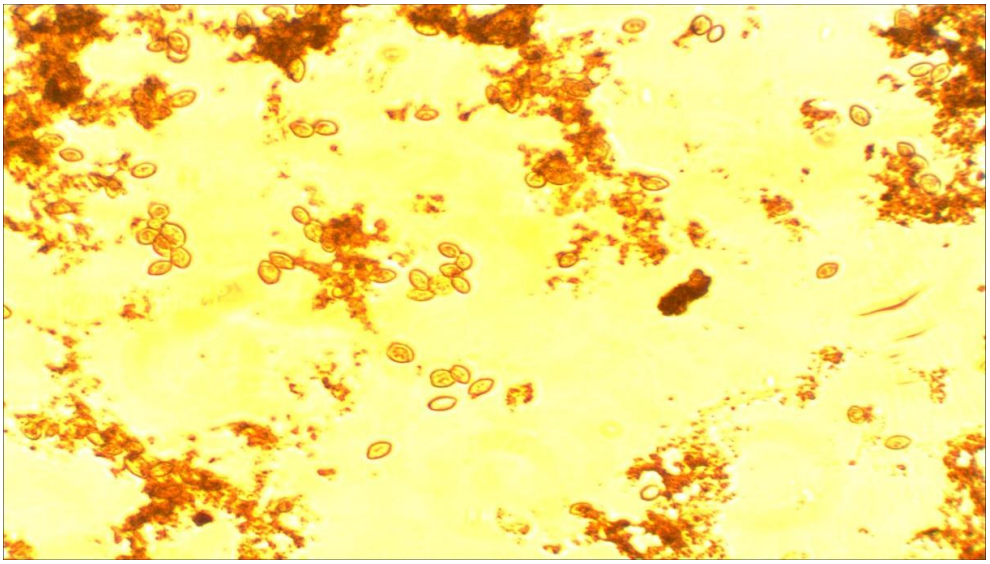


Fig. 4. *Monilia fructigena/Compound* ***5b*** *treated variant (1% (v/v) flowable dimethylsulfoxide/water concentrate, containing 0.1% (m/v) of the active substance)*

The results of the conducted biological tests showed that the 1% (v/v) flowable dimethylsulfoxide/water concentrates, containing 0.1% (m/v) of the active substance (**5a** and **5b**) completely inhibited the germination of the *Monilia fructigena* conidia. The control variant (1% (v/v) aqueous dimethylsulfoxide solution) did not show any effectiveness against the phytopathogen studied.

CONCLUSIONS

1. New naphthopyrandione derivatives with cycloalkanespirohydantoins, namely 3-(1,3-dioxo-1*H*,3*H*-naphtho[1,8-*cd*]pyran-6-yl)-1,3-diazaspiro[4.4]nonane-2,4-dione (**5a**, scheme 3) and 3-(1,3-dioxo-1*H*,3*H*-naphtho[1,8-*cd*]pyran-6-yl)-1,3-diazaspiro[4.5]decane-2,4-dione (**5b**, scheme 3) were successfully synthesized.

2. The structures of the compounds obtained were confirmed by physicochemical parameters, elemental analysis and IR spectral data.

3. The both products possessed a strong fungicidal activity against *Monilia fructigena*.

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