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SYNTHESIS AND FUNGICIDAL ACTIVITY OF SUBSTITUTED 2-(4-CHLOROPHENOXY)-1-(3-PYRIDYL)ETHAN-1-OLS

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A series of new substituted 2-(4-chlorophenoxy)-1-(3-pyridyl)ethan-1-ols has been obtained by the interaction of substituted 3-(oxiranyl)pyridines with 4-chlorophenol or sodium 4-chlorophenoxide for pharmacological and agrochemical screening. Fungicidal activity has been shown for the obtained compounds.

Keywords: substituted 2-chlorophenoxy-1-(3-pyridyl)ethan-1-ols, 1-(3-pyridyl)ethan-1-ols, 3-(2-oxiranyl)-pyridines, fungicides.

The fungicidal activity of 3-substituted pyridines was detected for the first time in the sixties of the last century (in α,α-disubstituted 3-pyridylcarbinols) [1]. Certain derivatives of 3-substituted pyridine disrupting the biosynthesis of ergosterol in fungi are used in agriculture [2]. Previously we synthesized a series of substituted 2-azolyl-1-(3-pyridyl)ethan-1-ols possessing fungicidal activity [3-5]. In the present work we have shown that the fungicidal activity of 1-(3-pyridyl)ethan-1-ols does not depend on the presence of an azole fragment in their structure.

The fungicidal activity of 2-phenoxy-1-(3-pyridyl)ethan-1-ols was detected comparatively recently [6]. Our investigations on the dependence of fungicidal activity of 1-(3-pyridyl)ethan-1-ols on their structure have led to the synthesis of 2-(4-chlorophenoxy)-1-(3-pyridyl)ethan-1-ols possessing high fungal toxicity.

For their synthesis we used the reaction of 2-substituted 3-(2-oxiranyl)pyridines with 4-chlorophenol or sodium 4-chlorophenoxide. Choice of just such a phenol for their synthesis is explained by the fact that the presence of a chlorine atom in position 4 of the phenyl nucleus is important for the display of fungal toxicity by compounds of this type [7].

We obtained 2,2-disubstituted oxiranes by the Corey–Chaykovsky reaction [8], by treating the appropriate ketones with trimethylsulfonium iodide [9, 10].

It was established experimentally that 2-(4-chlorophenoxy)-1-(3-pyridyl)ethan-1-ols **1-3** were obtained in good yield on heating the oxiranes to 60°C with 4-chlorophenol in DMF with NaOH as catalyst. However such a means of carrying out the reaction proved to be unsuitable for the synthesis of their vinylogs, the

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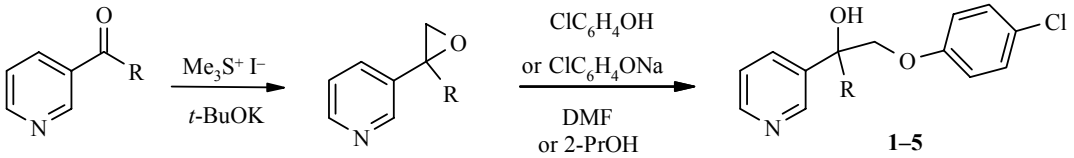
substituted 1-(4-chlorophenoxy)-4-phenyl-2-(3-pyridyl)but-3-en-2-ols. Due to the instability of the corresponding oxiranes the treated reaction mixtures contained many by-products, and isolation of the desired compounds was unsuccessful.



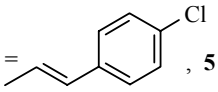
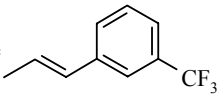
1 R = Ph, **2** R = *c*-Hex, **3 R =** *t*-BuCH$_2$, **4** R =  , **5** R = 

TABLE 1. Characteristics of Compounds **1-5**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
1	$C_{19}H_{16}ClNO_2$	69.94 / 70.05	5.03 / 4.95	4.33 / 4.30	Oil	72
2	$C_{19}H_{22}ClNO_2$	68.65 / 68.77	6.77 / 6.68	4.25 / 4.22	75-76	54
3	$C_{18}H_{22}ClNO_2$	67.52 / 67.60	6.98 / 6.93	4.41 / 4.38	145-146	60
4	$C_{21}H_{17}Cl_2NO_2$	65.17 / 65.30	4.52 / 4.44	3.70 / 3.63	92-93	22
5	$C_{22}H_{17}ClF_3NO_2$	62.83 / 62.94	4.16 / 4.08	3.37 / 3.34	Oil	13

TABLE 2. ^{1}H NMR Spectra of Compounds **1-5**

Compound	Chemical shifts, δ, ppm (*J*, Hz)
1	4.52-4.66 (2H, AB-system, *J* = 9.6, CH_2O); 6.3 (1H, s, OH); 7.0-7.5 (4H, A_2B_2-system, *J* = 8.8, C_6H_4Cl); 7.33 (6H, m, C_2H_5, H-4 Py); 7.86 (1H, d, *J* = 8.4, H-5 Py); 8.42 (1H, d, *J* = 4.2, H-6 Py); 8.68 (1H, s, H-2 Py)
2	0.8-1.9 (11H, m, CH cyclohexyl); 4.12-4.35 (2H, AB-system, *J* = 8.4, CH_2O); 5.3 (1H, s, OH); 6.93-7.28 (4H, A_2B_2-system, *J* = 9.5, C_6H_4Cl); 7.33 (1H, dd, J_1 = 7.6, J_2 = 3.8, H-5 Py); 7.83 (1H, d, *J* = 7.6, H-4 Py);
3	0.75 (9H, s, CH_3); 1.95-2.00 (2H, AB-system, *J* = 14.8, CH_2 aliph.); 4.02 (2H, AB-system, *J* = 8.1, CH_2O); 5.3 (1H, br. s, OH); 6.90-7.28 (4H, A_2B_2-system, *J* = 9.2, C_6H_4Cl); 7.32 (1H, dd, J_1 = 8.4, J_2 = 4.2, H-5 Py); 7.92 (1H, d, *J* = 8.4, H-4 Py); 8.41 (1H, d, *J* = 4.2, H-6 Py); 8.78 (1H, s, H-2 Py)
4	4.25 (2H, AB-system, *J* = 9.6, CH_2); 6.12 (1H, s, OH); 6.74-6.82 (2H, AB-system, *J* = 14.4, CH methine); 6.95-7.20 (4H, A_2B_2-system, *J* = 8.0, C_6H_4Cl); 7.06 (1H, m, 5-H Py); 7.38-7.50 (4H, A_2B_2-system, *J* = 8.0, C_6H_4Cl); 7.95 (1H, d, *J* = 4.2, 4-H Py); 8.45 (1H, d, *J* = 4.2, 6-H Py); 8.80 (1H, s, H-2 Py)
5	4.40 (2H, AB-system, *J* = 10.0, CH_2); 6.15 (1H, s, OH); 6.78-6.89 (2H, AB-system, *J* = 17, CH methine); 7.16 (1H, dd, J_1 = 8.4, J_2 = 4.2, H-5 Py); 7.40-7.54 (4H, A_2B_2-system, *J* = 8.0, C_6H_4Cl); 7.59-7.82 (4H, m, H Ph); 7.92 (1H, d, *J* = 4.2, H-4 Py); 8.48 (1H, d, *J* = 4.2, H-6 Py); 8.77 (1H, s, H-2 Py)

TABLE 3. Suppression of Radial Growth of Fungal Mycelia *in vitro* by Compounds **1-5** at c = 30 mg/l in Comparison with Untreated Control

Compound	Drop in radial growth of fungal mycelium, %				
	Venturia inaequalis	*Fusarium moniliforme*	*Fusarium oxysporum*	*Helmintho-sporium sativum*	*Sclerotinia sclerotiorum*
1	99-100	90-98	99-100	90-98	0-49
2	99-100	90-98	99-100	99-100	0-49
3	70-89	90-98	70-89	99-100	0-49
4	50-69	50-69	0-49	50-69	50-69
5	0-49	0-49	70-89	50-69	0-49
Standard*	50-69	90-98	70-89	50-69	50-69

*Standard was the commercial fungicide *triadimefon* (1-(4-chlorophenoxy)-3,3-dimethyl-1-(1H-1,2,4-triazol-1-yl)butan-2-one), containing 98% active substance ("Shchelkovo AgroKhim").

We obtained 1-(4-chlorophenoxy)-4-(4-chlorophenyl)-2-(3-pyridyl)but-3-en-2-ol (**4**) and 1-(4-chlorophenoxy)-2-(3-pyridyl)-4-[3-(trifluoromethyl)phenyl]but-3-en-2-ol (**5**), by treating oxiranes, obtained respectively from 3-(4-chlorophenyl)-1-(3-pyridyl)prop-2-en-1-one and 1-(3-pyridyl)-3-[3-(trifluoromethyl)phenyl]-prop-2-en-1-one, with sodium 4-chlorophenoxide by heating (50-60°C) for 6 h in 2-propanol. The oxiranes were not isolated in a pure form, but were put directly into the next reaction due to their instability. On using DMF as solvent in these reactions the isolation of compounds was markedly complicated and products separated as viscous oils on diluting the reaction mixture with water. Yields of alkyl- and aryl-substituted derivatives **1-3** proved to be significantly greater than the yields of compounds **4** and **5** containing a styryl group (Table 1).

In every case no isomeric products of addition of phenol to oxirane, the 2-(4-chlorophenoxy) 2-(3-pyridyl)ethan-1-ols, were detected.

The obtained compounds were tested *in vitro* for fungicidal activity against five phytopathogenic fungi, *viz. Venturia inaequalis* Wint, *Fusarium moniliforme* Sheldon, *Fusarium oxysporum* Schlecht, *Helminthosporium sativum* Pammel, King et Bakke, and *Sclerotinia sclerotiorum* (Lib.) de Bary, according to the procedure of the All-Russian Research Institute for Chemical Plant Protection Agents (Moscow) [11] (Table 3). The strains of fungi were obtained from the Institute mentioned. All compounds displayed high fungicidal activity.

EXPERIMENTAL

The ^{1}H NMR spectra of compounds were obtained on a Bruker AC-400 (400 MHz) instrument in DMSO-d_6, internal standard was TMS.

The synthesis and properties of 3-(2-phenyl-2-oxiranyl)pyridine [9], 3-(2-cyclohexyl-2-oxiranyl)-pyridine, 3-[2-(2,2-dimethylpropyl)-2-oxiranyl]pyridine [3], 3-(4-chlorophenyl)-1-(3-pyridyl)prop-2-en-1-one, and 1-(3-pyridyl)-3-[3-(trifluoromethyl)phenyl]prop-2-en-1-one [10] have been described previously.

2-(4-Chlorophenoxy)-1-phenyl-1-(3-pyridyl)ethan-1-ol (1). Sodium hydroxide (0.12 g) and water (0.05 ml) were added to a solution of 3-(2-oxiranyl-2-phenyl)pyridine (0.346 g, 1.76 mmol) and 4-chlorophenol (0.44 g, 3.4 mmol) in DMF (3 ml) and the mixture was heated at 120°C for 4 h. The reaction mixture was then poured into water (30 ml) with stirring, extracted with chloroform (3×15 ml), the extract was washed three times with 10% NaOH solution, with saturated NaCl solution, dried over $MgSO_4$, and evaporated in vacuum. Compound **1** (0.41 g, 72%) was obtained as an oil.

2-(4-Chlorophenoxy)-1-cyclohexyl-1-(3-pyridyl)ethan-1-ol (2) and 1-(4-Chlorophenoxy)-4,4-dimethyl-2-(3-pyridyl)pentan-2-ol (3) were obtained analogously.

1-(4-Chlorophenoxy)-4-(4-chlorophenyl)-2-(3-pyridyl)but-3-en-2-ol (4). A solution of potassium *t*-butylate (0.7 g, 6.27 mmol) in DMSO (3 ml) was added dropwise in an inert atmosphere during 30 min to a solution of 3-(4-chlorophenyl)-1-(3-pyridyl)prop-2-en-1-one (1.22 g, 5 mmol) and trimethylsulfonium iodide (1.43 g, 7 mmol) in DMSO (3.5 ml) cooling with an ice–salt mixture. The reaction mixture was then stirred for 15 min and diluted dropwise with water (30 ml), extracted with ether (4×50 ml), the extract was washed with saturated NaCl solution, and dried over $MgSO_4$. A solution of 4-chlorophenol (0.77 g, 6 mmol) and sodium isopropylate (0.23 g, 3 mmol) in 2-propanol (20 ml) was added to the obtained solution, and the ether distilled in vacuum. The resulting solution was heated for 6 h at 50-60°C, cooled, poured into water (25 ml), and left overnight. The separated oil was dissolved in chloroform, and the solution washed with 10% NaOH solution (4×14 ml). The organic phase was dried over $MgSO_4$, and the solvent distilled. The reaction product was purified by column chromatography on silica gel (eluent chloroform–ethanol, 20:1), and compound **4** (0.42 g, 22%) was obtained.

1-(4-Chlorophenoxy)-4-[3-(trifluoromethyl)phenyl]-2-(3-pyridyl)but-3-en-2-ol (5) was obtained analogously.

Yields and melting points of compounds **1-5** are given in Table 1, ^{1}H NMR spectra in Table 2, and results of biological testing in Table 3.

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