Synthesis, structure, and growth-promoting activity of 1-alkyl-4-(3-naphthyloxyprop-1-ynyl)piperidin-4-ols*

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Alkylation of 1- and 2-naphthols with propargyl bromide in acetone in the presence of potassium carbonate led to prop-2-ynyloxynaphthalenes, which upon reaction with 1-alkyl-piperidin-4-ones under the Favorsky conditions afforded the corresponding tertiary alcohols. 1-Methyl-4-[3-(2-naphthyloxy)prop-1-ynyl]piperidin-4-ol hydrochloride was found to possess a high growth-promoting activity in the concentration of 0.001% upon the pre-sowing treatment of beetroot seeds and potatoes and increase their productivity by ~20%.

Key words: alkylation, alkynylation, naphthyloxypropargylic piperidols, growth-promoting activity.

Continuing interest of synthetic chemists to the propargyl-type compounds $HC=C-CH_2-X-(X=O, N, S, Se, etc.)$ is due to their high reactivity, unique synthetic opportunities, and a wide scope of application of their derivatives.¹⁻⁴ In the last years, propargylic compounds were frequently used to prepare various heterocycles using Sonogashira reaction and Claisen rearrangement.⁵ Synthesis of triazoles using the "click chemistry" concept is also under rapid development.⁶ A propargyl group is believed to be a key substituent in the synthesis of various agrochemicals.⁷

In the present work, we report results on the synthesis and structure establishment of new naphthyloxypropargylic piperidols (Scheme 1) and study their effect on the growth and development of beetroots and potatoes.

The known propargyloxynaphthalenes 1 and 2 were obtained as described earlier.¹⁻⁴ Their Favorsky reaction with 1-methyl- and 1-propylpiperidin-4-ones in diethyl ether in the presence of potassium hydroxide led to 1-alkyl-4-(3-naphthyloxyprop-1-ynyl)piperidin-4-ols 3-6. The structure of the compounds synthesized was confirmed by IR and ¹H and ¹³C NMR spectroscopy.

¹H NMR spectra of compounds **3–6** contain three regions for the proton signals. The protons of the methyl and propyl substituents, as well as CH_2 protons of the piperidine rings, resonate in the region up to δ 2.5. The

Scheme 1



1-naphthyl (1, 3, 5); 2-naphthyl (2, 4, 6) R = Me (3, 4), Pr (5, 6)

Reagents and conditions: *i*. BrCH₂C=CH, K₂CO₃, acetone, reflux; *ii*. 1-alkyl-4-piperidone, KOH, Et₂O, 21 °C.

signals for the oxymethylene and hydroxyl (δ 5.7) protons are observed around δ 5.0. The protons of the naphthalene substituent with a total intensity of seven protons resonate in the low field. The signals with low intensities characteristic of quaternary carbon atoms are present in the ¹³C NMR spectra: the atoms of the acetylene fragment resonate at δ 79 and 92, atom C(4) of the piperidine fragment at δ 65, the naphthalene atoms C_{ipso} at δ 155. In general, the NMR spectra completely agree with the structure of the compounds synthesized in both the intensities

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of the corresponding protons in the ¹H NMR spectra and in the number of signals in the ¹³C NMR spectra, which is equal to the number of carbon atoms.

In continuation of the search of new plant protection chemicals, compounds 3-6 were converted to water-soluble *N*-hydrochlorides, which were studied for the influence on growth and development of beetroots and potatoes.

Under laboratory conditions, the effect of piperidinol hydrochlorides $3 \cdot \text{HCl}$, $4 \cdot \text{HCl}$, $5 \cdot \text{HCl}$, and $6 \cdot \text{HCl}$ on the sprouting energy and germinating capacity of potato and beetroot was studied. The concentration of the agents varied from 1.0 to 0.00001%. The optimal concentrations of the active compounds found in the laboratory experiments were further used under the field conditions to study their effect on the growth, development, and productivity of beetroots and potatoes. Four plots were used for each culture in the field trials, the account plot area for beetroots was 10 m², for potatoes 25 m². The most indicative data are given in Tables 1 and 2.

The results of the field trials show that the treatment of beetroot seeds with compounds $3 \cdot \text{HCl}$ and $4 \cdot \text{HCl}$ in the optimal doses accelerated appearance of shoots by 2–4 days. The plants grown from the seeds treated with agents in the concentrations of 0.001 and 0.0001% grew and developed better, that eventually led to the increase in the beetroot harvest. The highest increase in harvest as compared to the control (5.1 t ha⁻¹ or 22.2%) was obtained by the seed soaking in the solutions of compound $4 \cdot \text{HCl}$ with the concentration of 0.001%. Compound $4 \cdot \text{HCl}$ at the optimal doses increased productivity of potatoes by more than 20%, whereas the treatment with the reference compound (succinic acid) gave an 11% increase in productivity.

Analysis of the data on biological activity shows that compound **4** · HCl is the most active among those studied.

Table 1. Effect of the compounds synthesized on the productivity of beetroot^a

Agent ^b		Beetro	Addition				
		accour	nt plot		on average	to control	
	Ι	II	III	IV		/t ha ⁻¹	(%)
Control	22.7	23.0	23.2	23.1	23.0	_	_
3 ⋅ HCl	26.0	27.0	26.5	26.5	26.5	3.5	15.2
4 • HCl	27.9	28.2	28.1	28.2	28.1	5.1	22.2
5 · HCl	25.0	25.5	25.2	25.1	25.2	2.2	9.6
6 • HCl	25.0	25.5	25.1	26.0	25.4	2.4	10.4
Hetero- auxin	25.5	25.8	26.0	25.9	25.8	2.8	12.2

^{*a*} Experimental error P = 4.0%, the least mean difference HCP_{0.5} = 0.8 t ha⁻¹.

^{*b*} Control was water, the concentration of hydrochlorides 3-6 was 0.001%, the heteroauxin (reference) concentration was 0.06%.

Table 2. Effect of the compounds synthesized on the productivity of $potato^a$

Agent ^b		Pota	Addition				
		accou	nt plot		on average	to control	
						∕t ha ^{−1}	(%)
	I	П	III	IV			
Control	13.8	14.1	14.0	14.1	14.0	_	_
3 • HCl	15.5	15.8	16.2	16.5	16.0	2.0	14.3
4 • HCl	16.6	16.9	17.2	17.3	17.0	3.0	21.4
5 · HCl	15.0	15.5	16.0	15.1	15.4	1.4	10.0
6 • HCl	14.9	15.5	15.2	15.6	15.3	1.3	9.3
Succinic	15.5	15.7	15.2	16.0	15.6	1.6	11.4
acid							

^{*a*} Experimental error P = 3.4%, the least mean difference HCP_{0.5} = 0.7 t ha⁻¹.

^{*b*} Control was water, the concentration of hydrochlorides 3-6 was 0.001%, the concentration of succinic acid (reference) was 0.02%.

Experimental

IR spectra were recorded on a JES-25 Fourier-spectrometer in KBr pellets. ¹H and ¹³C NMR spectra were recorded on a Bruker DPX-400 spectrometer in DMSO-d₆ and CDCl₃ at room temperature, using hexamethyldisiloxane (δ 0.05) as an internal standard. High resolution mass spectra were obtained on a Bruker FTMS Solarix 7.0T instrument, using electrospray ionization. Melting points of compounds were determined on Boetius heating stage. Reaction progress and purity of compounds were monitored by TLC on Silufol 60 UV 254 plates.

1-Methyl-4-[3-(1-naphthyloxy)prop-1-ynyl]piperidin-4-ol (3). Potassium hydroxide (2.7 g, 48 mmol) was added to a solution of 1-(prop-2-ynyloxy)naphthalene (1) (2.9 g, 16 mmol) in diethyl ether (100 mL), and the mixture was stirred for 30 min at room temperature. Then, a solution of 1-methylpiperidin-4-one (1.8 g, 16 mmol) in diethyl ether (20 mL) was added slowly dropwise. After the reaction reached completion, the mixture was diluted with water (50 mL), extracted with diethyl ether (5×25 mL), the combined organic extracts were dried with K₂CO₃. After evaporation of the solvent, the residue was recrystallized from a mixture of hexane-benzene (10 mL, 4:1) to obtain product 3 (4.1 g, 88%) as a white powder with m.p. 105–107 °C. IR (KBr), v/cm⁻¹: 3477, 3053, 2944, 2796, 1596, 1581. ¹H NMR (DMSO-d₆), δ: 1.67 (m, 2 H, H(3')); 1.76 (m, 2 H, H(5[']); 2.08 (s, 3 H, NCH₃); 2.13 (m, 2 H, H(2['])); 2.47 (m, 2 H, H(6')), 5.08 (s, 2 H, OCH₂); 5.68 (s, 1 H, OH); 7.13 (d, 1 H, H(2), J = 7.6 Hz; 7.48 (t, 1 H, H(3), J = 8.0 Hz, J = 2.7 Hz); 7.53-7.60 (m, 3 H, H(4), H(6), H(7)); 7.93 (d, 1 H, H(5), J = 8.44 Hz; 8.20 (d, 1 H, H(8) J = 7.6 Hz). ¹³C NMR (DMSO-d₆), δ: 39.0 (C(3'), C(5')); 45.8 (NCH₃); 52.0 (C(2'), with (6')); 56.6 (OCH₂); 65.0 (C(4')); 79.3 (≡C); 91.9 (C≡); 106.8 (C(2)); 121.0 (C(4)); 121.7. (C(8)); 125.4 (C(9)); 125.8 (C(7)); 126.4 (C(3)); 126.9 (C(6)); 127.9 (C(5)); 134.4 (C(10)); 153.0 (C(1)). MS, m/z: 296.16459 [M]⁺. C₁₉H₂₂NO₂. Calculated: M = 296.16451.

Compounds **4**–**6** were obtained similarly.

1-Methyl-4-[3-(2-naphthyloxy)prop-1-ynyl]piperidin-4-ol(4). The yield was 78.4%, m.p. 143–145 °C (from hexane). IR (KBr), v/cm⁻¹: 3438, 3047, 2939, 2806, 1629, 1560. ¹H NMR (DMSO-d₆), δ : 1.65 (m, 2 H C(3')); 1.75 (m, 2 H, H(5')); 2.00 (s, 3 H, NCH₃); 2.12 (m, 2 H, H(2')); 2.45 (m, 2 H, H(6')); 4.99 (s, 2 H, OCH₂); 5.69 (s, 1 H, OH); 7.26 (dd, 2 H, H(3), $J_1 = 8.9$ Hz, $J_2 = 2.3$ Hz); 7.41 (s, 1 H, H(1)); 7.44 (m, 1 H, H(6)); 7.52 (t, 1 H, H(7), J = 7.5 Hz); 7.86 (d, 1 H, H(8), J = 8.2 Hz); 7.90 (d, 1 H, H(4), J = 7.8 Hz); 7.91 (d, 1 H, H(5), J = 9.1 Hz). ¹³C NMR (CDCl₃, δ : 39.0 (C(3'), C(5')); 45.6 (NCH₃); 51.9 (C(2'), C(6')); 56.1 (OCH₂); 65.0 (C(4')); 79.1 (=C); 91.9 (C=); 108.3 (C(1)); 119.0 (C(3)); 124.3 (C(6)); 126.9 (C(7)); 127.2 (C(8)); 127.9 (C(5)); 129.1 (C(10)); 129.8 (C(4)); 134.4 (C(9)); 155.4 (C(2)). MS, *m/z*: 296.16588 [M]⁺. C₁₉H₂₂NO₂. Calculated: M = 296.16451.

4-[3-(1-Naphthyloxy)prop-1-ynyl]-1-propylpiperidin-4-ol (5). The yield was 85%, m.p. 99-101 °C (from hexane). IR (KBr), v/cm⁻¹: 3436, 3056, 2939, 2827, 1598, 1580. ¹H NMR $(DMSO-d_6)$, δ : 0.82 (t, 3 H, CH₃, J = 7.4 Hz); 1.31–1.40 (m, 2 H, NCH₂CH₂CH₃); 1.65 (m, 2 H, H(3')); 1.76 (m, 2 H, H(5')); $2.10 (t, 2 H, NCH_2CH_2CH_3, J = 7.8 Hz)); 2.15 (m, 2 H, H(2'));$ 2.51 (m, 2 H, H(6')); 5.08 (s, 2 H, OCH₂); 5.67 (s, 1 H, OH); 7.12 (d, 1 H, H(2), J = 7.6 Hz); 7.47 (t, 1 H, H(3), J = 8.0 Hz); 7.53-7.60 (m, 3 H, H(4), H(6), H(7)); 7.92 (d, 1 H, H(5), J = 7.0 Hz); 8.19 (d, 1 H, H(8), J = 7.0 Hz). ¹³C NMR (CDCl₃), δ: 12.2 (CH₃); 19.8 (NCH₂<u>C</u>H₂CH₃); 39.1 (C(5'), C(3')); 49.9 (C(2'), C(6')); 56.6 (OCH₂); 59.9 (N<u>C</u>H₂CH₂CH₃); 65.6 C(4')); 79.3 (=C); 91.9 (C=); 106.9 (C(2)); 121.0 (C(4)); 121.8 (C(8)); 125.5 (C(9)); 125.8 (C(7)); 126.3 (C(3)); 126.9 (C(6)); 127.9 (C(5)); 134.5 (C(10)); 153.0 (C(1)). MS, *m/z*: 324.19581 [M]⁺. $C_{21}H_{26}NO_2$. Calculated: M = 324.19581.

4-[3-(2-Naphthyloxy)prop-1-ynyl]-1-propylpiperidin-4-ol (6). The yield was 75%, m.p. 78–80 °C (from hexane). IR (KBr), v/cm^{-1} : 3431, 3056, 2956, 2819, 1629, 1560. ¹H NMR (DMSO-d₆), δ: 0.76 (t, 3 H, CH₃, J = 7.3 Hz); 1.20–1.33 (m, 2 H, NCH₂CH₂CH₃); 1.62 (m, 2 H, H(3')); 1.75 (m, 2 H, H(5')); 1.97 (t, 2 H, NC \underline{H}_2 CH $_2$ CH $_3$, J = 7.5 Hz); 2.07 (m, 2 H, H(2)); 2.49 (m, 2 H, H(6')); 4.99 (s, 2 H, OCH₂); 5.67 (s, 1 H, OH); 7.24 (dd, 1 H, H(3), $J_1 = 9.0$ Hz, $J_2 = 2.4$ Hz); 7.41 (s, 1 H, H(1)); 7.43 (m, 1 H, H(6)); 7.51 (t, 1 H, H(7), J = 7.1 Hz); 7.84 (d, 1 H, H(8), J = 8.2 Hz); 7.88 (d, 1 H, H(4), J = 8.1 Hz); 7.88(d, 1 H, H(5), J = 9.1 Hz). ¹³C NMR (DMSO-d₆), δ : 12.1 (CH₃); 19.8 (NCH₂CH₂CH₃); 39.1 (C(3[']), C(5['])); 49.9 (C(2[']), C(6['])); 56.1 (OCH₂); 59.8 (NCH₂CH₂CH₃); 65.7 (C(4[′])); 79.3 (≡C); 91.9 (C=); 108.4 (C(1)); 119.0 (C(3)); 124.3 (C(6)); 126.8 (C(7));127.2 (C(8)); 127.9 (C(5)); 129.1 (C(10)); 129.8 (C(4)); 134.4 (C(9)); 155.3 (C(2)). MS, m/z: 324.19579 $[M]^+$. $C_{21}H_{26}NO_2$. Calculated: M = 324.19581.

1-Methyl-4-[3-(1-naphthyloxy)prop-1-ynyl]piperidin-4-ol hydrochloride (**3**•HCl). Diethyl ether saturated with hydrogen chloride was added dropwise to a solution of compound **3** (2.9 g, 0.01 mol) in diethyl ether (250 mL) to pH 2. The mixture was stirred on a magnetic stirrer for 25–30 min. A precipitate was filtered off and washed with diethyl ether (25 mL) to obtain hydrochloride **3**•HCl (3.1 g, 94%) as a white powder, m.p. 196–198 °C. Similarly were obtained **4**•HCl (73%, m.p. 168–170 °C, **5**•HCl (85%, m.p. 163–165 °C) and **6**•HCl (78%, m.p. 187–189 °C).

Biological trials. Beetroot seeds were soaked in freshly prepared solutions. Beetroot seeds soaked in water were used as a control, a 0.06% aqueous heteroauxin was used as a reference. The seeds were sprouted in Petri dishes in a thermostat, repeating trials 6 times. Germinated seeds were counted two times: first, five days after treatment to determine the sprouting energy, and second, ten days after to determine the germinating capacity of seeds.

Potato tubers were used to study the effect of the agents on the buds awakening. A 0.02% aq. succinic acid was used as a reference in this case. Potato tubers were sprouted in wet sawdust, 20 tubers were used in each trial, repeating each trial four times.

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