Synthesis of new derivatives of 5,6,7,8-tetrahydro-1,6-naphthyridines and their pharmacological properties

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1,5-Dicarbonyl derivatives of piperidine and tropane were studied in the heterocyclization with hydroxylamine hydrochloride. All the 5,6,7,8-tetrahydro-1,6-naphthyridines obtained exhibit a pronounced analgesic effect.

Key words: Michael reaction, *N*-benzylpiperidin-4-one, 8-methyl-2-(3-oxo-1,3-diphenylpropyl)-8-azabicyclo[3.2.1]octan-3-one, 1-methyl-3-(3-oxo-1,3-diphenylpropyl)piperidin-4-one, heterocyclization of 1,5-diketones, 5,6,7,8-tetrahydro-1,6-naphthyridines, opiate activity, agonists.

Substituted and polyfused piperidine derivatives exhibit ganglioblocking, anticholinesterase, neuroleptic, antihypertensive, and analgesic activities, depending on the type of substituents and their positions in the ring.[1—7] Fused pyrazolo[4,3-*c*]piperidines have a pronounced analgesic effect.[8] However, the pharmacological properties of 5,6,7,8-tetrahydro-1,6-naphthyridine systems with aromatic radicals in the pyridine ring have not been documented.

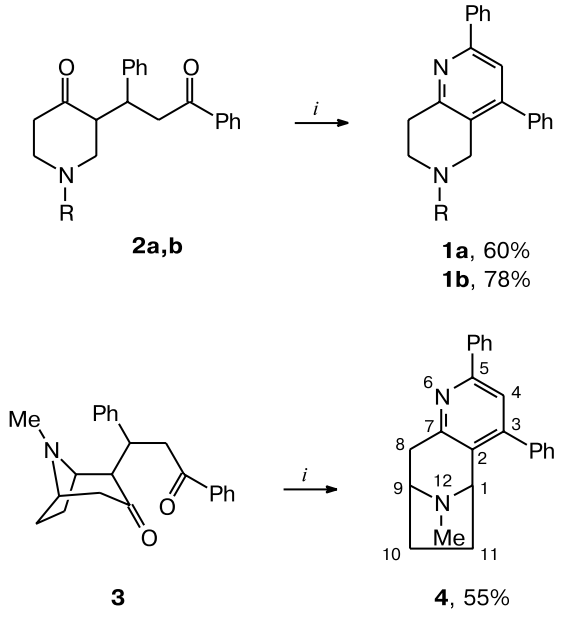
The synthesis of 3-(3-oxo-1,3-diphenylpropyl)piperidin-4-ones, their heterocyclization into 5,6,7,8-tetrahydro-1,6-naphthyridines, and the study of the pharmacological properties of the products obtained were of our interest.

6-Methyl-2,4-diphenyl-5,6,7,8-tetrahydro-1,6-naphthyridine (**1a**) was synthesized earlier[9] by the reaction of 4-amino-1-methyl-1,2,5,6-tetrahydropyridine-3-carbonitrile with chalcone. However, this synthesis is labor-consuming and use of chromatographic methods complicates isolation of both reaction intermediates and products.

For this reason, taking into account consideration that 1,5-dicarbonyl compounds serve as convenient precursors in the preparation of the dihydropyridine and pyridine systems,[10] we have recently[11] synthesized a number of 1,5-dicarbonyl derivatives of *N*-substituted piperidin-4-ones (**2a,b**) and 8-methyl-8-azabicyclo[3.2.1]octan-3-one (**3**).

We found that diketones **2a,b** and **3** under the action of $NH_2OH \cdot HCl$ in ethanol undergo heterocyclization into 5,6,7,8-tetrahydro-1,6-naphthyridine systems **1a,b** and **4**, respectively (Scheme 1). The reactions were carried out in ethanol at 70 °C.

Scheme 1



i. $NH_2OH \cdot HCl$, EtOH, 70 °C.
R = Me (**a**), CH_2Ph (**b**)

Cyclization of 1,5-dicarbonyl compounds proceeds smoothly without addition of catalytic amounts of *p*-toluenesulfonic acid.

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The 5,6,7,8-tetrahydro-1,6-naphthyridine structure of products **1a,b** was confirmed by ^{1}H NMR data. Their ^{1}H NMR spectra contain singlets at δ 3.50 (**1a**) and 3.65 (**1b**) for the protons of the piperidine ring at the C(5) atom and triplets at δ 2.85 and 3.20 (**1a**) and δ 2.80 and 3.15 (**1b**) for the protons at the C(7) and C(8) atoms, respectively. The aromatic protons appear at δ 7.20—7.50 and 7.90—8.0. The spectrum of compound **4** is complicated by the presence of multiplet signals for the tropane ring (see Experimental).

It was found that the reactions of 1,5-dicarbonyl compounds **2** and **3** with such nucleophiles as hydrazine hydrate, *n*-butylamine, ethanolamine, and ethylenediamine in ethanol or benzene in the presence of catalytic amounts of *p*-toluenesulfonic acid or CH_3COOH yield no dihydropyridine system. The resulting mixture of products (TLC data) was not separated by recrystallization.

Compounds **1**—**4** were tested for functional activity of opiate receptors with a model of separate organs (seminal duct MVD). Contractions of MVD were detected with a mechanotron and converted electrical signals were recorded on a recorder type. Compounds **1**—**4** were found to exhibit opiate activity and agonistic properties. Among the compounds studied, compounds **1b** and **2b** have the most pronounced pharmacological properties and will be tested additionally.

Experimental

The course of the reaction was monitored and the purity of the products was checked by TLC (Silufol UV-254) and GLC on a Tsvet-152 chromatograph (L column 0.7 m × 3 mm, liquid phase 5% SE-30 on Chromaton N-AW (0.16—0.20 mm), nitrogen as a carrier gas, programmed temperature rise from 75 to 325 °C at a rate of 22 deg min^{-1}). ^{1}H NMR spectra were recorded on a Bruker A-250 instrument (250 MHz) in $CDCl_3$. Chemical shifts are given in ppm on the δ scale with reference to HMDS as the internal standard. Melting points were determined on a Boetius instrument of the Kofler system.

All solvents were purified according to common standard procedures.[12]

6-Methyl-2,4-diphenyl-5,6,7,8-tetrahydro-1,6-naphthyridine (1a). Hydroxylamine hydrochloride (0.25 g, 3.5 mmol) was added to a solution of 1-methyl-3-(3-oxo-1,3-diphenylpropyl)piperidin-4-one (**2a**) (0.3 g, 1 mmol) in 10 mL of ethanol. The reaction mixture was heated at 70 °C for 12 h. Then the solvent was evaporated by half and 10% NaOH (15 mL) was added. The crystals that formed were filtered off, repeatedly washed with water, and recrystallized from Pr^{i}OH to give compound **1a** (0.18 g, 60%), m.p. 79—82 °C. ^{1}H NMR ($CDCl_3$), δ: 2.40 (s, 3 H, N—CH_3); 2.85 (t, 2 H, H(8), J = 7.8 Hz); 3.25 (t, 2 H, H(7), J = 7.8 Hz); 3.50 (s, 2 H, H(5)); 7.20—7.45 (m, 9 H, Ar—H+Py—H); 7.95—8.00 (m, 2 H, Ar—H). Found (%): C, 84.13; H, 6.82; N, 9.61. $C_{21}H_{20}N_2$. Calculated (%): C, 83.96; H, 6.71; N, 9.33.

6-Benzyl-2,4-diphenyl-5,6,7,8-tetrahydro-1,6-naphthyridine (1b). Hydroxylamine hydrochloride (0.25 g, 3.5 mmol) was added to a solution of 1-benzyl-3-(3-oxo-1,3-diphenylpropyl)piperidin-4-one (**2b**) (0.3 g, 7.5 mmol) in 10 mL of ethanol. The reaction mixture was heated at 70 °C for 8 h and treated as described above to give compound **1b** (0.22 g, 78.5%), m.p. 143—145 °C. ^{1}H NMR ($CDCl_3$), δ: 2.80 (t, 2 H, H(8), J = 8.0 Hz); 3.15 (t, 2 H, H(7), J = 8.0 Hz); 3.55 (s, 2 H, N—CH_2—Ph); 3.65 (s, 2 H, H(5)); 7.20—7.45 (m, 13 H, Ar—H+Py—H); 7.90—8.00 (m, 2 H, Ar—H). Found (%): C, 86.45; H, 6.81; N, 7.71. $C_{27}H_{24}N_2$. Calculated (%): C, 86.13; H, 6.43; N, 7.44.

12-Methyl-3,5-diphenyl-6,12-diazatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene (4). Hydroxylamine hydrochloride (0.5 g, 7 mmol) was added to a solution of 8-methyl-2-(3-oxo-1,3-diphenylpropyl)-8-azabicyclo[3.2.1]octan-3-one (**3**) (0.5 g, 1.4 mmol) in 7 mL of ethanol. The reaction mixture was heated at 70 °C for 8 h. Then the solvent was evaporated by two thirds and 10% KOH (15 mL) was added. The crystals that formed were filtered off, repeatedly washed with water, and recrystallized from Pr^{i}OH—water (1 : 0.25) to give compound **4** (0.25 g, 55%), m.p. 95—98°C. ^{1}H NMR ($CDCl_3$), δ: overlapping multiplets for the protons of the tropane ring appear at 1.70—2.05 (m, 4 H, trop.ring—H(10),H(11)); 2.37 (s, 3 H, N—CH_3); 2.40 (br.d, 1 H, H(8) J = 12.6 Hz); 2.80 (br.d, 1 H, H(8) J = 12.6 Hz); 3.10—3.70 (m, 2 H, H(1), H(9)); 7.20—7.50 (m, 9 H, Ar—H+Py—H); 7.95—8.00 (m, 2 H, Ar—H). Found (%): C, 84.98; H, 6.92; N, 8.71. $C_{23}H_{22}N_2$. Calculated (%): C, 84.63; H, 6.79; N, 8.58.

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