Chemistry of Natural Compounds, Vol. 47, No. 5, November, 2011 [Russian original No. 5, September-October, 2011]

SYNTHESIS OF α-CHLOROPYRIDINE DERIVATIVES OF γ-AMINOBUTYRIC ACID

N. V. Kovganko,* S. N. Sokolov, and Yu. G. Chernov

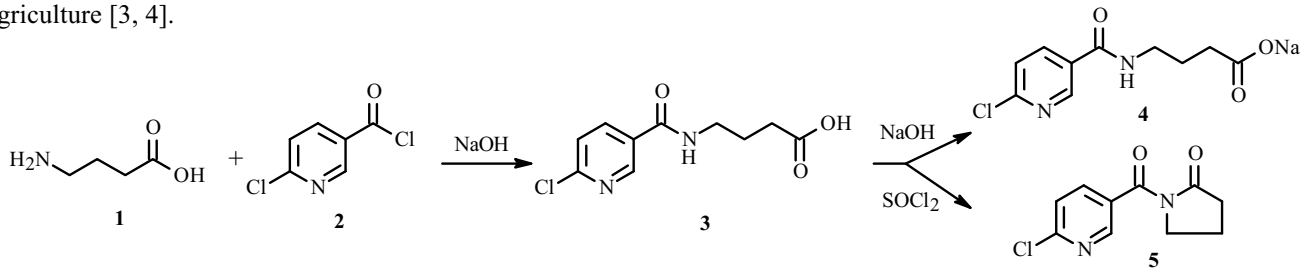
UDC 547.466.3

The sodium salt of N-*(6-chloronicotinoyl)-γ-aminobutyric acid, a structural analog of the known nootropic and vasidilating drug picamilon, was synthesized via Schotten–Baumann acylation of γ-aminobutyric acid with 6-chloronicotinoyl chloride and subsequent neutralization of the* N-*(6-chloronicotinoyl)- γ-aminobutyric acid that was obtained in >60% yield.*

Keywords: γ-aminobutyric acid, picamilon, analogs, synthesis.

γ-Aminobutyric acid (**1**) is a natural compound that is well known as a nervous system mediator. The unique physiological properties of **1** and several of its derivatives enable them to be used in medicine as nootropic drugs [1]. Our attention was drawn to drugs that were derivatives of γ-aminobutyric acid such as picamilon, the chemical structure of which is the sodium salt of *N*-nicotinoyl-γ-aminobutyric acid. Because the structure of picamilon includes portions of γ-aminobutyric acid and nicotinic acid, this drug in a pharmacological sense combines the properties of these two natural bioregulators.

We synthesized a close structural analog of picamilon. Its molecule includes γ-aminobutyric acid and a portion of not nicotinic but 6-chloronicotinic acid. We assumed that such substitution could produce compounds with unique biological activity profiles because the chloropyridine moiety is largely responsible for the occurrence of biological activity in neonicotinoid compounds, in particular, the natural analgesic epibatidine [2] and the insecticide imidacloprid, which is widely used in agriculture [3, 4].



According to our plan, Schcotten–Baumann acylation of **1** by 6-chloronicotinoylchloride (**2**) in the presence of NaOH synthesized in >60% yield *N*-(6-chloronicotinoyl)- γ-aminobutyric acid (**3**). The structure of **3** was proved using spectral data. Subsequent neutralization of **3** by methanolic NaOH produced in quantitative yield the sodium salt **4**.

Compound **3** could also be used as a convenient intermediate in the synthesis of other α-chloropyridine-containing derivatives of γ-aminobutyric acid. Thus, reaction of **3** with thionylchloride in dioxane synthesized in about 85% yield pyrrolidone **5**, the formation of which was due to facile intramolecular cyclization to a five-membered γ-lactam ring of the acid chloride that was initially produced by the action of thionylchloride on **3**.

EXPERIMENTAL

IR spectra were recorded on a Bomem-Michelson 100 FTIR spectrometer in the range 700–3600 cm^{-1}. PMR and ^{13}C NMR spectra were taken on a Bruker Avance 500 NMR spectrometer (operating frequency 500.13 MHz for ^{1}H and

Institute of Bioorganic Chemistry, National Academy of Sciences of Belarus, 220141, Belarus, Minsk, Ul. Akad. Kuprevicha, 5/2, e-mail: kovganko@iboch.bas-net.by. Translated from Khimiya Prirodnykh Soedinenii, No. 5, September–October, 2011, pp. 686–687. Original article submitted February 24, 2011.

125.75 MHz for ^{13}C). Chemical shifts are given relative to TMS as an internal standard. Mass spectra were measured on an Accela HPLC system with an LCQ-Fleet mass detector (three-dimensional ion trap) using chemical ionization at atmospheric pressure (APCI) (detection of positive and negative ions). The reactive gas was N_2. The *m*/*z* values are given for the strongest peaks. The course of reactions and purity of products were monitored using Kieselgel $60F_{254}$ plates (Merck). Melting points were determined on a Kofler block.

***N*-(6-Chloronicotinoyl)-γ-aminobutyric Acid (3).** A solution of **1** (2.89 g, 0.028 mol) in aqueous NaOH (10%, 12.3 mL, 0.034 mol) and H_2O (20 mL) was cooled in a salted ice-bath to –7–(–5)°C, stirred, and treated simultaneously with solutions of aqueous NaOH (10%, 12.3 mL, 0.034 mol) and 6-chloronicotinoylchloride (**2**, 5.00 g, 0.028 mol) (prepared by the literature method [5]) in THF (9 mL). The solutions of NaOH and 6-chloronicotinoylchloride were added simultaneously in equal portions of 2 mL at 5–7 min intervals, keeping the temperature of the reaction mixture at –7–(–5)°C. When the addition of the solutions was finished, the reaction mixture was stirred for another 30 min, treated dropwise with HCl solution (23 mL, 2N) until the pH was ~1–2, and stirred at –7–(–5)°C for another hour. The resulting precipitate was filtered off, washed with cold water (3 × 15 mL), and dried in air to afford crude *N*-(6-chloronicotinoyl)- γ-aminobutyric acid (**3**, 4.92 g). The aqueous filtrate was extracted with dichloroethane (5 × 20 mL). The combined organic extract was dried over $MgSO_4$. The desiccant was removed. The dichloroethane was evaporated *in vacuo* to produce another portion of crude **3** (0.82 g). The combined portions of the product were recrystallized from EtOAc to afford **3** (4.2 g). Yield 61%, mp 133–134°C. IR spectrum (KBr, ν, cm^{-1}): 3317 (NH), 1706 (COOH), 1642 (CO–NH). Mass spectrum (*m*/*z*): 243, 245 $[M + H]^+$.

PMR spectrum (DMSO-d_6, δ, ppm, J/Hz): 1.76 (2H, q, J = 7, H-3), 2.30 (2H, t, J = 7, H-2), 3.30 (2H, dt, J_1 = 7, J_2 = 5.5, H-4), 7.65 (1H, d, J = 8, H-5_{Py}), 8.23 (1H, dd, J_1 = 8, J_2 = 2.5, H-4_{Py}), 8.75 (1H, t, J = 5.5, CO–NH), 8.82 (1H, d, J = 2.5, H-2_{Py}), 12.12 (1H, br.s, COO<u>H</u>).

^{13}C NMR spectrum (DMSO-d_6, δ, ppm): 24.3 (C-3), 31.0 (C-2), 38.7 (C-4), 124.0 (C-5_{Py}), 129.4 (C-3_{Py}), 138.5 (C-4_{Py}), 148.8 (C-2_{Py}), 152.3 (C-6_{Py}), 163.7 (Py–CO–NH), 174.1 (C-1).

***N*-(6-Chloronicotinoyl)-γ-aminobutyric Acid, Sodium Salt (4).** A solution of NaOH (0.082 g, 2.06 mmol) in anhydrous MeOH (5 mL) was treated in several portions with **3** (0.5 g, 2.06 mmol). The MeOH was evaporated *in vacuo*. The solid was dried *in vacuo* (0.5 mm Hg) to constant mass to afford **4** (0.54 g, 99%), double mp 220–222 and 228–229°C (MeOH).

PMR spectrum (DMSO-d_6, δ, ppm, J/Hz): 1.72 (2H, q, J = 6.5,H-3), 2.12 (2H, t, J = 6.5, H-2), 3.26 (2H, dt, J_1 = 6.5, J_2 = 4.0, H-4), 7.61 (1H, d, J = 8, H-5_{Py}), 8.28 (1H, dd, J_1 = 8, J_2 = 2.5, H-4_{Py}), 8.85 (1H, d, J = 2.5, H-2_{Py}), 10.00 (1H, br.s, CO–NH).

^{13}C NMR spectrum (DMSO-d_6, δ, ppm): 24.7 (C-3), 35.7 (C-2), 40.6 (C-4), 123.9 (C-5_{Py}), 129.5 (C-3_{Py}), 138.3 (C-4_{Py}), 148.9 (C-2_{Py}), 152.1 (C-6_{Py}), 163.0 (Py–CO–NH), 176.7 (C-1).

Mass spectrum (*m*/*z*): 241, 243 $[M - Na]^-$.

1-(6-Chloronicotinoyl)pyrrolidone-2 (5). A suspension of **3** (0.5 g, 2.06 mmol) in dichloroethane (1 mL) was treated with thionylchloride (0.17 mL, 2.27 mmol), heated for 5 h at 50–55°C, evaporated *in vacuo*, and co-evaporated with dichloroethane (2 × 3 mL). The solid was crystallized from petroleum ether:EtOAc (3:1, 4 mL) to afford **5** (0.39 g, 1.74 mmol, 85%), mp 106–108°C (petroleum ether:EtOAc, 80–90°C). IR spectrum (KBr, ν, cm^{-1}): 1747 (CO–N), 1673 (Py–CO). Mass spectrum (*m*/*z*): 225, 227 $[M]^+$, $C_{10}H_9ClN_2O_2$.

PMR spectrum (DMSO-d_6, δ, ppm, J/Hz): 2.05 (2H, q, J = 8, H-4), 2.55 (2H, t, J = 8, H-3), 3.83 (2H, t, J = 8, H-5), 7.61 (1H, d, J = 8, H-5_{Py}), 8.00 (1H, dd, J_1 = 8, J_2 = 2.5, H-4_{Py}), 8.56 (1H, d, J = 2.5, H-2_{Py}).

^{13}C NMR spectrum (DMSO-d_6, δ, ppm): 16.9 (C-4), 32.6 (C-3), 45.8 (C-5), 123.4 (C-5_{Py}), 130.3 (C-3_{Py}), 139.5 (C-4_{Py}), 149.4 (C-2_{Py}), 152.0 (C-6_{Py}), 166.6 (Py–CO–N), 175.1 (C-2).

REFERENCES

1. M. D. Mashkovskii, *Drugs* [in Russian], Vol. 1, Novaya Volna, Moscow, 2002, pp. 110–117.
2. T. F. Spande, H. M. Garraffo, M. W. Edwards, H. J. C. Yeh, L. Panel, and J. W. Daly, *J. Am. Chem. Soc.*, **114**, 3475 (1992).
3. N. V. Kovganko and Zh. N. Kashkan, *Zh. Org. Khim.*, **40**, No. 12, 1759 (2004).
4. P. Jeschke and R. Nauen, *Pest Manage. Sci.*, **64**, No. 11, 1084 (2008).
5. N. V. Kovganko, Yu. G. Chernov, S. N. Sokolov, Zh. N. Kashkan, and V. L. Survilo, *Khim. Prir. Soedin.*, 175 (2009).