Chemistry of Natural Compounds, Vol. 46, No. 1, 2010

SYNTHESIS OF PYRIDINE-CONTAINING DERIVATIVES OF THE ALKALOIDS CYTISINE AND *d*-PSEUDOEPHEDRINE

I. V. Kulakov

UDC 547.94:547.822.5

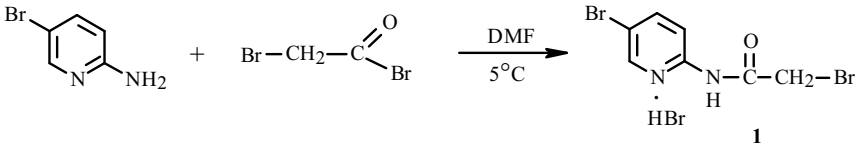
N-*(5-Bromopyridyl-2)-2-*N′*-cytisino- and* N′-d-*pseudoephedrineoacetamides were synthesized by reaction of the alkaloids cytisine and* d-*pseudoephedrine with* N-*(5-bromopyridin-2-yl)-2-bromoacetamide hydrobromide. The compositions and structures of the products were confirmed by IR and PMR spectroscopy and mass spectrometry.*

Keywords: alkaloids, cytisine, *d*-pseudoephedrine, 2-amino-5-bromopyridine, PMR spectroscopy.

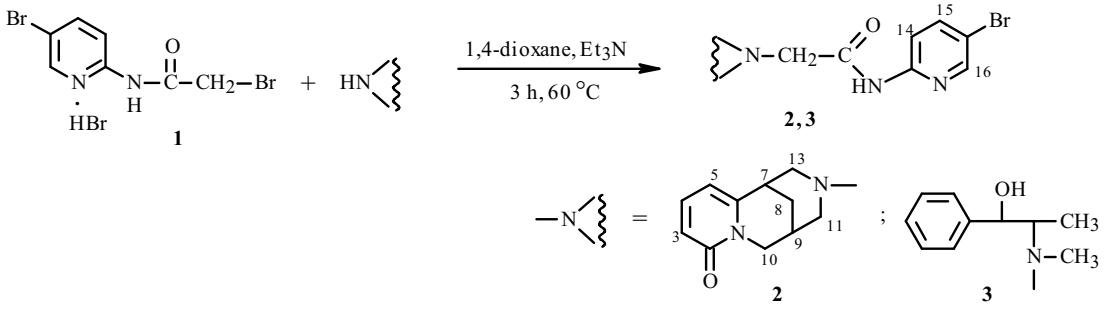
The combination in a molecule of two and more pharmacophores is one of the principal approaches to the chemical design of new biologically active compounds. Compounds with heterocyclic structural fragments, a special place among which is occupied by pyridine derivatives, which comprise about 5% of all known drugs, are most numerous among all drugs. Pyridine derivatives occur in essential vitamins (B_5 and B_6) and are widely used not only in medical practice as drugs with a variety of therapeutic activity (antituberculosis, antibacterial, antihistamine, antidepressant, analgesic, nootropic, psychotropic, and others) [1–3] but also in agriculture as effective fungicides, herbicides, and growth-stimulating compounds [4, 5]. More effective and safer drugs based on pyridine are currently continuously sought in practically all areas of chemotherapy.

We chose 2-amino-5-bromopyridine as the starting synthon for preparing new derivatives of the alkaloids cytisine and *d*-pseudoephedrine, which contain a pharmacologically active pyridine in their structures, and carried out the following transformations.

First acylation of 2-amino-5-bromopyridine by bromoacetic acid bromide in anhydrous DMF with cooling to 5°C produced *N*-(5-bromopyridin-2-yl)-2-bromoacetamide hydrobromide.



Next, the resulting *N*-(5-bromopyridin-2-yl)-2-bromoacetamide hydrobromide (**1**) was used to alkylate the alkaloids cytisine and *d*-pseudoephedrine with slight (to 60°C) heating of **1** hydrobromide and the alkaloids in anhydrous 1,4-dioxane in the presence of a 3-fold excess of Et_3N according to the scheme:



Institute of Organic Synthesis and Carbon Chemistry of the Republic of Kazakhstan, 100008, Karaganda, fax: (87212) 41 38 66, e-mail: kulakov_iv@mail.ru. Translated from Khimiya Prirodnykh Soedinenii, No. 1, pp. 59–60, January–February, 2010. Original article submitted July 20, 2009.

 0009-3130/10/4601-0066

The excess of Et_3N was necessary for conversion of **1** hydrobromide into the base and then as an acceptor for the HBr released during the reaction. The selection of 1,4-dioxane was based on its solubilizing ability for the starting hydrobromide of **1**. Also, the products were isolated from the dioxane solution as the bases.

IR spectra of products **2** and **3** contained a strong absorption band for the amide carbonyl at 1695 and 1706 cm^{-1} (1650 for the amide N–C=O of cytisine) and the hydroxyl at 3300–3410.

PMR spectra of **2** and **3** showed resonances for protons of the alkaloid fragments in their characteristic regions. Aromatic protons of the 5-bromopyridine ring for **2** and **3** were recorded at weak field of 6.55-8.08 ppm as two doublets and a singlet. Methylene protons near the carbonyl group were inequivalent and appeared as a doublet of doublets at 3.15 and 3.48 with SSCC 15.9 and 16.7 Hz.

EXPERIMENTAL

PMR spectra were recorded in DMSO-d_6 on a Bruker DRX500 spectrometer at 500 MHz relative to TMS internal standard. IR spectra were taken in KBr disks on an Avatar-320 Fourier-transform spectrometer (Nicolet). Mass spectra were obtained in a Finnigan Mat.Incos 50 instrument by direct sample introduction with ionizing energy 70 eV. Melting points were determined on a Boetius apparatus. TLC was performed on Sorbfil plates with development by iodine vapor. 2-Amino-5-bromopyridine and bromoacetic acid bromide (98%) were obtained commercially (Aldrich) and used without further purification. Elemental analyses of the products agreed with those calculated.

***N*-(5-Bromopyridin-2-yl)-2-bromoacetamide Hydrobromide (1).** A stirred cooled (5°C) solution of 2-amino-5-bromopyridine (1.73 g, 0.01 mol) in DMF (5 mL) was treated dropwise with bromoacetic acid bromide (2.42 g, 0.012 mol) and stirred for 2 h at room temperature. The resulting finely crystalline light-beige precipitate was cooled, filtered off, and washed several times with cold benzene to afford **1** (2.99 g, 80%), mp 230–232°C (dec.), $C_7H_7Br_3N_2O$.

***N*-(5-Bromopyridin-2-yl)-2-*N′*-cytisinoacetamide (2).** A stirred suspension of *N*-(5-bromopyridin-2-yl)-2-bromoacetamide hydrobromide (1.50 g, 4 mmol) in anhydrous 1,4-dioxane (10 mL) was treated with Et_3N (1.21 g, 12 mmol) and cytisine (0.76 g, 4 mmol) and heated for 3 h at 60–70°C. The resulting precipitate of $Et_3N{\cdot}HBr$ was filtered off and washed with warm dioxane. Solvent was distilled from the combined mother liquor. The resulting oily residue was ground with hexane. The resulting powder was recrystallized from benzene:hexane (1:1) to afford **2** (1.14 g, 71%) as a white crystalline compound, mp 171–173°C, $C_{18}H_{19}BrN_4O_2$. Mass spectrum (EI, 70 eV, *m*/*z*, I_{rel}, %): 402 (16) $[M]^+$, 404 (12) $[M]^+$, 230 (31), 203 (53), 160 (16), 146 (15), 58 (98), 42 (29).

PMR spectrum (500 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.72, 1.82 (2H, dd, $J_{8,7}$ = 12.8, $J_{8,9}$ = 12.9, H-8), 2.42 (1H, br.s, H-9), 2.60 (2H, m, H-11), 2.84 (1H, br.d, J = 10.6, H-7), 3.00 (2H, m, H-13), 3.10, 3.19 (2H, dd, $J_{a,b}$ = 15.9, N–CH_2), 3.75 (1H, dd, $J_{10a,9}$ = 6.6, H-10a), 3.87 (1H, d, $J_{10e,10a}$ = 15.3, H-10e), 6.06 (1H, d, $J_{5,4}$ = 6.8, H-5), 6.26 (1H, d, $J_{3,4}$ = 9.0, H-3), 7.29 (1H, dd, J = 6.8, 9.0, H-4), 7.96 (2H, d, $J_{14,15}$ = 8.9, H-14, H-15), 8.34 (1H, s, H-16), 9.65 (1H, s, N–H).

***N*-(5-Bromopyridin-2-yl)-2-*N′*-*d*-pseudoephedrinoacetamide (3)** was synthesized analogously to **2** from *N*-(5-bromopyridin-2-yl)-2-bromoacetamide hydrobromide (0.94 g, 2.5 mmol), *d*-pseudoephedrine (0.41 g, 2.5 mmol), and Et_3N (0.76 g, 7.5 mmol). The oily residue that was obtained after removing solvent was ground with ice. The resulting powder was filtered off to afford **3** (0.62 g, 66%) as white needle-like crystals, mp 68–70°C (30% EtOH), $C_{17}H_{20}BrN_3O_2$. Mass spectrum (EI, 70 eV, *m*/*z*, I_{rel}, %): 272 (9), 270 (9), 174 (15), 172 (15), 79 (15), 77 (25), 71 (100), 70 (22), 56 (45), 42 (47).

PMR spectrum (500 MHz, DMSO-d_6, δ, ppm, J/Hz): 0.67 (3H, d, J = 6.7, C$\underline{H}_3$–CH), 2.33 (3H, s, N–CH_3), 2.78 (1H, m, CHN), 3.17, 3.48 (2H, dd, $J_{a,b}$ = 16.7, N–C$\underline{H}_2$), 4.39 (1H, dd, J = 9.0, C$\underline{H}$(OH)), 5.49 (1H, d, J = 3.2, OH), 7.28 (5H, m, H_{arom}), 8.03 (1H, d, $J_{15,14}$ = 8.9, H-15), 8.12 (1H, d, $J_{14,15}$ = 8.9, H-14), 8.44 (1H, s, H-16), 10.53 (1H, s, N–H).

REFERENCES

1. A. T. Soldatenkov, N. M. Kolyadina, and I. V. Shendrik, *Principles of the Organic Chemistry of Drugs* [in Russian], Khimiya, Moscow, 2001.
2. M. D. Mashkovskii, *Drugs of the XXth Century* [in Russian], OOO Izd. Novaya Volna, Moscow, 1998.
3. M. D. Mashkovskii, *Drugs* [in Russian], OOO RIA Novaya Volna, 15th Ed., Moscow, 2007.
4. N. N. Mel′nikov, *Pesticides. Chemistry, Technology and Application* [in Russian], Khimiya, Moscow, 1987.
5. M. V. Shimanskaya and L. Ya. Leitis, *Khim. Geterotsikl. Soedin.*, **5**, 579 (1989).