CERTAIN TRANSFORMATIONS OF ANABASINE AND NICOTINE

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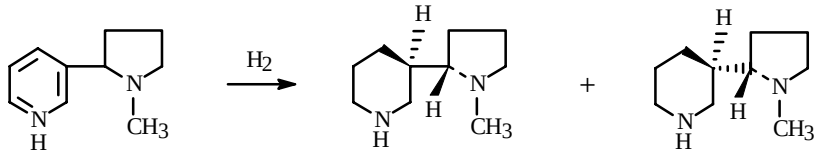
Electrocatalytic reduction of the alkaloids anabasine and nicotine was investigated. 1-α,β′-Dipiperidyl and hexahydronicotine were prepared. The reactions of anabasine and the hydrogenated alkaloids with dicarboxylic acid anhydrides were studied.

Key words: anabasine, nicotine, dicarboxylic acid anhydrides, 1-α,β′-dipiperidyl, hexahydronicotine, amidoacids.

Research has demonstrated the promise of using wild and cultivated plant material for preparing medicines. Thus it is important to apply new methods for transforming such an available class of compounds as alkaloids. For example, the pyridine alkaloids anabasine and nicotine are not used much because of their high toxicity. However, modification of the anabasine structure can produce reversible and irreversible cholinesterase inhibitors [1], among which anabasinylphosphamides are interesting [2]. The observation of bactericidal and pesticidal activities in synthetic nicotine derivatives drew the attention of researchers to the development of synthetic methods of these compounds [3-5].

In order to prepare new physiologically active compounds based on these pyridine alkaloids, we studied catalytic hydrogenation and the reactions of the resulting compounds with dicarboxylic acid anhydrides.

Electrocatalytic reduction of anabasine (**1**) and nicotine (**2**) on nickel sponge formed the hydrogenated products, 1-α,β′-dipiperidyl (**3**) and hexahydronicotine (**4**), respectively. The latter was a mixture of the 2′*S*,3*R*′- (**5**) and 2′*S*,3*S*′-isomers (**6**) [6]:



2 **5** **6**

These were separated by column chromatography on reversed-phase sorbents. The ratio of isomers in **4** was 83:17. The effect of the conditions of the electrocatalytic hydrogenation, e.g., concentration of starting alkaloid, cathode and anode electrolytes, catalyst mass, temperature, and current density, on the yields of **3** and **4** was determined.

Piperidines and pyridine amines are known to react readily with dicarboxylic acid anhydrides to give the corresponding amidoacids in good yields [7-9]. Several of these compounds have distinct hypoglycemic [7-9], hypertensive [8, 10], and anti-inflammatory [11] activities.

Considering this feature, we studied the reactions of **1**, **2**, and **4** with dicarboxylic acid anhydrides. This produced N′-anabasinyl- (**7-9**) and N-hexahydronicotinylamido acids (**10-12**) and N,N′-dipiperidylamido-*bis*-acids (**13-15**):

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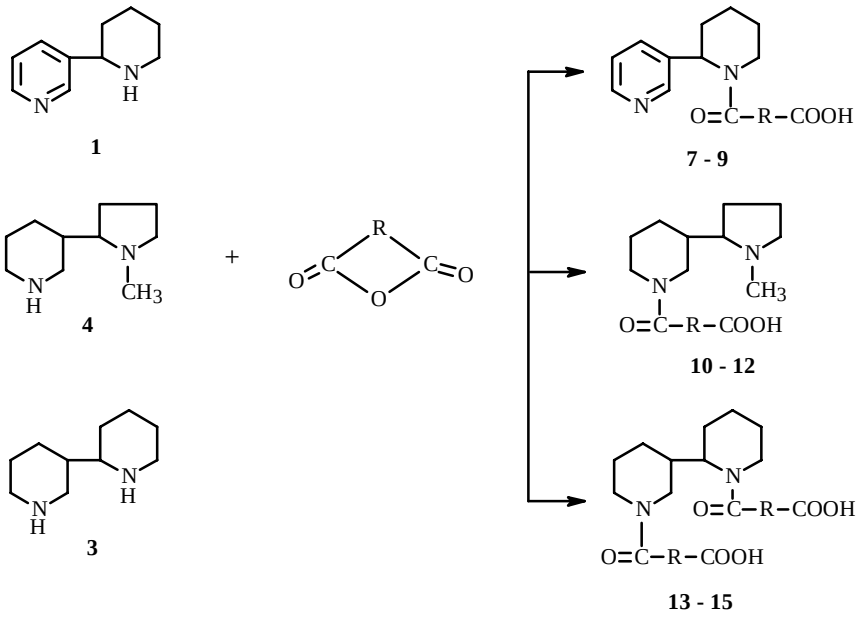

R = *o*-C_6H_4 (**7, 10, 13**); CH_2CH_2 (**8, 11, 14**); CH=CH (**9, 12, 15**)

The resulting amidoacids, with a rare exception, are crystalline compounds that are very soluble in water. The structures of the synthesized compounds were confirmed by IR and PMR spectroscopies and mass spectrometry.

The biological activities of these amidoacids showed that they possess moderate antibacterial activity toward gram-positive and gram-negative microorganisms and analgetic activity, especially evident for succinic acid 1-α,β'-dipiperidyl-N,N′-diamide (**14**). An investigation in white mongrel mice at doses of 1 and 5 mg/kg showed that it is several times more active than the known preparation analgine.

EXPERIMENTAL

The course of reactions and purity of products were monitored by TLC on Silufol UV-254 plates using chloroform:alcohol:aqueous ammonia (25%) (3:1:0.5) and (4:1:0.5) for 1-α,β'-dipiperidyl; for N′-anabasinylamidoacid, (4:1:1); for hexahydronicotine, chloroform:alcohol (3:1) and (2:1). Chromatography of the hydrogenation products was performed on a Chrom-5 instrument (for 1-α,β'-dipiperidyl, glass column 3.5 m in length with 3 mm internal diameter packed with celite-545 with 15% silicone elastomer PMS-100, sensitivity 4, argon carrier-gas flow rate 30 mL/min, flame-ionization detector, detector temperature 200°C, vaporizer 350°C, column 150°C; for hexahydronicotine, column with chromaton NAW HMDS with 5% silicone elastomer SE-30, column temperature 165°C, vaporizer 200°C, detector 180°C). Melting points were determined on a Boetius stage. IR spectra were recorded on a Fourier spectrophotometer (Nicolet Avotar) in KBr disks; PMR and ^{13}C NMR, on AC 200 [working frequencies 200.13 (^1H) and 50.32 MHz (^{13}C)] and DRX 500 spectrometers (Bruker) [working frequencies 500.13 (^1H) and 125.76 MHz (^{13}C)] for solutions (5%) in $CDCl_3$, CD_3OD, and $(CD_3)_2SO$. Signals in NMR spectra were assigned using various types of proton—proton and carbon—proton shift correlation spectroscopies (COSY, COLOC). Mass spectra were obtained in a MAT 8200 spectrometer (Finnigan) with electron-impact ionization. Elemental analyses corresponded to those calculated.

Electrocatalytic Hydrogenation of Anabasine. 1-Anabasine with melting point 274°/715 mm Hg was used. Electrocatalytic reduction of anabasine was performed in an electrocatalytic cell with an MA-40 diaphragm in aqueous NaOH (2%) on nickel sponge. The anode electrolyte was NaOH (20%); catalyst mass, 1.0 g; anabasine concentration, 0.065 M. The best results were achieved at 30°C and current density 30 A/dm^2. Compound **3** was extracted with benzene. The solid after removal of solvent was recrystallized from hexane to afford 1-α,β'-dipiperidyl (**3**, 72%), mp 66-68°C, which agrees with the literature [12].

IR spectrum (KBr, ν, cm^{-1}): 3318-3207 $(NH)_{str}$, 2957-2815 (CH_{alk}), 1589-1470 $(NH)_{def}$, 1233-1027 $(C–N)_{str}$.

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.07 (2H, t, ^2J = 7.5, H-3), 1.10 (2H, t, H-4′), 1.28 (2H, t, H-5), 1.29 (2H, d, H-5′), 1.36 (2H, t, H-4), 1.39 (2H, t, H-3′), 2.23 (2H, m, H-2), 2.33 (2H, t, ^2J = 11.5, H-2′), 2.45 (2H, m, H-6′), 2.53 (2H, d, ^2J = 2, H-6), 2.94 (2H, d, ^2J = 11.5, H-6′), 3.03 (2H, d, ^2J = 12.5, H-6), 3.10 (2H, d, ^2J = 11.5, H-2′). ^{13}C NMR spectrum (δ, ppm): 24.8 (C-5), 26.5 (C-5′), 26.7 (C-4), 27.6 (C-4′), 28.8 (C-3), 42.8 (C-3′), 46.9 (C-6′), 47.2 (C-6), 49.6 (C-2′), 59.9 (C-2).

Electrocatalytic hydrogenation of nicotine was carried out by an analogous method with a nicotine concentration of 0.185 M, 20°C, and current density 20 A/dm^2. Yield of **4**, 62%; melting point, 6°C. Hexahydronicotine was purified by column chromatography over silica gel using gradient elution with hexane:chloroform.

IR spectrum (ν, cm^{-1}): 3303 (NH), 2931-2857 (CH_{alk}), 2793 $(CH_3–N)$, 1573 (NH), 1370 (CH_3).

N′-Amides of Dicarboxylic Acids and *bis*-Acids (General Method). A solution of anabasine (6.5 mmol) in absolute EtOAc (10 mL) was treated with an equimolar amount of dicarboxylic acid anhydride and the same amount of ethylacetate and left for 5 h. The resulting amidoacid precipitate was separated, washed with the same solvent, and dried to constant mass. For hexahydronicotine, absolute diethylether was used. The reaction with 1-α,β′-dipiperidyl was performed in benzene.

This method produced:

***o*-Phthalic Acid N′-Anabasinylamide (7).** Yield 65%, mp 219-221°C. IR spectrum (KBr, ν, cm^{-1}): 3030, 725 (benzene ring), 2948-2857 (CH_{alk}), 2620-2550, (COOH), 1714 (CO), 1640 (CO), 1597, 1572, 1480, 771 (pyridine ring).

PMR spectrum (CD_3OH, δ, ppm, J/Hz): 1.5 (2H, s, H-4′), 1.8 (2H, d, H-3′), 2.56 (2H, s, J = 7, H-2′), 3.28 (2H, s, H-2′), 7.60 (1H, td, J_1 = 3.5, H-3), 7.70 (1H, td, J = 3.5, H-2), 8.13 (1H, dd, J = 19, H-5), 8.50 (1H, br.s, H-4). Mass spectrum (*m*/*z*, %): 311, 310 (9.4) $[M]^+$, 163 (20), 162 (80), 161 (100), 134 (21), 133 (25), 105 (42), 104 (85), 92 (17), 85 (31), 84 (39), 76 (63), 52 (11), 51 (16), 50 (39), 28 (17).

Maleic Acid N′-Anabasinylamide (8). Yield 70%, mp 150-152°C. IR spectrum (KBr, ν, cm^{-1}): 2952-2869 (CH_{alk}), 2650-2500 (COOH), 1700 (CO), 1650 (CO), 1618 (CH=CH-*cis*), 1599, 1582, 1470, 783 (pyridine ring).

PMR spectrum (CD_3OH, δ, ppm, J/Hz): 1.20 (2H, t, H-3′), 1.30 (2H, t, H-5′), 1.60 (2H, d, ^2J = 3.2, H-3′), 2.49 (2H, t, H-6′), 6.16 (2H, d, ^2J = 12, CH=CH), 6.81 (1H, d, J = 11.6, H-3), 7.50 (1H, t, J_1 = 2.8, J_2 = 8.0, H-4), 8.00 (1H, d, J = 7.6, H-6), 8.67 (1H, br.s, H-2). Mass spectrum (*m*/*z*, %): 243 (3.3), 242 (1), 215 (1), 188 (3), 163 (9), 162 (40), 161 (100), 144 (3), 134 (14), 133 (28), 120 (14), 119 (26), 106 (45), 85 (26), 84 (54), 65 (11), 55 (18), 54 (25), 39 (13), 29 (11), 28 (33).

Succinic Acid N′-Anabasinylamide (9). Yield 59%, mp 191-193°C. IR spectrum (KBr, ν, cm^{-1}): 2938-2862 (CH_{alk}), 2620-2520 (COOH), 1721 (CO), 1651 (CO), 1599, 1577, 1481, 780 (pyridine ring).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.52 (4H, m, H-3′, H-5′), 1.85 (1H, m, H-4′), 2.30 (1H, m, H-4′), 2.67 (5H, 2H, m, H-6′, 2H, CH_2 and 1H, H-2′), 3.68 (2H, m, CH_2), 5.94 (1H, br.s, OH), 7.27 (1H, dd, H-5, J = 7.5), 7.56 (1H, d, H-4, J = 7.3), 8.42 (1H, d, H-6, J = 7.5), 8.44 (1H, br.s, H-2).

^{13}C NMR spectrum (δ, ppm): 19.04 (t, C-4′), 25.55 (t, C-3′), 26.53 (t, C-5′), 41.75 (t, C-6′), 49.04 (d, C-2′), 57.74 (CH_2×2), 123.77 (d, C-5), 135.30 (s, C-3), 135.76 (d, C-4), 146.48 (d, C-2), 146.83 (d, C-6), 171.15 (s, C=O), 175.59 (s, C=O). Mass spectrum (*m*/*z*, %): 262 (22), 161 (100), 133 (25), 84 (32), 55 (17), 18 (14).

***o*-Phthalic Acid N′-Hexahydronicotinylamide (10).** Yield 80%, mp 158-160°C. IR spectrum (KBr, ν, cm^{-1}): 3030 (benzene ring), 2940-2860 (CH_{alk}), 2793 $(CH_3–N)$, 2400 (COOH), 1696 (CO), 1649 (CO), 1370 (CH_3).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.50 (2H, d, H-3′), 1.80 (3H, br.t, ^3J = 6.8, CH_3), 2.55 (2H, t, H-6), 2.79 (2H, d, H-6′), 3.08 (2H, d, H-2′), 3.6 (2H, br.t, CH_2), 7.31 (1H, d, H-3), 7.60 (1H, m, H-2), 7.80 (1H, dd, H-5), 8.4 (1H, t, H-4).

Maleic Acid N′-Hexahydronicotinylamide (11). Yield 86%, oil. IR spectrum (KBr, ν, cm^{-1}): 2941-2864 (CH_{alk}), 2741 $(CH_3–N)$, 2533 (COOH), 1712 (CO), 1650 (CO), 1610 (CH=CH), 1380 (CH_3).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.25 (2H, t, $^2J_2$ = 7.2, $^2J_1$ = 7.0, H-4′), 1.60 (2H, d, H-3′), 1.80 (2H, br.t, ^3J = 6.8, H-6), 1.98 (2H, br.s, H-2), 2.11 (2H, br.t, $^2J_1$ = 4.8, $^3J_2$ = 11.0, H-2′), 2.31 (1H, br.s, H-2), 2.39 (3H, t, J_1 = 7.6, J_2 = 16.8, $N–CH_3$), 2.79 (2H, d, H-6), 3.08 (2H, d, H-2′), 6.22 (2H, q, CH=CH), 9.7 (1H, br.s, COOH).

***bis*-*o*-Phthalic Acid α,β′-Dipiperidyl-N,N′-diamide (13).** Yield 82%, mp 180-182°C. IR spectrum (KBr, ν, cm^{-1}): 3030, 747 (benzene ring), 2936-2870 (CH_{alk}), 2560-2500 (COOH), 1710 (CO), 1640 (CO).

PMR spectrum (CD_3OD, δ, ppm, J/Hz): 1.21 (2H, t, $^2J_2$ = 7.2, $^2J_1$ = 6.8, H-5′), 1.44 (2H, br.t, H-3′), 1.87 (2H, br.s, H-2), 2.22 (2H, d, H-2′), 2.90 (2H, d, H-6′), 3.20 (2H, s, H-4′), 7.20 (1H, q, H-3), 7.48 (1H, m, H-2), 7.90 (1H, m, H-5), 7.96 (1H, t, J_1 = 5.2, J = 9.2, H-4). Mass spectrum (*m*/*z*, %): 2.32 (7), 169 (2), 168 (9), 149 (9), 125 (2), 124 (5), 112 (3), 110 (12), 104 (44), 96 (17), 85 (12), 84 (100), 76 (17), 68 (9), 57 (5), 56 (35), 41 (18), 30 (37), 28 (49), 18 (32).

***bis*-Maleic Acid α,β'-Dipiperidyl-N,N′-diamide (14).** Yield 81.5%, mp 72-75°C. IR spectrum (KBr, ν, cm^{-1}): 2925-2850 (CH_{alk}), 2610-2510 (COOH), 1698 (CO), 1620 (CH=CH).

PMR spectrum [$(CD_3)_2SO$, δ, ppm, J/Hz]: 1.39 (2H, m, H-5), 1.59 (2H, m, H-4), 1.99 (1H, m, H-3′), 2.74 (2H, t, H-6′), 2.88 (1H, d, H-2′), 3.25 (2H, t, H-6), 3.32 (1H, m, H-2), 6.1 (4H, s, CH=CH).

^{13}C NMR spectrum (δ, ppm): 21.35 (t, C-5), 21.65 (t, C-5′), 23.05 (t, C-4), 24.53 (t, C-3), 35.99 (d, C-3′), 43.23 (t, C-2′), 44.74 (t, C-6′), 44.93 (t, C-6), 135.64 (d, CH×4), 167.52 (s, C=O). Mass spectrum (*m*/*z*, %): 363, 347, 168, 84 (100).

***bis*-Succinic *A*cid α,β'-Dipiperidyl-N,N′-diamide (15).** Yield 81.5%, mp 72-75°C. IR spectrum (KBr, ν, cm^{-1}): 2925-2850 (CH_{alk}), 2510-2500 (COOH), 1700 (CO), 1650 (CO).

PMR spectrum (δ, ppm, J/Hz): 1.21 (2H, t, J = 6.8, H-4′), 1.27 (2H, t, J = 7.0, H-5), 1.43 (2H, br.s, H-3′), 2.10 (2H, d, H-2), 2.52 (2H, t, H-6), 2.83 (2H, t, H-6′), 4.50 (4H, d, CH_2–CH_2).

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