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Synthesis of Di-(N-tropinonyl)pyridines and Di-(N-tropinonyl)benzenes

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As a part of a research program related to the synthetic study of pharmacologically interesting tropane compounds, we synthesized di-(N-tropinonyl)pyridines **7**, **8**, **9** and di-(N-tropinonyl)benzenes **12**, **14**. *p*-Dipyrrolylbenzene **10**, 8-(4-pyrrol-1-yl-phenyl)-8-azabicyclo[3.2.1]octan-3-one **11** and 8-(3-pyrrol-1-yl-phenyl)-8-azabicyclo[3.2.1]-octan-3-one **13** as byproducts were synthesized. However, the reaction of 1,2-phenylene diamine with 2,5-dimethoxy tetrahydrofuran, acetone dicarboxylic acid and conc. HCl in water did not give 1,2-di-(8-azabicyclo[3.2.1]octan-3-onyl)benzene **15**. We suppose that the major reason is the steric hindrance of tropane rings.

Key Words: Tropane alkaloids, Di-(N-tropinonyl)pyridines, Di-(N-tropinonyl)benzenes, Anticonvulsant activity, Steric hindrance.

INTRODUCTION

Tropane alkaloids have received a great deal of attention because of their remarkable pharmaceutical significance[1-4]. Therefore a variety of synthetic approaches to tropane alkaloids have been investigated. Especially, a series of tropanes showed anticonvulsant activity against pentylenetetrazol-induced convulsions in mice and antiarrhythmic activity in rabbit previously treated with ouabain[5-8].

As a part of a research program related to the synthetic study of pharmacologically interesting tropane compounds, we now report the synthesis of di-(N-tropinonyl)pyridines and di-(N-tropinonyl)benzenes in the reaction of pyridine diamines (or phenylene diamines) with 2,5-dimethoxy tetrahydrofuran and acetone dicarboxylic acid at 0 ºC.

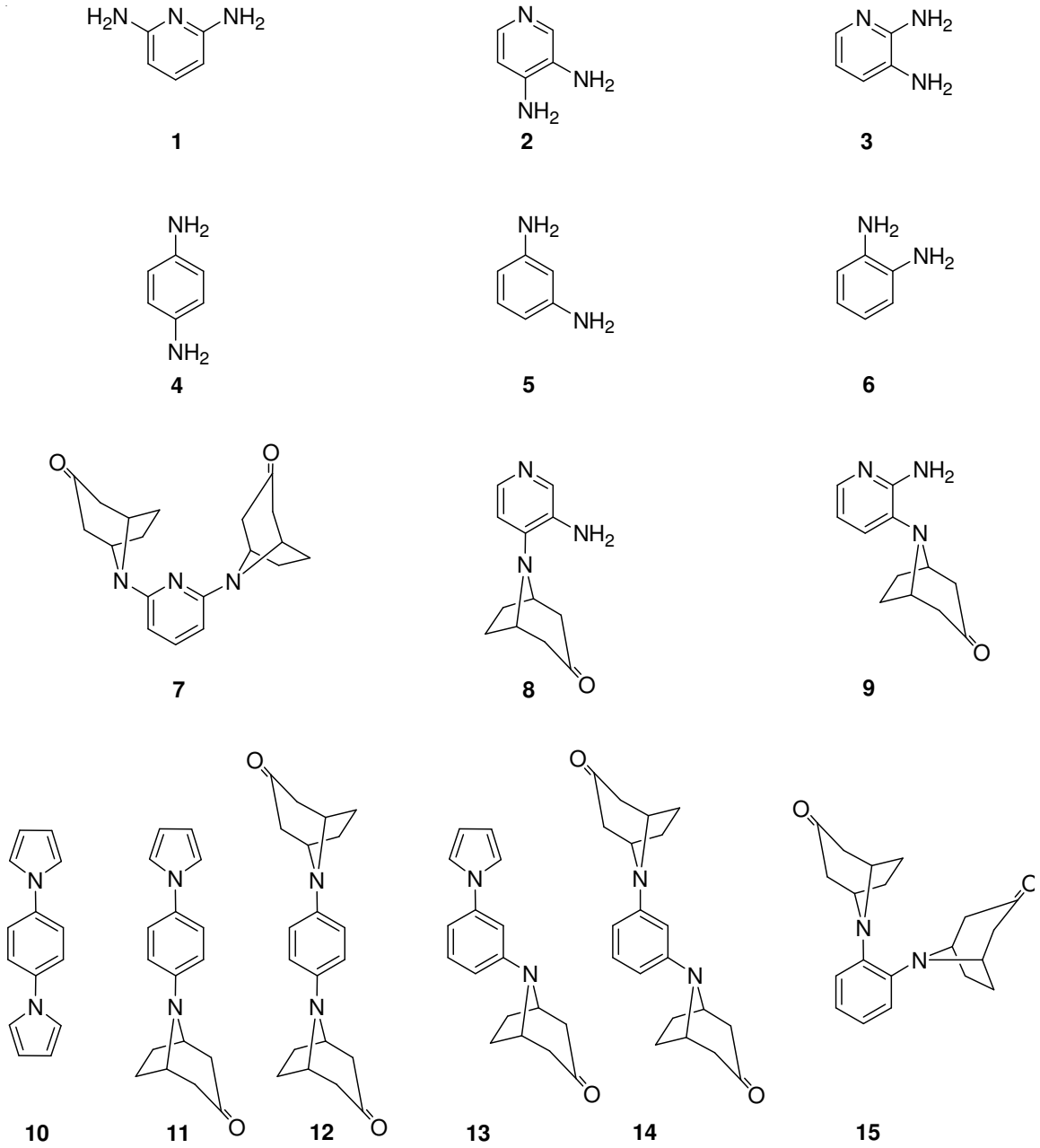
EXPERIMENTAL

Melting points were determined on an electrothermal capillary melting point apparatus and uncorrected. TLC was performed on glass plates coated with silicon oxide (silica gel 60 F_{254}) and compounds were visualized using a UV lamp. ^{1}H NMR and ^{13}C NMR spectra were obtained with Bruker AC 200 (200 MHz) and Varian Gemini (200 or 300 MHz) spectrometers. Mass spectra were measured with HP 5890 GC/mass (70 eV, EI). The organic solvents and chemicals were obtained from commercial products and purified by the appropriate methods before use.

Synthesis of 2,6-di-(8-azabicyclo[3.2.1]octan-3-onyl)-pyridine (7): Yield 67 %; m.p. 139-140 ºC; R_f 0.68 (TLC eluent; EtOAc: CH_2Cl_2 = 1:2, v/v); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.42 (t, *J* = 7.9 Hz, 1H), 6.11 (d, *J* = 8.1 Hz, 2H), 4.70 (s, 4H), 2.74 (dd, *J* = 4.3, 15.5 Hz, 4H), 2.33 (dd, *J* = 1.6, 15.5 Hz, 4H), 2.17 (m, 4H), 1.81 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 208.94, 155.80, 139.74, 98.17, 97.55, 53.61, 46.90, 28.79; mass (70 eV), m/z (rel. intensity %) 325 (100), 268 (20), 210 (28), 160 (21), 92 (9), 41 (9); Anal. calcd. (%) for $C_{19}H_{23}N_3O_2$: C, 70.13; H, 7.12; N, 12.91. Found (%): C, 70.27; H, 7.04; N, 12.73.

Synthesis of 8-(3-amino-pyridin-4-yl)-8-azabicyclo-[3.2.1]octan-3-one (8): Yield 48 %; m.p. 199-200 ºC; R_f 0.10 (TLC eluent; EtOAc: CH_2Cl_2 = 1:1, v/v); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.02 (s, 1H), 7.98 (d, *J* = 2.6 Hz, 1H), 6.61 (d, *J* = 5.3 Hz, 1H), 4.46 (s, 2H), 3.99 (s, 2H), 2.77 (dd, *J* = 4.3, 16.4 Hz, 2H), 2.44 (dd, *J* = 1.6, 17.3 Hz, 2H), 2.15 (m, 2H), 1.82 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 208.83, 147.80, 145.46, 139.58, 133.52, 109.54, 58.34, 50.68, 29.20; mass (70 eV), m/z (rel. intensity %) 217 (80), 160 (96), 120 (100), 92 (21), 53 (11); Anal. calcd. (%) for $C_{12}H_{15}N_3O$: C, 66.34; H, 6.96; N, 19.34. Found (%): C, 66.38; H, 7.01; N, 19.22.

Synthesis of 8-(2-amino-pyridin-3-yl)-8-azabicyclo-[3.2.1]octan-3-one (9): Yield 52 %; m.p. 193-194 ºC; R_f 0.25 (TLC eluent; EtOAc: CH_2Cl_2 = 1:1, v/v); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.79 (d, *J* = 5.0 Hz, 1H), 6.99 (d, *J* = 7.6 Hz, 1H), 6.63 (t, *J* = 7.5 Hz, 1H), 4.73 (s, 2H), 4.05 (s, 2H), 2.77 (dd, *J* = 4.9, 16.5 Hz, 2H), 2.43 (dd, *J* = 1.6, 17.4 Hz, 2H), 2.11 (m, 2H), 1.83 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 210.64, 153.98, 141.88, 131.85, 24.85, 114.32, 57.90, 57.83, 50.49, 28.90. Mass (70 eV), m/z (rel. intensity %) 217 (4), 160 (12),



Structures of products synthesized from pyridinediamines and phenylenediamines

120 (66), 93 (36), 81 (29), 66 (82), 53 (100); anal. calcd. (%) for $C_{12}H_{15}N_3O$: C, 66.34; H, 6.96; N, 19.34. Found (%): C, 66.27; H, 6.76; N, 19.39.

Synthesis of *p*-dipyrrolylbenzene (10): Yield 4 %; m.p. 213-214 ºC; R_f 0.48 (TLC eluent ; EtOAc: CH_2Cl_2: *n*-hexane = 1:1:2, v/v/v); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.36 (m, 4H), 6.93 (m, 4H), 6.20 (t, 4H); mass (70 eV), m/z (rel. Int. %) 208 (100), 180 (32), 152 (7), 115 (12), 28 (36); anal. calcd. (%) for $C_{14}H_{12}N_2$: C, 80.74; H, 5.81; N, 13.45. Found (%): C, 80.55; H, 5.73; N, 13.40.

Synthesis of 8-(4-pyrrol-1-yl-phenyl)-8-azabicyclo-[3.2.1]octan-3-one (11): Yield 12 %; m.p. 230-231 ºC; R_f 0.35 (TLC eluent; EtOAc: CH_2Cl_2: *n*-hexane = 1:1:2, v/v/v); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.33 (m, 2H), 7.05 (m, 4H), 6.32 (t, 2H), 4.50 (s, 2H), 2.70 (dd, *J* = 3.1, 15.0 Hz, 2H), 2.25 (m, 4H), 1.83 (m, 2H); mass (70 eV), m/z (rel. int. %) 266 (100), 209 (93), 169 (32), 142 (25), 115 (38), 68 (57); anal. calcd. (%) for $C_{17}H_{18}N_2O$: C, 76.66; H, 6.81; N, 10.52. Found (%): C, 76.42; H, 6.55; N, 10.37.

Synthesis of 1,4-di-(8-azabicyclo[3.2.1]octan-3-onyl)-benzene (12): Yield 69 %; m.p. 246-247 ºC; R_f 0.45 (TLC eluent; EtOAc only); IR (KBr, ν_{max}, cm^{-1}) 3037, 2923, 1730 (C=O), 1590; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.86 (m, 4H), 4.49 (s, 4H), 2.70 (dd, *J* = 3.0, 15.0 Hz, 4H), 2.22 (dd, *J* = 1.6, 15.2 Hz, 4H), 2.17 (m, 4H), 1.78 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 208.93, 138.05, 117.18, 55.08, 55.35, 45.76, 29.20; mass (70 eV), m/z (rel. intensity, %) 324 (100), 267 (58), 214 (28), 117 (14), 68 (15); anal. calcd. (%) for $C_{20}H_{24}N_2O_2$: C, 74.04; H, 7.46; N, 8.64. Found (%): C, 73.92; H, 7.41; N, 8.69.

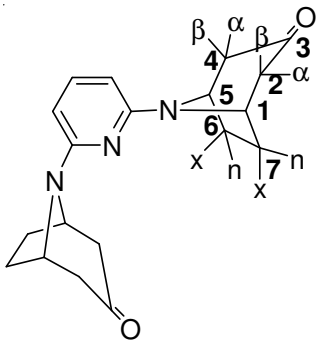
Synthesis of 8-(3-pyrrol-1-yl-phenyl)-8-azabicyclo-[3.2.1]octan-3-one (13): Yield 2 %; m.p. 163-164 ºC; R_f 0.69 (TLC eluent; EtOAc: *n*-hexane = 1:2, v/v); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.42 (m, 2H), 7.21 (m, 2H), 6.34 (t, 2H), 4.49 (s, 4H), 2.75 (dd, *J* = 3.2, 15.0 Hz, 4H), 2.34 (dd, *J* = 1.7, 15.3 Hz, 4H), 2.19 (m, 4H), 1.81 (m, 4H); mass (70 eV), m/z (rel. intensity, %) 266 (100), 209 (93), 169 (30), 142 (22), 115 (47), 68 (58); anal. calcd. (%) for $C_{17}H_{18}N_2O$: C, 76.66; H, 6.81; N, 10.52. Found (%): C, 75.98; H, 6.62; N, 10.39.

Synthesis of 1,3-di-(8-azabicyclo[3.2.1]octan-3-onyl)-benzene (14): Yield 38 %; m.p. 176-178 ºC; R_f 0.41 (TLC eluent; EtOAc: *n*-hexane = 1:2, v/v); IR (KBr, ν_{max}, cm^{-1}): 3040, 2920, 1728 (C=O), 1595; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.23 (t, *J* = 7.4 Hz, 1H), 6.39 (d, *J* = 7.0 Hz, 3H), 4.49 (s, 4H), 2.74 (dd, *J* = 3.1, 15.2 Hz, 4H), 2.32 (dd, *J* = 1.6, 15.3 Hz, 4H), 2.18 (m, 4H), 1.80 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 208.69, 147.06, 131.54, 106.17, 101.79, 54.90, 46.11, 29.16; mass, m/z (rel. intensity, %) 324 (100), 281 (21), 267 (52), 225 (15), 209 (52), 143 (16), 117 (17), 68 (16); anal. calcd. (%) for $C_{20}H_{24}N_2O_2$: C, 74.04; H, 7.46; N, 8.64. Found (%): C, 73.95; H, 7.32; N, 8.48.

RESULTS AND DISCUSSION

Earlier we reported the synthesis of N-substituted nortropinones in the reaction of amines with 2,5-dimethoxy tetrahydrofuran and acetone dicarboxylic acid[9-11].

A representative experimental procedure for the synthesis of 2,6-di-(8-azabicyclo[3.2.1]octan-3-onyl)pyridine **7** is as follows: A mixture of 2,5-dimethoxy tetrahydrofuran (1.32 g, 0.01 mol), acetone dicarboxylic acid (1.46 g, 0.01 mol), water (20 mL) and conc. HCl (0.5 mL) was stirred for 0.5 h. Pridine-2,6-diamine **1** (1.65 g, 1.5×10^{-2} mol) in water (10 mL) was added by using a dropping funnel at 0 ºC. After the reaction mixture was stirred under N_2 at room temperature for 28 h, a crude brown solid was precipitated. The reaction mixture was diluted with water (20 mL) and neutralized with saturated $NaHCO_3$ solution. The neutralized solution was extracted with CH_2Cl_2 (100 mL × 3). The organic layer was dried (Na_2SO_4), filtered and concentrated. The residue was chromatographed on a silica gel (EtOAc:*n*-hexane = 1:2, v/v) to yield **7** (3.27 g, 67 %) as a brown crystalline solid. ^{1}H NMR showed a singlet at δ 4.70 for four protons of C1 and C5, a doublet at δ 1.76 for four protons of $C6_n$ and $C7_n$, a doublet at δ 2.17 for four protons of $C6_x$ and $C7_x$, a double doublet at δ 2.33 (H-2(4)$_\alpha$, *J* = 1.6, 15.5 Hz) for four protons of $C2_\alpha$ and $C4_\alpha$ and a double doublet at δ 2.74 (H-2(4)$_\alpha$, *J* = 4.3, 15.5 Hz) for four protons of $C2_\beta$ and $C4_\beta$. Aromatic protons were at δ 7.42 and δ 6.11.



Mass spectra showed a protonated molecular ion at m/z 325 corresponding to the molecular formular $C_{19}H_{24}N_3O_2$. From these observations, this product was proposed to have the structure of **7**.

An experimental procedure for the synthesis of 1,4-di-(8-azabicyclo[3.2.1]octan-3-onyl)-benzene **12** is as follows: A mixture of 2,5-dimethoxy tetrahydrofuran (6.6 g, 0.05 mol), acetone dicarboxylic acid (5.84 g, 0.04 mol), water (20 mL) and c-HCl (0.5 mL) was stirred for 0.5 h. *p*-Phenylene diamine (2.16 g, 0.02 mol) in water (10 mL) was added by using a dropping funnel at 0 ºC. After the reaction mixture was stirred under N_2 at room temperature for 22 h, a crude brown solid was precipitated. The reaction mixture was diluted with water (20 mL) and neutralized with saturated $NaHCO_3$ solution. The neutralized solution was extracted with CH_2Cl_2 (100 mL × 3). The organic layer was dried (Na_2SO_4), filtered and concentrated. The residue was chromatographed on a silica gel (EtOAc: *n*-hexane = 3:1, v/v) to yield **12** (4.47 g, 69 %) as a brown crystalline solid. ^{1}H NMR showed a singlet at δ 4.49 for four protons of C1 and C5, a double at δ 1.78 for four protons of $C6_n$ and $C7_n$, a doublet at δ 2.17 for four protons of $C6_x$ and $C7_x$, a double doublet at δ 2.22 (H-2(4)$_\alpha$, *J* = 1.6, 15.2 Hz) for four protons of $C2_\alpha$ and $C4_\alpha$ and a double doublet at δ 2.70 (H-2(4)$_\alpha$, *J* = 3.0, 15.0 Hz) for four protons of $C2_\beta$ and $C4_\beta$. Aromatic protons were at δ 6.89 as a singlet.

Mass spectra showed a protonated molecular ion at m/z 324 corresponding to the molecular formular $C_{20}H_{24}N_2O_2$. Form these observations, this product was proposed to have the structure of **12**. *p*-Dipyrrolylbenzene **10** and 8-(4-pyrrol-1-yl-phenyl)-8-azabicyclo[3.2.1]octan-3-one **11** were synthesized as byproducts. However, the reaction of 1,2-phenylenediamine with 2,5-dimethoxy tetrahydrofuran, acetone dicarboxylic acid and conc. HCl in water did not give the expected product, 1,2-di-(8-azabicyclo[3.2.1]octan-3-onyl)benzene **15**. We suppose that the major reason is the steric hindrance of tropane rings.

Structures of all other products are suggested by the similar manner as **7** and **12** and Table-1 shows some physical data of the products.

TABLE-1
PHYSICAL DATA OF PRODUCTS SYNTHESIZED FROM PYRIDINEDIAMINES AND PHENYLENEDIAMINES

Starting material	Product	Reaction time (h)	m.p. (ºC)	Yield (%)*
1	**7**	28	139-140	67
2	**8**	30	199-200	48
3	**9**	28	193-194	52
4	**10**	22	213-214	4
4	**11**	22	230-231	12
4	**12**	22	246-247	69
5	**13**	31	–	2
5	**14**	31	176-178	38
6	**15**	35	–	–

*Isolated yields.

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