Synthesis of Di-(*N*-tropinonyl)alkanes and Di-(*N*-tropinonyl)benzenes

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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]

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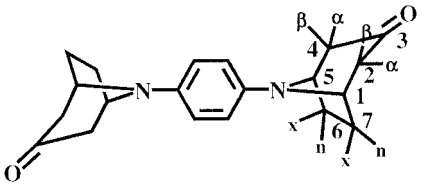
As a part of a research program related to the synthetic study of pharmacologically interesting tropane compounds, we now report the synthesis of di-(*N*-tropinonyl)- benzenes and di-(*N*-tropinonyl)alkanes in the reaction of phenylenediamines (or diaminoalkanes) with 2,5-dimethoxytetrahydrofuran, and acetonedicarboxylic acid at 0 °C.

Earlier we reported the synthesis of *N*-substituted nortropinones in the reaction of amines with 2,5-dimethoxytetrahydrofuran, and acetonedicarboxylic acid.[9,10]

A representative experimental procedure for the synthesis of 1,4-di-(8-azabicyclo[3,2,1]octan-3-onyl)benzene (**7**) is as follows: A mixture of 2,5-dimethoxytetrahydrofuran (6.6 g, 0.05 mol), acetonedicarboxylic acid (5.84 g, 0.04 mol), water (20 mL), and c-HCl (0.5 mL) was stirred for 30 min. *p*-Phenylenediamine (2.16 g, 0.02 mol) in water (10 mL) was added by using a dropping funnel at 0 °C. 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 dichloromethane (100 mL × 3). The organic layer was dried (Na_2SO_4), filtered and concentrated. The residue was chromatographed on a silica gel (*n*-hexane : ethyl acetate = 1 : 3, v/v) to yield **7** (4.47 g, 69%) as a brown crystalline solid. ^{1}H-NMR showed a singlet at δ4.49 for four protons of C1 and C5, a doublet at δ1.78 for four protons of $C6_n$ and $C7_n$, a doublet at δ2.17 for four protons of $C6_x$ and $C7_x$, a doublet at δ2.22 (H-2(4)$_\alpha$, J = 3 Hz). for four protons of C2$_\alpha$ and C4$_\alpha$, and a doublet at δ2.70 (H-2(4)$_\alpha$, J = 10 Hz) for four protons of C2$_\beta$ and C4$_\beta$. Aromatic protons were at δ 6.89 as a singlet.



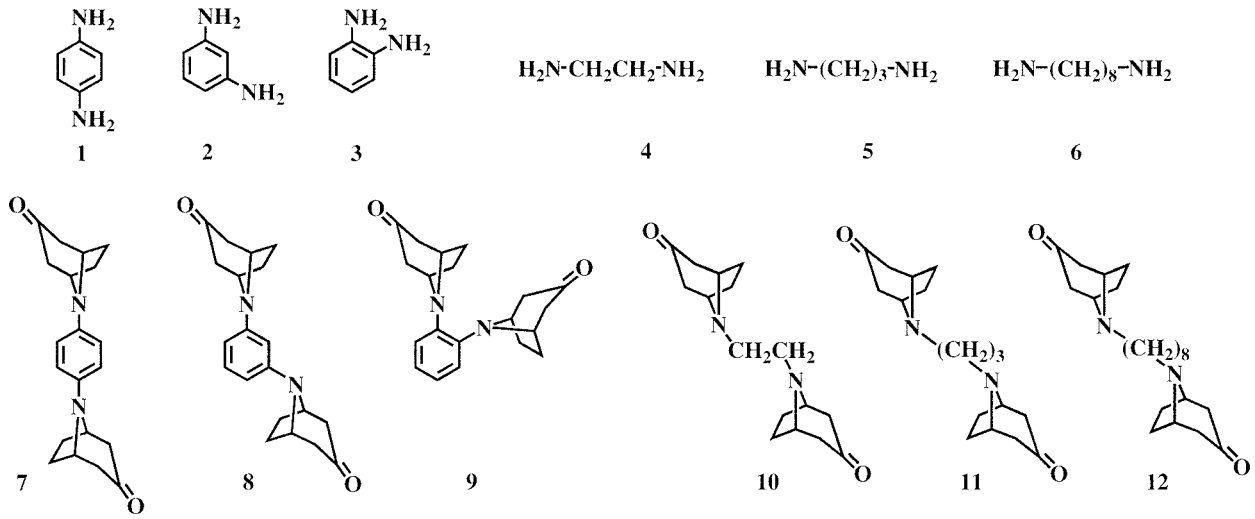


Figure 1. Structure of Di-(*N*-tropinonyl)benzenes and Di-(*N*-tropinonyl)alkanes.

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Table 1. Physical Data of Di-(*N*-tropinonyl)benzenes and Di-(*N*-tropinonyl)alkanes

Starting Meterial	Product	Reaction time (h)	Melting point (°C)	Yield* (%)
1	7	22	246~247	69
2	8	31	176~178	38
3	9	–	–	–
4	10	24	140~142	27
5	11	27	Liq.	31
6	12	67	Liq.	35

*Isolated yield

MS showed a protonated molecular ion at m/z 324 corresponding to the molecular formular $C_{20}H_{24}N_2O_2$. From these observations, this product was proposed to have the structure of **7**. However, the reaction of 1,2-phenylene diamine with 2,5-dimethoxytetrahydrofuran, acetonedicarboxylic acid, and c-HCl in water did not give the expected product, 1,2-di-(8-azabicyclo[3,2,1]octan-3-onyl)-benzene (**9**). We suppose that the major reason is the steric hindrance of tropane rings.

When various diaminoalkanes were used as the diamine source di-(8-azabicyclo[3,2,1]octan-3-onyl)alkanes **10-12** were obtained and characterized. In the case of **11**, ^{1}H-NMR showed a singlet at δ 3.57 for four protons of C1 and C5, a doublet at δ 1.60 for four protons of $C6_n$ and $C7_n$, a doublet at δ 2.03 for four protons of $C6_x$ and $C7_x$, a doublet at δ 2.64 (H-2(4), J = 4 Hz) for four protons of $C2_\alpha$ and $C4_\alpha$, a doublet at δ 2.72 (H-2(4)$_\beta$, J = 10 Hz) for four protons of $C2_\beta$ and $C4_\beta$, a clear quintet at δ 1.83 for two protons at the middle carbon of propane, and a triplet at δ 2.69 for four protons at C1 and C3 of propane. And, MS showed a protonated molecular ion at m/z 290 corresponding to the molecular formular $C_{17}H_{26}N_2O_2$. From these observations, this product was proposed to have the structure of 1,3-di-(8-azabicyclo[3,2,1]octan-3-onyl)-propane (**11**).

Structures of all other products are suggested by the similar manner as **7** and **11**, and Table 1 shows some physical data of the products.

Experimental Section

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 60F_{254}) and compounds were visualized using a uv lamp. Proton nuclear magnetic resonance 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 1,4-Di-(8-azabicyclo[3,2,1]octan-3-onyl)-benzene (7): mp 246-247 °C. IR (ν, KBr, cm^{-1}); 3037, 2923, 1730 (C=O), 1590. ^{13}C-NMR ($CDCl_3$); 208.93, 138.05, 117.18, 55.22, 45.76, 29.20. Mass, m/z (rel. intensity, %); 324 (100), 267 (58.3), 214 (27.8), 117 (13.9), 68 (14.8).

Synthesis of 1,3-Di-(8-azabicyclo[3,2,1]octan-3-onyl)-benzene (8): In the procedure described for the preparation of **7**, *m*-phenylenediamine (2.16 g, 0.02 mol) gave a crude brown solid after 31 h stirring. The residue was chromatographed on a silica gel (*n*-hexane : ethyl acetate = 5 : 1, v/v) to yield **8** (2.46 g, 38%) as a light brown crystalline solid. m.p. 176-178 °C. IR (ν, KBr, cm^{-1}); 3040, 2920, 1728 (C=O), 1595. ^{1}H-NMR ($CDCl_3$); δ 7.23 (t, 1H), 6.39 (d, 3H), 4.49 (s, 4H), 2.74 (d, 4H), 2.32 (d, 4H), 2.18 (d, 4H), 1.80 (d, 4H). ^{13}C-NMR ($CDCl_3$); 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 (21.3), 267 (51.9), 225 (14.8), 209 (51.9), 143 (15.7), 117 (16.7), 68 (15.7).

Synthesis of 1,2-Di-(8-azabicyclo[3,2,1]octan-3-onyl)-ethane (10): In the procedure described for the preparation of **7**, ethylenediamine (1.2 g, 0.02 mol) gave a crude deep brown solid after 24h stirring. The residue was chromatographed on a silica gel (*n*-hexane : dichloromethane : methanol = 10 : 10 : 1, v/v/v) to yield **10** (1.51 g, 27%) as a light yellow brown crystalline solid. m.p. 140-142 °C. IR (ν, KBr, cm^{-1}); 3030, 2920, 2905, 1725 (C=O). ^{1}H-NMR ($CDCl_3$); δ 3.55 (s, 4H), 2.77 (s, 4H), 2.62 (d, 4H), 2.16 (d, 4H), 2.02 (d, 4H), 1.57 (d, 4H). ^{13}C-NMR ($CDCl_3$); δ 209.61, 59.24, 50.25, 47.37, 27.83. Mass, m/z (rel. intensity, %); 276 (2), 138 (100), 96 (13), 54 (8).

Synthesis of 1,3-Di-(8-azabicyclo[3,2,1]octan-3-onyl)-propane (11): In the procedure described for the preparation of **7**, 1,3-diaminopropane (1.48 g, 0.02 mol) gave a crude deep brown solid after 27 h stirring. The residue was chromatographed on a silica gel (*n*-hexane : ethyl acetate = 1 : 3, v/v) to yield **11** (1.82 g, 31%) as a deep brown oil. IR (ν, KBr, cm^{-1}); 3035, 2920, 2909, 1723 (C=O). ^{1}H-NMR ($CDCl_3$); δ 6.68 (d, 2H), 6.15 (t, 2H), 3.57 (s, 4H), 2.74 (s, 4H), 2.67 (dd, 4H), 2.20 (dd, 4H), 2.05 (m, 4H), 1.82 (m, 2H), 1.60 (m, 4H). ^{13}C-NMR ($CDCl_3$); δ 210.31, 58.98, 48.51, 47.63, 28.55. Mass, m/z (rel. intensity, %); 290 (10.3), 165 (11.2), 152 (20.6), 138 (100), 122 (44.9), 108 (16.8), 96 (22.4), 81 (16.8), 68 (15), 55 (16.8).

Synthesis of 1,8-Di-(8-azabicyclo[3,2,1]octan-3-onyl)-octane (12): In the procedure described for the preparation of **7**, 1,8-diaminooctane (2.88 g, 0.02 mol) gave a crude deep brown solid after 67 h stirring. The residue was chromatographed on a silica gel (dichloromethane : ethyl acetate = 1 : 1, v/v) to yield **12** (2.53 g, 35) as a deep brown oil. IR (ν, KBr, cm^{-1}); 3030, 2925, 2910, 1726 (C=O). ^{1}H-NMR ($CDCl_3$); δ 3.52 (s, 4H), 2.67 (d, 4H), 2.54 (t, 4H), 2.15 (d, 4H), 2.00 (d, 4H), 1.53 (d, 4H), 1.33 (s, 12H). ^{13}C-NMR ($CDCl_3$); δ 210.23, 58.42, 50.08, 47.10, 29.48, 29.07, 27.88, 27.46. Mass, m/z (rel. intensity, %); 360 (12.9), 303 (100), 275 (9.3), 245 (7.4), 138 (68.5), 96 (13.8), 68 (11.1), 55 (12.9).

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