

Synthesis of 4,5-dihydro-1,6:3,8-dimethano-1,3,6,8-benzotetraazecine

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Three-component condensation of formaldehyde, *o*-phenylenediamine, and ethylenediamine gave for the first time 4,5-dihydro-1,6:3,8-dimethano-1,3,6,8-benzotetraazecine. Its structure was proved by X-ray diffraction analysis. A similar condensation of formaldehyde with a mixture of ethylenediamine and 1,2-diamino-4-methylbenzene yielded 10-methyl-4,5-dihydro-1,6:3,8-dimethano-1,3,6,8-benzotetraazecine and a condensation with a mixture of *o*-phenylenediamine and propane-1,2-diamine yielded 4-methyl-4,5-dihydro-1,6:3,8-dimethano-1,3,6,8-benzotetraazecine.

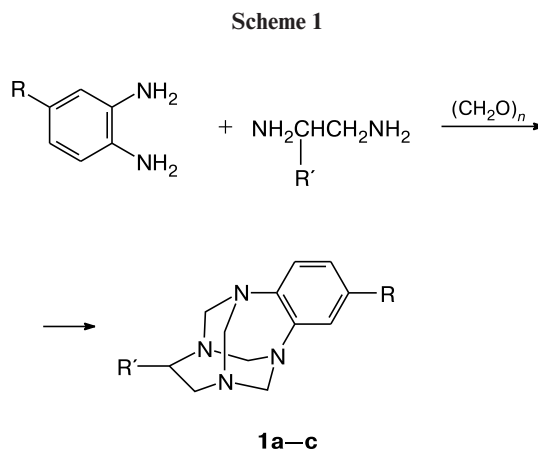
Key words: *o*-phenylenediamine, 1,2-diamino-4-methylbenzene, ethylenediamine, propane-1,2-diamine, formaldehyde, X-ray diffraction analysis, condensation.

For design and synthesis of complex polycyclic framework molecules, first one should realize how several simple molecules organize themselves into a larger one. In 1860, A. M. Butlerov discovered condensation of formaldehyde with ammonia in the ratio 6 : 4 into hexamethylenetetramine, the reaction producing no other stable products.¹ Previously,² we have found that a mixture of these reagents and aromatic 1,2-diamines yields, along with hexamethylenetetramine and condensation products from formaldehyde and diamines, products of three-component condensation of formaldehyde, ammonia, and aromatic 1,2-diamines. It was interesting to try to replace ammonia by aliphatic diamines in this reaction.

We discovered that a reaction of formaldehyde with a mixture of ethylenediamine and *o*-phenylenediamine gives not only formaldehyde–diamine condensation products but also 4,5-dihydro-1,6:3,8-dimethano-1,3,6,8-benzotetraazecine (**1a**) via three-component condensation (Scheme 1). Using 1,2-diamino-4-methylbenzene instead of *o*-phenylenediamine, we obtained 10-methyl-4,5-dihydro-1,6:3,8-dimethano-1,3,6,8-benzotetraazecine (**1b**). Its isomer containing the Me group in the ethylene bridge rather than in the benzene ring (4-methyl-4,5-dihydro-1,6:3,8-dimethano-1,3,6,8-benzotetraazecine (**1c**)) was obtained as a racemate by condensation of formaldehyde, *o*-phenylenediamine, and propane-1,2-diamine.

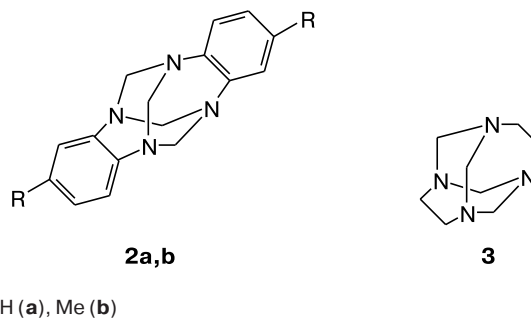
The structures of compounds **1a–c** were confirmed by elemental analysis data and ¹H NMR and mass spectra.

Parallel two-component condensation reactions of formaldehyde with *o*-phenylenediamine, 1,2-diamino-4-methylbenzene, and ethylenediamine gave compounds



R = R' = H (**a**); R = Me, R' = H (**b**); R = H, R' = Me (**c**)

2a, **2b**,² and **3**,^{3–7} respectively. Condensation of formaldehyde with propane-1,2-diamine yielded a mixture of liquid products⁸ easily separable from the target crystalline product **1c**.



We also developed a simplified procedure for the synthesis of product **3** from ethylenediamine and formaldehyde.

The structure of compound **1a** was determined from X-ray diffraction data (Fig. 1). Its geometrical parameters are comparable with those for compounds **2a** (see Ref. 4) and **3** (see Ref. 5), which suggests their structural similarity.

The C(sp²)—N bond lengths in structure **1a** (1.437 Å) equal those in structure **2a**. The C(sp³)—N bond lengths in structures **1a** and **3** are 1.464 and 1.470 Å, respectively. The angles N—C—N (the mean is 118.8°) and the angles C—N—C (they range from 112.2° to 115.6°; the mean is 114.3°) are comparable with those in 1,3,6,8-tetraazatricyclo[4.4.1.1^{3,8}]dodecane (**3**) (the mean values of the angles N—C—N and C—N—C are 118.6° and 114.8°, respectively).

Compounds **1a–c** belong to a specific group of aromatic amines in which the lone electron pairs on the N atoms bound to the benzene ring cannot efficiently interact with its electron system because of geometrical factors.

Experimental

¹H NMR spectra were recorded on a Bruker WM-500 spectrometer (500.13 MHz) for 2–3% solutions in CDCl₃. Mass spectra were recorded on a Finnigan MAT-90 instrument (direct inlet probe, voltage 5.0 kV, cathode emission current 100 μA, ionizing electron energy 70 eV, ionization chamber temperature 200 °C). Perfluorokerosene was used as a standard. The resolution was

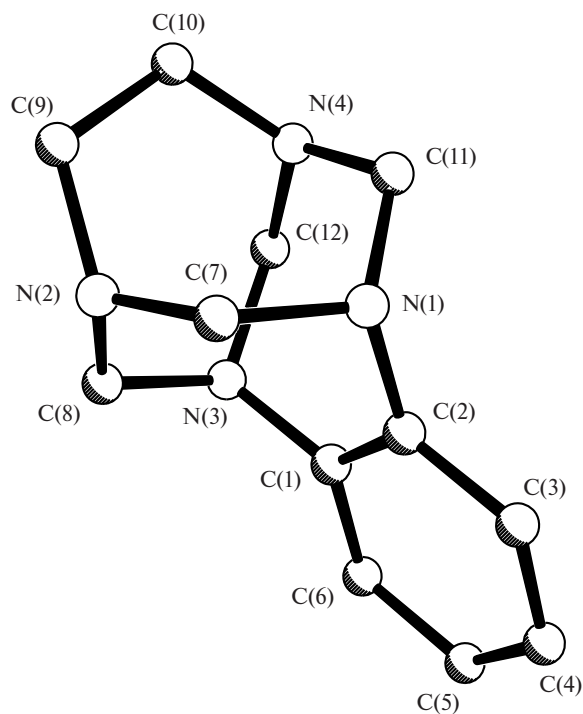


Fig. 1. Structure **1a**.

$M/\Delta M = 10\,000$. The injector temperature was 20 °C. The course of the reactions was monitored and the purity of the products was checked by TLC on Silufol UV-254 plates. Spots were visualized with the iodine vapor in a moist chamber or under UV light.

4,5-Dihydro-1,6:3,8-dimethano-1,3,6,8-benzotetraazecine (1a). Paraformaldehyde (3.3 g, 108 mmol) was added in small portions to a stirred solution of *o*-phenylenediamine (3.0 g, 27 mmol) and ethylenediamine (2 mL, 27 mmol) in hexane (20 mL). The reaction mixture was heated to complete homogenization. The organic layer was separated by decanting and the product was extracted from the aqueous layer with hot hexane (4×20 mL). The combined extracts were concentrated and the residue was recrystallized successively from water and isopropyl alcohol. The yield was 1.0 g (17%), white crystals, m.p. 103–104 °C (subl.). Found (%): C, 65.57; H, 7.03; N, 27.40. C₁₂H₁₆N₄. Calculated (%): C, 65.63; H, 6.97; N, 27.70. ¹H NMR, δ: 3.40 (s, 4 H, NCH₂CH₂N); 4.20 (d, 8 H, 4 NCH₂N, ²J = 13.5 Hz); 7.18 (s, 4 H, C₆H₄). MS, *m/z* (*I*_{rel} (%)): 216 [M]⁺ (48), 174 (24), 147 (22), 131 (100), 118 (46), 104 (45), 85 (43), 77 (51), 55 (69), 51 (35).

Table 1. Selected crystallographic parameters and a summary of data collection for structure **1a**

Parameter	Value
Molecular formula	C ₁₂ H ₁₆ N ₄
M	216.29
Crystal size/mm	0.21×0.24×0.35
Crystal system	Monoclinic
Space group	<i>P</i> 2 ₁ / <i>c</i>
<i>a</i> /Å	12.090(2)
<i>b</i> /Å	16.092(3)
<i>c</i> /Å	12.533(3)
α/deg	90
β/deg	113.27(3)
γ/deg	90
<i>V</i> /Å ³	2240.0(8)
<i>Z</i>	8
<i>d</i> _{calc} /g cm ⁻³	1.283
μ _{Mo} /mm ⁻¹	0.081
<i>F</i> (000)	928
Diffractometer	«Enraf–Nonius CAD-4»
<i>T</i> /K	293
Radiation (λ/Å)	Mo-Kα (0.71073), graphite monochromator
Scan mode	ω
Range of θ/deg	2.17–27.90
Ranges of <i>h</i> , <i>k</i> , <i>l</i> indices	–15 < <i>h</i> < 1, 0 < <i>k</i> < 21, –14 < <i>l</i> < 16
Number of measured reflections	2343
Number of independent reflections	2130
Number of parameters refined	(<i>R</i> _{int} = 0.0206) 289
GOOF по <i>F</i> ²	0.659
<i>R</i> (<i>I</i> > 2σ(<i>I</i>))	<i>R</i> ₁ = 0.0371, <i>wR</i> ₂ = 0.1023
<i>R</i> (for all reflections)	<i>R</i> ₁ = 0.0382, <i>wR</i> ₂ = 0.1029
Residual electron density (max/min)/e Å ⁻³	0.127/–0.188

10-Methyl-4,5-dihydro-1,6:3,8-dimethano-1,3,6,8-benzotetrazeine (1b). 1,2-Diamino-4-methylbenzene (3.0 g, 24.6 mmol) and ethylenediamine (1.72 mL, 24.6 mmol) were dissolved with heating in water (10 mL). The resulting solution was mixed with light petroleum (20 mL). Paraformaldehyde (2.95 g, 98.4 mmol) was added in small portions to the stirred mixture, which was heated to complete homogenization. The organic layer was separated by decanting and the product was extracted from the aqueous layer with hot light petroleum (4×20 mL). The combined extracts were concentrated and the residue was recrystallized successively from water and light petroleum. The yield was 1.5 g (27%), white crystals, m.p. 115–116 °C (subl.). Found (%): C, 67.32; H, 7.55; N, 24.80. C₁₃H₁₈N₄. Calculated (%): C, 67.79; H, 7.87; N, 24.32. ¹H NMR, δ: 2.35 (s, 3 H, Me); 3.45 (s, 4 H, NCH₂CH₂N); 4.25 (d, 8 H, 4 NCH₂N, ²J = 13.5 Hz); 7.00 (m, 3 H, C₆H₃). MS, *m/z* (*I*_{rel} (%)): 230 [M]⁺ (12), 202 (4), 147 (9), 146 (49), 145 (100), 132 (14), 119 (8), 70 (10), 67 (10), 56 (39), 42 (77).

4-Methyl-4,5-dihydro-1,6:3,8-dimethano-1,3,6,8-benzotetrazeine (1c). Paraformaldehyde (7.0 g, 230 mmol) was added in small portions to a solution of *o*-phenylenediamine (3.35 g, 60 mmol) and propane-1,2-diamine (4.35 g, 60 mmol) in light petroleum (20 mL). The reaction mixture was stirred for 30 min. The organic layer was separated by decanting and the product was extracted from the residue with light petroleum (3×20 mL). The combined extracts were concentrated and the residue was recrystallized from hexane. The yield was 3.0 g (22%), white crystals, m.p. 90–91 °C. Found (%): C, 67.32; H, 7.55; N, 24.80. C₁₃H₁₈N₄. Calculated (%): C, 67.79; H, 7.87; N, 24.32. ¹H NMR, δ: 1.25 (d, 3 H, Me, *J* = 7.8 Hz); 3.60 (m, 1 H, NCH₂CH₂); 2.90, 3.70 (both dd, 2 H, NCH₂C, *J* = 7.2 Hz, *J* = 15.0 Hz, *J* = 9.6 Hz, *J* = 15.0 Hz); 4.20 (d, 8 H, 4 NCH₂N, *J* = 15.6 Hz); 7.15 (s, 4 H, C₆H₄). MS, *m/z* (*I*_{rel} (%)): 230 [M]⁺ (36), 160 (17), 133 (69), 132 (72), 131 (100), 118 (36), 104 (22), 97 (100), 78 (51), 77 (55), 56 (21).

1,3,6,8-Tetraazatricyclo[4.4.1.1^{3,8}]dodecane (3). Paraformaldehyde (1289 g, 43 mol) was added in small portions for 6 h to vigorously stirred ethylenediamine (1500 mL, 21.5 mol) so that the reaction temperature was no higher than 50 °C. The reaction mixture was left for 12 h. The precipitate that formed was filtered off and recrystallized from isopropyl alcohol. The yield was 1400 g (78%), white crystals, m.p. 183–184 °C (*cf.* Refs 6, 7: m.p. 181–182 °C).

X-ray diffraction analysis. Selected crystallographic parameters and a summary of data collection for structure **1a** are given in Table 1. The structure was solved by the direct method and refined

by the least-squares method in the full-matrix anisotropic approximation for all non-hydrogen atoms. The H atoms were located geometrically and refined in the rider model with fixed isotropic thermal parameters (*U*_{iso} = 0.08 Å²). The calculations were performed with the SHELX-86 (see Ref. 9) and SHELX-93 programs.¹⁰ Comprehensive X-ray diffraction data have been deposited with the Cambridge Crystallographic Data Center.

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