ISSN 1070-3632, Russian Journal of General Chemistry, 2015, Vol. 85, No. 9, pp. 2080–2086. © Pleiades Publishing, Ltd., 2015.
Original Russian Text © N.A. Anisimova, E.I. Khristoforova, Yu.G. Trishin, 2015, published in Zhurnal Obshchei Khimii, 2015, Vol. 85, No. 9, pp. 1499–1505.

To the 85th Anniversary of birthday of late Yu.G. Gololobov

Cyclocondensation of Ethylenediamine with Acetone and Methyl Ethyl Ketone as a Synthetic Route to 14-Membered Azamacrocyclic Compounds

N. A. Anisimova, E. I. Khristoforova, and Yu. G. Trishin

St. Petersburg State Technological University of Plant Polymers, ul. Ivana Chernykh 4, St. Petersburg, 198095 Russia
e-mail: trish@YT4470.spb.edu

Received July 17, 2015

Abstract—14-Membered azamacrocyclic compounds, substituted 1,4,8,11-tetraazacyclotetradeca-4,11-diene and 1,4,8,11-tetraazacyclotetradeca-4,14-diene containing azomethine cycle and amine nitrogen atoms, were obtained as a mixture of *trans*- and *cis*-isomers by reacting ethylenediamine with acetone and methyl ethyl ketone. More stable *trans*-isomers were isolated individually by vacuum distillation.

Keywords: cyclocondensation, ethylenediamine, acetone, methyl ethyl ketone, azamacrocyclic compounds

DOI: 10.1134/S1070363215090108

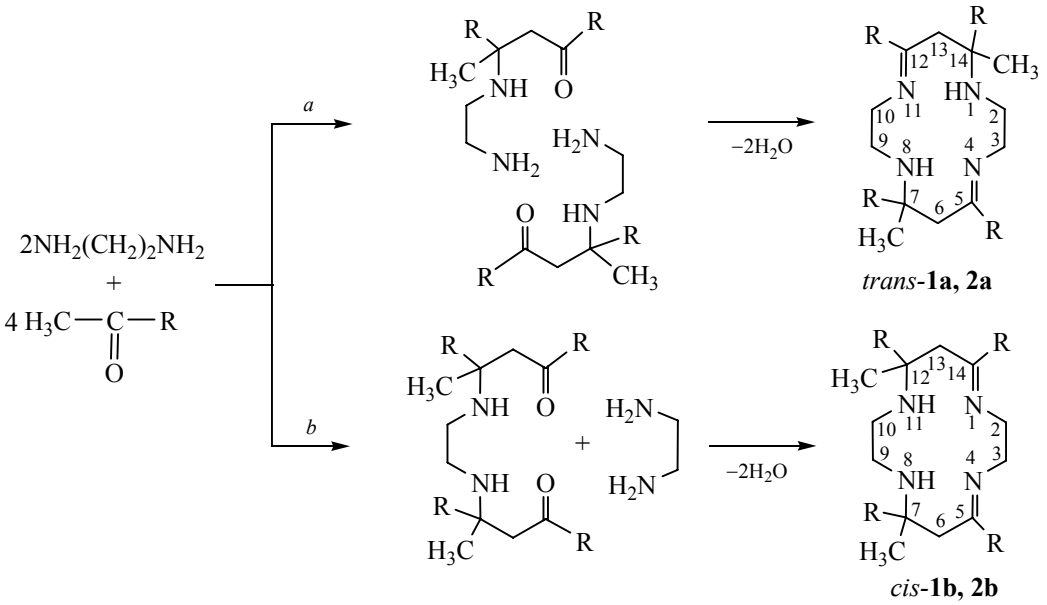
Azamacrocyclic compounds are important objects of supramolecular chemistry [1] due in particular to their wide spectrum of practically important properties. So, they tend to form discotic liquid crystals [2] and exhibit selective binding of metal cations and anions, acting as artificial anion receptors [3]. Metal complexes of macrocyclic Schiff bases are characterized by unusual magnetic and optical properties [4, 5], as well as by catalytic activity in redox reactions and inhibitory activity towards auto-oxidation reactions [6, 7]. Some of them show biological activity and are potential drugs. For example, complexes of 14-membered azamacrocycle exhibit antibacterial activity and are available for the use as analogs of antifungal drug Fluconazole [8].

In this regard, the development of new methods for the synthesis of macrocyclic nitrogen-containing compounds is an urgent task.

Recently, we obtained $[LNi]^{2+}Cl_2$ complex (L was 5,7,7,12,14,14-hexamethyl-1,4,8,11-tetraazacyclotetradeca-4,11-diene) via reaction of nickel(II) trisethylenediaminate complex with acetone and alongside the complex free ligand L was isolated in a 35% yield of [9]. It should be noted that attempts to synthesize aliphatic diene ligands as free Schiff bases have been unsuccessful due to their ability to hydrolysis and aldol-crotonic condensation [10, 11]. However, azamacrocyclic ligand we obtained was a stable compound. This fact prompted us to investigate the possibility of azamacrocycles synthesis by reacting ethylenediamine with acetone and other aliphatic ketones, by passing the intermediate step of producing their perchlorate salts or metal complexes, wherefrom free ligands can be prepared by the action of alkali solution [12, 13] or by reaction with potassium cyanide [14, 15], respectively.

Cyclocondensation of ethylenediamine with acetone and methyl ethyl ketone was found to form 14-membered azamacrocyclic compounds as a mixture of *trans*- and *cis*-isomers: 5,7,7,12,14,14-hexamethyl-1,4,8,11-tetraazacyclotetradeca-4,11-diene **1a**, 5,7,7,12,12,14-hexamethyl-1,4,8,11-tetraazacyclotetradeca-4,14-diene **1b** and 7,14-dimethyl-5,7,12,14-tetraethyl-1,4,8,11- tetraazacyclotetradeca-4,11-diene **2a**, 7,12-dimethyl-5,7,12,14-tetraethyl-1,4,8,11-tetraazacyclotetradeca-4,14-diene **2b**, respectively. Reacting ethylenediamine with acetone in a ratio of 1 : 2 under reflux in ethanol for 10 h resulted in the formation of *trans*- (**1a**) and *cis*-isomers (**1b**) in a ratio of 1.3 : 1.0. By ^{1}H NMR, the reaction was not complicated by side transformations (Fig. 1). The total yield of compounds **1a** and **1b** was 63%.

Scheme 1.



R = CH_3 (**1a**, **1b**), C_2H_5 (**2a**, **2b**).

Cyclocondensation of ethylenediamine with acetone proceeded successfully at room temperature in 24 h to form *trans*- (**1a**) and cis-isomers (**1b**) in a ratio of 1.5 : 1.0 (according to ^{1}H NMR spectrum) in a quantitative yield.

The formation of isomeric compounds **1a** and **1b** occurred probably through the pre-condensation of ethylenediamine with one (direction *a* for *trans*-isomer) or two (direction *b* for *cis*-isomer) acetone molecules according to Scheme 1.[1]

Similarly, ethylenediamine reacted with methyl ethyl ketone to form the corresponding isomeric macrocycles **2a** and **2b** in a ratio of 1.5 : 1.0 in a total yield of 58%.

It should be noted that *cis*-isomers **1b** and **2b** were unstable and underwent decomposition on prolonged storage or under a vacuum distillation. These compounds were only detected spectrally in a mixture with *trans*-isomers **1a** or **2a**. The latter were isolated in a pure state by distillation in a vacuum as yellowish oily substances. Contrary to the statement in [10, 11] on the instability of the azamacrocyclic compounds containing alkyl substituents on the carbon atoms of the macrocycle, *trans*-isomers **1a** and **2a** were stable, were stored at 4–20°C for over a year and did not undergo degradation even after prolonged boiling in ethanol solution.

To compare spectral characteristics of the resulting compounds **1a** and **1b** and the known salts of these macrocyclic compounds we obtained perchlorate salt $L{\cdot}2HClO_4$ by condensation of monoperchlorate salt of ethylenediamine and acetone by procedures [10, 18]. In contrast to the literature data [10, 18], the reaction afforded not *trans*-diene L salt, but a mixture of its structural isomers **3a** and **3b** with different mutual arrangement of azomethine groups (*trans*-**3a**, *cis*-**3b**) in 1 : 1 ratio (Scheme 2).

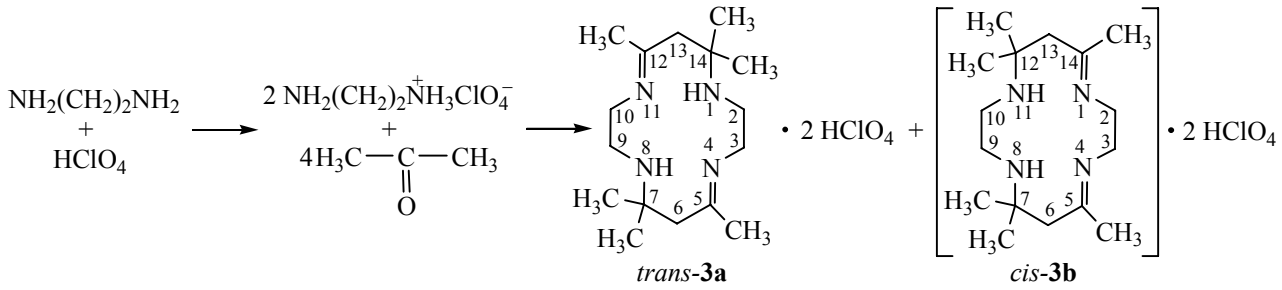
Formation of isomers **3a** and **3b** was proved by doubling of the signals of protons and carbon atoms of all the structural fragments in the ^{1}H and ^{13}C NMR spectra (see table).

The structures of compounds **1**–**3** were confirmed by means of IR, ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry, and by comparison of their spectral characteristics with those of parent compounds [19].

In the ^{1}H NMR spectra of compounds **1**–**3** there were the signals of protons of all the structural fragments of the molecules (see table). The signals of four CH_3 groups in compounds **1** and **3** or two CH_3 groups of compounds **2** attached at sp^3-hybridized

[1] Hereinafter, the numbering of ring atoms was carried out in accordance with recommendations [16, 17] used for naming these heterocyclic compounds.

Scheme 2.



carbon atom were equivalent and appeared as one singlet in the range of 0.93–1.30 ppm. Protons of two CH_3 groups bound with azomethine carbon resonated in weaker field (1.90–2.09 ppm). The signals of ethyl protons of compounds **2a** and **2b** attached to the sp^3-hybridized carbon atoms appeared in the upfield area [CH_3 proton were seen as triplets at 0.77 and 0.88 ppm; CH_2 protons being diastereotopic resonated as two multiplets at 1.26 and 1.33 ppm, 1.45 and 1.51 ppm (Fig. 2)]. The protons of ethyl moieties attached to the sp^2-hybridized carbon atoms resonated in more downfield region [0.95, 1.02 ppm (CH_3); 2.14, 2.23 ppm (CH_2)]. The signals of methylene bridge protons (H^6, H^{13}) of compounds **1** and **3** were observed as singlets in the range of 2.40–2.69 ppm. In the spectra of compounds **2a** and **2b** these protons were diastereotopic and appeared as multiplets at 2.45 (**2a**) and 2.36 ppm (**2b**) (Fig. 2). The methylene protons of $NHCH_2$ and $=NCH_2$ groups in compounds **1**–**3** resonated as multiplets in the regions of 2.54–3.26 and 3.20–3.66 ppm, respectively. The broadened signals in the range of 4.40–4.50 ppm corresponded to the protons of two amino groups.

Analyzing ^{1}H NMR spectral data of compounds **1**–**3**, we conclude that the chemical shifts of the protons of methylene groups bound to the amino and azomethine nitrogen atoms may be used as a criterion of the identification of *trans*- and *cis*-isomers, since in all the cases the difference values of the chemical shifts (e. g., $\Delta = \delta_{H^3,H^{10}} - \delta_{H^2,H^9}$ for compounds **1a**–**3a** or $\Delta = \delta_{H^3,H^2} - \delta_{H^{10},H^9}$ for compounds **1b**–**3b**), is significantly larger in the case of the *trans*-isomers (0.63–0.80 ppm) than in the case of the *cis*-isomers (0.25–0.30 ppm).

Unequivocal assignment of the proton signals was provided by two-dimensional HMQC and HMBC spectroscopy. So, in ^{1}H–^{13}C HMQC spectrum of **1a** (Fig. 3) a correlation existed between the corresponding protons and carbon atoms: δ_H 1.03 ppm and δ_C 28.0 ppm, δ_H 1.90 ppm and δ_C 31.0 ppm for the

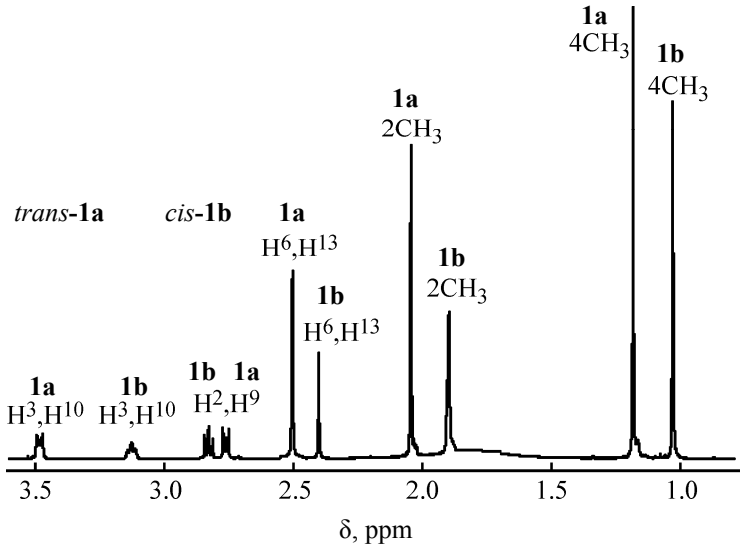
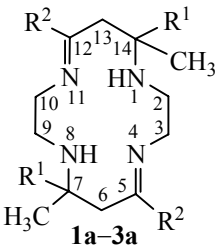
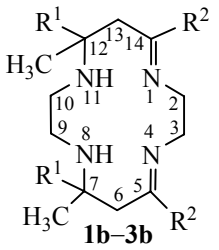


Fig. 1. ^{1}H NMR spectrum of the reaction mixture of *trans*- and *cis*-isomers **1a** and **1b**.

^{1}H and ^{13}C NMR spectral data for compounds **1–3**



1a–3a



1b–3b

Comp. no.	δ_H(CDCl$_3$), ppm							δ_C(CDCl$_3$), ppm					
	CH_3	R^1	R^2	H^6, H^{13}	H^2, H^9 (H^9, H^{10})	H^3, H^{10} (H^2, H^3)	NH	C^7, C^{14} (C^7, C^{12})	C^6, C^{13}	C^5, C^{12} (C^5, C^{14})	C^3, C^{10} (C^2, C^3)	C^2, C^9 (C^9, C^{10})	CH_3, =CCH_3
1a	1.03 s	1.03 s (CH_3)	1.90 s (CH_3)	2.40 s	2.75 t	3.50 t	4.50 br.s	52.20	50.0	174.00	54.58	42.70	28.00 31.00
					$\Delta = 0.75$[a]								
1b	1.12 s	1.12 s (CH_3)	2.00 s (CH_3)	2.49 s	(2.83 t)	(3.13 t)	4.40 br.s	(52.00)	46.19	(168.82)	(54.11)	(41.26)	28.12 30.62
					$\Delta = 0.30$[b]								
2a	0.93 s	0.77 t ($C\underline{H}_3CH_2$), 1.26 m and 1.45 m ($CH_3C\underline{H}_2$)	0.95 m ($C\underline{H}_3CH_2$), 2.14 q ($CH_3C\underline{H}_2$)	2.45 m	2.80 m	3.60 m	–	49.20	44.89	170.85	54.78	42.85	25.57 35.58
					$\Delta = 0.80$[a]								
2b	1.00 s	0.88 t ($C\underline{H}_3CH_2$), 1.33 m and 1.51 m ($CH_3C\underline{H}_2$)	1.02 m ($C\underline{H}_3CH_2$), 2.23 q ($CH_3C\underline{H}_2$)	2.36 m	(2.94 m)	(3.19 m)	–	(48.80)	46.24	(172.37)	(54.04)	(41.10)	26.33 33.37
					$\Delta = 0.25$[b]								
3a[c]	1.30 s	1.30 s (CH_3)	2.09 s (CH_3)	2.69 s	3.03 m	3.66 m	4.20	58.26	49.40	174.62	58.26	50.03	25.39 31.85
					$\Delta = 0.63$[a]								
3b[c]	1.22 s	1.22 s (CH_3)	2.02 s (CH_3)	2.50 s	(3.25 m)	(3.50 m)	–	(55.26)	47.37	(174.60)	(54.26)	(43.45)	24.73 30.99
					$\Delta = 0.25$[b]								

[a] $\Delta = \delta_{H^3,H^{10}} - \delta_{H^2,H^9}$. [b] $\Delta = \delta_{H^3,H^2} - \delta_{H^{10},H^9}$. [c] The spectra were recorded in DMSO-d_6.

CH_3-groups attached to the sp^3- and sp^2-hybridized carbon atoms, respectively; H^6,H^{13} (2.40 ppm)/C^6,C^{13} (50.0 ppm); H^2,H^9 (2.75 ppm)/C^2,C^9 (42.70 ppm); H^3,H^{10} (3.50 ppm)/ C^3,C^{10} (54.58 ppm). The ^{1}H–^{13}C HMBC spectrum of **1a** contained the following correlations between the protons and adjacent carbons: H^3,H^{10} (3.50 ppm)/C^2,C^9 (42.70 ppm) and C^5,C^{12} (174.0 ppm); H^2,H^9 (2.75 ppm)/C^7,C^{14} (52.2 ppm); H^6,H^{13} (2.40 ppm)/C^5,C^{12} (174.0 ppm) and C^7,C^{14} (52.2 ppm); CH_3 (1.03 ppm)/C^7,C^{14} (52.2 ppm); CH_3 (1.90 ppm)/C^5,C^{12} (174.0 ppm) and C^6,C^{13} (50.0 ppm). In ^{1}H–^{1}H COSY spectrum of **1a** (Fig. 4) a correlation was observed between the signals of the protons H^2, H^9 and H^3, H^{10} of CH_2 groups of the ethylene bridge.

The ^{13}C NMR spectra of compounds **1–3** contained the signals of all carbon atoms (see the table).

In the mass spectrum (ESI) of compound **1a** the most intense peak with *m*/*z* 281.2701 corresponded to the ion $[M - H]^+$. Besides, there were the following peaks, *m*/*z*: 282.2722 $[M - 2H]^+$, 283.2528 $[M - 3H]^+$, and 284.2525 $[M - 4H]^+$. IR spectra of compounds **1** and **2** contained absorption of the secondary amino groups (3180–3255 cm^{-1}) and C=N bond (1600–1670 cm^{-1}).

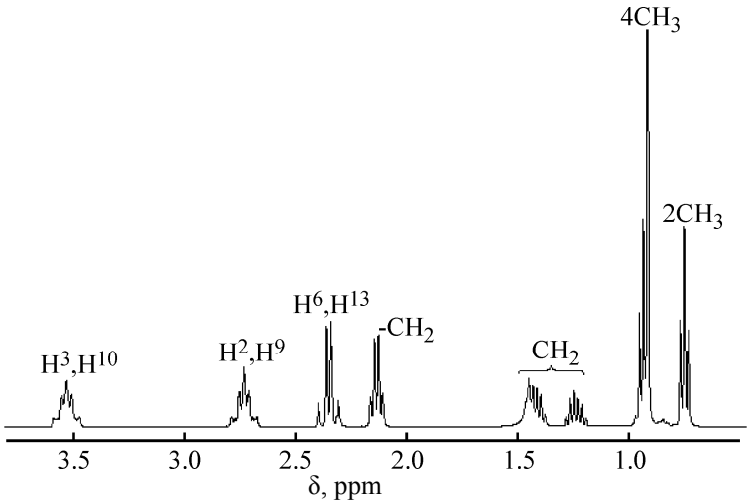


Fig. 2. ^{1}H NMR spectrum of compound **2a**.

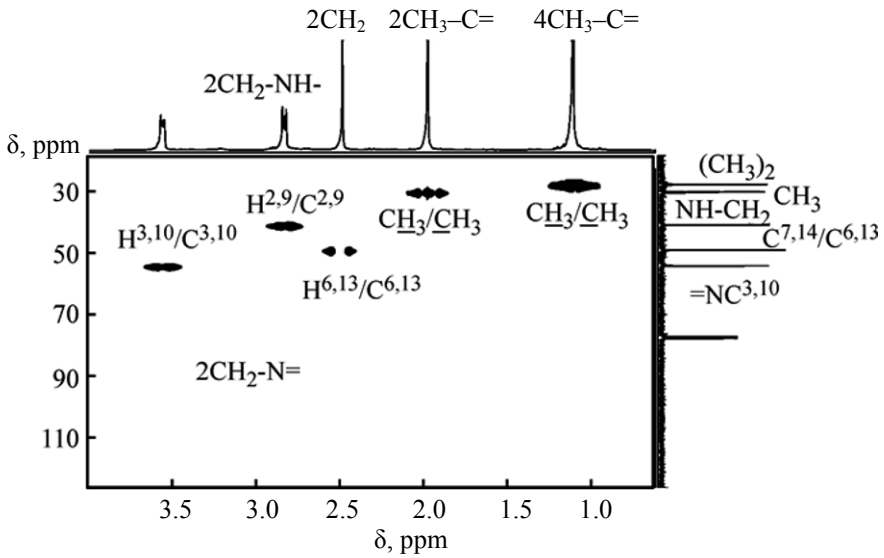


Fig. 3. ^{1}H–^{13}C HMQC spectrum of compound **1a**.

Hence, the reaction of ethylenediamine with aliphatic ketones as exemplified by methyl ethyl ketone and acetone is a simple method of the synthesis of 14-membered azamacrocyclic compounds containing amino and azomethine ring nitrogen atoms.

EXPERIMENTAL

^{1}H, ^{13}C, ^{1}H–^{13}C HMQC, ^{1}H–^{13}C HMBC NMR spectra were recorded on a Jeol ECX400A spectrometer operating at 100.52 (^{13}C) and 399.78 MHz (^{1}H) in $CDCl_3$. IR spectra were taken on a Shimadzu IR Prestige-21 Fourier spectrometer in chloroform. Mass spectrum (ESI) was registered on a Bruker Customer microtof 10223 (solvent methanol) instrument. TLC analysis was performed on Silufol UF-254 plates, eluting with hexane–acetone mixture, 3 : 2. Elemental analysis was made on a Carlo Erba 1106 instrument.

Ethylenediamine monohydroperchlorate and perchlorates **3a** and **3b** were prepared according to [9].

5,7,7,12,14,14-Hexamethyl-1,4,8,11-tetraazacyclotetradeca-4,11-diene (1a) and 5,7,7,12,12,14-hexamethyl-1,4,8,11-tetraazacyclotetradeca-4,14-diene (1b). *a. Under heating.* A solution of 10.2 g (0.17 mol) of ethylenediamine in 50 mL of anhydrous acetone and ethanol (1 : 1) was refluxed for 10 h. The reaction mixture was evaporated on a rotary eva-

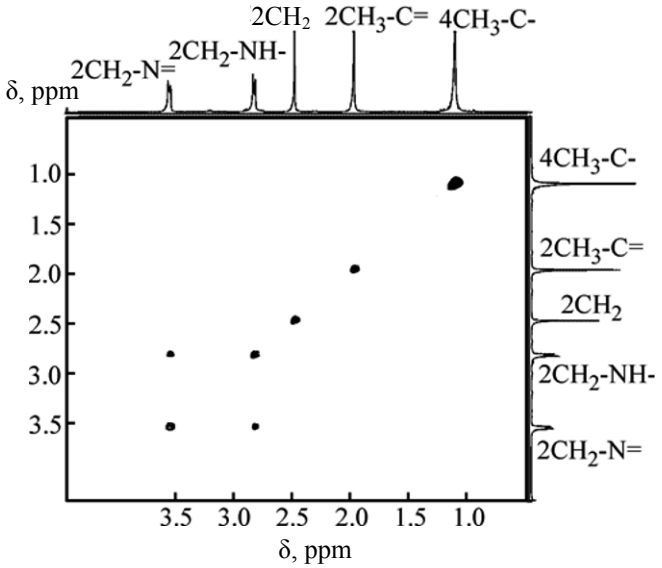


Fig. 4. ^{1}H–^{1}H COSY spectrum of compound **1a**.

porator. The residue, a mixture of *cis*- and *trans*-isomers in a ratio of **1a** : **1b** = 1.3 : 1.0 (^{1}H NMR), was distilled in a vacuum to yield 14.9 g (63%) of a mixture of *trans*- and *cis*-isomers **1a** and **1b** in a ratio of 3.0 : 1.0, bp 40–60°C (2 mmHg). Additional distillation of the mixture in a vacuum gave *trans*-isomer **1a**, bp 60–62°C (2 mmHg). Mass spectrum (ESI): *m*/*z* 281.2701 $[M - H]^+$. Found, %: C 68.31, 68.38; H 11.54, 11.56; N 20.05, 20.10. $C_{16}H_{32}N_4$. Calculated, %: C 68.52; H 11.50; N 19.98.

b. At room temperature. A solution of 10.2 g (0.17 mol) of ethylenediamine in 50 mL of anhydrous acetone and ethanol (1 : 1) was stirred for 10 h and left standing at room temperature for 24 h. The reaction mixture was evaporated on a rotary evaporator. The residue, a mixture of *cis*- and *trans*-isomers in a ratio of **1a** : **1b** = 1.5 : 1.0 (^{1}H NMR), was distilled in a vacuum (2 mmHg) to yield three fractions: 3.40 g of a mixture of isomers **1a** and **1b** in a ratio of 3.0 : 1.0, bp 28–40°C; 4.87 g of a mixture of isomers **1a** and **1b** in a ratio of 10.0 : 1.0, bp 40–60°C and 8.74 g of *trans*-isomer **1a**, bp 60–62°C. The overall yield of compounds **1a** and **1b** was 72%.

7,14-Dimethyl-5,7,12,14-tetraethyl-1,4,8,11-tetraazacyclotetradeca-4,11-diene (2a) and 7,12-dimethyl-5,7,12,14-tetraethyl-1,4,8,11-tetraazacyclotetradeca-4,14-diene (2b). *a. Under heating.* A solution of 10.2 g (0.17 mol) of ethylenediamine in 60 mL of anhydrous methyl ethyl ketone and ethanol (1 : 1) was refluxed for 10 h. The reaction mixture was evaporated on a rotary evaporator. The residue was distilled in a vacuum to give 16.5 g (58%) of a mixture of *trans*- and *cis*-isomers **2a** and **2b** in a ratio of 4.0 : 1.0, bp 22–29°C (3 mmHg). Additional distillation of the resulting mixture in a vacuum gave *trans*-isomer **2a**, bp 25–28°C (3 mmHg). Found, %: C 71.51, 71.56; H 11.80, 11.84; N 16.74, 16.80. $C_{20}H_{40}N_4$. Calculated, %: C 71.37; H 11.98; N 16.65.

b. At room temperature. A solution of 10.2 g (0.17 mol) of ethylenediamine in 60 mL of anhydrous methyl ethyl ketone and ethanol (1 : 1) was stirred for 10 h and left standing at room temperature for 24 h. The reaction mixture was evaporated on a rotary evaporator. The residue, a mixture of *trans*- and *cis*-isomers in a ratio **2a** : **2b** = 1.7 : 1.0 (^{1}H NMR), was distilled in a vacuum (3 mmHg) to yield three fractions: 8.9 g of a mixture of isomers **2a** and **2b** in a ratio of 4.0 : 1.0, bp 25–27°C; 5.8 g of a mixture of isomers **2a** and **2b** in a ratio of 7.0 : 1.0, bp 28–29°C and 5.2 g of *trans*-isomer **2a**, bp 29–30°C. The overall yield of compounds **2a** and **2b** was 70%.

Ethylenediamine monohydroperchlorate. To 37 mL of 70% solution of freshly distilled ethylenediamine was added with stirring 72 mL of 43.3% solution of perchloric acid at cooling with ice-salt mixture. Then, the temperature of the reaction mixture was adjusted to 20°C and mixture was evaporated on a rotary evaporator at a temperature below 60°C. The resulting residue was left standing to complete crystallization. The obtained crystals were filtered off, washed with ethanol, and dried in air. Yield 54 g (84%), mp 150°C.

5,7,7,12,14,14-Hexamethyl-1,4,8,11-tetraazacyclotetradeca-4,11-diene perchlorate (3a, 3b). A solution of 10 g of ethylenediamine monohydroperchlorate in 100 mL of anhydrous acetone was allowed to stand for 12 h at 20°C. The formed crystals were filtered off and washed with acetone and then with ethanol. According to ^{1}H NMR, the obtained crystals were a mixture of *trans*- and *cis*-isomers **3a** and **3b** in a ratio of 1.0 : 1.0. Yield 12 g (80%), mp 147–150°C (mp 158°C [10]).

ACKNOWLEDGMENTS

Spectral analysis was performed using the equipment of the Center for Joint Use of the Herzen State Pedagogical University of Russia.

This work was financially supported by the Russian Foundation for Basic Research (grant no. 14-03-00588).

REFERENCES

1. Steed, J.W. and Atwood, J.L., *Supramolecular Chemistry*, Wiley, 2009.
2. Gallant, A.J., Hui, J.K.-H., and Zahariev, F.E., *J. Org. Chem*., 2005, vol. 70, p. 7936. DOI: 10.1021/jo050742g.
3. Sessler, J.L., Katayev, E., Pantos, G.D., and Ustynyuk, Yu.A., *Chem. Commun*., 2004, no. 11, p. 1276. DOI: 10.1039/B403665D.
4. Brooker, S., *Eur. J. Inorg. Chem*., 2002, vol. 10, p. 2535. DOI: 10.1002/1099-0682(200210)2002:10.
5. Di Bella, S., *Chem. Soc. Rev*., 2001, vol. 30, p. 355. DOI: 0.1039/b100820j.
6. Nam, W. and Muller, J.G., *Inorg. Chem*., 1996, vol. 35, p. 6632. DOI: 10.1021/ic9513651.
7. Tsymbal, L.V., Andriichuk, I.L., Lampeka, Ya.D., and Pritzkow, H., *Russ. Chem. Bull*., 2010, vol. 59, no. 8, p. 1572. DOI: 10.1007/s11172-010-0280-3.
8. Singh, D. and Kumar, K., *J. Serb. Chem. Soc*., 2010, vol. 75, no. 4, p. 475. DOI: 10.2998/JSC091021028S.
9. Anisimova, N.A., Gomzyakova, E.N., Kondrat'eva, R.R., and Trishin, Yu.G., *Butlerovsk. Soobshch.*, 2013, vol. 12, no. 36, p. 22.
10. Yatsimirskii, K.B., Kol'chinskii, A.G., Pavlishchuk, V.V., and Talanova, G.G., *Sintez makrotsiklicheskikh soedinenii* (Synthesis of Macrocyclic Compounds), Kiev: Naukova Dumka, 1987.
11. Borisova, N.E., Reshetova, M.D., and Ustynyuk, Yu.A., *Russ. Chem. Rev*., 2007, vol. 76, no. 9, p. 785. DOI: 10.1070/RC2007v076n09ABEH 003705.
12. Hay, R.W. and Pujari, M.P., *Inorg. Chim. Acta*, 1986, vol. 121, p. 57. DOI: 10.1016/S0020-1693(00)87740-3.
13. Kolinski, R.A. and Korybut-Daszkiewicz, B., *Polish J. Chem*., 1982, vol. 56, p. 1033.
14. Love, J.L. and Powell, H.K.J., *Chem. Commun*., 1968, no. 1, p. 39. DOI: 10.1039/C19680000039.
15. Curtis, N.F., *J. Chem. Soc. (C)*, 1967, no. 20, p. 1979. DOI: 10.1039/j39670001979.
16. Hay, R.W. and Gidney, P.M., *J. Chem. Soc. Dalton. Trans*., 1976, p. 974. DOI: 10.1039/DT9760000974.
17. Cook, D.F., Curtis, N.F., and Hay, R.W., *J. Chem. Soc. Dalton. Trans*., 1973, p. 1160. DOI: 10.1039/DT9730001160.
18. Hay, R.W., Lawrance, G.A., and Curtis, N.F., *J. Chem. Soc. Perkin Trans. 1*, 1975, no. 3, p. 591. DOI: 10.1039/P19750000591.
19. Warner, L.G. and Busch, D.H., *J. Am. Chem. Soc*., 1968, vol. 90, no. 25, p. 6938. DOI: 10.1021/ja01027a008.