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Synthesis of 2-Oxa-4,6,8-triazabicyclo[3.3.0]octanes

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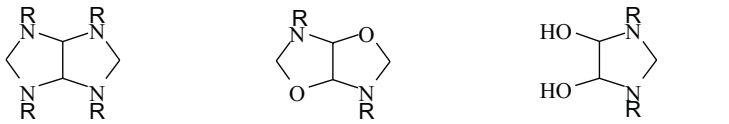
4,6,8-Triaryl-2-oxa-4,6,8-triazabicyclo[3.3.0]octanes **(4)** and 6,8-diaryl-2,4-dioxa-6,8--diazabicyclo[3.3.0]octanes **(5)** were synthesized by condensation of arylamines with glyoxal and formaldehyde in CH_3CN. Change of the reaction solvent to CH_3OH leads to dimethoxy imidazolidine **(7)**. Depending on the reaction conditions, intermediates with different configuration are formed. The X-ray crystal structure determination of **5** shows a *cis* fusion of the two five member rings, in line with two anomeric effect; a strong $n_N \rightarrow \sigma^*_{C\text{-}O}$ interaction and a weak $n_O \rightarrow \sigma^*_{C\text{-}N}$. The compound **5** is a rare molecule containing N-C-N and O-C-O units adjacent to N-C-O anomeric moiety. The results show, that in the presence of anomeric unit of N-C-O, the anomeric effect of N-C-N and O-C-O moieties are negligible.

Key words: 2-oxa-4,6,8-triazabicyclo[3.3.0]octanes, 2,4-dioxa-6,8-diazabicyclo[3.3.0]octane, dimethoxy imidazolidine, X-ray analysis, glyoxal condensation

A few reports on the synthesis of 2,4,6,8-tetraazabicyclo[3.3.0]octanes **(1)** [1–8], 2,6-dioxa-6,8-diazabicyclo[3.3.0]octane **(2)** and 1,3-disubstituted-4,5-dihydroxy imidazolidine **(3)** with substitutes only on nitrogen (N) atom have appeared [1,9–11]. Molecules showing anomeric effect in R-X-C-Y-R′ system (where X = N, Y = N, O) have been subject of studies during the last two decades [12–15].



1: R = Alkyl, Aryl, Acyl, Benzyl **2**: R = Pyridyl **3**: a R = Pyridyl, b R = Acyl

Formulae of the molecules **1**, **2** and **3**.

Experimental results and molecular mechanics calculations for N-C-O moiety are consistent with the following interactions: aromatic conjugation with N atoms and two unequal anomeric; a strong $n_N \rightarrow \sigma^*_{C\text{-}O}$ anomeric interaction and a weak $n_O \rightarrow \sigma^*_{C\text{-}N}$

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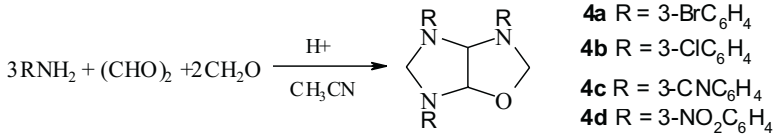
[7,9–10]. In this article we report results obtained in the synthesis of 4,6,8-triaryl-2-oxa-4,6,8-triazabicyclo[3.3.0]octanes **(4)**, 6,8-diaryl-2,4-dioxa-6,8-diazabicyclo[3.3.0]octanes **(5)** and 1,3-diaryl-4,5-dimethoxy imidazolidine **(7)**. Also, based on structural analysis of X-ray diffraction data, the anomeric interactions of adjacent N-C-O, O-C-O and N-C-N moieties in molecules **5e** is discussed.

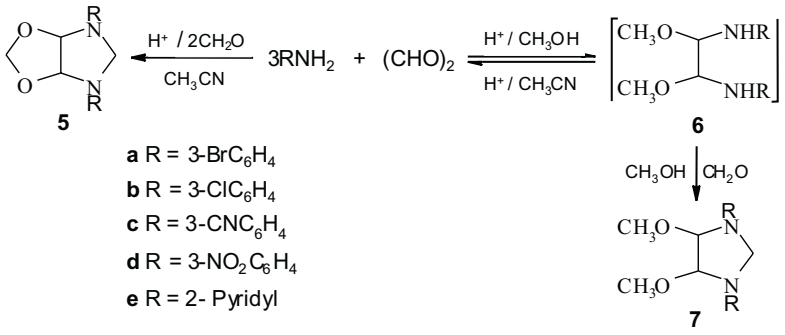
RESULTS AND DISCUSSION

By condensation of 3-substituted anilines, glyoxal, and formaldehyde in equimolar ratio, using formic acid as catalyst, in CH_3CN, at 40–60°C 4,6,8-triaryl-2-oxa-4,6,8-triaza–bicyclo[3.3.0]octane (**4a–d**) were formed (Scheme 1).



Scheme 1. Synthesis of compounds **4**.

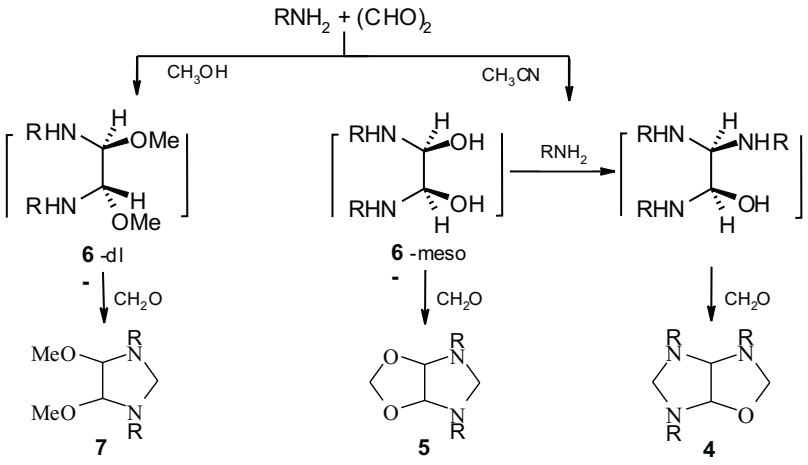
Best results were obtained at pH = 8–9.5. These reactions were completed in 48 h at room temperature. The ^{1}H NMR spectra of **4a–d** exhibit AB quartet for *cis* CH protons and two AB systems for the two CH_2 protons, in agreement with a *cis* configuration at the ring junction. Reaction of 3-nitroaniline (2 mol) with of glyoxal (1 mol) and of formaldehyde (2 mol) gave a yellow precipitate of 6,8-di-(3-nitrophenyl)-2,4-dioxa-6,8-diazabicyclo[3.3.0]octane (**5d**) (Scheme 2).



Scheme 2. Synthesis of compounds **5**, **6** and **7**.

In the case of **5d**, ^{1}H NMR spectrum showed two AB quartets for methylene groups, which is indicative of the *cis* canfiguration at the ring junction. Furthermore, the reaction of 3-nitro and 3-aminobenzonitrile with glyoxal in CH_3OH leads to **6c–d** [17]. The compound **6d** was transformed to **5d** in the presence of aqueous formaldehyde and formic acid in CH_3CN. In addition, by concentration the extract of reaction of

2-aminopyridine with glyoxal and formaldehyde in CH_3CN, 6,8-di-(2-aminopyridyl)-2,4-dioxa-6,8-diazabicyclo[3.3.0]octane (**5e**) was obtained [10]. The spectral data of **5e** are similar to **5d**. Addition of formaldehyde to **6c** produces a white precipitate of 1,3-di(3-cyanophenyl)-4,5-dimethoxy-imidazolidine (**7c**). The previous investigations [1,9,10] show that compounds (**3a**,**b**) with structure similar to **7c** were obtained in protic solvent. Considering the above results, the condensation of arylamine with glyoxal and formaldehyde in CH_3CN (aprotic solvent) gives **4** or **5**, but the reaction in CH_3OH (protic solvent) gives product **6** or **7**. A proposed reaction mechanism, which may accounts for all the observed products, is presented in the Scheme 3. Our results as well as previous works on the condensation of amines with glyoxal suggest that mechanism of their reactions involves the formation of intermediate **6** [9], that depending on the reaction conditions can exist in the form of *meso* or *dl* isomers. Thus, in aprotic solvents such as CH_3CN, the **6**-*meso* is formed, which then leads to products **4** or **5** (Scheme 3).



Scheme 3. A proposed way of formation of compounds **4**, **5**, **6** and **7**.

In protic solvents such as CH_3OH, the **6**-*dl* configuration is favorable, which leads to **7**. The crystal structure of **5e** was solved to confirm the stereochemistry and determine the overall molecular conformation. Details regarding the data collection and structural solution and refinement are presented in the experimental section. The atomic coordinates and thermal parameters are available from the authors on request. Figure 1 shows a computer-generated view of **5e** with atom numbering. A plot of the ring juncture in Figure 1 shows more clearly *cis* configuration.

There are some unusual structural features in this molecule. The ring bond angles N_4-C_5-N_6, N_4-C_{3a}-C_{6a} are shortened and C_{3a}-N_4-C_{12}, C_5-N_4- C_{3a} and C_5-N_4-C_{12} deviate significantly from 109° and are all rather large. It is most noteworthy that both pyridyl rings lie in the plane of the central ring (torsion angle involving the atoms

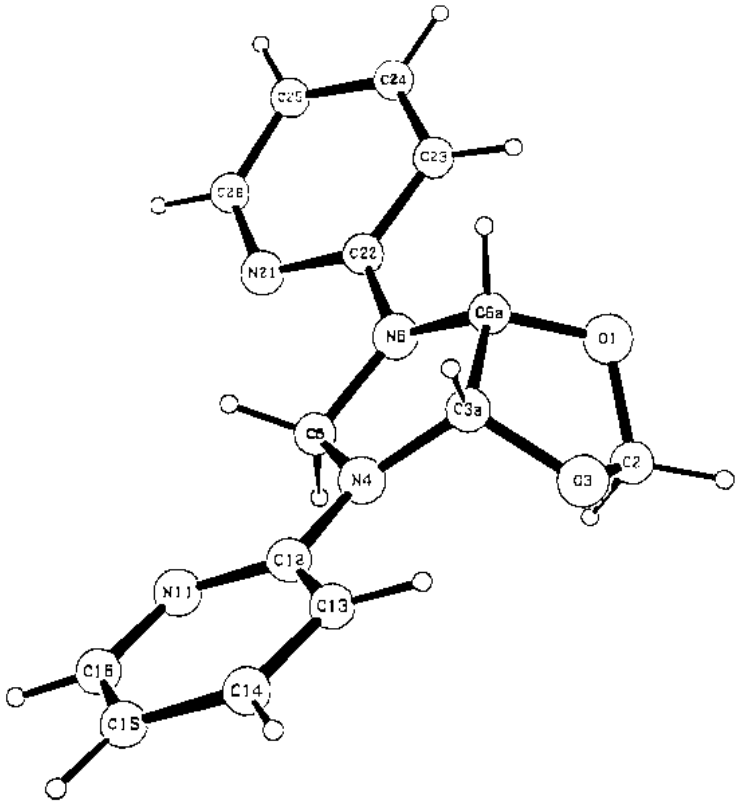


Figure 1. X-ray crystal structure of **5e**. Selected bond lengths (Å), bond angles (°) and torsion angles (°): N4-C_{23} 1.443, N4-C_5 1.445, N4-C_{12} 1.374, N_6-C_5 1.445, N_6-C_{6a} 1.439, N_6-C_{22} 1.375, O_1-C_2 1.413, O_1-C_{6a} 1.424, O_3-C_{3a} 1.420, N_4-C_5-N_6 103.1, C_5-N_4-C_{3a} 114, C_5-N_4-C_{12} 120.6, C_{3a}-N_4-C_{12} 122.8, N_4-C_{3a}-O_3 114, C_{3a}-O_3-C_2 105.4, O_1-C_2-O_3 105.1, C_{3a}-N_4-C_5-N_6 1.98, C_{6a}-N_6-C_5-N_4 –1.35, C_5-N_6-C_{6a}-C_{3a} 0.32, C_5-N_4-C_{3a}-C_{6a} –1.82, N_4-C_{3a}-C_{6a}-N_6 0.87, C_5-N_6-C_{6a}-O_1 113.88, N_6-C_{6a}-O_1-C_2 –91.73, O_3-C_{3a}-C_{6a}-O_1 1.00, C_{3a}-C_3-C_2-O_1 38.8, C_{6a}-O_1-C_2-O_3 –38.09.

C_{3a}-N_4-C_5-N_6 and C_{6a}-N_6- C_5-N_4 are 1.98° and –1.35° respectively). The central imidazolidine is essentially planar with maximum deviation of 0.0333 Å from the mean plane comprised of the atoms C_{3a}-N_4-C_5-N_6-C_{6a}. The results show that the resonance of aromatic rings with N atom is due to reduced N-pyramidality. It therefore reduces the bond length of N_4-C_{12}. Short C-O and C-N bonds as well as tightened N_4-C_3-N_6 bond angle (103.1°) leads to an anticipated anomeric effect in N-C-O moiety due two cross hyperconjugation from $n_{N4} \rightarrow \sigma^*_{C\text{-}O}$ and $n_O \rightarrow \sigma^*_{C\text{-}N}$ Back donation of electron from N atom drastically decrease N-pyramidality, which leading to an increase in p character of the 1p's. Experimental results and molecular mechanic calculation show that molecules having O-C-O or N-C-N units undergo an anomeric interaction. The molecules having adjacent N-C-O and N-C-N units as shown earlier, due to better anomeric interaction in N-C-O units the anomeric effect of N-C-N is negligible [9–11,13–16]. **5e** is a rare molecule having O-C-O and N-C-N units adjacent to N-C-O anomeric moiety. Bond angles of N_4-C_5-N_6, N_4-C_{3a}-C_{6a}, O_1-C_2-O_3 and

O_3-C_{3a}-C_{6a} are less than 109° and C_{3a}-N_4-C_{12}, C_5-N_4-C_{12}, C_{3a}-N_4-C_5 and O_3-C_{3a}-N_4 are more than 109°. Variation of the bond lengths and the bond angles of N-C-N, O-C-O has no significant anomeric effect that is seen for these units. The results show that in the presence of anomeric N-C-O unit that is a donor (N) and an acceptor (O), the anomeric effect of N-C-N and O-C-O moieties are negligible.

EXPERIMENTAL

All commercially available chemical reagents were used without further purification. Melting points were determined with an Electrothermal 9200 apparatus and uncorrected. IR spectra were recorded on a Shimadzu 4300 spectrometer. NMR spectra were recorded with a Bruker DRX- 500 AVANCE instrument. Mass analysis of the product was conducted with a FISONS TRIO 1000 GC-Mass instrument. Elemental analysis were carried out with a C, H, N, O Rapid-Heraeus apparatus.

Synthesis of 4,6,8-tri(3-bromophenyl)-2-oxa-4,6,8-triazabicyclo[3.3.0]octane (4a): To a stirred solution of 3-bromoaniline (5.16 g, 30 mmol), in CH_3CN (50 ml) at 40–60°C, glyoxal (1.45 g, of 40% aqueous solution, 10 mmol) is slowly added. The mixture was stirred at room temperature for 24 h, then formic acid (0.11 g, of 98% aqueous solution, 2 mmol) and formaldehyde (1.62 g, of 37% aqueous solution, 20 mmol) was gradually added in a period of five minutes. The solution was stirred for 24 h at room temperature until precipitate was formed. The precipitate was filtered and the filtrate concentrated to got residual precipitate. Overall yield of crude product is 2.98 g (51%). Recrystallization from CH_3CN gave crystals of **4a**, m.p. 216–217°C. ^{1}H NMR (DMSO-d_6) δ: 6.77–7.43 (m, 12H, CH_{Ar}), 6.02–6.28 (AB_q, 2H, J = 4.6 Hz, CH), 4.56–5.09 (AB_q, 2H, J = 7.1 Hz, O-CH_2-N), 4.72–4.91 (AB_q, 2H, J = 4.5 Hz, N-CH_2-N). ^{13}C-NMR (DMSO-d_6) δ: 149.53, 146.14, 145.42, 131.63, 131.38, 131.25, 125.31, 123.06, 122.98, 121.71, 121.24, 118.02, 116.77, 116.37, 113.16, 113.10, 87.74, 83.39, 77.53, 65.50. The CH_2 and CH carbons are distinguished by performing DEPT ^{13}C-NMR experiment. The EI-MS, m/z: 583 (M^+). Elemental analysis for $C_{22}H_{18}N_3OBr_3$ calculated: C, 45.28; H, 3.08; N, 7.20; Br, 41.68; found: C, 45.26; H, 3.10; N, 7.21; Br, 41.59.

Condensation of 3-chloro-, 3-cyano- and 3-nitro-aniline with glyoxal and formaldehyde under similar conditions leads to **4b–d**.

4b: yield 36%; m.p. 213–214°C; ^{1}H-NMR (DMSO-d_6) δ: 6.73–7.36 (m, 12H, CH_{Ar}), 6.02–6.28 (AB_q, 2H, J = 4.5 Hz, CH), 4.58–5.10 (AB_q, 2H, J = 7.1 Hz, O-CH_2-N), 4.73–4.93 (AB_q, 2H, J = 4.4 Hz, N-CH_2-N). ^{13}C-NMR (DMSO-d_6) δ: 149.41, 145.99, 145.28, 134.46, 134.36, 131.35, 131.08, 130.95, 122.37, 118.33, 117.60, 116.96, 115.82, 113.94, 113.62, 112.76, 112.69, 87.76, 83.41, 77.55, 65.55. The EI-MS, m/z: 451 (M^+). Elemental analysis for $C_{22}H_{18}N_3OCl_3$ calculated: C, 58.54; H, 3.94; N, 9.31; Cl, 24.61; found: C, 58.51; H, 4.01; N, 9.32; Cl, 24.29.

4c: yield 39%; m.p. 240–241°C; ^{1}H NMR (DMSO-d_6) δ: 7.06–7.73 (m, 12H, CH_{Ar}), 6.18–6.49 (AB_q, 2H, J = 4.1 Hz, CH), 4.59–5.16 (AB_q, 2H, J = 7.0 Hz, O-CH_2-N), 4.86–4.96 (AB_q, 2H, J = 4.3 Hz, N-CH_2-N). The EI-MS, m/z: 418 (M^+). Elemental analysis for $C_{25}H_{18}N_6O$, calculated: C, 71.77; H, 4.30; N, 20.10; found: C, 71.69; H, 4.31; N, 20.12.

4d: yield 44%; m.p. 251–252°C. ^{1}H NMR (DMSO-d_6) δ: 7.28–8.07 (m, 12H, CH_{Ar}), 6.25–6.62 (AB_q, 2H, J = 4.2 Hz, CH), 4.70–5.27 (AB_q, 2H, J = 7.1 Hz, O-CH_2-N), 4.99–5.14 (AB_q, 2H, J = 4.1 Hz, N-CH_2-N). The EI-MS, m/z: 478 (M^+). Elemental analysis for $C_{22}H_{18}N_6O_7$ calculated: C, 55.23; H, 3.76; N, 17.57; found: C, 55.20; H, 3.75; N, 17.49.

Synthesis of 4,6,8-tri(3-nitrophenyl)-2-oxa-4,6,8-triazabicyclo[3.3.0]octane (4d) from 1,2-dimethoxy-1,2-di(3-nitrophenylamino)ethane (6d) [17]: To a stirred solution of **6d** (3.62 g, 10 mmol), formic acid (0.11 g, of 98% solution, 2 mmol) and 3-nitroaniline (1.38 g, 10 mmol) in CH_3CN (50 ml), formaldehyde (1.62 g, of 37% aqueous solution, 20 mmol) was added dropwise. The solution was stirred at 20–25°C for 60 h until a yellow precipitate was appeared. The mixture was filtered and precipitate was washed with cold CH_3CN to give 2 g of the product (44% yield). Recrystallization from H_2O-THF gave yellow crystals of **4d**, m.p. 251–252°C (dec).

Synthesis of 6,8-di(3-nitrophenyl)-2,4-dioxa-6,8-diazabicyclo[3.3.0]octane (5d): To a stirred solution of 3-nitroaniline (2.76 g, 20 mmol) and formic acid (0.05 g of 98% aqueous solution, 1.1 mmol) in CH_3CN (100 ml) at 25°C, glyoxal (1.45 g of 40% aqueous solution, 10 mmol) was added slowly. After 2 h, to the resulting mixture, formaldehyde (1.62 g of 37% aqueous solution, 20 mmol) was added slowly. The solution was stirred at room temperature for 60 h until a yellow precipitate was formed. The mixture was filtered and precipitate was washed with cold CH_3CN to give 1.78 g (50% yield) of **5d**. Recrystallization from H_2O-THF gave yellow crystals of **5d**, m.p. 235–236°C (dec). ^{1}H-NMR (DMSO-d_6) δ: 7.43–7.78 (m, 8H, CH_{Ar}), 6.2 (s, 2H, CH), 4.95–5.16 (AB_q, 2H, J = 3.6 Hz, N-CH_2-N), 4.84–5.21 (AB_q, 2H, J = 0.8 Hz, O-CH_2-O). ^{13}C-NMR (DMSO-d_6) δ: 148.01, 144.04, 130.05, 119.03, 113.00, 107.02, 92.08, 78.00, and 65.00. The CH_2 and CH carbons are distinguished by performing DEPT ^{13}C-NMR experiment. The EI-MS, m/z: 358.6 (M^+). Elemental analysis for $C_{16}H_{14}N_4O_6$ calculated: C, 53.6; H, 3.9; N, 15.6; found: C, 53.4; H, 4.1; N, 15.1.

Synthesis of 5d from 6d: To a stirred solution of 6d (3.62 g, 10 mmol) and formic acid (0.05 g, of 98% aqueous solution 1.1 mmol) in CH_3CN (100 ml) at 20–25°C, formaldehyde (1.62 g, of 37% aqueous solution, 20 mmol) was added slowly. The solution was stirred for about 48 h at 20–25°C, then 40 ml of water was added to the solution and the yellow precipitates were filtered off, 1.8 g of crude product was obtained (50% yield, m.p. 230–233°C). Recrystallization from THF-H2O gave yellow crystals of 5d (m.p. 235–236°C).

Synthesis of 6,8-di(2-aminopyridyl)-2,4-dioxa-6,8-diazabicyclo[3.3.0]octane (5e): This compound was obtained by reaction of 2-aminopyridine with glyoxal and formaldehyde in CH_3CN [9]. ^{1}H NMR (DMSO-d_6) δ: 6.75–8.27 (m, 8H, $CH_{pyridyl}$), 6.22 (s, 2H, CH), 5.01–5.27 (AB_q, 2H, J = 6.2 Hz, N-CH_2-N), 4.82–5.15 (AB_q, 2H, J = 0.9 Hz, O-CH2-O). ^{13}C-NMR ($CDCl_3$) δ: 155.09, 148.08, 138.23, 115.65, 108.24, 93.66, 87.93, 64.55. Mass spectrum, m/z: 270 (M^+). Elemental analysis for $C_{14}H_{14}N_4O_2$ calculated: C, 62.22; H, 5.19; N, 20.74; found: C, 62.19; H, 5.19; N, 20.71.

Synthesis of 1,3-di(3-cyanophenyl)-4,5-dimethoxy-imidazolidine (7c): To a stirred solution of 3-aminobenzonitrile (2.36 g, 20 mmol) in CH_3OH (40 ml) at 25°C, glyoxal (1.45 g of 40% aqueous solution, 10 mmol) was added slowly. The solution was stirred at room temperature for 1 h, then, formic acid (0.05 g of 98% solution, 1.1 mmol) and formaldehyde (0.81 g of 37% aqueous solution, 10 mmol) was added. After 24 h stirring at room temperature, the mixture was filtered and white precipitate was washed with cold EtOH to give 1.97 g (59% yield) of **7c**. Recrystallization from CH_3OH-THF gave white pure crystals of **7c**, m.p. 172–172.5°C (dec). ^{1}H NMR (acetone-d_6) δ: 7.15–7.51 (m, 8H, CH_{Ar}), 5.5 (s, 2H, CH) 5.1 (s, 2H, CH_2), 3.43 (s, 6H, CH_3). ^{13}C NMR (acetone-d_6) δ: 186.08, 131.8, 123.57, 119.21, 117.48, 114.48, 91.93 (CH), 66.52 (CH_2), and 54.5 (CH_3). The CH_3, CH_2 and CH carbons are distinguished by performing DEPT ^{13}C-NMR experiment. The EI-MS, m/z: 334 (M^+). Elemental analysis for $C_{19}H_{18}N_4O_2$ calculated: C, 68.26; H, 5.38; N, 16.7; found: C, 68.18 H, 5.1; N, 16.83.

X-ray structure analysis of 6,8-di(2-aminopyridyl)-2,4-dioxa-6,8-diazabicycelo[3.3.0] octane (5e). $C_{14}H_{14}N_4O2$, FW = 270.29. Clear colorless crystal (0.25×0.28×0.88 mm) crystallized from CH_3CN was used for data collection on an Enraf-Nonius CAD4 diffractommeter at the Hoffmann-La Roche laboratory using graphite monochromated CuKα radiation and ω-2θ scan. Unit cell; a = 11.792(1) Å, b = 5.860(1) Å, c = 18.611(1) Å, β = 93.08(1), V = 1284.07(16) Å^{-3}. Space group: $P2_{1/c}$ (monoclinic crystals), Z = 4, D (X-ray, calcd) = 1.398 g cm^{-3}, (CuKα) = 7.59 cm^{-1}. Least-squares refinement of 181 structural parameters gave agreement factors of R = 0.044, Rw = 0.062 for 2021 unique observed reflections (another reflections, with $I > 3\sigma(I)$, were considered unobserved). No significant features, only ripples from –0.20 to 0.23 e Å^{-3}, were observed in the final difference map. The structure was solved by a multiple solution procedure with the aid of the program multan 11/82 and was refined by full matrix least square. The non-hydrogen atoms were refined anisotropically. Atomic coordinates, temperature factors, bond distances, bond angles and torsion have been deposited at the Cambridge Crystallographic Data Center. Number CCDC... These data can be obtained free of charge *via* www.ccdc.cam.ac.uk/conts/retrieving; html (or from the Cambridge Crystallographic Data Centre; deposit@ccdc.cam.ac.uk).

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