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Succinonitrile Activated by Thiating Agents as Precursor of Bis-cyclic Amidines, Tectons for Molecular Engineering

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Summary. Modification of the thio-*Pinner*'s method *via in situ* activation of a nitrile by thiating agents, S_8, P_4S_{10}, *Lawesson* reagent, or $Na_2S \cdot 9H_2O$, was applied in the syntheses of bis(4,5-dihydro-1*H*-imidazol-2-yl)alkanes and bis(1,4,5,6-tetrahydropyrimidin-2-yl)alkanes.

Keywords. Bis(4,5-dihydro-1*H*-imidazol-2-yl)alkane; Bis-(1,4,5,6-tetrahydropyrimidin-2-yl)alkane; Alkanedinitrile; Thio-*Pinner*'s method; Bis(cycloamidinium-2-yl)alkane salt.

Introduction

Cyclic amidines possess a broad variety of biological activities while bis(cycloamidin-2-yl)alkanes are interesting tectons for crystal engineering of molecular solids [1–4]. Thus, the study of an efficient procedure for their synthesis is important. The general method of the synthesis of amidines is based on the reaction of nitriles with ammonia, amines, and diamines. In these procedures amines or nitriles are usually activated to facilitate the addition of a nucleophile. Ammonia and amines are activated *via* formation of alkali metal amides, and metalated amines, or silylimines, whereas the nitrile group is converted to imidate or thioimidate salts (*Pinner*'s and thio-*Pinner*'s method), nitrilium complexes, nitrilium salts, or thioamides [5].

The use of the thio-*Pinner*'s method is usually much more efficient because the thiolates are good leaving groups and the reactions could proceed under mild conditions. However, this two-step procedure is based on the addition and elimination of toxic, pungent-smelling thiols. A similar activation is possible due to the sulfur containing catalysts, S_8 [5, 6] and P_4S_{10} [5, 7] (Scheme 1), used in the synthesis of cyclic amidines. Catalysts promote the formation of amidine in a more convenient one-step procedure, but this reaction requires an excess of the diamine and higher temperature.

Results and Discussion

Lever et al. [7] demonstrated that the reaction of succinonitrile and 1,2-diaminoethane at a molar ratio of 1:2 in presence of a catalytic amount of phosphorus pentasulfide leads to **1** in 60% yield. We improved this procedure by using an excessive amount of the diamine (up to 5 equiv) obtaining **1** in excellent 97% yield and successfully applied this method in the synthesis of bis(cycloamidin-2-yl)alkanes **1** [7–9], **2** [8, 10], **3** [8, 9, 11, 12], **4** [8, 13], **5** [4], and **6** starting from alkanedinitriles. We extended the *in situ* nitrile group activation by other sulfur containing catalysts such as sulfur, *Lawesson* reagent and sodium sulfide nonahydrate (Scheme 1). The results are compared in Table 1.

A probable mechanism of the nitrile group activation starts from the formation of corresponding thiols from catalysts and the amine group, *i.e.* *R*NHP(S)S-(P_2S_5)-SP(S)SH, *R*NHP(S)(*Ar*)SH, *R*NHS-S_6-SH

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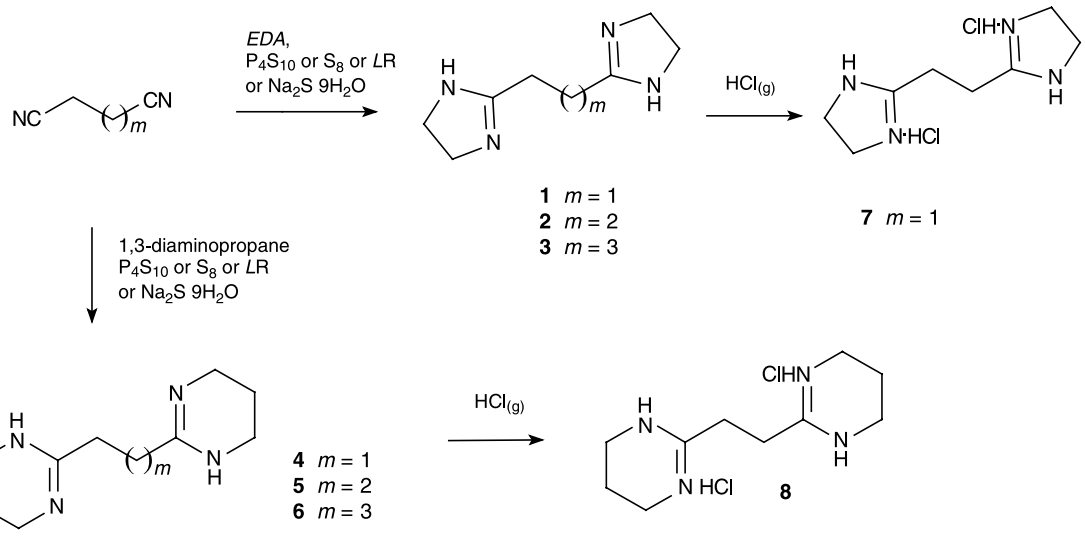


Scheme 1

Table 1. Synthesis of bis(cycloamidin-2-yl)alkanes with catalytic amounts of S_8, P_4S_{10}, *Lawesson* reagent (*L*R), and $Na_2S \cdot 9H_2O$ (Scheme 1)

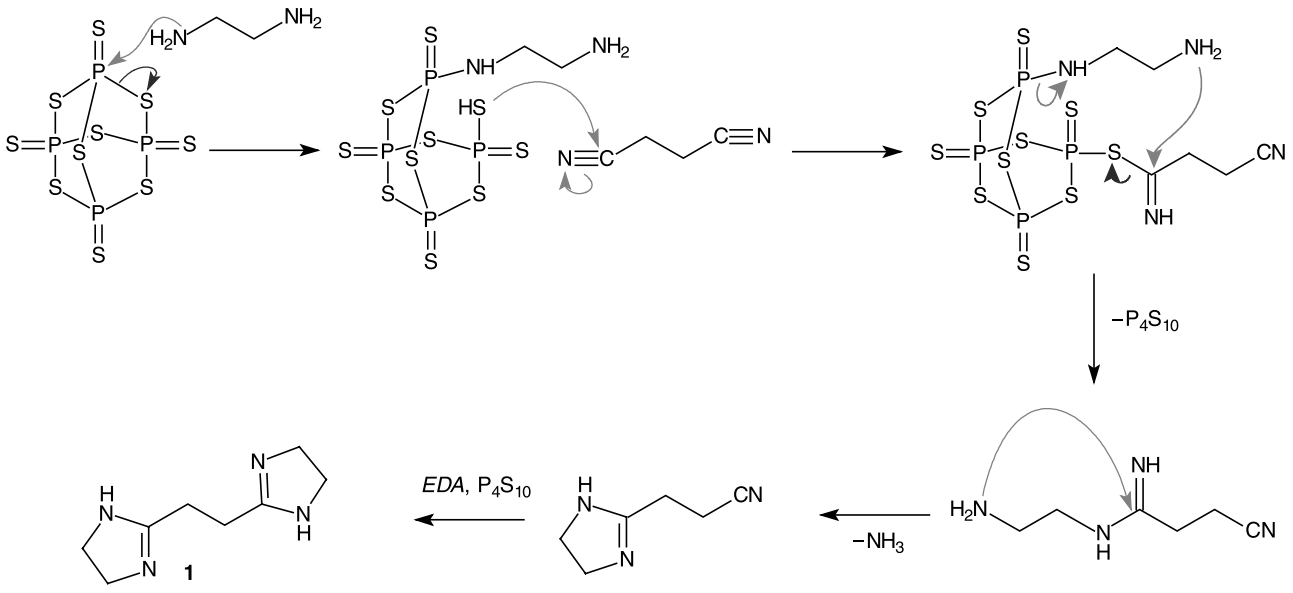
	S_8/conditions	Yield/%	P_4S_{10}/ conditions	Yield/%	*L*R/ conditions	Yield/%	$Na_2S \cdot 9H_2O$/ conditions	Yield/%
1	A	96	A	97	A	60	C, Al_2O_3	58
	C	34			C	42		
2	A	98	A	80	A	17	A, Al_2O_3	–
			B	39				
3	A	82	A	29	A	18	A, Al_2O_3	33
4	A	45	C	94	A	98	C, silica gel	44
	C	21			C	31		
5	A	98	A	90	A	–	A	–
6	A	45	A	89	A	–	A	–

Conditions A: toluene; equiv (1:5); 90°C, 10 h
Conditions B: toluene; equiv (1:4); 90°C, 10 h
Conditions C: toluene; equiv (1:5); 70°C, 10 h

(Scheme 2). According to the thio-*Pinner*'s method, thiol is added to the nitrile group, followed by substitution and transamination, whereas in the case of the sodium sulfide nonahydrate catalyst, sulfide anion and alkanedinitriles first form diiminotetrahydrothiophene or diiminothiepane intermediates. That probably explains the low yields of these reactions.

The results showed that sulfur is the best catalyst in the synthesis of bis(4,5-dihydro-1*H*-imidazol-2-yl)alkanes **1**, **2**, and **3**, and phosphorus pentasulfide in the synthesis of bis(1,4,5,6-tetrahydropyrimidin-2-yl)alkanes **4**, **5**, and **6**. The reaction should be carried out with an excessive amount of the diamine (up to 5 equiv) at 90°C for a period of 10 h. *Lawesson* reagent and sodium sulfide nonahydrate failed to be catalysts in the synthesis of **5** and **6**. Crude hygroscopic bis(cycloamidine-2-yl)alkanes **1**, **2**, **4**, **5**, and **6** are also purified by the formation of bis(cycloamidinium-2-yl)alkane dichlorides **7**, **8** (for **1**, **4**) and oxalates **9**, **10**, **11** (for **2**, **5**, and **6**).

A single crystal X-ray structure analysis was performed for compound **8**. The crystal architecture shown in Fig. 1B is an example of the self-assembly of the bis-1,2-(hexahydropyrimidinium-2-yl)ethane dichloride dihydrate molecules which are tectons [3], organized in three dimensions *via* hydrogen bonds. The water molecules and chloride anions are necessary linkers in this molecular system. The inorganic and organic parts of the crystal structure are organized in an alternatively repeating layers system



Scheme 2

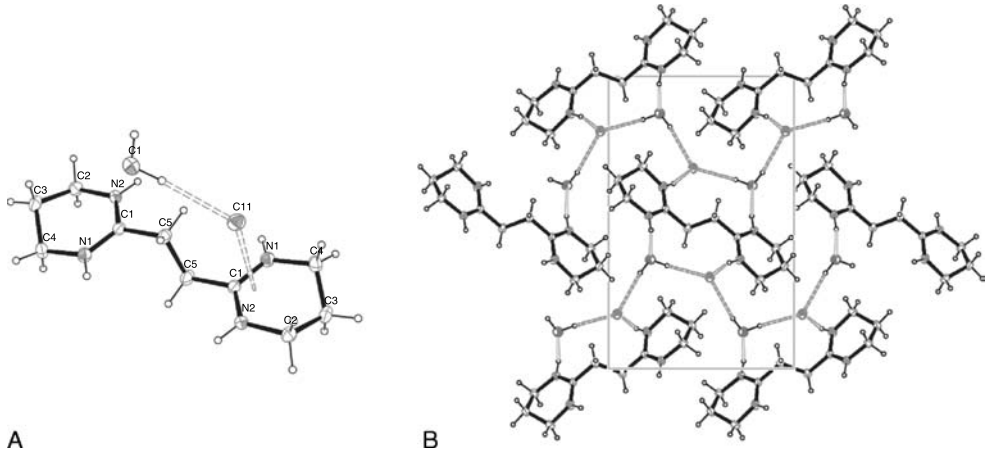


Fig. 1. A) Molecule of **8** obtained with transformation of asymmetric unit *via* inversion centre in the middle of C5–C5$^{i)}$ bond (i: $-x+1, -y, -z$), showing the interaction between Cl^- and the tetrahydropyrimidine ring, B) crystal packing projected along the [100] direction, showing the hydrogen bond system with zigzag chains along the *b* axis (visualisation made with ORTEP-3.0 [16]). Ellipsoids are drawn at 20% probability level

perpendicular to [100] direction. Bond length analysis shows that the nitrogen atoms in the heteroatomic ring are both in sp^2 hybridization [14, 15], which is a consequence of the double protonation of the molecule. The appearing positive charge is delocalized in the N1–C1–N2 region. This is additionally confirmed by the short distance between this region and the negative charged chloride ion, suggesting *Coulomb* interaction.

In conclusion, the modification of the thio-*Pinner*'s method *via in situ* activation of nitrile by the thiating agents S_8 and P_4S_{10} is very efficient in the synthesis of bis(cycloamidin-2-yl)alkanes and seems to be competitive to *Oxley*'s procedure [8].

Experimental

Melting points were determined on a *Boetius* PHMK 05 melting point apparatus. IR spectra: Bruker IFS 48 in KBr pellets or Nujol. NMR spectra: Bruker AMX 500 NMR (^{1}H: 500.14 MHz, ^{13}C: 125.76 MHz) or Bruker Avance II 300 (^{1}H: 300.18 MHz, ^{13}C: 75.48 MHz) in *DMSO*-d_6, D_2O, and $CDCl_3$ with *TMS* as an internal standard. Mass spectra: Finningan Mat 95 (EI, 70 eV). Microanalyses were performed with an Euro EA 3000 Elemental Analyzer; their results

agreed satisfactorily with the calculated values. X-Ray intensities were collected at room temperature on a Nonius Kappa CCD area detector diffractometer using Mo-K_α radiation ($\lambda = 0.7107$ Å).

*General Procedure for the Synthesis of 1,2-Bis(4,5-dihydro-1H-imidazol-2-yl)alkanes **1**, **2**, and **3** and 1,2-Bis(1,4,5,6-tetrahydropyrimidin-2-yl)alkanes **4**, **5**, and **6***

Method A: To a solution of 0.03 mol alkanedinitrile and 0.15 mol diamine in 8 cm^3 anhydrous toluene a catalytic amount of the catalyst (S_8, P_4S_{10}, *Lawesson* reagent, $Na_2S \cdot 9H_2O$) was added. The mixture was heated at 90°C for 10 h. The precipitate was filtered off, washed with acetone, and crystallized (*Et*OH for **1**, **3**; *Et*OH/acetone (1/3) for **2**; *Et*OH/acetone (1/5) for **4**, (3/1) for **5**, **6**).

1,2-Bis(4,5-dihydro-1H-imidazol-2-yl)ethane (**1**)
Yield for **1** Table 1; mp 235–236°C (Ref. [8] 235°C); IR and MS were found to be identical with the one described in Ref. [7]; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 2.55$ (s, 4H, CH_2–C(=N)NH), 2.8 (s, 2H, NH), 3.57 (s, 8H, NCH_2) ppm; ^{13}C NMR (500 MHz, $CDCl_3$): $\delta = 25.72$ (*C*H_2–C(=N)NH), 49.78 (N*C*H_2), 167.57 (CH_2–*C*(=N)NH) ppm.

1,3-Bis(4,5-dihydro-1H-imidazol-2-yl)propane (**2**)
Yield for **2** Table 1; mp 162–164°C (Ref. [10] 162–163°C); IR (KBr): $\bar{\nu} = 3191$, 2856–2956, 1611 cm^{-1}; ^{1}H NMR (300 MHz, *DMSO*-d_6): $\delta = 1.76$ (m, 2H, $CH_2CH_2CH_2$), 2.10 (t, 4H, CH_2–C(=N)NH), 3.37 (s, 8H, NCH_2) ppm; ^{13}C NMR (300 MHz, *DMSO*-d_6): $\delta = 23.59$ ($CH_2CH_2CH_2$), 28.60 (*C*H_2–C(=N)NH), 49.69 (N*C*H_2), 167.38 (CH_2–*C*(=N)NH) ppm; MS (EI, 70 eV): m/z (%) = 97.2 (100), 180.2 (19) M^+.

1,4-Bis(4,5-dihydro-1H-imidazol-2-yl)butane (**3**)
Yield for **3** Table 1; mp 210–212°C (Ref. [8] 218.5–219°C); IR (KBr): $\bar{\nu} = 3155$, 2833–2963, 1611 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.70$ (m, 4H, (CH_2CH_2)$_2$), 2.34 (m, 4H, CH_2–C(=N)NH), 3.62 (s, 8H, NCH_2) ppm; ^{13}C NMR (300 MHz, $CDCl_3$): $\delta = 25.21$ (*C*H_2CH_2)$_2$, 28.19 (*C*H_2–C(=N)NH), 48.92 (NCH_2), 168.27 (CH_2–*C*(=N)NH) ppm.

1,2-Bis(1,4,5,6-tetrahydropyrimidin-2-yl)ethane (**4**)
Yield for **4** Table 1; mp 206–208°C (Ref. [8] 200°C); IR (nujol): $\bar{\nu} = 3100$, 2750–3000, 1600 cm^{-1}; ^{1}H NMR and MS were found to be identical with the one described in Ref. [13]; ^{13}C NMR (300 MHz, $CDCl_3$): $\delta = 20.45$ (*C*H_2–C(=N)NH), 32.60 (NCH_2CH_2), 41.22 (N*C*H_2), 158.43 (CH_2–*C*(=N)NH) ppm.

1,3-Bis(1,4,5,6-tetrahydropyrimidin-2-yl)propane (**5**)
Yield for **5** Table 1; mp 214–216°C; IR (KBr): $\bar{\nu} = 3275$, 2853–2932, 1641 cm^{-1}; ^{1}H NMR (300 MHz, *DMSO*-d_6): $\delta = 1.53$ (m, 4H, (CH_2CH_2)$_2$), 1.64 (q, 4H, $CH_2CH_2CH_2$), 1.89 (t, 4H, CH_2–C(=N)NH), 3.08 (t, 8H, NCH_2), 4.51 (NH + H_2O) ppm; ^{13}C NMR (300 MHz, *DMSO*-d_6): $\delta = 21.13$ (*C*H_2CH_2C(=N)NH), 24.85 (*C*H_2–C(=N)NH), 35.22 (NCH_2CH_2), 41.35 (N*C*H_2), 157.165 (CH_2–*C*(=N)NH) ppm; MS (EI, 70 eV): m/z (%) = 98.2 (43.5), 111.2 (100), 208.2 (17) M^+.

1,4-Bis(1,4,5,6-tetrahydropyrimidin-2-yl)butane (**6**, $C_{12}H_{22}N_4$)
Yield for **6** Table 1; mp 182–183°C; IR (KBr): $\bar{\nu} = 3218$, 2858–2924, 1629 cm^{-1}; ^{1}H NMR (300 MHz, *DMSO*-d_6): $\delta = 1.45$ (m, 4H, (CH_2CH_2)$_2$), 1.60 (m, 4H, $CH_2CH_2CH_2$), 1.95 (t, 4H, CH_2–C(=N)NH), 3.13 (t, 8H, NCH_2), 3.69 (NH + H_2O) ppm; ^{13}C NMR (300 MHz, *DMSO*-d_6): $\delta = 20.98$ (*C*H_2CH_2C(=N)NH), 26.64 (*C*H_2–C(=N)NH), 35.51 (NCH_2CH_2), 41.21 (N*C*H_2), 157.55 (CH_2–*C*(=N)NH) ppm; MS (EI, 70 eV): m/z (%) = 98.1 (63), 111.2 (55), 124.1 (100), 125.2 (83.8), 222.2 (32) M^+.

*General Procedure for the Synthesis of 1,2-Bis(tetrahydroimidazolium-2-yl)ethane dichloride hydrate (**7**) and 1,2-Bis(hexahydropyrimidinium-2-yl)ethane dichloride dihydrate (**8**)*
A suspension of 6 mmol **1** or **4** in 10 cm^3 anhydrous toluene was saturated with dry $HCl_{(g)}$ at 0°C for 1 h. The mixture was stirred at rt for 2 h. The precipitate was filtered off and washed with acetone.

1,2-Bis(tetrahydroimidazolium-2-yl)ethane dichloride hydrate (**7**, $C_8H_{16}N_4Cl_2 + H_2O$)
Yield 1.49 g (97%); mp 109°C; IR (KBr): $\bar{\nu} = 3100$, 2750–3000, 1600 cm^{-1}. ^{1}H NMR (300 MHz, *DMSO*-d_6): $\delta = 2.81$ (s, 4H, (CH_2–C(=N)NH)$_2$), 3.69 (s, 8H, NCH_2) 10.0 (sb, 4H, N^+H) ppm; ^{13}C NMR (300 MHz, *DMSO*-d_6): $\delta = 23.18$ (*C*H_2–C(=N)NH), 45.18 (N*C*H_2), 168.67 (CH_2–*C*(=N)NH) ppm.

1,2-Bis(hexahydropyrimidinium-2-yl)ethane dichloride dihydrate (**8**, $C_{10}H_{20}N_4Cl_2 + 2H_2O$)
Yield 1.65 g (91%); mp 116°C; IR (KBr): $\bar{\nu} = 3100$, 2750–3000, 1600 cm^{-1}; ^{1}H NMR (500 MHz, *DMSO*-d_6): $\delta = 1.81$ (m, 4H, $CH_2CH_2CH_2$), 2.814, 2.39 (s, 4H, CH_2–C(=N)NH), 3.29 (t, 8H, NCH_2); 3.38 (s,H_2O) 10.20 (s, 4H, N^+H) ppm; ^{13}C NMR (500 MHz, *DMSO*-d_6): $\delta = 17.89$ (*C*H_2–C(=N)NH), 29.53 (NCH_2CH_2), 38.44 (N*C*H_2), 161.23 (CH_2–*C*(=N)NH) ppm.

X-Ray structure analysis of **8**: The dihydrochloride dihydrate **8** was crystallized from an ethanol solution *via* slow evaporation of the solvent. The obtained crystals are colourless and stable in air. Crystal data: moiety formula $C_{10}H_{20}N_4^{2+} \cdot 2Cl^- \cdot 2H_2O$, crystal size: $0.23 \times 0.23 \times 0.27$ mm^3, $M = 303.23$, monoclinic, space group $P2_1/c$, $a = 5.8691(1)$ Å, $b = 9.2086(2)$ Å, $c = 14.5180(2)$ Å, $\beta = 90.4614(9)°$, $V = 784.62(2)$ Å^3, $Z = 4$, $D_c = 1.284$ g/cm^3, μ(Mo-K_α) = 0.42 mm^{-1}, $F(000) = 324$, $T = 293(2)$ K. The phase problem was solved with direct methods (SIR92) [17]. The structure was refined by full-matrix least-squares on F^2 (SHELXL) [18]. All non-hydrogen atoms were refined anisotropically. The positions of hydrogen atoms bonded to carbon atoms were calculated while those bonded to nitrogen atoms and to oxygen of water molecule were found in the difference *Fourier* map. The hydrogen atoms were refined with isotropic displacement parameter equal 1.2 times that of the parent atom with the use of the riding model. The refinement parameters are: $R1 = 0.032$

for 1471 reflections with $F_o > 4\sigma(F_o)$, $wR2 = 0.085$, $S = 1.059$ for 1928 unique reflections ($R(\text{int}) = 0.012$). Atomic coordinates, displacement parameters and all bond lengths, bond angles, as well as the lists of structure factors have been deposited with Cambridge Crystallographic Data Center (deposition numbers: CCDC 293246).

*General Procedure for the Synthesis of 1,3-Bis(tetrahydroimidazolium-2-yl)propane Oxalate (**9**) and 1,3-Bis(hexahydropyrimidinium-2-yl)propane Oxalate (**10**), and 1,4-Bis(hexahydropyrimidinium-2-yl)butane Oxalate Tetrahydrate (**11**)*

To a solution of 2 mmol bis(cycloamidin-2-yl)alkanes in 5 cm^3 ethanol 0.22 g oxalic acid (2.44 mmol) was added. The mixture was refluxed for 5 min, and cooled. The precipitate was filtered off, washed with ethanol, and crystallized (*Et*OH for **9**, *Me*OH for **10**, **11**).

1,3-Bis(tetrahydroimidazolium-2-yl)propane oxalate (**9**, $C_{11}H_{18}N_4O_4$)

Yield 0.46 g (85%); mp 208–210°C; IR (KBr): $\bar{\nu} = 3156$, 2700–3010, 1650, 1592 cm^{-1}; ^{1}H NMR (500 MHz, D_2O): $\delta = 1.92$ (m, 2H, $CH_2CH_2CH_2$), 2.56 (t, 4H, CH_2–C(=N)NH), 3.84 (s, 8H, NCH_2) ppm; ^{13}C NMR (500 MHz, D_2O): $\delta = 21.38$ ($CH_2CH_2CH_2$), 25.10 (CH_2–C(=N)NH), 44.32 (NCH_2), 170.08 (CH_2–C(=N)NH), 173.40 (C=O) ppm.

1,3-Bis(hexahydropyrimidinium-2-yl)propane oxalate (**10**, $C_{13}H_{22}N_4O_4$)

Yield 0.54 g (90%); mp 290–291°C; IR (KBr): $\bar{\nu} = 3151$, 2700–3021, 1651, 1593 cm^{-1}; ^{1}H NMR (300 MHz, D_2O): $\delta = 1.80$–1.93 (m, 2H, CH_2CH_2, 4H, $CH_2CH_2CH_2$), 2.39 (t, 4H, CH_2–C(=N)NH), 3.29 (t, 8H, NCH_2), 4.71 (H_2O) ppm; ^{13}C NMR (300 MHz, D_2O): $\delta = 17.41$ ($CH_2CH_2CH_2$), 23.28 (CH_2–C(=N)NH), 31.31 (NCH_2CH_2), 38.52 (NCH_2), 162.56 (CH_2–C(=N)NH), 173.42 (C=O) ppm.

1,4-Bis(hexahydropyrimidinium-2-yl)butane oxalate tetrahydrate (**11**, $C_{14}H_{24}N_4O_4 + 4H_2O$)

Yield 0.71 (92%); mp 98–100°C; IR (KBr): $\bar{\nu} = 3182$, 2800–3000, 1654, 1595 cm^{-1}; ^{1}H NMR (300 MHz, D_2O): $\delta = 1.57$ (m, 4H, $(CH_2CH_2)_2$), 1.87 (m, 4H, $CH_2CH_2CH_2$), 2.35 (t, 4H, CH_2–C(=N)NH), 3.31 (t, 8H, NCH_2), 4.71 (H_2O) ppm; ^{13}C NMR (300 MHz, D_2O): $\delta = 17.48$ ($CH_2CH_2CH_2$), 25.05 (CH_2–C(=N)NH), 31.85 (NCH_2CH_2), 38.46 (NCH_2), 163.34 (CH_2–C(=N)NH), 173.32 (C=O) ppm.

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