Synthesis of 2-monofunctionalized 2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-diones

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New (1*R**,5*S**)-2-R-2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-diones containing the terminal carboxy or hydroxy group in the substituent R were synthesized by cyclocondensation of 4,5-dihydroxyimidazolidin-2-one with 1-R-ureas. Single-crystal X-ray diffraction analysis showed that 2-carboxyethyl-2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dione crystallizes as a racemate.

Key words: synthesis, 2-monofunctionalized 2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-diones, glycolurils, carboxy- and hydroxyalkyl groups, racemate, X-ray diffraction analysis.

Earlier, we have demonstrated that *N*-substituted bicyclic bis-ureas represent a new promising class of compounds possessing psycho- and cardiotropic activities.[1,2] 2,4,6,8-Tetramethyl-2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dione belonging to bicyclic bis-ureas of the octane series, *viz.*, 2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-diones (glycolurils), has been already integrated into medical practice as a daytime tranquilizer (Mebicar).[2] Other glycolurils exhibiting various psychotropic activities were also synthesized. Due to rigidity of the heterocyclic core and *cis*-fusion of the five-membered rings, these compounds adopt a conformation of a half-open book.[3,4] Because of this, many glycoluril derivatives contain the asymmetric C(1) and C(5) atoms. Only glycolurils having a symmetry plane (σ^1 or σ^2, Fig. 1) are achiral.

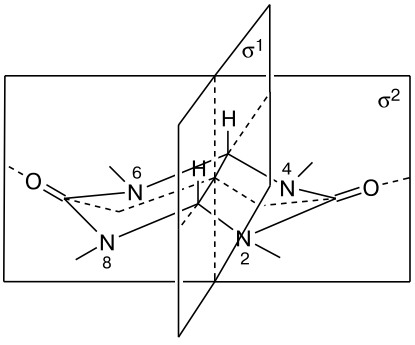

Fig. 1. Symmetry planes in glycolurils.

Chiral 2,6-dimethyl- and diethylglycolurils form conglomerates and, consequently, these compounds are capable of spontaneous separation into enantiomers.[5,6] The preparation of individual enantiomers is necessary for the design of chiral drugs.[7]

The present study was aimed at synthesizing new types of chiral glycolurils, *viz.*, 2-monosubstituted derivatives **1** containing functional groups (COOH or OH)* in the substituents. Only di- and tetra-*N*-hydroxymethyl derivatives of glycolurils containing similar substituents were described in the literature.[9] Data on the synthesis of mono-*N*-hydroxymethylglycolurils are lacking. A series of 2-*N*-monoalkylglycolurils (R = Me,[6,10] Et,[6] Pr,[6] Bu,[11] or CH_2Ph[6,10,12]) were synthesized as powders, whereas their high-quality crystals were not prepared.[6]

Derivatives of type **1** are of interest as potential physiologically active compounds and synthons for the construction of compounds containing fragments of glycolurils and other biologically active compounds.[13] In addition, one would expect that the introduction of functional groups into the alkyl substituents will facilitate the preparation of crystals suitable for X-ray diffraction analysis and allow one to elucidate their ability to form conglomerates.

Compounds **1a—g** were synthesized by condensation of monosubstituted ureas **2** with 4,5-dihydroxyimidazolidin-2-one (**3**) (Scheme 1).

* The synthesis of some of these compounds has been described earlier.[8]

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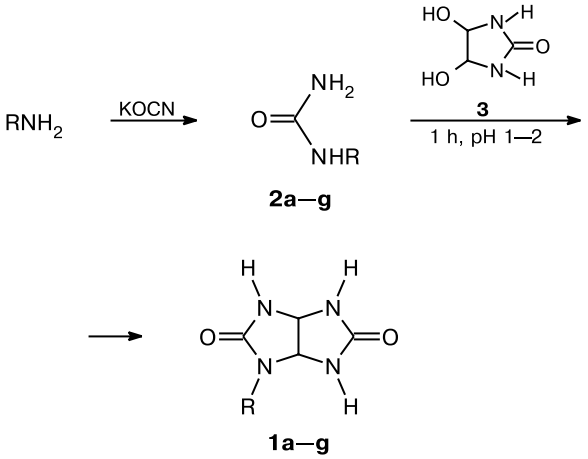
Scheme 1



R = CH_2COOH (**a**), $(CH_2)_2COOH$ (**b**), $(CH_2)_3COOH$ (**c**), $(CH_2)_4COOH$ (**d**), $CH_2C(O)NHCH_2COOH$ (**e**), $(CH_2)_2OH$ (**f**), CMe_2CH_2OH (**g**)

We intended to introduce fragments of amino acids (glycine, β-alanine, γ-aminobutyric, and δ-aminovaleric acids), dipeptide (glycylglycine), and amino alcohols (ethanolamine and 2-hydroxy(1,1-dimethyl)ethylamine) into ureas **2a—g**. The most general procedure for the preparation of compounds **2** involves the reactions of urea with the corresponding amino acids[14] or amino alcohols.[15] According to the known data, these reactions are carried out in a concentrated alkaline solution (~50%) at 110—140 °C during several hours. In addition, the procedure for the synthesis of mono(2-hydroxyalkyl)ureas **2f,g** by the reaction of nitrourea with ethanolamine or 2-hydroxy(1,1-dimethyl)ethylamine (at 100—170 °C in argon) was covered by a patent.[16] Ureas based on glycine and β-alanine were also prepared by *N*-carbomoylation of amino acids with KOCN at 40—50 °C and pH 7—10 for 5—15 h.[17] We modified the latter method and applied it to the synthesis of ureas **2a—g** (see Scheme 1). The reactions of KOCN with amino acids, dipeptide, and amino alcohols were carried out on refluxing in water for 20—30 min. Under these conditions, ureido acids **2a—e** and ureas **2f,g** were obtained in virtually quantitative yields.

Table 1. Yields and selected characteristics of 2-monosubstituted glycolurils **1a—g**

Compound	Yield (%)	M.p. /°C	Found / Calculated (%)			Molecular formula
			C	H	N	
1a	60	273—275	35.87 36.00	4.03 4.03	28.04 27.99	$C_6H_8N_4O_4$
1b	58	215—217	37.72 37.67	4.92 4.97	25.16 25.10	$C_7H_{10}N_4O_4 \cdot 0.5\ H_2O$
1c	58	145—147	42.12 42.10	5.41 5.30	24.61 24.55	$C_8H_{12}N_4O_4$
1d	52	220—222	44.46 44.63	5.77 5.83	23.20 23.13	$C_9H_{14}N_4O_4$
1e	40	251—252	37.38 37.36	4.40 4.31	27.18 27.23	$C_8H_{11}N_5O_5$
1f	55	172—173	38.80 38.71	5.45 5.41	30.11 30.09	$C_6H_{10}N_4O_3$
1g	47	227—229	44.91 44.85	6.63 6.59	26.13 26.15	$C_8H_{14}N_4O_3$

Cyclocondensation of substituted ureas **2a—g** with imidazolidinone **3** was carried out in a aqueous-acidic medium for 1 h (see Scheme 1). Compounds **1a—e** precipitated from the reaction mixtures upon cooling. After recrystallization from water, these compounds were obtained in 40—60% yields (Table 1). Compounds **1f,g** were isolated only after the removal of water and recrystallization from a MeOH—AcOEt mixture.

The structures of products **1a—g** were confirmed by the results of elemental analysis and spectroscopic data (Tables 1 and 2, respectively). The IR spectra of the resulting compounds have characteristic intense absorption bands of the CO groups in the region of 1640—1740 cm^{-1}

Table 2. Spectroscopic characteristics of compounds **1a—g**

Compound	IR, ν/cm^{-1}	^1H NMR (DMSO-d_6), δ (*J*/Hz)	MS, *m*/*z* (I_{rel} (%))
(1*R**,5*S**)-(3,7-Dioxo-2,4,6,8-tetraazabicyclo[3.3.0]oct-2-yl)ethanoic acid (**1a**)	624, 652, 700, 744, 760, 768, 804, 824, 848, 888, 896, 904, 920, 960, 1032, 1108, 1128, 1136, 1160, 1232, 1284, 1308, 1324, 1344, 1380, 1404, 1432, 1456, 1464, 1500, 1560, 1648, 1676, 1700, 1712, 2536, 2688, 2928, 3032, 3256	3.64, 4.00 (both d, 1 H each, CH_2, *J* = 18.2); 5.27 (s, 2 H, CHCH); 7.24, 7.26, 7.50 (all s, 1 H each, 3 NH); 12.72 (br.s, 1 H, COOH)	200 $[M]^+$ (2), 159 (2), 142 (8), 129 (4), 113 (52), 112 (34), 99 (24), 84 (24), 70 (19), 58 (100), 56 (52), 55 (34)

(*to be continued*)

Table 2 (*continued*)

Compound	IR, ν/cm^{-1}	^1H NMR (DMSO-d_6), δ (J/Hz)	MS, m/z (I_{rel} (%))
(1*R**,5*S**)-3-(3,7-Dioxo-2,4,6,8-tetraazabicyclo[3.3.0]oct-2-yl)propanoic acid (**1b**)	608, 672, 708, 736, 752, 768, 800, 808, 848, 884, 896, 920, 976, 1056, 1068, 1096, 1120, 1132, 1156, 1204, 1228, 1252, 1296, 1328, 1344, 1360, 1400, 1408, 1416, 1440, 1460, 1500, 1552, 1664, 1684, 1700, 1720, 2568, 2640, 2936, 3000, 3304, 3600, 3640	2.50★ (m, 2 H, CH_2CO); 3.22, 3.42 (both m, 2 H, NCH_2); 5.19 (d, 1 H, C(5)H, ^3J = 8.2); 5.29 (d, 1 H, C(1)H, ^3J = 8.2); 7.29, 7.34, 7.38 (all br.s, 1 H each, 3 NH); 12.30 (br.s, 1 H, COOH)	214 [$M^+ - 0.5\ H_2O$] (3), 171 (9), 153 (38), 125 (38), 112 (38), 99 (63), 84 (66), 70 (22), 59 (10), 55 (100)
(1*R**,5*S**)-4-(3,7-Dioxo-2,4,6,8-tetraazabicyclo[3.3.0]oct-2-yl)butanoic acid (**1c**)	664, 720, 736, 796, 816, 840, 888, 908, 928, 976, 1008, 1020, 1068, 1080, 1112, 1156, 1196, 1208, 1224, 1232, 1252, 1272, 1284, 1296, 1304, 1320, 1328, 1336, 1352, 1392, 1508, 1564, 1680, 1690, 1712, 1720, 2656, 2736, 2944, 2944, 3008, 3264, 3384, 3456	1.67 (m, 2 H, CCH_2C); 2.17 (t, 2 H, CH_2CO, ^3J = 7.5); 2.97, 3.17 (both m, 1 H each, NCH_2); 5.19, 5.25 (both d, 1 H each, CHCH, ^3J = 8.3); 7.28, 7.30, 7.41 (all s, 1 H each, 3 NH); 12.06 (br.s, 1 H, COOH)	—
(1*R**,5*S**)-5-(3,7-Dioxo-2,4,6,8-tetraazabicyclo[3.3.0]oct-2-yl)pentanoic acid (**1d**)	664, 712, 736, 752, 760, 800, 816, 848, 888, 964, 1076, 1088, 1120, 1152, 1208, 1220, 1256, 1296, 1348, 1376, 1408, 1424, 1504, 1564, 1692, 2840, 2860, 2980, 2952, 3000, 3210, 3248	1.44 (br.s, 4 H, $C(CH_2)_2C$); 2.22 (br.s, 2 H, CH_2CO); 2.94, 3.16 (both br.s, 1 H each, NCH_2); 5.19 (br.m, 2 H, CHCH); 7.25 (br.s, 2 H, 2 NH); 7.41 (s, 1 H, NH); 12.00 (br.s, 1 H, COOH)	—
(1*R**,5*S**)-*N*-[(3,7-Dioxo-2,4,6,8-tetraazabicyclo[3.3.0]oct-2-yl)acetyl]aminoethanoic acid (**1e**)	612, 624, 648, 668, 688, 724, 740, 752, 768, 796, 816, 848, 880, 888, 904, 924, 944, 960, 992, 1024, 1052, 1068, 1116, 1164, 1248, 1288, 1296, 1312, 1336, 1352, 1368, 1384, 1400, 1416, 1432, 1440, 1496, 1500, 1520, 1540, 1580, 1664, 1672, 1704, 1720, 1728, 1740, 2544, 2696, 2928, 2952, 3008, 3296, 3368, 3392	3.53, 3.96 (both d, 1 H each, NCH_2, ^2J = 17.2); 3.77 (d, 2 H, $NHC\underline{H}_2$, ^3J = 5.6); 5.33, 5.38 (both d, 2 H, CHCH, ^3J = 8.3); 7.32 (br.s, 2 H, 2 NH); 7.52 (s, 1 H, NH); 8.30 (t, 1 H, $N\underline{H}CH_2$, ^3J = 5.6); 12.70 (br.s, 1 H, COOH)	—
(1*R**,5*S**)-2-(2-Hydroxyethyl)-2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dione (**1f**)	684, 716, 736, 784, 792, 844, 864, 876, 888, 928, 1016, 1032, 1064, 1084, 1112, 1168, 1248, 1256, 1264, 1288, 1344, 1360, 1368, 1388, 1500, 1560, 1680, 1712, 1732, 2928, 2992, 3280, 3392, 3416	3.03, 3.21 (both m, 2 H, NCH_2); 3.45 (m, 2 H, CH_2O); 4.75 (t, 1 H, OH, ^3J = 5.2); 5.19 (d, 1 H, C(5)H, ^3J = 8.2); 5.30 (d, 1 H, C(1)H, ^3J = 8.2); 7.29 (br.m, 3 H, 3 NH)	186 $[M]^+$ (2), 156 (82), 155 (70), 143 (13), 126 (6), 113 (20), 112 (100), 100 (20), 98 (6), 84 (56), 83 (63), 82 (20), 71 (16), 69 (57), 58 (80), 56 (58)
(1*R**,5*S**)-2-[2-Hydroxy-(1,1-dimethyl)ethyl]-2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dione (**1g**)	720, 748, 764, 860, 888, 928, 1016, 1028, 1064, 1080, 1112, 1160, 1184, 1208, 1260, 1312, 1348, 1384, 1498, 1560, 1664, 1676, 1692, 2928, 2960, 3008, 3240	1.22, 1.24 (both s, 3 H each, 2 Me); 3.34, 3.62 (both dd, 1 H each, CH_2, ^2J = 10.7, ^3J = 4.2); 4.89 (br.t, 1 H, OH, ^3J = 4.2); 5.11 (d, 1 H, C(5)H, ^3J = 8.2); 5.46 (d, 1 H, C(1)H, ^3J = 8.2); 7.17 (br.s, 1 H, NH); 7.26 (br.s, 2 H, 2 NH)	—

★ The signals overlap with the signal of the solvent; because of this, the ^1H NMR spectrum in D_2O and the ^{13}C NMR spectrum were additionally recorded. ^1H NMR (D_2O), δ: 2.14 (t, 2 H, CH_2CO, J = 6.7 Hz); 2.82—2.12 (m, 2 H, NCH_2); 5.02 and 5.10 (both d, 1 H each, CHCH, ^3J = 8.5 Hz). ^{13}C NMR, δ: 32.7, 36.7 (2 CH_2); 62.4, 68.1 (2 CH); 159.2, 161.3 (2 CO); 173.1 (COOH).

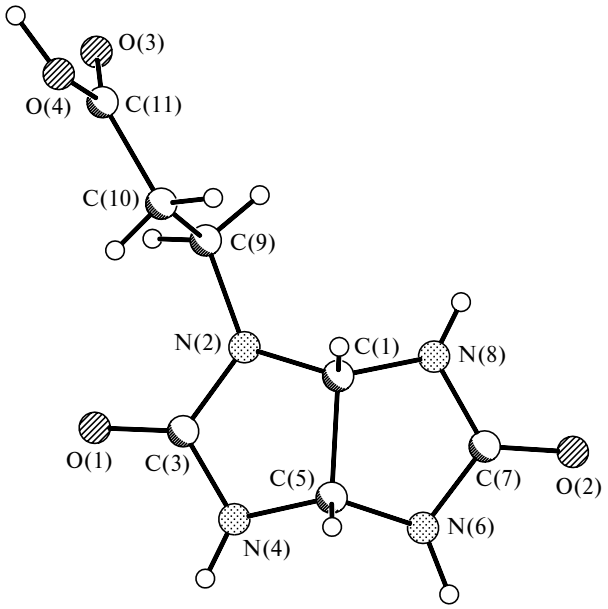


Fig. 2. Overall view of molecule **1b**.

and bands, which might be assigned to skeletal vibrations of the bicyclic systems (1500—1508 cm^{-1}). In the ^1H NMR spectra of compounds **1b,c,e—g**, the signals for the methine protons (CH—CH fragment) are observed as an AB system (δ 5.0—5.5). A singlet for these protons in the spectrum of compound **1a** and a broadened multiplet in the spectrum of compound **1d** are attributed to the similarity of their chemical shifts. The protons of the NCH_2 groups are diastereotopic and are manifested as an AMX_2 system due to spin-spin coupling with the protons of the adjacent CH_2 group. The positions of other signals and their intensities are in complete agreement with their structures (see Table 2).

Attempts to crystallize compounds **1a—g** from water allowed us to grow crystals of **1a,b** and **1d** suitable for X-ray diffraction analysis. X-ray diffraction study demonstrated that product **1b** crystallized as a water solvate in the centrosymmetrical space group $P2_1/c$. The principal bond lengths and bond angles in the bicyclic system (Fig. 2, Table 3) are close to the expected values.[5] The introduction of the $(CH_2)_2COOH$ group has virtually no effect on the conjugation in the N—C(=O)—N fragment, which is manifested in the similarity of the corresponding N—C and C=O bond lengths. By contrast, the N—C(H) bond length appears to be more sensitive to the introduction of the substituent.

Both five-membered rings adopt a strongly flattened envelope conformation with the C(3) and C(7) atoms deviating from the corresponding planes by 0.08 and 0.11 Å. The dihedral angle between the planes of the five-membered rings is 119.1°.

The presence of four protons and three carbonyl groups capable of hydrogen bonding gives rise to the expected

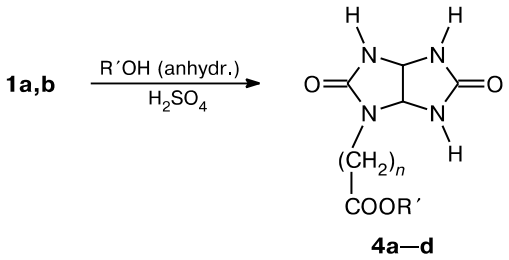
Table. 3. Selected bond lengths (*d*) and bond angles (ω) in the structure of **1b**

Bond	*d*/Å	Bond	*d*/Å
O(1)—C(3)	1.238(2)	C(5)—N(4)	1.437(2)
O(2)—C(7)	1.236(2)	C(5)—N(6)	1.441(2)
C(1)—N(2)	1.451(2)	C(7)—N(6)	1.345(2)
C(1)—N(8)	1.442(2)	C(7)—N(8)	1.355(2)
C(1)—C(5)	1.559(2)	O(3)—C(11)	1.212(2)
C(3)—N(2)	1.354(2)	O(4)—C(11)	1.322(2)
C(3)—N(4)	1.353(2)	N(2)—C(9)	1.456(2)
Angle	**ω/deg**	**Angle**	**ω/deg**
N(8)—C(1)—C(5)	103.3(1)	N(4)—C(5)—N(6)	114.4(1)
N(2)—C(1)—C(5)	102.8(1)	N(4)—C(5)—C(1)	103.1(1)
C(3)—N(2)—C(1)	111.9(1)	N(6)—C(5)—C(1)	102.3(1)
C(3)—N(2)—C(9)	122.5(1)	C(7)—N(6)—C(5)	112.8(1)
C(1)—N(2)—C(9)	123.1(1)	O(2)—C(7)—N(6)	125.7(1)
O(1)—C(3)—N(4)	125.4(1)	O(2)—C(7)—N(8)	125.3(1)
O(1)—C(3)—N(2)	125.3(1)	N(6)—C(7)—N(8)	108.9(1)
N(4)—C(3)—N(2)	109.3(1)	C(7)—N(8)—C(1)	111.9(1)
C(3)—N(4)—C(5)	112.5(1)		

H-bonded three-dimensional framework. It should be noted that not only the NH and COH groups but also the methine H atom at the C(5) atom can be involved in hydrogen bonding (Table 4).

Of chemical transformations of glycolurils **1**, we studied esterification of products **1a,b** (Scheme 2). Compounds **4a—d** were prepared according to standard procedures and their structures were confirmed by elemental analysis and spectroscopic methods.

Scheme 2



4a—d

4: R′ = Me, *n* = 1 (**a**); R′ = Et, *n* = 1 (**b**); R′ = Me, *n* = 2 (**c**); R′ = Et, *n* = 2 (**d**)

To summarize, cyclocondensation of 4,5-dihydroxyimidazolidin-2-one with 1-R-ureas afforded new monofunctionally substituted glycolurils, which are of interest as potentially physiologically active compounds and synthons for the preparation of other derivatives of this class. Single-crystal X-ray diffraction study showed that 2-carboxyethyl-2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dione (**1b**) crystallized as a racemate.

Table 4. Principal geometric parameters (bond lengths (*d*) and bond angles) of the hydrogen bonds (D—H...A) in the structure of **1b**

Bond	*d*(D...A)	*d*(H...A)	D—H—A angle /deg
	Å		
N(4)—H(4N)...O(1) (–*x* + 1, –*y* + 1, –*z*)	2.882(2)	2.06	163
N(6)—H(6N)...O(3) (*x* + 1, –*y* + 1.5, *z* – 0.5)	2.924(2)	2.06	156
N(8)—H(8N)...O(1) (–*x* + 1, *y* + 0.5, –*z* + 0.5)	3.054(2)	2.29	165
O(4)—H(4O)...O(2) (*x* – 1, –*y* + 1.5, *z* + 0.5)	2.626(2)	1.69	170
O(1W)—H(1WA)...O(1)	2.780(3)	1.85	152
O(1W)—H(1WB)...N(4) (*x* – 1, *y*, *z*)	3.310(3)	2.36	152
C(5)—H(5)...O(2) (2 – *x*, *y* – 0.5, –*z* + 0.5)	3.231(3)	2.17	172

Note. D is a donor and A is an acceptor. The symmetry operations are given in parentheses.

Experimental

The IR spectra were recorded on a Specord M-80 spectrometer in KBr pellets. The NMR spectra were measured on Bruker AM-250 (250 MHz (^{1}H)) and Bruker AM-300 (300 MHz for ^{1}H and 75.5 MHz for ^{13}C) spectrometers in DMSO-d_6; the chemical shifts are given in the δ scale relative to Me_4S as the internal standard. The mass spectra were obtained on an MS-30 mass spectrometer. The melting points were measured on a Boetius PHMK-05 instrument.

Synthesis of monosubstituted ureas 2a—g (general procedure). An aqueous solution of the corresponding amino acid (dipeptide or amino alcohol) (0.05 mol) was heated to boiling and then KOCN (4.5 g, 0.052 mol) was added in five portions to the gently refluxing solution. After the addition of a total amount of KOCN, the reaction mixture was refluxed for 20 min (in the case of dipeptide, for 30 min), cooled to ~20 °C, and treated with an equimolar amount (4.5 mL) of concentrated HCl to pH ~1. Then the reaction mixture was kept at ~20 °C for 7 h and crystals of compounds **2a—e** that precipitated were filtered off. In the case of **2f**,**g**, the reaction mixture was concentrated to dryness *in vacuo*, MeOH (20 mL) was added, and a precipitate of KCl was filtered off. The filtrate was concentrated *in vacuo*, the oily residue was triturated with a 1 : 2 MeOH—Et_2O mixture (15 mL), and products **2f,g** that formed were filtered off.

Ureidoethanoic acid (2a). The yield was 95%, m.p. 173—175 °C (*cf.* lit. data[17]: m.p. 165 °C).

3-Ureidopropanoic acid (2b). The yield was 96%, m.p. 178—180 °C.

4-Ureidobutanoic acid (2c). The yield was 92%, m.p. 190—192 °C.

5-Ureidopentanoic acid (2d). The yield was 87—88%, m.p. 195—197 °C.

Ureidoacetylaminoethanoic acid (2e). The yield was 85—86%, m.p. 220—222 °C.

1-(2-Hydroxyethyl)urea (2f). The yield was 78—80%, m.p. 85—86 °C.

1-[2-Hydroxy(1,1-dimethyl)ethyl]urea (2g). The yield was 76—77%, m.p. 60—62 °C.

Synthesis of 2-substituted (1*R,5*S**)-2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-diones 1a—g (general procedure).** Concentrated HCl was added to an aqueous solution of the corresponding urea **2** (0.05 mol) and 4,5-dihydroxyimidazolidin-2-one (**3**) (0.05 mol) to pH 1—2. The solution was refluxed for 1 h, cooled to ~20 °C, and kept for 12 h. The precipitates of compounds **1a—e** that formed were filtered off and recrystallized from water. In the case of compounds **1f,g**, the reaction mixture was concentrated *in vacuo* until an oily residue formed. The precipitate was triturated with a 1 : 3 Me_2CO—Et_2O mixture (10 mL). Products **1f,g** that precipitated were filtered off and recrystallized from a 4 : 1 MeOH—AcOEt mixture (15 mL). The yields and physicochemical characteristics of compounds **1a—g** are given in Table 1. The spectroscopic characteristics of these compounds are listed in Table 2.

Synthesis of methyl esters of 2-substituted (1*R,5*S**)-2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-diones 4a,c (general procedure).** Concentrated H_2SO_4 (1 mmol) was added to a solution of compounds **1a,b** (5 mmol) in MeOH (0.5 mol) and the reaction mixture was refluxed for 5 h under conditions precluding exposure to atmospheric moisture. Then the reaction mixture was concentrated to ~1/3 of the initial volume and kept at ~20 °C for 7 h. The precipitates that formed were filtered off and washed with MeOH (3—5 mL). Compounds **4a** and **4c** were obtained in yields of 0.95 g (88%) and 0.85 g (75%), respectively.

Methyl (1*R,5*S**)-(3,7-dioxo-2,4,6,8-tetraazabicyclo[3.3.0]oct-2-yl)ethanoate (4a).** M.p. 250—252 °C. Found (%): C, 39.31; H, 4.65; N, 26.27. $C_7H_{10}N_4O_4$. Calculated (%): C, 39.25; H, 4.71; N, 26.16. ^{1}H NMR, δ: 3.64 (s, 3 H, OMe); 3.77 and 4.06 (both d, 1 H each, CH_2, ^2J = 18.1 Hz); 5.27 (s, 2 H, CHCH); 7.30, 7.32, and 7.60 (all s, 1 H each, 3 NH). MS, *m*/*z* (I_{rel} (%)): 214 $[M]^+$ (5), 185 (5), 171 (17), 156 (79), 155 (72), 143 (5), 126 (12), 113 (16), 112 (100), 100 (24), 84 (19), 83 (71), 82 (24), 70 (21), 69 (60), 58 (92), 56 (63).

Methyl (1*R,5*S**)-3-(3,7-dioxo-2,4,6,8-tetraazabicyclo[3.3.0]oct-2-yl)propanoate (4c).** M.p. 196—197 °C. Found (%): C, 42.24; H, 5.35; N, 24.47. $C_8H_{12}N_4O_4$. Calculated (%): C, 42.10; H, 5.30; N, 24.55. ^{1}H NMR, δ: 2.53 (m, 2 H, CH_2CO); 3.32 and 3.45 (both m, 2 H each, NCH_2); 3.66 (s, 3 H, OMe); 5.17 (d, 1 H, C(5)H, ^3J = 8.2 Hz); 5.25 (d, 1 H, C(1)H, ^3J = 8.2 Hz); 7.19, 7.25, and 7.31 (all br.s, 1 H each, 3 NH).

Synthesis of ethyl esters of 2-substituted (1*R,5*S**)-2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-diones 4b,d (general procedure).** Concentrated H_2SO_4 (10 mmol) was added to a solution of compounds **1a,b** (5 mmol) in anhydrous EtOH (0.5 mol). The reaction mixture was refluxed for 2 h and then toluene (0.25 mol) was added. The mixture was concentrated to dryness by azeotropic distillation and the residue was dissolved in anhydrous EtOH (5 mL). The resulting solution was kept at ~20 °C

for 12 h and the precipitates of esters **4b,d** that formed were filtered off and washed with anhydrous EtOH. Compounds **4b** and **4d** were obtained in yields of 0.91 g (77%) and 0.89 g (74%), respectively.

Ethyl (1*R,5*S**)-(3,7-dioxo-2,4,6,8-tetraazabicyclo[3.3.0]oct-2-yl)ethanoate (4b).** M.p. 224—225 °C. Found (%): C, 42.15; H, 5.27; N, 24.57. $C_8H_{12}N_4O_4$. Calculated (%): C, 42.10; H, 5.30; N, 24.55. ^{1}H NMR, δ: 1.21 (t, 3 H, Me, ^3J = 7.2 Hz); 3.73 and 4.05 (both d, 1 H each, CH_2, ^2J = 18.1 Hz); 4.12 (q, 2 H, MeC$\underline{H}_2$, ^3J = 7.2 Hz); 5.29 (s, 2 H, CHCH); 7.26, 7.36, and 7.62 (all s, 1 H each, 3 NH). MS, *m*/*z* (I_{rel} (%)): 228 $[M]^+$ (2), 199 (5), 186 (15), 185 (83), 171 (5), 156 (21), 155 (85), 126 (10), 112 (100), 99 (7), 84 (36), 83 (30), 82 (21), 69 (46), 58 (64), 56 (39).

Ethyl (1*R,5*S**)-3-(3,7-dioxo-2,4,6,8-tetraazabicyclo[3.3.0]oct-2-yl)propanoate (4d).** M.p. 205—207 °C. Found (%): C, 44.41; H, 5.75; N, 23.26. $C_9H_{14}N_4O_4$. Calculated (%): C, 44.63; H, 5.83; N, 23.13. ^{1}H NMR, δ: 1.18 (t, 3 H, Me, ^3J = 7.3 Hz); 2.63 (m, 2 H, CH_2CO); 3.19 and 3.34 (both m, 2 H, NCH_2); 4.05 (q, 2 H, MeC$\underline{H}_2$, ^3J = 7.3 Hz); 5.18 (d, 1 H, C(5)H, ^3J = 8.0 Hz); 5.29 (d, 1 H, C(1)H, ^3J = 8.0 Hz); 7.29 (br.s, 1 H, NH); 7.37 (br.s, 2 H, 2 NH).

X-ray diffraction analysis of compound 1b. Single crystals were prepared by crystallization from H_2O. Crystals of **1b** ($C_7H_{10}N_4O_4 \cdot 0.5\,H_2O$, M = 223.20) are monoclinic, space group $P2_1/c$, at T = 163 K: a = 7.656(2) Å, b = 11.263(4) Å, c = 10.764(3) Å, β = 101.45(2)°, V = 909.7(5) Å^3, Z = 4, d_{calc} = 1.630 g cm^{-3}. The intensities of 1912 independent reflections were measured on an automated Syntex $P2_1$ diffractometer (graphite monochromator, λ(Mo-Kα) = 0.71073 Å, θ/2θ scan technique, θ_{max} = 26°). The structure was solved by direct methods and refined by the full-matrix least-squares method based on F^2_{hkl} with anisotropic thermal parameters for all nonhydrogen atoms. The H atoms were revealed from the difference electron density synthesis and refined isotropically. Analysis of the difference electron density synthesis in the region of the water molecule of solvation located in an inversion center showed disordering of the H atoms, and their positions were refined using the riding model. The final reliability factors were as follows: R_1 = 0.0427 (based on F^2 for 1585 observed reflections with $I > 2\sigma(I)$), wR_2 = 0.1282, GOF = 1.082, the number of the refinable parameters was 188. All calculations were carried out on a personal computer with the use of the SHELXTL PLUS program package.

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