Synthesis of First Representatives of 3,3'-Bi(6,8-dialkyl-2,4-dioxa-6,8-diazabicyclo[3.3.0]octan-7-ones)

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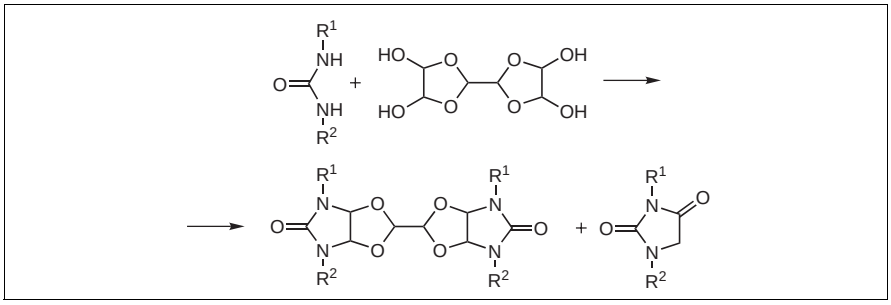

The first representatives of 3,3'-bi(2,4-dioxa-6,8-diazabicyclo[3.3.0]octan-7-ones) have been synthesized by a reaction of glyoxal as form of 2,2′-bi(4,5-dihydroxy-1,3-dioxalane) with N,N'-dialkylureas. Their structures have been supported by X-ray analysis. 1,3-Dialkylimidazolidine-2,4-diones (hydantoins) have been isolated as by-products and their formation mechanism has been experimentally confirmed.

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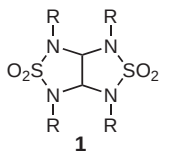
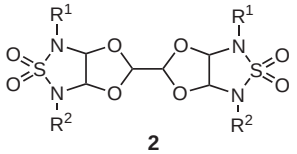
Introduction.

For several years we have been interested in chemistry and stereochemistry of 2,4,6,8-tetraazabicyclo[3.3.0]octan-3,7-diones (glycolurils) [1-9], possessing a wide range of biological activity [9-12]. In particular, they represent a novel class of neurotropic compounds [2,3,9,10]. The synthesis of glycolurils is based on the reaction of glyoxal or 4,5-dihydroxyimidazolidin-2-ones with *N*-nucleophiles containing urea fragments in the water or water-methanol at pH 1 [4-7,13,14]. Recently [15], looking for new biologically active compounds, we have tried to synthesize derivatives of 3,7-dithia-2,4,6,8-tetraazabicyclo[3.3.0]octan-3,3,7,7-tetraoxide **1** – sulfoanalogues of glycolurils. But instead of the expected bicyclic compounds **1**, reaction of 40% water solution of glyoxal with 1,3-dialkylsulphamides at pH 1 gave derivatives of a new heterocyclic system — 1,3-dioxolano[4,5-*c*]-1,2,5-thiadiazolidine — 3,3'-bi(6,8-dialkyl-2,4-dioxa-7-thia-6,8-diazabicyclo[3.3.0]octan-7,7-dioxides) **2** (5-11% yield). The structure of bisbicycles **2** with two 1,3-dioxolano[4,5-*c*]-1,2,5-thiadiazolidine fragments connected by the C(3)-C(3') bond was proved by spectroscopic methods and the structure of **2g** by X-ray analysis.



1



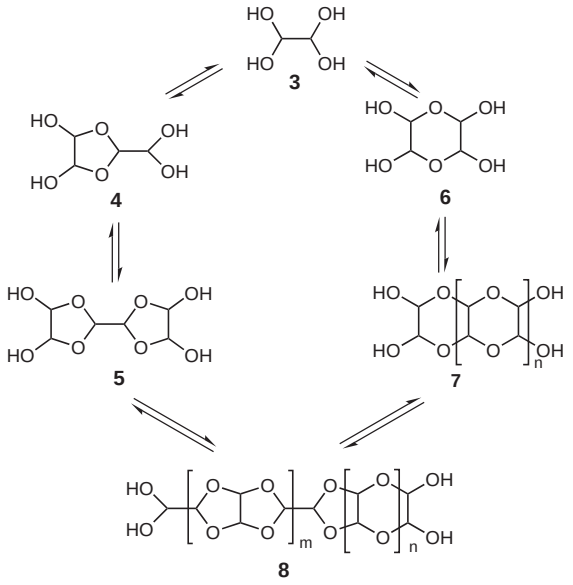
2

$R^1 = R^2$ = Me (**a**); $R^1 = R^2$ = Et (**b**); R^1 = Me, R^2 = Et (**c**);
$R^1 = R^2$ = *n*-Pr (**d**); $R^1 = R^2$ = *i*-Pr (**e**);
$R^1 = R^2$ = *n*-Bu (**f**); $R^1 = R^2$ = *s*-Bu (**g**).

In the same paper [15] we suggested that formation of **2** could be explained by reaction of sulfamides with glyoxal in one of its hydrated forms — 2,2'-bi(4,5-dihydroxy-1,3-dioxolane) or trimer dihydrate **5**. It is known [16-20], that in water solutions glyoxal exists in different hydrated forms: bisgem-diol **3**, dimer dihydrate **4** with a dioxolane cycle, trimer dihydrate **5** with bisdioxolane fragment, and in the form of the dioxane structure **6** and other oligomers **7** & **8**, including both dioxolane and dioxane cycles (Scheme 1). Structure of these hydrates and their contents

in solutions were established by ^{1}H and ^{13}C NMR in D_2O and DMSO-d_6.

Scheme 1



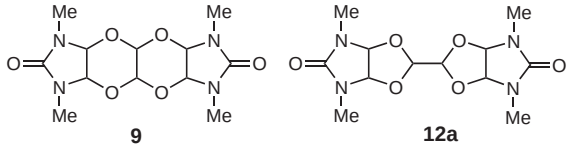
Assuming that the trimer dihydrate **5** played a key role in the formation of **2**, we used solid glyoxal for their synthesis. That resulted in an increased in their respective yields to 54-85%.

Electron Impact Ionization Mass Spectrometry (EIMS) shows that all compounds **2** produce a fragment equal to a half of the molecular ion. It means that such electron-affected fragmentation involves the C(3)-C(3') bond breakage. Moreover, we discovered that EIM spectrum of solid glyoxal also contained a fragmentary ion equal to a half of the molecular ion corresponding to the structure **5**. This factor may be decisive for the determination of the structure of similar compounds.

We intend to continue this research to explore reactions of glyoxal in the form of 2,2'-bi(4,5-dihydroxy-1,3-dioxolane) **5** with other *N*-bisnucleophiles (*e.g.* 1,3-dialkylureas) as a route to a novel heterocyclic system 3,3′-bi(2,4-dioxa-6,8-diazabicylo[3.3.0]octan-7-one)

Results and Discussion.

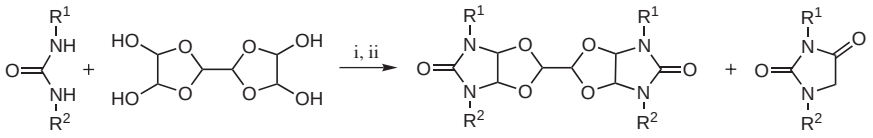
Analysis of the available literature showed that there is only one paper [21] describing compound with structure distinguishes from glycolurils. It was obtained in a low yield by the reaction of 40% glyoxal with 1,3-dimethylurea **10a** or 1,3-dimethyl-4,5-dihydroxyimidazolidin-one **11a** at RT and pH 2 (3-19 days). Authors of paper [21] ascribed to this compound the structure of **9** with four annelated heterocycles only on the basis of the elemental analysis, IR- and ^{1}H NMR spectroscopy. These data, however, do not prove that the reported compound **9** is not an isomeric bisbicyclic system **12a** with the central dioxolane fragment.



The first step of this investigation included an attempt to obtain structures **12** under conditions used for synthesis of bisbicycles **2** and to repeat the published synthesis of **9** in order to re-investigate its structure with modern methods.

The reaction of 1,3-dimethyl- or 1,3-diethylurea **10a,b** with glyoxal in the form of 2,2'-bi(4,5-dihydroxy-1,3-dioxolane) **5** in conc. HCl (20 ºC, 1 h.) led to gum-like products of the unknown structure. The investigation of precipitates obtained after 7 days from a solution of ureas **10a,b** and glyoxal, under conditions described in the literature for formation of **9**, showed characteristic ^{1}H NMR spectra of 3,3'-bi(2,4-dioxa-6,8-diazabicylo[3.3.0]-octan-7-ones) **12** (Scheme 2). Singlets at 4.78-4.79 ppm, can be attributed to the C(3)H-C(3')H groups connecting two identical 6,8-dialkyl-2,4-dioxa-6,8-diazabicyclo-[3.3.0]octan-7-one fragments. The ratio of integral intensities of these signals, N-Me (N-Et) groups, and bridging C(1)H-C(5)H & C(1')H-C(5') fragments did not contradict the structure of the desired bisbicycles **12a,b**. The value of the chemical shift of C(3)H-C(3')H group also does not contradict the structures **12a,b** as chemical shifts of the bridging CH-CH protons in bisdioxane

Scheme 2



$R^1 = R^2$ = Me (**a**), $R^1 = R^2$ = Et (**b**), R^1 = Me, R^2 = *t*-Bu (**c**), R^1 = Me, R^2 = *c*-C_6H_{11} (**d**).

Reagents and conditions. (i) H_2O or H_2O:MeOH (1:5), 20 °C, pH 5, 60 days (49-56%); (ii) H_2O or H_2O:MeOH (1:5), 60 °C, pH 6, 2 h (41-45%).

fragment of the 1,4,5,8-tetraoxadecaline derivatives are equal to 4.4-4.6 ppm. [22]. High resolution mass (HRM) spectra show the expected molecular ions. EIM spectra contain typical for **12** fragmentary ions with mass equal to a half of the molecular ions, corresponding to a break of the central C(3)-C(3') bond.

Finally, the structure of heterocyclic systems **12a,b** (on the example of **12b**) was established by the X-ray diffraction study. It showed unambiguously that the obtained products were not triply annelated tetracycles **9**. In fact, they contained two identical bicyclic parts — 6,8-dialkyl-2,4-dioxa-6,8-diazabicyclo[3.3.0]octan-7-ones linked by a carbon-carbon bond (Figure 1).

According to XRD of the **12b** crystallize with two independent molecules both of which are located in the center of symmetry and thus correspond to meso-form. The imidazolidine cycles are almost planar (the r.m.s deviation is not more than 0.01Å) and dioxane ones are characterized by the envelope conformation with the deviation of C(3) atom by 0.46 and 0.51Å.

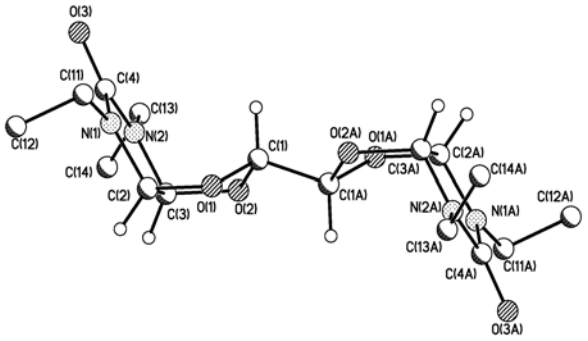


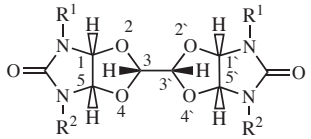
Figure 1. General view of one of the independent molecules of **12b.** Selected bond lengths (Å): C(1)-N(8) 1.422(2), C(1)-O(2) 1.428(2), C(1)-C(5) 1.543(3), O(1)-C(7) 1.214(2), O(2)-C(3) 1.407(2), C(3)-O(4) 1.410(2), O(4)-C(5) 1.424(2), C(5)-N(6) 1.424(2), N(6)-C(7) 1.363(2), N(6)-C(9) 1.457(2), N(8)-C(11) 1.453(2).

The yields of compounds **12a,b** obtained by the published procedure are pretty low (14-16%). In order to optimize the yields, the influence of different parameters on the reaction of 1,3-dialkylureas **10a-d** with glyoxal in the form of 2,2'-bi(4,5-dihydroxy-1,3-dioxolane) **5** was studied (Scheme 2). Since the content of **5** in water solution depends its concentration, pH and temperature, we hoped to find conditions providing preferential formation of the desired bisbicycles **12**. In order to achieve this, we varied pH of the water solution of glyoxal (2, 5 or 6), temperature (20 or 60 °C), duration of the reaction (1-7 h at 60 °C or 2 months at 20 °C), and the ratio of reagents. Trimer dihydrate of glyoxal **5** was dissolved in a minimal volume of water (solution with pH 5). After adjustment of pH with concentrated HCl or 20% $NaHCO_3$ when necessary, it was combined with a solution of ureas **10a,b** in a 5-fold amount of water or a 5-fold amount of MeOH for low soluble ureas **10c,d**.

Thin-layer chromatography of the reaction masses has shown that in all cases at pH 2 and 20 ºC two months were needed to achieve full conversion of initial ureas. Moreover, targeted bisbicycles **12a-d** were produced in the yields as low as 14-16%. The same reactions conducted at pH 5 and at 20 °C during 2 months led to an increase in the yields of compounds **12a-d** up to 49-56%.

In order to reduce the reaction duration an interaction of ureas **10a,c** with glyoxal **5** was studied at pH 5 or 6 and at 60 °C during 1-7 h. It was established that at pH equal to 5 urea **10a** is fully exhausted to the end of the fourth hour, and urea **10c** — to the end of the second hour, and at pH 6 ureas **10a,c** are in fact not visible at the end of the second hour. Probably, in these conditions the concentration of glyoxal in the form **5** in the reaction mass is more than twice higher that at pH 5 and at the same temperature. The yields of bisbicyles **12b,d**, obtained by the reaction of trimer dihydrate glyoxal **5** with the ureas **10b,d** under the same conditions have the same order and comprise 41 and 45% respectively. Although the conducting of the reactions at pH 5, 20 °C during two months occurs with the slightly bigger yields of compounds **12a-d** (49-56%), these conditions are not preparative enough. Thus, the optimal conditions for the synthesis of 3,3'-bi(6,8-dialkyl-2,4-dioxa-6,8-diazabicyclo[3.3.0]octan-7-ones) **12** are pH 6 of the fresh water glyoxal solution in the form **5**, 60 °C and duration of the reaction 2 hours.

^{1}H NMR Spectra of bisbicycles **12c,d** represent a more complicated case than the ones for the compounds **12a,b**. The appearance of the signals of protons at C(1, 1') and C(5, 5') in the form of systems AB (dd) in the in the area of 5.53-5.82 ppm testifies to their inequivalence what is connected with the peculiarities of the stereochemistry of these compounds. Thus, compounds **12a,b** (with the same substituents at the nitrogen atoms) contain 4 asymmetric carbon atoms — 1, 5, 1', 5', and compounds **10c,d** (with different substituents by the nitrogen atoms) — 6 asymmetric carbon atoms: 1, 3, 5, 1', 3', 5'. In the compounds **12a,b** carbon atoms 3 and 3' are pseudoasymmetric.



12a-d

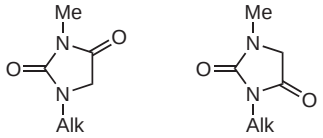
$R^1 = R^2$ = Me (**a**), $R^1 = R^2$ = Et (**b**),
R^1 = Me, R^2 = *t*-Bu (**c**), R^1 = Me, R^2 = *c*-C_6H_{11} (**d**).

Moreover, the configuration of the C(1) – (*S*), C(5) – (*R*), C(1') – (*R*) and C(5') — (*S*) atoms is strictly set and does not depend on the priority or configuration of the substituents at the nitrogen atoms as it is fully determined by the sequence of atoms O, N, C in each 6,8-dialkyl-2,4-

dioxa-6,8-diazabicyclo[3.3.0]octan-7-one fragment of bisbicycle **12**. The hydrogen atoms in the bridging fragmentes C(1)H-C(5)H and C(1')H-C(5')H are *cis*-oriented. Besides, for the pseudoasymmetric atoms C(3) and C(3') three combinations of their configurations are possible: *s*,*r* (= *r*,*s*); *r*,*r* and *s*,*s*. In case of equal non-chiral substituents by the nitrogen atom (R = Me, Et), molecules of compounds **12a,b** have a plane of symmetry and appear to be *meso*-forms, what was confirmed by the X-ray diffraction data for bisbicycle **12b**. If the substituents at the nitrogen atoms are structurally different, like in the case of **12c,d**, then for them theoretically one can suppose the formation of the mixture of diastereomeric *meso*-forms and racemates: 2 *meso*-forms and 4 racemates.

Indeed the ^{1}H NMR spectra of crude compounds **12c,d** fix the protons signals in the field 4.78-4.79 ppm a mixture of the diastereoisomers with the prevalence of one of them. The prevailing stereoisomers were obtained in the individual state after their crystallization from methanol and fully determined spectrally. However, the obtained data don't allow relating them to any concrete stereoisomer.

Since the yields of **12** were not quantitative, we looked into structure of by-products. Oily residues from the mother solutions were studied by ^{1}H NMR. Their spectra contained signals similar to those of the reported NMR spectra of unsubstituted hydantoin [23,24] and 1,3-dimethylhydantoin [25], suggesting presence of hydantoins **13a,b** or structural isomers (ratio 9:1) **13c,d** and **14c,d**. A general feature of these spectra is the presence of CH_2 singlets at 3.89-4.05 ppm.



13c,d **14c,d**

Alk = *t*-Bu (**c**), R = *c*-C_6H_{11} (**d**).

Compounds **13a,b** were obtained form the oily remains by extraction with ether. The solid mixtures of hydantoins **13c,d** and **14c,d** are precipitated from methanol. After the crystallization of the latter from the methanol only the dominating isomers were obtained. The yields of hydantoins **13a-d** are equal to 18-20%. The physical-chemical characteristics and the ^{1}H NMR spectrum of compound **13a** are consistent with the literature data for the 1,3-dimethylgidantoin [25]. Hydantoins **13b-d** are described in the literature [26-28] but were characterized only by the element analysis and melting points (**13b** — boiling point). So, we have characterized compounds **13b-d** by ^{1}H NMR spectroscopy.

To prove the structure of compound **13c**, difference mode NOE experiments [29] were applied (Figure 2). Saturation of *t*-Bu signal results in decreasing of CH_2 signal intensity. On the other hand, saturation of Me signal does not affect signals of any other groups. Comparing **13c** and **14c** NOE experiments point to **13c**, since in **14c** one can expect decreasing in of CH_2 signal intensity after saturation of Me signal.

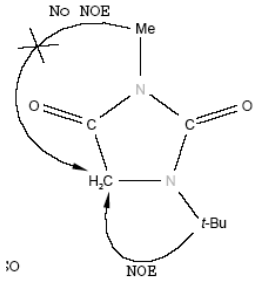


Figure 2. Difference mode NOE experiments of **13c** in DMSO-d6

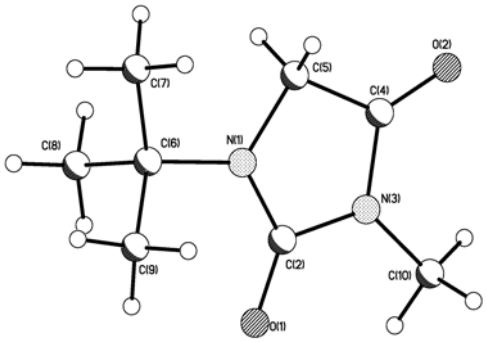


Figure 3. General view of **13c**. Selected bond lengths (Å): O(1)-C(2) 1.2231(19), N(1)-C(2) 1.355(2)N(1)-C(5) 1.462(2), N(1)-C(6) 1.488(2), O(2)-C(4) 1.212(2), C(2)-N(3) 1.410(2), N(3)-C(4) 1.371(2), N(3)-C(10) 1.453(2), C(4)-C(5) 1.511(2); bond angles(°): C(2)-N(1)-C(5) 110.6(1), C(2)-N(1)-C(6) 124.8(1), C(5)-N(1)-C(6) 123.2(1), O(1)-C(2)-N(1) 129.1(15), O(1)-C(2)-N(3) 123.1(14), N(1)-C(2)-N(3) 107.8(13), C(4)-N(3)-C(2) 111.9(1), C(4)-N(3)-C(10) 124.7(1), C(2)-N(3)-C(10) 123.6(1), O(2)-C(4)-N(3) 126.2(2), O(2)-C(4)-C(5) 127.7(1), N(3)-C(4)-C(5) 106.1(1), N(1)-C(5)-C(4) 103.3(1).

In addition, the structure of the obtained hydantoins was established by the X-ray diffraction study. According to XRD the hydantoin cycle is characterized by the envelope conformation with the deviation of methylene atom C(5) by 0.099(3)Å from the plane of N(1), C(2), N(3) and C(4). The bonds lengths in the N(1)-C(2)- N(3)-C(4) fragment alternate with the maximum value observed for C(2)-N(3) one 1.410(2)Å (Figure 3). The pronounced acidity of the hydrogen atoms at C(5) atom leads to the formation in crystal of the relatively strong C-H…O contacts with H…O distances equal to 2.26-2.35Å.

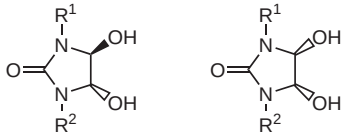
The formation of hydantoins **13** and **14** during the synthesis of bisbicycles **12** can be explained by a pinacolin-like rearrangement of the corresponding 4,5-dihydroxyimidazolidin-2-ones **11a-d**. The latter could form as a result of the transformation of **5** under reaction

conditions to other forms of glyoxal (*e.g.* bisgem-diol **3**, Scheme 1) followed by reaction with ureas **10**. Usually, 4,5-dihydroxyimidazolidin-2-ones are not used as precursors for the synthesis of hydantoins **13** and **14**. Other methods are preferred for this purpose [27,28,30]. At the same time, the formation of hydantoins as by-products of glycolurils synthesis from ureas and 40% solution of glyoxal or 4,5-dihydroxyimidazolidin-2-ones at pH 1 has been observed by us earlier [5].

To confirm the fact of the formation of hydantoins **13a-d** and **14c,d** in the optimal conditions for obtaining bisbicycles **12** we synthesized 1,3-dialkyl-4,5-dihydroxyimidazolydin-2-ones **11a-d** by the condensation of ureas **10a-d** with 40% glyoxal water solution under standard conditions [5]. Compounds **11a,b** have been reported earlier [14,31,32], and **11c,d** have been obtained and characterized for the first time.

Then, the synthesized compounds **11** were treated with water (**11a,b**) or with the water-methanol mixture (**11c,d**) at pH 6 and 60 °C for 2 h, which resulted in hydantoins **13** and **14** in 75-80% yield (Scheme 3).

are different or equivalent. The carbon atoms in compounds **11′** with the *cis*-disposition of the hydroxyl groups have an opposite configuration. In the case of the same substituents at the nitrogen atoms these compounds have a symmetry plane and represent *meso*-form. If the substituents at the nitrogen atoms in the *cis*-isomers are different then these compounds are chiral. Earlier [33] *cis*- and *trans*-isomers have been obtained for the compound **11a**.

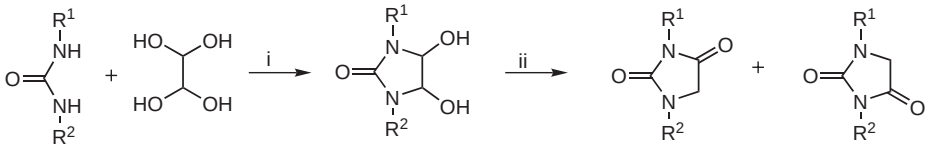


11a-d **11'a-d**

$R^1 = R^2$ = Me (**a**), $R^1 = R^2$ = Et (**b**), R^1 = Me, R^2 = *t*-Bu (**c**), R^1 = Me, R^2 = *c*-C_6H_{11} (**d**).

Besides, it is known [34,35] that 4,5-dihydroxyimidazolydin-2-ones **11** belong to that class of compounds which is capable of crystallizing

Scheme 3



10a-d **3** **11a-d** **13a-d** **14c,d**

$R^1 = R^2$ = Me (**a**), $R^1 = R^2$ = Et (**b**), R^1 = Me, R^2 = *t*-Bu (**c**), R^1 = Me, R^2 = *c*-C_6H_{11} (**d**).

Reagents and conditions. (i) H_2O or H_2O:MeOH (1:5), 45-50 °C, pH 4-5, 2 h (35-52%); (ii) pH 6, 2 h, 60 °C (75-80%).

The physical-chemical characteristics of the obtained hydantoins **13a,b** and mixture of hydantoins **13c,d** and **14c,d** (also in the ratio 9:1) corresponded to the above-described. In the latter case after the crystallization from methanol the dominating isomers **13c,d** were obtained. The presence of the isomers **14c,d** was established only spectrally. This result shows that dehydratation of 1-alkyl-3-methyl-4,5-dihydroxyimidazolydin-2-ones **11c,d** is a regioselective process that leads the predominating formation of **13c,d.**

1,3-Dialkyl-4,5-dihydroxyimidazolydin-2-ones **11a-d** as well as bisbicyclic systems **12** are of interest from the point of view of stereochemistry. Compounds **11** contain two asymmetric carbon atoms C(4), C(5) with OH in *trans*- and *cis*-positions. In the *trans*-isomers these atoms have the same configuration and such compounds are racemates, which can be theoretically resolved into enantiomers, regardless of the fact that the N-substitutents as conglomerates (a mixture of gomochiral crystals). In order to find the conglomerates among the synthesized compounds **11** the crystallization of the earlier unknown 1-alkyl-3methyl-4,5-dihydroxy-imidazolydin-2-ones **11c,d** was investigated. We have managed to obtain a suitable for the X-ray diffraction study single crystal of only compound **11c**. The X-ray diffraction study of **11c** has revealed that it crystallized as a racemate (sp. group Pbca). The hydroxyl groups are characterized by the *trans*-disposition with the torsion angle O(3)C(5)C(4)O(2) equal to 143.6º. The five-membred cycle is characterized by twist conformation with the deviation of C(4) and C(5) atoms by –0.18 and 0.25Å, respectively. In crystal molecules are assembled in zig-zag layers parallel to crystallographic plane ab by the O-H…O bonds (O…O 2.669(2) and 2.809(2)Å).

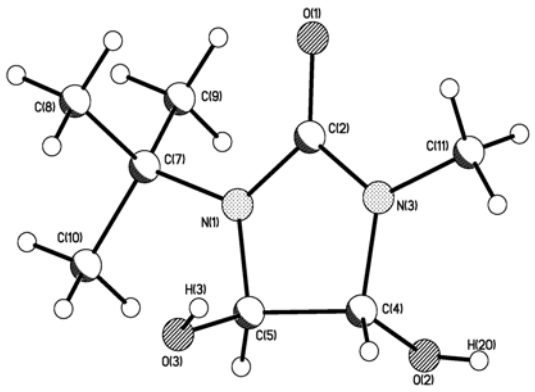


Figure 4. General view of **11c**. Selected bond lengths(Å): N(1)-C(2) 1.368(3), N(1)-C(5) 1.452(3), O(1)-C(2) 1.228(3), O(2)-C(4) 1.409(3), O(3)-C(5) 1.409(3), C(2)-N(3) 1.358(3), N(3)-C(4) 1.433(3); bond angles(°): C(2)-N(1)-C(5) 109.7(2), C(2)-N(1)-C(7) 123.7(2), C(5)-N(1)-C(7) 124.4(2), O(1)-C(2)-N(3) 125.1(2), O(1)-C(2)-N(1) 126.4(2), N(3)-C(2)-N(1) 108.4(2), C(2)-N(3)-C(4) 111.2(2), C(2)-N(3)-C(11) 123.2(2), C(4)-N(3)-C(11) 124.4(2).

Thus, for the first time the interaction of 1,3-dialkylureas **10** with glyoxal in the hydrate form of 2,2'-bi(4,5-dihydroxy-1,3-dioxolan) **5** was studied in details and the first representatives of the previously unknown bisbicylcic systems of 3,3'-bi(6,8-dialkyl-2,4-dioxalan-6,8-diazabicyclo[3.3.0]octan-7-one **12a-d** were prepared. Their structure was confirmed by the combination of the data for the element analysis, NMR-spectroscopy, MSEI, HMRS and X-ray analysis. Besides, it was established that the corresponding hydantoins are formed as the by-products. The suggested scheme of their formation was confirmed experimentally.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-300 instrument in a DMSO-d_6 at 300.13 MHz and 75.47 MHz respectively. The chemical shifts value (δ) were expressed

Table 1
Crystal data and structure refinement parameters for **11c**, **12b** and **13c**.

Compound	**11c**	**12b**	**13c**
Empirical formula	$C_8H_{16}N_2O_3$	$C_{16}H_{26}N_4O_6$	$C_8H_{14}N_2O_2$
Formula weight	188.23	370.41	170.21
Diffractometer	Siemens P3	Siemens P3	Syntex $P2_1$
Wavelength	Mo-Kα	Mo-Kα	Mo-Kα
Crystal colour, habit	colorless prism	Colorless prism	colorless prism
Temperature (K)	298(2)	298(2)	173(2)
Crystal system	Orthorhombic	Triclinic	Monoclinic
Space group	Pbca	P-1	$P2_1/n$
a (Å)	10.834(2)	6.0438(12)	6.3028(13)
b (Å)	8.501(2)	11.825(2)	16.862(3)
c (Å)	22.128(4)	13.825(3)	8.8358(18)
α(°)		101.55(3)	
β (°)		97.35(3)	104.13(3)
γ (°)		93.19(3)	
V (Å^3)	2038.0(7)	956.7(4)	910.7(3)
$Z(Z')$	8(1)	2(1)	4(1)
F(000)	816	396	368
D_{calc} (g cm^{-1})	1.227	1.286	1.242
Linear absorption, μ (cm^{-1})	0.94	0.99	0.90
Scan type	$\theta/2\theta$	$\theta/2\theta$	$\theta/2\theta$
$2\theta max$ (°)	64	56	56
Completeness of dataset (%)	99.8	99.7	98.7
Reflections measured	3551	5041	2355
Independent reflections	3551 [0.000]	4606 [0.0261]	2172 [0.0630]
Observed reflections [$I > 2\sigma(I)$]	1679	3195	1665
Parameters	130	239	121
Final $R(F_{hkl})$: R_1	0.042	0.0532	0.0545
WR_2	0.1312	0.0880	0.1421
GOF	1.052	1.037	0.962
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.201, -0.168	0.203,-0.162	0.397, –0.214

relative to chemical shifts for the deuterated solvent (2.50 ppm and 39.51 ppm for the proton and carbon NMR, respectively). Mass spectra were measured on an MS 30 spectrometer.

The crystal structures **11c, 12b** and **13c** were solved by a direct method and refined by the full-matrix least-squares against F^2 in anisotropic approximation for nonhydrogen atoms. All hydrogen atoms were located from the Fourier density synthesis and refined in isotropic approximation. Crystal data and structure refinement parameters for **11c, 12b** and **13c** are given in Table 1. All calculations were performed using the SHELXTL software. The crystallographic data have been deposited with the Cambridge Crystallographic Data Center, CCDC293638 for 11c, CCDC293639 for 12b and CCDC293640 for 13c. Copies of this information may be obtained free of charge from: The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (Fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or *http://www.ccdc.cam.ac.uk*).

The Optimal Procedure for the Synthesis of 3,3'-Bi(6,8-dialkyl-2,4-dioxa-6,8-diazabicyclo[3.3.0]octan-7-ones) **12a-d**

The trimer dihydrate of glyoxal **5** (0.01 mol) was dissolved at 50 °C in the minimal volume of water (4 ml).The 20% water solution of $NaHCO_3$ was added to the solution up to pH value 6. The corresponding dialkylurea (0.02 mol) **10** was dissolved in H_2O (for **10a,b**) or MeOH (for **10c,d**) in the 5-fold amount to the glyoxal solution in water. The obtained solutions were combined and held during 2 hours at 60 ºC. The reaction masses were left at room temperature overnight. The residues **12a-d** were collected by filtration and were crystallized from MeOH to give **12a**, **12b**, **12c** and **12d** in 42, 41, 43 and 45% yields, respectively.

3,3'-Bi(6,8-dimethyl-2,4-dioxa-6,8-diazabicyclo[3.3.0]octan-7-one (**12a**).

Mp 237-238 °C. R_f = 0.68 (MeOH:CH_3Cl=1:5, v/v); ^{1}H nmr (DMSO-d_6): δ 2.76(s, 12, 4CH_3), 4.79 (s, 2, 2CH), 5.61 (s, 4, 4N-*CH*-O). ^{13}C nmr ([$^2H_6$]DMSO), δ: 28 (CH_3), 87 (CH), 99 (CH), 157 (CO)

Anal. Calcd. for $C_{12}H_{18}N_4O_6$ (314.29): C, 45.86; H, 5.77; N, 17.83. Found: C, 45.59; H, 5.97; N, 17.91.

3,3'-Bi(6,8-diethyl-2,4-dioxa-6,8-diazabicyclo[3.3.0]octan-7-one (**12b**).

Mp 225-227 ºC. R_f = 0.73 (MeOH:CH_3Cl=1:5, v/v);^{1}H nmr (DMSO-d_6): δ 1.11 (m, 12, 4CH_3), 3.24 (m, 8, 4CH_2), 4.78 (s, 2, 2CH), 5.72 (s, 4, 4CH). ^{13}C nmr ([$^2H_6$]DMSO), δ: 13 (CH_3), 36 (CH_2), 86 (CH), 99 (CH), 157 (CO). ms: m/z: 185 (M^+/2), 157 (M^+/2-CH_2O), 141, 140, 112, 86, 58, 56.

Anal. Calcd. for $C_{16}H_{26}N_4O_6$ (370,40): C, 51.88; H, 7.08; N, 15.13. Found: C, 52.02; H, 7.20; N, 14.96.

3,3'-Bi(6-*tert*-butyl-8-methyl-2,4-dioxa-6,8-diazabicyclo[3.3.0]-octan-7-one (**12c**).

Mp 247-249 ºC. R_f = 0.82 (MeOH:CH_3Cl=1:5, v/v); ^{1}H nmr (DMSO-d_6): δ 1.34 (s, 18, 6C-CH_3), 2.69 (s, 6, 2N-CH_3), 4.74 (s, 2, 2CH), 5.54 (d, 2, 2N-*CH*-O, J = 5.0 Hz), 5.82 (d, 2, 2N-*CH*-O, J = 5.0 Hz). ^{13}C nmr ([$^2H_6$]DMSO), δ: 27 (C-CH_3), 28 (N-CH_3), 53 (CH_2), 85 (C(5),C(5')) 86 (C(1),C(1')), 98 (C(3),C(3')), 157 (CO). ms: m/z: 199 (M^+/2), 155, 154, 143, 115, 98, 84, 72, 70. HMRS, Found $(M+H)^+$, 399.2237. $C_{18}H_{30}N_4O_6$ requires M, 398.2165.

Anal. Calcd. for $C_{18}H_{30}N_4O_6$ (398,45): C, 54.26; H, 7.59; N, 14.06. Found: C, 54.11; H, 7.71; N, 13.95.

3,3'-Bi(6-cyclohexyl-8-methyl-2,4-dioxa-6,8-diazabicyclo-[3.3.0]octan-7-one (**12d**)

Mp 314-316 ºC. R_f = 0.75 (MeOH:CH_3Cl=1:5, v/v); ^{1}H nmr (DMSO-d_6): δ 0.98-1.37(br.m, 8, 4CH_2), 1.42-1.90 (br.m, 12, 6CH_2), 2.75(s, 6, 2N-CH_3), 3.49(m, 2, 2N-*CH*-(CH_2)$_2$), 4.82(s, 2, 2CH), 5.53(d, 2, 2N-*CH*-O, J = 4.9 Hz), 5.71(d, 2, 2N-*CH*-O, J = 4.9 Hz). ^{13}C nmr ([$^2H_6$]DMSO), δ: 25 (CH_2), 28 (CH_2), 30 (CH_3), 32 (CH_2), 52 (CH), 85 (C5,C5') 87 (C1,C1'), 99 (C3,C3'), 157 (CO). ms: m/z: 225 (M^+/2), 153, 115, 98, 82, 68.

Anal. Calcd. for $C_{22}H_{34}N_4O_6$ (450,53): C, 58.65; H, 7.61; N, 12.44. Found: C, 58.79; H, 7.80; N, 12.57

General Procedure for the Synthesis of 1,3-dialkyl-4,5-dihydroxyimidazolidin-2-ones **11a-d**.

A small amount of the concentrated HCl was added drop wise to pH 4-4.5 to the solution of 0.04 mol glyoxal (the 40% water solution) and the corresponding urea **10** (0.04 mol). The reaction mass was held at 45-50 °C during 2 hours. The reaction masses for the synthesis of **11a,b** were evaporated *in vacuo* to give oily residues and were crystallized from MeOH to give **11a** and **11b** in 32 and 25% yields, respectively. The reaction masses for the synthesis of **11c,d** were evaporated *in vacuo* to half of their volume. By the cooling a crystalline precipitates were obtained. The residues **11c,d** were collected by filtration and were crystallized from MeOH to give **11c** and **11d** in 35 and 52% yields, respectively.

1-*tert*-Butyl-3-methyl-4,5-dihydroxyimidazolidin-2-one (**11c**).

Mp 156-158 ºC; ^{1}H nmr (DMSO-d_6): δ 1.31 (s, 9, 3C-CH_3), 2.63 (s, 3, N-CH_3), 4.40 (br.m, 1, CH), 4.65 (br.m, 1, CH), 5.83 (br.m, 1, OH), 6.00 (br.m, 1, OH).

Anal. Calcd. for $C_8H_{16}N_2O_3$ (188,22): C, 51.05; H, 8.57; N, 14.88. Found: C, 50.94; H, 8.69; N, 14.99

1-Cyclohexyl-3-methyl-4,5-dihydroxyimidazolidin-2-one (**11d**).

Mp 164-166 ºC; ^{1}H nmr (DMSO-d_6): δ 0.8-1.76(br.m, 10, 5CH_2), 2.60 (s, 3, N-CH_3), 4.37 (br.m, 1, CH), 4.66 (br.m, 1, CH), 5,90 (br.m, 1, OH), 6.05 (br.m, 1, OH)

Anal. Calcd. for $C_{10}H_{18}N_2O_3$ (214,26): C, 56.06; H, 8.47; N, 13.07. Found: C, 55.90; H, 8.25; N, 12.95

General Procedure for the Synthesis of 3-alkyl-1-methylimidazolidin-2,4-diones **13a-d**.

1,3-Dialkyl-4,5-dihydroxyimidazolidin-2-ones **11a-d** (0.02 mol) were dissolved at RT in the minimal amount of H_2O (for **11a,b**) or H_2O-MeOH mixture (1:5) (for **11c,d**). A 20% water solution of $NaHCO_3$ was added to the solution up to pH 6. The reaction masses were held at 60 °C during 2 h. The reaction masses for the synthesis of **13a,b** were evaporated *in vacuo* to give oily residues, which were extracted with the ether. The obtained solutions evaporated *in vacuo* to give a crystalline precipitates, which were crystallized from MeOH to give **13a,b** in 77 and 75% yields, respectively. The reaction masses for the synthesis of **13c,d** were placed in the refridgerator. The residues **13c,d** were collected by filtration and were crystallized from MeOH to give **13c** and **13d** in 78 and 80% yields, respectively.

1,3-Diethylimidazolidin-2,4-dione (**13b**).

Bp 260-261 °C; ^{1}H nmr (DMSO-d_6): δ 1.04 (t, 6, CH_3, J = 6.0 Hz), 3.32 (m, 4, N-CH_2), 3.85 (s, 2, CH_2).

Anal. Calcd. for $C_7H_{12}N_2O_2$ (156,18): C, 53.83; H, 7.74; N, 17.94. Found: C, 53.76; H, 7.82; N, 18.01.

1-*tert*-Butyl-3-methylimidazolidin-2,4-dione (**13c**).

Mp 104-106 ºC; ^{1}H nmr (DMSO-d_6): δ 1.46(s, 9, 3C-CH_3), 2.80(s, 3, N-CH_3), 4.05(s, 2, CH_2)

Anal. Calcd. for $C_8H_{14}N_2O_2$ (170,21): C, 56.45; H, 8.29; N, 16.46. Found: C, 56.57; H, 8.45; N, 16.28.

1-Cyclohexyl-3-methylimidazolidin-2,4-dione (**13d**).

Mp 112-114 ºC; ^{1}H nmr (DMSO-d_6): δ 0.9-1.75(br.m, 10, 5CH_2), 2.79(s, 3, CH_3), 3,69(m, 1, N-CH), 3.89(s, 2, CH_2)

Anal. Calcd. for $C_{10}H_{16}N_2O_2$ (196,25): C, 61.20; H, 8.22; N, 14.27. Found: C, 61.01; H, 8.35; N, 14.39

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