4,5-Dihydroxyimidazolidin-2-ones in α-ureidoalkylation of *N*-carboxyalkyl-, *N*-hydroxyalkyl-, and *N*-aminoalkylureas

5.* Synthesis of *N*-hydroxyalkyl-1,5-diphenylglycolurils

G. A. Gazieva, V. V. Baranov, and A. N. Kravchenko*

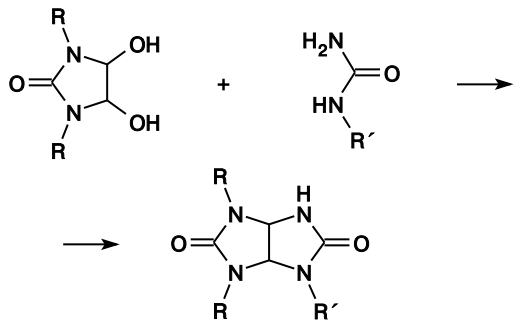
N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences,
47 Leninsky prosp., 119991 Moscow, Russian Federation.
Fax: +7 (499) 135 5328. E-mail: gaz@ioc.ac.ru

A systematic investigation of α-ureidoalkylation of *N*-hydroxyalkylureas with 4,5-dihydroxy-1,3-dimethyl-4,5-diphenylimidazolidin-2-one allowed the discovery of a synthetic route to earlier unknown *N*-hydroxyalkyl-1,5-diphenylglycolurils. The yields of these compounds decrease with lengthening and branching of the alkyl chain in the starting ureas.

Key words: α-ureidoalkylation, glycolurils, *N*-hydroxyalkylureas, 4,5-dihydroxy-1,3-dimethyl-4,5-diphenylimidazolidin-2-one.

In the last few years, our investigations have dealt with the synthesis of functionalized glycolurils (2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-diones). Earlier,[1—4] we have reported on our systematic investigations of α-ureidoalkylation of *N*-carboxyalkyl-, *N*-hydroxyalkyl-, and *N*-aminoalkylureas with either unsubstituted or N-substituted 4,5-dihydroxyimidazolidin-2-ones as ureidoalkylating reagents (Scheme 1). 4,5-Diphenyl analogs were used only in coupling reactions with *N*-aminoalkylureas.[1,4]

Scheme 1



R = H, Alk; R′ is carboxy-, hydroxy-, and aminoalkyl

A pharmacological study of the previously obtained *N*-carboxyalkyl-, *N*-hydroxyalkyl-, and *N*-aminoalkylglycolurils revealed anxiolytic, sedative, and nootropic effects of *N*-carboxypropyl derivatives.[5] *N*-Hydroxyalkylglycolurils are bacteriostatic for Gram-positive microflora.[6] 2-(2-Acetylaminoethyl)-4-methylglycoluril exhibits nootropic activity.[1] In addition, some 1,5-diphenylglycolurils containing alkyl substituents at the N atoms are known to affect the cytochrome P450-dependent monooxygenase system of liver.[7] That is why development of synthetic methods leading to functionalized glycolurils that contain alkyl and hydroxyalkyl substituents at the N atoms and phenyl substituents at the C atoms of the glycoluril framework is of current interest.

With the aim of determining the scope of these reactions and searching for new biologically active compounds among glycolurils, here we studied α-ureidoalkylation of *N*-hydroxyalkylureas (ureidoalkanols) with 4,5-dihydroxy-1,3-dimethyl-4,5-diphenylimidazolidin-2-one (DHI **1**).

Earlier,[3] we have found that *N*-hydroxyalkylglycolurils can be obtained by an acid-catalyzed reaction of ureidoalkanols with unsubstituted or 1,3-dialkyl-4,5-dihydroxyimidazolidin-2-ones in hot water. The yields of glycolurils depend on the length and branching of the carbon chain in the starting ureas, the presence of substituents at the N atoms of DHI, and the reaction times.[3]

Because DHI **1** is insoluble in water, α-ureidoalkylation of ureido alcohols **2a—f** (Scheme 2) (prepared by *N*-carbamoylation of appropriate amino alcohols according to our procedure[8]) was carried out in boiling methanol in the presence of different amounts of conc. HCl for 1 and 2 h. The yields of compounds **3a—d** increase with an increase in the molar ratio HCl/DHI **1** from 0.2 to 0.5 (Table 1, entries *1*, *2*; *5*, *6*; *9*, *10*; *13*, *14*) and remain virtually insensitive to an extension of the reaction time from 1 to 2 h and to a further increase in the above ratio (from 0.5 to 1) (Table 1, entries *2—4*, *6—8*, *10—12*, and *14—16*). Based on the results obtained, we synthesized glycolurils **3a—e** under optimized conditions (HCl/DHI **1** = 0.5, 1 h). The

* For Part 4, see Ref. 1.

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 6, pp. 1267—1270, June, 2010.

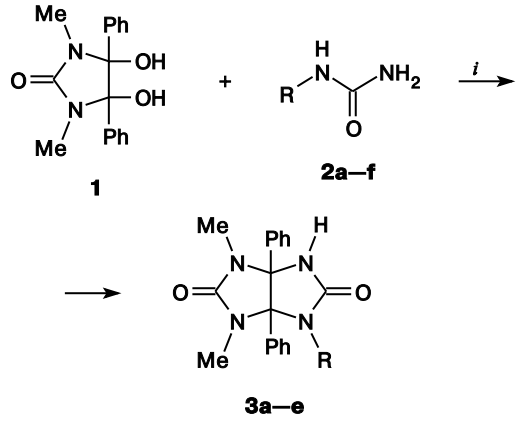
1066-5285/10/5906-1296

Table 1. Influence of the reaction time and the amount of HCl on the yields of *N*-hydroxyalkylglycolurils **3a—d**

Entry	τ/h	HCl /mol equiv^{-1}	Product	Yield (%)
1	1	0.2	**3a**	78
2	1	0.5	**3a**	89
3	1	1	**3a**	90
4	2	0.5	**3a**	90
5	1	0.2	**3b**	61
6	1	0.5	**3b**	72
7	1	1	**3b**	73
8	2	0.5	**3b**	71
9	1	0.2	**3c**	67
10	1	0.5	**3c**	81
11	1	1	**3c**	81
12	2	0.5	**3c**	82
13	1	0.2	**3d**	82
14	1	0.5	**3d**	88
15	1	1	**3d**	89
16	2	0.5	**3d**	88

Note. τ is the reaction time.

Scheme 2



2, **3**: R = $(CH_2)_2OH$ (**a**), $(CH_2)_3OH$ (**b**), $CH_2CH(OH)Me$ (**c**), $(CH_2)_2C_6H_4OH$-*p* (**d**), $CH(Et)CH_2OH$ (**e**), $C(Me)_2CH_2OH$ (**f**)

Reagents and conditions: *i*. MeOH, HCl, reflux, 1 h.

more branched the alkyl chain in the starting ureido alcohol, the lower the yields of glycolurils **3a—e**. For instance, the yields of compounds **3a—d** are 72—89% (Table 2), while the yield of glycoluril **3e** with the α-ethyl substituent is 64%; α,α-disubstituted urea **2f** remains inert in this reaction.

The ^{1}H NMR spectra of compounds **3a—e** show signals of the alkyl fragments at δ 0.8—4.1, signals of the OH protons at δ 4.4—5.1 (for **3d**, δ 9.18), multiplets of the phenyl protons at δ 6.6—7.2, and singlets of the NH protons at δ 8.3—8.6. The ^{13}C NMR spectra exhibit signals of the bridgehead atoms C(Ph)—C(Ph) at δ 82.5—88.5, signals of the phenyl C atoms at δ 127.3—135.1, and two signals from two carbonyl C atoms at δ 158.6—158.8 and δ 159.5—161.0. The signals of the C atoms of the alkyl fragments correspond to the structures of the glycolurils obtained. The spectra of compounds **3c** and **3e** containing three asymmetric C atoms show double sets of signals of the protons and the carbon atoms in a ratio of 1 : 1, which is due to their structural features. Since the bicyclic framework of glycolurils is rigid and their imidazolidine rings are *cis*-fused,[2—4] the diastereomers of **3c** are 6-(2(*R**)-hydroxypropyl)-2,4-dimethyl-1(*S**),5(*S**)-diphenyl-2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dione and 6-(2(*R**)-hydroxypropyl)-2,4-dimethyl-1(*R**),5(*R**)-diphenyl-2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dione and the diastereomers of **3e** are 6-(1-hydroxybut-2(*R**)-yl)-2,4-dimethyl-1(*S**),5(*S**)-diphenyl-2,4,6,8-tetraazabicyclo[3.3.0]-

Table 2. Yields, melting points, elemental analysis data, and mass spectra of compounds **3a—e**

Compound	Yield (%)	T_m/°C	Found / Calculated (%)			Molecular formula	MS, m/z (I_{rel} (%))
			C	H	N		
3a	89	263—264	65.33 65.56	6.16 6.05	15.27 15.29	$C_{20}H_{22}N_4O_3$	366 (5) $[M]^+$, 335 (100)
3b	72	218—220	66.22 66.30	6.41 6.36	14.67 14.73	$C_{21}H_{24}N_4O_3$	380 (7) $[M]^+$, 264 (100)
3c	81	266—268[a] 277—279[b]	66.25 66.30	6.31 6.36	14.69 14.73	$C_{21}H_{24}N_4O_3$	363 (4) $[M - 17(H_2O)]^+$, 264 (100)
3d	88	315—317	70.59 70.57	5.88 5.92	12.62 12.66	$C_{26}H_{26}N_4O_3$	—
3e	64	261—263[a] 302—304[b]	66.80 66.69	6.62 6.64	14.19 14.20	$C_{22}H_{26}N_4O_3$	365 (10) $[M - 29(Et)]^+$, 363 (100)

[a] The mixture of diastereomers.
[b] The first racemate.

octane-3,7-dione and 6-(1-hydroxybut-2(*R**)-yl)-2,4-dimethyl-1(*R**),5(*R**)-diphenyl-2,4,6,8-tetraazabicyclo-[3.3.0]octane-3,7-dione. Repeated recrystallization from methanol allowed one racemate to be separated from the other for both compounds **3c** and **3e**; the racemates were characterized by melting points and ^{1}H and ^{13}C NMR spectra (Tables 2, 3).

The mass spectra of glycolurils **3a,b** with unbranched hydroxyalkyl chains at the N atom contain molecular ion peaks. In the mass spectra of 6-(2-hydroxypropyl)- (**3c**) and 6-(1-hydroxybut-2-yl)glycolurils (**3e**), the highest-mass peaks correspond to the fragments $[M - H_2O]^+$ and $[M - Et]^+$, respectively (see Table 2).

N-Hydroxyalkylglycolurils **3a**—**e** are amorphous white powders; we failed to obtain crystals suitable for X-ray diffraction study by crystallization from various solvents.

6-(2-Hydroxyethyl)- (**3a**) and 6-[2-(4-hydroxyphenyl)-ethyl]-2,4-dimethyl-1,5-diphenyl-2,4,6,8-tetraazabi-cyclo[3.3.0]octane-3,7-diones (**3d**) are being tested with mice for acute toxicity and biological activity at the Institute of Technical Chemistry (Ural Division of the Russian Academy of Sciences). To date, it has been found that both compounds have $LD_{50} > 1000$ mg kg^{-1} and produce no anxiolytic effect in a dose of 100 mg kg^{-1}.

Thus, we studied for the first time the α-ureidoalkylation of ureidoalkanols **2** with 4,5-diphenyl-DHI **1** and

Table 3. ^{1}H and ^{13}C NMR spectra of compounds **3a**—**e** in DMSO-d_6

Compound	^{1}H (δ, *J*/Hz)	^{13}C (δ)
3a	2.59 (s, 3 H, NMe); 2.75—2.88 (m, 1 H, OCH_2); 2.83 (s, 3 H, NMe); 3.32—3.42 (m, 1 H, OCH_2); 3.48—3.58 (m, 1 H, NCH_2); 3.60—3.70 (m, 1 H, NCH_2); 4.78 (t, 1 H, OH, *J* = 5.5); 6.78—6.90 (m, 4 H, Ph); 7.05—7.13 (m, 6 H, Ph); 8.54 (s, 1 H, NH)	26.24 (NMe); 28.04 (NMe); 45.34 (NCH_2); 59.33 (OCH_2); 82.64 (CPh); 87.74 (CPh); 127.32, 127.92, 128.01, 128.25, 128.32, 128.50, 133.01, 134.74 (all Ph); 158.62 (C=O); 159.86 (C=O)
3b	1.59—1.71 (m, 1 H, CH_2); 1.84—1.96 (m, 1 H, CH_2); 2.60 (s, 3 H, NMe); 2.75—2.88 (m, 1 H, OCH_2); 2.80 (s, 3 H, NMe); 3.31—3.48 (m, 3 H, OCH_2 + NCH_2); 4.47 (t, 1 H, OH, *J* = 5.6); 6.76—6.90 (m, 4 H, Ph); 7.05—7.15 (m, 6 H, Ph); 8.45 (s, 1 H, NH)	26.17 (NMe); 28.09 (NMe); 32.60 (CH_2); 40.40 (NCH_2); 58.44 (OCH_2); 82.51 (CPh); 87.81 (CPh); 127.31, 127.91, 127.99, 128.23, 128.29, 128.45, 133.16, 134.76 (all Ph); 158.60 (C=O); 159.57 (C=O)
3c	First racemate: 1.00 (d, 3 H, Me, *J* = 5.6); 2.61 (s, 3 H, NMe); 2.75 (dd, 1 H, NCH_2, *J* = 14.7, *J* = 4.4); 2.81 (s, 3 H, NMe); 3.25—3.35 (m, 1 H, NCH_2); 4.01—4.09 (m, 1 H, CH); 4.92 (d, 1 H, OH, *J* = 3.7); 6.76 (m, 2 H, Ph); 6.87 (m, 2 H, Ph); 7.09 (br.s, 6 H, Ph); 8.64 (s, 1 H, NH)	First racemate: 21.30 (Me); 26.46 (NMe); 28.67 (NMe); 51.20 (CH_2); 65.95 (CH); 83.12 (CPh); 88.30 (CPh); 127.45, 128.07, 128.31, 128.36, 128.51, 128.59, 128.66, 132.86, 134.65 (all Ph); 158.81 (C=O); 161.03, (C=O)
	Second racemate: 1.02 (d, 3 H, Me, *J* = 5.6); 2.60 (s, 3 H, NMe); 2.60—2.66 (m, 1 H, NCH_2); 2.84 (s, 3 H, NMe); 3.25—3.35 (m, 1 H, NCH_2); 3.88—3.97 (m, 1 H, CH); 4.87 (d, 1 H, OH, *J* = 4.4); 6.76 (m, 2 H, Ph); 6.87 (m, 2 H, Ph); 7.09 (br.s, 6 H, Ph); 8.48 (s, 1 H, NH)	Second racemate: 22.02 (Me); 26.17 (NMe); 28.35 (NMe); 50.78 (CH_2); 65.38 (CH); 82.71 (CPh); 88.46 (CPh); 127.45, 128.07, 128.31, 128.36, 128.51, 128.59, 128.66, 133.19, 134.74 (all Ph); 158.72 (C=O); 160.14 (C=O)
3d	2.61 (s, 3 H, NMe); 2.63—2.73 (m, 1 H, CH_2); 2.79—2.88 (m, 1 H, CH_2); 2.82 (s, 3 H, NMe); 2.93—3.01 (m, 1 H, NCH_2); 3.35—3.46 (m, 1 H, NCH_2); 6.63 (d, 2 H, ArOH *J* = 7.7); 6.74 (m, 2 H, Ph); 6.87 (m, 2 H, Ph); 6.94 (d, 2 H, ArOH, *J* = 7.9); 7.07 (br.s, 6 H, Ph); 8.55 (s, 1 H, NH); 9.18 (s, 1 H, OH)	26.29 (NMe); 28.16 (NMe); 34.30 (CH_2); 45.19 (NCH_2); 82.53 (CPh); 87.77 (CPh); 115.19, 127.31, 127.87, 127.97, 128.18, 128.26, 128.42, 128.80, 129.50, 132.97, 134.79, 155.77 (all Ar); 158.63 (C=O); 159.57 (C=O)
3e	First racemate: 0.82 (t, 3 H, Me, *J* = 7.4); 1.83—1.88 (m, 1 H, CH_2); 2.17—2.24 (m, 1 H, CH_2); 2.55 (s, 3 H, NMe); 2.70—2.76 (m, 1 H, CH); 2.90 (s, 3 H, NMe); 3.63—3.70 (m, 1 H, OCH_2); 3.75—3.82 (m, 1 H, OCH_2); 4.79 (t, 1 H, OH, *J* = 5.1); 6.87—6.92 (m, 4 H, Ph); 7.02—7.10 (m, 6H, Ph); 8.36 (s, 1 H, NH)	First racemate: 10.89 (Me); 25.76 (CH_2); 26.28 (NMe); 29.29 (NMe); 57.24 (NCH); 62.42 (OCH_2); 83.20 (CPh); 88.09 (CPh); 127.40, 127.84, 127.93, 127.95, 128.21, 128.35, 128.43, 128,57, 133.42, 134.72 (all Ph); 158.63 (C=O); 159.53 (C=O)
	Second racemate: 0.87 (t, 3 H, Me, *J* = 7.4); 1.52—1.59 (m, 1 H, CH_2); 2.04—2.11 (m, 1 H, CH_2); 2.60 (s, 3 H, NMe); 2.84—2.89 (m, 1 H, CH); 2.85 (s, 3 H, NMe); 3.86—3.92 (m, 2 H, OCH_2); 5.03 (t, 1 H, OH, *J* = 5.1); 6.87—6.92 (m, 4 H, Ph); 7.02—7.10 (m, 6 H, Ph); 8.45 (s, 1 H, NH)	Second racemate: 12.60 (Me); 23.21 (CH_2); 26.44 (NMe); 29.15 (NMe); 57.40 (NCH); 63.44 (OCH_2); 83.50 (CPh); 87.91 (CPh); 127.40, 127.84, 127.93, 127.95, 128.21, 128.27, 128.35, 128,57, 133.70, 135.11 (all Ph); 158.78 (C=O); 159.78 (C=O)

developed a method for the synthesis of glycolurils **3a—e** containing alkyl and hydroxyalkyl substituents at the N atoms and phenyl substituents at the bridgehead C atoms.

Experimental

NMR spectra were recorded on a Bruker AM-300 spectrometer (300.13 (^{1}H) and 75.5 MHz (^{13}C)) in DMSO-d_6. The chemical shifts δ are referenced to Me_4Si as the internal standard. Mass spectra were recorded on a Kratos MS-30 mass spectrometer (EI, 70 eV). Melting points were determined on a GALLENKAMP instrument (Sanyo).

Compound **1** was prepared from 1,3-dimethylurea and diphenylglyoxal in boiling methanol in the presence of aqueous KOH according to a known procedure.[9]

Synthesis of 6-hydroxyalkyl-2,4-dimethyl-1,5-diphenyl-2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-diones 3a—e (general procedure). Concentrated HCl (0.21 mL, 0.0025 mol) was added to a suspension of DHI **1** (1.49 g, 0.005 mol) and an appropriate ureidoalkanol **2a—e** (0.005 mol) in methanol (15 mL). The reaction mixture was refluxed with stirring for 1 h and then cooled. The precipitate that formed was filtered off and recrystallized from methanol. The physicochemical characteristics of glycolurils **3a—e** are given in Tables 2 and 3.

References

1. G. A. Gazieva, P. V. Lozhkin, V. V. Baranov, A. N. Kravchenko, N. N. Makhova, *Izv. Akad. Nauk, Ser. Khim.*, 2010, 628 [*Russ. Chem. Bull.*, *Int. Ed.*, 2010, **59**, 642].
2. A. N. Kravchenko, K. A. Lyssenko, I. E. Chikunov, P. A. Belyakov, M. M. Il´in, V. V. Baranov, Yu. V. Nelyubina, V. A. Davankov, T. S. Pivina, N. N. Makhova, M. Yu. Antipin, *Izv. Akad. Nauk, Ser. Khim.*, 2009, 390 [*Russ. Chem. Bull.*, *Int. Ed.*, 2009, **58**, 395].
3. A. N. Kravchenko, A. S. Sigachev, P. A. Belyakov, M. M. Il´in, K. A. Lyssenko, V. A. Davankov, O. V. Lebedev, N. N. Makhova, V. A. Tartakovsky, *Izv. Akad. Nauk*, *Ser. Khim.*, 2009, 1229 [*Russ. Chem. Bull.*, *Int. Ed.*, 2009, **58**, 1264].
4. G. A. Gazieva, P. V. Lozhkin, V. V. Baranov, Yu. V. Nelyubina, A. N. Kravchenko, N. N. Makhova, *Izv. Akad. Nauk*, *Ser. Khim.*, 2009, 2408 [*Russ. Chem. Bull.*, *Int. Ed.*, 2009, **58**, 2488].
5. Yu. B. Vikharev, L. V. Anikina, I. E. Chikunov, A. S. Sigachev, A. N. Kravchenko, Yu. V. Shklyaev, N. N. Makhova, *Vopr. Biol. Med. Farm. Khim.* [*Problems in Biological, Medicinal, and Pharmaceutical Chemistry*], 2006, No. 2, 12 (in Russian).
6. G. A. Aleksandrova, A. N. Kravchenko, A. S. Sigachev, V. V. Baranov, *Trudy Mezhdunarodnoi konferentsii "Innovatsionnyi potentsial estestvennykh nauk"* [*Proc. Int. Conf. "Innovative Potential of Natural Sciences"*], Perm, 2006, **1**, 243 (in Russian).
7. A. A. Bakibaev, R. R. Akhmedzhanov, A. Yu. Yagovkin, T. P. Novozheeva, V. D. Filimonov, A. S. Saratikov, *Khim.-Farm. Zh.*, 1993, **27**, No. 6, 29 [*Russ. Pharm. Chem. J.* (*Engl. Transl.*), 1993, **27**, No. 6, 401].
8. A. N. Kravchenko, E. Yu. Maksareva, P. A Belyakov, A. S. Sigachev, K. Yu. Chegaev, K. A. Lyssenko, O. V. Lebedev, N. N. Makhova, *Izv. Akad. Nauk, Ser. Khim.*, 2003, 180 [*Russ. Chem. Bull.*, *Int. Ed.*, 2003, **52**, 192].
9. R. Neville, *J. Org. Chem.*, 1958, **23**, 1588.

Received December 9, 2009;
in revised form April 26, 2010