Chemistry of Heterocyclic Compounds, Vol. 42, No. 3, 2006

REACTION OF N-ALKYLGLYCOLURILS WITH ELECTROPHILIC REAGENTS

A. N. Kravchenko[1], A. S. Sigachev[1], G. A. Gazieva[1], E. Yu. Maksareva[1], N. S. Trunova[1], K. A. Chegaev[1], K. A. Lyssenko[2], D. V. Lyubetsky[2], M. I. Struchkova[1], M. M. Il'in[2], V. A. Davankov[2], O. V. Lebedev[1], N. N. Makhova[1], and V. A. Tartakovsky[1]

The N-hydroxymethylation, N-acetylation, and N-acetoxymethylation of mono-, di-, and trialkylglycolurils by reaction with the electrophilic reagents formaldehyde and acetaldehyde have been studied. General methods have been developed for the preparation of mono-, di-, and tri-N-hydroxymethylglycolurils by treatment of differently substituted N-alkylglycolurils with formaldehyde (as hemiformal in methanol) and the synthesis of di-N- and tri-N-acetyl- or N-acetoxymethylglycolurils via the electrophilic substitution of hydrogen atoms for an acetyl group at the nitrogen or oxygen atoms in the hydroxymethyl groups of glycolurils using acetic anhydride. The regioselectivity of the reaction of the 2-t-Bu- and 2-c-C_6H_{11}-glycolurils with formaldehyde has been shown to yield a 4,6-di(hydroxymethyl) derivative. It was found that the hydroxymethylation of 2,4- and 2,6-dialkylglycolurils occurs regioselectively with a stoichiometric ratio of glycoluril to hemiformal and permits preparation of their mono- and dihydroxymethyl derivatives. The enantiomeric analysis of the obtained compounds has been carried out for the first time using HPLC on chiral phases. X-ray analysis has been carried out on the previously unreported racemic 2,6-diacetoxymethyl-4,8-dimethylglycoluril.

Keywords: N-Hydroxymethyl(acetyl, acetoxymethyl)glycolurils, acetic anhydride, formaldehyde, electrophilic reagents, hydroxymethylation and electrophilic substitution of N-alkylglycolurils, regioselectivity, regiospecificity, X-ray analysis, enantiomeric analysis.

The preparation of enantiomerically pure biologically active compounds is an important goal in organic and medicinal chemistry. In recent years this problem has being resolved by us in the case of glycoluril (2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dione) derivatives which are a promising class of neurotropic compounds [1-4]. For access to enantiomers of glycolurils we have developed two basic methods, *viz*. the diastereoselective and diastereospecific synthesis using optically pure precursors (asymmetric induction) [5, 6] and the separation of racemates *via* spontaneous crystallization [7-11]. A necessary condition for the spontaneous separation into enantiomers is the ability of the racemates to form conglomerates (crystallization as a mixture of homochiral crystals). Both N-alkyl- [7, 8, 11], N-carboxy- [9, 11], and N-hydroxyalkylglycolurils [10] show this property. However, N-alkylglycolurils are basically finely dispersed powders [8, 10] while glycolurils with functional groups in the substituent generally form coarser crystals fully suited to X-ray

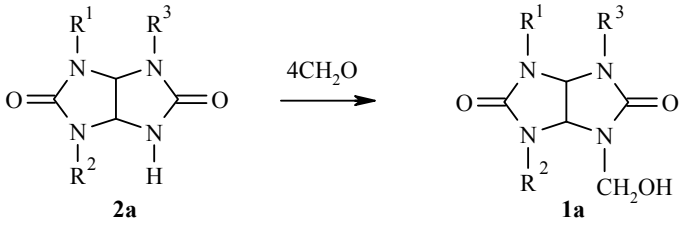
[1] N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Moscow 117913; e-mail: kani@ioc.ac.ru. [2] A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, Moscow 119991; e-mail: kostya@xray.ineos.ac.ru. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 411-423, March, 2006. Original article submitted July 15, 2005.

analytical investigation [9, 12]. In particular, it has been shown that 2-carboxypropyl- and 2-(2-hydroxy-1,1-dimethylethyl)glycolurils among this type of derivative crystallize as conglomerates [9, 11, 12]. In addition we have developed an enantiomeric analysis of chiral N-alkyl (carboxyalkyl-, hydroxylalkyl)glycolurils by HPLC on chiral phases [10-13].

In a continuation of our study of the synthesis of racemic functionally substituted glycolurils the aims of this work were to develop general methods for preparation of previously unrecorded racemic N-acetyl- and N-hydroxymethylglycolurils and their O-acetyl derivatives, the enantiomeric analysis of the compounds obtained by HPLC, and an investigation of their crystallization processes from different solvents. The preparation of conglomerates might be expected in this series because it has previously been shown that 2,6-diacetyl-4,8-dinitroglycoluril crystallizes in a noncentrosymmetric space group $P2_12_12_1$ [14] which is most typical of glycolurils forming conglomerates [7-9, 11].

The reactions of glycolurils with different electrophilic reagents in N-hydroxymethylation, acylation, chlorination, and nitration processes has only been described for glycoluril and isolated N-alkylglycolurils [15-51]. The processes of chlorination [17-32] and nitration [33-35] have been known for a long time and mostly reported in the patent literature [17, 19, 22-32, 34, 35]. It is known that the synthesis of N-hydroxymethyl derivatives of glycolurils occurs by treatment of glycolurils with formaldehyde [36-45]. This reaction is only known in some detail for glycoluril. Thus the synthesis of 2,4,6,8-tetra-(hydroxymethyl)glycoluril (**1a**) occurs in 80% yield by condensation of the glycoluril **2a** in a suspension of paraformaldehyde in aqueous base solution at pH 10-12 and a temperature of 50-60°C, the length of the process not being reported [45]. Compound **1a** was separated and characterized by melting point. In another example the reaction occurs over 2 h at pH 9-10 and temperature of 50°C with the formaldehyde being used as a 40% solution in water (Scheme 1). A 50% solution of the glycoluril **1a** was obtained and was used in a subsequent reaction without separation [15].

Scheme 1



2a **1a**

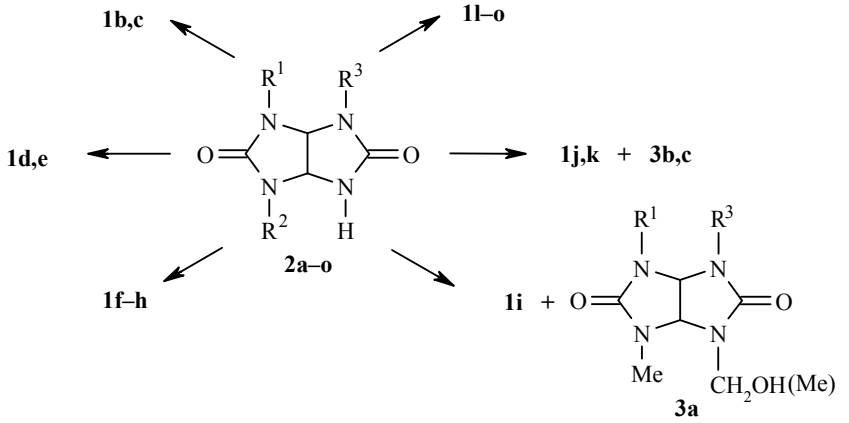
1a $R^1 = R^2 = R^3 = CH_2OH$; **2a** $R^1 = R^2 = R^3 = H$

The N-acylation of glycolurils is carried out using acid chlorides or acetic anhydride and with either BuLi in absolute solvents or $HClO_4$ [15, 16, 46-51] as catalysts. Examples of the O-acylation of the hydroxymethylglycolurils are absent in the literature.

As targets for the study we chose the mono- (**2b-e**), di- (**2f-k**), and tri-N-alkylglycolurils **(2l-o**) (Scheme 2). The synthesis of the starting glycolurils **2b-o** was carried out by methods developed by us before [10, 52]. Mono- (**2b-e**), 2,4-di- (**2i**), and 2,4,6-trialkylglycolurils (**2l-o**) were prepared by the α-ureidoalkylation of mono- and 1,3-dialkylureas and using as ureidoalkylating agents the corresponding 4,5-dihydroxyimidazolidin-2-ones [10, 52]. The 2,6- (**2f-h**), and 2,8-dialkyl derivatives (**2j,k**) were prepared by condensation of the corresponding monoalkylureas with glyoxal [10].

It is known that 2-mono-, 2,4-, 2,6-, and 2,8-dialkylglycolurils **2b-k** are poorly soluble in water [10] and hence their complete hydroxymethylation in conditions similar to the literature method will also occur in

Scheme 2



1 b R^1 = Me, $R^2 = R^3 = CH_2OH$; **c** R^1 = Et, $R^2 = R^3 = CH_2OH$; **d** R^1 = *t*-Bu, $R^2 = CH_2OH$, R^3 = H; **e** R^1 = *c*-C_6H_{11}, $R^2 = CH_2OH$, R^3 = H; **f** $R^1 = CH_2OH$, $R^2 = R^3$ = Me; **g** $R^1 = CH_2OH$, $R^2 = R^3$ = Et; **h** $R^1 = CH_2OH$, $R^2 = R^3$ = Pr; **i** $R^1 = R^2$ = Me, $R^3 = CH_2OH$; **j** $R^1 = R^3$ = Me, $R^2 = CH_2OH$; **k** $R^1 = R^3$ = Et, $R^2 = CH_2OH$; **l** $R^1 = R^2$ = Me, R^3 = Et; **m** $R^1 = R^2 = R^3$ = Me; **n** $R^1 = R^2 = R^3$ = Et; **o** $R^1 = R^2$ = Et, R^3 = Me; **2 a** $R^1 = R^2 = R^3$ = H; **b** R^1 = Me, $R^2 = R^3$ = H; **c** R^1 = Et, $R^2 = R^3$ = H; **d** R^1 = *t*-Bu, $R^2 = R^3$ = H; **e** R^1 = *c*-C_6H_{11}, $R^2 = R^3$ = H; **f** R^1 = H, $R^2 = R^3$ = Me; **g** R^1 = H, $R^2 = R^3$ = Et; **h** R^1 = H, $R^2 = R^3$ = Pr; **i** $R^1 = R^2$ = Me, R^3 = H; **j** $R^1 = R^3$ = Me, R^2 = H; **k** $R^1 = R^3$ = Et, R^2 = H; **l** $R^1 = R^2$ = Me, R^3 = Et; **m** $R^1 = R^2 = R^3$ = Me; **n** $R^1 = R^2 = R^3$ = Et; **o** $R^1 = R^2$ = Et, R^3 = Me; **3a** R^1 = Me, R^3 = H; **b** $R^1 = R^3$ = Me; **c** $R^1 = R^3$ = Et

suspension complicating the method of carrying out the TLC monitoring and thus the optimization of the process. We therefore studied the possible hydroxymethylation of these compounds using hemiformal as a methanol solution prepared from paraformaldehyde in the presence of K_2CO_3.

Development of the method for the hydroxymethylation of compounds **2b-k** was carried out in the case of 2-methylglycoluril **2b** and a methanol solution of hemiformal taken in stoichiometric amounts at 60°C over 1-2 h in two different pH ranges (8-9 and 10-12). TLC analysis showed that the optimum time for the reaction was 1 h. After separation in the pure state (crystallization from methanol) the yield of the target glycoluril **1b** in the pH 10-12 experiment was 70-75% and in the range 8-9 it was 82-85%. Hence the hydroxymethylation processes were carried out subsequently at pH 8-9.

We carried out the targeted full hydroxymethylation of the glycolurils **2c-j** in the optimum conditions (pH 8-9, 1 h, 60°C) and the yields of the glycolurils were 65-95%. The hydroxymethylation of the 2-*t*-Bu- and 2-cyclohexylglycolurils **2d,e** gave the products of partial hydroxymethylation 2-alkyl-4,6-di(hydroxymethyl)glycolurils **1d,e*** independently of the molar ratio of **2d,e** to formaldehyde (1:3 or 1:2). The regiospecific substitution of only the *cis*-related hydrogen atoms on atoms $N_{(4)}$ and $N_{(6)}$ in compounds **2d,e** and the absence of hydroxymethyl groups on atom $N_{(8)}$ infers steric hindrance to hydroxymethylation at the $N_{(8)}$ atom due to the bulky *t*-Bu and *c*-C_6H_{11} substituents in the starting glycolurils **2d,e**.

The presence of products of incomplete substitution was observed in the ^{1}H NMR spectra of the unpurified products of hydroxymethylation of the glycolurils **2i-k**. Fractional crystallization from methanol gave the pure achiral compounds **1i-k** in 65-70% yield and compounds **3a-c** (20-25% yield) as the products of incomplete hydroxymethylation of the starting **2i-k**. The ratio of the products of full **1i-k** and partial

* The structure of the compounds prepared was confirmed by us by a chemical route through their use in the synthesis of tricyclic glycoluril derivatives 3-Alk-7-*t*-Bu-(*c*-C_6H_{11})-1,3,5,7,9-pentaazatricyclo[5.3.1.$0^{8.10}$]-dodecane-6,10-diones which will be reported later on.

hydroxymethylation **3a-c** was 2.4:1 or 3.25:1 which shows the regioselectivity of this reaction. In the reaction of **2i** with hemiformal the glycoluril **3a** could not be separated but the methyl ether **3a'** was obtained, evidently formed *via* etherification of the hydroxymethyl group by methanol in the prolonged crystallization process.

With the aim of studying a possible regioselectivity in the hydroxymethylation of one of the nitrogen atoms in 2,4- and 2,8-dimethylglycolurils **2i** and **2j,k** we have looked at their reaction with 1 mol of formaldehyde under these conditions. From the ^{1}H NMR analysis in the region for the NH group proton signals (6.5-7.5 ppm) and CH_2 groups (4.0-4.7 ppm) of the reaction mass evaporated to dryness it is evident that the signals for three products appear in each: the starting glycolurils **2i** or **2j,k**, the products of incomplete substitution **3a** and **3b,c**, and the fully substituted products **1i** and **1j,k**. The starting glycolurils **2i** and **2j,k** precipitate from the reaction mixtures. The di- (**1i** and **1j,k**) and monohydroxymethylglycolurils (**3a** and **3b,c**) were prepared in the pure state by fractional crystallization from methanol. The separated products **1i** (**j,k**), **2i** (**j,k**), and **3a** (**b,c**) show that a change in the ratio of glycoluril **2i** (**j,k**) to hemiformal does not lead to regiospecificity in their N-hydroxymethylation processes.

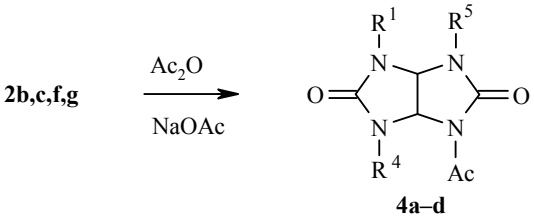
Hydroxymethylation of the readily water soluble 2,4,6-trialkylglycolurils **2l-o** was studied by us for two variants using a methanol solution of hemiformal according to the developed method (Method A) or using formaldehyde as a 37% aqueous solution (formalin) (Method B).

Method B was developed in the case of the reaction of 6-ethyl-2,4-dimethylglycoluril **2l** with formalin. The reaction was carried out in formalin at pH 8-9 and pH 10-12 and a temperature of 60°C over 1-3 h. TLC was used to monitor the process. It was found that the optimal reaction time was 1 h. At pH 10-12 the reaction mass darkened and the separation of product **1l** was hindered by the need to carry out the extraction with $CHCl_3$, the yield being 70%*. The hydroxymethylated derivatives **1m-o** were synthesized from the trialkylglycolurils **2m-o** in 79-97% yields by a similar method.

The hydroxymethylation of **2l-o** using hemiformal as a methanol solution (pH 8-9, 1 h, 60°C, Method 1) gives compounds **1l-o** in similar yields. For the separation of the products **1l-o** it was not necessary to use $CHCl_3$ extraction hence the glycolurils **1l-o** were separated as oily residues (after evaporation of methanol) giving solid products upon trituration with ether.

The N-acetylation of the racemic 2-methyl(ethyl)- and 2,6-dialkyl(dimethyl and diethyl)glycolurils **2b,c** ad **2f,g** respectively were optimized by us using a method based on their reaction with acetic anhydride (as reagent and solvent) in the presence of a ten-fold excess of NaOAc. The reaction was performed by refluxing for 0.5-1.5 h (Scheme 3). The dependence of the yields of **4a-d** on the duration of the acetylation was evaluated after separation of the final products **4a-d** in the pure state. The N-acetyl derivatives **4a-d** were obtained in 61-78% yields with a reaction time of 1.5 h. The yields of the compounds synthesized by us 2,4,6-triacetyl-2-methyl- (**4a**) (75-78%) or 2,6-diacetyl-4,8-dimethylglycolurils (**4c**) (64-66%) were comparable or greater than those reported in the literature [46] for preparation of these compounds (**4a** – 45%, **4c** – 65%) from 2-methyl- or 2,6-dimethylglycolurils using acetic anhydride in the presence of $HClO_4$.

Scheme 3



4a–d

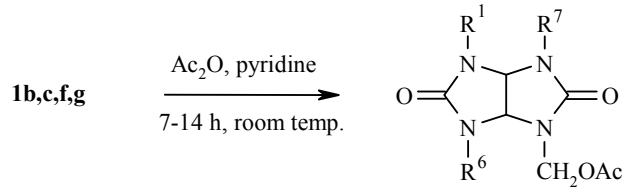
4 a R^1 =Me, $R^4 = R^5$ = Ac; **b** R^1 = Et, $R^4 = R^5$ = Ac; **c** R^1 = Ac, $R^4 = R^5$ = Me;
d R^1 = Ac, $R^4 = R^5$ = Et

* Here and subsequently averaged product yields are given.

However, the introduction of an acetyl group at the $N_{(8)}$ atom of 2,4,6-trialkylglycolurils **2l-o** was unsuccessful either with the use of acetic anhydride in the presence of $HClO_4$ or NaOAc or with acetyl chloride in the presence of triethylamine and this may be related to steric factors.

To investigate the O-acetylation we have chosen the most readily available chiral N-hydroxymethylated derivatives **1b,c,f,g**. O-Acetylation was carried out using acetic anhydride in pyridine at room temperature over 24 h. On the basis of the ^1H and ^{13}C NMR spectroscopic data it was found that all of the hydroxymethyl groups had undergone acetylation. The yields of the N-acetoxymethylglycolurils **5a-d** were 54-70% (Scheme 4).

Scheme 4



5a–d

5 a R^1 = Me, $R^6 = R^7 = CH_2OAc$; **b** R^1 = Et, $R^6 = R^7 = CH_2OAc$; **c** $R^1 = CH_2OAc$, $R^6 = R^7$ = Me; **d** $R^1 = CH_2OAc$, $R^6 = R^7$ = Et

With the aim of clarifying the ability of the synthesized glycolurils **1, 4, 5** to crystallize as conglomerates we have studied their crystallization processes from 50% aqueous methanol, methanol, chloroform and ethyl acetate. The hydroxymethylated glycolurils **1** are finely dispersed powders and the N-acetyl derivatives **4** and O-acetylglycolurils **5** crystallize as very fine, needle-like crystals thus it was not possible to evaluate the ability of the obtained compounds to form conglomerates at this stage. Crystals suitable for X-ray analysis were prepared only in the crystallization of the glycoluril **5c** from methanol. X-ray analysis showed that compound **5c** crystallizes in a centrosymmetric space group *C*2/*c*, i.e. it is a racemate.

The crystal **5c** is characterised overall as having *C*2 symmetry in this molecule, the second order axis passing through the center of the $C_{(1)}$–$C_{(1A)}$ bond. The basic bond lengths in the **5c** molecule are close to those expected for this class of compounds (Table 1). The conformation of the 5-membered ring (Fig. 1) is a flattened

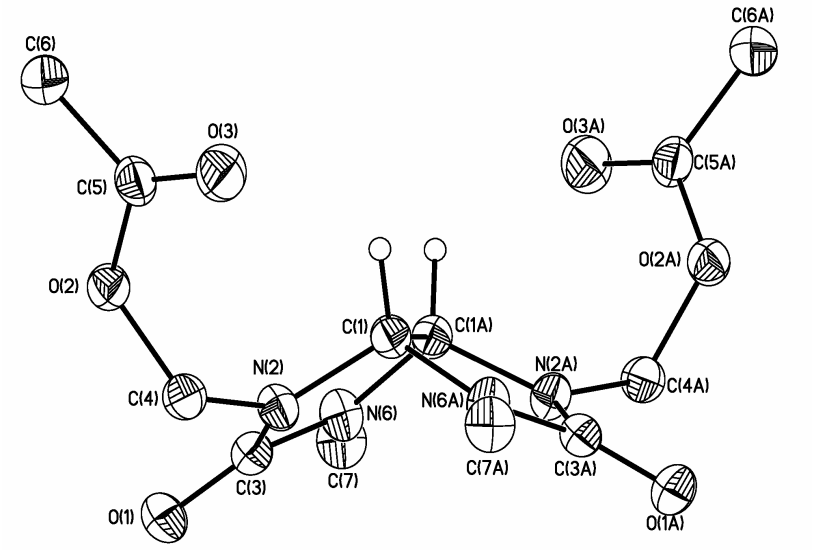


Fig. 1. Overall view of the molecule of compound **5c**
(atoms are shown with thermal vibration ellipsoids having 50% probability).

TABLE 1. Basic Bond Lengths (*l*) and Valence Angles (ω) in the Molecule of Compound **5c**

Bond	*l*, Å	Angle	ω, deg.
O(1)–C(3)	1.219(2)	C(3)–N(2)–C(4)	120.3(1)
N(2)–C(3)	1.386(2)	C(3)–N(2)–C(1)	111.7(1)
N(2)–C(4)	1.426(2)	C(4)–N(2)–C(1)	124.8(1)
N(2)–C(1)	1.453(2)	C(3)–N(6)–C(7)	123.4(1)
N(6)–C(3)	1.356(2)	C(3)–N(6)–C(1A)	113.7(1)
N(6)–C(7)	1.438(2)	C(7)–N(6)–C(1A)	122.7(1)
N(6)–C(1A)	1.446(2)	N(6A)–C(1)–N(2)	112.9(1)
C(1)–C(1A)	1.555(3)	N(6A)–C(1)–C(1A)	102.7(1)
		N(2)–C(1)–C(1A)	103.7(1)
		O(1)–C(3)–N(6)	126.4(1)
		O(1)–C(3)–N(2)	125.5(1)
		N(6)–C(3)–N(2)	108.0(1)

"envelope" with the atom $C_{(1A)}$ deviating from the plane of the $C_{(1)}$, $N_{(2)}$, $C_{(3)}$, $N_{(6)}$ atoms by 0.06 Å (which are coplanar with 0.003 Å). The acetyl groups in the molecule are placed to one side of the mean plane of the ring and are characterized by a *cis*-orientation relative to the bridging hydrogen atoms.

The atoms $N_{(2)}$ and $N_{(6)}$ in the molecule **5c** are somewhat different (the deviation of the $N_{(2)}$ and $N_{(6)}$ atoms from the plane formed by atoms linked with these atoms are 0.15 and 0.03 Å respectively). The difference in degree of pyramidalization of the nitrogen atoms in turn leads to a lengthening of the $N_{(2)}$–$C_{(3)}$ (1.386(2)) bond when compared with $N_{(6)}$–$C_{(3)}$ (1.356(2) Å) bond.

Analysis of the crystal packing has shown that, beside a series of weak C–H···O interactions of all the remaining intermolecular distances correspond to conventional van der Waal contacts.

The synthesized racemic compounds **1f-h, 4b, 5c** were subjected to chromatography on several chiral HPLC columns (OJ-H, OD, AD, ChirobioticTAG, β-CD) and on a C18 ligand exchange column modified by C_{10}-L-Hyp. However, only when using the OJ-H HPLC column, elution with a mixture of hexane and *i*-PrOH, and UV detection at 210 nm were the enantiomeric peaks for the compounds **1g** and **1h** base line separated after 6-9 min with good resolution. These conditions were fully suited to a rapid enantiomeric analysis of the given compounds.

Hence a study of the N-acylation, N-hydroxymethylation, and N-acetoxymethylation of mono-, di-, and trialkylglycolurils has shown that the use of a methanol solution of hemiformal in condensation reactions with N-glycolurils or acetic anhydride in the electrophilic substitution at the nitrogen or oxygen atoms of the hydroxymethyl groups of N-glycolurils give this process applicability to differently substituted at the nitrogen atom N-glycolurils.

The regioselectivity of the reaction of 2-*t*-Bu- and 2-*c*-C_6H_{11}-glycolurils with formaldehyde giving the 4,6-di(hydroxymethyl) derivative was found. It was shown that hydroxymethylation of 2,4- and 2,6-dialkylglycolurils occurs regioselectively with a stoichiometric ratio of glycoluril to hemiformal and leads to formation of monohydroxy- and dihydroxymethylglycolurils. The possibility of carrying out the enantiomeric analysis of racemates of these synthesized compounds using HPLC on chiral phases has been shown for the first time. Using X-ray analysis it was found that the previously unrecorded 2,6-diacetoxymethyl-4,8-dimethylglycoluril is a racemate.

TABLE 2. Characteristics of the Synthesized Compounds **1b-o, 3a', 3b,c, 4a-d, 5a-d**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
1b	$C_8H_{14}N_4O_5$	38.92 / 39.02	5.79 / 5.73	22.81 / 22.75	130-132	80-82
1c	$C_9H_{16}N_4O_5$	41.65 / 41.54	6.18 / 6.20	21.47 / 21.53	114-116	70-73
1d	$C_{10}H_{18}N_4O_4$	46.48 / 46.50	7.08 / 7.02	21.64 / 21.69	198-200	78-80
1e	$C_{12}H_{20}N_4O_4$	50.75 / 50.69	7.14 / 7.09	19.65 / 19.71	170-172	70-72
1f	$C_8H_{14}N_4O_4$	41.67 / 41.74	6.19 / 6.13	24.21 / 24.34	159-161	82-85
1g	$C_{10}H_{18}N_4O_4$	46.59 / 46.50	6.95 / 7.02	21.61 / 21.69	119-121	88-90
1h	$C_{12}H_{22}N_4O_4$	50.29 / 50.34	7.77 / 7.74	19.52 / 19.57	89-91	75-78
1i	$C_8H_{14}N_4O_4$	41.78 / 41.74	6.09 / 6.13	24.28 / 24.34	163-165	62-65
1j	$C_8H_{14}N_4O_4$	41.69 / 41.74	6.17 / 6.13	24.38 / 24.34	135-137	85-87
1k	$C_{10}H_{18}N_4O_4$	46.55 / 46.50	7.06 / 7.02	21.62 / 21.69	124-126	89-91
1l	$C_9H_{16}N_4O_3$	47.32 / 47.36	6.98 / 7.07	24.69 / 24.55	108-110	93-95
1m	$C_8H_{14}N_4O_3$	44.92 / 44.85	6.61 / 6.59	26.09 / 26.15	132-134	90-92
1n	$C_{11}H_{20}N_4O_3$	51.49 / 51.55	7.91 / 7.87	21.93 / 21.86	97-99	89-91
1o	$C_{10}H_{18}N_4O_3$	49.72 / 49.58	7.53 / 7.49	23.03 / 23.13	106-108	83-85
3a'	$C_8H_{14}N_4O_3$	44.82 / 44.85	6.61 / 6.59	26.19 / 26.15	181-183	20-22
3b	$C_7H_{12}N_4O_3$	42.02 / 42.00	6.01 / 6.04	27.17 / 27.99	151-153	23-25
3c	$C_9H_{16}N_4O_3$	47.33 / 47.36	6.99 / 7.07	24.44 / 24.55	143-145	21-22
4a	$C_{11}H_{14}N_4O_5$	46.92 / 46.81	4.93 / 5.00	19.95 / 19.85	172-174	75-78
4b	$C_{12}H_{16}N_4O_5$	48.81 / 48.65	5.29 / 5.44	19.06 / 18.91	165-167	63-65
4c	$C_{10}H_{14}N_4O_4$	47.19 / 47.24	5.58 / 5.55	22.07 / 22.04	159-161	64-66
4d	$C_{12}H_{18}N_4O_4$	51.11 / 51.06	6.38 / 6.43	19.84 / 19.85	144-146	61-62
5a	$C_{14}H_{20}N_4O_8$	45.58 / 45.61	5.44 / 5.41	15.03 / 15.05	169-171	68-70
5b	$C_{15}H_{22}N_4O_8$	46.66 / 46.63	5.79 / 5.74	14.47 / 14.50	133-135	57-58
5c	$C_{12}H_{18}N_4O_6$	45.98 / 45.86	5.85 / 5.77	17.81 / 17.83	162-164	65-67
5d	$C_{14}H_{22}N_4O_6$	49.04 / 49.12	6.52 / 6.48	16.41 / 16.37	120-122	54-56

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Bruker AM-300 instrument (300 MHz) using DMSO-d_6. Mass spectroscopic investigation was carried out using an MS-30 mass spectrometer.

TABLE 3. ^{1}H NMR Spectra of the Synthesized Glycolurils **1b-o, 3a', 3b,c, 4a-d, 5a-d**

Glycoluril	Chemical shifts, δ, ppm (*J*, Hz)
1	2
2,4,6-Tri(hydroxymethyl)-8-methylglycoluril (**1b**)	2.85 (3H, s, CH_3); 4.69 (6H, m, $3NCH_2$); 5.29 and 5.49 (each 1H, both d, *J* = 8.5, 2CH); 5.92 (3H, m, 3OH)
8-Ethyl-2,4,6-tri(hydroxymethyl)-glycoluril (**1c**)	1.08 (3H, t, *J* = 6.7, CH_3); 3.20 (2H, m, NCH_2); 4.60 (6H, m, $3NCH_2$); 5.44 (2H, m, CHCH); 5.95 (3H, br. s, 3OH)
2-*tert*-Butyl-4,6-di(hydroxymethyl)glycoluril (**1d**)	1.31 (9H, s, $3CH_3$); 4.65 (4H, m, $2CH_2$); 5.36 and 5.43 (each 1H, both d, *J* = 8.6, 2CH); 5.78 (2H, br. s, 2OH); 7.70 (1H, br. s, NH)
2-Cyclohexyl-4,6-di(hydroxy-methyl)glycoluril (**1e**)	1.17 (4H, m, $2CH_2$); 1.62 (8H, 6H, m, $3CH_2$); 3.43 (1H, m, CH); 4.55 (4H, m, $2CH_2$); 5.25 and 5.67 (each 1H, both d, *J* = 8.0, 2CH); 5.78 (2H, br. s, 2OH); 7.48 (1H, s, NH)
2,6-Di(hydroxymethyl)-4,8-dimethylglycoluril (**1f**).	2.83 (6H, s, $2NCH_3$); 4.37 (4H, m, $2NCH_2$); 5.24 (2H, s, CHCH); 5.94 (1H, t, *J* = 5.0, OH)
4,8-Diethyl-2,6-di(hydroxy-methyl)glycoluril (**1g**)	1.11 (6H, t, *J* = 6.62, $2CH_3$); 3.23 (2H, m, NCH_2); 3.38 (2H, m, NCH_2); 4.59 and 4.71 (each 1H, both d, *J* = 11.0, $2NCH_2$); 5.46 (2H, s, 2CH); 5.95 (2H, br. s, 2OH)
2,6-Di(hydroxymethyl)-4,8-dipropylglycoluril (**1h**)	0.85 (6H, t, *J* = 7.4, $2CH_3$); 1.48 (4H, m, $2CH_2$); 3.17 (2H, m, NCH_2); 3.35 (2H, m, NCH_2); 4.58 and 4.72 (each 1H, both d, *J* = 11.0, $2NCH_2$); 5.41 (2H, br. s, 2CH); 6.05 (2H, br. s, 2OH)
2,4-Di(hydroxymethyl)-4,8-dimethylglycoluril (**1i**)	2.82 (6H, s, $2NCH_3$); 4.66 (4H, m, $2NCH_2$); 5.46 (2H, br. s, 2CH); 6.05 (2H, br. s, 2OH)
2,8-Di(hydroxymethyl)-4,6-dimethylglycoluril (**1j**)	2.81 (6H, s, $2NCH_3$); 4.38 (4H, m, $2NCH_2$); 5.11 and 5.49 (each 1H, d, *J* = 7.9, 2CH); 5.82 (2H, m, 2OH)
4,6-Diethyl-2,8-di(hydroxy-methyl)glycoluril (**1k**)	1.7 (6H, m, $2CCH_3$); 3.07 (4H, m, $2CCH_2$); 4.56 (4H, m, $2NCH_2$); 5.21 and 5.48 (each 1H, both d, *J* = 7.0, 2CH); 5.87 (2H, m, OH)
4-Ethyl-2-hydroxymethyl-6,8-dimethylglycoluril (**1l**)	1.00 (3H, t, *J* = 7.3, CH_3); 2.81 (3H, s, NCH_3); 2.83 (3H, s, NCH_3); 3.16 (2H, m, NCH_2); 4.67 (2H, d, *J* = 6.7, NCH_2); 5.20 and 5.26 (each 1H, both d, *J* =8.5, 2CH); 5.90 (1H, t, *J* = 6.5, OH)
2-Hydroxymethyl-4,6,8-trimethylglycoluril (**1m**)	2.81 (9H, m, $3CH_3$); 4.66 (2H, m, NCH_2O); 5.09 and 5.26 (each 1H, both d, *J* = 8.1, CH); 5.73 (1H, br. s, OH)
4,6,8-Triethyl-2-hydroxymethyl-glycoluril (**1n**)	0.91 (3H, br. s, CH_3); 1.02 (3H, br. s, CH_3); 1.08 (3H, br. s, CH_3); 3.02 (6H, m, $3NCH_2$); 5.04 (2H, br. s, NCH_2O); 5.07 and 5.19 (each 1H, both d, *J* = 7.9, 2CH); 7.42 (1H, br. s, OH)
6,8-Diethyl-2-hydroxymethyl-4-methylglycoluril (**1o**)	1.11 (6H, m, $2CH_3$); 2.85 (3H, s, NCH_3); 2.00 (4H, m, $2NCH_2$); 4.68 (2H, br. s, NCH_2O); 5.16 and 5.28 (each 1H, both d, *J* = 8.5, 2CH); 5.91 (1H, br. s, OH)
6-Methoxymethyl-2,4-dimethyl-glycoluril (**3a'**)*	2.67 (3H, s, NCH_3); 2.78 (3H, s, NCH_3); 3.18 (3H, s, OCH_3); 4.53 and 4.67 (each 1H, both d, *J* = 11.0, NCH_2); 5.18 (2H, m, CHCH); 7.98 (1H, s, NH)
2-Hydroxymethyl-4,6-dimethylglycoluril (**3b**)	2.67 (3H, s, NCH_3); 2.78 (3H, s, NCH_3); 4.43 and 4.75 (each 1H, both d, *J* = 9.0, NCH_2); 5.12 and 5.22 (each 1H, both d, *J* = 7.5, 2CH); 5.55 (1H, br. s, OH); 7.49 (1H, s, NH)
4,6-Diethyl-2-hydroxymethyl-glycoluril (**3c**)	1.12 (6H, m, $2CH_3$); 3.32 (4H, m, $2NCH_2$); 4.40 and 4.65 (each 1H, both d, *J* = 9.1, NCH_2); 5.02 and 5.21 (each 1H, both d, *J* = 7. 0, CH); 5.59 (1H, br. s, OH); 7.51 (1H, s, NH)
2,4,6-Triacetyl-8-methylglycoluril (**4a**)	2.33 (3H, s, $C(O)CH_3$); 2.40 (3H, s, $C(O)CH_3$); 2.47 (3H, s, $C(O)CH_3$); 2.79 (3H, s, NCH_3); 5.81 and 6.39 (each 1H, both d, *J* = 4.5, CHCH)
2,4,6-Triacetyl-8-ethylglycoluril (**4b**)	1.07 (3H, t, *J* = 6.64, CH_3); 2.31 (3H, s, $C(O)CH_3$); 2.39 (3H, s, $C(O)CH_3$); 2.47 (3H, s, $C(O)CH_3$); 3.10 (1H, m, NCH_2); 3.40 (1H, m, NCH_2); 5.93 and 6.37 (each 1H, both d, *J* = 7.4, 2CH)
2,6-Diacetyl-4,8-dimethylglycoluril (**4c**)	2.41 (6H, s, $2COCH_3$); 2.80 (6H, s, $2NCH_3$); 5.75 (2H, s, CH–CH)

TABLE 3 (continued)

1	2
2,6-Diacetyl-4,8-diethylglycoluril (**4d**)	1.07 (6H, t, J = 6.6, $2CH_3$); 2.40 (6H, s, $2COCH_3$); 3.22 (2H, m, NCH_2); 3.40 (2H, m, NCH_2); 5.56 (2H, s, 2CH)
2,4,6-Triacetoxymethyl-8-methylglycoluril (**5a**)	1.98 (3H, s, $COCH_3$); 2.03 (6H, s, $2COCH_3$); 2.75 (3H, s, NCH_3); 4.56–5.12 (6H, m, $3NCH_2$); 5.28 and 5.36 (2H, both d, J = 7.5, CHCH)
2,4,6-Triacetoxymethyl-8-ethylglycoluril (**5b**)	1.10 (3H, t, J = 7.3, CCH_3); 2.04 (6H, s, $COCH_3$); 2.08 (3H, s, $COCH_3$); 3.33 (2H, m, CH_2); 4.81 (6H, m, $3NCH_2$); 5.20 and 5.45 (each 1H, both d, J = 11.8, 2CH)
2,6-Diacetoxymethyl-4,8-dimethylglycoluril (**5c**)	2.03 (6H, s, $2COCH_3$); 2.85 (6H, s, $2NCH_3$); 5.28 (2H, d, J = 11.6, NCH_2); 5.36 (2H, s, 2CH); 5.47 (2H, d, J = 11.6, NCH_2)
2,6-Diacetoxymethyl-4,8-diethylglycoluril (**5d**)	1.10 (3H, t, J = 7.3, C-CH_3); 2.04 (6H, s, $COCH_3$); 3.22 and 3.44 (each 2H, both m, $2CH_2$); 5.20 and 5.45 (each 2H, both d, J = 11.8, $2CH_2$); 5.47 (2H, s, 2CH)

* Mass spectrum, *m/z* (*I*, %): 214 (5), 183 (29), 182 (100), 154 (44), 140 (33), 139 (36), 113 (39), 112 (96), 111 (28), 98 (26), 97 (36), 84 (28), 82 (39), 69 (25), 45 (48), 43 (56), 42 (64).

X-ray Diffraction Experiment for Compound 5c ($C_{14}H_{18}N_4O_8$) was carried out at temperature of 120 K on a Smart CCD 1000K three circle automatic diffractometer (MoKα irradiation, graphite monochromator, ω-scanning to $2\theta_{max} \leq 56°$). The crystals are monoclinic at 120 K: a = 18.238(3), b = 9.397(1), c = 8.387(1) Å; β = 96.810(5)°; V = 1427.3(3) Å^3; d_{calc} = 1.723 g/cm^3; M = 242.20; F(000) =776; μ = 1.43 cm^{-1}; Z = 4 (Z' = 0.5); space group $C2/c$. Of the overall number of 6482 reflections, 1742 independent reflections (R_{int} = 0.0567) were used in subsequent calculations and refinement. The structure was solved by a direct method and refined using a least squares analysis in an anisotropic, full matrix approximation for F^2_{hkl}. Hydrogen atoms were localized from difference electron density Fourier synthesis and refined using the "riding" model. The final difference factors were 0.0485 for 1460 reflections with $I > 2\sigma(I)$, wR_2 = 0.1217 and GOF = 1.081 for all reflections. All calculations were performed using the SHELXTL PLUS program package [53].

N-Hydroxymethylation of Glycolurils 2a-o (General Method). A. K_2CO_3 on the tip of a spatula and methanol (5 ml) were added to a solution containing the calculated amount of paraformaldehyde (0.005 mol for each NH group) heating until complete solution of the paraformaldehyde. The stoichiometric amount of 2-alkyl- (**2a-e**), 2,4- (**2i**), 2,6- (**2f-h**), 2,8-dialkyl- (**2j,k**) or 2,4,6-trialkylglycolurils **2l-o** and water (1 ml) (pH 8-9) was added and the product was refluxed for 1 h, cooled, evaporated in vacuo, and the residue was triturated with ether or acetone, filtered, and crystallized from methanol. When the mixture of precipitates formed from the N-hydroxymethylation of the glycolurils **2i,j,k** was crystallized from methanol **3a-c** initially precipitated and then **1i,j,k**. Recrystallization of **3a** from methanol gave **3a'** (Tables 2 and 3).

The course of the reaction of **2b** was monitored every 15 min using TLC on Silufol plates in the system $CHCl_3$–MeOH (9:1); R_f 0.42 for the starting glycoluril **2b** and 0.85 for compound **1b**. At the end of 1 h at both pH 8-9 and also at pH 10-12 the reaction mixture contained virtually no starting glycoluril **2b** while at pH 10-12 traces of contaminant products appeared. At the end of 2 h the picture had not changed but the reaction mixture showed contaminants with R_f 0.36-0.25 in the experiment at pH 8-9 and at 0.32-0.15 at pH 10-12 and this can be explained by partial oligomerization of the products **1b**.

B. Potassium carbonate was added in small portions to an aqueous solution (37%, d = 1.083) of formalin (0.005 mol) to pH 8-9 followed by the corresponding compound **2l-o** (0.005 mol). The reaction mixture was heated to 60°C for 1 h. Solvent was distilled off on a rotary evaporator to half volume and the product was

extracted with $CHCl_3$ (5 × 5 ml). Solvent was distilled off and the product was precipitated from the oily residue by ether. The precipitated **1l-o** was filtered off and recrystallized from methanol.

In the case of the reaction of glycoluril **2l** with formalin the course of the reaction was monitored by TLC on Silufol plates using the system $CHCl_3$–MeOH (10:1); R_f 0.58 for the starting glycoluril **2l** and 0.75 for compound **1l**. At the end of 1 h the reaction mixture contained virtually no remaining glycoluril and after 2 h the picture was unchanged. At the end of 3 h hydrolysis of the hydroxymethylation product **1l** to the starting glycoluril **2l** had begun.

N-Acetylation of 2-Alkyl- (2b,c) and 2,6-Dialkylglycolurils (2f,g) (General Method). The 2-alkyl, 2,4-, 2,6-, or 2,8-dialkylglycoluril (0.005 mol), anhydrous sodium acetate (a 3-fold excess for each amino group), and acetic anhydride (10 ml) were placed in a round bottomed flask. The suspension was stirred at 100-110°C for 1.5 h, cooled, the solvent distilled off, and the residue was extracted with chloroform (2 × 15 ml). The chloroform extracts were evaporated to give the N-acetylglycolurils **4a-d** which were recrystallized from methanol (Tables 2 and 3).

O-Acetylation of 2-Alkyl-4,6,8-tri(hydroxymethyl)- (1b,c) and 2,6-Dialkyl-4,8-di(hydroxymethyl)glycolurils (1f,g) (General Method). Acetic anhydride (5 ml) and the hydroxy derivative (0.005 mol) were added to dry pyridine (5 ml) and the product was stirred to complete solution at 20°C and held at this temperature for 1 day. The solvent was distilled off and the residue was triturated with ether of give the precipitated **5a** (**5b-d**) which was filtered off and recrystallized from methanol (Tables 2 and 3).

This work was carried out with the support of the Chemistry Division program OKh-10 of the Russian Academy of Sciences.

REFERENCES

1. M. D. Mashkovskii, *Drugs* [in Russian], Vol. 1, Novaya Volna, Moscow (2000), p. 86.
2. S. S. Novikov, *Izv. Akad. Nauk SSSR. Ser. Khim.*, 2261 (1979).
3. O. V. Lebedev, L. I. Khmel'nitskii, L. V. Epishina, L. I. Suvorova, I. V. Zaikonnikova, I. E. Zimakova, S. V. Kirshin, A. M. Karpov, V. S. Chudnovskii, M. V. Povstyanoi, and V. A. Eres'ko, in *Targeted Search for Novel Neurotropic Preparations* [in Russian], Zinatne, Riga (1983), p. 81.
4. Yu. V. Vicharev, L. V. Anikina, I. E. Chikunov, Yu. V. Shklyaev, and A. N. Kravchenko, in *Abstracts Book of the 7th International Seminar "Scientific Advances in Chemistry: Heterocycles, Catalysis and Polymers as Driving Forces"* [in Russian], Yekaterinburg (2004), p. 129.
5. A. N. Kravchenko, K. Yu. Chegaev, I. E. Chikunov, P. A. Belyakov, E. Yu. Maksareva, K. A. Lyssenko, O. V. Lebedev, and N. N. Makhova, *Mendeleev Commun.*, 269 (2003).
6. I. E. Chikunov, A. N. Kravchenko, P. A. Belyakov, K. A. Lyssenko, V. V. Baranov, O. V. Lebedev, and N. N. Makhova, *Mendeleev Commun.*, 253 (2004).
7. R. G. Kostyanovsky, K. A. Lyssenko, G. K. Kadorkina, O. V. Lebedev, A. N. Kravchenko, I. I. Chervin, and V. R. Kostyanovsky, *Mendeleev Commun.*, 231 (1998).
8. R. G. Kostyanovsky, K. A. Lyssenko, A. N. Kravchenko, O. V. Lebedev, G. K. Kadorkina, and V. R. Kostyanovsky, *Mendeleev Commun.*, 134 (2001).
9. K. A. Lyssenko, D. G. Golovanov, A. N. Kravchenko, I. E. Chikunov, O. V. Lebedev, and N. N. Makhova, *Mendeleev Commun.*, 105 (2004).
10. A. N. Kravchenko, A. S. Sigachev, E. Yu. Maksareva, G. A. Gazieva, N. S. Trunova, B. V. Lozhkin, T. S. Pivina, M. M. Il'in, K. A. Lyssenko, Yu. V. Nelyubina, V. A. Davankov, O. V. Lebedev, N. N. Makhova, and V. A. Tartakovsky, *Izv. Akad. Nauk, Ser. Khim.*, 680 (2005).

11. N. N. Makhova, A. N. Kravchenko, I. E. Chikunov, A. V. Shevtsov, V. Yu. Petukhova, A. S. Sigachev, O. V. Lebedev, and G. A. Gazieva, in *Plenary Lectures and Proceedings of the 7th International Seminar "Scientific Advances in Chemistry: Heterocycles, Catalysis and Polymers as Driving Forces"* [in Russian], Yekaterinburg (2004), p. 127.
12. A. S. Sigachev, B. V. Lozhkin, and A. N. Kravchenko in: *Abstracts of VII Youth Science-School Conference of Organic Chemistry* [in Russian], Yekaterinburg (2004), p. 166.
13. M. M. Il'in, V. A. Davankov, O. V. Lebedev, A. N. Kravchenko, A. S. Sigachev, and E. Yu. Maksareva, in *Russian Symposium "Chromatography and Chromatographic Equipment"* [in Russian], Moscow (2004), p. 243.
14. P. J. Boileau, E. Wimmer, M. Pierrot, A. Baldy, and R. Gallo, *Acta Crystallogr.*, **C41**, 1680 (1978).
15. H. Petersen, *Synthesis*, 273 (1973).
16. A. A. Bakibaeva (editor), *Progress in the Chemistry in the Design of Novel Biologically Active Compounds* [in Russian], Tomsk (1998), p. 72.
17. F. B. Slesak, P. Bluestone, and H. H. Bluestone, US Pat. 3187005; *Chem. Abstr.*, **63**, 11570 (1965).
18. F. B. Slezak, A. Hirach, and J. Rosen, *J. Org. Chem.*, **25**, 660 (1960).
19. H. B. Adkins, US Pat. 2654763; *Chem. Abstr.*, **48**, 10778 (1954).
20. D. F. Kutepov and D. N. Khokhlov, *Zh. Obshch. Khim.*, **31**, 793 (1961).
21. Ch. Hasee and D. Kuchling, *Liebigs Ann. Chem.*, 95 (1975).
22. G. Laurene and O. Petersen, *US Pat. 2779764; Chem. Abstr.*, **58**, 7947 (1963).
23. J. W. Williams, US Pat. 2649389; *Chem. Abstr.*, **48**, 8267 (1954).
24. L. Gandon and P. H. Williame, Fr. Patent 1345699; *Chem. Abstr.*, **60**, 14513 (1964).
25. A. J. Stokes, US Pat. 2777856; *Chem. Abstr.*, **52**, 9705 (1958).
26. I. Rosen and F. Slezak, US Pat. 3019075; *Chem. Abstr.*, **57**, 3461 (1962).
27. K. Yagimoto, Y. Zhimizu, and M. Mitomi, Jpn. Patent 7495992; *Chem. Abstr.*, **82**, 156298 (1975).
28. F. B. Slezak, I. Rosen, and C. A. Neros, Fr. Patent 1360998; *Chem. Abstr.*, **61**, 13333 (1964).
29. P. Palitzsch, East Ger. Patent 123467; *Chem. Abstr.*, **87**, 135329 (1977).
30. H. Ulrid, East Ger. Patent 99788; *Chem. Abstr.*, **80**, 26782 (1974).
31. T. Inoi, K. Shoji, and T. Takahashi, Jpn. Patent 7040291; *Chem. Abstr.*, **74**, 112053 (1971).
32. K. Nonaka and K. Shoji, Jpn. Patent 6928871; *Chem. Abstr.*, **72**, 101818 (1970).
33. A. Franchimont and E. A. Rlobbie, *Rec. Trav. Chim.*, **7**, 236 (1887).
34. J. Boileau, J. M. Emeury, and J. P. Kehren, Ger. Patent 2462330; *Chem. Abstr.*, **86**, 75499 (1976).
35. J. Boileau, J. M. Emeury, and J. P. Kehren, Ger. Patent 2435651; *Chem. Abstr.*, **83**, 30483 (1975).
36. H. Petersen and H. Bille, Ger. Patent 2027203; *Chem. Abstr.*, **76**, 114770 (1979).
37. J. Boileau, J. M. Emeury, and J. P. Kehren, US Pat. 4487938; *Chem. Abstr.*, **73**, 46604 (1984).
38. W. R. Hausch, US Pat. 4435456; *Chem. Abstr.*, **100**, 193372 (1984).
39. R. Toepfl, H. Abel, and A. Maeder, Ger. Patent 1954358; *Chem. Abstr.*, **73**, 46604 (1970).
40. H. Rongzu, L. Yanjun, F. Yingao, and W. Jinsheng, *J. Therm. Analysis,* **46**, 1283 (1996).
41. H. Rongzu, D. Yang. H. Zhao, Sh. Gao, and Q. Shi, *Thermochimica Acta,*, **389**, 65 (2002).
42. Y. Fang and G. Wu, *Hanneng Cailiao,* **5**, 9 (1997); *Chem. Abstr.*, **126**, 295252 (1997).
43. G. A. Gazieva, A. N. Kravchenko, K. Y. Chegaev, Yu. A. Strelenko, and O. V. Lebedev, *Mendeleev Commun.*, 28 (2000).
44. H. Gattner and K. Wagner, Eur. Patent 60471; *Chem. Abstr.*, **98**, 1663 (1983).
45. H. G. Goodman, US Pat. 2697714; *Chem. Abstr.*, **49**, 73683 (1955).
46. D. Kuhling, *Liebigs Ann. Chem.*, 263 (1973).
47. S. Sun, L. Edwards, and P. Harrison, *J. Chem. Soc., Perkin Trans 1*, 437 (1998).

48. C. F. Matta, C. C. Cow, S. Sun, J. F. Dritten, and P. H. M. Yarrison, *J. Mol. Struct.*, **523**, 241 (2000).
49. D. Kuehling, Ger. Patent 19966502; *Chem. Abstr.*, **78**, 97655 (1973).
50. J. Boileau, E. Wimmer, M. Carail, and R. Gallo, *Bull. Soc. Chim. Fr.*, 465 (1986).
51. Henkel and Cie GmbH, Ger. Patent 1909876; *Chem. Abstr.*, **70**, 33002 (1969).
52. A. N. Kravchenko, O. V. Lebedev, and E. Yu. Maksareva, *Mendeleev Commun.*, 27 (2000).
53. G. M. Sheldrick, *SHELXTL-97. Version 5.10*, Bruker AXS Inc., Madison, WI-53719, USA.