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α-UREIDOALKYLATION OF 1,3-BIS(HYDROXYMETHYL)-IMIDAZOLIDIN-2-ONE

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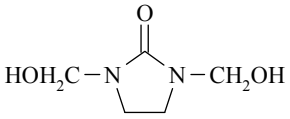
The α-ureidoalkylation of imidazolidine-2,4-dione, urea, carboxylic acid amides, and sulfonamides has been studied using 1,3-bis(hydroxymethyl)-imidazolidin-2-one as ureidoalkylating agent. Methods have been developed for the synthesis of 1,3-bis(2,4-dioxoimidazolidin-1-ylmethyl)-, 1,3-bis(acetylaminomethyl)-, 1,3-bis(benzoylaminomethyl)-, 1,3-bis(phenylsulfonylaminomethyl)-, and 1,3-bis(p-toluenesulfonylaminomethyl)imidazolidin-2-ones.

Keywords: 1,3-bis(R-aminomethyl)imidazolidin-2-ones, 1,3-bis(hydroxymethyl)imidazolidin-2-one, 1,3-bis(2,4-dioxoimidazolidin-1-yl)methylimidazolidin-2-one, α-ureidoalkylation.

Derivatives of imidazolidin-2-one display antispasmodic, analgetic, herbicidal, and other forms of activity [1-4]. In the course of several years we have broadly investigated the α-ureidoalkylation of alkyl-, hydroxyalkyl, and carboxyalkylureas, sulfamides, thiosemicarbazides, and aminoguanidine using 4,5-dihydroxyimidazolidin-2-ones as ureidoalkylating reagents and have developed general methods for the directed synthesis of 1,3,4,6-tetrahydroimidazo[4.5-*d*]imidazole-2,5-diones [5-7] and their heteroanalogs [8, 9] substituted at the nitrogen atom.

The aim of the present work is the investigation of the α-ureidoalkylation of 2,4-dioxoimidazolidine, ureas, sulfamides, and acid amides using 1,3-bis(hydroxymethyl)imidazolidin-2-one (**1**). It is known that compound **1** is used for cross-linking cellulose [10] and also covalent fixing on cellulose fibers of dyestuffs containing nucleophilic groups in the molecule, including –NHR and –NHCOR. However a check on the reaction process was effected only by UV and IR spectroscopic methods of the obtained powders [11].



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Furthermore, by the reaction of imidazolidin-2-one (ethylene urea) with formaldehyde in acid medium in a variant of the one-stage synthesis (without isolating the N-hydroxymethyl derivatives of ethylene urea), analogs of cucurbiturils [12] and linear oligomers [13, 14], have been obtained and used for cross-linking or stabilizing polymers. There are isolated examples in the literature of aminomethylation of ethylene urea with N-hydroxymethyl or N-methoxymethyl derivatives of amines [14, 15].

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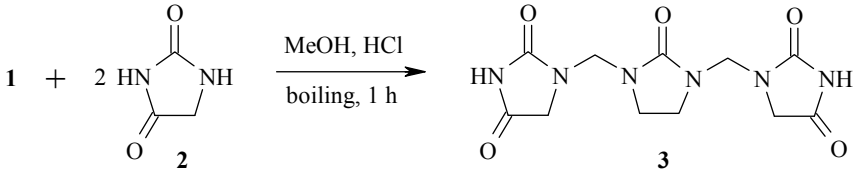
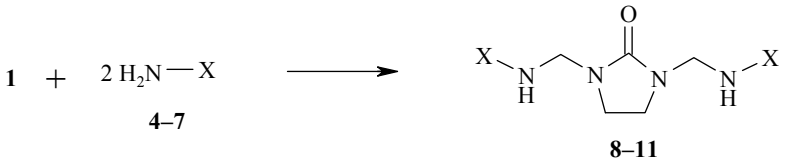
In the first stage we studied the α-ureidoalkylation of 2,4-dioxoimidazolidine (hydantoin). Choice of hydantoin **2** as a model compound was due to the fact that the NH group of hydantoin, located between two carbonyl groups, is distinguished by a low reactivity, which enables avoidance of the formation of oligomers and polymers reported in the literature [12-14]. Reactions were carried out by a procedure analogous to the α-ureidoalkylation of ethylene urea with 4,5-dihydroxyimidazolidin-2-ones [16], under conditions of acid catalysis during 1 h on boiling equimolar quantities of the reactants in methanol, water, and a water–isopropyl alcohol mixture. Solids were isolated in all cases, the ^{1}H and ^{13}C NMR spectra of which corresponded to the expected 1,3-bis(2,4-dioxoimidazolidin-1-ylmethyl)imidazolidin-2-one (**3**). The signal of the NH groups protons was located at 10.86 ppm and corresponds to the signal of a proton at a nitrogen atom situated between two carbonyl groups. The intensities of the signals of the protons of the methylene and ethylene groups, being singlets, and also the NH groups, correspond completely to the structure of compound **3**.



The yields of product **3** in methanol (70), water (64), and in the water-isopropyl alcohol mixture (59%) were comparable. Analogous results were obtained on carrying the reaction of bis(hydroxymethyl)ethylene urea **1** with acetamide **4** in these solvents.

In the reaction of compound **1** with acid amides **4-7** in methanol in the presence of HCl the previously undescribed 1,3-bis(acetylaminomethyl)imidazolidin-2-one (**8**), 1,3-bis(benzoylaminomethyl)imidazolidin-2-one (**9**), 1,3-bis(phenylsulfonylaminomethyl)imidazolidin-2-one (**10**), and 1,3-bis(*p*-toluenesulfonylamino-methyl)imidazolidin-2-one (**11**) were obtained.



4, **8** X = C(O)Me; **5**, **9** X = C(O)Ph; **6**, **10** X = SO_2Ph; **7**, **11** X = Ts

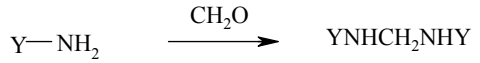
TABLE 1. Characteristics of Compounds **3, 8-11, 18**

Compound	Empirical formula	Found, % / Calculated, %				mp, °C (solvent)	Yield, %
		C	H	N	S		
3	$C_{11}H_{14}N_6O_5$	42.60 42.58	4.56 4.55	27.07 27.09		302-304 (DMSO-H_2O, 1:1)	68-71
8	$C_9H_{16}N_4O_3$	47.35 47.36	7.09 7.07	24.56 24.55		164-166 (MeOH)	62-64
9	$C_{19}H_{20}N_4O_3$	64.77 64.76	5.70 5.72	15.91 15.90		207-209 (MeOH)	48-50
10	$C_{17}H_{20}N_4O_5S_2$	48.12 48.10	4.74 4.75	13.21 13.20	15.08 15.11	188-191 (Me_2CO-$CHCl_3$, 1:3)	39-42
11	$C_{19}H_{24}N_4O_5S_2$	50.41 50.43	5.34 5.35	12.39 12.38	14.15 14.17	198-200 (Me_2CO-H_2O, 1:1)	62-65
18	$C_7H_{12}N_4O_6$	33.85 33.88	4.90 4.87	22.56 22.57		210-212 (H_2O)	60-63

TABLE 2. Spectral Characteristics of Compounds **3**, **8-11**, **17**, **18**

Compound	^{1}H NMR spectrum, δ, ppm (*J*, Hz)	^{13}C NMR spectrum, δ, ppm (*J*, Hz)
3	3.30 (4H, s, $2CH_2$); 3.86 (4H, s, $2CH_2$); 4.60 (4H, s, $2CH_2$); 10.86 (2H, br. s, 2NH)	40.8 (CH_2), 50.0 (CH_2), 50.5 (CH_2), 157.5 (C=O), 159.6 (C=O), 171.9 (C=O)
8	1.79 (6H, s, $2CH_3$); 3.21 (4H, s, $2CH_2$); 4.41 (4H, d, *J* = 6.1, $2CH_2$); 8.38 (2H, t, *J* = 6.1, 2NH)	
9	3.33 (4H, s, $2CH_2$); 4.70 (4H, d, *J* = 6.1, $2CH_2$); 7.46 (6H, m, C_6H_5); 7.86 (4H, d, *J* = 6.7, C_6H_5); 9.01 (2H, t, *J* = 6.1, 2NH)	41.6 (CH_2), 48.5 (CH_2), 127.4 (C_6H_5), 128.3 (C_6H_5), 131.5 (C_6H_5), 133.7 (C_6H_5), 158.9 (C=O), 167.1 (C=O)
10	2.79 (4H, s, $2CH_2$); 4.23 (4H, d, *J* = 6.1, $2CH_2$); 7.57 (6H, m, C_6H_5); 7.74 (4H, d, *J* = 7.4, C_6H_5); 8.37 (2H, t, *J* = 6.1, 2NH)	
11	2.38 (6H, s, $2CH_3$); 2.88 (4H, s, $2CH_2$); 4.23 (4H, s, $2CH_2$); 7.37 (4H, d, *J* = 7.1, Ts); 7.65 (4H, d, *J* = 7.1, Ts); 8.22 (2H, br. s, 2NH)	20.9 (CH_3), 39.8 (CH_2), 51.8 (CH_2), 126.2 (Ts), 129.4 (Ts), 138.6 (Ts), 142.6 (Ts), 157.5 (C=O)
17	4.43 (2H, t, *J* = 6.1, CH_2); 6.82-6.92 (4H, m, 2H(C_6H_5)+2NH); 7.21 (4H, t, *J* = 7.4, C_6H_5); 7.37 (4H, d, *J* = 7.4, C_6H_5); 8.61 (2H, s, 2NH)	
18	3.69 (4H, d, *J* = 5.5, $2CH_2$); 4.24 (2H, t, *J* = 5.8, CH_2); 6.28 (2H, br. s, 2NH); 6.72 (2H, t, *J* = 5.8, 2NH)	

On introducing urethane **12**, ureas **13, 14**, and butylsulfamide **15** into analogous reactions, products were formed the ^{1}H NMR spectra of which did not contain signals for the protons of the ethylene urea fragment, but in them there were signals for the ethyl group of urethane **12**, the phenyl fragment of urea **13**, the ethoxycarbonyl fragment of the N-carbamoylglycine **14**, or the butyl group of sulfamide **15**, for the NH groups of all the compounds listed, and triplet signals for protons at 4.12-4.41 ppm. From their chemical shifts they may be assigned to CH_2 groups protons linking the fragments of the initial compounds **12-15**. The intensities of all the groups of protons correspond to the structure of methylene bisderivatives **16-19**. This fact indicates that the urethane, ureas, and butylsulfamide were condensed not with compound **1**, but with formaldehyde. This may be explained by the reversible hydroxymethylation reaction, due to which a certain amount of formaldehyde is always present in solutions of compound **1**.



12–15 **16–19**

12, **16** Y = COOEt, **13**, **17** Y = CONHPh, **14**, **18** Y = $CONHCH_2COOH$, **15**, **19** Y = SO_2NHBu

Methylenebiscarbamates, ureas, and sulfamides, including compounds **16, 17**, and **19** have been obtained as by-products, initial, or intermediate products in the synthesis of various linear and heterocyclic compounds [17-21].

Study of the α-ureidoalkylation of hydantoin, ureas, and acid amides with 1,3-bis(hydroxymethyl)imidazolidin-2-one **1** therefore led to the previously unknown 1,3-disubstituted imidazolidin-2-ones, which has confirmed the possibility of using 1,3-bis(hydroxymethyl)imidazolidin-2-one as a ureidoalkylating agent.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer (at 300 and 75 MHz respectively) in DMSO-d_6, internal standard was TMS. Melting points were determined on a Gallenkamp instrument (Sanyo).

α-Ureidoalkylation with 1,3-Bis(hydroxymethyl)imidazolidin-2-one (1) (General Method). Compound **1** (0.73 g, 5 mmol) and the appropriate compound **2**, **4-7**, **12-15** (10 mmol) were dissolved in methanol (5 ml), conc. HCl (2 drops) was added and the mixture was boiled for 1 h. After cooling the reaction mixture, the precipitated solid compound **3**, **8-11**, **16-19** was filtered off, and recrystallized. Compound **10** (R_f = 0.23, for benzenesulfamide R_f = 0.48) was purified by column chromatography on silica gel (40/100) using acetone–chloroform, 1:3. The characteristics of the obtained compounds are given in Tables 1 and 2.

Bis(ethoxycarbonylamino)methane 16. Yield 15-17%; mp 130-132°C (MeOH) (lit. mp 130°C from *n*-C_6H_{14} [17]).

1,1′-Methylenebis(3-phenylurea) 17. Yield 48-53%; mp 222-223°C (MeOH) (lit. mp 210-211°C [18], mp 221-223°C [19]).

1,1′-Methylenebis(3-butylsulfamide) 19. Yield 7-9%; mp 136-138°C (MeOH) (lit. mp 124°C from Et_2O [20]).

The data of ^{1}H NMR spectra of compounds **16** and **19** correspond to those given in [17, 20].

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