The reaction of salts of *N*-(β-hydroxyalkyl)-*N'*-hydroxydiazene *N*-oxides with dihalomethanes

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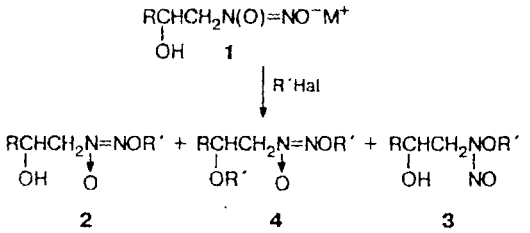
Methylene-bis[*N'*-oxydiazene-*N*-(β-hydroxyalkyl) *N*-oxides] were synthesized by the reaction of salts of *N*-(β-hydroxyalkyl)-*N'*-hydroxydiazene *N*-oxides with dihalomethanes. The effect of the nature of the starting reagents and the reaction conditions on the yields of the target compounds was studied.

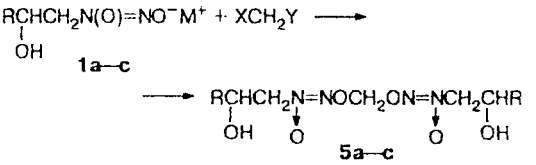
Key words: methylene-bis[*N'*-oxydiazene-*N*-(β-hydroxyalkyl) *N*-oxides], salts of *N*-(β-hydroxyalkyl)-*N'*-hydroxydiazene *N*-oxides, dihalomethanes, methylenation.

We have shown previously[1,2] that reactions of salts of *N*-(β-hydroxyalkyl)-*N'*-hydroxydiazene *N*-oxides (**1**) with unsubstituted and β-substituted alkyl halides mostly result in *N*-(β-hydroxyalkyl)-*N'*-alkoxydiazene *N*-oxides (**2**) and/or *O*-substituted *N*-(β-hydroxyalkyl)-*N*-nitrosohydroxylamines (**3**). If halogenated derivatives incorporating an atom with an unshared electron pair (O, N) in the α-position are used as alkylating agents, products of their alkylation on the hydroxy group are formed along with compounds **2**.[2]



The dependence of the yield of reaction products on the nature of the initial reagents and reaction conditions is complex and cannot be interpreted unequivocally. Nevertheless, in many cases it is possible to direct the reaction towards the preferred formation of alkoxydiazene *N*-oxides (**2**). Taking this into consideration, we studied the possibility to obtain the previously unknown methylene-bis[*N'*-diazene-*N*-(β-hydroxyalkyl) *N*-oxides] (**5**), *i.e.*, azoxyformals, by the reaction of salts **1** with dihalomethanes, and determined the major features of this reaction. CH_2Cl_2, CH_2Br_2, CH_2I_2, $ClCH_2Br$, $ClCH_2I$, and $BrCH_2F$ were studied as the dihalomethanes, and diverse salts of *N*-(2-hydroxypropyl)- (**1a**), *N*-(2-hydroxy-3-methylbutyl)- (**1b**), and *N*-(2-hydroxy-3,3-dimethylbutyl)-*N'*-hydroxydiazene *N*-oxide (**1c**) were used as substrates to be methylenated.

It was found that the reactions under study give the desired methylene-bis(diazene *N*-oxides) (**5a—c**) as the only stable products.



R = Me (**a**), Pr^i (**b**), Bu^t (**c**)
X, Y = F, Cl, Br, I

The conclusion about the structure of compounds **5a—c** was made on the basis of elemental analysis data, spectral characteristics (Table 1) and the negative qualitative reaction on the N—NO group (with a mixture diphenylamine—concentrated H_2SO_4).

The resulting azoxyformals **5a—c** are rather high-melting, quite stable compounds. Their yields depend on a combination of factors: the nature of the cation in salts **1a—c**, the character of the methylenating reagent, the solvent, the structure of the alkyl substituent in **1a—c**, and the reaction temperature and duration (Table 2).

The highest yields of azoxyformals were observed in the methylenation of tetramethylammonium salts **1** in acetonitrile. In the optimum variant the yields were ~30—60%. On going from tetramethylammonium salts to ammonium salts, the yields of azoxyformals decreased several times, while replacement of even one methyl group in the tetramethylammonium cation with $C_{16}H_{33}$ prevented the formation of the desired compounds completely. Acetonitrile was the best of the solvents studied, while aprotic dipolar solvents had lower efficiency, and hydroxyl-containing solvents were unsuitable. Moreover, even an insignificant content of

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Table 1. Physicochemical properties and element analysis data of azoxyformals $[RCH(OH)CH_2N(O)=NO]_2CH_2$ (**5a—c**)

5	*R*	M.p./°C (solvent)	R_f	IR, ν/cm^{-1}	NMR, δ (acetone-d_6) ^{1}H (*J*/Hz)	^{14}N ($\Delta\nu_{1/2}$/Hz)	^{13}C [a]	Found / Calculated (%) C	H	N	Molecular formula
a	Me	91—93 (EtOAc)	0.10[b] 0.34[c]	3420 (OH); 1515, 1320 (N=N—O, O)	1.2 (d, 6 H, CH_3, J = 5.9); 4.05 (m, 4 H, CH_2N); 4.3 (m, 2 H, CH); 4.45 (br.s, 2 H, OH); 5.58 (s, 2 H, CH_2O)	−62.2 (162.7)		34.06 / 33.33	6.67 / 6.39	22.32 / 22.21	$C_7H_{16}N_4O_6$
b	Pr^i	137—141 ($CHCl_3$—hexane)	0.60[b] 0.37[c]	3428 (OH); 1512, 1312 (N=N—O, O)	1.1 (dd, 12 H, CH_3, J = 3.2); 1.8 (m, 2 H, C<u>H</u>(CH_3)$_2$); 3.98 (m, 2 H, OH); 4.1 (dd, 4 H, CH_2N, J = 6.4); 4.3 (dd, 2 H, CHO, J = 6.4); 5.8 (s, 2 H, OCH_2O)	−61.2 (183.1)	17.3 (CH_3); 18.7 (CH_3); 31.7 (<u>C</u>H(CH_3)$_2$); 67.7 (<u>C</u>H_2N); 71.0 (<u>C</u>HOH); 95.5 (<u>C</u>H_2O);	42.00 / 42.85	7.90 / 7.85	18.10 / 18.17	$C_{11}H_{24}N_4O_6$
c	Bu^t [d]	175—180 (acetone)	0.74[b] 0.32[c]	3480 (OH); 1525, 1320 (N=N—O, O)	0.94 (s, 18 H, CH_3); 3.51 (br.s, 2 H, OH); 3.84 (dd, 2 H, CH, J = 8); 4.1 (m, 4 H, CH_2N); 5.85 (s, 2 H, CH_2O)	−61.0 (198.3)		46.15 / 46.42	8.21 / 8.39	16.75 / 16.66	$C_{13}H_{28}N_4O_6$

[a] $(CD_3)_2SO$ as the solvent. Signals were assigned using the DEPT-135 procedure. [b] EtOAc as the eluent.
[c] $CHCl_3$—MeOH (9 : 1) as the eluent. [d] NMR spectra were recorded in acetonitrile-d_3.

water in acetonitrile decreased the yield of azoxyformals several times.

Of alkaline metal salts, we studied the lithium and potassium salts **1a**. It was found that the lithium salt does not form azoxyformal **5a** even on heating with $ClCH_2I$ in DMSO at 50 °C for ten days. On the contrary, the potassium salt gives the desired azoxyformal **5a** after keeping for 24 h at ~70 °C, but the yield is low (~20%). The potassium salt, unlike the tetramethylammonium salt, does not react with dihalomethanes at room temperature. However, if the reaction is carried out in the presence of crown ethers, azoxyformals can be formed; their yields vary from 0 to 13% and are determined, among other factors, by the type of the crown ether and the solvent used.

When silver salts **1a—c** were used, the azoxyformals could be obtained (in dry ether-type solvents) only in the case of chloroiodomethane, but the yields did not exceed 3.5—16%.

In the series of dihalomethanes studied, the highest yields of azoxyformals were observed in the reaction with dichloromethane. As regards other methylenating agents, it is apparently possible to arrange them in series according to efficiency, with the position of dihalomethanes in the series depending on the substrate to be methylenated.

For example, these series look as follows for compounds **1a**, **1b** and **1c**:

$CH_2Cl_2 > ClCH_2Br > ClCH_2I > CH_2Br_2 > FCH_2Br$

$CH_2Cl_2 > ClCH_2I \approx ClCH_2Br > CH_2I_2 \approx CH_2Br_2$

$CH_2Cl_2 > ClCH_2Br > ClCH_2I \approx CH_2I_2 > CH_2Br_2$

Finally, the highest yields of azoxyformals were mostly observed for alkylation of salts **1b**.

The structure of the products obtained in the reaction of salts **1a—c** with dihalomethanes and the complex dependence of their yield on the nature of the starting reagents and solvents are most likely determined by the presence of three centers of electrophilic attack in the anions of the starting salts, increased reactivity of intermediate halomethyl ethers, *i.e.*, primary products of the halomethylation of anions **1** (in comparison with the starting dihalomethanes), and the lability of the compounds formed that contain the *N*-nitrosohydroxylamine fragment.

When the experimental part of the present research had been practically completed, a detailed paper appeared on the reaction of a number of dihalomethanes (CH_2Cl_2, CH_2Br_2, $ClCH_2Br$) with the salts $AlkN(O)=NO^-M^+$ (Alk = Me, Bu^t, Bu^i, *n*-C_5H_{11}).[3] Comparison of data obtained by us and results of this paper allows us to estimate the effect of the β-hydroxy group in salts **1** on the regularities of their reactions with dihalomethanes. Though the corresponding azoxyformals were the sole stable products of both reactions, the laws of their formation differed much. In fact, while the maximum yields of azoxyformals from $AlkN(O)=NO^-M^+$ were observed for potassium salts, tetramethylammonium salts were optimal in the case of $RCH(OH)CH_2N(O)=NO^-M^+$; if potassium salts were used, the yields of azoxyformals were much smaller or they were not formed at all. In the methylenation of $AlkN(O)=NO^-M^+$, the nature of the solvent (DMSO, MeOH, MeCN) has practically no effect on the results of the reaction. Conversely, the choice of

Table 2. Effect of the conditions of reaction between $RCH(OH)CH_2N(O)NO^-M^+$ salts (**1a—c**) and XCH_2Y on the yield of $[RCH(OH)CH_2N(O)=NO]_2CH_2$ (**5a—c**)

XCH_2Y		M^+	Reaction conditions				Yield (%)		
X	Y		*T*/°C	τ/days	Solvent	Catalyst[a]	**5a**	**5b**	**5c**
Cl	I	Ag	~20	7	Ether	—	16	3.5	3.5
Cl	I	Ag	~100	7	Dioxane	—	14	—	—
Cl	I	Li	~20	6	MeCN	12C4	0	—	—
Cl	I	Li	~20	6	MeCN	B12C4	0	—	—
Cl	I	Li	~50	10	DMSO	—	0	—	—
Cl	I	K	~20	7	DMF	—	0	—	—
Cl	I	K	~20	10	$CHCl_3/H_2O$	Me_4NCl	0	—	—
Cl	I	K	~20	1	Benzene	15C5	6	—	—
Cl	I	K	~20	1	MeCN	15C5	0	—	—
Cl	I	K	~20	6	MeCN	15C5	0	—	—
Cl	I	K	~20	1	Benzene	DB18C6	3	—	—
Cl	I	K	~20	1	MeCN	DB18C6	0	—	—
Cl	I	K	~20	6	MeCN	DB18C6	5	—	—
Cl	I	K	~20	6	MeCN	18C6 · MeCN	13	—	—
Cl	I	Me_4N	~20	7	MeCN	—	18	31	22
Cl	I	Me_4N	~20	10	Dioxane	—	0	—	—
Cl	I	Me_4N	~20	12	DMF	—	0	—	—
Cl	I	Me_4N	~20	7	MeOH	—	2	—	—
Cl	I	Me_4N	~20	7	$MeCN/H_2O$	—	3	—	—
Cl	I	Me_3NEt	~20	5	MeCN	—	14	—	—
Cl	I	Me_3NCH_2Ph	~20	2	MeCN	—	9	—	—
Cl	I	Me_3NCH_2Ph	~20	4	MeCN	—	13	—	—
Cl	I	Me_3NCH_2Ph	~20	7	MeCN	—	14	—	—
Cl	I	Me_4N[b]	~20	7	—	—		20	<0.1
Cl	I	Me_4N	~60	7	MeCN	—		34	22.5
Cl	Br	Ag	~20	4	Ether	—	0	—	—
Cl	Br	K	~20	6	MeCN	18C6 · MeCN	11	—	—
Cl	Br	Me_4N	~20	7	MeCN	—	28	31.5	23
Cl	Br	Me_4N	~60	7	MeCN	—	30	28	24.5
Cl	Br	NH_4	~20	7	MeCN	—		15.5	5
F	Br	Me_4N	~20	7	MeCN	—	10.5	—	—
I	I	Me_4N	~20	7	MeCN	—		26	22
Br	Br	Me_4N	~20	7	MeCN	—	15	25.5	20
Br	Br	$Me_3NC_{16}H_{33}$	~20	6	MeCN	—	0	—	—
Cl	Cl	K	72	1	DMSO	—	21.5	—	—
Cl	Cl	Me_4N	~20	7	MeCN	—		11	16
Cl	Cl	Me_4N	~60	7	MeCN	—	41	57	28.5
Cl	Cl	Me_4N	~60	2	MeCN	—	—	35.5	—
Cl	Cl	Me_4N	~60	5	MeCN	—	—	45	—

[a] Molar ratio salt : catalyst = 10 : 1; 12C4 = 12-crown-4, 18C6 = 18-crown-6, 15C5 = 15-crown-5, 12C4 = 12-crown-4, DB18C6 = dibenzo-18-crown-6, B12C4 = benzo-12-crown-4.
[b] Silica gel as a support, without solvent.

the solvent can have a decisive role in the reaction of salts **1** with dihalomethanes. Finally, CH_2Br_2 was the best methylenating reagent studied for $AlkN(O)=NO^-M^+$, and CH_2Cl_2 was the best for salts **1**, while CH_2Br_2 was inferior in this respect to $ClCH_2Br$ and $ClCH_2I$.

Experimental

IR spectra were recorded on UR-20, Specord M-60, and Specord M-82M spectrophotometers in KBr pellets or in thin films on KBr glasses. NMR spectra were obtained on Bruker AM-300, Bruker WM-250, and Bruker AC-200C instruments (^1H — 300.13; 255.13; 200.13 MHz; ^{14}N — 21.69 MHz; ^{13}C — 62.9 MHz). ^1H and ^{13}C NMR chemical shifts were measured relative to the signal from the solvent (acetone-d_6 — 2.07 and 30.0 ppm, acetonitrile-d_3 — 1.96 and 1.3 ppm, DMSO-d_6 — 2.50 and 39.5 ppm), and that of ^{14}N relative to an external standard ($MeNO_2$). Melting points were determined between glasses on a Boëtius hot stage.

PTLC was carried out on Silpearl UV-254 silica gel with a fluorescent indicator (λ 254 nm) or on a Silufol UV-254 plate with silica gel deposited on it. Solvents used in the work and some starting reagents of "analytically pure" grade were purified by standard methods.

The salts of *N*-(β-hydroxyalkyl)-*N'*-hydroxydiazene *N*-oxides **1a—c** used in the work were obtained according to known procedures.[1]

Alkylations of salts of *N*-(β-hydroxyalkyl)-N'-hydroxydiazene *N*-oxides $RCH(OH)CH_2N(NO)O^-M^+$ (1a—c).

1. Alkylation of silver salts 1a—c. An appropriate dihalomethane (0.002 mol) was added to a suspension of compound **1a—c** (0.002 mol) in 10 ml of dry ether or dioxane. The reaction mixture was stirred at a certain temperature (see Table 2). The mixture was filtered, and the solid residue was washed with 5 mL of MeOH. The filtrate was concentrated *in vacuo*. The remaining oily compound was fractionated by PTLC to afford 2,12-dihydroxy-6,8-dioxa-4,5,9,10-tetraazatrideca-4,9-diene 4,10-dioxide (**5a**), 3,13-dihydroxy-2,14-dimethyl-7,9-dioxa-5,6,10,11-tetraazapentadeca-5,10-diene 5,11-dioxide (**5b**), and 3,13-dihydroxy-7,9-dioxa-5,6,10,11-tetraaza-2,2,14,14-tetramethylpentadeca-5,10-diene 5,11-dioxide (**5c**). The reaction conditions, yields, and some physicochemical characteristics of the compounds obtained are listed in Tables 1 and 2.

2. Alkylation of alkaline metal salts 1a—c. ***A.*** A mixture of salts **1a** (0.0025 mol) and 0.003 mol of the appropriate alkylating agent in 10 mL of the appropriate solvent were mixed under dry nitrogen. The resulting solution was concentrated *in vacuo*. The remaining oil was fractionated by PTLC. The reaction conditions and the yields of azoxyformals **5a—c** are listed in Table 2.

B. A suspension of potassium salt **1a** (0.003 mol) and tetramethylammonium chloride (0.00015 mol) was stirred for 15 min in 20 mL of a $CHCl_3$—H_2O mixture. Chloroiodomethane (0.003 mol) was added to this emulsion, and the mixture was stirred at ~20 °C for a certain period of time. The organic phase was separated, and the aqueous phase was carefully washed with EtOAc. The combined extracts were dried with $MgSO_4$. The drying agent was separated, and the filtrate was concentrated. Compound **5a** was isolated from the residue by PTLC.

C. A suspension of potassium or lithium salt **1a** (0.003 mol) and 0.0001 mol of the appropriate crown ether in 20 mL of the appropriate solvent was stirred for 2 h at 20 °C. Then the corresponding dihalomethane (0.003 mol) was added, and stirring was continued at 20 °C. After a certain period of time, the solid phase was separated. The filtrate was concentrated *in vacuo*. PTLC of the residue gave compound **5a**.

3. Alkylation of tetraalkylammonium salts 1a—c. ***A.*** A suspension of salt **1a—c** (0.002 mol) and 0.002 mol of the appropriate alkylating agent in 20 mL of dry MeCN was stirred under dry nitrogen. The precipitate was filtered off and washed on the filter with 5 mL of dry MeCN. The filtrate was concentrated *in vacuo*. The oily residue was suspended in 20 mL of acetone and kept for 30 min. The precipitate that formed was separated and washed with 5 mL of acetone. The filtrate was concentrated *in vacuo*. The residue was fractionated by PTLC to give compounds **5a—c**.

B. A solution of Me_4N-salt **1b** or **1c** (0.005 mol) in 100 ml of dry methanol was mixed with 15 g of silica gel (100—160 mm), dried at 180 °C and a residual pressure ~2 Torr, and stirred for ~30 min. The methanol was removed *in vacuo*, and the residue was carefully dried at ~60 °C and a residual pressure 2—3 Torr for 2 h. The resulting dry mixture was treated with vigorous shaking with 5 ml of chloroiodomethane, purged with dry nitrogen, and the flask was closed tightly. The reaction mixture was heated with vigorous shaking for 30 min at 40 °C, then kept for 7 days at ~20 °C. After a certain period of time, the mixture was treated with 100 mL of dry MeCN. The silica gel was separated, and the filtrate was concentrated *in vacuo*. Compounds **5b** or **5c** were isolated from the residue by PTLC.

4. Alkylation of ammonium salts 1b—c. A mixture of NH_4-salt **1b—c** (0.005 mol) and bromochloromethane (0.005 mol) in ~20 mL of dry MeCN was stirred at ~20 °C. After a certain period of time, the solid precipitate was separated and washed with 10 mL of dry MeCN. The filtrate was concentrated *in vacuo*. Compounds **5b—c** were isolated from the residue by PTLC.

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