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N-(β-HYDROXYALKYL)DIAZENE-N'-OXIDES AND SOME OF THEIR TRANSFORMATIONS

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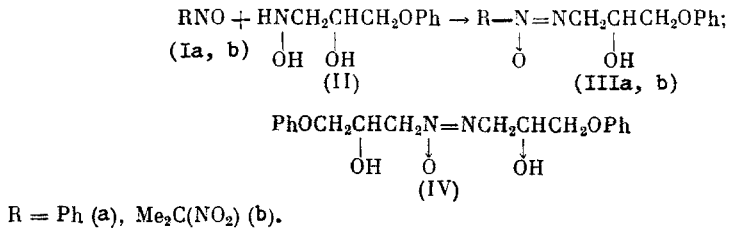
The majority of known N-hydroxyalkyldiazene-N'-oxides (HADO's) are isolated from natural sources (see for example [1-3]), which is explained by the absence of general methods for their synthesis.

In this paper we have proposed two general methods for synthesis of HADO's. The first method consists of reaction of aromatic or aliphatic nitroso compounds (Ia, b) with N-(β-hydroxyalkyl) hydroxylamine (II) [4]



R = Ph (a), $Me_2C(NO_2)$ (b).

Contrary to literature data on the reaction of nitroso compounds with N-alkylhydroxysilamines, which usually gives mixtures of regioisomeric diazene oxides [5, 6], the reactions of (Ia, b) with (II) proceed regioselectively and lead to isomers with the hydroxyl group in the distant position relative to the "oxidized" nitrogen atom.

Upon reaction of (Ib) with (II), together with (IIIb) a compound is formed in comparable amounts which, according to elemental analysis and spectral characteristics may be a mixture of either cis—trans- or diasteroisomers of N,N'-bis(2-hydroxy-3-phenoxypropyl)diazene oxide (IV).

The IR spectrum of (IV) (Table 1) has absorption bands of the azoxy group at 1300 and 1510 cm^{-1} and the mass spectrum of (IV) contains the molecular ion. Probably due to the long relaxation times of nitrogen atoms no signals were detected in the ^{15}N NMR spectrum and the ^{14}N NMR spectrum has one signal with a half-height width ($\Delta\nu_{\frac{1}{2}}$) of ∿1400 Hz centered at −45.5 ppm (from $MeNO_2$), i.e., in the region of chemical shifts characteristic of the oxidized nitrogen atom of diazene oxides. The ^{13}C NMR spectrum (IV) contains four signals which belong to OCH, CHOH, and NCH_2 groups and pairs of C_{ipso} and C_{para} signals. This spectrum does not contradict the assumption of a mixture of either cis—trans- or diastereoisomers. The PMR spectrum of (IV) contains a great number of multiplets the most intense of which change gradually in ratio upon boiling of (IV) in toluene (without decomposition), achieving an equilibrium state.

Formation of (IV) can be explained by oxidation of some of (II) by pseudonitrol (Ib) to 2-hydroxy-1-phenoxy-3-nitrosopropane and condensation of the latter with starting (II)

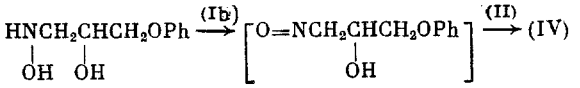


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TABLE 1. Data of Elemental Analysis and IR Spectra of the Obtained Compounds

Compound	Yield %	Mp or Bp, °C (p, mm Hg)	Molecular formula	Found/Calculated % C	H	N	IR spectrum (ν, cm^{-1})
(IIIa)	50	46–47 (hexane)	$C_{15}H_{16}N_2O_3$	66,59 / 66,18	6,27 / 5,88	10,67 / 10,29	3600–3210, 3080, 2945, 1605, 1590, 1490, 1465, 1410, 1305, 1295, 1250, 780, 765, 695
(IIIb)	27	Oil	–	–	–	–	3600–3200, 2940, 1605, 1595, 1575, 1510, 1465, 1400, 1380, 1355, 1295, 1250, 1050, 860, 760
(IV)	11	130 (AcOH – water 1 : 1)	$C_{18}H_{22}N_2O_5$	62,84 / 62,43	6,52 / 6,54	8,53 / 8,09	3600–3300, 2945, 2885, 1610, 1595, 1505, 1465, 1300, 1255, 1200, 1175, 1085, 1050, 750
(Vb)	60	40,5–41,5(1)	–	–	–	–	–
(VIa)	64	Oil	–	–	–	–	3600–3200, 2985, 2920, 1740, 1575, 1520, 1510, 1470, 1405, 1380, 1355, 1195, 1160, 1035
(VIb)	98	60–61 hexane – chloroform 4 : 1)	$C_8H_{10}N_2O_2$	58,27 / 57,83	6,11 / 6,02	16,79 / 16,87	3300–3100, 2950, 1495, 1450, 1400, 1350, 1310, 1070, 890, 850, 780, 695
(VIc)	91	106–109(1)	$C_9H_{12}N_2O_2$	59,60 / 60,00	6,82 / 6,67	15,85 / 15,56	3400, 2960, 1475, 1445, 1300, 1070, 765, 680
(VIII)	62	78–79 (CCl_4 – hexane 3 : 2)	$C_{13}H_{18}N_4O_5$	50,32 / 50,32	6,02 / 5,81	17,69 / 18,06	3300, 1730, 1710, 1605, 1570, 1560, 1505, 1450, 1405, 1380, 1320, 1310, 1255, 1240, 1195, 1160, 1080, 750, 690
(IX)	63	Oil	–	–	–	–	2975, 2940, 2885, 1720, 1605, 1505, 1480, 1370, 1250, 760
(X)	100	125–126 (MeOH)	$C_{18}H_{19}N_7O_8$	46,60 / 46,85	4,18 / 4,12	–	–

A second method of HADO synthesis consists in reaction of nitroso derivatives (Ia, b) with N,N-dichloro-2-hydroxyalkylamines (Va, b) in the presence of $CuBr_2$ (as is known [7], N,N-dichloroamines in reaction with nitroso compounds form regioisomers, in which the oxide nitrogen atom is bound to the same nitrogen atom as in the starting nitroso compounds)

$$RNO + Cl_2NCH_2CHR' \xrightarrow[MeCN]{CuBr_2} RN{=}NCH_2CHR'$$

(Ia, b) (Va, b) (VIa–c)

R = $Me_2C(NO_2)$, R′ = Me (a); R = Ph, R′ = H(b); R = Ph, R′ = Me (c).

The structure of (III) and (VI) was studied in most detail by NMR spectroscopy, using the example of (IIIb) which contains an asymmetric carbon atom (CHOH), in consequence of which the protons of the two neighboring CH_2 groups are nonequivalent. The proton spectrum of the $N{-}CH_2{-}CHOH{-}CH_2O$ fragment corresponds to a ABMNX spin system, in which long range splitting $^4J_{HH}$ does not appear. The two-fold difference in the geminal constants in the CH_2 groups is noteworthy. Thus, in the OCH_2 and NCH_2 groups these constants are respectively −9.5 and −18.0 Hz. In our opinion there are differing mechanisms in this case for transfer of the influence of the neighboring electronegative substituent on the geminal constant [8]: for the OCH_2 group it is inductive {the $^2J_{H-H}$ value is increased compared to the constant in methane (−12.4 Hz) and for the CH_2 group hyperconjugation is operative (the constant is decreased)}.

TABLE 2. ^{13}C NMR Data of Compounds $R^1N(O)=NCH_2CH(OH)CH_2R^2$

Compound	Solvent (δ, ppm)	R^1	R^2	Chemical shifts				
				OCH_2	$CHOH$	NCH_2	R^1	R^2
(IIIa) *	$CDCl_3$ (77,00)	Ph	OPh	70,00	66,14	55,34	146,79 (*i*) 121,87 (*o*) 128,59 (*m*) 131,62 (*p*)	158,33 (*i*) 114,47 (*o*) 129,34 (*m*) 121,03 (*p*)
(IIIb)	DMS, DMSO-d_6 (39,50)	$Me_2C(NO_2)$	OPh	70,18	66,53	55,98	24,00 (Me) 111,74 (C)	158,55 (*i*) 119,55 (*o*) 129,48 (*m*) 120,68 (*p*)
(IV)	$CDCl_3$	$PhOCH_2CHCH_2$ OH	CH_2CHCH_2OPh OH	72,20 70,43 69,76 69,56	66,80 66,64 64,94 64,85	60,92 60,83 55,25 55,21		158,61 (*i*) 158,36 (OPh) 114,60 (*o*) 129,54 (*m*) 120,83 (*p*) 120,65 (*p*)
(VIa)	$CDCl_3$	$Me_2C(NO_2)$	H	–	65,10	59,85	24,45 (Me†) 24,50 111,03 (C)	20,87 (Me)
(VIb)	$CDCl_3$	Ph	H	–	64,96	59,47	146,35 (*i*) 121,34 (*o*) 128,04 (*m*) 131,01 (*p*)	20,67 (Me)

*^{14}N NMR Spectrum of (IIIa) (solution in $CDCl_3$) has a signal at δ 48.14 ppm ($\Delta\nu_{\frac{1}{2}}$ = 280 Hz), which corresponds to the oxidized nitrogen atom of the N=N → O fragment.

†Two signals of approximately equal intensity. The cause of nonequivalency of the methyl groups is unknown.

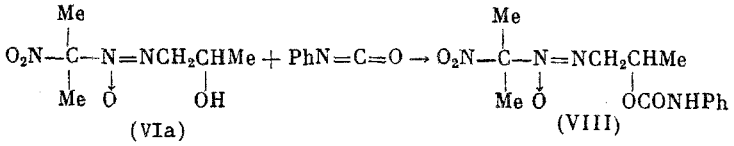
The assignment of signals of the CH_2 groups in the proton spectrum was confirmed by observing the coupling constant through three bonds $^3J_{Cipso-OCH_2}$ = 2.2 Hz using two-dimensional $^{13}C-^1H$ spectroscopy [9]. In the ^{14}N NMR spectrum of (IIIb) two signals are present: one from the NO_2 group with chemical shift of 3.9 ppm ($\Delta\nu_{\frac{1}{2}}$ = 240 Hz) and another from the =N

atom with chemical shift of −43.3 ppm ($\Delta\nu_{\frac{1}{2}}$ = 320 Hz relative to $MeNO_2$). To determine the oxygen atom position in the azoxy group we proceeded from the fact that only the nitrogen atom carrying it gives a detectable signal in the ^{14}N NMR spectrum. The signal of the carbon atom bound with it in the ^{13}C NMR spectrum should be broadened due to spin–spin interaction $^1J_{^{14}N-^{13}C}$. Upon irradiation at the ^{14}N frequency in the ^{13}C NMR spectrum only the signal of the quaternary carbon atom of the Me_2CNO_2 group (111.74 ppm) is noticeably narrowed with increase of peak intensity, i.e., the oxygen atom of the azoxy group is on the side of this substituent. The other confirmation of this conclusion is the identical multiplicity of the ^{15}N NMR signals of the NO_2 and $=\overset{\rightarrow O}{N}$ groups. Both signals (δ = 3.1 and −44.2 ppm) are

septets with coupling constants $^2J_{^{15}N-CH_3}$ of 3.0 and 2.4 Hz respectively. The same spectrum contains a signal at −30.0 ppm belonging to the second "unoxidized" azoxy nitrogen atom. The structure of (IIIa) was assigned by analogy to (IIIb) on the basis of their similar spectral data

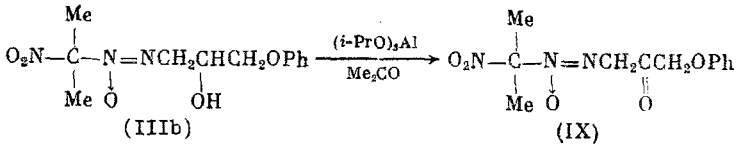
N,N-dichloroaminoisopropanol (Vb), not previously described, was obtained similarly to (Va) [10] by chlorination of aminoisopropanol (VIIb) [11] with chlorine in acetate buffer. Compound (Vb) is a lemon yellow liquid distillable under vacuum, which decomposes during storage even at temperatures below −10°C.

The hydroxyl group in HADO's has typical chemical properties. Thus, upon reaction of (VIa) with phenyl isocyanate the corresponding urethane (VIII) is formed. This reaction can be used for obtaining crystalline derivatives of HADO's



(VIa) (VIII)

Treatment of (IIIb) with excess of aluminum isopropylate in boiling benzene yielded the corresponding ketone (IX), which was characterized as the 2,4-dinitrophenylhydrazone (X)



(IIIb) (IX)

It should be noted, however, that we were unable to find conditions for the analogous oxidation of (IIIa) and (VIb, c).

EXPERIMENTAL

PMR spectra were taken on a Tesla BS-467 instrument with working frequency of 60 MHz and a Bruker AM-300 with working frequency of 300 MHz in solutions in $CDCl_3$ or acetone-d_6 using HMDS as internal standard. ^{13}C (75.5 MHz), ^{14}N (21.7 MHz), and ^{15}N (30.4 MHz) NMR spectra were recorded on a Bruker AM-300 instrument. IR spectra were obtained on UR-20 and Specord IR instruments using KBr pellets for crystalline substances and neat smears for liquid substances. The mass spectrum was taken on an MS-30 instrument

For column chromatography (CC) under pressure and for TLC Silpearl silica gel was used (for TLC with Luminofor). Melting point was determined on a Koffler table. Compounds (Ia, b) were synthesized by the method of [12, 13] respectively. Elemental analysis and IR spectral data are shown in Table 1 and ^{13}C NMR spectra in Table 2.

1-Phenyl-2-(2-hydroxy-3-phenoxypropyl)diazene-1-oxide (IIIa). A mixture of 0.75 g of (Ia) and 1.3 g of (II) in 25 ml of abs. CH_2Cl_2 was kept for 3 days at 10°C and evaporated. From the residue by TLC (C_6H_6:EA, 2:1) 1.27 g (50%) of (IIIa) (R_f 0.58, mp 46-47°C, hexane)

was isolated. PMR spectrum (δ, ppm from HMDS, unspecified solvent – acetone-d_6): 8.20 m (N–Ph, o-H), 7.42 m (NPh, m- and p-H), 7.25-6.77 m (Ph), 4.45 m (CHOH), 4.23-3.67 m (NCH_2 and OCH_2).

1-(1-Methyl-1-nitroethyl)-2-(2-hydroxy-3-phenoxypropyl)diazene-1-oxide (IIIb) and 1,2-bis(2-hydroxy-3-phenoxypropyl)diazene oxide (IV). A solution of 2.58 g of (Ib) and 4 g of (II) in 100 ml of dry CH_2Cl_2 was kept for 3 days at 0°C and evaporated. The residue was treated with ether and by filtration there was separated 0.82 g {11% based on (II)} of a colorless crystalline precipitate (IV) with mp of 130°C (50% AcOH). The filtrate was evaporated and by column chromatography 1.47 g {15% based on (Ib)} of colorless oil (IIIb) was isolated. PMR spectrum of (IIIb) (δ, ppm): 7.42-6.64 m (Ph), 4.43 m (CH), 4.11-3.73 m (OCH_2 and NCH_2), 2.83 s (OH), 32.3 s (Me). PMR spectrum of (IV) (δ, ppm): 4.74-4.32 m, 4.17-4.02 m, 3.66-3.61 m (NCH_2–CHOH–CH_2O), 7.32-7.24 m (Ph), o-H), 6.99-6.89 m (Ph, m- and p-H).

1-(N,N-Dichloroamino)propan-2-ol (Vb). A solution of 5 g of 1-aminopropan-2-ol in 100 ml of acetate buffer (30.8 g AcONa and 1.5 g AcOH in 0.5 liter water) was bubbled with Cl_2 for 2 h at ≤ 6°C and extracted with CH_2Cl_2. The extract was dried above $MgSO_4$. Solvent was removed and the residue was distilled under vacuum at 40.5-41.5°C (1 mm). There was obtained 5.7 g (60%) of (Vb), n_D^{20} 1.4835. PMR spectrum (δ, ppm): 4.58 s (OH), 4.03 m (CH), 3.64 m (CH_2N), 1.17 d (Me). For comparison we cite PMR spectra of N,N-dichloroaminoethanol (Va), aminoethanol (VIIa), and aminoisopropanol (VIIb) (δ, ppm): (Va): 3.78 m (NCH_2, OCH_2), 4.25 s (OH); (VIIa): 4.11 s (OH), 3.47-2.85 m (CH_2N, OCH_2), 2.58 t (NH_2); (VIIb): 3.72 m (NCH_2, CHOH), 2.48 m (NH_2/OH), 1.03 d (Me).

1-Phenyl-2-(2-hydroxypropyl)diazene-1-oxide (VIc). Into a solution of 1.23 g of $CuBr_2$ in 35 ml of abs. MeCN at 5°C a solution of 0.54 g of 2-nitro-2-nitrosopropane (Ia) in abs. MeCN was added, then at 0-2°C 0.79 g of (Vb) was added dropwise (color was changing from dark-green to brown-purple). The mixture was stirred at 2°C for 30 min more, heated at ∿ 20°C, poured into 150 ml of water, and extracted with CH_2Cl_2. The extract was dried above $MgSO_4$ and solvent was removed. By chromatography of the residue (eluent-benzene:EA, 1:2) 0.82 g (91%) of yellowish oil (VIc) was isolated, which was additionally purified by distillation at 106-109°C (1 mm), n_D^{20} 1.5547. Analogously (VIa, b) were synthesized. PMR spectra (δ, ppm, $CHCl_3$): (VIa): 4.14 m (CH), 3.47 m (NCH_2), 2.83 s (MeCN), 1.21 d (MeCH); (VIb): 8.1 m (Ph, o-H), 7.45 m (Ph, m- and p-H), 4.30 s (OH), 3.85 m (NCH_2, OCH_2); (VIc): 8.03 m (Ph, o-H), 7.40 m (Ph, m- and p-H), 4.30 s (OH), 4.28 m (CH), 3.62 m (NCH_2), 1.22 d (Me).

1-(2-Methyl-2-nitroethyl)-2-[2-(N-phenylcarbamoyloxy)propyl]diazene-1-oxide (VIII). To a solution of 0.25 g of PhNCO in 10 ml of abs. C_6H_6 a solution of 0.4 g of (VIa) in 5 ml of abs. C_6H_6 was added and the mixture was boiled for 1 h, then at ∿ 20°C evaporated for 18 h, and (VIII) was obtained, which was recrystallized from a mixture of hexane:CCl_4 (2:3), mp 78-79°C.

1-(2-Methyl-2-nitroethyl)-2-(2-oxo-3-phenoxypropyl)diazene-1-oxide (IX) and Its 2,4-dinitrophenylhydrazone (X). A mixture of 0.45 g of (VIa) and 1.62 g of $(i\text{-PrO})_3Al$ was boiled for 10 h in a mixture of 20 ml of C_6H_6 and 24 ml of acetone. After cooling the reaction mixture was washed with diluted H_2SO_4. After solvent removal there was obtained 0.31 g of dark oil, from which by TLC 0.16 g (41%) of (IX) was isolated. Eluent C_6H_6:EA (2:1), R_f 0.72. (X), yield quantitative (in the presence of H_3PO_4), mp 125-126°C (MeOH).

The authors express gratitude to N. F. Karpenko for taking spectra and aiding in their interpretation.

CONCLUSIONS

1. Regioselective methods are proposed for synthesis of N-(β-hydroxyalkyl)diazene-N'-oxides by reaction of nitroso compounds with N-(β-hydroxyalkyl)hydroxylamines or with N,N-dichloro-2-hydroxyalkylamines.

2. The possibility was shown of obtaining N-β-oxo- and β-arylaminocarboxyl derivatives of diazene-N'-oxides by treatment of N-(β-hydroxyalkyl)diazene-N'-oxides with aluminum isopropylate and phenyl isocyanate respectively.

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ASYMMETRIC SYNTHESIS OF AMINO ACIDS BY CATALYTIC REDUCTION OF AZLACTONES OF SUBSTITUTED ACYLAMINOACRYLIC ACIDS.

22. EFFECT OF SUBSTITUTION ON THE RATE OF AMINOLYSIS OF Δ^2-OXAZOLIN-5-ONES

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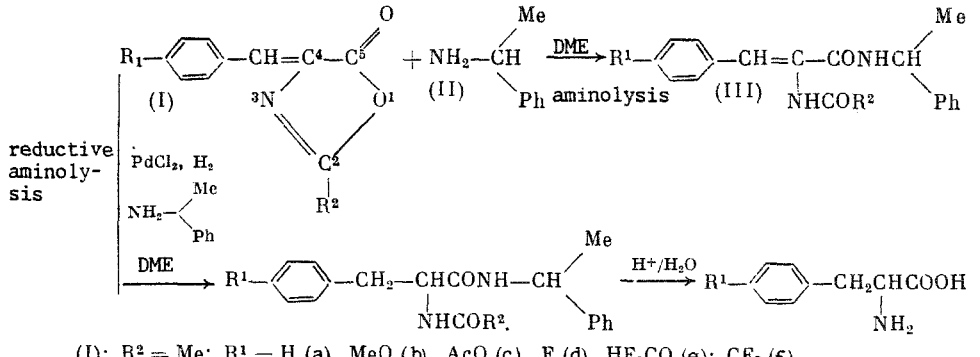
There has recently been a considerable increase in interest concerning the structure and reactivity of unsaturated Δ^2-oxazolin-5-ones (I) [1-3]. This is due to the large group of products with practical importance that are obtained from (I), in particular, optically active amino acids and dipeptides, by catalytic reductive aminolysis of (I) [4]. The kinetics of the opening of the oxazolone ring in (I) on treatment with benzylamine in an aprotic solvent has been studied in [5] using UV spectroscopy.

The present work is devoted to an IR spectroscopic study of the opening of the oxazolone ring by treatment with α-phenylethylamine (II) and the effect of substituents in (I) on the rate of the reaction.

RESULTS AND DISCUSSION

The aminolysis study was carried out using the (Z)-isomer of 2-methyl- and 2-phenyl-4-benzylideneoxazolin-5-ones (I) with different substituents in the aromatic ring of the benzylidene group. These compounds had previously been used for the asymmetric synthesis of substituted amino acids by reductive aminolysis of (I) (Scheme 1) [4, 6, 7]

Scheme I



(I): R^2 = Me; R^1 = H (a), MeO (b), AcO (c), F (d), HF_2CO (e); CF_3 (f).
R^2 = Ph; R^1 = H (g), MeO (h), AcO (i), HF_2CO (j).

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