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Reaction of Certain α,β-Unsaturated Terpenic Oximes with Sodium Nitrite in Acetic Acid: a Facile Synthesis of Allylic Nitro Compounds.

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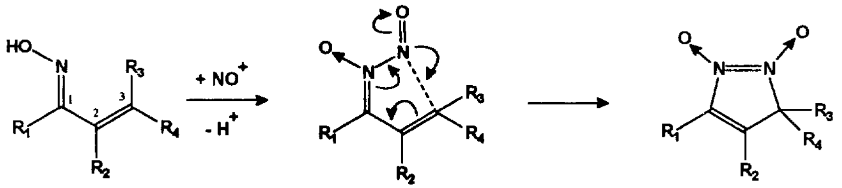
Abstract: Reaction of nitrous acid with α,β-unsaturated oximes having the structural fragment of 2-methyl-3-hydroxyimino-1-cyclohexene is described. A set of the oximes studied includes simple monocyclic derivatives (2-methyl-2-cyclohexenone oxime and carvone oxime) as well as more complex bicyclic compounds (car-2-en-4-one oxime and a-muurolen-3-one oxime). The reaction was shown to give allylic nitro compounds either with the retention of the carbon frame or with the rearranged skeleton. Chemical structure and stereochemistry of the products obtained are established by ^{1}H, ^{13}C and ^{14}N NMR spectroscopy together with IR and UV data. Possible mechanisms of the reaction are discussed. Molecular mechanics and MNDO-calculations are used for the mechanistic study.

INTRODUCTION

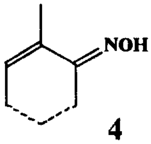
Nitrogen-containing derivatives hold a particular place among the derivatives of terpene hydrocarbons and are considered as potential biologically active substances. α,β-Unsaturated oximes, easily obtained either from unsaturated hydrocarbons by nitrosochlorination - dehydrochlorination or from the corresponding α,β-unsaturated carbonyl compounds, are adaptable to the synthesis of diverse nitrogen-containing derivatives. One of the most thoroughly studied reactions of α,β-unsaturated oximes is the reaction with nitrous acid generated from sodium nitrite in the acetic acid solutions. The starting oxime **1** is transformed to pyrazole derivative **3** under reaction conditions[1,2,3,4] (Scheme 1)[5].

Scheme 1.



1 **2** **3**

In this case the capacity of the starting oxime **1** (and/or intermediate N-nitroso derivatives **2**) to exist in s-*cis*-conformation is a necessary condition for the formation of the heterocyclic compound. This condition is easily fulfilled in the case of acyclic α,β-unsaturated oximes that react with nitrous acid giving rise to pyrazole derivatives. However the majority of α,β-unsaturated oximes to be obtained starting from the accessible natural terpene hydrocarbons have a double bond in the cyclic fragment of the molecule, so



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the fulfillment of this condition is impossible to be achieved. In the present study the chemical transformations of some α,β-unsaturated oximes, having structural fragment **4** with fixed *s-trans*-conformation of diene system, under the action of nitrous acid are studied.

RESULTS AND DISCUSSION

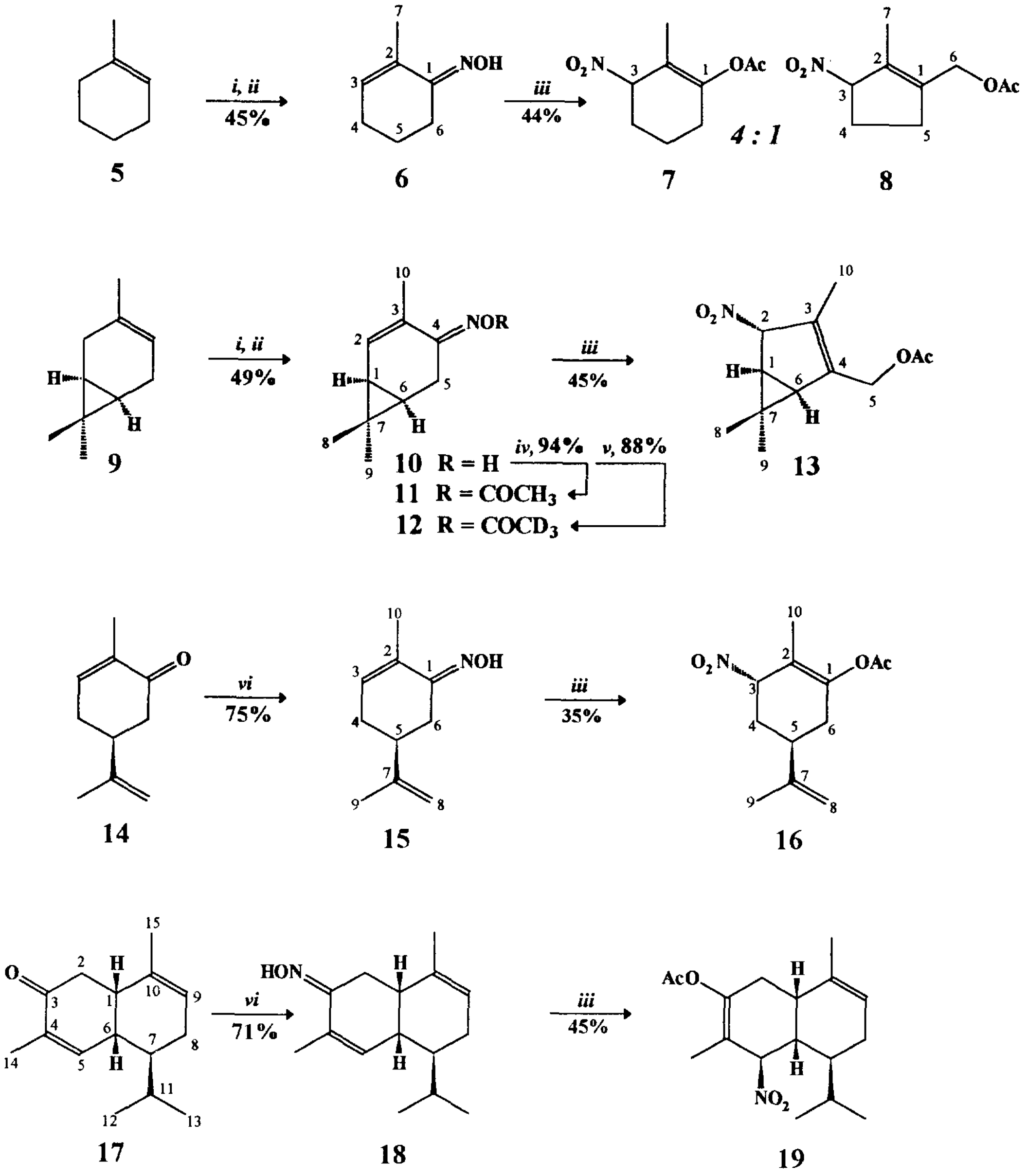
Structure elucidation of the nitrosation products

We studied the transformations of a number of unsaturated oximes, namely, 2-methyl-2-cyclohexenone oxime (**6**), car-2-en-4-one oxime (**10**), carvone oxime (**15**) and α-muurolen-3-one oxime (**18**) under the action of nitrous acid. The reactions of all the listed oximes with sodium nitrite in acetic acid are similar in visual appearance: the first portions of powdered sodium nitrite being added, the colorless solution of oxime is first painted yellow, and as sodium nitrite is further added, a gas is evolved with the reaction mixture changing to a more intense colour and a fine crystalline precipitate (sodium acetate) arising. The starting oxime is completely utilized (according to TLC) only after 3 equivalents of sodium nitrite were added. The crude reaction product is a red-brown viscid oil containing the sole product (according to TLC), which can be isolated by silica gel chromatography with the yield 35-45%. All the studied oximes are transformed to unsaturated nitro acetates, having similar R_f values on TLC and being slowly pitched when stored at room temperature. Transformation of oxime **6** gives a chromatographically homogeneous mixture of isomeric nitro acetates **7** and **8**, while oximes **10**, **15** and **18** give individual compounds **13**, **16** and **19** correspondingly. The resulting nitro acetates belong to two different structure types (***Scheme 2***): derivatives of 1-acetoxy-2-methyl-3-nitrocyclohexene type (compounds **7**, **16** and **19**) and derivatives of 1-acetoxymethyl-2-methyl-3-nitrocyclopentene type (compounds **8** and **13**). Structures and stereochemistry of the products obtained were established by NMR spectroscopy and IR and UV data. ^{1}H, ^{13}C and ^{14}N NMR data of the compounds are listed in ***Tables 1-4***.

The availability of bicyclo[3.1.0]hexene system in compound **13** was established from the values of the $^1J_{C\text{-}C}$ coupling constants in ^{13}C-NMR spectrum (INADEQUATE technique, ***Table 2***). The presence of a nitro group was confirmed by ^{14}N NMR spectroscopy: δ_N +13 ppm[6]. The attachment of acetate group to the CH_2-group and nitro group to the C-4 atom (and not the reverse) in this compound is supported by the data of selective heteronuclear double resonance: under selective irradiation of the protons of the acetate group carbonyl carbon gives triplet (J = 3.5 Hz) due to the vicinal constants $^3J_{C\text{-}O\text{-}CH_2}$. For a closely corresponding bicyclo[3.1.0]hexene derivative the coupling constant $^3J_{H\text{-}H}$ comprises 7.5 Hz, **H**-1 and **H**-2 being in *cis*-configuration, and 1.5 Hz, the protons being in *trans*-configuration[7]. The availability of the coupling constants $J_{H^1\text{-}H^2}$=2.6 Hz for compound **13** indicated the *trans*-configuration of the nitro group in cyclopentene fragment with respect to the cyclopropane unit.

NMR and IR spectra show compound **16** to be an aliphatic nitro derivative (δ_N +11 ppm) with a enolacetate structural fragment ($\delta_{Me\underline{C}OOR}$ 167.4 ppm[8], $\nu_{C=O}$ 1762 cm^{-1} and $\nu_{C=C}$ 1700 cm^{-1} [9]). The shape of **H**-5 signal in NMR ^{1}**H** spectrum (***Table 3***) indicates a half-chair conformation of the six-membered ring, isopropenyl group aligned equatorial, while the shape of **H**-3 signal indicates pseudoequatorial orientation of **H**-3 atom. Thus, nitro and isopropenyl groups are *trans* situated in the molecule **16**.

Scheme 2.



i = NOCl
ii = NEt_3
iii = $NaNO_2$ /AcOH
iv = $Ac_2O/Et_3N/Et_2O$
v = $CD_3COCl/Et_3N/Et_2O$
vi = NH_2OH x $HCl/MeOH/Na_2CO_3$

Table 1. **^1H and ^{13}C NMR Data for Compounds 6-8^{a,b}.**

	6^c		7^d		8^d	
i	δC^i	δH^i (J, Hz)	δC^i	δH^i (J, Hz)	δC^i	δH^i (J, Hz)
1	155.68	-	149.79	-	140.97	-
2	130.80		114.59	-	131.20	-
3	132.80	5.97 *tq* (5.0, 1.5)	86.06	4.93 *t* (4.0)	96.17	5.24 *m*
4	25.25	2.15 *m*	27.37	1.6-2.7	32.42	1.6-2.7
5	21.37	1.73 *tt* (6.5, 6.5)	18.03	1.6-2.7	27.37	1.6-2.7
6	22.51	2.58 *t* (6.5)	26.43	2.15 *m*	59.58	4.55 *d* (12.4)
						4.67 *d* (12.4)
7	18.11	1.81 *dt* (1.5, 1.5)	13.16	1.51 *dd* (1.8, 1.8)	10.96	1.67 *br.s*
$CH_3\underline{CO}$			167.29	-	169.83	-
$\underline{CH_3}CO$			19.85	2.08 *s*	19.92	1.97 *s*
$O\underline{H}$		9.2 *br.s*				

^{a} *Bruker AC 200*; ^{b} chemical shifts are given in ppm; ^{c} in $CDCl_3$-CCl_4 (1:1 v/v); ^{d} in $CDCl_3$-C_6D_6 (1:1 v/v).

Table 2. **NMR Data for Compounds 11 - 13^{a,b}.**

	11^c	12^d		$13^{d,e}$	
i	δC^i	δC^i	δH^i (J, Hz)	δC^i ($J_{C^i\text{-}C^j}$)	δH^i (J, Hz)
1	22.92	23.22	1.19 *dd.* (8.0, 5.4)	31.10 (44.3, 15.0, 9.5)	1.97 *dd* (5.8, 2.6)
2	134.75	135.75	6.21 *d* (5.4)	93.93 (44.3, 42.0)	4.71 *d* (2.6)
3	126.70	126.98	-	132.21 (74.2, 45.3, 42.0)	-
4	159.11	160.13	-	141.24 (74.2, 51.5, 50.4)	-
5	19.42	19.88	Ha: 2.63 *dd* (20.0, 8.0) Hb: 2.88 *d.* (20.0)	59.69 (51.5)	Ha: 4.57 *d* (13.0) Hb: 4.63 *d* (13.0)
6	19.93	20.19	1.01 *dd* (8.0, 8.0)	37.82 (50.4, 14.0, 9.5)	1.79 *d* (5.8)
7	23.19	23.64	-	28.08 (46.1, 42.4, 15.0, 14.0	-
8	12.93	13.27	0.70 *s*	13.44 (46.1)	0.71 *s*
9	26.92	27.23	1.05 *s*	25.82 (42.4)	1.06 *s*
10	17.25	17.67	1.84 *s*	11.10 (45.3)	1.70 *br.s*
$CH_3\underline{CO}$	167.75	168.91		170.37 (59.2)^f	
$\underline{CH_3}CO$	18.95	-^{g}	2.08 *br.s* (resid.)	20.54 (59.2)	1.99 *s*

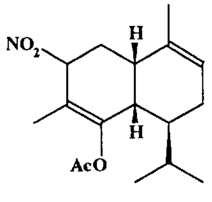
^{a} *Bruker AC 200;* ^{b} chemical shifts are given in ppm; ^{c} in $CDCl_3$-CCl_4 (1:1 v/v); ^{d} in $CDCl_3$; ^{14}N NMR: δ +13 ppm; ^{e} carbon-carbon (±0.1 Hz) and carbon-proton (±0.3 Hz) coupling constants were measured for 60% solution in acetone-d_6; ^{f} $^2J_{C\text{-}H}$ = 6.5 Hz, $^3J_{C\text{-}H}$ = 3.5 Hz; ^{g} chemical shift for CD_3-group has not been measured because of the low intensity of the signal.

***Table 3.* NMR Data for Compounds 15 and 16[a].**

	15[b]	**16**[c]		
i	δC^i	δC^i	δH^i (*J*, Hz)	$J_{H^i\text{-}H^j}$, Hz (H^j)[d]
1	156.14	149.66	-	
2	132.63	114.29	-	
3	130.12	85.91	4.99 *ddtq* (5.5, 2.0, 1.2, 0.6)	5.6 (H4β), 2.0 (H4α), -1.4 (H6β), -0.7 (H6α), ±0.6 (3H10)
4	30.25	31.79[e]	α**H**: 2.39 *ddd* (14.4, 2.7, 2.0) β**H**: 1.94 *ddd* (14.4, 12.7, 5.5)	-14.6 (H4β), 2.0 (H3), 2.7 (H5), 1.0 (H6α) -14.6 (H4α), 5.6 (H3), 12.7 (H5)
5	40.12	36.14	2.62 *dtddqd* (12.7, 8.4, 2.7, 0.6, 0.4, 1.2)	12.7 (H4β), 2.7 (H4α), 11.0 (H6β), 5.3 (H6α)
6	27.22	32.05[e]	2.25 *ddq* (8.4, 1.2, 2.0)	α**H**: -17.3 (H6β), 5.3 (H5), -0.7 (H3), 1.0 (H4α) β**H**: -17.3 (H6α), 11.0 (H5), -1.4 (H3)
7	147.41	145.67	-	
8	110.05	110.17	**H**a: 4.72 *ddq* (1.2, 1.2, 0.8) **H**b: 4.77 *dqd* (1.2, 1.2, 0.6)	1.2 (H8b), -0.8 (3H9) 1.2 (H8a), -1.2 (3H9)
9	20.67	20.08	1.70 *ddd* (1.2, 0.8, 0.4)	-0.8 (H8a), -1.2 (H8b)
10	17.65	13.51	1.62 *td* (2.0, 0.6)	
$CH_3\underline{CO}$	-	167.39	-	
$\underline{CH_3}CO$	-	19.89	2.16 *s*	

[a] chemical shifts are given in ppm; [b] *Bruker AC 200*; in **$CDCl_3$-CCl_4** (1:1 v/v); [c] *Bruker AM 400*; in **$CDCl_3$**; ^{14}**N** NMR: δ +11 ppm; [d] the coupling constants (±0.3 Hz) were calculated using *PANIC* program, for **C_6D_6** solution (*Bruker AM 400*), $\Delta\delta H^6_{\alpha,\beta}$ = 10 Hz; [e] assignment may have to be reversed.

Two structures for the product of oxime **18** nitrosation are possible according to NMR data (***Table 4***): structure **19** shown on ***Scheme 2*** and alternative structure **20**. Structure **19** is supported by the availability of the indirect coupling constants of **H**-5 atom with **C**-6 atom ($^2J_{C\text{-}H}$-type, 3.5 Hz) and **C**-7 atom ($^3J_{C\text{-}H}$-type, 2.7 Hz). Determination of configuration for **C**-5 atom requires preliminary refinement of the bicyclic system's conformation. Such derivatives may come in two stable conformations both having half-chair conformations of the six-membered rings "A" and "B", but with different isopropyl group orientation (axial and equatorial)[10,11]. Analysis of ^{13}C NMR spectra of the derivatives of this series shows methyl carbon atoms of the isopropyl fragment to give signals within δ 14.8-15.7 ppm (**C**-12) and δ 21.0-21.2 ppm (**C**-13) in the case of equatorial isopropyl group orientation and within δ 19.3-19.6 ppm (**C**-12) and δ 20.9-21.1 ppm (**C**-13) in the case of axial



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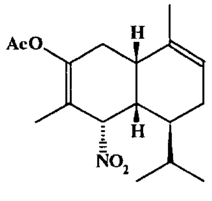

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orientation[10,12,13]. The magnitude of chemical shifts of these methyls in compound **19** being equal to δ 14.3 and 20.5 ppm favours an equatorial orientation of isopropyl. Besides, the coupling constant $^3J_{H^6\text{-}H^7}$ = 11.2 Hz for compound **19** indicates 1,2-*trans*-diaxial orientation of the corresponding protons, possible only in the case of the equatorial isopropyl orientation. ***Table 5*** represents the calculated values of some characteristic coupling constants for two epimers at C-5 atom (compounds **19** and **21**) and the experimental ones for compound **19**. Comparison of the calculated and experimental data indicates β-configuration of the nitro group in compound **19**.

Nitrosation of oxime **6** results in chromatographically pure product, displaying two sets of signals in NMR spectra (the intensities are in ratio 4:1). Correlation of the spectral characteristics obtained (***Table 1***) with those of 1-acetoxy-2-methyl-3-nitrocyclohexene derivatives (compounds **16** and **19**) and 1-acetoxymethyl-2-methyl-3-nitrocyclopentene derivative (compound **13**) allows structures **7** and **8** for the mixture components.

***Table 4.* ^{1}H and ^{13}C NMR Data for Compounds 17-19[a].**

	17[b]	**18**[b,c]		**19**[c]	
i	δC^i	δC^i	δH^i (*J*, Hz)	δC^i	δH^i (*J*, Hz)
1	39.57	37.10		34.67	[2.40]
2	39.69	24.52	3.23 *dd* (16.4, 3.8) 2.11 *d* (16.4)	31.05	eq.: [2.38] ax.: [2.07]
3	199.27	156.36		149.91	-
4	134.87	129.65		113.25	-
5	140.01	137.12	6.10 *d* (5.5)	88.74	4.98 *br.s*
6	37.75	37.54		40.68	2.28 *ddd* (11.2, 4.2, 2.0)
7	39.37	39.59		34.88	[1.64]
8	24.73	24.66		24.85	[1.73, 1.86]
9	121.95	121.76	5.40 *br.s*	120.94	5.20 *br.s*
10	134.64	135.71		135.71	-
11	27.33	27.27		27.44	[1.67]
12	16.00	15.75	0.84 *d* (6.5)	14.96	0.85 *d* (6.8)
13	20.94	21.01	0.88 *d* (6.5)	20.83	0.84 *d* (6.8)
14	15.90	17.87	1.87 *br.s*	14.61	1.52 *br.s*
15	20.94	21.32	1.69 *br.s*	21.56	1.51 *br.s*
O$\underline{H}$			10.1 *br.s*		
$CH_3\underline{CO}$				167.89	-
$\underline{CH_3}CO$				20.47	1.90 *s*

[a] chemical shifts are given in ppm; [b] *Bruker AC 200*; in **$CDCl_3$**; [c] LRJMD-technique[14] was used for the signal assignment; [d] *Bruker AM 400*; in **$CDCl_3$-C_6D_6** (δ$C_{benzene\text{-}d6}$ = 128.00 ppm, δ $H_{benzene\text{-}d6}$ = 7.24 ppm); [e] chemical shifts put in square brackets were taken from the 2D heteronuclear ^{13}C-^1H chemical shift correlation spectra ($^1J_{CH}$ = 125 Hz); [f] $^nJ_{H^5\text{-}C^i}$, ±0.1 Hz (C^i): 5.5 (C-1), 5.7 (C-3), 5.1 (C-4), 3.5 (C-6), 2.7 (C-7), 3.3 (C-14); the coupling constants were obtained from the selective 2D J(C,H)-resolved spectrum[15].

Table 5. **Selected Experimental and Calculated Values of the Vicinal Coupling Constants (Hz) for Compounds 19 and 21.**

	experimental	calculated[a]	
Vicinal coupling constant	**19**	**19**	**21**
H^1-H^6	4.2	4.3	9.8
H^5-H^6	2.0	2.5	6.9
H^6-H^7	11.2	11.6	11.9
C^1-H^5	5.5	5.5	4.3
C^7-H^5	2.7	3.2	0.7

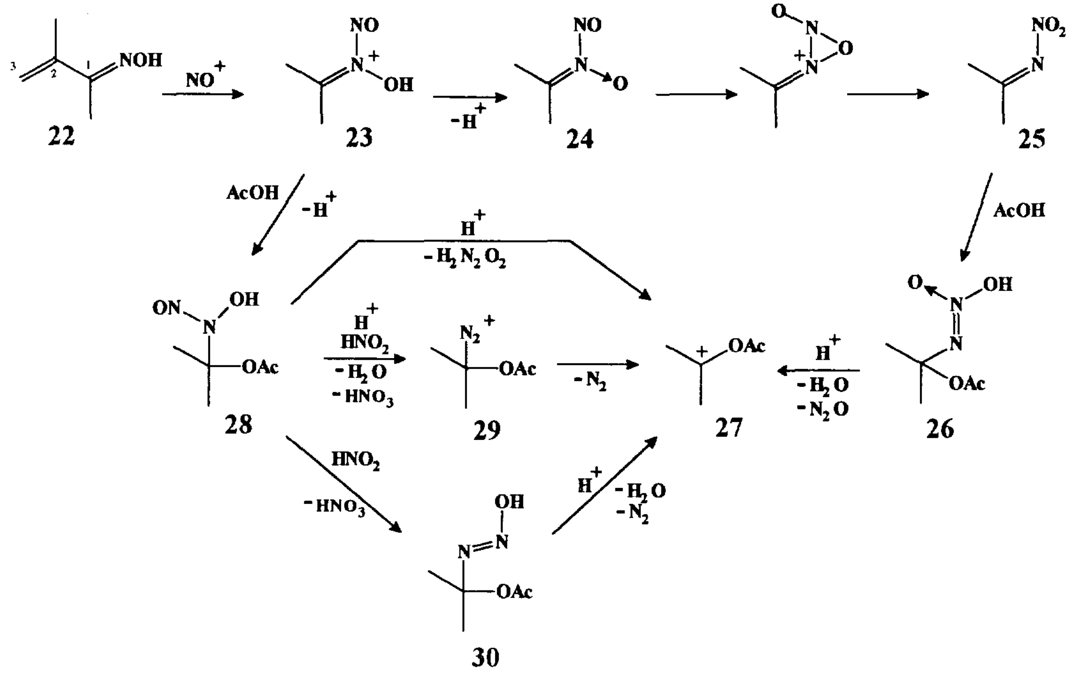
[a] The coupling constants were calculated by known procedure[16] using well-known Karplus equation: $^3J_{H\text{-}H} = 7 - cos\phi + 5cos2\phi$ (with the correction on the electronegativity of the substituent: $J = 0.9J_0$ for NO_2-group) for the proton-proton coupling and the Karplus-type equation[17]: $^3J_{C\text{-}H} = 4.26 - cos\phi + 3.56cos2\phi$ for the carbon-proton coupling.

Possible mechanism of the reaction

With introducing in all the above reactions of the unsaturated oximes, having the same structural fragment **4**, with all the reactions being conducted in the same conditions and proceeding identically (in appearance), and with the reaction products being compounds of the same type (nitro acetates), we suppose all the studied unsaturated oximes **6**, **10**, **15** and **18** to react similarly in that the NO^+ cation is primarily attached to the nitrogen atom of the oxime group, and all the transformations of the nitrous function in intermediate compounds occur similarly. Thus the differences in structure of the resulting products should depend on the peculiarities of spatial structure of the intermediate products, emerging on the final steps of the transformations. It is worth noting that other species are discussed as nitrosating agents, such as AcONO[18,19], HNO_2, $H_2NO_2^+$, N_2O_3[20] whose formation would be expected here, but their action also resides in the transferring of NO^+ to the substrate molecule. Thus from this point on we shall speak about NO^+-attack bearing only the result formally expressed in attachment of nitrosyl cation, but not the mode of the reaction and not the vector participating in it. The primary NO^+-attack is applied to nitrogen atom of oxime fragment in unsaturated oxime **22** and leads to N-nitroso derivative **23**[21]. Two variants of deoximation, shown on ***Scheme 3***, varying in the character of nitrogen-containing function being eliminated and the amount of sodium nitrite required for the completion of the reaction, are possible.

N-nitroso oxime **23** can be deprotonated into **24**, leading to rearrangement of nitrogen function and formation of nitrimine **25** (compare with ref.[4,22,23], that might give adduct **26** on the addition of nucleophile[24], the above adduct can lead to cation **27** by ejection of N_2O molecule[25,26]. On this mode of reaction one equivalent of sodium nitrite is utilized (as NO_2^-) - for the generation of the nitro group of the ultimate product. In the product of nucleophile addition to nitroso oxime **28** a reduction of nitrogen-containing function might occur (here one more equivalent of nitrite is required) with formation of either diazo compounds **29** or corresponding diazo acetate **30**, these latter decomposing into the deoximation product **27**. The complete transformation of all the studied oximes (that is for the complete elimination of the starting material from the reaction mixture, TLC) requires three equivalents of sodium nitrite, contradicting the mode of deoximation, including ejection of N_2O molecule[27]. Furthermore, mass

Scheme 3.



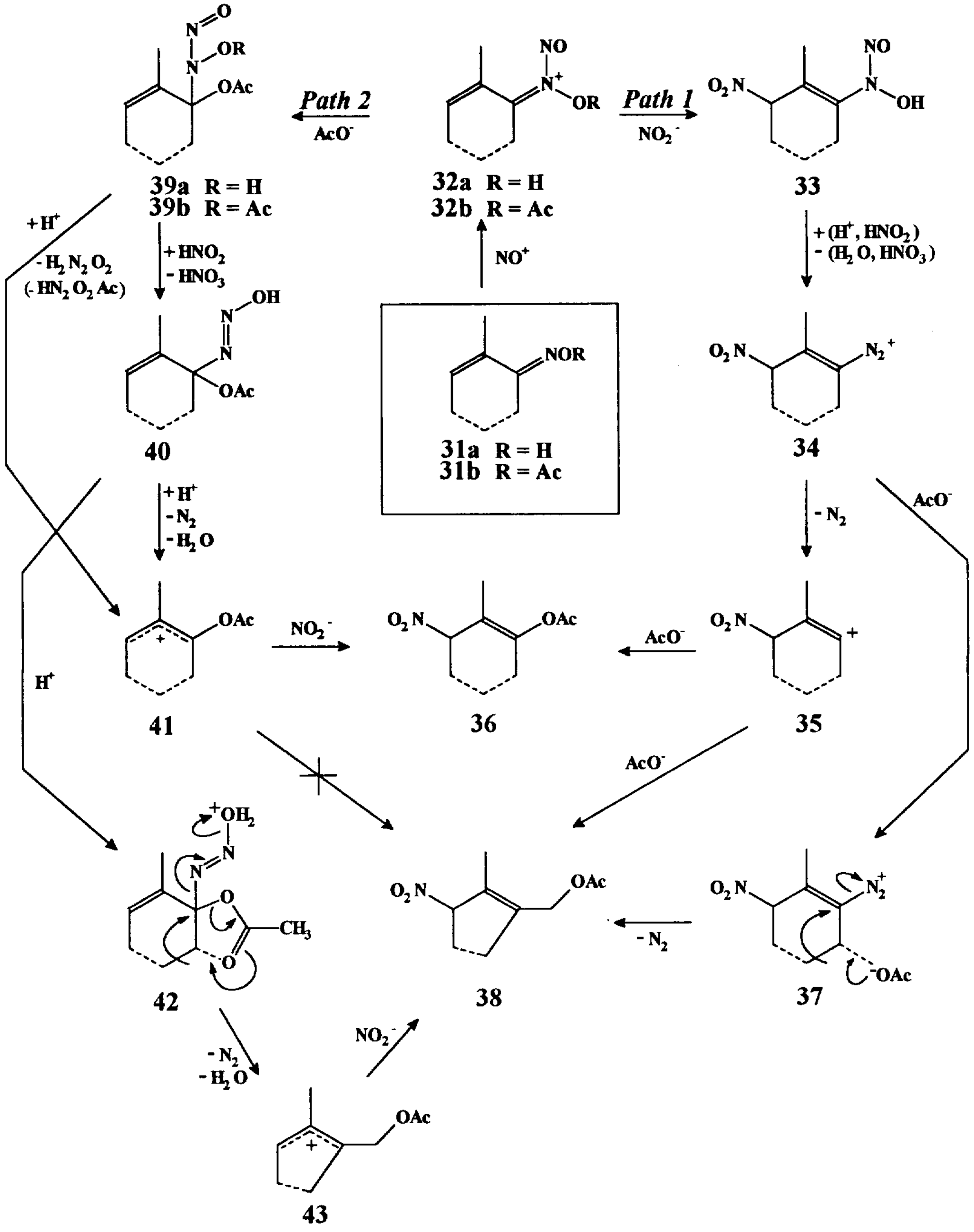
spectrum of the gases evolving in the course of the nitrosation showed main components of the mixture to be nitrogen and nitrogen oxide in the ratio 2:1, nitrous oxide escaped detection. Thus the overall equation may be written as:

$$\text{oxime} + 3NaNO_2 + 3CH_3COOH = \text{nitro acetate} + N_2\uparrow + NaNO_3 + 2CH_3COONa + H_2O$$

Nevertheless the emergence of molecular nitrogen among the reaction products may be caused not by direct elimination of N_2 from diazo compound of the **29**-type, but by the reduction of hyponitrous acid $H_2N_2O_2$, known to be easily reduced to N_2, when acted upon by the excess of nitrous acid[28].

Scheme 4 may be suggested to explain the formation of the reaction products. All versions of a mechanism involving O-acylated forms over oxime group are eliminated from the consideration, although O-acylated oxime derivatives are capable to arise in the course of the reaction. Comparison of the nitrosation reaction of car-2-en-4-one oxime (**10**) and its acetate **11** showed oxime **10** to react well faster, though O-acetylated compound **11** resulted in the same product **13** under the reaction conditions. Besides that, O-acetate-d_3 **12** is transformed to the unenriched product **13**, so any intramolecular transferring of acetyl group during the transformation of O-acetyl oxime derivatives is also out of consideration. The conversion of adduct **32** may follow two different pathways (*Scheme 4*). *Pathway 1.* Addition of NO_2-group leads to allylic nitro derivative **33**, the nitrous function being further reduced to give diazo compound **34**; the latter compound is deazotized either to give vinyl-type cation **35**[29] being transformed into acetate **36**, or is accompanied by rearrangement (**35**→**38** or **37**→**38**)[30]. *Pathway 2.* Addition of

Scheme 4.


39a R = H
39b R = Ac
N=O
N-OR
OAc
Path 2
AcO⁻
NO
N⁺
OR
32a R = H
32b R = Ac
Path 1
NO₂⁻
O₂N
NO
N
OH
33
+H⁺
-H₂N₂O₂
(-HN₂O₂Ac)
+HNO₂
-HNO₃
N
N
OH
OAc
40
NO⁺
NOR
31a R = H
31b R = Ac
+(H⁺, HNO₂)
-(H₂O, HNO₃)
O₂N
N₂⁺
34
+H⁺
-N₂
-H₂O
-N₂
AcO⁻
OAc
+
41
NO₂⁻
O₂N
OAc
36
AcO⁻
O₂N
+
35
H⁺
AcO⁻
⁺OH₂
N
N
O
CH₃
O
42
O₂N
OAc
38
-N₂
O₂N
N₂⁺
⁻OAc
37
-N₂
-H₂O
NO₂⁻
OAc
+
43

acetate group leads to adduct **39**, the nitrous function being further reduced to diazohydroxide group (compound **40**)[31]; the latter compound is decomposed either to give product **36** with the retention of the carbon skeleton, or to lead to the rearrangement of allylic cation **43**, being converted into anomalous product **38**.

Analysis of the reaction products stereochemistry gives no way of choosing between these two pathways. For the reaction of oximes **10** and **18**, where spatial arrangement is essential for addition of nitro group, nitro group is brought into the least hindered side, providing both **32**→**33** transformation and **41**→**36** and **43**→**38** transformations. But pathway 1 leaves unexplained differences in the ratio of isomeric nitro acetates **36** and **38**, resulting from various initial oximes. Diazo compound of the **34**-type and vinyl-type cation **35** in the case of the nitrosation of oxime **10**, are structurally similar to 3-carene (**9**), having a planar six-membered ring[32]. Such a geometry of the molecule is the most favorable to rearrangement (antiperiplanar alignment of migrating bond C_5-C_6 with respect to the leaving group (in **34**) or vacant orbital (in **35**)). Rearrangement product **13** is actually generated alone on nitrosation of oxime **9**. But on the nitrosation of all the rest oximes vinyl-type diazo compound **34** (or corresponding vinylic cation **35**) being the cyclohexene derivative should be shaped essentially alike in six-membered ring (half-chair). But as this takes place it is obscure why a mixture of "normal" **7** and "anomalous" **8** isomers results in the case of cyclohexene derivative, while only "normal" products **16** and **19** are formed in the case of *p*-menthane and muurolane derivatives correspondingly.

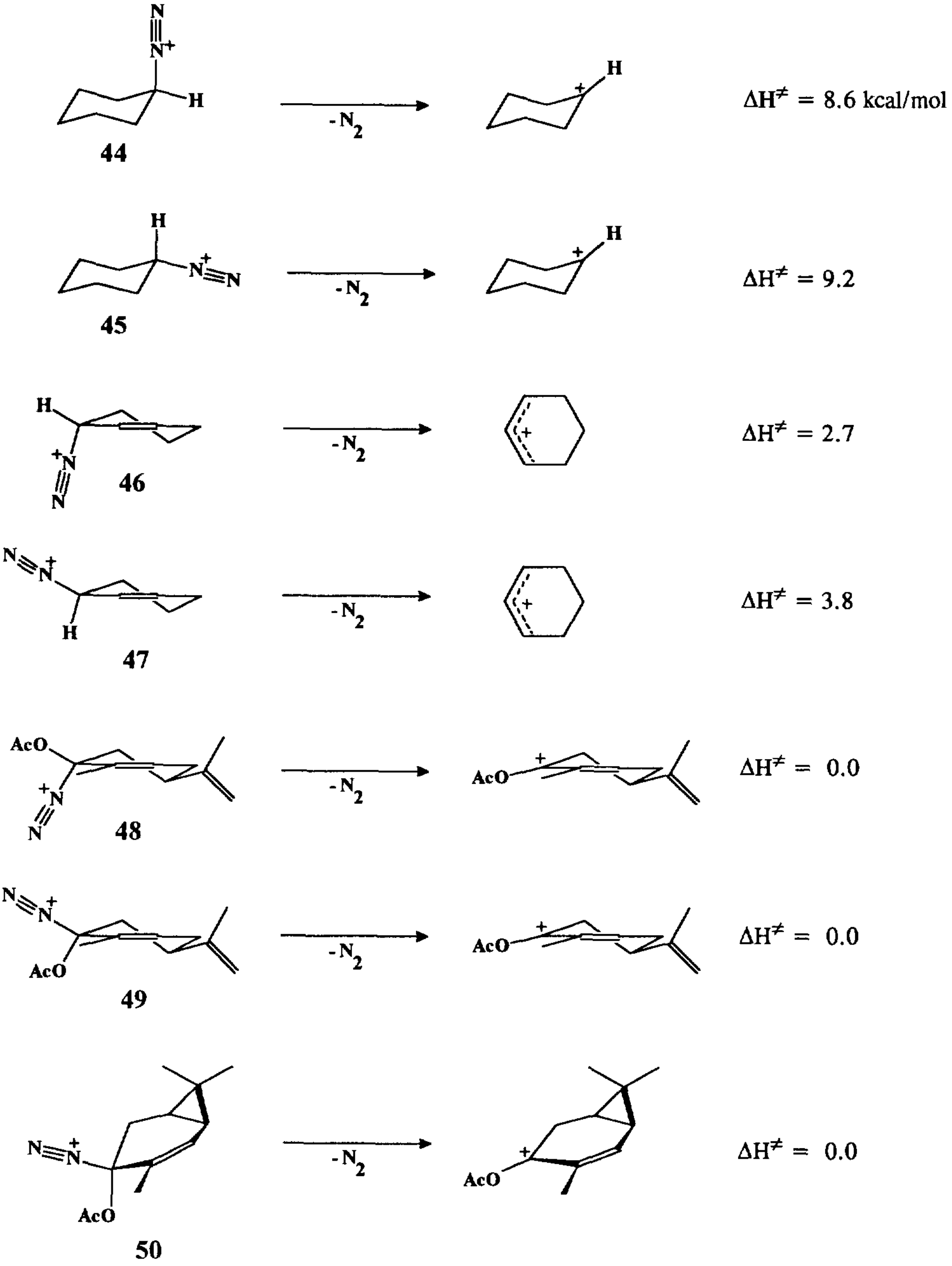
The reaction path 2 (see *Scheme 4*) seems to be more favoured. Transformation like **40**→**41** and **40**→**42** is in fact the reaction similar to the last stage of deamination of aliphatic amines[33]. The literature data on different aspects of the deamination reaction are extensive and diverse, but to the data there is no consensus on fine mechanism of deamination itself, that is the elimination of nitrogen-containing function from substrate molecule and the attendant structure modifications. However, being conformationally controlled reaction, the process of deamination is obvious to impose stringent requirements upon the neighboring group assistance[34]: the group migration takes place inevitable when the group occupies an antiperiplanar position relative to the cleaved C-N bond irrespectively of the group ability to migrate.

According to the quantum chemical calculations by the MNDO technique (*Scheme 5*), the adducts of type **29** in the reaction of the unsaturated oximes should exhibit unusual characteristics.

The calculations for the decomposition of cyclohexane-type diazo compounds **44** and **45** predict the availability of sensible activation barrier, being considerably lowered in the case of allylic diazo compounds **46** and **47**. At the same time, the decomposition of isomeric terpene diazo compounds **48-50** is to occur without any barriers. In other words, diazo compounds of **48-50** type should not be intermediates on calculation evidence, and may be considered as transition states, if at all. If this is the case, to evaluate the influence of conformational equations on the course of reaction and to decide between two competing processes (transformation through involvement of neighboring group in **42** (*Scheme 4*) and formation of allylic ion **41**) calculations should be performed not for the diazo compounds themselves but for their immediate precursors. Corresponding diazohydroxides of **30** type (*Scheme 3*) postulated to be short-lived intermediates in the reaction of amine diazotization[18] are the most likely ones. Calculated data for the conformational equilibriums in these diazohydroxides may be used to explain the results of the nitrosation reaction of the oximes, having regard to an extremely high-rate conversion of

Scheme 5.

Parameters of the Decomposition of Some Diazonium Ions According to the MNDO-Calculations.

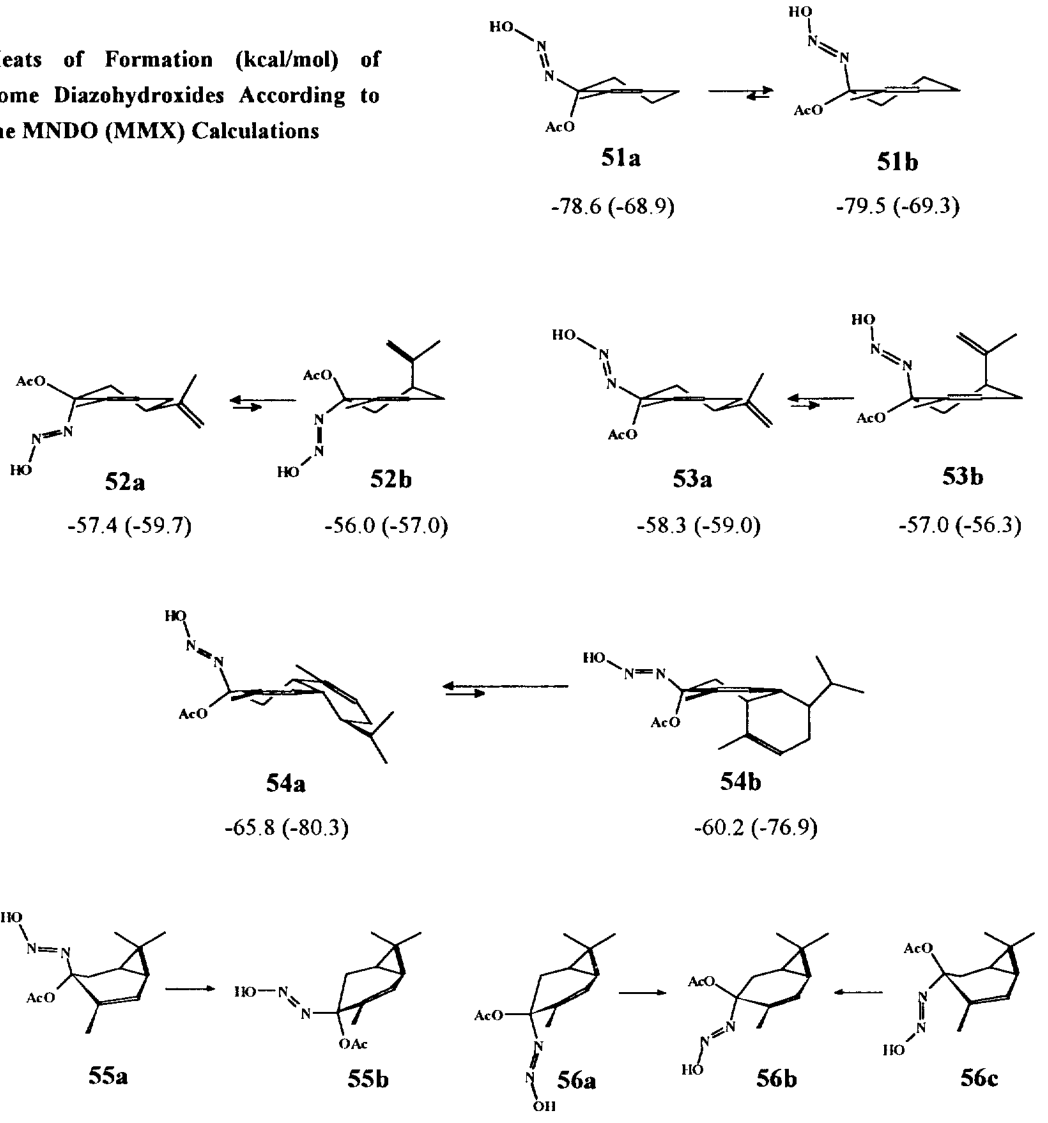


diazohydroxides in acidic medium[35,36,37]. More over, diazohydroxides may turn to be real intermediates, undergoing a breakdown without formation of diazonium ion[38], and it is this course of reaction that can explain a discrepancy between composition of the deamination products and conformational equilibrium in the initial compounds[39].

The calculated heats of formation of diazohydroxides derived from methylcyclohexene, limonene, 3-carene and muurolene-type unsaturated oximes are shown on *Scheme 6*.

Scheme 6.

Heats of Formation (kcal/mol) of Some Diazohydroxides According to the MNDO (MMX) Calculations



51a -78.6 (-68.9)

51b -79.5 (-69.3)

52a -57.4 (-59.7)

52b -56.0 (-57.0)

53a -58.3 (-59.0)

53b -57.0 (-56.3)

54a -65.8 (-80.3)

54b -60.2 (-76.9)

55a

55b

56a

56b

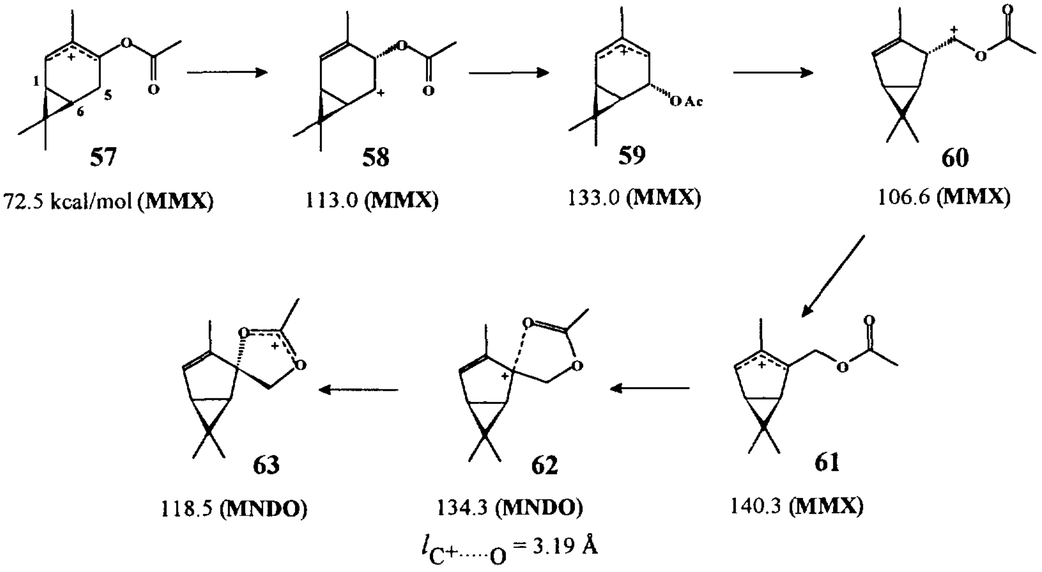
56c

Conformers **51a** and **51b** of the methylcyclohexene type diazohydroxides are comparable in energy, though conformer **51b** with pseudoequatorial acetate group is more stable (by 0.4 - 0.9 kcal/mol). Nitrous function in **51a** is situated unfavorably for rearrangement, hence the reaction products are dominated by "normal" product 7 (*Scheme 2*). Two stereoisomeric diazohydroxides **52** and **53** can result from the limonene derivative. If stereochemistry of acetate group addition is assumed to result in formation of only (or mainly) isomer **52** here[40], "normal" product **16** is readily appreciated to be the only product of oxime **14** transformation: conformer **52a** is by 1.4 - 2.7 kcal/mol more stable than **52b** conformer that is bound to give product of rearrangement. The muurolene derivative react similarly: if the acetate group attachment to the intermediate nitroso oxime is assumed to occur similar to the above case (attachment of **AcO$^-$** from the side of the neighboring pseudoaxial hydrogen), the reaction should lead to isomer **54**, whose conformation **54a** is more stable by 3.4 - 5.6 kcal/mol and nitrogen function arranged unfavorably for the rearrangement. In the case of 3-carene derivative **9** having acetate group *trans*-situated relative to the cyclopropane fragment, there is the only stable conformer **55b**, wherein nitrogen-bearing function is most favorable for the rearrangement. Conformer **56b**, having a nearly planar six-membered ring and nitrogen function arranged unfavorably for rearrangement, is also the only stable conformer for *cis*-isomer **56**. All the known reactions of addition to C-3 and C-4 atoms for 3-carene derivatives occur however on the least hindered α-side (the side opposite to cyclopropane fragment)[41]. Hence only formation of isomer **55**, wherein rearrangement should be easily take place, is expected on oxime **10** nitrosation, which is actually observed.

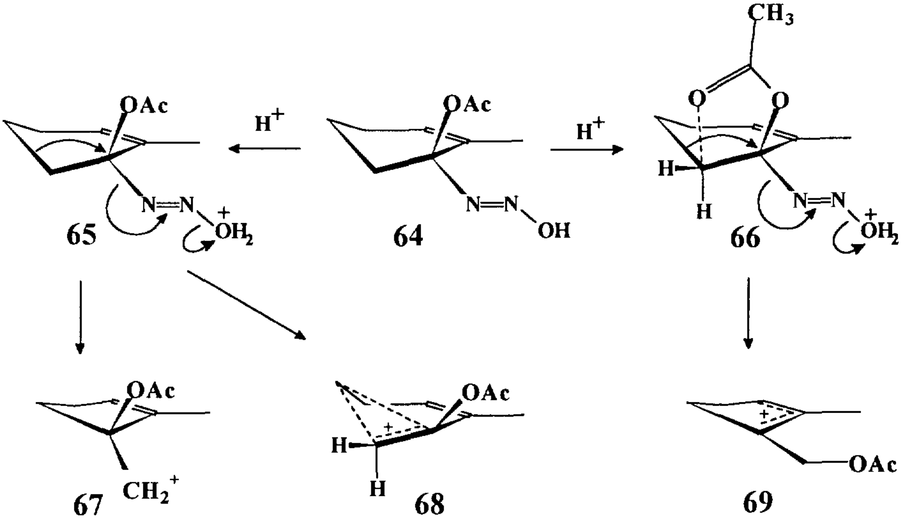
It should be noted that it is the anchimeric assistance[34] of the neighboring group in the decomposition of type **40** compound and not subsequent stages of the process (that is conversion of type **41** ion) that should be associated with the course of carbon skeleton rearrangement in the reaction under investigation. A hypothetical scheme of such allylic ion transformation by 1,2-shifts[42] into a rearrangement product is shown on *Scheme 7* for the case of oxime **10** nitrosation. Apart from the fact that ion **57** is a rather stable ion[43], six-membered cycle in the ion **57** molecule is estimated to be nearly planar, and dihedral angle between C5-C6 bond and C4 vacant orbital is about 90 degrees, being extremely unfavorable for the rearrangement[44]. Next according to the calculated heats of formation of the initial ion **57** and ions **58-61**, resulting from ion **57** through a number of sequential 1,2-shifts, ion **57** is an extremely stable one (evidently due to the participation of the acetate group) and is not likely to lead to the rearrangement of the carbon skeleton with the formation of far more strained ions, and even supplementary interaction with the acetate group in the terminal product (ions **62** and **63**) giving less gain of energy than required.

As for the rearrangement **64→69** itself (*Scheme 8*), this stage seems to be synchronous not only in regard to the simultaneous nitrogen elimination and migration of the neighboring **C-C** bond, but considering the attack of acetate group also simultaneous with the above stages as shown in **66**[45]. Otherwise (that is without simultaneous involvement of acetate group as shown for **65→67** transformations) an extremely unstable primary cation **67** would have to be involved. Although cationic species formed in the latter case may have a nonclassical structure **68**[34], the stabilization of this type for a primary ion is too weak to take this route into consideration.

Scheme 7.



Scheme 8.



EXPERIMENTAL

General experimental procedures

All the solvents used were reagent quality. Petroleum ether refers to that fraction which boils in the range 40-70°C. Diethyl ether was freshly distilled. Removal of all solvents was carried out under reduced pressure and all commercial reagents were used without additional purification. Preparative column chromatography was performed on SiO_2 ("KSK", Russia, 100-200 mesh, air dried and activated at 140°C for 5h). Purity of the reaction products was controlled by TLC together with ^1H and ^{13}C NMR data. Analytical TLC plates were **Silufol**® (Silpearl on aluminum foil, Czechoslovakia). IR spectra were obtained using a ***UR-20*** spectrometer. UV spectra were obtained for **EtOH** solutions using a ***Specord UV VIS*** spectrometer. Refractive indices were measured using a ***IRF-454B*** refractometer. A ***Polamat A*** polarimeter was used to measure optical rotation at 580 nm. Melting points were obtained using a ***Kofler*** melting point apparatus. Mass spectra were obtained on a ***Finnigan MAT 8200*** instrument using the Electron Impact Ionization technique (50-100°C, 70eV). For some of the new compounds, precise mass determination for the molecular ion of a pure sample were obtained instead of combustion analyses. Purity was determined from constancy of melting point together with GLC and NMR data. ^1H and ^{13}C NMR spectra were recorded at room temperature for 5-10% solutions using standard Bruker NMR Software System on a ***Bruker WP 200 SY*** or ***Bruker AC 200*** (^1H 200.13 MHz, ^{13}C 50.32 MHz) and a ***Bruker AM 400*** (^1H 400.13 MHz, ^{13}C 100.61 MHz) instruments locked to the deuterium resonance of the solvent. The chemical shifts were calculated relative to the solvent signal using as internal standard ($CDCl_3$): δ_H 7.24 ppm and δ_C 76.90 ppm. ^{14}N NMR spectra were recorded at room temperature on a ***Bruker AM 400*** (^{14}N 28.904 MHz) instrument; ^{14}N chemical shifts were measured relative to the resonance for a liquid formamide $HCONH_2$ (δ_N 267.8 ppm) using as external standard. Molecular mechanics calculations were carried out using MMX program[46]. MNDO calculations were performed using **MNDO-89** program[47].

General nitrosation procedure

Sodium nitrite powder was added portionwise during a certain period of time to a stirred solution of an oxime in glacial acetic acid at +5-10°C. After complete reaction (TLC), the mixture was diluted with water and extracted with diethyl ether. The combined ethereal extracts were washed with 0.5M aq. Na_2CO_3, brine and dried ($MgSO_4$). The solvent was evaporated to leave a yellow oil. The crude product was chromatographed on a silica gel column (Et_2O - light petroleum ether) to give pure substances.

2-Methyl-2-cyclohexen-1-one oxime (**6**) was prepared by nitrosochlorination-dehydrochlorination of *1-methylcyclohexene* (**5**) and had m.p. 63-64°C (CH_3CN, lit.[48]: 63-64°C).

(±)-2-Methyl-3-nitrocyclohexen-1-yl acetate (**7**) and *(±)-1-acetoxymethyl-2-methyl-3-nitrocyclopentene* (**8**). Methylcyclohexenone oxime **6** (1.00g, 7.99 mmol) in **AcOH** (20 ml) was treated with $\mathbf{NaNO_2}$ (1.66g, 24.0 mmol) according to the standard nitrosation procedure (2 h) affording 0.70g (3.51 mmol, 44%) of a mixture of the *title compounds* as a yellowish oil: found **C** 54.93, **H** 6.36, **N** 6.72; $\mathbf{C_9H_{13}NO_4}$ requires **C** 54.26, **H** 6.58, **N** 7.03; n_D^{23} 1.4807; IR (ν, cm^{-1}, film): 1755 and 1745 (**C=O**), 1695 (**C=C**), 1545 and 1362 ($\mathbf{NO_2}$), 1440, 1202 (**C-O-C**), 1132, 1110, 1075, 1000; UV ($\lambda_{max.}$, nm): 208 (ε 7700); MS (m/z): 153 (M^+-NO_2, 10%), 112 (8), 111 (100), 93 (20), 82 (7), 55 (5), 54 (5), 43 (49), 41 (7), 39 (7).

(+)-1S,6R-Car-2-en-4-one oxime (**10**) was prepared from (+)-3-carene (**9**) as described in ref.[49]: m.p. 93-94°C (**EtOAc**), 94-95°C (petroleum ether, lit.[49]: 97-98°C); $[\alpha]_{580}^{24}$ +265 (*c* 2.37, $\mathbf{CHCl_3}$, lit.[49]: $[\alpha]_D^{25}$ +374 (**EtOH**)).

(+)-1S,6R-Car-2-en-4-one oxime acetate (**11**). Acetic anhydride (1 ml, 10.60 mmol) was added dropwise to a stirred solution of carenone oxime **10** (1.02g, 6.17 mmol) and $\mathbf{NEt_3}$ (2.3 ml, 16.5 mmol) in $\mathbf{Et_2O}$ (20 ml). The reaction mixture was stirred at r.t. for 4 h and poured into water (20 ml). The organic layer was separated and the aqueous phase was extracted with $\mathbf{Et_2O}$ (2 × 10 ml). The combined organic extracts were washed with aq. **HCl** (1M, 10 ml), $\mathbf{Na_2CO_3}$ (0.5M, 15 ml), brine and dried with $\mathbf{MgSO_4}$. The solvent was distilled off to give 1.20 g (5.80 mmol, 94%) of the *title compound* as a colourless oil: found **C** 70.82, **H** 8.42, **N** 6.81; $\mathbf{C_{12}H_{17}NO_2}$ requires **C** 69.54, **H** 8.27, **N** 6.76; n_D^{22} 1.5194; $[\alpha]_{580}^{25}$ +166 (*c* 3.84, $\mathbf{CHCl_3}$); IR (ν, cm^{-1}, film): 3012 (**H-C=C**), 1776 (**C=O**), 1645 (**C=C**), 1580 (**C=N**), 1370, 1274, 1201 (**C-O-C**), 1012, 945 (**N-O**), 900; UV ($\lambda_{max.}$, nm): 205 (ε 5900), 273 (ε 12000); MS (m/z): 207 (M^+, 0.6%), 149 (21), 148 (12), 147 (42), 134 (75), 133 (10), 132 (47), 123 (11), 119 (13), 117 (10), 106 (18), 91 (10), 77 (11), 60 (59), 58 (27), 45 (68), 43 (100), 42 (13), 41 (11).

(+)-1S,6R-Car-2-en-4-one oxime acetate-d_3 (**12**). Carenone oxime **10** (1.54g, 9.32 mmol) was treated with **AcCl**-d_3 (0.73 ml, 10.3 mmol) and $\mathbf{NEt_3}$ (5 ml, 35.9 mmol) in $\mathbf{Et_2O}$ (25 ml) at -10°C for 1 h to give the *title compound* (1.84g, 8.76 mmol, 88%) as colourless oil: n_D^{27} 1.5104; MS (m/z): 210 (M^+, 0.2%), 149 (10), 147 (19), 146 (10), 134 (33), 132 (32), 106 (12), 103 (10), 73 (16), 63 (13), 62 (12), 59 (100), 58 (27), 46 (42), 45 (79), 44 (17), 43 (20), 41 (12).

(-)-1R,4S,5R-2-Acetoxymethyl-4-nitro-3,6,6-trimethylbicyclo[3.1.0]hex-2-ene (**13**). Carenone oxime **10** (5.06g, 30.6 mmol) was treated with $\mathbf{NaNO_2}$ (6.34g, 91.9 mmol) in **AcOH** (30 ml) according to the standard nitrosation procedure (4 h). The chromatography yielded 3.28g (13.7 mmol, 45%) of the *title compound* as a yellowish oil: found **C** 61.31, **H** 7.26, **N** 5.91; $\mathbf{C_{12}H_{17}NO_4}$ requires **C** 60.24, **H** 7.16, **N** 5.85; n_D^{25} 1.4933; $[\alpha]_{580}^{24}$ -210 (*c* 2.17, $\mathbf{CHCl_3}$); IR (ν, cm^{-1}, film): 1751 (**C=O**), 1644 (**C=C**), 1554 and 1386 ($\mathbf{NO_2}$), 1445, 1239 (**C-O-C**), 1036, 771; UV ($\lambda_{max.}$, nm): 210 (ε 9300); MS

(m/z): 166 (9%), 151 (7), 149 (8), 148 (9), 134 (13), 133 (100), 121 (16), 105 (24), 93 (10), 91 (23), 79 (9), 77 (10), 43 (67), 41 (13).

A mixture of the gases evolved was analyzed by mass-spectrometry (the range of masses measured was m/z = 4-70; intensities less than 0.3% were not registered): m/z = 18 (**H_2O**, rel.int. 7%), m/z = 28 (**N_2**, 100%), m/z = 29 (1%), m/z = 30 (**NO**, 62%), m/z = 32 (**O_2**, 0.5%), m/z = 40 (0.3%), m/z = 44 (**CO_2**, 1%).

Carenone oxime acetate **11** (0.60g, 2.89 mmol) in **AcOH** (15 ml) was treated with **$NaNO_2$** (4.00g, 58.0 mmol) according to the standard nitrosation procedure (4 h). The chromatography yielded 0.18g of the starting material and 0.16g (0.67 mmol, 33%) of the *title compound*.

Carenone oxime acetate-d_3 **12** (0.30g, 1.39 mmol) in **AcOH** (25 ml) was treated with **$NaNO_2$** (7.30g, 109 mmol) according to the standard procedure (12 h). The chromatography yielded 0.16g (0.67 mmol, 48%) of the *title compound*.

(+)-4S-p-Mentha-1(6),8-dien-2-one oxime {carvone oxime} (**15**) was prepared from (+)-carvone (**14**) ($[\alpha]_{580}^{23}$ +59.8 (*c* 5.15, **$CHCl_3$**)) and had m.p. 71-72°C (aq.**EtOH**, lit.[50]: 72°C) and $[\alpha]_{580}^{22}$ +50.5 (*c* 4.63, **$CHCl_3$**), lit.[50]: $[\alpha]_D^{20}$ +39.2 (**EtOH**).

(-)-4S,6S-6-Nitro-p-mentha-1,8-dien-2-yl acetate (**16**). Carvone oxime **15** (3.00g, 18.2 mmol) in **AcOH** (30 ml) was treated with **$NaNO_2$** (3.78g, 54.8 mmol) according to standard nitrosation procedure (2 h). The chromatography yielded 1.50g (19.2 mmol, 35%) of the *title compound* as a yellowish oil: found **C** 61.19, **H** 7.09, **N** 6.23; **$C_{12}H_{17}NO_4$** requires **C** 60.24, **H** 7.16, **N** 5.85. n_D^{25} 1.4940; $[\alpha]_{580}^{25}$ -133.9° (*c* 9.20, **$CHCl_3$**); IR (ν, cm^{-1}, film): 3080 (**H-C=**), 1763 (**C=O**), 1700 (**C=C**), 1647 (**C=C**), 1550 and 1368 (**NO_2**), 1443, 1205 (**C-O-C**), 1148, 1120, 1067, 895 (**H-C=**); UV ($\lambda_{max.}$, nm): 209 (ε 8000); MS (m/z): 193 (14), 152 (11), 151 (100), 123 (22), 109 (76), 107 (10), 95 (12), 91 (9), 82 (15), 54 (10), 53 (9), 43 (60), 41(14).

(-)-1S,6S,7S-Muurolan-4,9-dien-3-one (**17**) was prepared from (-)-muurolene with $[\alpha]_{580}^{21}$ -55.2 as described in ref.[51]: m.p. 46-49°C (hexane); $[\alpha]_{580}^{22}$ -71.8 (*c* 2.09, **$CHCl_3$**, lit.[51]: $[\alpha]_D$ -42.9).

(-)-1S,6S,7S-Muurolan-4,9-dien-3-one oxime (**18**). Treatment of muurolenone **17** (2.70g, 12.4 mmol) with **$NH_2OH\times HCl$** (1.96g, 28.1 mmol) and **Na_2CO_3** (3.00g, 28.3 mmol) in boiling methanol (30 ml) for 6 h followed by chromatography of the crude product gave the *title compound* 2.05 g (8.79 mmol, 71%) as a yellowish glass: $[\alpha]_{580}^{22}$ -126 (*c* 2.38, **$CHCl_3$**); IR (ν, cm^{-1}, 1% in **$CHCl_3$**): 3585 (**H-O**), 3048 (**H-C=**), 1722, 1668, 1644 (**C=C, C=N**), 956 (**N-O**); UV ($\lambda_{max.}$, nm): 203 (ε 6400), 238 (ε 18800); MS (m/z): 233.1772 {**$C_{15}H_{23}NO$** requires 233.1780} (M^+, 50%), 216 (15), 190 (38), 172 (11), 158 (10), 157 (15), 147 (21), 146 (19), 145 (12), 137 (77), 135 (14), 132 (31), 123 (24), 119 (16), 106 (19), 105 (100), 99 (18), 93 (51), 91 (26), 79 (14), 77 (19), 69 (12), 55 (21), 53 (12), 43 (37), 41 (34).

(+)-1S,5R,6S,7S-5-Nitromuurolan-3,9-dien-3-yl acetate (**19**). Muurolenone oxime **18** (1.00g, 4.29 mmol) was treated with **$NaNO_2$** (1.70g, 24.6 mmol) in **AcOH** (20 ml) according to the standard nitrosation procedure (3 h). The chromatography yielded 0.60g (1.95 mmol, 45%) of the *title compound* as a yellow viscous oil: $[\alpha]^{21}_{580}$ +130 (*c* 3.32, **$CHCl_3$**); IR (ν, cm^{-1}, film): 3043 (**H-C=**), 1758 (**C=O**), 1708 and 1676 (**C=C**), 1551 and 1372 (**NO_2**), 1440, 1210 (**C-O-C**), 1159, 1130; UV ($\lambda_{max.}$, nm): 204 (ε 13700); MS (m/z): 261.1858 {**$C_{17}H_{25}O_2$** requires 261.1855} (**M^+-NO_2**, 12%), 220 (17), 219 (100), 159 (11), 147 (11), 135 (33), 123 (18), 121 (10), 119 (10), 109 (13), 105 (14), 93 (46), 91 (12), 85 (19), 83 (17), 69 (16), 55 (10), 43 (47), 41 (15).

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