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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 2methyl-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 ¹H, ¹³C and ¹⁴N 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.



In this case the capacity of the starting oxime 1 (and/or intermediate N-nitroso derivatives 2) to exist in scis-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



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-2cyclohexenone 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 Rf 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. ¹H, ¹³C and ¹⁴N 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 ${}^{1}J_{C-C}$ 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 ppm⁶. The attachment of acetate group to the CH₂-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 ${}^{3}J_{C-O-CH_2}$. For a closely corresponding bicyclo[3.1.0] hexene derivative the coupling constant ${}^{3}J_{H-H}$ comprises 7.5 Hz, H-1 and H-2 being in *cis*-configuration, and 1.5 Hz, the protons being in *trans*configuration⁷. The availability of the coupling constants $J_{H^1-H^2}=2.6$ 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 (δ_{MeCOOR} 167.4 ppm⁸, $v_{C=0}$ 1762 cm⁻¹ and $v_{C=C}$ 1700 cm⁻¹ ⁹). The shape of H-5 signal in NMR ¹H 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 = NOCI $iv = Ac_2O/Et_3N/Et_2O$ $ii = NEt_3$ $v = CD_3COCI/Et_3N/Et_2O$ $iii = NaNO_2 /ACOH$ $vi = NH_2OH \times HCI/MeOH/Na_2CO_3$

	6 ^c		7 <i>d</i>		8 d	
i	δC ⁱ	δ H ^{<i>i</i>} (<i>J</i> , Hz)	δC ⁱ	δ H ^{<i>i</i>} (<i>J</i> , Hz)	δC ⁱ	δ H ^{<i>i</i>} (<i>J</i> , 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
СН <u>3СО</u> <u>СН</u> 3СО О <u>Н</u>		9.2 br.s	167.29 19.85	2.08 s	169.83 19.92	- 1.97 s

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

^a Bruker AC 200; ^b chemical shifts are given in ppm; ^c in CDCl₃-CCl₄ (1:1 v/v); ^d in CDCl₃-C₆D₆ (1:1 v/v).

	11 ^C	12 ^d		13 ^{d,e}		
i	δ C ⁱ	δC ⁱ	δ Η ⁱ (J, Hz)	$\delta \mathbf{C}^{i} (J_{\mathbf{C}^{i} \cdot \mathbf{C}^{j}})$	δ Ηⁱ (<i>J</i> , 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 <i>dd</i> (20.0, 8.0) Hb: 2.88 <i>d</i> . (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	
Сн <u>3СО</u> <u>СН</u> 3СО	167.75 18.95	168.91 - <i>8</i>	2.08 <i>br.s</i> (resid.)	170.37 (59.2) <i>f</i> 20.54 (59.2)	1.99 s	

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

^{*a*} Bruker AC 200; ^{*b*} chemical shifts are given in ppm; ^{*c*} in CDCl₃-CCl₄ (1:1 v/v); ^{*d*} in CDCl₃; ¹⁴N 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 ; $f^2 J_{C-H} = 6.5$ Hz, ³ $J_{C-H} = 3.5$ Hz; ^{*g*} chemical shift for CD₃-group has not been measured because of the low intensity of the signal.

	15 ^b	16 ^c				
i	8C ⁱ	δC ⁱ	δ Ηⁱ (<i>J</i> , Hz)	$J_{\mathbf{H}^{i}-\mathbf{H}^{j}}$, Hz (\mathbf{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. 7 9 ^e	αH: 2.39 ddd (14.4, 2.7, 2.0) βH: 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 <i>dtddqd</i> (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)	αΗ: -17.3 (Η6β), 5.3 (Η5), -0.7 (Η3), 1.0 (Η4α) βΗ: -17.3 (Η6α), 11.0 (Η5), -1.4 (Η3)		
7	147.41	145.67	-			
8	110.05	110.17	Ha: 4.72 ddq (1.2, 1.2, 0.8) Hb: 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)			
Сн <u>3СО</u>	-	167.39	-			
<u>СН</u> 3СО	-	19.89	2.16 s			

Table 3. NMR Data for Compounds 15 and 16^a.

^{*a*} chemical shifts are given in ppm; ^{*b*} Bruker AC 200; in CDCl₃-CCl₄ (1:1 v/v); ^{*c*} Bruker AM 400; in CDCl₃; ¹⁴N NMR: δ +11 ppm; ^{*d*} the coupling constants (±0.3 Hz) were calculated using PANIC program, for C₆D₆ solution (Bruker AM 400), $\Delta\delta H^{\delta}_{\alpha,\beta} = 10$ 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 (${}^{2}J_{C-H}$ -type, 3.5 Hz) and C-7



atom $({}^{3}J_{C-H}$ -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 ¹³C 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

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 ${}^{3}J_{\rm H6-H7} = 11.2$ 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.

	17 ^b		18 ^{b,c}		19 ^c
i	δ C ⁱ	δC ⁱ	δ Ηⁱ (<i>J</i> , Hz)	δC ⁱ	δ Ηⁱ (<i>J</i> , Hz)
1	39.57	37.10		34.67	[2.40]
2	39.69	24.52	3.23 <i>dd</i> (16.4, 3.8) 2.11 <i>d</i> (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
О <u>Н</u> СН <u>3СО</u> <u>СН</u> 3СО			10.1 br.s	167.89 20.47	- 1.90 s

Table 4. ¹H and ¹³C NMR Data for Compounds 17-19^a.

^{*a*} chemical shifts are given in ppm; ^{*b*} Bruker AC 200; in CDCl₃; ^{*c*} LRJMD-technique¹⁴ was used for the signal assignment; ^{*d*} Bruker AM 400; in CDCl₃-C₆D₆ (δ C_{benzene-d6} = 128.00 ppm, δ H_{benzene-d6} = 7.24 ppm); ^{*e*} chemical shifts put in square brackets were taken from the 2D heteronuclear ¹³C-¹H chemical shift correlation spectra (¹J_{CH} = 125 Hz); ^{fn}J_H5_{-Cⁱ}, ±0.1 Hz (Cⁱ): 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 spectrum¹⁵.

	experimental	calculated ^a		
Vicinal coupling constant	19	19	21	
H1-H6	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	
С ⁷ -Н ⁵	2.7	3.2	0.7	
		ļ		

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

^{*a*} The coupling constants were calculated by known procedure¹⁶ using well-known Karplus equation: ${}^{3}J_{H-H} = 7 - \cos\phi + 5\cos 2\phi$ (with the correction on the electronegativity of the substituent: $J = 0.9J_{0}$ for NO₂-group) for the proton-proton coupling and the Karplus-type equation¹⁷: ${}^{3}J_{C-H} = 4.26 - \cos\phi + 3.56\cos 2\phi$ 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}, HNO₂, H₂NO₂⁺, N₂O₃²⁰ 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 23²¹. 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 nucleophile²⁴, the above adduct can lead to cation 27 by ejection of N₂O molecule^{25,26}. On this mode of reaction one equivalent of sodium nitrite is utilized (as NO₂⁻) - 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 N₂O molecule²⁷. 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:

oxime + $3N_aNO_2$ + $3CH_3COOH$ = nitro acetate + N_2 + N_aNO_3 + $2CH_3COON_a$ + H_2O

Nevertheless the emergence of molecular nitrogen among the reaction products may be caused not by direct elimination of N₂ from diazo compound of the 29-type, but by the reduction of hyponitrous acid $H_2N_2O_2$, known to be easily reduced to N₂, when acted upon by the excess of nitrous acid²⁸.

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 NO₂-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 $(35\rightarrow38 \text{ or } 37\rightarrow38)^{30}$. Pathway 2. Addition of

Scheme 4.



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 $32\rightarrow33$ transformation and $41\rightarrow36$ and $43\rightarrow38$ 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 ring³². Such a geometry of the molecule is the most favorable to rearrangement (antiperiplanar alignment of migrating bond C₃-C₆ 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 derivatives correspondingly.

The reaction path 2 (see Scheme 4) seems to be more favoured. Transformation like $40\rightarrow41$ and $40\rightarrow42$ is in fact the reaction similar to the last stage of deamination of aliphatic amines³³. 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 assistance³⁴: 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 diazotization¹⁸ 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 ion³⁸, and it is this course of reaction that can explain a discrepancy between composition of the deamination products and conformational equilibrium in the initial compounds³⁹.

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.



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 here⁴⁰, "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 3carene 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 assistance³⁴ 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-shifts⁴² 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 ion⁴³, 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 rearrangement⁴⁴. 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 $64\rightarrow 69$ 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 $65\rightarrow 67$ 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 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 SiO₂ ("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 ¹³C 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 ¹³C 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, 13C 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 (CDCl₃): δ_H 7.24 ppm and δ c 76.90 ppm. ¹⁴N NMR spectra were recorded at room temperature on a Bruker AM 400 (¹⁴N 28.904 MHz) instrument; ¹⁴N chemical shifts were measured relative to the resonance for a liquid formamide HCONH₂ (δ_N 267.8 ppm) using as external standard. Molecular mechanics calculations were carried out using MMX program⁴⁶. MNDO calculations were performed using MNDO-89 program⁴⁷.

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 (MgSO₄). The solvent was evaporated to leave a yellow oil. The crude product was chromatographed on a silica gel column (Et₂O - 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 (CH₃CN, 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 NaNO₂ (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; C9H₁₃NO₄ requires C 54.26, H 6.58, N 7.03; n_D^{23} 1.4807; IR (v, cm⁻¹, film): 1755 and 1745 (C=O), 1695 (C=C), 1545 and 1362 (NO₂), 1440, 1202 (C-O-C), 1132, 1110, 1075, 1000; UV (λ_{max} , nm): 208 (ϵ 7700); MS (m/z): 153 (M⁺-NO₂, 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, CHCl₃, 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 NEt₃ (2.3 ml, 16.5 mmol) in Et₂O (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 Et₂O (2 × 10 ml). The combined organic extracts were washed with aq. HCl (1M, 10 ml), Na₂CO₃ (0.5M, 15 ml), brine and dried with MgSO₄. 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; C₁₂H₁₇NO₂ requires C 69.54, H 8.27, N 6.76; n_D^{22} 1.5194; $[\alpha]_{580}^{25}$ +166 (c 3.84, CHCl₃); IR (v, 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 (λ_{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-d₃ (12). Carenone oxime 10 (1.54g, 9.32 mmol) was treated with AcCl-d₃ (0.73 ml, 10.3 mmol) and NEt₃ (5 ml, 35.9 mmol) in Et₂O (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 NaNO₂ (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; C₁₂H₁₇NO₄ requires C 60.24, H 7.16, N 5.85; n_D^{25} 1.4933; $[\alpha]_{580}^{24}$ -210 (c 2.17, CHCl₃); IR (v, cm⁻¹, film): 1751 (C=O), 1644 (C=C), 1554 and 1386 (NO₂), 1445, 1239 (C-O-C), 1036, 771; UV (λ_{max} , nm): 210 (ϵ 9300); MS 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 (H₂O, rel.int. 7%), m/z = 28 (N₂, 100%), m/z = 29 (1%), m/z = 30 (NO, 62%), m/z = 32 (O₂, 0.5%), m/z = 40 (0.3%), m/z = 44 (CO₂, 1%).

Carenone oxime acetate 11 (0.60g, 2.89 mmol) in AcOH (15 ml) was treated with NaNO₂ (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 NaNO₂ (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, CHCl₃)) and had m.p. 71-72°C (aq.EtOH, lit.⁵⁰: 72°C) and $[\alpha]_{580}^{22}$ +50.5 (c 4.63, CHCl₃), 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 NaNO₂ (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; C₁₂H₁₇NO₄ requires C 60.24, H 7.16, N 5.85. n_D^{25} 1.4940; [α_{1580}^{25} -133.9° (c 9.20, CHCl₃); IR (v, cm⁻¹, film): 3080 (H-C=), 1763 (C=O), 1700 (C=C), 1647 (C=C), 1550 and 1368 (NO₂), 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, CHCl₃, lit.⁵¹: $[\alpha]_D$ -42.9).

(-)-15,65,75-Muurolan-4,9-dien-3-one oxime (18). Treatment of muurolenone 17 (2.70g, 12.4 mmol) with NH₂OH×HCl (1.96g, 28.1 mmol) and Na₂CO₃ (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, CHCl₃); IR (v, cm⁻¹, 1% in CHCl₃): 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 {C₁₅H₂₃NO 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 NaNO₂ (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: $[\alpha]_{580}^{21}$ +130 (c 3.32, CHCl₃); IR (v, cm⁻¹, film): 3043 (H-C=), 1758 (C=O), 1708 and 1676 (C=C), 1551 and 1372 (NO₂), 1440, 1210 (C-O-C), 1159, 1130; UV ($\lambda_{max.}$, nm): 204 (ϵ 13700); MS (m/z): 261.1858 {C₁₇H₂₅O₂ requires 261.1855} (M⁺-NO₂, 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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