Chemistry of Natural Compounds, Vol. 50, No. 2, May, 2014 [Russian original No. 2, March–April, 2014]

(*R*)-*n*-MENTH-4-EN-3-ONE AND ITS DERIVATIVES IN REACTIONS WITH *N*-CONTAINING REAGENTS

G. Yu. Ishmuratov,[1,2*] V. S. Tukhvatshin,[2] M. P. Yakovleva,[1] R. R. Muslukhov,[1] A. V. Allagulova,[2] and G. R. Talipova[2]

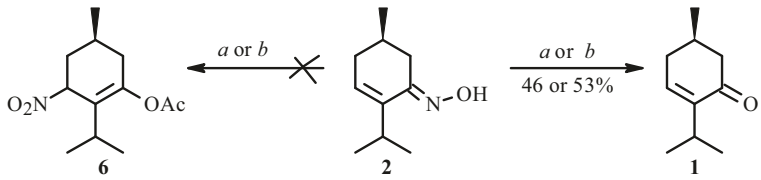
The reactions of (R)-n-*menth-4-en-3-one and its derivatives with* N-*containing reagents were studied. New menthane-type acetamides were synthesized.*

Keywords: (*R*)-*n*-menth-4-en-3-one and its derivatives, nitrosation, Ritter reaction, menthane-type acetamides.

We determined earlier that (*R*)-*n*-menth-4-en-3-one (**1**) was less reactive than ordinary cyclic α,β-unsaturated ketones in conjugated addition of organometallic reagents, Michael addition, and pyrazoline-formation reactions [1].

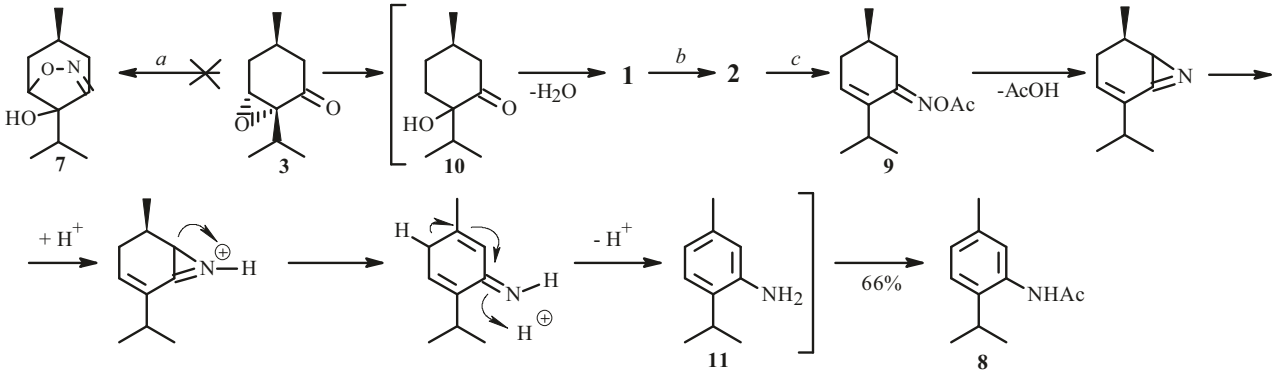
In continuation of studies on the elaboration of the synthetic potential of **1**, we studied the behavior of its anti-oxime (**2**) [2], epoxide (**3**) [3], (1*R*,3*R*)-*n*-menthen-3-ol (**4**) [4], and acetate (**5**) [5] in reactions with *N*-containing reagents. The transformations studied herein also had practical application because it is known [6] that *N*-containing derivatives of monoterpenoids exhibit various types of biological activity.

It was found that nitrosation of **2** by $NaNO_2$–AcOH in MeOH or $CHCl_3$ did not give the expected unsaturated nitroacetate (**6**) [6], like (–)-carvone oxime [7]. Regeneration of starting **1** was observed.



a. $NaNO_2$, AcOH, $CHCl_3$, 20°C; *b*. $NaNO_2$, AcOH, MeOH, 20°C

The reaction of **3** with $NH_2OH{\cdot}HCl$ in the presence of NaOAc formed an aromatic acetamide (**8**) and not the proposed 1,2-dioxopyrazole derivative (**7**), like (*S*)-pulegone [8]. Evidently, this was due to the steric influence of the *i*-Pr group and the lower reactivity of the endocyclic double bond in **1**. Compound **8** was probably formed by the following scheme. Ketoalcohol **10** was dehydrated through sequential steps to enone **1**, reaction of which with $NH_2OH{\cdot}HCl$ gave oxime **2** and then its *O*-acyl derivative **9**. The last underwent Semmler–Wolf conversion to amine **11** with further acylation to the desired acetamide **8** [2].



a. $NH_2OH{\cdot}HCl$, AcONa, H_2O, Δ; *b*. $NH_2OH{\cdot}HCl$; *c*. AcONa

1) Institute of Organic Chemistry, Ufa Scientific Center, Russian Academy of Sciences, 450054, Ufa, Prosp. Oktyabrya, 71, e-mail: insect@anrb.ru; 2) Bashkir State University, 450074, Ufa, Ul. Z. Validi, 32, e-mail: vadimtukhvatshin@yandex.ru.
Translated from *Khimiya Prirodnykh Soedinenii*, No. 2, March–April, 2014, pp. 241–243. Original article submitted October 9, 2013.

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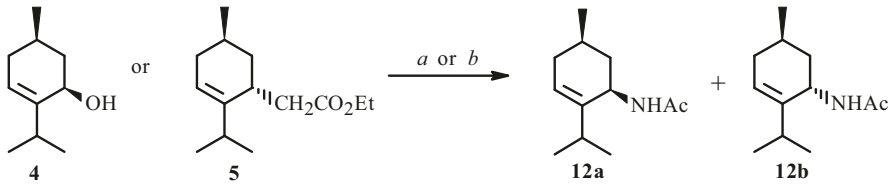
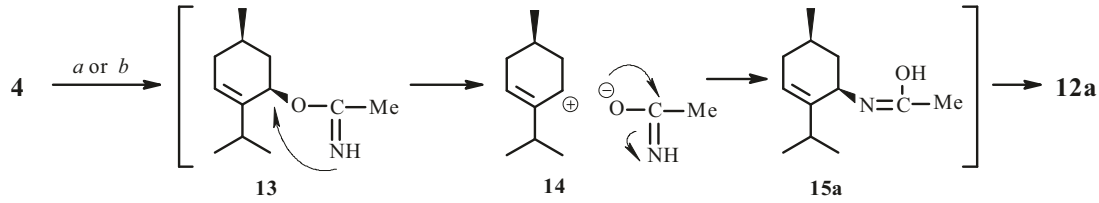
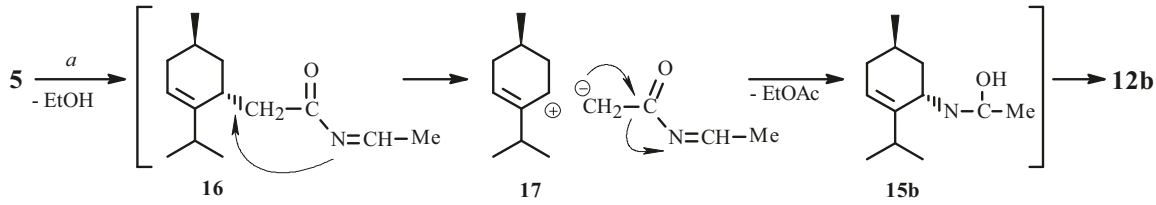


a. MeCN, H_2SO_4, 20°C; *b*. MeCN, $BF_3 \cdot OEt_2$, 80°C

The Ritter reaction involving terpene derivatives is a convenient and common synthetic method for potentially biologically and pharmacologically active acetamides [9]. Therefore, the behavior of (1*R*,3*R*)-*n*-menthen-3-ol (**4**) and acetate **5** in this reaction was studied. Capillary GC and PMR showed that alcohol **4** formed mixtures of acetamides **12a** and **b** in ratios of 55:45 and 69:31 if H_2SO_4 and $BF_3 \cdot Et_2O$, respectively, were used as catalysts. However, **5** with H_2SO_4 catalyst was transformed into a 57:43 mixture of these same stereoisomers with **12b** dominating. Apparently, this was due to simultaneous occurrence of S_N1 and S_Ni substitution mechanisms.



a. MeCN, H_2SO_4, 20°C; *b*. MeCN, $BF_3 \cdot OEt_2$, 80°C



a. MeCN, H_2SO_4, 20°C

Thus, a mixture of equal amounts of acetamides **12a** and **b** formed according to the S_N1 mechanism. The enrichment of the mixture with the **12a** stereomer for **4** or **12b**, for acetate **5**, was obviously due to occurrence of the S_Ni mechanism [10, 11], according to which adduct **13** formed initially from alcohol **4** and then dissociated to form contact ion pair **14**, which decomposed through unstable **15a** into the **12a** isomer.

Acetamide **12b** was formed analogously via an S_Ni mechanism from acetate **5**. The ethoxy group in **5** was replaced by –N=CHMe in product **16**, which converted to contact ion pair **17** and eliminated ethylacetate to form **15b**.

Thus, a Ritter reaction involving (1*R*,3*R*)-*n*-menthen-3-ol (**4**) or its Claisen orthoester rearrangement product **5** under H_2SO_4 or $BF_3 \cdot Et_2O$ catalysis occurred simultaneously according to S_N1 and S_Ni mechanisms to form an enriched mixture of acetamides **12a** and **b**. The S_Ni substitution mechanism dominated to produce diastereomeric acetamides (**12a** and **b**) if a Lewis acid ($BF_3 \cdot Et_2O$) was used as the catalyst rather than a protic acid (H_2SO_4).

EXPERIMENTAL

IR spectra were recorded from thin layers on a Prestige-21 instrument (Shimadzu). NMR spectra were obtained in $CDCl_3$ with TMS internal standard on a Bruker Avance III 500 spectrometer (operating frequency 500.13 MHz for PMR and 125.20 MHz for ^{13}C NMR). PMR and ^{13}C NMR spectra were analyzed and resonances were assigned by two-dimensional correlation spectroscopy COSY (H–H), HSQC, and HMBC. Chromatographic analysis was performed on Chrom-5 [column length 1.2 m, stationary phase silicone SE-30 (5%) + OV-225 (3%) on Chromaton N-AW-DMCS (0.16–0.20 mm), operating temperature 50–300°C] and GC-9A [Shimadzu, quartz capillary column length 25 m, stationary phase OV-101, operating temperature 80–280°C] instruments with He carrier gas. Optical rotation was measured on a PerkinElmer 241-MC polarimeter. Column chromatography was carried out over silica gel L (60–200 μm, Sorbfil, Russia). TLC used Sorbfil plates (Russia). Mass spectra were taken on a 2010 EV LC MS instrument (Shimadzu, syringe injection, sample solution in MeCN at flow rate

60 μL/min) using electrospray ionization (ESI) with simultaneous recording of positive and negative ions at capillary potentials of 4.5 and 3.5 kV, respectively. The capillary interface temperature was 230°C; nebulizer gas (dry N_2) at flow rate 1.5 L/min. Petroleum ether (PE, bp 40–70°C) was used for chromatography. Solvents were dried by standard methods. Elemental analyses of newly synthesized compounds agreed with those calculated.

Transformation of (*R*)-4-Menthen-3-one Antioxime (2) under Nitrosation Reaction Conditions. *a*) A suspension of oxime **2** (0.50 g, 3.0 mmol) and $NaNO_2$ (0.71 g, 10.3 mmol) in anhydrous $CHCl_3$ (10 mL) was treated dropwise with stirring at room temperature with glacial HOAc (1.5 mL), stirred for 2 h, diluted with H_2O (10 mL), and extracted with EtOAc (3 × 30 mL). The combined organic layer was washed successively with saturated solutions of Na_2CO_3 (3 × 5 mL) and NaCl (2 × 5 mL), dried over $MgSO_4$, and evaporated. The solid (0.33 g) was chromatographed (SiO_2, PE–EtOAc, 30:1) to afford **1** (0.21 g, 46%), $[\alpha]_D^{21}$ –66.9° (*c* 4.95, $CHCl_3$) {lit. [12], $[\alpha]_D^{25}$ –67.5° (*c* 5.3, $CHCl_3$)}. The IR, PMR, and ^{13}C NMR spectral data were identical to those published earlier [12].

b) A suspension of oxime **2** (0.50 g, 3.0 mmol) and $NaNO_2$ (0.71 g, 10.3 mmol) in anhydrous MeOH (12 mL) was treated dropwise with stirring at room temperature with glacial HOAc (1.4 mL), stirred for 5 h, and evaporated in *vacuo*. The solid was diluted with H_2O (10 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layer was washed successively with saturated solutions of Na_2CO_3 (3 × 5 mL) and NaCl (2 × 5 mL), dried over $MgSO_4$, and evaporated. The solid (0.38 g) was chromatographed (SiO_2, PE–EtOAc, 30:1) to afford **1** (0.24 g, 53%) that was identical to that obtained in *a*).

Transformation of 3 under Oximation Reaction Conditions. Epoxide **3** (1.50 g, 8.9 mmol) was dissolved in MeOH (8 mL); treated sequentially with $NH_2OH{\cdot}HCl$ (7.50 g, 107.9 mmol), NaOAc (15.0 g, 182.9 mmol), and H_2O (23 mL); refluxed for 2 h, cooled to room temperature, and extracted with EtOAc (3 × 90 mL). The combined organic layer was washed with saturated NaCl solution (2 × 15 mL), dried over Na_2SO_4, and evaporated. The solid (1.50 g) was chromatographed (SiO_2, PE–EtOAc, 20:1) to afford **8** (1.12 g, 66%), R_f 0.51 (PE–EtOAc, 2:1). The IR, PMR, and ^{13}C NMR spectral data were identical to those published earlier [2].

Transformations of 4 and 5 in a Ritter Reaction. Enol **4** (0.46 g, 3.0 mmol) or acetate **5** (0.67 g, 3.0 mmol) was dissolved in MeCN (12 mL), cooled to 0°C, stirred, and treated with $BF_3{\cdot}Et_2O$ (0.4 mL) or conc. H_2SO_4 (0.8 g, 7.7 mmol). The reaction mixture was held at 20°C (for H_2SO_4) or 80°C (for $BF_3{\cdot}Et_2O$) for 12 h, poured into cold (0°C) H_2O (15 mL), washed with NaOH solution (15%, 3 × 5 mL), and extracted with EtOAc (3 × 30 mL). The combined organic layer was washed with saturated NaCl solution (2 × 5 mL), dried over Na_2SO_4, and evaporated. The solid was purified by column chromatography (SiO_2, PE–EtOAc, 20:1) to afford diastereomeric acetamides **12a** and **b**. For enol **4**, yield 0.41 g (70%) of a mixture (55:45) of **12a** and **b** (H_2SO_4); 0.27 g (46%) of a mixture (69:31) of **12a** and **b** ($BF_3{\cdot}Et_2O$). For acetate **5**, yield 0.45 g (77%) of a mixture (43:57) of **12a** and **b** (H_2SO_4). R_f 0.27 (PE–EtOAc 2:1). IR spectrum (KBr, ν, cm^{-1}): 1539 (NHAc), 1620 (C=C), 1651 (C=O), 3350–3196 (NH). ESI mass spectrum ESI, *m/z* (I_{rel}, %), MeCN – H_2O 95:5, ($Scan^+$): 410.0 ($2[M + H]^+ + H_2O$], 37.5), 196.0 ($[M + H]^+$, 100.0), 137.0 ($[M – NHCOMe]^+$, 12.5).

***N*-[(1*R*,5*R*)-2-(1-Methylethyl)-5-methyl-2-cyclohexenyl]acetamide (12a) from a Mixture with 12b.** PMR spectrum (500.13 MHz, CD_3OD, δ, ppm, J/Hz): 0.96 (3H, d, J = 6.6, CH_3-5′), 0.98 (3H, d, J = 6.9, H-3″), 1.04 (3H, d, J = 6.9, H-2″), 1.31 (1H, dd, ^2J = 13.3, ^3J = 4.7, H_a-4′), 1.52–1.60 (1H, m, H-5′), 1.59 (1H, d, J = 12.4, H_a-6′), 1.79 (1H, d, J = 13.3, H_e-4′), 1.92 (3H, s, NHCOC$\underline{H}_3$), 2.12 (1H, dd, ^2J = 12.4, ^3J = 4.1, H_e-6′), 2.19 (1H, sept, J = 6.9, H-1″), 4.75 (1H, m, H_a-1′), 5.54 (1H, d, J = 2.0, H-3′), 7.93 (1H, br.s, N$\underline{H}$COCH$_3$). ^{13}C NMR spectrum (125.20 MHz, $CDCl_3$, δ, ppm): 21.16 (q, C-3″), 21.71 (q, C-2″), 22.90 (q, CH_3-5′), 23.51 (d, C-5′), 23.95 (s, NHCO$\underline{C}$H$_3$), 31.56 (d, C-1″), 33.86 (t, C-4′), 38.00 (t, C-6′), 45.62 (d, C-1′), 123.65 (d, C-3′), 142.70 (s, C-2′), 169.19 (s, C-1).

***N*-[(1*S*,5*R*)-2-(1-Methylethyl)-5-methyl-2-cyclohexenyl]acetamide (12b) from a Mixture with 12a.** PMR spectrum (500.13 MHz, CD_3OD, δ, ppm, J/Hz): 0.96 (3H, d, J = 6.6, CH_3-5′), 0.98 (3H, d, J = 6.9, H-3″), 1.04 (3H, d, J = 6.9, H-2″), 1.31 (1H, dd, ^2J = 13.3, ^3J = 4.7, H_a-4′), 1.52–1.60 (1H, m, H-5′), 1.59 (1H, d, J = 12.4, H_a-6′), 1.79 (1H, d, J = 13.3, H_e-4′), 1.92 (3H, s, NHCOC$\underline{H}_3$), 2.12 (1H, dd, ^2J = 12.4, ^3J = 4.1, H_e-6′), 2.19 (1H, sept, J = 6.9, H-1″), 4.52 (1H, m, H_e-1′), 5.61 (1H, d, J = 4.5, H-3′), 8.07 (1H, br.s, N$\underline{H}$COCH$_3$). ^{13}C NMR spectrum (125.20 MHz, $CDCl_3$, δ, ppm): 21.16 (q, C-3″), 21.71 (q, C-2″), 22.90 (q, CH_3-5′), 23.51 (d, C-5′), 23.95 (s, NHCO$\underline{C}$H$_3$), 31.56 (d, C-1″), 33.98 (t, C-4′), 40.08 (t, C-6′), 47.87 (d, C-1′), 121.85 (d, C-3′), 143.42 (s, C-2′), 169.58 (s, C-1).

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