ISSN 1070-4280, Russian Journal of Organic Chemistry, 2006, Vol. 42, No. 8, pp. 1151–1156. © Pleiades Publishing, Inc. 2006.
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Verbenone in the Synthesis of *o*-Menth-1-en-3-one and 5,7,7-Trimethylazabicyclo[4.1.1]octane Derivatives

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Received February 21, 2005

Abstract—At treatment with sulfuric acid in acetonitrile solution the verbenone (4,6,6-trimethylbicyclo[3.1.1]hept-3-en-2-one) suffers an opening of the four-membered ring with the rupture of the C^1–C^6 bond of the pinane skeleton and transforms into *o*-menthene derivatives, *o*-mentha-1,6-dien-3-one and 8-acetamido-*o*-menth-1-en-3-one, whose ratio depends on the reaction conditions. *E*- and *Z*-isomers of verbenone oxime under the same conditions undergo the Beckmann rearrangement leading to the formation of 5,7,7-trimethyl-3-azabicyclo[4.1.1]oct-4-en-2-one and 5,7,7-trimethyl-2-azabicyclo[4.1.1]oct-4-en-3-one, respectively.

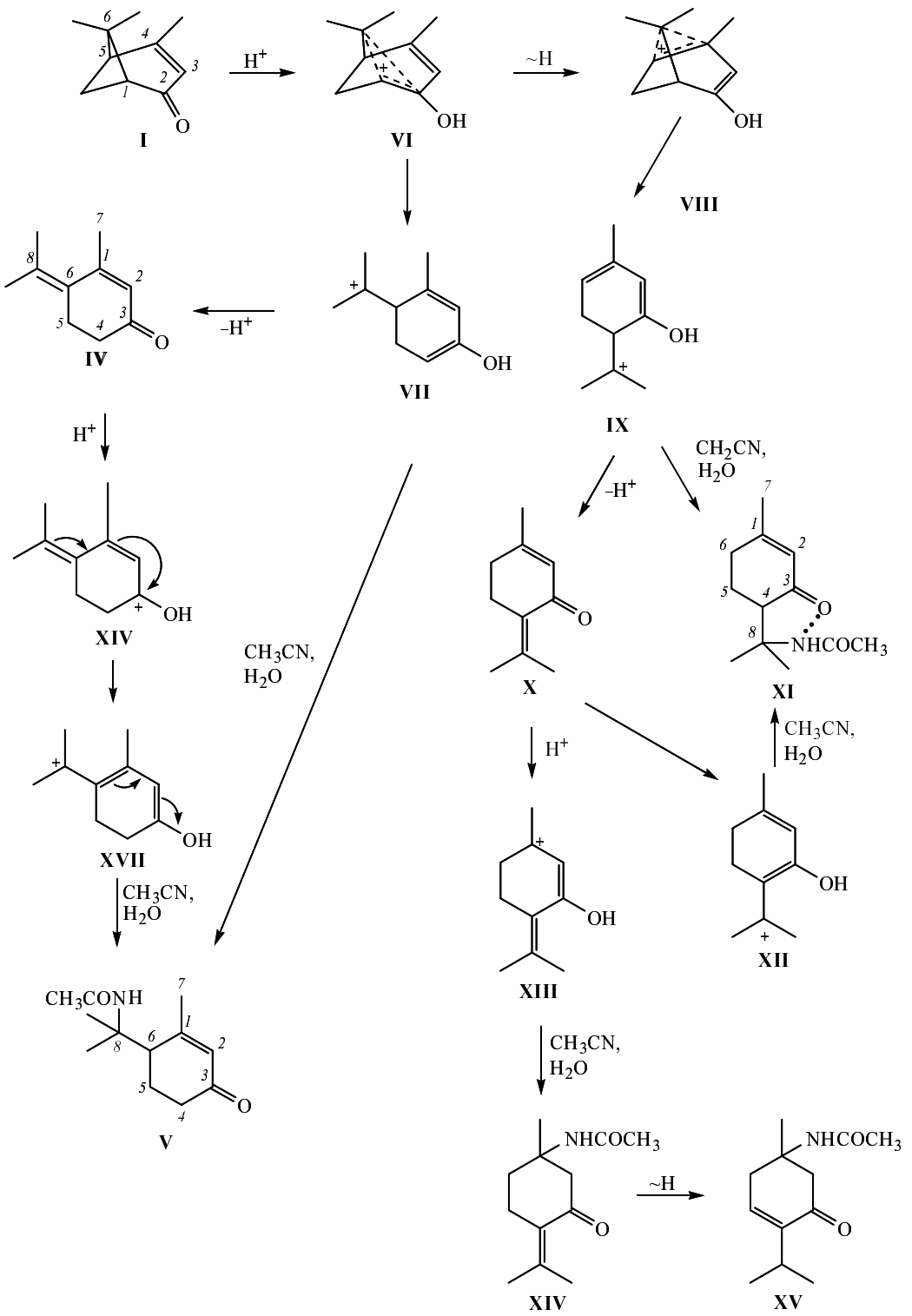
DOI: 10.1134/S1070428006080082

We formerly [1] studied the transformations under conditions of the acid catalysis of a large set of pinane (2,6,6-trimethylbicyclo[3.1.1]heptane) derivatives. The main route of transformations of the oxygen-containing derivatives of this series with reaction centers at the C^2 and C^3 was the formation of *p*-menthane derivatives resulting from the opening of the cyclobutane ring. Ketone oximes of the pinane series, like verbanone, pinocamphone, and isopinocamphone oximes on the contrary underwent at the treatment with the sulfuric acid in acetonitrile a classical Beckmann rearrangement with the retention of the four-membered ring giving bicyclic lactams [2, 3].

In this study we investigated the transformations under the Ritter reaction conditions of verbenone (4,6,6-trimethylbicyclo[3.1.1]hept-3-en-2-one) (**I**), and also of *E*- and *Z*-isomers of its oxime **II** and **III**. The possible routes of transformation of these compounds are governed by the presence in their structures of two potential reaction sites: a double bond and a functional group (carbonyl or oximine). Verbenone (**I**) under these conditions selectively converted into *o*-menthene derivatives. In the presence of 4 equiv of sulfuric acid the main product was *o*-mentha-1,6-dien-3-one (**IV**), a compound resulting formally from the opening of the four-membered ring by the *o*-menthane type conserving the enone fragment present in the initial structure. The minor component of the reaction mixture in this case was a product of a nucleophilic stabilization of the intermediate *o*-menthenone carbocation, 8-acetamido-*o*-menth-1-en-3-one (**V**). In the presence of 8 equiv of sulfuric acid amidoketone **V** formed predominantly, and dienone **IV** became the minor component of the reaction mixture. *o*-Mentha-1,6-dien-3-one (**IV**) under these conditions converted selectively into 8-acetamido-*o*-menth-1-en-3-one (**V**). The presumable mechanism of these reactions is shown on the scheme.

The verbenone protonation at the most electronegative oxygen of the carbonyl group led to the formation of a nonclassical cation **VI**. The opening of the four-membered ring with the rupture of C^1–C^6 gave *o*-mentha-diene carbocation **VII**. In a moderately acidic medium the thermodynamically preferred stabilization of this cation consisted in a proton ejection providing dienone **IV**. The thermodynamic feasibility of this stabilization of cation **VII** originates from the resulting formation of a completely conjugated 6π-electron system. At the high concentration of acid the deprotonation process is hampered by kinetic factors, and cation **VII** undergoes nucleophilic stabilization taking up the acetonitrile molecule and forming amidoenone **V** on hydration.

Presumably the verbenone transformation might lead also to the formation of *p*-menthene derivatives: carboca-



tion **VI** could transform into ion **VIII** by a hydride shift, the four-membered ring should open with the cleavage of the C^5–C^6 bond and give carvomenthyl cation **IX**. The latter stabilized either by deprotonation or a nucleophile addition would have given *p*-mentha-1,4-dien-3-one (**X**) and 8-acetamido-*p*-menth-1-ene (**XI**) respectively, *p*-analogs of dienone **IV** and amidoenone **V**.

The *o*-isomers structure was assigned to compounds obtained based on IR and ^{1}H NMR spectra. The IR spectrum of dienone **IV** contains absorption bands at 1660

and 1610 cm^{-1} corresponding to vibrations of conjugated carbonyl and double C=C bond. Therewith the integral intensity of the 1610 cm^{-1} band is considerably smaller than that of the carbonyl group vibrations. As known, this relative intensity of the bands suggests the *s-trans*-configuration of the enone fragment [4]. At the formation of a cross-conjugated *p*-dienone **X** one of the double bonds should have a *cis*-configuration with respect to the carbonyl group, and the intensity of the corresponding band should be at least comparable with that of the intensity of the carbonyl vibrations band. The data of ^{1}H NMR spectroscopy also testify to the structure **IV** of the isolated dienone. We previously discovered that in the case of an *s-cis*-configuration of the dimethylenone fragment the signal of a methyl group in a *syn*-orientation with respect to the carbonyl appeared notably downfield compared to the signal of an *anti*-oriented group (δ ~2.18 and 1.86 ppm respectively) [5]. Therefore at the formation of *p*- dienone **X** the most downfield signal should belong to the methyl group C^8–CH$_3$-*syn*. However in the spectrum of the compound obtained the most downfield signal corresponds to the methyl group attached to the C^1 (2.10 ppm, doublet, allyl coupling constant 1.2 Hz). The chemical shifts of the geminal methyl groups are relatively close (δ 1.93 and 1.86 ppm), and the signals of the methylene groups on the contrary are considerably different (δ 2.67 and 2.29 ppm, two 2-proton triplets, ^3J 6.2 Hz). The latter fact indicates the significant distinctions in their spatial arrangement and also is in a better agreement with the *o*-menthadiene structure **IV** than with structure **X**. The equivalence of the geminal protons at the atoms C^4 and C^5 in the compound obtained suggests that the menthadienone ring exists in a nearly planar conformation. In the mass spectrum of compound **IV** appeared a molecular ion peak M^+ 150 of integral intensity 36% relative to the most abundant one.

In the IR spectrum of amidoenone **V** appear absorption bands at 3450, 3310, and 3215 cm^{-1}, belonging to the stretching vibrations of the NH group; a band at 1660 cm^{-1} corresponding to vibrations of an amide and a conjugated keto carbonyl groups ; a band of C=C bond vibrations at 1620 cm^{-1}, and a band at 1550 cm^{-1} from the NH group vibrations in the substituted amides (amide **II** band). The position of the latter band indicates a moderate association of the NH groups and testifies to the *o*-menthane structure **V** of the amidoenone since in the case of the *p*-menthane analog **XI** an internal chelation should take place, and the corresponding band should be observed at 1570 cm^{-1} [4]. The *o*-menthane structure of amidoketone **V** is also confirmed by the data of ^{1}H NMR spectroscopy. The chemical shift value of the methine proton in this compound equal to 3.07 ppm (doublet of doublets, $^3J_{a,a}$ 12.0, $^3J_{a,e}$ 3.6 Hz) is well consistent with structure **V** where this proton is attached to atom C^6, namely, in a vicinal position with respect to the amido group and the C=C double bond. The signal of proton at the C^4 atom in the spectrum of *p*-menthane analog **XI** should appear considerably downfield (~ 3.6 ppm) due to the shielding by the α-carbonyl group. The observed vicinal coupling constants of this proton (12 and 3.6 Hz) indicate its axial orientation and therefore the equatorial orientation of the amidoisopropyl group of compound **V**. The chemical shift of the NH group proton equal to 6.2 ppm reveals the absence of a chelating hydrogen bond (the signal of NH group in a chelate appears at 10–12 ppm); as already mentioned, this fact testifies to *o*-menthene structure of amidoenone **V** obtained. The position and multiplicity of the other signals also are well consistent with the assumed structure (see EXPERIMENTAL). In the mass spectrum of this compound appeared a molecular ion peak M^+ 209 of integral intensity 2% relative to the most abundant one.

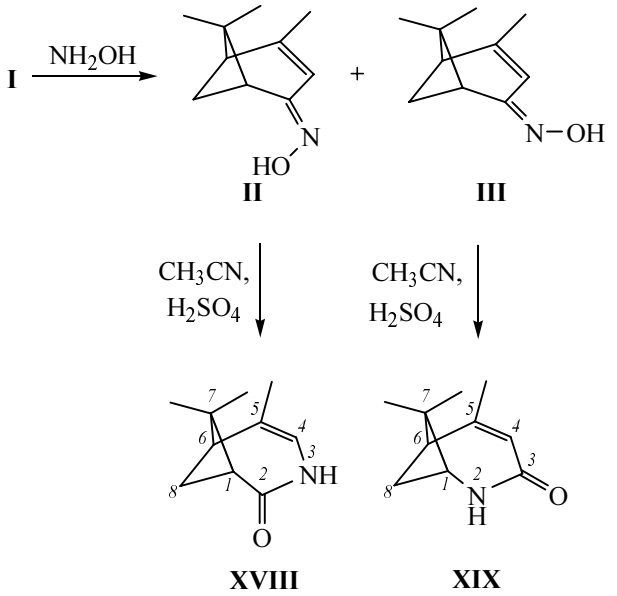
The *o*-menthene structure of compounds **IV** and **V** is also confirmed by the transformations of dienone **IV** under the Ritter reaction conditions. As already mentioned, the verbenone transformation yielded a single amidoenone. It is apparent that in the cross-conjugated dienone **X** the double C=C bonds are of comparable reactivity, and the protonation of the carbonyl group in this compound should lead to the formation of comparable amounts of cationic intermediates **XII** and **XIII**. The nucleophilic stabilization with acetonitrile of the first among these cations should result in amidoenone **XI**, and cation **XIII** should give rise to amide **XIV** or its isomerization product **XV**. However even traces of compounds with the geminal location of the methyl and amide group were lacking in the reaction mixture. This result is quite sensible for *o*-menthane dienone **IV** for cation **XVI** arising at protonation of its carbonyl group can transform only in ion **XVII**. The formation of a cation with a positive charge on the C^1 atom indispensible for transformation into a compound bearing the amido group on this atom is thermodynamically unfavorable since the conjugation of the double bonds in the molecule is completely broken in this case.

Thus verbenone (**I**) transformation under the Ritter reaction conditions open a convenient and efficient path to preparation of rare and difficultly available *o*-menthene derivatives. The presence in the structure of compounds

IV and **V** of activated carbonyl groups and double bonds recommends them as promising synthons for designing molecules possessing *o*-menthane fragment.

The oximation of ketone **I** results in formation of a mixture of *E*- and *Z*-isomers of oximes **II** and **III** in a ratio 2:5 (according to ^{1}H NMR data; see EXPERIMENTAL). The stereoisomere were separated by crystallization: in crystallization from hexane precipitated the mixture enriched with the *E*-isomer of the oxime, and from acetonitrile, with the *Z*-isomer.

We demonstrated formerly [1–3] that bicyclic terpene oximes which did not undergo under the conditions of acid catalysis the classical Beckmann rearrangements into the corresponding lactams, under the Ritter reaction conditions were cleanly converted into azabicyclic products due to the nucleophilic stabilization of the intermediate cations. We studied the transformations of both stereoisomeric oximes **II** and **III** under the Ritter reaction conditions. The only reaction products obtained were unsaturated bicyclic lactams: 5,7,7-trimethyl-3-azabicyclo-[4.1.1]oct-4-en-2-one (**XVIII**) and 5,7,7-trimethyl-2-azabicyclo[4.1.1]oct-4-en-3-one (**XIX**) respectively.



The synthesis of 2-azalactam **XIX** by the rearrangement of the corresponding oxime tosylate in pyridine was previously described [6]. The treating of oxime **II** with protic acids in the absence of acetonitrile led to the formation of a mixture of monocyclic nitriles of unidentified structure.

The structure of lactams **XVII** and **XIX** was derived from the data of IR, ^{1}H NMR and mass spectra. In the IR spectra of both isomeric lactams an absorption band is present at 1640 cm^{-1}, corresponding to the vibrations of the carbonyl group in the α,β-unsaturated lactams, and also a vibration band of the double C=C bond (1600 for 2-azalactam and 1610 cm^{-1} for 3-azaanalog). In the mass spectra of both compounds molecular ion peaks M^+ 166 are observed with an integral intensity ~ 40% relative to the most abundant one. In the ^{1}H NMR spectrum of 2-azalactam **XIX** a signal of an olefin proton attached to C^4 atom appeared as a quartet. Its chemical shift (5.78 ppm) indicates the proximity of the carbonyl group; the coupling constant 1.5 Hz corresponds to the allyl coupling of this proton with the protons of a methyl attached to the C^5 atom (doublet, δ 1.86 ppm). The signal of the proton linked to C^1 adjacent to the NH group is observed as a doublet of triplets at δ 3.61 ppm; the coupling constant 5.8 Hz corresponds to the coupling of the proton with protons H$^{8\text{-}syn}$ and H^6, and the constant 1.8 Hz, to the coupling with the proton H$^{8\text{-}anti}$. The position and multiplicity of the other signals also are well consistent with the assumed structure of compound **XIX** (see EXPERIMENTAL). The quartet resonance corresponding to the olefin proton of 3-azalactam **XVIII** appeared in a weaker field (δ 6.46 ppm). The coupling constant of the allyl coupling with the protons of a methyl attached to the C^5 atom (doublet, δ 1.90 ppm) amounted to 1.4 Hz. The signal of the proton attached to C^1 that in this compound is adjacent to the carbonyl is on the contrary shifted upfield compared to the 2-azaanalog and appears at δ 2.64 ppm. Its multiplicity is the same as in the signal of the analogous proton of compound **XIX**, like the position and multiplicity of the other proton signals (see EXPERIMENTAL).

The above stated shows that the method we have developed before [1–3] for lactams preparation from the labile oximes of bicyclic terpenes gives good results also with the oximes of α,β-unsaturated bicyclic ketones.

EXPERIMENTAL

IR spectra were recorded on a Fourier-spectrophotometer Nicolet Protege-460. ^{1}H NMR spectra were registered on a spectrometer Tesla BS-567 (100 MHz) from solutions in $CDCl_3$, internal reference HMDS. Mass spectra were measured on a GC-MS Hewlett-Packard 5890/5972 instrument, colunm HP-5MS (70 eV). The

reaction progress was monitored and the composition of products synthesized was checked by GLC on a chromatograph Chrom-5 equipped with a glass column (2000×2 mm) packed with a Chromaton-N-AW-DMCS carrier (0.16–0.20), liquid phase Apiezon L.

The initial verbenone (commercial product) was distilled at the atmospheric pressure, bp 224–225°C (750 mm Hg), n_D^{18} 1.4976.

Verbenone *E*- and *Z*-oximes (II) + (III) were obtained by a common procedure [2]. The stereoisomers ratio (2:5) was estimated from NMR spectra by the ratio of the integral intensity of olefin protons signals: δ 6.44 ppm at the *syn*-orientation of the oximine hydroxy group (*Z*-isomer) and 5.79 ppm at its *anti*-orientation (*E*-isomer) [7]. The separation of the stereoisomeric oximes **II** and **III** was performed by recrystallization. Therewith the precipitate from hexane was enriched with the minor component, *E*-isomer **II**. After two subsequent crystallization the sample obtained contained no less than 90% of compound **II**, mp 102–104°C. The mixture obtained by evaporation of the mother liquor was recrystallized from acetonitrile. After three-fold recrystallization the *Z*-isomer of the oxime was of 94% purity (according to NMR data), mp 119–120°C [6].

Ritter reaction with compounds **I–III** was carried out by a conventional procedure [1, 2].

***o*-Mentha-1,6-dien-3-one (IV).** A light oily substance obtained from verbenone (**I**) by the Ritter reaction in the presence of 4 equiv of sulfuric acid and isolated after evaporating ether contained prevailingly compound **IV** with a small impurity of amidoketone **V** (~4–5%). To remove the latter the reaction product was dissolved in a 5-fold volume of hexane. The minor component was practically insoluble in hexane and precipitated after cooling the solution in a refrigerator. On evaporating the hexane solution pure diene-3-on **IV** was obtained. Yield 75%, n_D^{18} 1.5230. IR spectrum, ν, cm^{-1}: 3030 v.w (=C–H), 2970, 2915, 2855 (C–$H_{aliph.}$), 1660 (C=$O_{conjug.}$), 1610 (C=$C_{conjug.}$). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.86 s and 1.93 s (3H each, both 8-CH_3), 2.10 d (3H, 1-CH_3, ^4J 1.2 Hz), 2.29 t (2H, C^5H_2, ^3J 6.2 Hz), 2.67 t (2H, C^4H_2, ^3J 6.2 Hz), 5.89 d (1H, H^2, ^4J 1.2 Hz). Mass spectrum, *m/z* (I_{rel}, %): 150 [*M*]$^+$ (36), 135 [*M*– CH_3]$^+$ (24), 122 (4), 110 (100), 95, 82, 70, 55, 43.

8-Acetamido-*o*-menth-1-en-3-one (V) was obtained by carrying out the Ritter reaction in the presence of 8 equiv of sulfuric acid. The reaction mixture was neutralized with ammonia solution, extracted with hexane to remove the impurity of dienone **IV**, then with ether. On evaporating the ether the fine crystalline product obtained was recrystallized from ethanol. Yield 72%, mp 108–109°C. IR spectrum, ν, cm^{-1}: 3310, 3215, 3080 (NH), 3030 v.w (=C–H), 2975, 2915, 2870, 2830 (C–H_{aliph}), 1660 v.s (C=O_{amide} + C=$O_{conjug.ketone}$), 1620 (C=$C_{conjug.}$), 1550 (NH_{amide}). ^{1}H NMR spectrum, δ, ppm: 1.34 s and 1.47 s (3H each, 8-CH_3), 1.72 m(1H, H^{5a}, ^2J 13.6, $^2J_{a,a'}$ 12.0 and 10.5 Hz, $^2J_{a,e'}$ 3.6 and 5.4 Hz), 1.92 s (6H, $COCH_3$ and =C–CH_3), 2.06 d.d.d (1H, H^{4a}, ^2J 14.8, $^3J_{a,a'}$ 10.5, $^3J_{a,e'}$ 5.4 Hz), 2.33 m(2H, H^{4e} + H^{5e}) 3.07 d.d (1H, H^{6a}, $^3J_{a,a'}$ 12.0, $^3J_{a,e'}$ 3.6 Hz), 5.78 q (1H, =C–H, ^WJ 1.2 Hz), 6.20 (1H, NH). Mass spectrum, *m/z* (I_{rel}, %): 209 [*M*]$^+$ (2), 194 [*M*– CH_3]$^+$ (<1), 181 (<1), 166 *M*–$COCH_3$]$^+$ (1), 152 [*M*–$NCOCH_3$]$^+$ (8), 150 [*M*–NH_2COCH_3]$^+$ (27), 135 [*M*–NH_2COCH_3–CH_3]$^+$ (15), 124 (3), 110 (40), 95, 82, 70, 58 (100), 43.

5,7,7-Trimethyl-3-azabicyclo[4.1.1]oct-4-en-2-one (XVIII) was obtained by rearrangement of *E*-isomer of oxime **II** in a 72% yield, mp 111–112°C. IR spectrum, ν, cm^{-1}: 3300 (NH), 3060 (=C–H), 2955, 2925, 2855 (C–H_{aliph}), 1640 (C=$O_{conjug.lactam}$), 1610 (C=$C_{conjug.}$). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.86 s (3H, 7-CH_3-*syn*), 1.40 s (3H, 7-CH_3-*anti*), 1.65 d.t (1H, $H^{7a'}$, ^2J 10.2, $^3J_{1,7}$ and $^3J_{6,7}$ 1.8 Hz), 1.89 d (3H, 5-CH_3, ^4J 1.4 Hz), 2.25 d.t (1H, H^6, $^3J_{6,8e'}$ and $^4J_{6,1}$ 5.6, $^3J_{6,8a'}$ 1.8 Hz), 2.64 d.t (1H, H^1, $^3J_{1,8e'}$ and $^4J_{1,6}$ 5.6, $^3J_{1,8a'}$ 1.8 Hz), 2.75 d.t (1H, $H^{8e'}$, ^2J 10.2, $^3J_{8e',1}$ and $^3J_{8e',6}$ 5.6 Hz), 6.46 q (1H, H^4, $^4J_{CH_3}$ 1.4 Hz). Mass spectrum, *m/z* (I_{rel}, %): 166 [*M*]$^+$ (38), 151 [*M* – CH_3] (17), 138 (6), 110 (100), 95, 84, 77, 63, 43.

5,7,7-Trimethyl-2-azabicyclo[4.1.1]oct-4-en-3-one (XIX) was obtained by rearrangement of *Z*-isomer of oxime **III** in a 76% yield, mp 144–145°C (publ.: mp 143–144°C [6]). IR spectrum, ν, cm^{-1}: 3280 (NH), 3060 (=C–H), 2955, 2925, 2865 (C–H_{aliph}), 1645 (C=$O_{conjug.lactam}$), 1600 (C=$C_{conjug.}$). ^{1}H NMR spectrum, δ, ppm: 0.85 s (3H, 7-CH_3-*syn*), 1.44 s (3H, 7-CH_3-*anti*), 1.68 d.t (1H, $H^{7a'}$, ^2J 10.2, $^3J_{7a',1}$ and $^3J_{7a',6}$ 1.8 Hz), 1.85 d (3H, 5-CH_3, ^4J 1.5 Hz), 2.22 d.t (1H, H^6, $^3J_{6,8e'}$ and $^4J_{6,1}$ 5.6, $^3J_{6,8a'}$ 1.8 Hz), 3.61 d.t (1H, H^1, $^3J_{1,8e}$ and $^4J_{1,6}$ 5.6, $^3J_{1,8a'}$ 1.8 Hz), 2.76 d.t (1H, $H^{8e'}$, ^2J 10.2, $^3J_{1,8e}$ and $^3J_{6,8e}$ 5.6 Hz), 5.78 q (1H, H^4, $^4J_{CH_3}$ 1.5 Hz). In the ^{1}H NMR spectrum published in [6] were assigned only the methyl groups signals and the signal of the olefin proton at C^4 atom. Mass spectrum, *m/z* (I_{rel}, %): 166 [*M*]$^+$ (42), 151 [*M* – CH_3] (19), 138 (7), 110 (100), 95, 84, 63, 43.

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