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Verbanone in the Synthesis of Amidoketones from *o*-Menthane Series

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Abstract—A verbanone reaction with acetonitrile under Ritter reaction conditions led to a selective formation of *o*-menthane derivatives, a mixture of stereoisomeric *cis*- and *trans*-8-acetamido-*o*-menthones. The streoisomers ratio depends on the reaction conditions and the character of acid catalyst used.

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We formerly demonstrated that terpene ketones from the bicyclo[2.2.1]heptane series, like camphor [1], isocamphanone [2], isofenchone [3], and 3-bromoisocamphanone [4], in contrast to the other alicyclic ketones were capable to enter into reaction with nitriles via carbonyl group under acid catalysis (Ritter reaction) providing the corresponding geminal diamides with nonrearranged initial carbon skeleton. Fenchone was an exception to this rule. The sterical shielding of the carbonyl in this compound prevented the geminal introduction of two bulky acetamide substituents leading to a rearrangement of the initial carbon skeleton and to the formation of a mixture of three diamides with nongeminal position of the functional substituents [5].

The higher reactivity of the carbonyl group in the above mentioned ketones as compared with monocyclic and acyclic analogs we ascribed to the formation of "nonclassical" carbocations by protonation of the carbonyl in these compounds which consequently were far more stable. The corresponding increase in the "life time" of these cations significantly increased the probability of the reaction with a weak nucleophile, nitrile. Thus we suggested a reaction mechanism with the first stage consisting in the protonation of a carbonyl group and formation of a hydroxy-substituted nonclassical carbocation.

S.M. Luk'yanov and A.B. Koblik [6] suggested an alternative mechanism where the first stage of the reaction was an addition of a protonated nitrile molecule to the C=O double bond resulting in the formation of an intermediate with a geminal position of a hydroxy group and a cation-iminium moiety. We believe that this mechanism is unconvincing was above all since it does not provide an understanding of the higher reactivity of the norbornane ketones, also these with the sterically hindered reaction site, as compared, for instance, with monocyclic ketones with considerably more accessible sterically carbonyl group.

In this research we investigated the reaction with acetonitrile under the conditions of the Ritter reaction of a bicyclic terpene ketone with a pinane (bicyclo[3.1.1]-heptane) skeleton: verbanone (**I**). Inasmuch as the bicyclic pinane skeleton also could provide nonclassical carbocations with a positive charge delocalized over the skeleton we presumed that the carbonyl group of the compound also would be sufficiently active to be involved into this reaction. At the same time the lability of the pinane skeleton that under acid catalysis as a rule opened into a menthane structure [7] did not permit to hope for formation of unrearranged geminal diamides. The reaction occurring by each of the above discussed mechanisms should lead to the formation of menthane derivatives with different functional substituents. Therefore the structure of the reaction products would serve as a proof of one among the two probable mechanisms.

Verbanone (**I**) was subjected to Ritter reaction under milder condition than those used with terpene ketones of the bicyclo[2.2.1]heptane series (see EXPERIMENTAL), for under the conditions common for this reaction a large amount of polymers formed due to the lability of the pinane skeleton. The verbanone reaction with acetonitrile led to

the formation of a stereoisomeric mixture of amidoketones from the *o*-menthane series, *cis*- and *trans*-8-acetamido-*o*-menthones (**II**) and (**III**), whose ratio depended on the reaction conditions and on the character of the applied acid catalyst. At the use of sulfuric acid as catalyst under moderately mild conditions (5°C during the acid addition, 15°C at the subsequent stirring) the ratio of amidoketones **II** and **III** in the mixture obtained was 1:1. At lower temperature the mixture formed contained a higher fraction of the *cis*-isomer **II** (2:1 and 3:1, see EXPERIMENTAL), but the reaction therewith strongly decelerated. A mixture of stereoisomers **II** and **III** in a 3:1 ratio was also obtained using boron trifluoride etherate as an acid catalyst at 15°C.

The structure of stereoisomeric *cis*- and *trans*-8-acetamido-*o*-menthones (**II**) and (**III**) was proved based on ^{1}H and ^{13}C NMR, IR, and mass spectra. The negligible difference in the structure of stereoisomeric amidoketones **II** and **III** prevented their isolation in an individual state by all the procedures available to us (vacuum distillation and column chromatography). Therefore the IR spectra were recorded from mixtures. Inasmuch as no significant distinctions were observed in the spectra of different composition we concluded that the characteristic absorption bands in the IR spectra of stereoisomeric amidoketones **II** and **III** coincided. The IR spectra contain the bands at 1720 and 1650 cm^{-1}, characteristic of ketone and amide carbonyl groups respectively, and also bands at 3310, 3200, and 1540 cm^{-1} corresponding to the NH vibrations in amides. The molecular ion peak $[M]^+$ appeared in the mass spectrum with an integral intensity of 8% relative to the most abundant one.

The adequate proof that the amidoketones synthesized belong to the rare and difficultly available series of the *o*-menthane derivatives [8], and the conformation of their spatial arrangement were obtained with the use of NMR spectroscopy. To the assignment of the signals in the ^{1}H NMR spectra the procedure was applied of the direct estimation of the spin-spin coupling constants ^{1}H–^{1}H COSY-45. The most upfield signal in the spectrum of *cis*-8-acetamido-*o*-menthone (**II**) is the resonance of a methyl group (δ 0.92 ppm, ^3J 7.0 Hz). At the frequency corresponding to this signal a response was observed at 2.48 ppm corresponding to the signal of the proton H^3 adjacent to the methyl group. According to the correlation spectrum the proton H^3 is coupled to three protons whose signals appear at 2.79, 2.60, and 2.10 ppm. The presence of only three protons in the α-position with respect to H^3 indicates the *ortho*-location of the methyl and isopropyl substituents, and the corresponding coupling constants of this proton equal to 2.5–4.5 Hz testify to the equatorial orientation of the proton H^3, and consequently to the axial position of the methyl group in compound **II**. The correlation spectrum indicates the existence of a geminal coupling between the protons whose signals appear at δ, ppm: 2.60 d.d (^2J 14.0, ^3J 4.5 Hz) and 2.10 d.d (^2J 14.0, ^3J 2.5 Hz). These protons lack any coupling save that with the proton H^3, and the values of their chemical shifts point to their proximity to the carbonyl group. The signal at δ 2.79 ppm obviously belongs to the proton H^4 adjacent to the isopropylamide substituent. One of the coupling constants (J 12 Hz) indicates the coupling of this proton with the axial proton attached to the atom C^5 (1.75 ppm, m) and reveals the axial orientation of the proton H^4 and therefore the equatorial orientation of the amidoisopropyl group. The resonance of the equatorial proton at C^5 gives rise to a signal at 1.90 ppm (m, ^2J 12.0, $^2{}^3J_{a,e}$ 3.0, $^3J_{e,e'}$ 4.5 Hz). A coupling of protons H^{5e} and H^{5a} was found with a pair of geminal protons corresponding to a signal at 2.35 ppm (m, 2H) and originating from the second methylene group neighboring to the carbonyl. Thus the cited data unambiguously prove the structure of amidoketone **II** as a derivative of the *o*-menthane series with an equatorial isopropylacetamido group and an axial methyl at C^3. The data of the ^{13}C NMR spectroscopy also evidence this spatial arrangement of amidoketone **II**. The assignment of the signals in the spectrum was performed with the use of *J*-modulation and by comparison with the published [7] spectra of menthane derivatives. The signal of the methyl group 3-CH_3 of *cis*-8-acetamido-*o*-menthone (**II**) appeared in the strong field (δ 15.2 ppm) pointing to its axial orientation [9]. The appearance in the spectra of two downfield (50.8 and 41.3 ppm) and only one upfield (22.3 ppm) triplets indicates the presence of two methylene groups in the α-position relative to a carbonyl (211.7 ppm), thus also supporting the *o*-menthane structure. The chemical shifts and multiplicity of the other carbon signals (see EXPERIMENTAL) are also well consistent with the assumed structure of *cis*-8-acetamido-*o*-menthone (**II**).

The structure of the second component of the reaction mixture, *trans*-8-acetamido-*o*-menthone (**III**), was established in the same fashion. The analysis of the correlation spectrum ^{1}H–^{1}H of compound **III** shows that the difference is only in the orientation of the methyl group: its signal appears in a weaker field as is characteristic of an equatorially directed methyl (δ 1.02 ppm, d, ^3J 7.0 Hz). The signal of proton H^3 coupled with the methyl is

observed on the contrary upfield from that in compound **II** (δ 2.02 ppm) and has a different multiplicity because it takes part in two axial-axial couplings: with an axial proton at the atom C^4 ($^3J_{a,a}$ 12.0 Hz) and a pseudoaxial proton attached to atom C^2 ($^3J_{a,a'}$ 9.0 Hz). The signals of the axial protons neighboring to the carbonyl group are also identified in the spectrum: δ 2.12 (d.d, H^{2a}, ^2J 14.0, $^3J_{a,a'}$ 9.0 Hz) and 2.20 ppm (d.d.d, H^{6a}, ^2J 14.0, $^3J_{a,a'}$ 9.0, $^3J_{e,a'}$ 3.5 Hz).

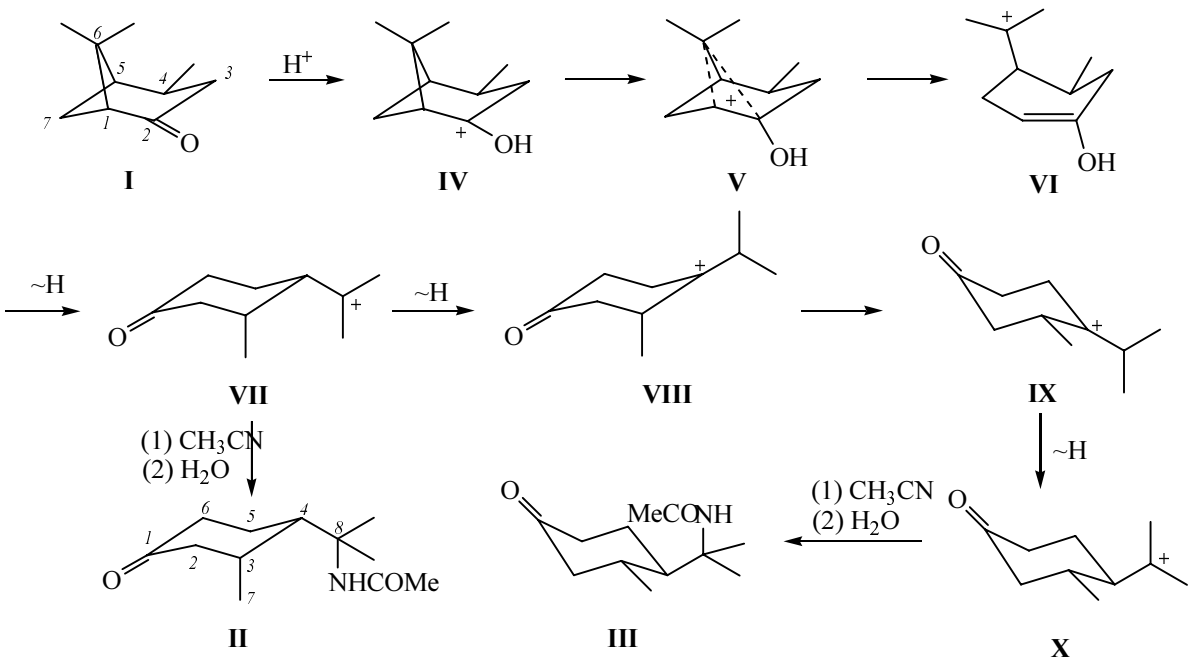
The signals of the equatorial protons attached to these atoms, and also of the proton H^{4a} appear as a combined multiplet at 2.40 ppm. The multiplicity of signals of protons at the C^5 atom of *trans*-amidoketone **III** is the same as in the spectrum of compound **II**. Some variations in the chemical shifts of the corresponding protons originate from the difference in the shielding effect of the axially and equatorially oriented methyl groups and also from the distinctions in the hydrocarbon skeletons strain. In the ^{13}C NMR spectrum of *trans*-8-acetamido-*o*-menthone (**III**) the signal of the methyl group at C^3 appeared considerably downfield compared to the corresponding signal in the spectrum of compound **II** (δ 24.3 ppm) also proving its equatorial orientation. Like the spectrum of analog **II**, the spectrum of amidoketone **III** contains three triplets: two downfield signals (46.6 and 38.6 ppm) and one upfield resonance (24.3 ppm) in conformity to the *o*-menthone sructure of compound obtained as has been discussed above. The chemical shifts and multiplicity of the other carbon signals (see EXPERIMENTAL) are also well consistent with the assumed structure of compound **III**.

It should be stressed that the *o*-menthane derivatives are very rare and difficultly available. Their content in the natural sources is as a rule negligibly small [8]. On the contrary, the verbanone is relatively accessible compound for it is pproduced industrially from cheap and available α-pinene. Therefore the above described reactions constitute a good procedure for selective preparation of *o*-menthane derivatives. The previously developed syntheses of these compounds [10] were not selective and as a rule led to the formation of mixtures *o*- and *p*-menthane derivatives, the latter prevailing.

The selective formation of amidoketones of the *o*-menthane series from the verbanone occurs apparently in keeping with Scheme 1.

The protonation of the carbonyl oxygen in compound **I** causes an appearance of an efficient positive charge on atom C^2. The arising conjugation with the cyclobutane ring results in the formation of a nonclassical carbocation **V** that in keeping with the scheme common for pinane derivative should suffer the opening giving cationic intermediate **VI** with an *o*-menthane skeleton, a hydroxy group at the double bond, and a positive charge on the atom C^8. Under mild conditions a hydride shift leads to

Scheme 1.



the formation of *o*-menthone carbocation **VII** that by an addition of a nucleophile molecule (acetonitrile) addition followed by hydration converts into *cis*-8-acetamido-*o*-menthone (**II**), the main reaction product.

The formation of the *trans*-isomeric amidoketone **III** occurs likely as a result of a reversible transformation of *O*-menthone cation **VII** with a positive charge on C^8 into carbocation **VIII** with a positive charge on C^4. The latter through a ring inversion transforms into a thermodynamically more feasible cation **IX** with an equatorial orientation of the methyl group. The reverse 8,4-hydride shift provides *o*-menthone carbocation X that undergoes the nucleophilic stabilization as above to form *trans*-8-acetamido-*o*-menthone (**III**) with the thermodynamically preferred equatorial orientation of both substituents.

The reduced relative content of isomer **III** with the *trans*-menthane skeleton at lower reaction temperature is presumably due to a greater drop in the rate of hydride shift than of velocity of nucleophile addition at decreasing temperature. The higher reaction selectivity at the catalysis with BF_3 is probably observed because of formation of conformationally less labile intermediates.

The formation of compounds **II** and **III** containing a carbonyl in the ring completely rules out the reaction mechanism suggested in [6]. When to a verbanone molecule adds a protonated acetonitrile molecule obviously the first intermediate with a positive charge in the pinane skeleton would be acetamido-substituted cation **XII** whose subsequent transformations should lead to the formation either to *of o*-menthene diamides **XIV** or of products of their further conversions (Scheme 2).

The absence of compounds of this structure among the reaction products makes possible to prefer the mechanism involving the formation of nonclassical carbocation with a hydroxy group.

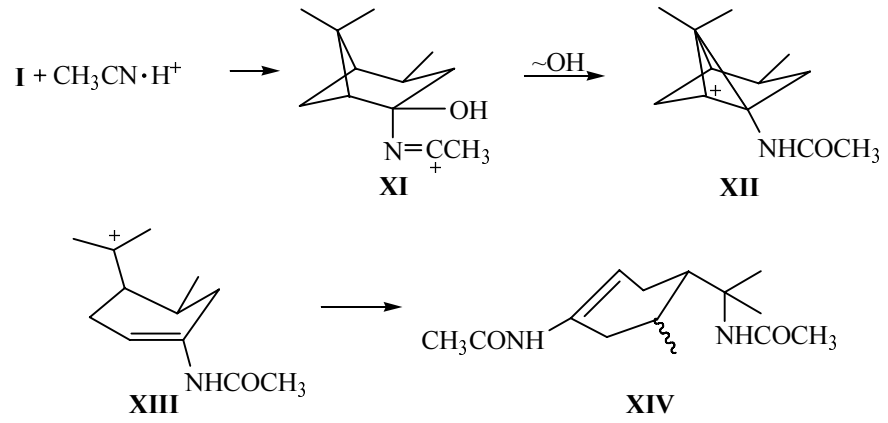
EXPERIMENTAL

IR spectra were recorded on a Fourier-spectrophotometer Nicolet Protege-460. ^1H and ^{13}C NMR spectra were registered on a spectrometer Bruker DRX-500 (500.132 and 125.758 MHz respectively) 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 isomeric 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.

Ritter reaction with verbanone (I) catalyzed by H_2SO_4 was carried out by the common procedure [1–3] adding carefully 2.8 ml of sulfuric acid to 3.0 g of verbanone dissolved in 5 ml of acetonitrile at 5 (*a*), –5 (*b*), or –15°C (*c*). After the addition of the acid was completed the reaction mixture was stirred at 15 (*a*), 5 (*b*), or –5°C (*c*). On completion of the reaction (GLC monitoring) the reaction mixture was poured in excess of aqueous ammonia, the reaction products were extracted with ether, and the extract was dried with $MgSO_4$. The oily substance obtained by evaporating the solvent was passed through a thin bed of chromatography-grade silica gel to remove polymeric compounds. The yield of the mixture of *cis*- and *trans*-8-acetamido-menthones (**II**) and (**III**) 56 (*a,* isomers ratio ~1:1), 59 (*b*, isomers ratio 2:1), 64% (*c*, isomers ratio 3:1).

Ritter reaction with verbanone (I) catalyzed by BF_3 etherate was performed by method *a*, but instead of the sulfuric acid 7.0 ml of the boron trifluoride etherate was added, and the quenching of the reaction mixture was done with excess diluted NaOH water solution. The yield of the mixture of amidoketones **II** and **III** 68%, isomers ratio 3:1.

Scheme 2.



Amidoketones II and III. IR spectrum, ν, cm^{-1}: 3310, 3200, 3080 (NH), 2965, 2930, 2870 (C–H), 1720 ($C{=}O_{ketone.}$), 1650 ($C{=}O_{amide}$), 1540 (NH).

On the GC-MS instrument we succeeded to register the individual mass spectra of stereoisomeric amidoketones **II** and **III**, but these spectra proved to be practically identical with minor difference in the intensity of some peaks. Mass spectrum, *m/z* (I_{rel}, %): 195 $[M]^{+\cdot}$ (8), 180 $[M - CH_3]^+$, 163, 154, 152 $[M - COCH_3]^+$, 136 $[M - NH_2COCH_3]^+$ (100), 134, 120, 106, 93, 83, 69, 59 $[NH_2COCH_3]$ (85), 55, 44, 43.

^1H and ^{13}C NMR spectra of *cis*-8-acetamido-*o*-menthone (**II**) were obtained from the registered spectrum of the mixture containing 75% of this isomer. The assignment of proton signals in the ^1H NMR spectrum was based on the direct correlation spectrum ^1H–^1H COSY-45. ^1H and ^{13}C NMR spectra of *trans*-8-acetamido-*o*-menthone (**III**) were obtained by subtraction of the signals of the main component from the spectra of the isomer mixture.

***cis*-8-Acetamido-*o*-menthone (II).** ^1H NMR spectrum, δ, ppm: 0.92 d (3H, 3-CH_3, ^3J 7.0 Hz), 1.35 s and 1.36 s [3H each, 8-$(CH_3)_2$], 1.75 m (1H, H^{5a}, ^2J 12.0, $^3J_{a,a}$ 12.0, $^3J_{a,a'}$ 9.0, $^3J_{a,e'}$ 4.5 Hz), 1.90 m (1H, H^{5e}, ^2J 12.0, $^3J_{e,a} = {}^3J_{e,a'} = {}^3J_{e,e'}$ = 3–4 Hz), 1.98 s (3H, $COCH_3$), 2.11 d.d (1H, H^{2a}, ^2J 14.0, $^3J_{a',e}$ 2.5 Hz), 2.35 m (2H, $H^{6a} + H^{6e}$), 2.48 m (1H, H^{3e}, $^3J_{e,a}$ 3.0, $^3J_{\varepsilon,a'}$ 2.5, $^3J_{e,e'}$ 4.5, $^3J_{3,Me}$ 7.0 Hz), 2.60 d.d (1H, H^{2e}, ^2J 14.0, $^3J_{e',e}$ 4.5 Hz), 2.79 d.t (1H, H^{4a}, $^3J_{a,a}$ 12.0, 2 $^3J_{a,e}$ 3.0 Hz), 5.60 br.s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 15.2 q (3-CH_3), 22.3 t (C^5), 25.5 q [8-$(CH_3)_2$], 26.5 q ($CO\underline{C}H_3$), 32.3 d (C^3), 41.3 t (C^2), 45.1 d (C^4), 50.8 t (C^6), 56.9 C (C^8), 169.8 s (CO_{amide}), 211.7 s (C^1).

***trans*-8-Acetamido-*o*-menthone (III).** ^1H NMR spectrum, δ, ppm: 1.02 d (3H, 3-CH_3, ^3J 7.0 Hz), 1.31 s and 1.37 s [3H each, 8-$(CH_3)_2$], 1.52 m (1H, H^{5a}, ^2J 12.0, $^3J_{a,a}$ 12.0, $^3J_{a,a'}$ 9.0, $^3J_{a,e'}$ 4.5 Hz), 1.90 m (1H, H^{5e}, ^2J 12.0, $^3J_{e,a} = {}^3J_{e,a'} = {}^3J_{e,e'}$ = 3–4 Hz), 1.97 s (3H, $COCH_3$), 2.02 m (1H, H^{3a}, $^3J_{a,a}$ 12.0, $^3J_{a,a'}$ 9.0, $^3J_{a,e'}$ 2.5, $^3J_{3,Me}$ 7.0 Hz), 2.12 d.d (1H, H^{2a}, ^2J 14.0, $^3J_{a',a}$ 9.0 Hz), 2.20 d.d.d (1H, H^{6a}, ^2J 14.0, $^3J_{a',a}$ 9.0, $^3J_{a',e}$ 2.5 Hz), 2.40 m (3H, $H^{2e} + H^{6e} + H^{4a}$), 5.65 br.s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 23.0 t (C^5), 24.3 q [3-CH_3 + 8-$(CH_3)_2$], 25.4 q ($CO\underline{C}H_3$), 30.1 d (C^3), 38.6 t (C^2), 45.6 d (C^4), 46.6 t (C^6), 56.9 C (C^8), 169.7 s (CO_{amide}), 211.6 s (C^1).

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