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Transformations of 2-(Phenylethynyl)isocamphanol under Acid Catalysis

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Abstract—2-*exo*-(Phenylethynyl)isocamphanol prepared from lithium phenylacetylide and isocamphanone suffered under conditions of Ritter reaction a conversion predominantly into a mixture of 2-(benzoylmethylene)isocamphane and 2-(benzoylmethylene)bornane that formed as a result of rearrangements of the initial acetylene alcohol by Meyer–Schuster and partially by Wagner–Meerwein. The enones ratio depends on the reaction conditions and varies from 5:4 to 1:3. The product of nucleophilic substitution, *N*-(4-benzoylmethyl-2-isobornyl)acetamide, formed in a yield no higher than 10%. Analogous rearrangements occurred at treating 2-phenylethynylisocamphanol with formic acid; here the mixture of the above enones formed in a ratio 1:2. The initial acetylene alcohol treated with Beckmann mixture gave rise to the same enones in a ratio 1:1, and the target 2-*endo*-(phenylethynyl)-isocamphanol acetate formed as minor product (~15%). The individual α,β-unsaturated ketones under the Ritter reaction conditions were selectively converted into *N*-(4-benzoylmethyl-2-isobornyl)acetamide.

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We showed formerly that terpene acetylene alcohols from the series of bicyclo[2.2.1]heptane could under conditions of Ritter reaction undergo various transformations involving both rearrangement of the carbon skeleton and hydration of the triple bond giving amides with substituents possessing a triple bond and/or a carbonyl group. The direction of the transformations is governed by the spatial arrangement of the initial alcohol and does not depend on the reaction conditions [1, 2]. For instance, 2-(phenylethynyl)isoborneol (2-*endo*-phenylethynyl-1,7,7-trimethylbicyclo[2.2.1]-heptan-2-ol) (**I**) reacted with acetonitrile in the presence of sulfuric acid (Ritter reaction) giving 4-substituted bornane derivatives: *N*-[4-(phenylethynyl)isobornyl]acetamide and *N*-[4-(benzoylmethyl)isobornyl]acetamide (**II**) in a ratio 8:3 [2].

We report here on the study of transformations under acid catalysis conditions of a structural analog of acetylene alcohol **I**, 2-(phenylethynyl)isocamphanol (2-*exo*-phenylethynyl-5,5,6-trimethylbicyclo-[2.2.1]heptan-2-ol) (**III**) obtained from lithium phenylacetylide and isocamphanone. This spatial arrangement was ascribed to the acetylene alcohol obtained based on two reasons: Firstly, we had shown previously that organolithium compounds had added to isocamphanone exclusively from the *exo*-side of the molecule [3]. Secondly in the ^{1}H NMR spectrum of this compound the signal of proton linked to C^6 atom appeared in abnormally weak field (δ 2.12 ppm) indicating that it was spatially close to the hydroxy group on C^2 atom which evidently had the *endo*-orientation [4]. Therefore compound **III** is distinguished from the previously studied alcohol **I** by the spatial orientation of the substituents at the reaction site. We previously established that at this stereochemistry of the reaction site the protonation is thermodynamically more favorable not at the hydroxy group but at the triple bond resulting in the exhaustive hydration of the latter and the formation of amidoketones [1]. It turned out however that the Ritter reaction carried out by standard procedure brought about prevailing formation of polymeric products, and only at strong dilution of the reaction mixture (see EXPERIMENTAL) we succeeded in preparation from the acetylene alcohol **III** of its adduct with acetonitrile, *N*-(4-benzoylmethyl-2-isobornyl)acetamide (**II**), but even in this event it formed only as a minor product. The main reaction products were α,β-unsaturated ketones resulting from rearrangement of initial acetylene alcohol **III**, 2-(benzoylmethylene)-isocamphane (**IV**) and 2-(benzoylmethylene)bornane (**V**). The ratio of compounds **II, IV**, and **V** in the reaction products depended on the reaction conditions. At cooling (see EXPERIMENTAL) in the presence of 4 equiv of sulfuric

acid prevailed enone **IV** with unchanged isocamphane skeleton, and the content of amide **II** did not exceed 4%. At room temperature in the presence of 8 equiv of sulfuric acid a mixture was formed containing 67% of bornane enone **V** and 10% of amidoketone **II**. At the use of boron trifluoride etherate as catalyst we also obtained a mixture with prevailing compound **V** (65%), and only trace amounts of amide **II**.

The minor component **II** was isolated from the reaction mixture by freezing from a hexane solution. α,β-Unsaturated ketones **IV** and **V** were isolated in individual state by column chromatography on silica gel.

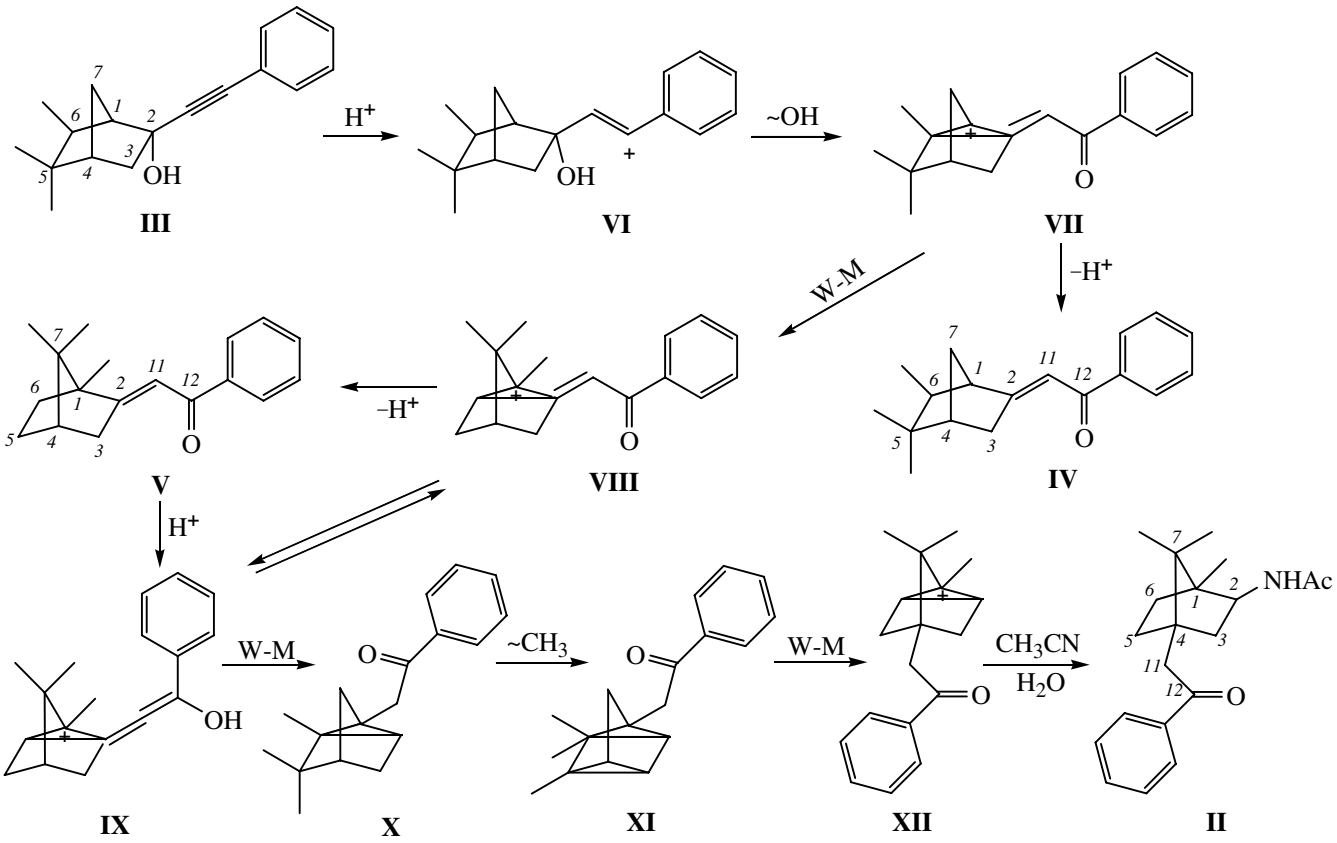
The structure of compounds obtained was established based on IR, ^{1}H NMR, and mass spectra. Physicochemical and spectral characteristics of amidoketone **II** and 2-(benzoylmethylene)bornane (**V**) were identical to those previously described for amidoketone and enone obtained from 2-(phenylethynyl)isoborneol [2]. In the IR spectrum of isocamphane compound **IV** bands are also present characteristic of an enone fragment: 1665 (C=O conjugated) and 1610 (C=C) cm^{-1}. The comparable integral intensity of these bands indicated that the system of conjugated double bonds of this compound possessed *s-cis*-configuration like in bornane analog **V**. The mass spectrum of compound **IV** contained the molecular ion peak 254 $[M]^+$ of relative intensity 30% with respect to the most abundant peak. The structure of enone with retained isocamphane skeleton was attributed to this compound based on the ^{1}H NMR spectrum. The spectrum contained two singlets (δ 0.91 and 1.00 ppm) and one doublet (δ 0.92 ppm, ^3J 7.2 Hz) frpom methyl groups and also a quartet belonging to proton H^6 contiguous to a methyl group (1.48 ppm, ^3J 7.2 Hz). A signal of an olefin proton located at a conjugated C=C bond (δ 6.96 ppm, triplet) was also identified in the spectrum. The coupling constant 2.2 Hz corresponds to the *trans*-allyl coupling with the protons attached to C^3 atom. The signals of the latter appeared at 2.75 ppm (double d.d, H^3_{endo}, ^2J 19.8, $^4J_{3,11}$ 2.2, $^WJ_{3,7\text{-}anti}$ 1.6 Hz) and 3.19 ppm (double d.d, H^3_{exo}, ^2J 19.8 , $^3J_{3,4}$ 4.0, $^4J_{3,11}$ 2.2 Hz).

This products mixture formed from 2-phenylethynylisocamphanol (**III**) under Ritter reaction conditions as a result of the following transformations. As already mentioned above, the *endo*-orientation of the hydroxy group does not favor its elimination, and therefore the protonation occurs at the triple bond C≡C. In this case unlike the previously described protonation of such bond in 2-ethynylisocamphanol forms carbocation **VI** with a positive charge on C^{12} atom stabilized by the mesomeric effect of the phenyl substituent. The migration of hydroxy group to the cation center leads to the formation of a benzoyl-substituted nonclassic carbocation **VII**. The latter is stabilized by proton ejection to give isocamphane enone **IV**. In this event the driving force of the reaction is the formation of totally conjugated 10π-electron bond system. The formation of compound **IV** is favored by low temperature reducing the rate of further transformations (first of all, of the Wagner–Meerwein rearrangement), and medium concentration of acid not hampering kinetically the deprotonation of cation **VII**. Wagner–Meerwein rearrangement of this cation provides a bornane intermediate **VIII** that, stabilized by loosing a proton, gives the second conjugate ketone, 2-(benzoylmethylene)bornane (**V**).

The formation of the minor component of the products mixture, amidoketone **II**, apparently occurs with a similar rearrangement of the carbon skeleton like that we have previously described for 2-(phenylethynyl)isoborneol (**I**) via intermediate formation of carbocations **IX–XII**. The low yield of the compound is due apparently to the very short life time of cationic intermediates **VIII** or **IX** in the reaction carried out in a dilute acetonitrile solution and at relatively low concentration of acid. We already mentioned that without dilution an excessive amount of polymer products was formed. It is presumable that this fact is caused by the high nucleophilicity of compounds **IV** and **V**. Yet the isolated α,β-unsaturated ketones **IV** and **V** reacted under mild conditions with acetonitrile in the presence of sulfuric acid giving compound **II** in a preparative yield (~65%) without dilution of the reaction mixture. The formation of large amount of polymer is probably due to the high reactivity of cationic intermediates and not enones **IV** or **V**.

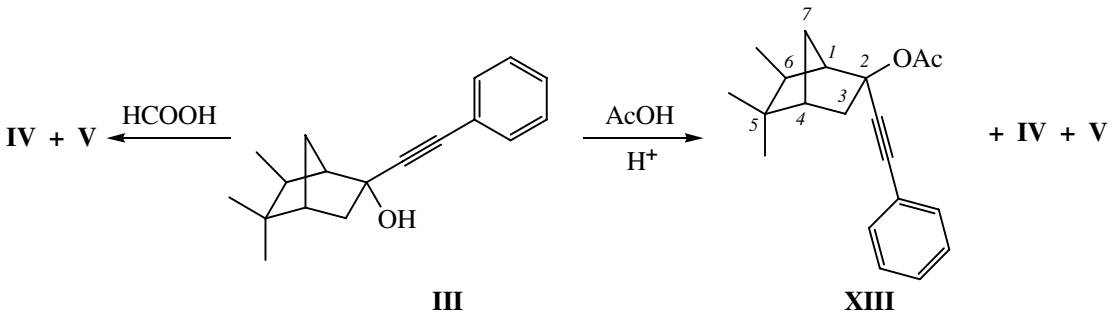
The treatment of 2-(phenylethynyl)isocamphanol (**III**) with formic acid at reflux also resulted in the Meyer–Schuster rearrangement [5] and partially in Wagner–Meerwein rearrangement giving a mixture of enones **IV** and **V** in a ratio 1:2. The Wagner–Meerwein rearrangement is believed to occur only at catalysis with strong mineral acids [6]. In this event the occurrence of the rearrangement is favored evidently by the easy formation of the corresponding carbocation even in the presence of weak organic acid.

Thus the triple bond of 2-(phenylethynyl)isocamphanol (**III**) under the conditions of acid catalysis suffers exhaustive hydration as a result of intramolecular rearrangement leading to the formation of benzoyl-substituted derivatives.



In order to obtain compounds with a triple bond acetylene alcohol **III** was treated with Beckmann mixture (acetic acid in the presenc of catalytic quantity of sulfuric acid) under mild conditions (without heating of the reaction mixture). We formerly showed that the *endo*-oriented hydroxy group of tertiary alcohols from the norbornane series under these conditions could be replaced by acetoxy group by S_N2 mechanism[7] due to the involvement into the reaction of a strong nucleophile (acetic acid) whose addition did not require cationic intermediate formation. This mechanism gave hope to conserve the triple bond in the structure of the initial compound. In this way we expected to obtain an acetate of acetylene alcohol with an *exo*-orientation of the departing group favoring its elimination under the conditions of nucleophilic substitution like in the case of phenylethynylisoborneol (**I**). We actually obtained 2-*exo*-acetate of 2-(phenylethynyl)isocamphanol (**XIII**), but only as a minor component of the reaction mixture (~15%). The main reaction products were the same α,β-unsaturated ketones **IV** and **V** that formed here in nearly equal amounts.

The IR and mass spectra of compound **XIII** obtained are consistent with the suggested structure. The *exo*-acetate structure was assigned to the ester based on the ^{1}H NMR spectrum. The signal of *exo*-proton H^3 in the spectrum of this compound is considerably shifted downfield as compared with the corresponding proton



signal in the spectrum of initial alcohol (Δ ~0.35 ppm) indicating that this atom is located in the region of deshielding caused by the ester group and thus syggesting a change in the stereochemistry of the adjacent atom. On the contrary, the signal of proton at C^6 atom is shifted upfield (see EXPERIMENTAL) revealing the absence of a polar substituent in the position C^2-*endo*.

Inasmuch as neither the triple bond nor the isocamphane skeleton not suffer rearrangements in the course of preparation of acetate **XIII**, it is presumable that its formation occurs by the S_N2 mechanism. However the rate of this reaction is low and significantly less than that of the Meyer–Schuster rearrangement.

EXPERIMENTAL

IR spectra were recorded on a Fourier spectrophotometer Nicolet Protege-460, ^{1}H NMR spectra were regisrered on a spectrometer Tesla BS-567 (100 MHz) from solutions in $CDCl_3$, internal reference HMDS. Mass spectra were measured on a GC-MS instrument Hewlett Packard 5890/5972, column HP-5MS (70 eV). The reaction progress was monitored and the composition of the products obtained was checked by GLC on a chromatograph Chrom-5 equipped with a glass column (2000 × 2 mm), stationary phase Apiezon L on Chromaton-N-AW-DMCS (0.16–0.20).

2-(Phenylethynyl)isocamphanol (III) was obtained from lithium acetylide and isocamphanone as described in [2], mp 49–51°C. ^{1}H NMR spectrum, δ, ppm: 0.91 d (3H, 6-CH_3, ^3J 7.5 Hz), 0.95 s (3H, 5-CH_3-*endo*), 1.08 s (3H, 5-CH_3-*exo*), 1.72 m (2H, H^4 + H^7_{anti}), 2.00 m (4H, H^1 + H^3_2 + OH), 2.12 q (1H, H^6, ^3J 7.5 Hz), 7.32 m (5H, Ph).

Ritter reaction with 2-(phenylethynyl)isocamphanol (III). *a.* In 40 ml of acetonitrile was dissolved 5 g of acetylene alcohol **III**. At cooling to room temperature on a water bath was slowly added dropwise 8 ml of concn. H_2SO_4. The completion of reaction was monitored by GLC by consumption of the initial alcohol. Then the reaction mixture was poured into excess of cooled water solution of ammonia, extracted with ether, the extract was dried with $MgSO_4$. On evaporating a mixture was obtained containing up to 20% of polymeric product. To remove the polymer the reaction product was dissolved in methanol, and the flakes of the polymer were filtered off. On evaporating the filtrate we obtained 4.1 g of a mixture containing 23% of isocamphane enone **IV**, 67% of bornane enone **V**, and 10% of amidoketone **II**. To isolate pure ***N*-(4-benzoylmethyl-2-isobornyl)-acetamide (II)** the mixture obtained was dissolved in a 5-fold volume of hexane and the solution was cooled to –12°C. Amidoketone **II** virtually insoluble in hexane precipitated as fine colorless crystals. The use of a smaller hexane volume is unfavorable, for then compound **II** does not precipitate completely apparently due to its higher solubility in the mixture hexane–enones **IV** and **V** at a large quantity of the enones. The physicochemical and spectral characteristics of the isolated compound **II** were identical to those of the same amidoketone prepared from 2-(phenylethynyl)isoborneol (**I**) or 2-(benzoylmethylidene)-bornane (**V**) [2].

The mixture of α,β-unsaturated ketones that remained in the hexane solution was evaporated and subjected to column chromatography on silica gel (L 40/100, Chemapol, Czechia), eluent hexane. The greater chromatographic mobility corresponded to bornane enone **V**. Its NMR spectra were identical to those of enone obtained from 2-(phenylethynyl)isoborneol [2].

2-(Benzoylmethylene)isocamphane (IV) was isolated as thick yellow oily compound, n_D^{16} 1.5602. IR spectrum, cm^{-1}: 3060 w, 3025 w (C–H_{arom}), 2960, 2870 (C–H_{aliph}), 1665 s (C=$O_{conjug.}$), 1610 s (C=$C_{conjug.}$), 1580 w, 1490 w (C=C_{arom}), 760 s, 690 s [δ (H_{arom})]. ^{1}H NMR spectrum, δ, ppm: 0.91 s (3H, 5-CH_3-*endo*), 0.92 d (6-CH_3, ^3J 7.2 Hz), 1.00 s (3H, 5-CH_3-*exo*), 1.25 d.d (1H, H^7-*anti*, ^2J 9.8, ^WJ 1.6 Hz), 1.48 q (1H, H^6, ^3J 7.2 Hz), 1.72 d (1H, H^4, ^3J 4.0 Hz), 1.96 m (2H, H^1 + H^7-*sin*), 2.75 d.d.d (1H, H^3-*endo*, ^2J 19.8, $^4J_{3,11}$ 2.2 , ^WJ 1.6 Hz), 3.11 d.d.d (1H, H^3-*exo*, ^2J 19.8, $^3J_{3,4}$ 4.0, $^4J_{3,11}$ 2.2 Hz), 6.96 t (1H, H^{11}, $^4J_{11,3\text{-}exo}$ 2.2, $^4J_{11,3\text{-}endo}$ 2.2 Hz), 7.49 m ($3H_{arom}$), 7.90 m ($2H_{arom}$). Mass spectrum, *m/z* (I_{rel}, %): 254 $[M]^+$ (30), 239 $[M - CH_3]^+$ (16), 236 $[M - OH]^+$ (11), 221 (17), 207 (13), 194 (22), 172 (11), 149 $[M - C_6H_5CO]^+$ (32), 134 $[M - C_6H_5CO - CH_3]^+$ (17), 122 (100), 115 (10), 105 (91), 91 (37), 77 $[C_6H_5]$ (84), 51 (16), 41 (27).

b. Ritter reaction was carried out analogously, but 4 ml of acid was added at cooling on an ice bath (0... –5°C). We obtained 4.2 g of a mixture containing 53% of enone **IV**, 43% of enone **V**, and 4% of amidoketone **II**.

c. Ritter reaction catalyzed with BF_3 etherate (10 ml) was carried out analogously by procedure *a,* only the reaction mixture was quenched by excess water solution of NaOH. We obtained 4.25 g of a mixture containing 33% of isocamphane enone **IV**, 65% of enone **V**, and less than 2% of amide **II**.

d. Ritter reaction with enones **IV** or **V** was performed by dissolving 3.0 g of an appropriate enone or their mixture in 6 ml of acetonitrile. Further synthesis was carried out as in procedure *b*. The yield of amidoketone **II** was independent of the enone used and amounted to 2.4 g (65%).

Rearrangement of 2-(phenylethynyl)isocamphanol (III) under treatment with HCOOH. Compound **III** (5.0 g) was dissolved in 10 ml of 85% HCOOH, and the mixture was boiled till the completion of the reaction (GLC monitoring). The reaction mixture was cooled, neutralized with excess aqueous ammonia, the reaction products were extracted into hexane, the extract was dried with $MgSO_4$. On evaporating the solvent we obtained a mixture of **2-(benzoylmethylene)bornane (V)** and **2-(benzoylmethylene)isocamphane (IV)** in a ratio 2:1 (GLC data). Overall yield 80%.

Transformation of 2-(phenylethynyl)isocamphanol (III) under treatment with AcOH catalyzed by H_2SO_4. Compound **III** (5.0 g) was dissolved in 10 ml of glacial acetic acid, a drop of concn. H_2SO_4 was added, and the mixture was stirred till the completion of the reaction (GLC monitoring). The reaction mixture was neutralized with excess cooled aqueous ammonia, the reaction products were extracted into ether, and the extract was dried with $MgSO_4$. On evaporating the extract and removing the polymeric products (see above) we obtained a mixture containing 2-(benzoylmethylidene)bornane (**V**) (43%), 2-(benzoyl-methylidene)isocamphane (**IV**) (42%), and **2-(phenylethynyl)isocamphanol 2-*exo*-acetate (XIII)** (15%). Overall yield 4.4 g. A small quantity of ester **XIII** required for spectral analyses was isolated by chromatography on silica gel. n_D^{17} 1.5211. IR spectrum, cm^{-1}: 3060, 3025 w (C–H_{arom}), 2960, 2910, 2870 (C–H_{aliph}), 2190 w (C≡C), 1735 s (C=O_{ester}), 1580 w, 1490 (C=C_{arom}), 755 s , 690 s [δ (H_{arom})]. ^1H NMR spectrum, δ, ppm: 0.87 s (3H, 5-CH_3-*endo*), 0.90 d (6-CH_3, ^3J 7.2 Hz), 1.02 s (3H, 5-CH_3-*exo*), 1.50 d.d (1H, H^7-*anti*, ^2J 9.8, ^WJ 1.6 Hz), 1.70 m (2H, $H^6 + H^4$), 1.99 C (3H, $COCH_3$), 2.08 m (2H, $H^1 + H^7$-*sin*), 2.23 d.d (1H, H^3-*endo*, ^2J 15.6, ^WJ 2.0 Hz), 2.34 d.d (1H, H^3-*exo*, ^2J 15.6, $^3J_{3,4}$ 4.0 Hz) 7.36 m ($3H_{arom}$), 7.60 m ($2H_{arom}$). Mass spectrum, *m*/*z* (I_{rel}, %): 296 $[M]^+$ (11), 281 $[M - CH_3]^+$ (6), 237 $[M - CH_3COO]^+$ (70), 222 (19), 208 (23), 195 (12), 172 (23), 151 (34), 135 (37), 121 (100), 117 (14), 105 (67), 91 (39), 77 $[C_6H_5]$ (77), 59 (60), 44 (23).

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