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Unusual Products of the Reactions of Verbenone and Verbenol with *N*-Bromosuccinimide in the Presence of Water

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Abstract—The major products of the reactions of (–)-verbenone and (+)-*trans*-verbenol with *N*-bromosuccinimide in the presence of water were compounds having an oxabicyclo[3.2.1]octane skeleton but containing different numbers of bromine atoms in their molecules.

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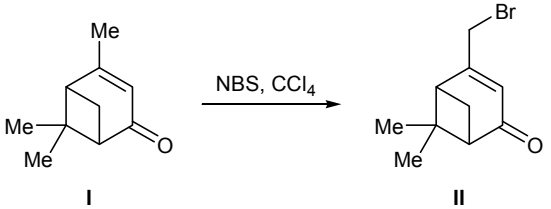
As a rule, olefins react with *N*-bromosuccinimide (NBS) in the presence of water to give the corresponding α-bromohydrins that are used in the synthesis of epoxides. This approach attracts interest, for it ensures formation of an epoxy group at more sterically hindered side of initial olefin. For example, 3-carene *cis*-epoxide was successfully synthesized in such a way, though this compound cannot be obtained by other methods [1, 2].

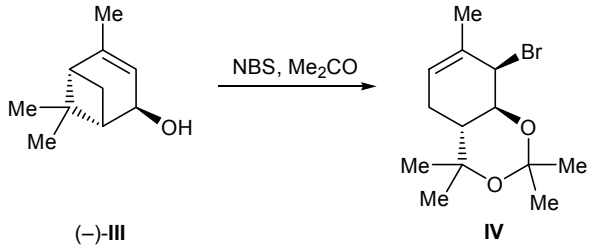
Published data on reactions of other widespread monoterpene, α-pinene, and its derivatives with NBS are very few in number and fragmentary. It was reported that α-pinene reacts with NBS to give complex mixtures of brominated and bromine-free compounds, among which verbenyl bromide, bornyl bromide, mirtenyl bromide, *p*-cymene, and probably fenchyl bromide were identified [3–6]. Furthermore, it was shown previously that the reaction of verbenone (**I**) with NBS in carbon tetrachloride is accompanied by allylic bromination with formation of compound **II** in which the pinane skeleton was conserved [7] (Scheme 1). On the other hand, (–)-*trans*-verbenol [(–)-**III**] reacted with NBS in acetone to give *O*,*O*′-isopropylidene derivative of bromo-substituted diol with a *p*-menthane skeleton (compound **IV**; Scheme 2). The reaction of *cis*-verbenol with NBS followed an analogous pattern [8].

Scheme 1.



I **II**

Scheme 2.

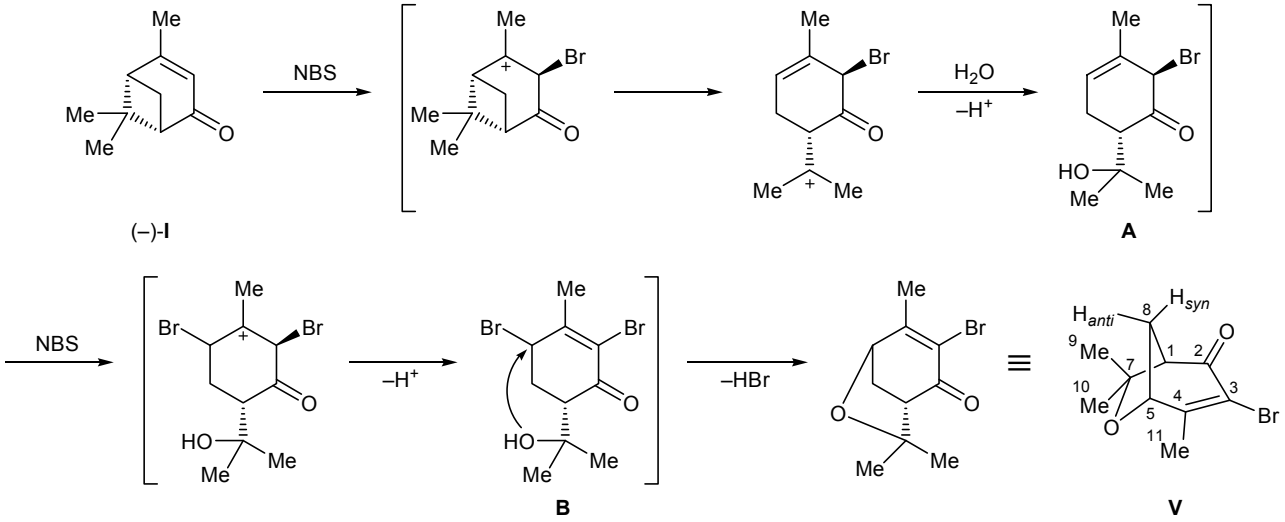


(–)-**III** **IV**

In the present work we examined for the first time the reactions of (–)-verbenone [(–)-**I**] and (+)-*trans*-verbenol [(+)-**III**] with *N*-bromosuccinimide in the presence of water and found that these reactions led to products whose structure differed considerably from the structure of compounds **II** and **IV** obtained previously by reactions of (–)-**I** and (+)-**III** with NBS under different conditions.

The reactions were carried out in aqueous dioxane in the presence of $CaCO_3$ at 50°C, i.e., under the conditions ensuring successful formation of bromohydrins from monoterpenes [2, 9]. (–)-Verbenone [(–)-**I**] reacted with NBS in the above system to produce a fairly complex mixture of products, the major of which was compound **V** having a 6-oxabicyclo[3.2.1]-

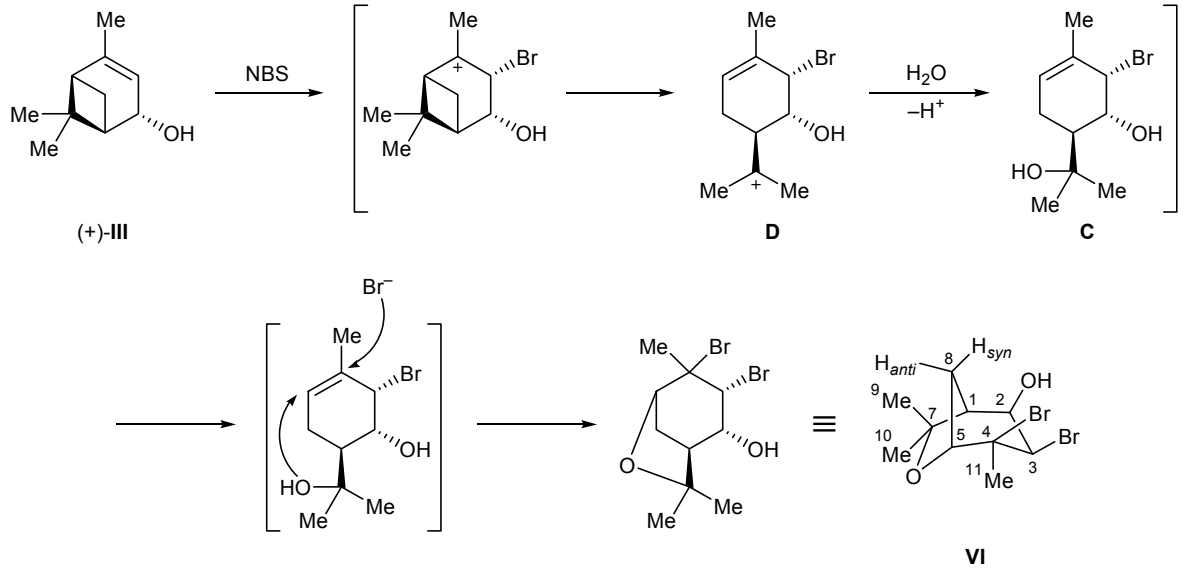
Scheme 3.



octane skeleton. Compound **V** was isolated by column chromatography on silica gel (yield 22%, Scheme 3). Obviously, the reaction begins with attack by bromine atom at the double bond in molecule (–)-**I**, which is followed by rearrangement into cationic species with *p*-menthane skeleton. The latter takes up water molecule to give intermediate enone **A** which is capable of reacting with the second NBS molecule. Dibromide **B** thus formed undergoes intramolecular nucleophilic substitution of bromine atom by oxygen atom in the hydroxy group, finally leading to compound **V**.

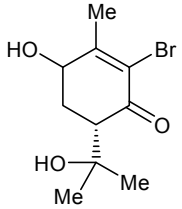
The reaction of (+)-*trans*-verbenol [(+)-**III**] with NBS under analogous conditions followed a different pattern (Scheme 4). In this case, the product was dibromo-substituted bicyclic alcohol **VI** which was isolated in 39% yield. Presumably, the reaction involves initial formation of intermediate **C** which may be regarded as an analog of **A** (Scheme 3). Acetonide **IV** (see above) is likely to be formed through another enantiomer of cation **D** which is precursor of **C**. However, in our case the reaction does not stop at the stage of formation of *p*-menthane derivative, but concerted addition of bromine cation at the double bond and intramolecular heterocyclization give compound **VI**. Compound **V** could also be formed according to a mechanism similar to that shown in Scheme 4; but in this case the heterocyclization should be followed by dehydrobromination.

Scheme 4.

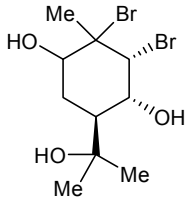


When the reaction of (+)-**III** with NBS was performed at room temperature over a period of 3 days, we obtained a more complex mixture of products, but the major product was again compound **VI**.

We have found no published data on compounds **V** and **VI**, and their structure was determined on the basis of the ^{1}H and ^{13}C NMR spectra and high-resolution mass spectra. Structure **VII** as an alternative to **V** was ruled out taking into account the ^{13}C NMR spectrum recorded from solution in $CDCl_3$ with addition of D_2O. The chemical shifts of carbon atoms attached to oxygen (δ_C 79.09 and 80.81 ppm) did not change upon addition of D_2O. If hydroxy groups were present, the corresponding signals would be displaced upfield due to isotope effect (replacement of OH by OD).



VII



VIII

In the ^{13}C NMR spectrum of compound **VI** in $CDCl_3$ only one signal at δ_C 70.45 ppm was displaced upfield ($\Delta\delta_C$ = 0.12 ppm) upon addition of D_2O, indicating the presence of only one hydroxy group in its molecule. These data reject alternative structure **VIII**.

The presence of a coupling constant between the 2-H and *anti*-8-H protons (J = 1.0 Hz, *W*-coupling) in the ^{1}H NMR spectrum of **VI** suggests that these protons occupy equatorial positions. Orientation of the 3-H proton cannot be determined on the basis of the vicinal coupling constant for 2-H and 3-H (J = 4.2 Hz). On the other hand, paramagnetic shift of the *syn*-8-H signal relative to the corresponding signal of compound **V** is likely to result from deshielding effect of the hydroxy group and bromine atom on C^2 and C^4, respectively, due to 1,3-diaxial interaction. Therefore, the 2-OH and 4-Br substituents are oriented *cis* with respect to each other and to the *syn*-8-H proton.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded from solutions in $CDCl_3$ or $CDCl_3$–CCl_4 (~1:1 by volume) on a Bruker DRX-500 spectrometer at 500.13 MHz for ^{1}H and 125.76 MHz for ^{13}C; the chemical shifts were determined relative to the solvent signals (δ 7.24, δ_C 76.90 ppm). The structure of the isolated compounds was determined by analysis of their ^{1}H NMR spectra with the use of ^{1}H–^{1}H double resonance techniques, as well as by analysis of the ^{13}C NMR spectra recorded with J modulation (JMOD) and off-resonance decoupling from protons and two-dimensional ^{13}C–^{1}H heteronuclear correlation spectra using direct and long-range couplings (C–H COSY, $^1J_{CH}$ = 135 Hz; COLOC, HMBC, $^{2,3}J_{CH}$ = 10 Hz). The high-resolution mass spectra (electron impact, 70 eV) were obtained on a DFS Thermo Scientific spectrometer with direct sample admission into the ion source (a.m.u. range 0–500). The optical rotations ($[\alpha]_D$) were measured on a PolAAr 3005 polarimeter.

(5*S*)-3-Bromo-4,7,7-trimethyl-6-oxabicyclo[3.2.1]-oct-3-en-2-one (V). *N*-Bromosuccinimide, 0.956 g (5.37 mmol), was added under stirring to a mixture of 0.400 g (2.67 mmol) of (–)-verbenone [(–)-**I**, $[\alpha]_D^{25}$ = –210.5° (*c* = 0.77, $CHCl_3$)], 0.265 g (2.65 mmol) of $CaCO_3$, 8 ml of water, and 16 ml of dioxane. The mixture was stirred for 2 h at 50–60°C and cooled to room temperature, 30 ml of water was added, and the product was extracted into diethyl ether (3×40 ml). The extracts were combined, washed with water (3×30 ml), 0.1 N aqueous $Na_2S_2O_3$ (2×20 ml), and water again (2×30 ml), and dried over Na_2SO_4. The drying agent was filtered off, the solvent was distilled off from the filtrate, and the residue was subjected to column chromatography on silica gel (Macherey–Nagel, 60–200 μm) using hexane–diethyl ether mixtures as eluent (gradient elution, 0 to 20% of diethyl ether). Yield 0.144 g (22%), $[\alpha]_D^{22}$ = –103.8° (*c* = 1.54, $CHCl_3$). ^{1}H NMR spectrum ($CDCl_3$–CCl_4), δ, ppm: 1.13 s ($C^{10}H_3$), 1.32 s (C^9H_3), 2.22 s ($C^{11}H_3$), 2.24 d.d (*syn*-8-H, ^2J = 11.5, $J_{8,1}$ = 0.5 Hz), 2.33 d.d.d (*anti*-8-H, ^2J = 11.5, $J_{8,5}$ = 4.8, $J_{8,1}$ = 4.1 Hz), 3.05 d.d.d (1-H, $J_{1,anti\text{-}8}$ = 4.1, $J_{1,5}$ = 1.3, $J_{1,syn\text{-}8}$ = 0.5 Hz), 4.49 d.d (5-H, $J_{5,anti\text{-}8}$ = 4.8, $J_{5,1}$ = 1.3 Hz). ^{13}C NMR spectrum ($CDCl_3$–CCl_4), δ_C, ppm: 59.23 d (C^1), 191.72 s (C^2), 124.43 s (C^3), 161.37 s (C^4), 79.09 d (C^5), 80.81 s (C^7), 38.05 t (C^8), 29.44 q (C^9), 25.84 q (C^{10}), 23.27 q (C^{11}). Found: *m*/*z* 244.0099 $[M]^+$. $C_{10}H_{13}BrO_2$. Calculated: *M* 244.0093.

3,4-Dibromo-4,7,7-trimethyl-6-oxabicyclo[3.2.1]-octan-2-ol (VI). *N*-Bromosuccinimide, 0.235 g (1.32 mmol), was added under stirring to a mixture of 0.100 g (0.66 mmol) of (+)-*trans*-verbenol [(+)-**III**, $[\alpha]_D^{23}$ = +115.2° (*c* = 0.12, $CHCl_3$)], 0.066 g (0.66 mmol) of $CaCO_3$, 2 ml of water, and 4 ml of dioxane. The mixture was stirred for 3 h at 50–60°C, cooled to room temperature, treated with 10 ml of water, and extracted with diethyl ether (2×20 ml). The

extracts were combined, washed with water (4×10 ml) and 0.1 N aqueous $Na_2S_2O_3$ (2×10 ml), and dried over Na_2SO_4, 7.5 ml of hexane and 4 ml of diethyl ether were added to the residue, the solution was separated by decanting, and the solvent was distilled off. Yield 0.086 g (39%), $[\alpha]_D^{22} = -1.9°$ (c = 0.94, $CHCl_3$). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.24 s (C^9H_3), 1.32 s ($C^{10}H_3$), 1.78 s ($C^{11}H_3$), 2.24 d.d.d.d (*anti*-8-H, ^2J = 13.0, $J_{8,5}$ = 6.1, $J_{8,1}$ = 4.2, $J_{8,2}$ = 1.0 Hz), 2.29 d.d (1-H, $J_{1,anti\text{-}8}$ = 4.2, $J_{1,2}$ = 4.2 Hz), 2.54 br.d (OH, $J_{OH,2}$ = 2.6 Hz), 3.14 d (*syn*-8-H, ^2J = 13.0 Hz), 4.05 d.d.d.d (2-H, $J_{2,1}$ = $J_{2,3}$ = 4.2, $J_{2,OH}$ = 2.6, $J_{2,anti\text{-}8}$ = 1.0 Hz), 4.30 d (5-H, $J_{5,anti\text{-}8}$ = 6.1 Hz), 4.51 d (3-H, $J_{3,2}$ = 4.2 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 46.68 d (C^1), 70.45 d (C^2), 62.00 d (C^3), 68.81 s (C^4), 83.37 d (C^5), 82.53 s (C^7), 28.56 t (C^8), 29.82 q (C^9), 22.27 q (C^{10}), 30.91 q (C^{11}). Found: m/z 325.9502 $[M]^+$. $C_{10}H_{16}Br_2O_2$. Calculated: M 325.9512.

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