

Ritter Reaction on Terpenoids, I

Stereospecific Preparation of (1S,5R,8R) and (1R,5S,8S) 8-Acetamido-2,4,4,8-tetramethyl-3-aza-bicyclo[3.3.1]non-2-ene Perchlorate

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Ritter Reaction, (+)Limonene, (–)β-Pinene, Terpinolene, Stereospecific Synthesis

Treatment of (+)limonene with diluted perchloric acid in acetonitrile solution afforded (1S,5R,8R) 8-acetamido-2,4,4,8-tetramethyl-3-aza-bicyclo[3.3.1]non-2-ene perchlorate while the same reaction on (–)β-pinene produced the (1R,5S,8S) enantiomer, and terpinolene gave the racemic mixture. The structure of the product is proposed on basis of its physical and spectroscopic (IR, ¹H and ¹³C NMR, MS) properties and its formation involves a Ritter reaction between the monoterpene and acetonitrile.

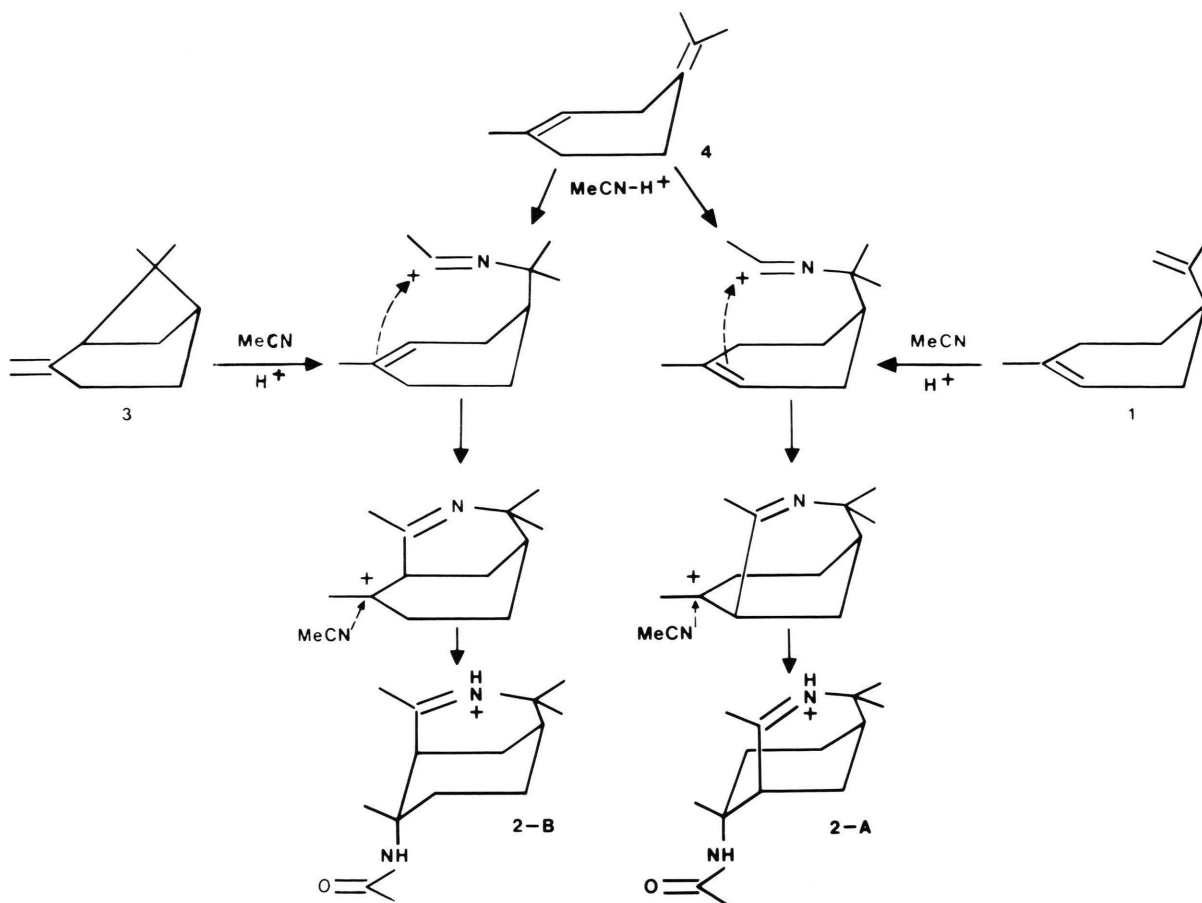
When studying the electrochemical behaviour of monoterpenes (limonene, β-pinene and terpinolene) in perchloric acid solutions employing acetonitrile-water as solvent, it was found that, at low water contents, stationary oxidation currents could be sustained [1]. However, when long term potentiostatic experiments and systematic cyclic voltammetry measurements were carried out, complicating features were observed which lead to the conclusion that additional chemical processes were taking place in the solution bulk and, therefore, it was decided to investigate the chemical behaviour of the mentioned monoterpenes in the chosen reaction medium.

Reaction of (+)limonene (**1**) in the conditions indicated in Experimental afforded an optically active, [α]_D –83.5°, crystalline product, C₁₄H₂₅N₂O₅Cl, for which structure **2a** is proposed on the basis of the following properties. The molecular formula together with the IR bands at 3280 and 1525 cm^{–1} indicate the presence of an acetamido group while bands at 2720–2660 and 1660 cm^{–1} point to an iminium salt

in a bicyclic structure, in which there are no signals of olefinic protons in the 100 MHz ¹H NMR spectrum, but presents a signal of a ketiminic carbon-atom at 190.9 ppm in the ¹³C NMR spectrum. This signal was assigned to the carbon of the iminium salt carrying a C-methyl group which resonates at δ 2.61 in the ¹H NMR spectrum. The presence of the acetamido residue was confirmed by signals at 172.5 ppm in the ¹³C NMR (amidic carbonyl) and of a methyl group at δ 2.02 in the ¹H NMR respectively. This spectrum also shows three methyl singlets which are indicative of substitution on the carbons of the starting compound that carried methyl groups, further confirmed by the fully decoupled and off-resonance ¹³C NMR spectrum. The mass spectrum of **2a** indicates the presence of a perchlorate salt whose acid moiety is lost giving the heaviest ion at *m/z* 236 (C₁₄H₂₄N₂O) which suffers further fragmentations indicative of the presence of the acetamido group and leading to a probable bicyclic fragment of *m/z* 177 which losses 55 amu (retro Diels-Alder and hydrogen transfer) giving the base peak at *m/z* 122.

The formation of compound **2a** from reaction of limonene with acetonitrile in acid medium could follow the pathway shown in Scheme 1, the Ritter reaction [2–4] being the first step in the sequence.

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When the same procedure was applied to $(-)\beta$ -pinene (**3**) (see Experimental) compound **2b** was obtained which has identical physical and spectroscopic properties as **2a** but shows an optical rotation value of $+85.2^\circ$. The stereospecificity of the reactions is consistent with the mechanism proposed in Scheme 1 which was further confirmed by the result obtained when terpinolene (**4**) was submitted to the same reaction affording the racemic mixture **2a–2b** with identical properties as **2a** and/or **2b** except for being optically inactive.

The present study shows a novel reaction of mono and bicyclic monoterpenes with acetonitrile – *via* the Ritter N-alkyl amide synthesis followed by intramolecular alkylation – to yield azabicyclic compounds which, in turn, could be applied to the synthesis of a variety of new aza products.

Work is in progress to extend the scope and to establish the limitations of the procedure.

Experimental

Melting points are uncorrected. The IR spectrum were registered in KBr pellets using a Beckman IR-33 spectrophotometer, ^1H and ^{13}C FT-NMR spectra were recorded at 100 MHz and 25.2 MHz respectively with a Varian XL-100-15 spectrometer; solvents are indicated in each case. Mass spectra were performed at 70 eV (direct inlet) with a Varian-Mat CH7-A spectrometer interfaced to a Varian-Mat Data System 166 computer.

(1*S*,5*R*,8*R*) 8-Acetamido-2,4,4,8-tetramethyl-3-azabicyclo[3.3.1]non-2-ene perchlorate (**2a**)

(+)-Limonene (Fluka, purum) purified as described elsewhere [1] (2.81 g) was dissolved in analytical grade acetonitrile (103.45 ml) containing concentrated perchloric acid (3.81 ml) and water (0.42 ml). After 6 h at room temperature the solvents were evaporated *in vacuo* and at room temperature affording a crystalline precipitate (1.92 g)

which was recrystallized from ethyl alcohol and from acetone-benzene. The pure compound had m.p. 252–253 °C, $[\alpha]_D^{22}$ –83.5° (c 0.85, methyl alcohol).

IR: 3280 (NH), 2720–2660 (NH), 1660 (C=N), 1525 (N–C = O) cm^{-1} , 1100 and 620 (ClO_4^-) cm^{-1} [5].

^1H NMR (CDCl_3 – CD_3OD –TMS): δ 1.48 (s, 3H, CH_3 -8), 1.51 (s, 3H, CH_3 -4), 1.54 (s, 3H, CH_3 -4), 1.94 (b.s., 8H, CH_2 and CH), 2.03 (s, 3H, CH_3 –CO–N), 2.61 (s, 3H, CH_3 -2), 3.68 (b.s., 1H, NH), 7.26 (s, 1H, =NH). The last two signals disappear by exchange with D_2O –DCl.

^{13}C NMR (CDCl_3 – CD_3OD –TMS): δ 22.39 (CH_3 –CO–N), 23.57 (two CH_3 at 4), 27.04 (C-7), 27.27 (C-6), 29.48 (CH_3 at 2 and CH_3 at 8), 32.25 (C-9), 34.02 (C-5), 42.55 (C-1), 56.24 (C-8), 62.42 (C-4), 172.47 (CH_3 –CO–N), 190.90 (C-2).

MS (m/z , %): 236 (M– HClO_4 , 70), 221 (236–15, 18), 177 (236–59, 52), 162 (236–15–59, 36), 150 (177–27, 59), 122 ($\text{C}_8\text{H}_{12}\text{N}$, 100), 43 ($\text{C}_2\text{H}_5\text{N}$, 23), 42 ($\text{C}_2\text{H}_4\text{N}$, 44).

Analysis for $\text{C}_{14}\text{H}_{25}\text{N}_2\text{O}_5\text{Cl}$

Calcd	C 49.92	H 7.48	N 8.31	Cl 10.52,
Found	C 50.01	H 7.28	N 8.30	Cl 10.89.

(1*R*,5*S*,8*S*) 8-Acetamido-2,4,4,8-tetramethyl-3-azabicyclo[3.3.1]non-2-ene perchlorate (**2b**)

(–) β -Pinene (2.50 g) was treated as already described for limonene. The crystalline product

(2.86 g) had m.p. 252–253 °C, $[\alpha]_D^{22}$ +85.2° (c 0.87, methyl alcohol). The IR, ^1H and ^{13}C NMR and MS were identical to those registered for the previously described product (**2a**).

Analysis for $\text{C}_{14}\text{H}_{25}\text{N}_2\text{O}_5\text{Cl}$

Calcd	C 49.92	H 7.48	N 8.31	Cl 10.52,
Found	C 49.73	H 7.51	N 8.24	Cl 10.54.

Racemic 8-acetamido-2,4,4,8-tetramethyl-3-azabicyclo[3.3.1]non-2-ene perchlorate (**2a–2b**)

Terpinolene (2.80 g) was submitted to the same reaction procedure giving a crystalline product (1.12 g) of m.p. 243–244 °C, $[\alpha]_D^{22}$ +0.23° (c 0.86, methyl alcohol) with spectroscopic properties identical to those obtained for **2a** or **2b**.

Analysis for $\text{C}_{14}\text{H}_{25}\text{N}_2\text{O}_5\text{Cl}$

Calcd	C 49.92	H 7.48	N 8.31	Cl 10.52,
Found	C 49.75	H 7.22	N 8.07	Cl 10.26.

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