NUCLEOPHILIC ADDITION OF NITRILES TO TERTIARY MONOCYCLIC TERPENES ALCOHOLS

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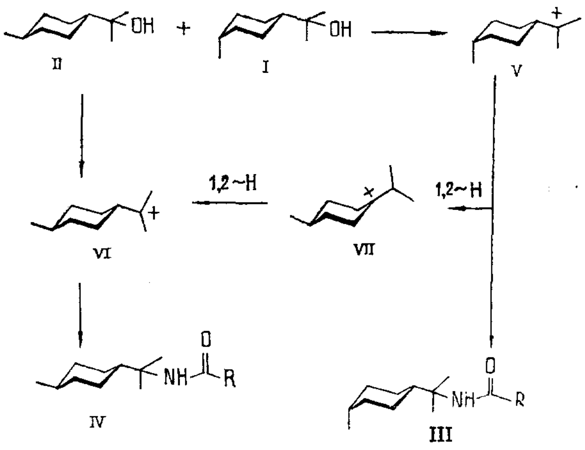
Previously unknown secondary amines have been synthesized by the Ritter reaction of p-menthan-8-ol with propio- and benzonitriles. The performance of this reaction with α-terpeneol and benzonitrile led to the formation of a mixture of N-(p-menth-1-en-8-yl)benzamide and N,N-(p-menth-1,8-diyl)dibenzamide. A trans-diamide was also obtained on the reaction of α-terpineol with isovaleronitrile. The use of propionitrile as the nucleophile with α-terpineol led to the formation of 2-ethyl-4,4,8-trimethyl-8-propionamido-3-azabicyclo[3.3.1]non-2-ene.

It is known [1] that a change in the conditions of performing the Ritter reaction has a decisive influence on the direction of the interaction of monoterpenoids with nitriles in the presence of acids. It has been shown previously [2] that the action of acetonitrile on p-menth-1-en-8-ol in the presence of concentrated sulfuric acid forms N-(p-menth-1-en-8-yl)acetamide. When limonene (p-mentha-1,8-diene) is heated with hydrocyanic acid in the presence of sulfuric acid, p-mentha-1,8-diyldiformamide is obtained [3]. Caram et al. [4] have shown that when the Ritter reaction of limonene with acetonitrile is performed in dilute perchloric acid solution (1S,5R,8R)-2,4,4,8-tetramethyl-8-acetamido-3-azabicyclo-[3.3.1]non-2-ene perchlorate is formed stereospecifically. cis- and trans-p-Menthan-8-ols and p-menthenes gave a N-(p-menth-8-yl)acetamide in which the trans isomer predominated [2]. cis-Carveol (5-isopropenyl-2-methylcyclohex-2-en-1-ol), on reacting with acetonitrile in the presence of perchloric acid, gave the corresponding trans-amide in quantitative yield [5]. It follows from the facts given the study of the interaction of terpenoids of the p-menthane series with nitriles under the conditions of the Ritter reaction is of undoubted interest for determining the reactivities of compounds of this path.



where $R = CH_2CH_3$ (a); $R = C_6H_5$ (b)

We have studied the reactions of the tertiary terpene alcohols cis- and trans-p-menthan-8-ols and α-terpineol with propio-, isovalero-, and benzonitriles. The reactions were carried out at room temperature (∿20°C) in the presence of concentrated sulfuric acid.

It was established that the reaction between cis- and trans-p-menthan-8-ols (I and II, respectively), in a ratio of 1:1 takes place with the formation of a mixture of cis- and trans-p-menth-8-ylacetamides (III and IV, respectively) in a ratio of 1:6. It is obvious

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TABLE 1. PMR Spectra of the Amides (IX-XII)

Compound	Solvent	Chemical shift, δ, ppm	Multiplicity	Assignment
IX	$CDCl_3$	1,41	s	9,10-CH_3
		1,43	s	9,10-CH_3
		1,51	s	7-CH_3
		1,74	m	6H
		2,22	m	2H
		5,77	s	C^2—H
		5,93	s	N—H
		7,43	m	5H aromatic protons
X	$CDCl_3$	1,38	s	9,10-CH_3
		1,47	s	7-CH_3
		1,62	m	5H
		1,74	m	2H
		2,19	m	2H
		5,94	s	2 NH
		7,64	s	10H aromatic protons
XI	CD_3OD	0,92	d	14,15-CH_3
		0,94	d	14,15-CH_3
		1,21	m	2C^{13}—H
		1,25	s	9,10-CH_3
		1,35	s	7-CH_3
		1,57	m	2C^{11}—CH_2
		2,00	m	9H
XII	$CDCl_3$	1,08	t	17-CH_3
		1,12	s	11-CH_3
		1,16	t	14-CH_3
		1,28	s	12-CH_3
		1,41	s	10-CH_3
		1,43	m	2H
		1,61	m	2H
		1,80	m	4H
		2,10	dd	13-CH_2
		2,29	dd	16-CH_2
		5,31	s	N—H

that the ion (V) initially formed from the cis-isomer of the alcohol (I) in an acid medium is converted by successive 1,2-hydride shifts into the thermodynamically more stable ion (VI).

The hydride-ion transfer in cation (VII) takes place extremely stereospecifically, leading to the formation mainly of the ion (VI) with the trans arrangement of the substituents, and not the ion (V) with their cis configuration, as can be seen from the ratio of the isomers of the reaction products — the secondary amides (III) and (IV). The yields of the amides (IIa), (IIIa) and (IIb), (IIIb) were somewhat lower than those of N-(p-menth-8-yl)acetamide [2], probably because of the lower nucleophilicity of propio- and benzonitriles as compared with acetonitrile, and also as the result of an increase in the steric hindrance.

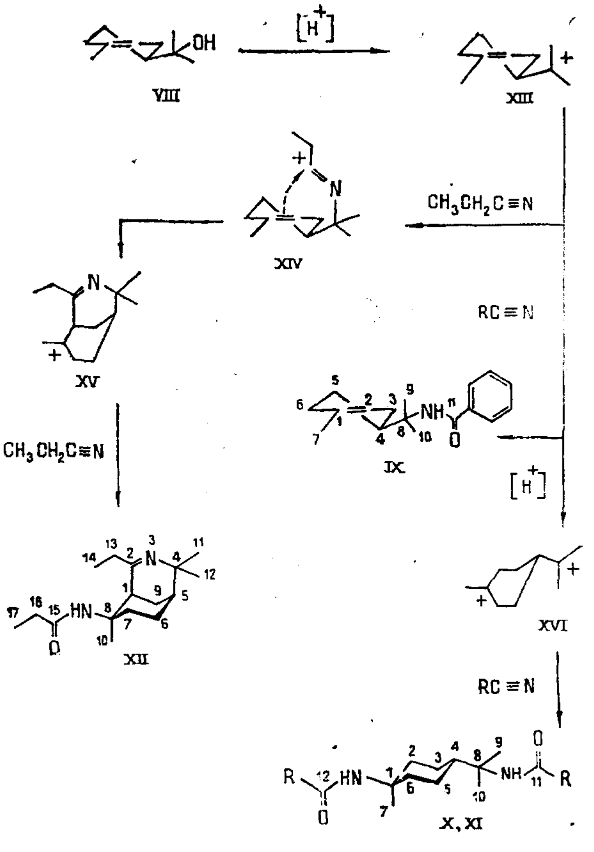
In a study of the interaction of α-terpineol (p-menth-1-en-8-ol) (VIII) with propio-, isovalero-, and benzonitriles we observed no analogy with the reaction of this tertiary alcohol with acetonitrile. The reactivities of each of the nitriles mentioned, and also spatial factors are probably responsible for the formation of different products. Thus, the interaction of P-terpineol (p-menth-1-en-8-ol) (VIII) with benzonitrile led to the formation of N-(p-menth-1-en-8-yl)benzamide (IX) and N,N-(p-menth-1,8-diyl)dibenzamide (X). The structures of the amides (IX) and (X) obtained were shown by the PMR spectroscopy. In the PMR spectrum of the amide (IX) the singlets of the three methyl groups at C^1 and C^8, a multiplet of eight protons of the hydrocarbon skeleton, a singlet of the vinyl proton at C^2, a singlet of the proton attached to the nitrogen atom and a multiplet of five protons of the aromatic ring were identified (Table 1). In the PMR spectrum of the diamide (X) (see Table 1) the signals of the three methyl groups at C^1 and C^8, a multiplet of nine protons of the cyclohexane ring, and a multiplet of ten protons of the two aromatic rings were assigned.

The action on α-terpineol of isovaleronitrile led with a yield of about 40% only to N,N-(p-menth-1,8-diyl)diisovaleramide (XI), the structure of which was confirmed unambiguously by its ^{1}H and ^{13}C NMR spectra. The PMR spectrum of the diamide (XI) had two doublets of four methyl groups of a substituted isovaleramide, the singlet of two methyl groups at C^8, the singlet of a methyl group at C^1, the multiplet of two methylene groups adjacent to carbonyl groups, and multiplets of the protons of the cyclohexane ring (see Table 1). We assume that the methyl group at C^1 of the diamide is present in the axial position on the basis of the fact that for 1,4-disubstituted dihexanes the trans-e,e conformation is more stable [6], while the more voluminous substituents — in the present case, the amide groups — must be present in the equatorial position.

The results of ^{13}C NMR spectroscopy well confirmed our hypothesis. In the ^{13}C NMR spectrum of the diamide (XI) the following signals were identified (δ, ppm): C^1 – 54.6 s, $C^{2,6}$ – 38.17 t, $C^{3,5}$ – 24.67 t, C^4 – 45.5 d, C^7 – 22.0 q, C^8 – 57.5 s, $C^{9,10}$ – 24.83 q, C^{11} – 175.0 s, C^{12} – 47.33 t, C^{13} – 27.67 d, C^{14} – 22.9 q, C^{15} – 23.0 q. The ^{13}C chemical shifts given for compound (XI) agree well with the chemical shifts given in the literature [7] for the structurally close trans-diequatorial 1,8-dichloro-p-menthane when the different contributions of the substituents are allowed for.

On the reaction of α-terpineol (VIII) with propionitrile, a considerable amount of resin formation was observed. However, it was possible to isolate from the reaction mixture the individual compound (XII) which, according to its IR spectrum, contained an amide group: amide I band, ν(C=O), s, 1642 cm^{-1}; amide II band, δ(N—H), s, 1550 cm^{-1}; and ν(N—H) bands at 3280 s, 3200 w, and 3070 m, cm^{-1}. We assigned the 1662 cm^{-1} band to the ν(C=N) bond vibrations. The mass spectrum of compound (XII) had the peak of the molecular ion M$^+$, at 264 m/z. Its PMR spectrum contained three singlets and two triplets of five methyl groups, two doublets of doublets of methylene groups, multiplets of eight protons, and a singlet of a proton attached to a nitrogen atom (see Table 1). On the basis of the facts presented, the compound (XII) that had been obtained was assigned the structure of 2-ethyl-4,4,8-trimethyl-8-propionamido-3-azabicyclo[3.3.1]non-2-ene.

The ^{13}C NMR spectrum confirmed the suggested structure of (XII). The following signals were identified in the ^{13}C NMR spectrum (δ, ppm): C^1 – 35.23 d, C^2 – 152.49 s, C^4 – 60.92 s, C^5 – 34.13 d, C^6 – 27.34 t, C^7 – 28.08 t, C^8 – 58.72 s, C^9 – 32.85 t, C^{10} – 25.69 q, $C^{11,12}$ – 25.87 q, C^{13} – 39.27 t, C^{14} – 13.58 q, C^{15} – 173.77 s, C^{16} – 36.33 t, C^{17} – 11.01 q. The assignment of the signals was made on the basis of the multiplicity of the lines



in the spectrum recorded without the suppression of coupling with protons and agreed well with the assignment of the ^{13}C signals in the spectrum of a substituted 3-azabicyclo[3.3.1]-non-2-ene perchlorate of similar structure [4].

The formation of 2-ethyl-4,4,8-trimethyl-8-propionamido-3-azabicyclo[3.3.1]non-2-ene (XII), from α-terpineol and propionitrile in the presence of sulfuric acid obviously takes place through the formation in the first stage of the ion (XIII), which, adding a molecule of the nitrile, is converted into the ion (XIV). As a result of successive 1,2 and trans-annular hydride shifts, the cation (XIV) cyclizes with the formation of the ion (XV), the stabilization of which takes place on the addition of a nucleophile (propionitrile) to the cationic center.

EXPERIMENTAL

^1H and ^{13}C NMR spectra were taken on a Bruker WM-360 spectrometer. Deuterated chloroform and deuterated methanol were used as solvents. The ^1H and ^{13}C chemical shifts were determined relative to the internal standard tetramethylsilane. IR spectra were taken on a UR-20 spectrometer, and mass spectra on a MKh-1320 instrument. GLC analysis was performed on a LKhM-7A chromatograph with programming of the temperature from 90 to 200°C in a column (0.5 mm × 2 m) filled with Chromosorb W (60-80 mesh) and crystalline KOH (9:1) impregnated with Apiezon K (12%).

The Ritter reaction of a mixture of cis- and trans-p-methan-8-ol and of α-terpineol with nitriles was carried out by a general procedure [8].

N-(p-Menth-8-yl)propionamide (III, IVa), $C_{13}H_{25}ON$, mp 96°C (from ethanol). Found, %: C 74.11, H 12.03, N 6.37. Calculated, %: C 73.88, H 11.92, N 6.23, λ_{max}^{KBr}, cm^{-1}: 3300, 3075 (N–H), 2960, 2930, 2880, 2850 (C–H), 1650 (C=O), 1550 (N–H).

Mass spectrum, m/z (%): 211 (M^+; 10), 196, 177, 168, 154, 140, 138, 136, 123, 112, 93 (100), 81. Yield 48%.

N-(p-Menth-8-yl)benzamide (III, IVb), $C_{16}H_{25}ON$, mp 121°C (from ethanol). Found, %: C 78.85; H 9.71; N 5.45. Calculated, %: C 78.72, H 9.72, N 5.40. λ_{max}^{KBr}, cm^{-1}: 3380, 3180 (N–H), 1680 (C=O), 1580 (N–H), 1610, 1450, 720 (benzene ring).

Mass spectrum, m/z (%): 259 (M^+; 16), 216, 141, 136, 121 (100), 105, 95, 76. Yield 37%.

N-(p-Menth-1-en-8-yl)benzamide (IX), $C_{17}H_{23}ON$, mp 193°C (from ethanol). Yield 45%. Found, %: C 79.45, H 9.11, N 5.52. Calculated, %: C 79.33, H 9.01, N 5.44. λ_{max}^{KBr}, cm^{-1}: 3340, 3065 (N–H), 2945, 2875 (C–H), 1640 (C=O), 1580 (N–H), 1535 (C=C), 3030, 1610, 1490, 720 (benzene ring).

Mass spectrum, m/z (%): 257 (M^+; 8), 242, 239, 217, 162, 136, 122, 105 (100), 93, 77.

N,N-(p-Menth-1,8-diyl)dibenzamide (X), $C_{24}H_{30}O_2N_2$, mp 235°C (from ethanol). Yield 15%. Found, %: C 76.01, H 8.12, N 7.31. Calculated, %: C 76.16, H 7.99, N 7.40. λ_{max}^{KBr}, cm^{-1}: 3330, 3070, (N–H), 2950, 2875 (C–H), 1650 (C=O), 1550 (N–H), 3020, 1610, 1455, 710 (benzene ring).

Mass spectrum, m/z (%): 389 (M^+; 5), 257, 273, 242, 217, 162, 136, 122, 105 (100), 77.

N,N-p-(Menth-1,8-diyl)diisovaleramide (XI), $C_{20}H_{38}O_2N_2$, mp 219°C (from ethanol). Yield 40%. Found, %: C 71.07, H 11.25, N 8.06. Calculated, %: C 70.96, H 11.31, N 8.28. λ_{max}^{KBr}, cm^{-1}: 3300, 3170 (N–H), 2960, 2875 (C–H), 1650 (C=O), 1550 (N–H).

Mass spectrum, m/z (%): 338 (M^+; 9), 323, 253, 237, 211, 197, 142, 136 (100), 121, 102, 93, 81, 70, 58, 41.

2-Ethyl-4,4,8-trimethyl-8-propionamido-3-azabicyclo[3.3.1]non-2-ene (XII), $C_{16}H_{28}ON_2$, mp 99°C (from ethanol). Yield 24%. Found, %: C 72.57, H 10.74, N 10.41. Calculated, %: C 72.68, H 10.68, N 10.59.

Mass spectrum, m/z (%): 264 (M^+; 15), 249, 209, 191, 176, 160, 150, 136 (100), 122, 97, 57, 41.

SUMMARY

By the Ritter reaction of p-menthan-8-ol with propio- and benzonitriles the corresponding secondary amides, not previously described have been synthesized. The use in this reaction of α-terpineol and benzonitrile led to the formation of a mixture of N-(p-menth-1-en-8-yl)-benzamide and N,N-(p-menth-1,8-diyl)dibenzamide. A trans-diamide was also obtained in the reaction of P-terpineol with isovaleronitrile. The use of propionitrile as the nucleophile led to the formation from P-terpineol of 2-ethyl-4,4,8-trimethyl-8-propionamido-3-azobicyclo[3.3.1]non-2-ene.

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STRUCTURE OF FERULIDE

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The structure of a new sesquiterpene lactone — ferulide from *Ferula penninervis* Regel et Schmalh — has been established on the basis of its spectral characteristics. This compound has the composition $C_{20}H_{24}O_5$, mp 135-137°C.

On standing, the mother liquor from ferolide — a sesquiterpene lactone isolated previously from the seeds of *Ferula penninervis* Regel et Schmalh [1] — deposited crystals of a new compound with mp 135-137°C, composition $C_{20}H_{24}O_5$ (I).

The IR spectrum of (I) had the absorption bands of the carbonyl of a γ-lactone ring (1790 cm^{-1}), of an α,β-conjugated C=O of an ester group (1720 cm^{-1}), and bands characteristic for a guaiadienone grouping (1690, 1650, and 1620 cm^{-1}). The mass spectrum showed, in addition to the peak of the molecular ion (M^+ 344), the peak of an ion with m/z 244 [M — 100]. The splitting out of an ion with m/z 100 is possible if the ester group in (I) contains a senecionic, angelic, or tiglic acid residue. This and other questions of the structure of the compound under investigation were solved by considering the characteristics of the proton magnetic resonance spectra.

The PMR spectrum of (I) ($CDCl_3$, 0 — TMS, Varian SC-300) had one-proton multiplets at 5.69 and 6.16 ppm with half widths of 4 Hz from two olefinic protons, and the signals of the protons of five methyl groups: 1.54 (s), 1.91 (d, ^4J = 1.2 Hz), 2.15 (d, ^4J = 1.2 Hz), 2.24, and 2.29 ppm (br.s). In the homonuclear double proton-proton resonance spectrum, when the transitions of the nuclei of the olefinic proton with a CS of 5.69 ppm were saturated, the doublets of methyl groups at 1.91 and 2.15 ppm were synchronously converted into singlets. Consequently, the ester group of the compound contains a semecionic acid residue (5.69, 1.91, and 2.15 ppm).

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