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DIELS—ALDER MODIFICATION OF MONOTERPENES AND ALDER—ENE SYNTHESIS INVOLVING 3-METHYL-3-CYANOCYCLOPROPENE

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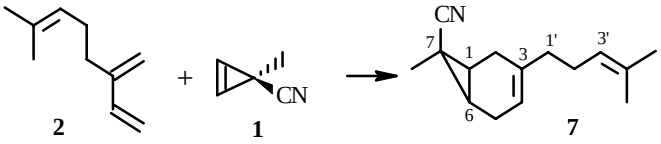
Monoterpene derivatives with a cyclopropane moiety in the molecule were prepared by reactions of 3-methyl-3-cyanocyclopropene with several monoterpenes and terpenoids (β-myrcene, neoalloocimene, alloocimene, β-pinene, carvone). They were formed using the Diels—Alder reaction, Alder—ene synthesis, conjugated Alder—ene addition, and Diels—Alder cyclization.

Key words: monoterpenes, Diels—Alder reaction, Alder—ene synthesis, 3-methyl-3-cyanocyclopropene.

We studied reactions of the most characeristic unsaturated monoterpenes (acylic, monocyclic, and bicyclic) with 3-methyl-3-cyanocyclopropenene (**1**) in order to prepare new synthetic derivatives of monoterpenoids with a cyclopropane moiety that in some instances exhibit important biological activity [1]. Compound **1** is formally a hemiterpene that can undergo cycloaddition reactions [2].

In the first part of the work, we studied reactions of 2,6-dimethyloctane monoterpenes *β*-myrcene (**2**), alloocimene (**3**), and neoalloocimene (**4**), for which **3** and **4** were used as the natural mixture. Acyclic triene monoterpenes **2**-**4** are widely distributed in natural sources and are accessible via thermal isomerization of pinenes. They are very interesting in various synthetic investigations, including for the preparation of compounds with practically useful properties [3-5]. All these compounds contain a conjugated diene system. Reaction with 3-methyl-3-cyanocyclopropene was proposed to produce new substances with a cyclopropane and a nitrile in the molecule using a Diels—Alder reaction.



2 **1** **7**

Reactions of **1** with monoterpenes **2**-**4** were carried out in sealed ampuls without solvent and with an equimolar ratio of reagents. They were completed after a few hours at 80°C. The reaction mixtures were analyzed by GC/MS. The products were isolated by column chromatography (CC) over silica gel using petroleum ether. The structures of the products were established using IR spectra, NMR spectra, and mass spectrometry and were confirmed by elemental analyses.

GC/MS of the products from reaction of **1** and terpene **2** detected two compounds with mass number 215 (corresponding to the 1:1 adduct) in a 10:1 ratio. The mass spectra of these had identical fragmentation patterns with respect to fragment-ion masses but differed with respect to the intensities of the peaks. This is usual for structural isomers. The principal isomer that was isolated by CC was assigned the structure of a sesquiterpenoid with the carane bicyclic moiety **7** based on spectral data. The *syn*-position of the CN group was assigned according to results of reactions of **1** with other dienes (Scheme 1) [6, 7]. The minor adduct probably had a structure differing from **7** only in the *anti*-position of the nitrile. It could not be isolated and characterized owing to its low content in the reaction mixture.

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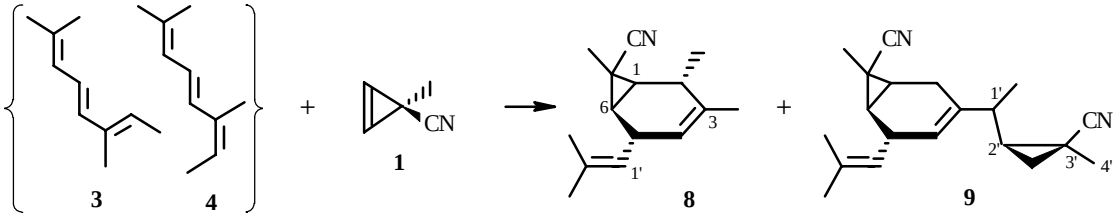
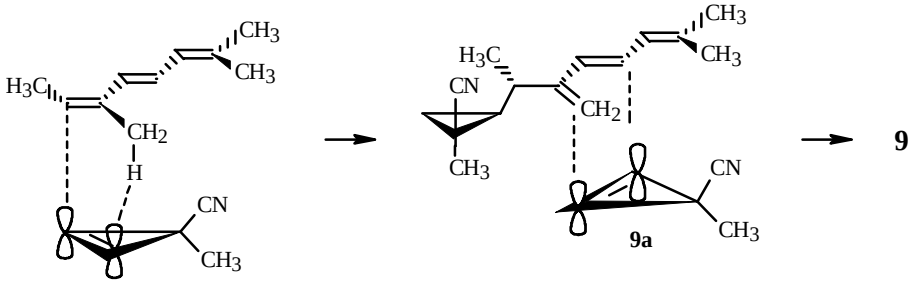
The reaction of **1** with **3** gave somewhat unexpected results. In addition to the normal cyclic Diels—Alder adduct **8**, the structure of which was previously established by an x-ray crystal structure (XCS) [8], an adduct with mass number 294 of formula $C_{20}H_{26}N_2$ was isolated. This corresponded to the addition of two molecules of **1** to one molecule of **4** to give **9**. Identical PMR spectra in the resonance region of the isobutenyl protons on C-5, among others, confirmed that **8** and **9** were structurally similar.



3 **4** **1** **8** **9**

Formation of the *bis*-adduct **9**, which at first glance seems paradoxical, can in fact be explained logically. Let us keep in mind the composition of alloocimene isolated from natural sources and produced synthetically, i.e., it is always a mixture of geomtric isomers **3** and **4** with the former usually predominating [9, 10] (in our experiment alloocimene was a 65:35 mixture of **3**:**4**). The former usually also undergoes Diels—Alder cyclization because it can adopt the *cis*-conformation required to carry out this reaction without significant energy losses. However, **4** (called recently neoalloocimene) cannot adopt this conformation because of steric hindrance and exists in the *trans*-conformation, which is favorable to reaction with **1** according to the Alder—ene addition. Adduct **9a** that formed by the Alder—ene reaction has a diene moiety in its structure that is favorable for cyclization with a second molecule of **1** but by a Diels—Alder reaction. It is unilkely that the first adduct of this reaction, **9a**, would be isolated because the Diels—Alder cyclization, as a rule, has a lower energy barrier than the Alder—ene addition and, therefore, the whole process will proceed to the final product **9** and can be defined as a conjugated Diels—Alder—ene reaction.

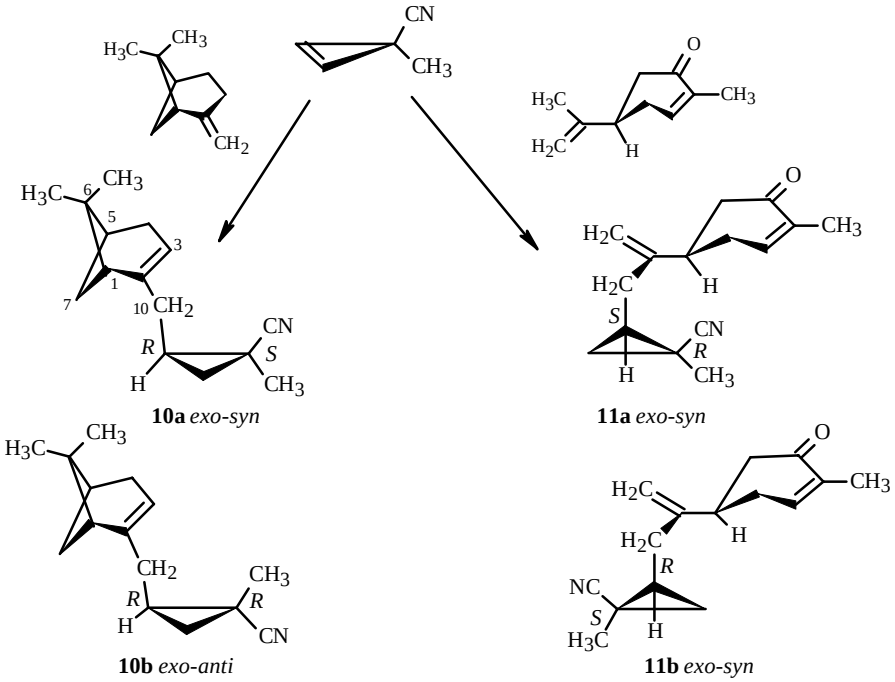


Having discovered that 3-methyl-3-cyanocyclopropene can undergo pericyclic reactions by the ene-synthesis mechanism, which was previously unknown for this compound, its reaction with cyclic terpenes without conjugated double bonds was then studied. Reactions of **1** with the bicyclic terpene β-pinene (**5**) and monocyclic terpenoid carvone (**6**) produced adducts that were formed by an Alder—ene synthesis mechanism.

The reactions of **1** with **5** and **6** were carried out with equimolar ratios of reagents and were completed in 3-5 h at 110-140°C, i.e., under more forcing conditions than for the studied acyclic terpenes. The reaction mixtures were analyzed analogously to those of the first part of the work.

The reaction products isolated by CC over silica gel were identified by GC/MS, which showed that product **10** with mass 215 from the reaction with β-pinene was a mixture of isomers in a 95:5 ratio whereas product **11** with mass 229 from the reaction with carvone was a mixture of isomers in a 55:45 ratio. Mass spectra of each isomeric pair had identical fragmentation patterns with small differences in the intensities of peaks for fragment ions. This indicated that the isomeric pairs were diastereomeric. The principal product of the reaction of **1** with **5** was identified as the *exo-syn*-addition product. The minor product was not identified.

The structure of **11** was assigned based on experimental data for nuclear Overhauser effects (NOE). Thus, the observed strong NOE between the CH group and the cyclopropane CH_3 indicated that these groups were spatially close, i.e., the CH group was situated on one side of the cyclopropane ring with the CH_3 group in the *trans*-position relative to the CN.



An attempt to separate the isomers of **11** was unsuccessful. Their mixture was analyzed.

Thus, the reaction of terpenes and terpenoids with 3-methyl-3-cyanocyclopropene produced chemical derivatives of monoterpenoids with a cyclopropane moiety in the molecule, the formation of which requires reaction of the starting components by Diels—Alder cyclization, ene synthesis, and a conjugated Diels—Alder—ene reaction. Furthermore, these results and those of previous work [6, 7] indicate that 3-methyl-3-cyanocyclopropene is promising as a mild prenylating agent.

EXPERIMENTAL

PMR and ^{13}C NMR spectra of compounds in $CDCl_3$ solution were recorded on an Avance-600 (Bruker) spectrometer (600 MHz for ^1H; 150.926 MHz for ^{13}C) at 30°C. Chemical shifts (CS) were measured relative to the solvent signal. Column chromatography used silica gel (L grade, 100-160 μm). GC/MS was carried out on an Agilent Technologies (USA) model 6890N gas chromatograph with a model 5973N mass-selective detector. IR spectra of samples in mineral oil were recorded on a Vector 22 spectrometer.

3-Methyl-3-cyanocyclopropene (1) was synthesized by the literature method [2].

7-Methyl-3-(4′methyl-3′-pentenyl)-7-cyano-3-bicyclo[4.1.0]heptene (7). Compound **1** (0.158 g, 2 mmol) was placed in an ampul with *β*-myrcene (**2**, 0.272 g, 2 mmol), treated with hydroquinone (5 mg), heated on a water bath at 80°C for 3 h, cooled, and chromatographed over silica gel (hexane eluent), R_f 0.3 (Silufol). Yield of **7** as an oil, 0.35 g (81.4%).

IR spectrum (KBr, ν, cm^{-1}): 2238 (CN).

PMR spectrum (600 MHz, $CDCl_3$,δ, ppm, J/Hz): 1.18-1.30 (2H, m, CH-1, CH-6), 1.35 (3H, s, CH_3-9), 1.55 and 1.62 (3H, s, CH_3-5′, 3H, s, CH_3-6′), 1.85-2.50 (8H, m, CH_2-2, CH_2-5, CH_2-1′, CH_2-2′), 5.13 (1H, t, ^3J = 5.3, CH-4).

Mass spectrum (EI, 60 eV, *m*/*z*, I_{rel}, %): 215 (54) $[M]^+$.

2,3,7-Trimethyl-5-(2′-methyl-1′-propenyl)-7-cyano-3-bicyclo[4.1.0]heptene (8) and 3-(3′-cyano-2′,3′-methylene-2′-butenyl)-5-(2′-methyl-1′-propenyl)-7-methyl-7-cyano-3-bicyclo[4.1.0]heptene (9). Compound **1** (0.237 g, 3 mmol) was placed in an ampul with technical alloocimene (**3**, 0.408 g, 3 mmol) treated with hydroquinone (5 mg), heated on a water bath at 80°C for 3 h, cooled, and chromatographed over silica gel (hexane:diethylether eluent, 1:1), R_f (**8**) 0.45 (Silufol); R_f (**9**) 0.3 (Silufol). Yield of **8** as colorless crystals 0.34 g (52,7%), mp 42-44°C.

IR spectrum (KBr, ν, cm^{-1}): 2240 (CN).

PMR spectrum (600 MHz, $CDCl_3$,δ, ppm, J/Hz): 1.05 (1H, d, ^3J = 8.6, CH-1), 1.14 (1H, d, ^3J = 8.6, CH-6), 1.20 (3H, d, CH_3-10, ^3J = 7.1), 1.34 (3H, s, CH_3-9), 1.64 (3H, s, CH_3-11), 1.67 and 1.69 (6H, s, s, CH_3-3′ and CH_3-4′), 2.34 (1H, m, CH-2), 3.30 (1H, m, CH-5), 4.87 (1H, d, ^3J = 9.7, CH-1′), 5.08 (1H, d, ^3J = 5.4, CH-4).

Mass spectrum (EI, 60 eV, *m*/*z*, I_{rel}, %): 215 (67), $[M]^+$.

These data agree with those reported previously [8] where the structure of the adduct of alloocimene with 3-methyl-3-cyanocyclopropene was established by an XCS.

Yield of **9** as an oil, 0.11 g, which crystallized after a week, mp 36-38°C. Yield 12.5% (calculated for starting alloocymene).

IR spectrum (KBr, ν, cm^{-1}): 2240 (CN).

PMR spectrum (600 MHz, $CDCl_3$,δ, ppm, J/Hz): 0.86-0.91 (1H, m, CH-1′), 0.97 (2H, m, CH_2-cyclopropane), 1.04 (1H, dd, ^3J = 8.6 and 6.0, CH-1), 1.12 (1H, d, ^3J = 8.6, CH-6), 1.26 (3H, d, CH_3 on C-1′), 1.28 (1H, m, CH-2′), 1.38 and 1.40 (6H, s, s, CH_3-4′ and CH_3-9), 1.73 and 11.74 [6H, s, s, $(CH_3)_2$–C=], 2.38 (1H, d, ^2J = 18.3, CH-2), 2.48 (1H, dd, ^2J = 18.3 and ^3J = 6.0, CH-2), 3.36 (1H, m, CH-5), 4.97 (1H, d, ^3J = 9.7, CH= on C-5), 5.30 (1H, s, CH-4).

^{13}C NMR spectrum (150.926 MHz, $CDCl_3$): 120.7 (s, CN), 122.7 (s, CN), 121.2 (d, C-4), 126.6 (d, C-1′ on C-5), 131.8 and 135.2 (s, s, C-3 and C-2′ on C-5), 43.12 (d, C-5), 31.97 (d, C-1′) and 31.94 (t, C-2), 29.73 (d, C-6), 25.70 and 24.68 (d, d, C-1 and C-2′), 21.66 (t, CH_2-cyclopropane), 23.00, 22.37, 21.71, 18.85, 17.87 (5q, C-4′, C-9, C-7, C-3′ and C-4′ on C-5), 13.33 (s, C-7), 10.24 (s, C-3′).

High-resolution mass spectrum (EI, 60 eV, *m*/*z*, I_{rel}, %): 294.20959 (60) $[M]^+$.

1-Methyl-1-cyano-2-(10-α-pinenyl)cyclopropane (10). Compound **1** (0.158 g, 2 mmol) was placed in an ampul with (-)-β-pinene (0.272 g, 2 mmol), treated with hydroquinone (5 mg), heated on a sand bath at 110°C for 3 h, and cooled. The reaction mixture was dissolved in hexane (3 mL) and chromatographed crudely over silica gel (hexane eluent), R_f 0.35 (Silufol). This purified the reaction mixture of a small amount of tars and hydroquinone. Solvent was distilled off to afford **10** as an oil, 0.38 g (88.4%) that crystallized after two days, mp 46-47°C.

PMR spectrum (600 MHz, $CDCl_3$,δ, ppm, J/Hz): 0.83 (2H, d, CH_2-3, ^3J = 8.5), 0.81 (3H, s, CH_3-9′), 0.96 (1H, q, CH-2), 1.23 (3H, s, CH_3-8), 1.29 (3H, s, CH_3-5), 1.99 (1H, m, CH-1′), 2.05 (1H, m, CH-5′), 1.14 [1H, m, CH(a)-6′], 2.31 [1H, m, CH(e)-6′], 2.09 (2H, m, CH_2-10), 2.16 [1H, dd, CH(a)-4′], 2.23 [1H, dd, CH(e)-4′], 5.28 (1H, s, CH-3′).

^{13}C NMR spectrum (150.926 MHz, $CDCl_3$): 10.03 (s, C-1), 24.13 (d, C-2), 20.65 (t, C-3), 121.4 (CN), 21.17 (q, C-5), 45.69 (d, C-1′), 145.6 (s, C-2′), 117.08 (d, C-3′), 31.04 (t, C-4′), 40.61 (d, C-5′), 37.75 (s, C-7′), 31.35 (t, C-7′), 26.15 (t, C-10′), 21.0 (q, C-9′), 37.77 (q, C-10′).

Mass spectrum (EI, 60 eV, *m*/*z*, I_{rel}, %): 215 (49) $[M]^+$.

1-Methyl-1-cyano-2-(10-carvonyl)cyclopropane (11). Compound **1** (0.158 g, 2 mmol) was placed in an ampul with carvone (0.300 g, 2 mmol), treated with hydroquinone (5 mg), heated on a sand bath at 140°C for 5 h, cooled, and chromatographed over silica gel (hexane:diethylether eluent, 1:1), R_f 0.45 (Silufol). Yield of **10** as a thick colorless oil, 0.31 g (67.7%).

PMR spectrum (600 MHz, $CDCl_3$,δ, ppm, J/Hz): 0.90-1.05 (2H, m, C-3), 1.15 (1H, m, C-2), 1.42 (3H, s, C-5), 1.79 (3H, s, C-7′), 2.27 (2H, dd, C-10′), 2.72 (1H, m, C-5′), 2.31 [1H, m, C(a)-4′], 2.51 [1H, m, C(e)-4′], 2.4 [1H, m, C(a)-6′], 2.61 [1H, m, C(e)-6′], 4.92 (1H, s, C-9′ *cis* to CH_2-10′), 5.02 (1H, s, C-9′ *trans* to CH_2-10′), 6.75 (1H, s, C-3′).

^{13}C NMR spectrum (150.926 MHz, $CDCl_3$): 10.69 (s, C-1), 24.77 (d, C-2), 21.29 (t, C-3), 122.38 (CN), 21.33 (q, C-5), 199.33 (s, C-1′), 136.5 (s, C-2′), 144.2 (d, C-3′), 31.74 (t, C-4′), 45.5 (d, C-5′), 43.3 (t, C-6′), 15.63 (q, C-7′), 148.91 (s, C-8′), 110.25 (t, C-9′), 35.55 (q, C-10′).

Mass spectrum (EI, 60 eV, *m*/*z*, I_{rel}, %): 229 (29) $[M]^+$.

Elemental analyses of all compounds agreed with those calculated.

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