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Synthesis and Molecular Structure of Alloocimene Adducts with Maleic and Citraconic Anhydrides

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Abstract—Reactions of alloocimene with maleic and citraconic anhydrides gave the corresponding Diels–Alder cycloaddition products which may be regarded as new synthetic sesquiterpenoids. The molecular structures of the adducts, determined by X-ray analysis, indicated *endo* addition of the dienophiles at the most sterically accessible diene system and *syn-boat* conformation of the bicyclic skeleton.

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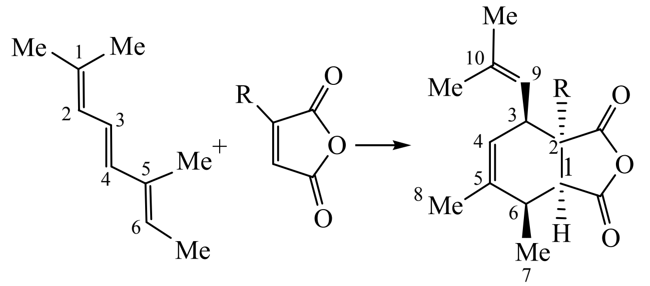
Alloocimene is an acyclic monoterpene which is fairly rarely encountered in natural sources but is synthetically accessible from pinenes [1–3]. Alloocimene molecule possesses a unique conjugated triene π-electron system which gives rise to wide synthetic potential. First of all, Diels–Alder reactions should be noted, where alloocimene acts as diene. Arbuzov [4] was the first to use the Diels–Alder reaction to prove the formation of alloocimene in the catalytic pyrolysis of α-pinene. In subsequent studies, Diels–Alder reactions of alloocimene were extended to various dienophiles [5]. Alloocimene usually exists as a mixture of *E* and *Z* isomers, the former prevailing [6], and Diels–Alder reaction involves the *E* isomer which more readily adopts cisoid conformation favorable for the cycloaddition process. The *Z* isomer is capable of reacting with the same electrophilic olefins according to the Alder–ene addition pattern [7].

In the present work we examined reactions of alloocimene with cyclic unsaturated carboxylic acid anhydrides, namely maleic and citraconic anhydrides **I** and **II**, with a view to develop a procedure for the synthesis of new synthetic sesquiterpenoids and determine the molecular structure of the adducts, which could provide information on the reaction mechanism. The products of the above reactions can be used in the synthesis of biphilic isoprenoid derivatives that are promising from the viewpoint of possible medicinal and biological applications. Maleic and citraconic anhydrides may be regarded as norhemiterpenoid **I** and hemiterpenoid **II**, respectively. The reactions were carried out at room temperature in tetrahydrofuran, the alloocimene–dienophile ratio being 3 : 2 (Scheme 1). The reaction with maleic anhydride (**I**) was complete in a few hours, whereas the reaction with citraconic anhydride (**II**) required several days. The process was assumed to be complete when the reaction mixture lost its orange color typical of charge-transfer complex formed upon mixing of the reactants. After appropriate treatment, crystalline Diels–Alder adducts **III** and **IV** were isolated in good yield, and their structure was determined on the basis of their elemental compositions and IR and NMR spectra. The molecular structures of crystalline samples of **III** and **IV** were determined by X-ray analysis. According to the X-diffraction data, adducts **III** and **IV** may be identified as synthetic sesquiterpenoids of the cyclohexene series.

The structure of adducts **III** and **IV** (Figs. 1, 2) indicates addition of dienophiles **I** and **II** at the $C^3=C^4-C^5=C^6$ diene fragment of alloocimene. Among two possible regioisomers, only one (compound **IV**) is formed from anhydride **II**, which may be due to hyperconjugation between the methyl group in citraconic anhydride and $\pi\text{-}C^1=C^2$ bond in the transition state; in this reaction, steric factors are equal at both orientations of the dienophile. The *cis* orientation of the

Scheme 1.



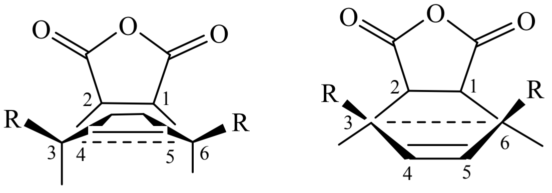
I, II III, IV

I, III, R = H; II, IV, R = Me.

anhydride fragment with respect to the methyl and isobutenyl groups in the cyclohexene ring of adducts **III** and **IV** suggests *endo* orientation of the addends in the transition state, which is typical of Diels–Alder reactions with conjugated triene as diene component.

Another important conclusion drawn from the X-ray diffraction data for compounds **III** and **IV** is related to conformation of their molecules. The bicyclic fragment in crystal has *syn-boat* conformation which is seemingly less favorable for steric reasons. Presumably, such structure is stabilized due to much more favorable staggered conformation about the C–C bonds in the anhydride fragment and substituents on C^3 and C^6 [the torsion angles $C^{13}C^2C^3C^7$ and $C^{13}C^2C^3C^4$ are, respectively, 60.4(2)° and –69.9(1)° in molecule **III** and –72.6(2)° and 56.5(2)° in molecule **IV**] as compared to eclipsed orientation of the same fragments in *anti-boat* conformer. Analogous con-formational pattern was observed by us previously for compounds of the carene series (bicyclo[4.1.0]hept-3-enes) where the three-membered ring was oriented *syn* with respect to the 2,5-disubstituted cyclohexene fragment [8] (Scheme 2).

Scheme 2.



syn-boat *anti-boat*

The presence of a methyl group on C^2 in molecule **IV** induces appreciable distortion of the bicyclic fragment. The five-membered ring in molecule **III** is planar within 0.030(1) Å, whereas deviation of atoms from the mean-square plane of the five-membered ring in **IV** increases to 0.098(1) Å. Analogous pattern is observed for the six-membered ring: the *boat* base in **III** and **IV** is planar within 0.022(2) and 0.065(1) Å, respectively.

To conclude, reactions of alloocimene with maleic and citraconic anhydrides gave the corresponding Diels–Alder adducts which may be regarded as new synthetic sesquiterpenoids. According to the X-ray diffraction data, the reaction involves *endo* addition of the dienophile at the most sterically accessible diene system and the adducts are characterized by *syn-boat* conformation of the bicyclic skeleton.

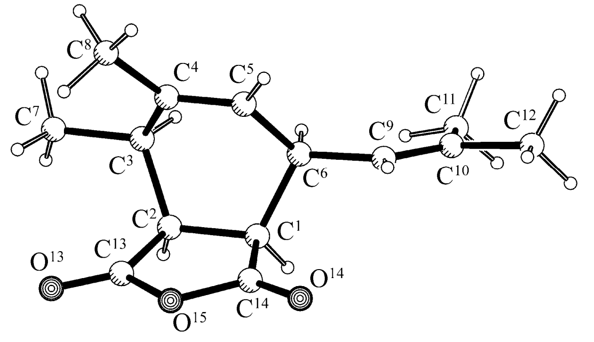


Fig. 1. Structure of the molecule of 5,6-dimethyl-3-(2-methyl-prop-1-en-1-yl)cyclohex-4-ene-1,2-dicarboxylic anhydride (**III**) according to the X-ray diffraction data.

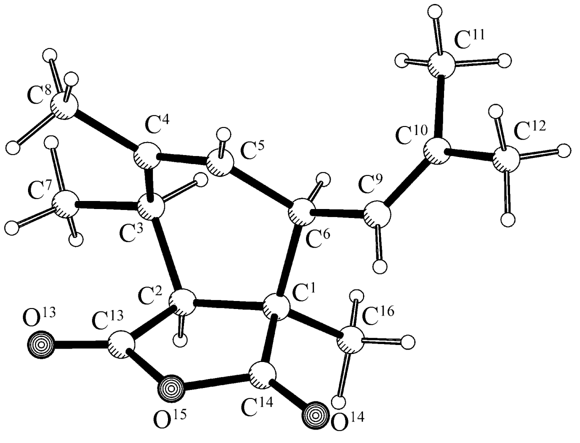


Fig. 2. Structure of the molecule of 2,5,6-trimethyl-3-(2-methyl-prop-1-en-1-yl)cyclohex-4-ene-1,2-dicarboxylic anhydride (**IV**) according to the X-ray diffraction data.

EXPERIMENTAL

The elemental compositions were determined using an EuroEA 3000 CHNS analyzer. The IR spectra of crystalline samples of adducts **III** and **IV** were recorded in KBr on a Bruker Vertex 70 spectrometer with Fourier transform. The ^{1}H NMR spectra were measured from solutions in chloroform-*d* on a Varian Unity instrument at 300 MHz. The melting points were determined on a Digital Mel-Temp 3.0 melting point apparatus.

The X-ray diffraction data for single crystals of compounds **III** and **IV** were acquired on a Bruker SMART Apex II diffractometer (graphite monochromator, λMoK_α 0.71073 Å). Absorption by the crystal was taken into account semiempirically using SADABS program [9]. The structures were solved by the direct method (SHELXS [10]). Non-hydrogen atoms were refined first in isotropic and then in anisotropic approximation (SHELXL-97 [11]). Hydrogen atoms were placed into calculated positions which were refined according to the riding model. All calculations were performed using WinGX [12] and APEX2 [13]. The molecular structures were plotted using PLATON [14]. The X-ray diffraction data for **III** and **IV** were deposited to the Cambridge Crystallographic Data Centre (entry nos. CCDC 772831 and 772832, respectively).

Compound **III**. Monoclinic crystals. Unit cell parameters (20°C): $a = 13.8339(17)$, $b = 5.9102(7)$, $c = 15.839(2)$ Å; $\beta = 95.131(1)°$; $V = 1289.8(3)$ Å^3; $Z = 4$; $d_{calc} = 1.206$ g/cm^3; space group $P2_1/n$; $\mu Mo = 0.84$ cm^{-1}. Intensities of 3062 independent reflections were measured, 2352 of which were characterized by $I \geq 2\sigma(I)$. Final divergence factors: $R = 0.0434$, $R_w = 0.1221$.

Compound **IV**. Monoclinic crystals. Unit cell parameters (20°C): $a = 10.066(4)$, $b = 10.110(4)$, $c = 14.184(5)$ Å; $\beta = 107.752(3)°$; $V = 1374.6(8)$ Å^3; $Z = 4$; $d_{calc} = 1.200$ g/cm^3; space group $P2_1/n$; $\mu Mo = 0.82$ cm^{-1}. Intensities of 2705 independent reflections were measured, 2044 of which were characterized by $I \geq 2\sigma(I)$. Final divergence factors: $R = 0.04,07$ $R_w = 0.0963$.

The X-ray diffraction study of compounds **III** and **IV** was performed at the Federal Collective Use Spectral Analytical Center for Physicochemical Studies on the Structure, Properties, and Composition of Substances and Materials.

5,6-Dimethyl-3-(2-methylprop-1-en-1-yl)cyclohex-4-ene-1,2-dicarboxylic anhydride (III). Maleic anhydride, 4.9 g, was dissolved in 10 ml of anhydrous tetrahydrofuran, and 10.2 g of stabilized technical-grade alloocimene was added. The mixture spontaneously warmed up and turned orange; the color gradually lost its intensity and became persistently lemon yellow in several hours. The mixture was left overnight at room temperature, the solvent was distilled off on a rotary evaporator, the residue was diluted with light petroleum ether (~100 ml), and the precipitate was filtered off, washed with petroleum ether, and recrystallized from warm ethanol. Yield 10.4 g (88%), mp 83–84°C. IR spectrum, ν, cm^{-1}: 1772.8, 1850.8 (C=O, C=C). ^{1}H NMR spectrum, δ, ppm: 1.48 d (3H, $J = 7.4$ Hz), 1.68 d (3H, $J = 1.0$ Hz), 1.76 d (3H, $J = 1.2$ Hz), 1.80 s (3H), 2.56 m (1H), 3.15 m (1H), 3.29 d. d (2H, $J = 2.2$, 4.0 Hz), 5.50–5.56 m (2H). Found, %: C 71.81; H 7.89. $C_{14}H_{18}O_3$. Calculated, %: C 71.79; H 7.69.

2,5,6-Trimethyl-3-(2-methylprop-1-en-1-yl)cyclohex-4-ene-1,2-dicarboxylic anhydride (IV). Citraconic anhydride, 5.6 g, was mixed at room temperature with 10.2 g of alloocimene. The mixture turned yellow–orange, and the color very slowly (during several days) turned lemon yellow. After 10 days, the mixture was diluted with petroleum ether (~100 ml), and the precipitate was filtered off, washed with cold petroleum ether, and recrystallized from warm ethanol. Yield ~9.5 g (77%). Repeated crystallization from a dilute solution in ethanol gave fairly large crystals with mp 80–81.5°C. IR spectrum, ν, cm^{-1}: 1769.5, 1841.7 (C=O, C=C). ^{1}H NMR spectrum, δ, ppm: 1.38 s (3H), 1.49 d (3H, $J = 7.3$ Hz), 1.64 d (3H, $J = 1.2$ Hz), 1.75 m (3H), 1.80 d (3H, $J = 1.2$ Hz), 2.57 m (1H), 2.80 m (1H), 2.84 d (1H, $J = 2.6$ Hz), 5.36–5.41 m (2H). Found, %: C 72.87; H 8.15. $C_{15}H_{20}O_3$. Calculated, %: C 72.58; H 8.06.

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