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Ionic Liquid-Catalyzed Diels–Alder Reaction of Levopimaric Acid with Quinones

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Abstract—Diels–Alder reactions of levopimaric acid with quinones are strongly accelerated in the presence of ionic liquids (imidazolium salts) as catalyst.

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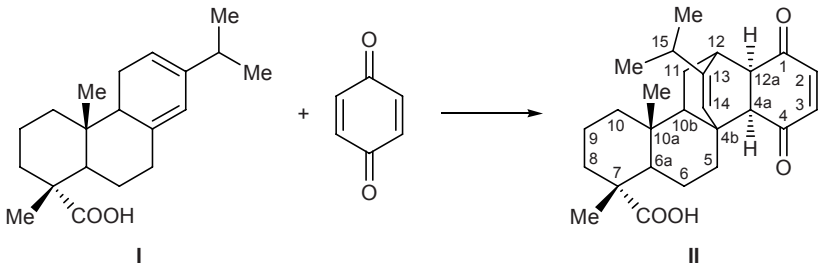
Synthetic transformations of natural compounds with a view to obtain biologically active substances are the subject of important studies in the field of fine organic synthesis and medicinal chemistry. In this respect diterpenoid rosin acids and their derivatives attract much interest [1–3]. Among these compounds, a prominent place is occupied by levopimaric acid which is the main component of pine pitch.

In the recent years ionic liquids have been widely used in organic synthesis as catalysts or solvents. Ionic liquids are salts consisting of an organic cation and inorganic anion that are liquid at room temperature [4]. They are inflammable, nonexplosive, and nontoxic; in addition, they are characterized by high dissolving capacity and possibility for repeated use [4].

We examined the Diels–Alder reaction of pine pitch containing ~30% of levopimaric acid (**I**) with quinones in the presence of a catalytic amount of ionic liquids; as the latter, salts consisting of 1-butyl-3-methylimidazolium cation (Bmim) and BF_4^-, PF_6^-, and $CF_3CO_2^-$ anions were used [5]. 1,4-Benzoquinone, 2-chloro-, 2-bromo-, and 2-acetylamino-1,4-benzoquinones, and 1,4-naphthoquinone were selected as dienophiles. It is known that compound **I** reacts with 1,4-benzoquinone in 5–7 days to give up to 92% of the corresponding Diels–Alder adduct [6–8] and that the reactions of **I** with 2-chloro- and 2-acetylamino-1,4-benzoquinones take 7 [9] and 5 days [7], respectively. We have found that ionic liquids exhibit different catalytic activities in the reactions of diene **I** with quinones. Solvent nature is also an important factor. We tried two solvent mixtures: benzene–hexane (10:1) and methylene chloride–hexane (10:1), taking into account that pine pitch is poorly soluble in acetonitrile–chloroform (10:1) [6]. In addition, the isolation procedure was also modified. A catalytic amount of ionic liquid Bmim-PF_6, Bmim-BF_4, or Bmim-CF_3CO_2 was added to a solution of pine pitch and 1,4-benzoquinone at room temperature. The progress of the reactions was monitored by thin-layer chromatography.

1-Butyl-3-methylimidazolium hexafluorophosphate(V) (Bmim-PF_6) turned out to be the most effective catalyst in the synthesis of quinopimaric acid (**II**) (Scheme 1). The latter was formed in quantitative

Scheme 1.



I **II**

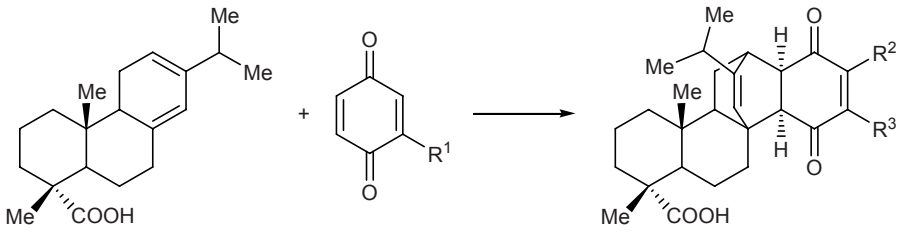
Reactions of levopimaric acid (**I**) with 1,4-benzoquinones and 1,4-naphthoquinone in the presence of ionic liquids

Quinone	Catalyst	Methylene chloride–hexane		Benzene–hexane	
		reaction time, h	yield, %	reaction time, h	yield, %
1,4-Benzoquinone	Bmim-PF_6	3	100	1	100
	Bmim-BF_4	6	90	3.5	54
	Bmim-CF_3COO	20	75	4	87
	No catalyst	216	100	168	90
2-Chloro-1,4-benzoquinone	Bmim-PF_6	3	100	43	5
	Bmim-BF_4	6	90	48	10
	Bmim-CF_3COO	20	75	54	7
	No catalyst	216	100	168	62
2-Bromo-1,4-benzoquinone	Bmim-PF_6	20	83	–	–
	Bmim-BF_4	20	72	–	–
	Bmim-CF_3COO	24	74	–	–
	No catalyst	216	0	–	–
2-Acetylamino-1,4-benzo-quinone	Bmim-PF_6	1	100	–	–
	No catalyst	120	100	–	–
1,4-Naphthoquinone	Bmim-PF_6	5	100	5	50
	Bmim-BF_4	7	87	5	47
	Bmim-CF_3COO	17	55	8	30
	No catalyst	216	100	216	93

yield in 1 h in benzene–hexane (10:1) (see table). The reaction in methylene chloride–hexane (10:1) was slower, and the isolation procedure was more difficult.

We also examined the reaction of **I** with 2-chloro-1,4-benzoquinone in the presence of Bmim-PF_6, Bmim-BF_4, and Bmim-CF_3CO_2 (Scheme 2). According to [9], the reaction of levopimaric acid (**I**) with 2-chloro-1,4-benzoquinone was carried out in chloroform–acetonitrile (25:1), and adduct **IIIa** was isolated as a single isomer in 50% yield. We found that the yield can be raised to quantitative by carrying out the reaction in methylene chloride–hexane (10:1) and increasing the reaction time to 9 days. Both in the presence of ionic liquids and in the absence of catalyst, two regioisomeric adducts **IIIa** and **IIIb** were formed at a ratio of 7:1, i.e., the presence of ionic liquids did not affect the regioselectivity of [4+2]-cycloaddition. Unlike the reaction with 1,4-benzoquinone, the use of methylene chloride–hexane mixture in the catalytic reaction ensured better results than in the reaction carried out in benzene–hexane. The best yield in the reaction with 2-chloro-1,4-benzoquinone was obtained in the

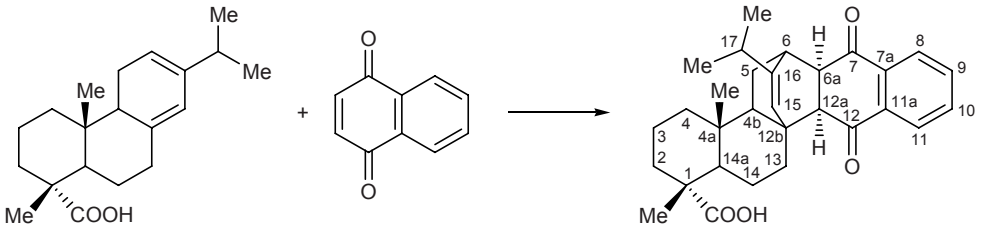
Scheme 2.



I **IIIa**, **IIIb**, **IVa**, **IVb**, **Va**, **Vb**

R^1 = Cl, Br, NHAc; **III**, R^2 = H, R^3 = Cl (**a**), R^2 = Cl, R^3 = H (**b**); **IV**, R^2 = H, R^3 = Br (**a**), R^2 = Br, R^3 = H (**b**); **V**, R^2 = Br, R^3 = AcNH (**a**), R^2 = AcNH, R^3 = H (**b**).

Scheme 3.



I **VI**

presence of Bmim-PF_6, while isolation of the product in the reaction catalyzed by Bmim-CF_3CO_2 was more difficult.

Bromoquinopimaric acid was not reported previously. No compound **IV** was formed in the reactions of **I** with 2-bromo-1,4-benzoquinone in the absence of ionic liquid (reaction time 9 days). We examined the reaction of diene **I** with 2-bromo-1,4-benzoquinone in methylene chloride–hexane in the presence of ionic liquids under the same conditions as in the reactions with 2-chloro-1,4-benzoquinone. Likewise, the product was a mixture of regioisomeric 2- and 3-bromo derivatives **IVa** and **IVb** at a ratio of 7:1. Unfortunately, we failed to separate the isomer mixture and isolate the major isomer as individual substance. As above, the best results were obtained using Bmim-PF_6 as catalyst.

3-Acetylaminoquinopimaric acid was synthesized previously in the system acetonitrile–chloroform (5 days, yield 92%) [7]. When the reaction of **I** with 2-acetylamino-1,4-benzoquinone was performed under the optimal conditions for 2-halo-1,4-benzoquinones, the complete conversion was attained in 1 h. The product contained mainly isomer **Va**, and the fraction of isomer **Vb** did not exceed 7%. Analogous result was obtained in the absence of imidazolium salt, i.e., under the conditions described in [7]. In the ^{13}C NMR spectrum of the product we observed the following signals of minor isomer **Vb**, δ_C, ppm: 184.69 s (COO), 145.06 s (C^{13}), 120.13 d (C^3), 122.31 d (C^{14}). The isomer ratio was determined from the intensities of signals from protons at the double C^{13}=C^{14} bond. The poor yield of the minor product did not allow us to characterize it by spectral data.

The cycloaddition of levopimaric acid (**I**) to 1,4-naphthoquinone was reported for the first time in [10, 11], and we found no other data on the cycloaddition product. Therefore, for the sake of brevity we propose to name adduct **VI** (Scheme 3) *naphthoquinopimaric acid* by analogy with quinopimaric acid (**II**). Spectral parameters of compound **VI** are given below (see Experimental). Exact assignment of signals from protons in structure **VI** was made on the basis of COSY HH 45° and CHCORR spectra. The coupling constant for the 6a-H and 12-H protons ($J \approx 8.5$ Hz) indicated their *cis* arrangement and hence *cis* junction of the **D** and **E** rings, as in other adducts of **I** with benzoquinones [6–9]. The orientation of the aromatic ring with respect to the double C^{15}=C^{16} bond [*syn* (*exo*) or *anti* (*endo*)] was determined by NOEDIFF experiments. Irradiation at a frequency corresponding to resonance of the 15-H proton gave more than 3% nuclear Overhauser effect for the 17-H proton in the isopropyl group. According to quantum-chemical calculations (GAUSSIAN), the distances between 12a-H and 4b-H and between 5-H_{ax} and 6a-H should range from 3.2 to 3.6 Å in the structure with *anti* (*endo*) orientation of the aromatic ring and C^{15}=C^{16} bond; i.e., NOE should be observed for these proton couples. Irradiation at the 4b-H resonance frequency gave 4.9% response on 12a-H, while saturation of the 5-H_{ax} signal increased the 6a-H signal intensity by 6.6%. Therefore, the aromatic ring is oriented *syn* (*exo*) with respect to the C^{15}=C^{16} double bond.

The optimal conditions for the reaction of compound **I** with 1,4-naphthoquinone imply methylene chloride–hexane (10:1) as solvent and Bmim-PF_6 as catalyst.

Thus the use of ionic liquids as catalysts in the Diels-Alder reactions of levopimaric acid with 1,4-benzoquinones and 1,4-naphthoquinones makes it possible to considerably shorten the reaction time (in some cases, by two orders of magnitude) and increase the product yield. In some reactions, catalysis by ionic liquids leads to insignificant contamination of the Diels–Alder adducts by imidazolium salts, but the latter can readily be removed by repeated crystallization. According to the ^1H NMR data, the purity of the Diels–Alder adducts with 1,4-benzoquinones and 1,4-naphthoquinone was about 95% after single recrystallization.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were recorded from 10–20% solutions in $CDCl_3$ or $(CD_3)_2CO$ on a Bruker AM-300 spectrometer at 300.13 and 75.47 MHz, respectively, using the residual proton and carbon signals of the solvent as reference. The IR spectra were measured on a Shimadzu instrument from neat substances or samples dispersed in Nujol. The progress of reactions was monitored by TLC on Sorbfil PTSKh-AF-A plates using chloroform–methanol (10:1) as eluent.

1,4-Benzoquinone was purified by sublimation. 2-Chloro- and 2-bromo-1,4-benzoquinones were prepared from the corresponding hydroquinones according to the procedure described in [12]; their properties were consistent with published data. Pine pitch from *Pinus Silvestris* containing ~30% of levopimaric acid was collected in the spring of 2006 in the Nizhnii Novgorod region. The concentration of levopimaric acid in pine pitch was determined by GLC from the ratio of resin acid methyl esters obtained by methylation with excess diazomethane. The physical properties and spectral parameters of the isolated compounds coincided with those reported in [6–9]. The yields were calculated on the initial quinone.

(4a*R*,7*R*,10a*R*,12a*R*)-13-Isopropyl-7,10a-dimethyl-1,4-dioxo-4,4a,5,6,6a,7,8,9,10,10a,10b,11,12,12a-tetradecahydro-1*H*-4b,12-ethenochrysene-7-carboxylic acid (II, quinopimaric acid). A solution of 0.05 mol of 1,4-benzoquinone in 2.5 ml of hexane and 0.5 g of ionic liquid (Bmim-PF_6, Bmim-BF_4, or Bmim-CF_3COO) were added to 5 g of pine pitch in 50 ml of methylene chloride. The mixture was kept for several hours, depending on the catalyst, at room temperature with protection from light. The solvent was distilled off under reduced pressure (water-jet pump), and the residue was recrystallized from petroleum ether (bp 40–70°C). The product was additionally recrystallized from acetone–petroleum ether. The reaction times and yields of quinopimaric acid (**II**) are given in table.

Reactions of levopimaric acid (I) with 2-chloro-, 2-bromo-, and 2-acetylamino-1,4-benzoquinones and 1,4-naphthoquinones in the presence of ionic liquids (*general procedure***).** A solution of 0.05 mol of the corresponding quinone in 2.5 ml of hexane and 0.5 g of ionic liquid (Bmim-PF_6, Bmim-BF_4, or Bmim-CF_3COO) were added to 5 g of pine pitch in 50 ml of methylene chloride, and the mixture was stirred at room temperature with protection from light. The progress of the reaction was monitored by TLC. The solvent was distilled off under reduced pressure (water-jet pump), and the residue was recrystallized from petroleum ether (bp 40–70°C). Chloro- and bromoquinopimaric acids **III** and **IV** were isolated as mixtures of regioisomers at a ratio of ~7:1, isomers **IIIa** and **IVa** prevailing. The yields and reaction times are given in table.

(4a*R*,4b*S*,7*R*,10a*R*,10b*S*,12*R*,12a*R*)-2-Chloro-13-isopropyl-7,10a-dimethyl-1,4-dioxo-1,4,4a,4b,5,6,-6a,7,8,9,10,10a,10b,11,12,12a-hexadecahydro-4b,12-ethenochrysene-7-carboxylic acid (IIIb, 2-chloroquinopimaric acid) was obtained as a mixture with 3-chloro isomer **IIIa** and was not isolated as individual substance due to its low fraction in the mixture. ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 15.90 q (Me), 16.42 q (Me), 19.80 q (Me), 16.89 t (C^9), 20.61 q (Me), 22.03 t (C^6), 28.14 t (C^{11}), 32.58 d (C^{15}), 35.02 t (C^5), 37.65 t (C^8), 37.83 s (C^{10a}), 38.11 t (C^{10}), 41.54 d (C^{12}), 42.40 s (C^{4b}), 46.61 s (C^7), 50.11 d (C^{4a}), 50.28 d (C^{6a}), 51.7 d (C^{10b}), 58.63 d (C^{12a}), 125.33 d (C^{14}), 141.21 d (C^3), 147.59 s (C^2), 150.61 s (C^{13}), 184.64 s (C=O, acid), 191.90 s (C^4=O), 195.02 s (C^1=O). Found, %: C 70.04; H 7.51; Cl 8.08. $C_{26}H_{33}ClO_4$. Calculated, %: C 70.18; H 7.47; Cl 7.97.

(4a*R*,4b*S*,7*R*,10a*R*,10b*S*,12*R*,12a*R*)-3-Bromo- and -2-bromo-13-isopropyl-7,10a-dimethyl-1,4-dioxo-1,4,4a,4b,5,6,6a,7,8,9,10,10a,10b,11,12,12a-hexadecahydro-4b,12-ethenochrysene-7-carboxylic acids (IVa/IVb, 3- and 2-bromoquinopimaric acids, mixture of isomers). R_f 0.66. IR spectrum, ν, cm^{-1}: 3300 (OH), 1695 (C=O, acid), 1600 (C=O), 1585 (C=C), 1458, 1377, 1278, 1230, 1168, 1153, 1103, 1072, 1037, 825. ^{13}C NMR spectrum ($CDCl_3$–CD_3OD), δ_C, ppm: isomer **IVa**: 15.52 q (Me), 16.17 q (Me), 16.66 t (C^9), 19.27 q (Me), 20.13 q (Me), 21.60 t (C^6), 27.72 t (C^{11}), 32.66 d (C^{15}), 36.33 t (C^5), 37.74 s (C^{10a}), 38.00 t (C^{10}), 40.92 d (C^{12}), 42.37 t (C^8), 46.33 s (C^{4b}), 47.51 s (C^7), 48.66 d (C^{6a}), 51.21 d (C^{10b}), 55.57 d (C^{4a}), 56.96 d (C^{12a}), 124.95 d (C^{14}), 143.14 d (C^2), 147.85 s (C^3), 150.05 s (C^{13}), 181.46 s (C=O, acid), 191.15 s (C^4=O), 196.55 (C^1=O); isomer **IVb***: 16.17 q (Me), 16.43 q (Me), 16.66 t (C^9), 20.33 q (Me), 20.89 q (Me), 22.09 t (C^6), 27.65 t (C^{11}), 32.52 d (C^{15}), 36.91 t (C^5), 37.43 s (C^{10a}), 38.21 t (C^{10}), 41.76 d (C^{12}), 42.45 t (C^8), 45.83 s (C^{4b}), 49.73 d (C^{6a}), 50.63 d (C^{10b}), 55.68 d (C^{4a}), 58.49 d (C^{12a}), 126.45 s (C^{14}), 145.37 s (C^2), 144.82 d (C^3), 146.29 d (C^{13}), 181.46 s (C=O, acid), 192.21 s (C^4=O), 195.14 s (C^1=O).

* The C^7 signal was overlapped by the solvent signal (CD_3OD).

Found, %: C 63.76; H 7.01; Br 16.08. $C_{26}H_{33}BrO_4$. Calculated, %: C 63.82; H 6.75; Br 16.34.

(1*R*,4a*R*,4b*S*,6*R*,6a*R*,12a*R*,12b*S*)-16-Isopropyl-1,4a-dimethyl-7,12-dioxo-1,2,3,4,4a,4b,5,6,6a,7,12,-12a,12b,13,14,14a-hexadecahydro-6,12b-ethenobenzo[*b*]chrysene-1-carboxylic acid (VI, naphthoquinopimaric acid). mp 175–178°C, $[\alpha]_D^{20}$ = –162° (*c* = 10, $CHCl_3$). IR spectrum, ν, cm^{-1}: 3446, 2914, 2852, 1712, 1693, 1674, 1658, 1589, 1462, 1377, 1321, 1290, 1271, 1255, 1230, 1190, 1170, 1149, 989, 844, 731. ^{1}H NMR spectrum [$(CD_3)_2CO$], δ, ppm: 0.53 d (3H, Me, ^3J = 6.9 Hz), 0.60 s (3H, 4a-CH_3), 0.88 d (3H, Me, ^3J = 6.9 Hz), 1.00 d.d.d (1H, 4-H_{ax}, ^2J = 13.2, $^3J_{4\text{-}ax,3\text{-}ax}$ = 3.0, $^3J_{4\text{-}ax,3\text{-}eq}$ = 1.2 Hz), 1.12 s (3H, 1-CH_3), 1.28 m (2H, 14-H), 1.32 d.d.d (1H, 5-H_{eq}, ^2J = –12.9, $^3J_{5\text{-}eq,4b}$ = 5.4, $^3J_{5\text{-}eq,6}$ = 3.2 Hz), 1.45 d.t (1H, 4-H_{eq}, ^2J = –13.2, $^3J_{4\text{-}eq,3\text{-}ax}$ = 2.5, $^3J_{4\text{-}eq,3\text{-}eq}$ = 2.5 Hz), 1.48 m (1H, 2-H_{ax}), 1.53 m (2H, 3-H), 1.58 m (1H, 2-H_{eq}), 1.61 d.d (1H, 4b-H, $^3J_{4b,5\text{-}ax}$ = 10.0, $^3J_{4b,5\text{-}eq}$ = 5.4 Hz), 1.74 m (1H, 17-H), 1.93 d.d.d (1H, 5-H_{ax}, ^2J = –12.9, $^3J_{5\text{-}ax,4b}$ = 10.0, $^3J_{5\text{-}ax,6}$ = 2.7 Hz), 2.92 d.d (1H, 12a-H, $^3J_{12a,6a}$ = 8.6, $^4J_{12a,15}$ = 1.6 Hz), 3.01 d.d.d.d (1H, 6-H, $^3J_{6,5\text{-}eq}$ = 3.2, $^3J_{6,6a}$ = 2.9, $^3J_{6,5\text{-}ax}$ = 2.7, $^4J_{6,15}$ = 1.6 Hz), 3.32 d.d (1H, 6a-H, $^3J_{6a,12a}$ = 8.6, $^3J_{6a,6}$ = 2.9 Hz), 5.16 t (1H, 15-H, $^4J_{15,12a}$ = 1.6, $^4J_{15,6}$ = 1.6 Hz), 7.67–7.78 m (4H, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 15.94 q (Me), 16.31 q (Me), 16.88 t (C^3), 18.87 q (Me), 20.49 q (Me), 21.91 t (C^{14}), 27.94 t (C^5), 32.99 d (C^{17}), 34.94 t (C^{13}), 36.54 t (C^2), 37.64 s (C^{4a}), 37.98 t (C^4), 42.02 d (C^6), 42.24 s (C^1), 46.77 s (C^{12b}), 48.98 d (C^{6a}), 51.96 d (C^{12a}), 56.10 d (C^{14a}), 59.19 d (C^{4b}), 125.00 d (C^8), 125.71 d (C^{15}, C^{11}), 133.02 d (C^{10}), 133.79 d (C^9), 136.67 s (C^{11a}), 138.44 s (C^{7a}), 147.36 s (C^{16}), 184.87 s (C=O, acid), 198.45 s and 198.77 s (C^7, C^{12}). Found, %: C 78.53; H 10.51. $C_{30}H_{36}O_4$. Calculated, %: C 78.16; H 9.98.

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