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p-COUMARATES OF *BETULA PENDULA* (*BETULACEAE*) VEGETATIVE BUDS SESQUITERPENE ALCOHOLS

© ***D.N. Vedernikov*, E.M. Ipanova***

Kirov St. Petersburg State Forest Technical University, Institutskiy per., 5, St. Petersburg, 194021 (Russia), e-mail: dimitriy-4@yandex.ru

The composition of coumarates sesquiterpene alcohols of *Betula pendula* Roth. birch vegetative buds was determined. Fraction was isolated from buds extract by preparative liquid chromatography. The extract was isolated by sequential extraction of an alcoholic extract of the buds with methyl tert-butyl ether. The new sesquiterpene derivatives were first detected in the birch vegetative buds. The structure of 6-hydroxyisocaryophyllene [(1R,4Z,6R,9S)-8-methylene-11,11-dimethylbicyclo[7.2.0]undec-4-ene-6-ol] trans-p-coumarate isolated from the birch buds was determined by NMR spectroscopy. The physico-chemical characteristics and NMR data of 6-hydroxyisocaryophyllene p-coumarate and others coumarates are demonstrated. The gas chromatographic retention indices of all identified compounds were determined. Birch buds contain derivatives of trans-coumaric acid. The antimicrobial activity of sesquiterpene alcohols coumarates was evaluated. The antimicrobial activity of sesquiterpene alcohols coumarates in relation to the following microorganisms: *Escherichia coli, Proteus mirabilis, Staphylococcus aureus, Staphylococcus pneumonia and Klebsiella pneumonia* was evaluated. The fraction of sesquiterpene alcohols coumarates showed activity against *Staphylococcus epidermidis*.

Keywords: *Betula pendula* Roth., vegetative buds, 6-hydroxyisocaryophyllene trans-p-coumarate, coumarates, NMR spectroscopy, data of GLC, antimicrobial activity, Extraction.

Introduction

Coumarates of sesquiterpene alcohols were first isolated from the *Verbesina virginica* L. roots [1]. Sesquiterpene alcohols coumarates composition of white birch (*Betula pendula* Roth.) vegetative buds consists [2, 3] of 6-hydroxy-β-caryophyllene, 14-hydroxyhumulene, 14-hydroxy-β-caryophyllene and t-betulenol ((1S,4R,8R)-9,9-dimethyl-2,5-dimethylenebiclo[6.2.0]decane-4-yl) methanol coumarates. This study determined that in addition to the listed compounds the fraction also consists of 6-hydroxyisocaryophyllene, 14-hydroxyisocaryophyllene, 14-hydroxy-4,5-dihydrocaryophyllene coumarates.

Experimental

Vegetative buds of *B. pendula* (425 g (293 g absolutely dry substance) of buds)) were collected in March 2018 in the Leningrad Region. The wet, crushed buds were extracted with isopropanol in a Soxhlet apparatus for 12 hours. The yield of extract from a.d.s. was 42%. The alcohol extract was evaporated and sequentially extracted with petroleum ether and methyl tert-butyl ether (MTBE) 4 times in 100 ml for 10 minutes at boiling.

The obtained MTBE-extract was separated by preparative liquid chromatography on silica gel with gradient elution using hexane as an eluent with the addition of up to 13% MTBE. Preparative liquid chromatography was performed for 90 hours. The fraction of coumarates (1.7 g, 0.34% from a.d.s) eluted from the PE column supplemented with 11-12% MTBE. The fraction was rechromatographed (3 times) to obtain the individual component – 6-hydroxyisocaryophyllene p-coumarate. Fraction chromatography was performed for 10 hours. The presence of coumarates was established by chromatography-mass spectrometry. Molecular weights of the isolated compounds – 366.

To analyze the alcohol component of the esters by chromatography-mass spectrometry, the fraction was hydrolyzed with an alkali solution. The reaction was carried out by boiling 50 mg of the substance in 10 ml of a 0.5 N solution of KOH in ethanol for 1.5 h.

Vedernikov Dmitriy Nikolaevich – Professor, Doctor of Chemistry, e-mail: public@spbftu.ru, dimitriy-4@yandex.ru
Ipanova Elizaveta Mihailovna – is the student working for master's degree, e-mail: lisaghost1@gmail.ru

* Corresponding author.

Qualitative and quantitative analysis of esters and sesquiterpene alcohols was carried out by gas chromatography-mass spectrometry. The device is an 6850A Agilent chroma-mass spectrometer (Agilent Technologies, Inc.) with a model G2629A gas chromatograph equipped with a model G2577A HP5973 Network selective mass spectrometry detector. The ionizing energy was 70 eV. The temperatures of a separator and an ion source were 280 and 230 °C, respectively. To fractionate samples, Rxi®-5 Sil MS column (30000 × 0.18 mm ID) with a 0.10 μm (low polarity crossbond® silarylene phase; similar to 5% phenyl/95% dimethyl polysiloxane) was used. The thermostat temperature was programmed to increase from 100 to 250 °C at a rate of 5 °C per min. The evaporator temperature was 270 °C. The flow rate of the carrier gas (helium) was 1 cm^3 per min. The dosed volume was 0.1 μL. The gas chromatographic retention indices of the analyzed substances were determined using the retention indices of *n*-alkanes as standard compounds (Aldrich). The standard compounds were chosen so that the retention times of the studied substances fell between those of the reference alkanes. Retention indices were calculated following the determination of the coefficients of the following equation: $I = a\tau^2 + b\tau + c$, where I and τ represent the retention index and retention time, respectively. All calculations were performed using an Advanced Grapher program (version 2.08).

High resolution mass spectrum (HR-ESI) was recorded on a Bruker-micrOTOF instrument using an electrospray method. The scanning interval is 50–1200 m/z. The ion polarity is positive, the voltage of the ion source capillary is 4500 V, the gas pressure at spraying is 1.0 bar, and the dry gas flow rate is 4.0 l/min. The solvent was methanol.

NMR spectra were recorded using a Device Jeol ECX-400A

spectrometer (400 and 100 MHz for ^1H and ^{13}C spectra, respectively) and Varian DirectDrive NMR System 700 MHz and $CDCl_3$ as a solvent (δ-scale). As internal standards residual signals $CHCl_3$ (δ H 7.25 ppm) were used.

UV spectra were recorded on a UV-2401PC Shimadzu

IR spectra were recorded on a FTIR-8400S Shimadzu instrument using the FT-IR reflection technique.

Optical rotation angle was determined on the device: Automatic Polarimeter AA65. Solvent-chloroform. The length of the cuvette is 3 cm.

Thin layer chromatography was performed on Merck Silica gel 60 F254 plates. The spots on the TLC plates were exposed to ultraviolet light and sprayed were sprayed with a 10% solution of sulfuric acid in ethanol with the addition of vanillin.

Antimicrobial activity. The microplate method and the agar diffusion method were used to determine antimicrobial activity. In this experiment, the test object was tested in concentrations: 1000, 500, 100, 50, 10, 1, 0.5, 0.1 μg/ml. Dimethyl sulfoxidewas used as a solvent to prepare a stock solution of the test object at a concentration of 20000 μg/ml,. The research was carried out at the "Adaptogen" Interregional Center.

Physic-chemical and Spectral Characteristics of the isolated compounds

6-Hydroxyisocaryophyllene *trans-p*-coumarate (1), 6-*trans-p*-coumaroxy-isocaryophyllene, (1R,4Z, 6R, 9S)-8-methylene-4,11,11-trimethylbicyclo[7.2.0]undec-4-ene-6-yl-(2*E*)-3-(4-hydroxyphenyl)prop-2-enoate.
M.p. 105–109 °C. $[\alpha]_D^{25}$ +73°(*c* 0.44, $CHCl_3$). Mass-spectrum (m/z, I_{rel}, %): 366 (<1) [M^+], 341(<1), 321(<1), 303(<1), 283(<1), 262(<1), 239(<1), 213(1), 187(1,3), 165(<1), 147(100), 118(5.7), 91(12.6), 65(3.9), 53(1.8).

High resolution mass spectrometry (HR-ESI): $C_{24}H_{30}O_3$ +Na: 389.2082(100), 390.2112(26.5), 391.2142 (3.7). Mass calculation: 389.21(100), 390.21(26.1), 391.22(3.3).

IR-spectrum (ν, $см^{-1}$): 3443, 2941, 2887, 2829,1701, 1651, 1618, 1593, 1574, 1489, 1298, 1269, 1143, 972, 787.

UV l_{max}/nm (EtOH) (log e): 203 (5.00), 228 (4.60), 205 (4.77); 314 (4.82)

TLC – chromatography: Brand TLC Sorbpolymer sorbfil plates for thin layer chromatography. Eluent mixture: hexane with the addition of 20% MTBE. R_f = 0.34 (UV detection).

(1R,4E,9S,6R)-6-Hydroxy-β-caryophyllene trans-p-coumarate (2), 6-trans-p-coumaroxy-(1R,4E,9S,6R) caryophyllene, (1R,4E,6R,9S)-8-methylene-4,11,11-trimethylbicyclo[7.2.0]undec-4-ene-6-yl (2E)-3-(4-hydroxyphenyl)prop-2-enoate.

^1H NMR in $CDCl_3$ (δ): 1.686 (H-14), 5.323 (1H, d, H-5), 5.700 (1H, dt, H-6).

^{13}C NMR in $CDCl_3$ (δ): 23.3 (q, C-14), 73.2 (d, C-6), 125.5 (d, C-5).

The mass spectrum was similar to the mass spectrum of 6-Hydroxyisocaryophyllene trans-p-coumarate [1].

14-Hydroxy-α-humulene *trans-p*-coumarate (3), 14-*trans-p*-coumaroxy-humulene, (1E,4E,8E)-4,8,11,11-tetramethylcycloundeca-1,4,8-trien-14-yl (2*E*)-3-(4-hydroxyphenyl)prop-2-enoate.

^1H NMR in $CDCl_3$ (δ): 1.06 (3H, s, H-12), 1.06 (3H, s, H-13), 1.444 (3H, s, H-15), 1.924 (2H, d, H-10), 2.14 (2H, t, H-7), 2.18 (2H, dt, H-6), 2.700 (2H, d, H-3), 4.667 (2H, d, H-14), 4.993 (1H, t, H-9), 5.205 (1H, d, H-1), 5.293 (1H, t, H-5), 5.621(1H, ddd, H-2).

^{13}C NMR in $CDCl_3$ (δ): 25.4 (q, C-12), 26.0 (t, C-6), 26.4 (q, C-15), 32.8 (q, C-13), 35.6 (t, C-10), 37,5 (s, C-11), 37.6 (t, C-13), 42.8 (t, C-7), 65.5 (t, C-14), 128.0 (d, C-9), 131.9 (d, C-2), 132.8 (s, C-8), 142.3 (s, C-4), 144.6 (D, C-1).

***t*-betulenol *trans-p*-coumarate (4), 14-*trans-p*-coumaroxy-*t*-betulenol, ((1S,4R,8R)-9,9-dimethyl-2,5-dimethylenebiclo[6.2.0]decane-4-yl)-methanyl-(2*E*)-3-(4-hydroxyphenyl)prop-2-enoate**.

^{1}H NMR in $CDCl_3$ (δ): 0.968 (3H, s, H-12), 0.978 (3H, s, H-11), 1.501 (1H, m, H-2), 1.672 (2H, m, H-9), 1.700 (1H, m, H-2), 1.717 (1H, m, H-1), 1.911 (1H, m, H-3), 2.220 (1H, m, H-5), 2.474 (1H, m, H-8), 2.475 (1H, m, H-3), 2.481 (1H, m, H-6), 2.741 (1H, m, H-6), 4.082 ($1H_a$, dd, H-13), 4.223 ($1H_b$, dd, H-13), 4.686 (1Ha, t, H-15), 4.784 (1Hb, brs s, H-15), 4.883 (1Hb, brs s, H-14), 4.975(1Ha, brs s, H-14).

^{13}C NMR in $CDCl_3$ (δ): 25.4 (q, C-12), 32.6 (q, C-11), 34.1 (t, C-2), 34.2 (s, C-10), 40.9 (t, C-9), 43.2 (t, C-6), 43.4 (t, C-3), 47.9 (d, C-8), 52.6 (d, C-1), 53.1 (d, C-5), 69.8 (t, C-13), 112.1 (t, C-15), 114.0 (t, C-14), 151.8 (s, C-7), 152.2 (s, C-4).

14-hydroxy-β-caryophyllene-*trans-p*-coumarate (5), 14-*trans-p*-coumaroxy-β-caryophyllene, (1R,4E,9S)-11,11-dimethyl-8-methylenebicyclo[7,2,0]undec-4-ene-14-yl (2*E*)-3-(4-hydroxyphenyl)prop-2-enoate.

^{1}H NMR in $CDCl_3$ (δ): 2.67 (2H, H-6), 4.59, 4.60 (H-14 ββ), 4.74, 4.75 (H-14, ββ βα), 4.78, 4.80 (H-14 βα), 4.79 (Ha, H-15 βα), 4.81 (Ha, H-15 ββ), 4.909 (Hb, H-15 βα), 4.96 (Hb, H-15 ββ), 5.619 (H-5 ββ), 5.641 (H-5 βα).

^{13}C NMR in $CDCl_3$ (δ): 37.5 (t, C-6), 63.8 (t, C-14), 63.9 (t, C-14), 111.6 (t, C-15 ββ), 113.9 (t, C-15 βα), 133.7 (d, C-5).

14-hydroxyisocaryophyllene-*trans-p*-coumarate (6), 14-*trans-p*-coumaroxyisocaryophyllene, (1R,4Z,9S)-11,11-dimethyl-8-methylenebicyclo[7,2,0]undec-4-ene-14-yl-(2*E*)-3-(4-hydroxyphenyl)prop-2-enoate.

^{1}H NMR in $CDCl_3$ (δ): 0.96 (3H, s, H-13), 0.98 (3H, s, H-12), 2.12 (2H, H-7), 2.40 (2H, , H-6), 4.619 (2H, H-14), 4.79 (H-15), 4.88 (H-15), 5.60 (1H, t, H-5).

^{13}C NMR in $CDCl_3$ (δ): 24.8 (q, C-12), 32.2 (q, C-13), 36.3 (t, C-6), 42.7 (t, C-7), 65.4 (t, C-14), 112.2 (t, C-15), 133.8 (d, C-5).

The mass spectrum was similar to the mass spectrum of 14-hydroxy-β-caryophyllene trans-p-coumarate [1].

14-hydroxy-4,5-dihydro-β-caryophyllene *trans-p*-coumarate (7), 14-*trans-p*-coumaroxy-4,5-dihydro-β-caryophyllene, (1R,9S)-11,11-trimethyl-8-methylenebicyclo[7,2,0]undeca-14-yl (2*E*)-3-(4-hydroxyphenyl)–prop-2-enoate.

Mass-spectrum (m/z, I_{rel}, %): 368(<1) [M^+], 354(<1), 340(<1), 321(<1), 309(<1), 295(<1), 279(<1), 262(<1), 239(<1), 204(6), 189(5), 176(4), 164(22), 147(100), 133(13), 119(20), 105(11), 91(20), 82(12), 67(7), 55(6), 50(2).

Mass-spectrum of **14-hydroxy-4,5-dihydro-β-caryophyllene**: 222(2), 207(9), 191(27), 189(11), 175(5), 161(9), 149(10), 147(9), 135(43), 133(34), 121(40), 119(32), 109(53), 107(53), 105(41), 95(100), 93(84), 91(64), 82(50), 81(60), 79(99), 77(42), 69(50), 67(71), 55(49), 53(24), 52(4).

Results and discussion

Separation of the coumarate fraction by preparative liquid chromatography and taking the NMR spectra of the fractions showes that trans- p- coumarates are contained in the buds: doublets from protons are observed at the double bond carbon associated with the aromatic ring with centers of 7.623 and 6.29 ppm and the spin-spin interaction constant is 16.0 Hz. Signals of cis-*p*- coumarates on the spectra of fractions with centers of 6.79–6.85 and 5.83 ppm and the spin-spin interaction constant is 12.3 Hz appear when the fractions are stored in the light, during liquid chromatography. The ability of coumaric acid to transform from trans to cis under the influence of UV light is noted in [4]. *Cis-p*-coumaric acid is also formed upon saponification of the coumarate fraction [2].

Individual coumarate was isolated by triplicate chromatography on silica gel with an eluent system: hexane – MTBE (11–12%). The proton signal, which was observed in the NMR spectrum with a center at 5.743 ddd, was similar to the proton signal at 6 carbon in the NMR^{1}H spectrum of 6- hydroxyisocaryophyllene recently isolated from birch bud [5].

The signals of other atoms were identified using NMR spectra: HMQC, HMBC, COZY H^1-H^1 and were similar to the signals of the corresponding sesquiterpene alcohol (Tab. 1). The magnetic interaction of protons in the two-dimensional NOESY NMR spectrum was similar to the interaction of protons in the corresponding spectrum of 6-hydroxyisocaryophyllene [5].

The magnetic interaction of protons in the two-dimensional NOESY NMR spectrum was similar to the interaction of protons in the corresponding spectrum of 6-hydroxyisocaryophyllene [5].

The composition of the other coumarates alcoholic half was established after saponification of the fraction, comparison of the mass spectra of alcohols with the mass spectra of sesquiterpenoids previously isolated from birch buds [6], as well as comparing NMR ^{1}H spectra of fractions with NMR spectra of 14-hydroxy-isocaryophyllene, 14-hydroxy-β-caryophyllene [7], 14-hydroxyhumulene [8], ((1S,4R,8R)-9,9-dimethyl-2,5-dimethylenebycyclo[6.2.0]decane-4-yl)methanol [1], 6-hydroxycaryophyllene [9]. The presence of the compound (7) in the composition of the coumarates was established by comparing the saponification product mass spectrum with the mass spectrum of 14-hydroxydihydrocaryophyllene. Compound was found in *Betula litwinowii* buds [10]. The discovery of most of these sesquiterpene alcohols in birch buds was previously reported [11–13].

The main contribution to the identification of compounds was made by the analysis of the TOCSY and HSQCAD spectra obtained using a spectrometer with a frequency of 700 MHz, on which the signals of individual alcohol components were viewed. The names of the alcohol constituents of coumarates, gas chromatographic retention indices of the compounds and the ratio of the components are shown in table 2.

Note. The assignment of a signal to a specific coumarate was made after comparing the chromatograms of sesquiterpene alcohols obtained by saponification of coumarates with the chromatogram of coumarates. The ratio of the areas of the peaks of coumarates in the chromatogram corresponded to the ratio of the peak areas of the corresponding alcohol half.

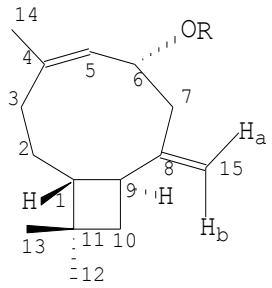
Table 1. Data on the ^{1}H NMR and ^{13}C NMR spectra of coumarate 6-hydroxyisocaryophyllene (1)

C atom	δC, ppm	δH ppm,	NOE correlations	HMBC results
1	50.1 d	1.728 dddd		C8, C13
2	30.1 d	α 1.249dddd β 1.003 dddd		C1
3	29.3 t	1.877 m	-H(C6); βH(C2)	
4	138.1 s	–		
5	125.6 d	5.228 dd	-αH(C7); H(C14)	C3, C14
6	73.4 d	5.743 ddd (5.693 ddd *cis*-kumarat)		
7	42.6 t	α 2.487 dd β 2.637 dd	β-H_a(C15)	β-C5, C6, C8, C15
8	151.0 s	–		
9	39.9 d	2.516 ddd	H(C12)	C8, C15, C10, C13
10	39.7 t	α 1.563 dd β 1.741 dd	β-H(C13); α-H(C12)	C1,C9, C13, C11
11	29.8 s	–		
12	25.5 q	1.006 s		
13	23.2 q	0.990 s		C1, C9, C12
14	23.0 q	1.651 d	αH(3C)	C4, C5, C3
15	113.3 t	H_a – 4.957 brs s. H_b – 4.998 brs s.		H_b-C9, C7
1`	127,1 s	–		
2`,6`	130.0 d	7.400 d		C4',
3`,5`	116.0 d	6.843 d		C1', C4'
4`	158.2 s	–		
α	144.8 d	7.623 d		Cβ, C2',C6', γ
β	115.8 d	6.291 d		C1'
γ	167.3 s	–		

J/Hz: for (**1**): 1-9=9.8; 1-2α=11.0; 1-2β=3.7; 2α-3β=8.9; 2β-3β=4.0; 2α-2β=13.8; 2β-3α=4.5; 3α-2α=4.6; 3α-3β=13.2; 5-14=0.8; 5-6=8.0; 6-7β=4.0; 6-7α=8.4; 7α-7β=13.0; 9-10α =9.1; 9-10β= 9.6

Table 2. Coumarates composition. Gas chromatographic retention indices

Alcohol component of ethers	RI of sesquiterpenol	RI of coumarate sesquiterpenol	p-Coumarate content, %
6-hydroxyisocaryophyllene	1574	3072	24
((1S,4R,8R)-9,9-dimethyl-2,5-dimethylenebicyclo[6.2.0]decane-4-yl)methanol (t-betulenol)	1587	3113	24
6-hydroxy-β-caryophyllene	1590	3122	6
14-hydroxyisocaryophyllene	1609	3128	9
14-hydroxy-β-caryophyllene	1611	3129	14
14-hydroxydihydrocaryophyllene	1645	3182	3
14-hydroxy- α-humulene	1660	3147	20



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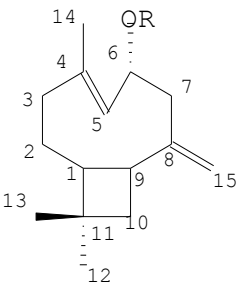

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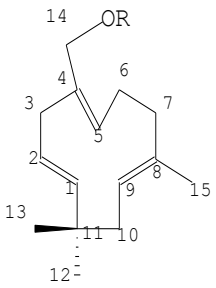

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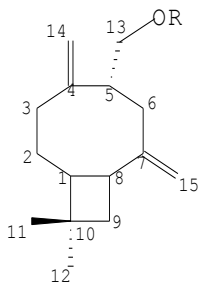

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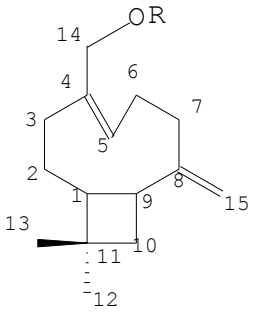

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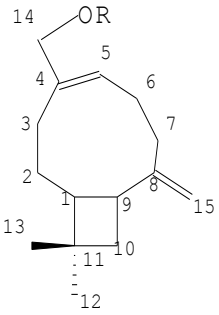

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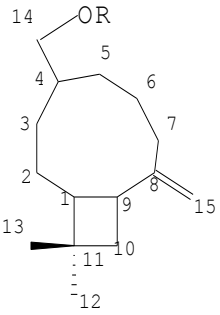

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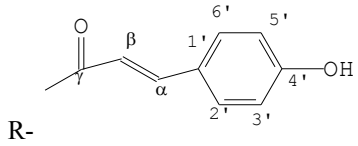

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Biological Activity

The biological activity of coumaric acid has been reported in recent years [14]. P-Coumaric acid shows anti-diabetic activity [15], antioxidant activity [16], antitumor activity [17]. p-Coumaric acid protect neurons against injury induced by 5-*S*-cysteinyl-dopamine [18], alleviate of the intestinal Ischemia/Reperfusion injury [19].

The coumarate fraction was investigated to determine antimicrobial activity, since the alcoholic extract of birch buds has biological activity against Staphylococcus aureus [19], and p-coumaric acid has antimicrobial activity against the gram-positive bacteria (*S. aureus*, *Staphylococcus epidermidis*, *Enterococcus faecalis*, *L. monocytogenes* and *Streptococcus agalactiae*) and the gram-negative bacteria (*E. coli*, *Proteus mirabilis*, *Morganella morganii*, *Pasteurella multocida* and *Neisseria gonorrhoeae*)[20].

Seeding on culture media from wells with a concentration of 1000 μg/ml of 96-well plate with microorganisms *Escherichia coli, Proteus mirabilis, Staphylococcus* aureus showed growth on plates, indicating the absence of antimicrobial activity of the studied object in relation to these microorganisms, the minimum inhibitory concentration (MIC) >1000 mcg/ml. Seeding on culture media from the wells of the tablet with concentrations of 1000, 500,100, 50 μg/ml with the microorganism *Staphylococcus epidermidis* showed the absence of microorganism growth, microorganism growth was detected from wells with concentrations of 10, 1, 0.5, 0.1 μg/ml in this case, the MIC ≤50 μg/ml.

The results of the agar diffusion study showed the absence of growth inhibition zones of *Streptococcus pneumonia* and *Klebsiella pneumonia* (-) microorganisms. In this case, the MIC >1000 μg/ml.

Conclusions

Trans-p-coumarates of 6-hydroxyisocaryophyllene, ((1S,4R,8R)-9,9-dimethyl-2,5-dimethylene-bicyclo[6.2.0]-decane-4-yl)methanol, 6-hydroxy-β-caryophyllene, 14-hydroxyisocaryophyllene, 14-hydroxy-β-caryophyllene, 14-hydroxydihydrocaryophyllene were identified in the fraction of coumarate sesquiterpene alcohols of the ethereal extract of *B. pendula* vegetative buds (0.5% of dry buds). The coumarate fraction has activity against the microorganism *Staphylococcus epidermidis* with a minimum inhibitory concentration (MIC) of 50 μg/ml. Not active against *Staphylococcus aureus* ATCC 6538-P, *Streptococcus pneumoniae* ATCC 6303, *Klebsiella pneumoniae* – ATCC 13883, *Escherichia coli* (-) ATCC 25922 (VKPM B-6645), *Proteus mirabilis* (-) 3177 (GKPM B-4488).

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