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Analgesic Activity of Some Furanoditerpenoids of Labdanum Series and Their Derivatives

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Abstract

Derivatives of labdanum triterpenoids – lambertianic and flomizoic acids and their esters, modified in the heterocyclic fragment of the molecule, were obtained. Their analgesic activity was investigated.

Key words: lambertianic acid, flomizoic acid, analgesic activity

INTRODUCTION

Some plants growing in Central Asia are used in folk medicine as neuroleptic and psychomimetic means. The active essence responsible for these kinds of action is furanoditerpenoids of clerodan, neoclerodan and labdan series [1–4]. During the recent decade, the attention of researchers has been attracted to the Brazilian plant of *Salvia minorum* genus (psychoactive mint) the leaves of which are applied by the peoples of the Amazonian regions during their traditional procedures leading to the state of hallucinations [5]. The plant produces a complicated mixture of diterpenoids of the neoclerodan series including 24 metabolites the molecules of which include the furan structural fragment [5, 6]. Special interest was caused by one of them – salvinorin A **I**, which exhibits unique activity as a powerful agonist of kappa-opioid receptors [5, 7]. Available plant furanolabdanoids are lambertianic acid **II** and its methyl ester **III** – metabolites of Siberian cedar [8]. Lambertianic acid is easily transformed into another furan-containing metabolite – flomizoic acid **IV**. This compound is formed as a result of enzymatic hydrolysis if plant glycosides present in the medical plants of Lamiaceae family: *Phlomis* sp. and *Eremostachys* sp. [9, 10]. Extracts from these plants are characterized by diverse kinds of biological activity including analgesic action.

Investigations performed by us previously into the pharmacological activity of lambertianic acid **II** and its ester **III**, as well as amino derivatives of labdanoids **V–VII** revealed antidepressant and neurotrophic activity of these compounds [11, 12].

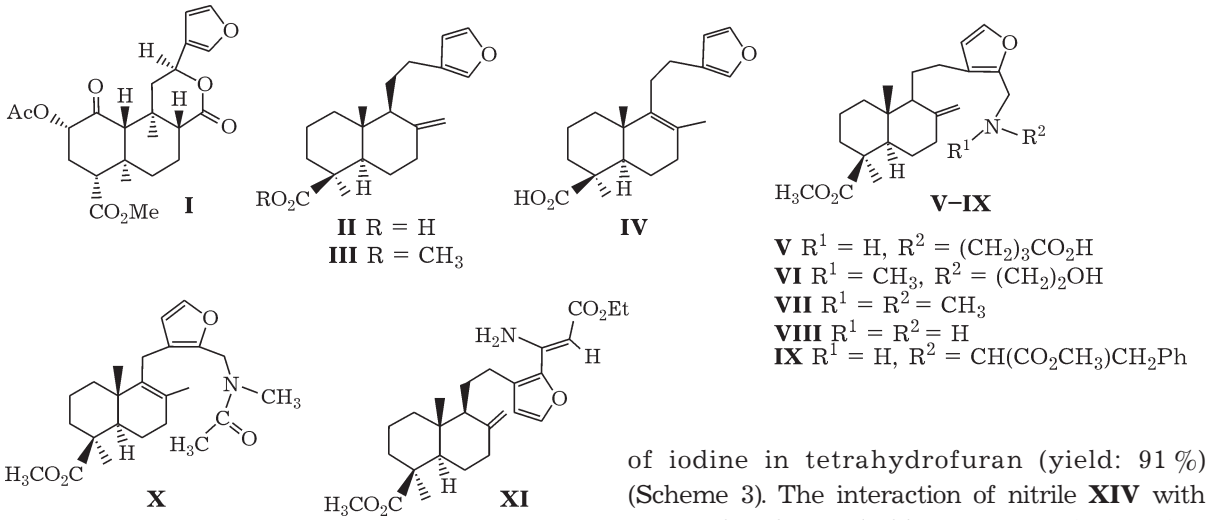
The goal of the present work was to study the analgesic activity of labdanoids **II–IV** and their synthetic nitrogen-containing derivatives **V–XI** (Scheme 1).

EXPERIMENTAL

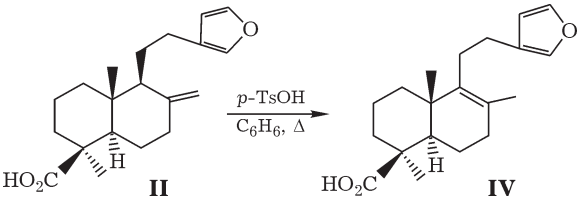
Chemistry

Various nitrogen-containing derivatives of lambertianic and flomizoic acids were synthesized for investigation. Flomizoic acid **IV** was obtained by isomerization of lambertianic acid **II** under the action of *p*-toluene sulphonic acid under heating in benzene (yield: 86 %).

Compounds **V–VII**, **IX** and **X** were obtained according to Mannich's reaction from methyllambertianate **III** with different amines using the procedures described in [13]. The synthesis of compound **VIII** was carried out according to Scheme 2 using 16-formylmethyllambertianate **XII** as the initial compound. The



Scheme 1.

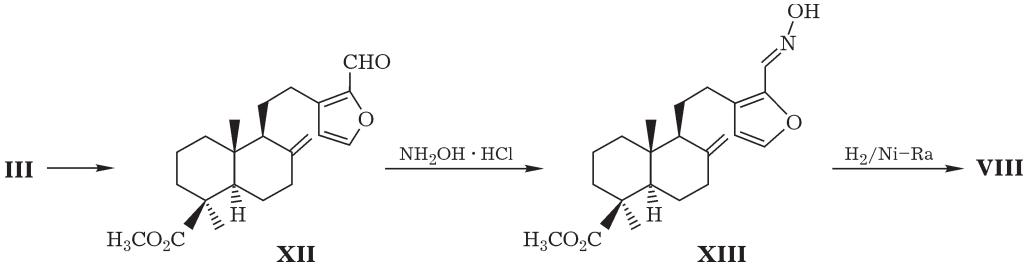


treatment of aldehyde **XII** with hydroxylamine leads to the quantitative formation of oxime **XIII**; its reduction leads to the formation of aminomethyllambertianate **VIII** (yield: 97 %).

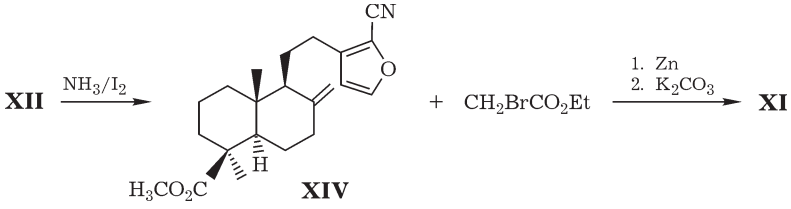
A key compound in the synthesis of diterpene enaminoester **XI** is 16-cyanomethyllambertianate **XIV** which was obtained by treating 16-formylmethyllambertianate **XII** with the aqueous solution of ammonia in the presence of iodine in tetrahydrofuran (yield: 91 %) (Scheme 3). The interaction of nitrile **XIV** with zinc enolate from ethyl bromoacetate (4 equiv.) in the THF solution followed by hydrolysis under the action of K_2CO_3 leads to the formation of enaminoester **XI**, which was isolated with a yield of 92 % after column chromatography. Compound **XI** is formed as an individual stereo isomer.

Lambertianic acid **II** was isolated using the procedure described in [14]. The physicochemical characteristics of compounds **V–II**, **IX** and **X** were reported in [13]. Compounds **VII** and **VIII** were isolated and then studied in the form of oxalates.

(1*S*,4a*S*,5*S*,8a*R*)-5-[2-furan-3-yl)ethyl]-1,4a,6-trimethyl-1,2,3,4,4a,7,8,8a-octahydronaphthalene-1-carboxylic acid [15,16-epoxy-8(9),13(16),14-labdatrien-18-oic acid, flomizoic acid] **IV.** The solution of 8.88 g (28.1 mmol) of lambertianic acid **II** in 30 mL of benzene was prepared; 0.24 g (1.4 mmol) of *p*-toluene sulphonic acid was added to the solution. The



Scheme 2.



Scheme 3.

reaction mixture was boiled for 8 h, the solvent was evaporated in vacuum, and the residue was passed through a column with silica gel (with chloroform as eluent). By crystallizing the fraction from hexane, 7.66 g (86 %) of compound **IV** was obtained. M. p. 119–122 °C $[\alpha]_{589}^{22.1}$ +181.50 (s 0.23, $CHCl_3$). (According to data reported in [9], $[\alpha]_D^{14}$ +116.9 (s 0.31, CH_3OH.) UV spectrum (ethanol), λ_{max}, nm (log ε): 203 (4.05). IR spectrum, cm^{-1}: 3430 (OH), 1695 (CO). NMR ^1H spectrum (δ, ppm, *J*, Hz): 0.91 s (3H, $C^{20}H_3$), 1.06 td (1H, H^3, *J* 13.9, 4.6), 1.24 t (1H, H^1, *J* 13.1), 1.30 s (3H, $C^{19}H_3$), 1.41 d (1H, H^5, *J* 11.9), 1.58 dm (2H, $H^{2,2}$, *J* 11.0), 1.66 s (3H, $C^{17}H_3$), 1.82 td (1H, H^{11}, *J* 12.3, 5.5), 1.93 dm (2H, $H^{1,11}$, *J* 13.3), 2.01 d (1H, H^7, *J* 5.7), 2.07–2.34 m (4H, $H^{3,6,6,7}$), 2.47 t (2H, $H^{12,12}$, *J* 7.0), 6.31 s (1H, H^{14}), 7.25 s (1H, H^{15}), 7.37 s (1H, H^{16}). NMR ^{13}C spectrum (δ, ppm): 17.41 q (C^{20}), 19.06 t (C^2), 19.29 q (C^{17}), 20.26 t (C^{11}), 25.27 t (C^{12}), 28.17 q (C^{19}), 28.48 t (C^6), 33.79 t (C^7), 36.72 t (C^1), 36.92 t (C^3), 39.32 s (C^{10}), 43.38 s (C^4), 53.13 d (C^5), 110.35 d (C^{14}), 125.09 s (C^{13}), 126.91 s (C^8), 137.94 d (C^{15}), 138.38 s (C^9), 142.21 d (C^{16}), 184.31 s (C^{18}). Mass spectrum, *m/z* (I_{rel}, %): 317 (21), 316 (94), 301 (22), 235 (37), 234 (36), 221 (31), 189 (100), 188 (36), 133 (62), 119 (45), 105 (33), 91 (35), 82 (39), 81 (60), 56 (37), 43 (61). Found: [*M*] 316.2040. $C_{20}H_{28}O_3$. Calculated: 316.2033.

(1*S*,10*R*,5*S*,9*S*)-Methyl-5-{2-[2-(hydroxyaminomethyl)-furan-3-yl]ethyl)-1,4a-dimethyl-6-methylenedecahydronaphthalene-1-carboxylate XIII. To the solution of 1.00 g (2.8 mmol) of aldehyde **XII** in aqueous ethanol ($EtOH/H_2O$ = 1 : 1), we added 0.20 g (2.8 mmol) of hydroxylamine hydrochloride and 0.12 g (2.8 mmol) NaOH. The reaction mixture was mixed at room temperature for 5 h, and then 50 mL of water was added. The product was extracted with chloroform (3 × 50 mL). The organic extract was washed with water (3 × 40 mL) dried with $MgSO_4$, and evaporated. In the residue, we obtained 1.04 g (100 %) of compound **VI** in the form of oil. NMR ^1H spectrum (δ, ppm, *J*, Hz): 0.49 s (3H, $C^{20}H_3$), 1.00 m (2H, $H^{1,3}$), 1.15 s (3H, $C^{19}H_3$), 1.26 dd (1H, H^5, *J* 12, 3), 1.46 m, 1.51 м (3H, $H^{2,9,11}$), 1.55 m (1H, H^{11}), 1.56 dd (1H, H^1, *J* 8, 2), 1.74 m, 1.78 m, 1.82 m, (3H, $H^{2,6,7}$), 1.88 m (1H, H^6), 1.96 m (1H, H^{12}), 2.13 dm (1H, H^3, J_{hem} 13), 2.41 m (1H, H^7), 2.50 m (1H, H^{12}), 3.59 s (3H, OCH_3), 4.57 s, 4.91 s (2H, $H^{17,17}$), 6.30 d (1H, H^{14}, *J* 2), 7.38 d (1H, H^{15}, *J* 2), 7.96 s (1H, CHNOH). NMR ^{13}C spectrum, δ, ppm: 12.19 q (C^{20}), 19.44 t (C^2), 22.56 t (C^{12}), 23.71 t (C^{11}), 25.78 t (C^6), 28.28 q (C^{19}), 37.65 t (C^3), 38.13 t (C^7), 38.54 t (C^1), 39.67 s (C^4), 43.82 s (C^{10}), 50.72 q (OCH_3), 54.27 d (C^9), 55.70 d (C^5), 106.17 t (C^{17}), 112.22 d (C^{14}), 128.69 s (C^{13}), 138.39 d (CH=), 142.37 s (C^{16}), 143.36 d (C^{15}), 147.23 s (C^8), 177.37 s (C^{18}).

(1*S*,10*R*,5*S*,9*S*)-Methyl-5-[2-[2-(aminomethyl)-furan-3-yl]ethyl}-1,4a-dimethyl-6-methylenedecahydronaphthalene-1-carboxylate VIII. To the solution of 1.00 g (2.8 mmol) of oxime **XIII** in ethanol, we added 10 mL of the aqueous solution of 2 M NaOH and 1 g of Raney nickel. The reaction mixture was stirred at room temperature in the atmosphere of hydrogen for 5 h. The catalyst was removed by filtering, and the solvent was evaporated. The solution of oxalic acid in ether was added to the residue. The precipitate was separated by filtering. Oxalate of amine **VIII** 1.17 g (97 %) was obtained. M. p. 165–168 °C. $[\alpha]_{580}$ +0.18° (s 13.90, $CHCl_3$). UV spectrum, λ_{max}, nm (log ε): 193 (2.55), 212 (2.30), 226 (2.37), 242 (2.39). IR spectrum, cm^{-1}: 1156, 1229, 1724 (C=O), 2946 (N_3^+H). NMR ^1H spectrum (δ, ppm, *J*, Hz): 0.49 s (3H, $C^{20}H_3$), 1.01 dt (1H, H^1, *J* 13.5, 3.2), 1.01 dt (1H, H^3 *J* 13.5, 3.2), 1.16 s (3H, $C^{19}H_3$), 1.28 d (1H, H^5, *J* 11.2), 1.51 m (3H, $H^{2,9,11}$), 1.57 m (1H, H^{11}), 1.74 m, 1.82 m, (3H, $H^{2,6,1}$), 1.87 m (1H, H^7), 1.98 m (1H, H^6), 2.13 dm (1H, H^3, J_{hem} 13.2), 2.28 m (1H, H^{12}), 2.40 d (1H, H^7, *J* 11.1), 2.53 m (1H, H^{12}), 3.60 s (3H, OCH_3), 4.03 ws (2H, CH_2N), 4.56 s, 4.90 s (2H, $H^{17,17}$), 4.76 ws (2H, NH_2), 6.28 s (1H, H^{14}), 7.24 s (1H, H^{15}). NMR ^{13}C spectrum, δ, ppm: 11.65 q (C^{20}), 19.01 t (C^2), 21.93 t (C^{12}), 23.33 t (C^{11}), 25.43 t (C^6), 27.81 q (C^{19}), 33.01 t (CH_2N), 37.20 t (C^3), 37.77 t (C^7), 38.14 t (C^1), 39.30 s (C^4), 43.89 s (C^{10}), 50.32 q (OCH_3), 54.11 d (C^9), 55.35 d (C^5), 105.67 t (C^{17}), 110.86 d (C^{14}), 124.49 s (C^{13}), 141.08 s (C^{16}), 142.46 d (C^{15}), 146.86 s (C^8), 177.54 s (C^{18}). Mass spectrum, *m/z* (I_{rel}, %): 359.3 (10), 342.3 (14), 330.3 (17), 329.2 (47), 269.2 (25), 161.1 (30), 160.1 (21), 147.1 (49), 123.1 (18), 122.1 (58), 121.1 (72), 119.1 (19), 109.1 (100), 108.1 (18), 107.1 (26), 105.1 (21), 95.1 (23), 94.1 (51), 93.1 (23), 91.1 (25), 83.1 (33), 81.1 (28), 79.1 (22), 67.1 (16), 55.0 (29), 46.0 (14), 45.0

(28), 41.0 (18), 30.0 (20). Found: $[M]^+$ 359.2450. Calculated: *M* 449.2408.

(1*S*,4a*R*,5*S*,8a*R*)-Methyl-5-[2-(2-cyanofuran-3-yl]-1,4a-dimethyl-6-methylene-decahydronaphthalene-1-carboxylate (methyl ester of 16-cyano-15,16-epoxy-8(9),13(16),14-labdatriene-18-ic acid) **XIV**. To the solution of 0.50 g (1.40 mmol) of 16-formylmethyllambertianate **XII** in 2 mL of THF under intense mixing we added 5 mL of the aqueous solution of NH_3 (70 mmol) and 0.39 g (1.54 mmol) of I_2. The reaction mixture was stirred for 5 h, diluted with 30 mL of water and extracted with chloroform (3 × 20 mL). The organic fractions were brought together, washed with water (3 × 20 mL) and dried with $MgSO_4$. Then the solvent was evaporated, and the residue was crystallized from hexane. Nitrile **XIV** was obtained in the amount of 0.45 g (91 %). M. p. 72–75 °C. $[\alpha]_D^{20}$ +34.92° (1.9, chlf.). UV spectrum, λ_{max} (log ε): 201 (4.06), 241 (4.02), 279 (3.06). IR spectrum, cm^{-1}: 788, 894, 1034, 1091, 1124, 1153, 1166, 1204, 1592, 1644, 1678, 1724, 2224, 3070, 3147. NMR ^1H spectrum (δ, ppm, *J*, Hz): 0.47 s (3H, $C^{20}H_3$), 0.97 m (1H, H^1), 1.00 m (1H, H^3), 1.14 s (3H, $C^{19}H_3$), 1.25 dd (1H, H^5, *J* 11.7, 2.6), 1.49 m (1H, H^2), 1.58 m (1H, H^9), 1.63 m (1H, H^{11}), 1.73 m, 1.77 m, 1.82 m, (4H, $H^{1,2,6,11}$), 1.87 m (1H, H^7), 1.96 m (1H, H^6), 2.12 dm (1H, H^3, J_{hem} 12.3), 2.39 m (2H, $H^{12,7}$), 2.69 m (1H, H^{12}), 3.57 s (3H, OCH_3), 4.54 s, 4.90 s (2H, H^{17}), 6.36 d (1H, H^{14}, *J* 1.8), 7.43 d (1H, H^{15}, *J* 1.8). NMR ^{13}C spectrum, δ, ppm: 12.13 q (C^{20}), 19.45 t (C^2), 23.35 t (C^{12}), 23.48 t (C^{11}), 25.77 t (C^6), 28.32 q (C^{19}), 37.68 t (C^3), 38.16 t (C^7), 38.63 t (C^1), 39.78 s (C^4), 43.80 s (C^{10}), 50.69 q (OCH_3), 54.80 d (C^9), 55.73 d (C^5), 106.22 t (C^{17}), 111.13 s (CN), 112.02 d (C^{14}), 123.12 s (C^{13}), 138.98 s (C^{16}), 146.63 d (C^{15}), 146.80 s (C^8), 177.15 s (C^{18}). Mass spectrum, *m*/*z* (I_{rel}, %): 357 (0.39), 356(2), 355 (9), 340 (10), 296 (15), 249 (13), 189 (26), 181 (12), 122 (11), 121 (100), 119 (11), 110 (37), 107 (22), 109 (19), 105 (14), 95 (11), 93 (17), 91 (15), 81 (27), 79 (15), 67.0 (12), 55.0 (14), 43.9 (19), 41.0 (14). Found: $[M]^+$ 355.2137. $C_{22}H_{29}O_3N$. Calculated: *M* 355.2142.

(1*S*,4a*R*,5*S*,8a*R*)-Methyl-5-{2-[2-(2-(*Z*)-1-amino-3-ethoxy-3-oxoprop-1-ene)furan-3-yl]ethyl}-1,4a-dimethyl-6-methylenedecahydronaphthalene-1-carboxylate XI. Ethyl ester of bromoacetic acid in the amount of two drops was added to the suspension of 0.55 g (8.46 mmol) of zinc in 3 mL of THF in argon flow. The mixture was boiled for 15 min (the mixture becomes green). Nitrile **XIV** 0.50 g (1.43 mmol) was added into the hot reaction mixture; the ethyl ester of bromoacetic acid was added dropwise: 0.94 g (5.63 mmol) during 1 h. The reaction mixture was again boiled for 15 min, and then cooled to room temperature; 10 mL of TGF and 2 mL of 50 % aqueous solution of K_2CO_3 were added. The mixture was stirred for 30 min. The organic layer was separated; the water layer was extracted with diethyl ether (3 × 20 mL). The organic extracts were brought together, washed with water (3 × 20 mL) and dried with $MgSO_4$. The solvent was evaporated, and the residue was chromatographed through silica gel (with chloroform as eluent). Compound **XI** was obtained in the amount of 0.58 g (92 %) as a light-yellow oil. $[\alpha]_D^{20}$ −11.3° (s 2.9, ethanol). UV spectrum, λ_{max} (log ε): 204 (3.98), 266 (3.81), 316 (2.18). IR spectrum, cm^{-1}: 757, 788, 893, 1032, 1093, 1164, 1238, 1312, 1496, 1550, 1610, 1663, 1723, 3329, 3460. NMR ^1H spectrum (δ, ppm, *J*, Hz): 0.50 c (3H, $C^{20}H_3$), 1.01 m (2H, $H^{1,3}$), 1.16 s (3H, $C^{19}H_3$), 1.26 m (1H, H^5), 1.28 t (3H, $OCH_2C\underline{H}_3$, *J* 7.0), 1.48 d.m (1H H^2, J_{hem} 14.3), 1.64 m (2H, $H^{9,11}$), 1.77 m, 1.80 m, (4H, $H^{11,1,2,6}$), 1.88 m (1H, H^7), 1.96 m (1H, H^6), 2.15 d.m (1H, H^3, J_{hem} 13.3), 2.42 m (1H, H^7), 2.51 m (1H, H^{12}), 2.71 m (1H, H^{12}), 3.60 s (3H, OCH_3), 4.10–4.50 m (2H, NH_2), 4.14 q (2H, OCH_2, *J* 7.0), 4.61 s, 4.91 s (2H, H^{17}), 4.95 s (1H, =CH), 6.34 d (1H, H^{14}, *J* 1.8), 7.37 d (1H, H^{15}, *J* 1.8). NMR ^{13}C spectrum, δ, ppm: 12.45 q (C^{20}), 14.46 q (CH_3), 19.81 t (C^2), 23.62 t (C^{12}), 24.80 t (C^{11}), 26.06 t (C^6), 28.62 q (C^{19}), 38.02 t (C^3), 38.50 t (C^7), 38.86 t (C^1), 40.16 s (C^{10}), 44.12 s (C^4), 50.95 q (OCH_3), 55.10 d (C^9), 56.04 d (C^5), 58.59 t (CH_2), 82.31 d (CH=), 106.51 t (C^{17}), 114.00 d (C^{14}), 127.06 s (C^{13}), 142.06 s (C^{16}), 143.76 d (C^{15}), 147.68 s (C^8), 149.83 s (C=), 170.47 s ($\underline{C}O_2CH_2CH_3$), 177.47 s (C^{18}). Mass spectrum, *m*/*z* (I_{rel}, %): 445 (3), 444 (17), 443 (53), 428 (4), 427 (8), 426 (28), 398 (16) 343 (20), 262 (11), 246 (10), 220 (35), 208(52), 195 (100), 123 (30). Found: $[M]^+$ 443.2668. $C_{26}H_{37}NO_5$. Calculated: *M* 443.2666.

Pharmacology

All the experiments were carried out with mature while outbred mice with body mass 20–25 g. To study the analgesic activity of compounds, standard models [15] were used: the tests for visceral pain "acetic convulsions" (AC) and "hot plate" (HP). The agents under study were introduced in the dose of 5 mg/kg once intragastrically in the form of water-Tween (Tween 80) suspension (0.5 %) 1 h before the reproduction of the model. The animals of the reference group received an equivalent volume of water.

Acetic convulsions were caused by the intraperitoneal introduction of acetic acid (0.75 %, in the amount of 0.1 mL per a mouse), the pain reaction was estimated as the number of convulsions since the 5th till the 8th minute after the introduction of acetic acid. The percentage of suppression of the pain reaction (SPR) was calculated according to equation: $100\,\% \cdot (A - B)/A$, where A, B are the average number of convulsions in the reference and test groups, respectively.

To reproduce the HP test, the animals were put on a platform heated to 54 °C; the time before licking the hind leg or jumping was measured.

RESULTS AND DISCUSSION

The parameters of acute toxicity for mice after single introduction into stomach were determined. It was shown that LD_{50} for the compounds under investigation is within the range 600–1200 mg/kg, which allows us to assign these compounds to the 3rd (moderately toxic) class of compounds.

One can see in the data presented in Table 1 that lambertianic acid **II** itself in the dose of 5 mg/kg does not exhibit analgesic activity in the tests for both visceral and thermal pain. The synthesized isomer of lambertianic acid **IV** suppressed by 36 % the pain reaction caused by the chemical irritation of peritoneum but does not affect the thermal sensitivity of animals. Methyl ester of lambertianic acid **III** possesses the analgesic activity in both tests: it suppresses the pain reaction in AC by 42 % and increases the latent response time in HP test by 57.5 %. It should be stressed that all further chemical transformations of methyl lambertianate cause only the loss of the analgesic activity of the compounds in the test for thermal pain. As far as the visceral pain is concerned, the introduction of the structural substitute into the furan ring of compound **III** causes almost no changes of the analgesic activity in the AC test with four compounds (**V**, **VII**, **IX** and **XI**), while in two compounds (**VI** and **X**) this causes the loss of the analgesic activity. Only agent **VIII** containing free amino group in the side chain exhibits a substantial increase in the activity (by 31.3 %) in comparison with methyl lambertianate itself.

TABLE 1

Analgesic activity of furanolabdanoids and their amino derivatives in the tests of "Acetic convulsions" (AC) and "Hol plate" (HP)

Agents	AC, % SPR	HP, rel. time of pain reaction, %
II	16.3	10.2
III	41.9**	57.5*
IV	35.9***	23.6
V	33.4**	−22.7
VI	0	−20.9
VII	38.9*	5.0
VIII	73.2**	17.7
IX	35.4*	−5.0
X	0	−6.1
XI	43***	29.1

Note. Signs. "+" and "−" mean an increase and decrease of the latent time of pain reaction with respect to the reference group, respectively.

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ with respect to the reference.

CONCLUSION

Thus, it may be stated on the basis of the performed screening of the analgesic activity of presented compounds that furanoditerpenoids of labdanum series are the analgesic agents of the novel structural type exhibiting rather high activity in the test for visceral pain.

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