ISSN 1068-1620, Russian Journal of Bioorganic Chemistry, 2010, Vol. 36, No. 6, pp. 762–770. © Pleiades Publishing, Ltd., 2010.
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Synthesis and Pharmacological Activity of Amides and the Ozonolysis Product of Maleopimaric Acid

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Received December 21, 2009; in final form, May 4, 2010

Abstract—The synthesis of a new group of maleopimaric acid amides containing fragments of methyl ethers of amino acids, aliphatic amines, imidazole, and *N*-methylpiperazine was carried out. The ozonolysis of methylmaleopimarate occurs via the cleavage of the double bond C18(19) and the opening of an anhydrous ring with the formation of secotriacid. As a result of the screening of the anti-inflammatory and antiulcer activity of maleopimaric acid derivatives, new effective compounds such as maleopimaric acid and its methyl ether, a product of ozonolysis—diterpenic secotriacid—and maleopimaric acid amide with *L*-leucine were found. An important advantage of the studied compounds is the low toxicity and the presence of bidirectional activity in the absence of adverse effects on the animal.

Keywords: levopimaric acid, maleopimaric acid, amides, ozonolysis, antiulcer activity, anti-inflammatory activity

DOI: 10.1134/S1068162010060130

INTRODUCTION

Maleopimaric acid (**II**), which is the adduct of diene synthesis of levopimaric acid (**I**) with maleic anhydride, is an accessible product for chemical modification [1–8]. The processes of the oxidation and regroupings of maleopimaric and the fumaropimaric acids associated with them were studied in [9–14]. Methods of the selective decarboxylation, including catalytic methods accompanied by a reaction of retrodiene synthesis, were developed [15]. The fungicidal properties of salts and ethers of *N*-replaced imides of maleopimaric acid were revealed [16]. Compounds with anti-inflammatory and heptaprotective activities were found among the amides of maleopimaric acid with piperazine, 4-methyl- and 4-hydroxyethylpiperazine, morpholine, and dimethylcarbamoyl.

While continuing the studies of the pharmacological properties of adducts of levopimaric acid [18–22], we modified maleopimaric acid (**II**) at the carboxyl group and bridging double bond and studied the antiulcer and anti-inflammatory activities of the obtained compounds.

RESULTS AND DISCUSSION

A new group of amides (**V**)–(**XIV**) were synthesized by the interaction of maleopimaryl chloride (**IV**) with ethers of amino acids, aliphatic amines, ^{1}H-imidazole, and *N*-methylpiperazine (scheme). The use of a quantity of amine equimolar to the acid allowed us to conduct the reaction selectively by the carboxyl function without involving the anhydrous ring.

One of the effective methods of the oxidation of double bonds is ozonolysis. The reaction of methyl maleopimarate (**III**) with ozone was mentioned in the work by L. Ruzicka [23]. We found that the ozonation of the methyl ether of maleopimaric acid (**III**) in methylene–methanol at 0°C produces a good yield of secotriacid (**XV**). The structure of the obtained acid was confirmed by the synthesis and determination of the physicochemical characteristics of its full methyl ether (**XVI**). The opening of the anhydrous ring of methylmaleopimarate with the formation of two carboxyl groups during ozonation probably occurs due to the participation of the anhydrous ring in the stabilization of the peroxide products of the interaction of ozone with the C18–C19 double bond spatially close to it. It should be noted that the aldehyde group, which forms in the C1 position during the cleavage of the C18–C19 double bond by ozone, is very easily oxidized to the carboxyl group. The compound (**XV**) can be obtained also during the ozonolysis of the trimethyl ether of fumaropimaric acid but with a low yield and after the chromatographic purification of the multicomponent mixture [24].

A study of the acute toxicity of the derivatives of maleopimaric acid (**II**), (**III**), and (**V**)–(**XV**) showed (see Experimental section) that their mean lethal dose is within 8000 to 12000 mg/kg. The introduction of

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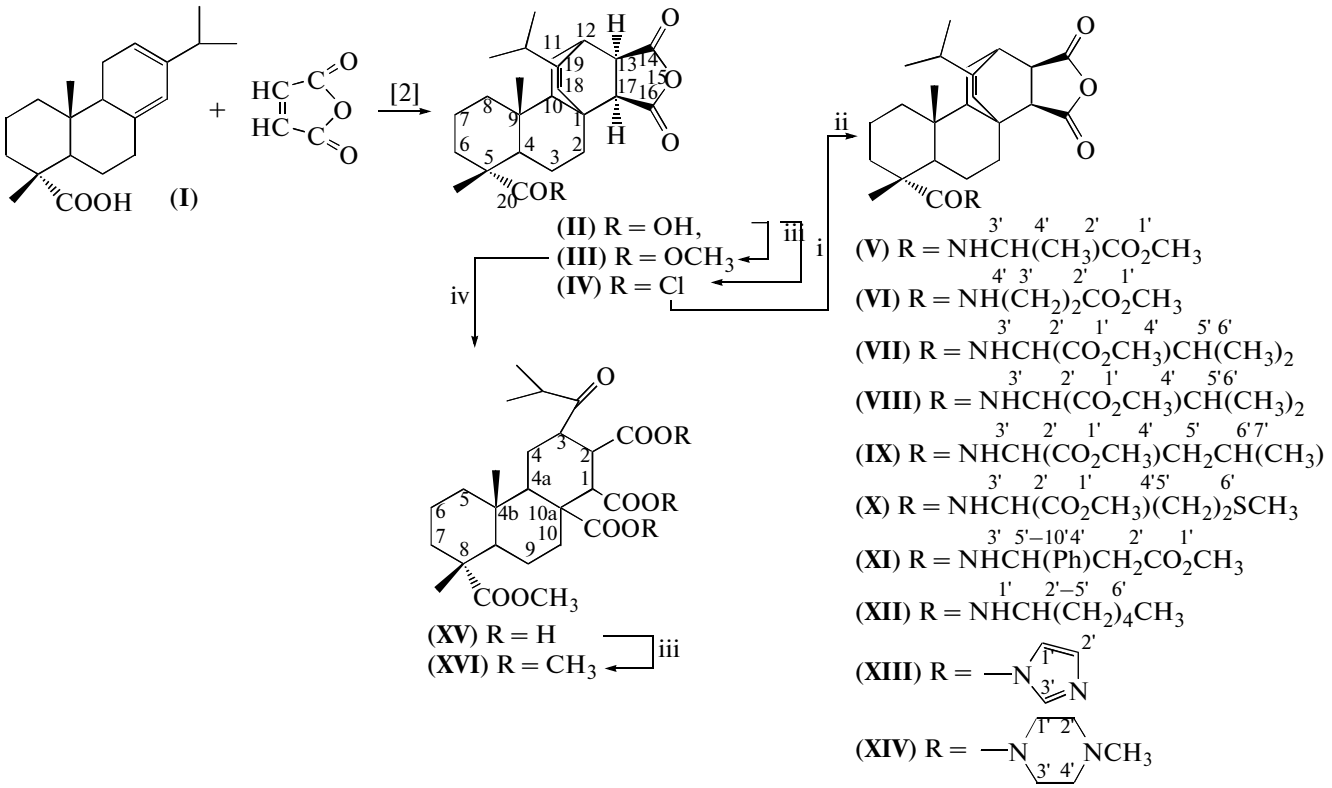

Reaction conditions: i. $(COCl)_2$, $CHCl_3$, 3 h; ii. $NH_2CH(CH_3)CO_2CH_3 \cdot HCl$ for **(V)**, $NH_2(CH_2)_2CO_2CH_3 \cdot HCl$ for **(VI)**, (*L*)-$NH_2CH(CO_2CH_3)CH(CH_3)_2 \cdot HCl$ for **(VII)**, (*DL*)-$NH_2CH(CO_2CH_3)CH(CH_3)_2 \cdot HCl$ for **(VIII)**, $NH_2CH(CO_2CH_3)CH_2CH(CH_3)_2 \cdot HCl$ for **(IX)**, (*L*)-$NH_2CH(CO_2CH_3)(CH_2)_2SCH_3 \cdot HCl$ for **(X)**, $NH_2CH(Ph)CH_2CO_2CH_3 \cdot HCl$ for **(XI)**, $NH_2CH(CH_2)_4CH_3$ for **(XII)**, $NH_2C_3H_3N_2$ for **(XIII)**, $NH_2C_5H_{11}N_2$ for **(XIV)**, Et_3N, $CHCl_3$; iii. CH_2N_2, Et_2O; iv. O_3, CH_2Cl_2-MeOH, 0°C.

Scheme.

doses close to LD_{16} to the stomachs of mice was accompanied by an insignificant inhibition in the experimental animals and a decrease in their locomotive activity ("freezing" on the spot). However, these signs disappeared within 1 to 2 h and the physiological activity was completely restored. After the administration of doses close to LD_{50}, a short-term increase in the motor activity of mice from experimental groups was registered for 20–30 min, after which inhibition followed, which lasted from 6 to 12 h. The intragastric introduction of absolutely lethal doses of compounds **(II)**, **(III)**, and **(V)**–**(XV)** caused the quick (within 5–10 min) depression of motor activity and a lethal outcome within 12 to 24 h. The variability coefficient of the lethal doses was 1.6–2.1, which indicates their significantly wide range. Thus, according to GOST 12.1.00.7-76, compounds **(II)**, **(III)**, and **(V)**–**(XV)** belong to class 4 of danger (low toxicity).

The anti-inflammatory properties of derivatives of maleopimaric acid were studied in three species of experimental inflammations induced by carrageenin, which is a phlogogen of a protein nature, and phlogogens of a nonprotein nature: silver nitrate and formalin. Ortophen was used for comparison. The data from Table 1 show that maleopimaric acid **(II)** manifests anti-inflammatory activity more pronouncedly as compared to ortophen, but less pronouncedly as compared to the product of ozonolysis **(XV)** in a dose of 50 mg/kg.

The derivatives of maleopimaric acid **(V)**–**(XIV)** have higher anti-inflammatory action than the acid itself (Table 1). The highest activity in this group is demonstrated by the amide of maleopimaric acid with methyl ether of *L*-leucine **(IX)** during argentonitrate inflammation (within doses of 25 to 100 mg/kg).

An interesting manifestation of the antiphlogistic activity was registered in compounds **(VII)**, **(VIII)**, which contain fragments of *L*- and *DL*-valine. It was established that the presence of a fragment of *DL*-valine decreases the pharmacological effectiveness during the acute stages of the inflammatory reaction as compared with compound **(VII)**. At the same time, the degree of the antiphlogistic activity of compound

Table 1. Anti-inflammatory activity* of compounds (**II**), (**III**), and (**V**)–(**XV**)

Compound	Carrageenin inflammation, the dose, mg/kg					
	25		50		100	
	A	B	A	B	A	B
(II)	38.7 ± 1.9	29.1 ± 1.4	40.6 ± 2.5	25.5 ± 1.6	40.0 ± 2.0	26.6 ± 1.3
(III)	37.6 ± 1.9	31.0 ± 1.5	38.8 ± 2.5	28.9 ± 1.9	35.9 ± 1.8	34.2 ± 1.7
(V)	40.3 ± 1.7	26.0 ± 1.1	39.7 ± 1.9	27.2 ± 1.3	41.1 ± 2.0	24.5 ± 1.1
(VI)	38.2 ± 1.6	30.0 ± 1.3	37.8 ± 1.9	30.6 ± 1.5	37.2 ± 1.8	31.8 ± 1.5
(VII)	37.9 ± 1.6	30.4 ± 1.3	36.3 ± 2.1	33.4 ± 1.9	39.1 ± 1.8	28.3 ± 1.3
(VIII)	52.8 ± 3.3	3.1 ± 0.2	52.2 ± 2.1	4.2 ± 0.2	53.2 ± 2.6	2.5 ± 0.1
(IX)	38.2 ± 1.6	30.0 ± 1.3	37.9 ± 2.1	30.4 ± 1.7	37.3 ± 1.8	31.6 ± 1.5
(X)	42.1 ± 1.6	22.9 ± 0.9	41.8 ± 1.9	23.3 ± 1.0	42.3 ± 1.9	22.5 ± 1.0
(XI)	44.7 ± 1.7	18.1 ± 0.7	43.3 ± 2.0	20.6 ± 0.9	44.6 ± 2.3	18.3 ± 1.0
(XII)	39.7 ± 2.5	27.2 ± 1.7	40.1 ± 1.8	26.4 ± 1.2	39.1 ± 2.0	28.2 ± 1.5
(XIII)	42.3 ± 2.5	22.3 ± 1.3	44.3 ± 1.8	18.7 ± 0.8	45.3 ± 1.9	16.8 ± 0.7
(XIV)	41.1 ± 1.7	24.6 ± 1.0	40.8 ± 1.8	25.2 ± 1.1	49.4 ± 2.0	9.4 ± 0.4
(XV)	39.4 ± 2.5	27.7 ± 1.7	34.5 ± 1.7	36.7 ± 1.8	34.7 ± 2.2	36.4 ± 2.3
Ortophen	40.7 ± 1.3	25.4 ± 0.8	40.7 ± 1.3	25.4 ± 0.8	40.7 ± 1.3	25.4 ± 0.8
Control	54.5 ± 1.1	n.s.	54.5 ± 1.1	n.s.	54.5 ± 1.1	n.s.
Compound	Argentonitrate inflammation, the dose, mg/kg					
	25		50		100	
	A	B	A	B	A	B
(II)	35.2 ± 2.2	18.2 ± 1.1	34.3 ± 1.9	20.4 ± 1.2	34.0 ± 1.9	21.0 ± 1.1
(III)	33.7 ± 2.2	21.8 ± 1.4	31.6 ± 1.5	26.7 ± 1.2	34.0 ± 0.7	21.1 ± 0.4
(V)	35.4 ± 2.0	17.7 ± 1.0	35.8 ± 1.4	16.9 ± 0.7	37.2 ± 1.3	13.7 ± 0.5
(VI)	34.2 ± 1.9	20.7 ± 1.1	34.6 ± 1.5	19.6 ± 0.9	35.0 ± 1.8	18.8 ± 0.9
(VII)	29.3 ± 1.4	31.9 ± 1.6	28.1 ± 1.8	34.7 ± 2.2	30.2 ± 1.5	29.8 ± 1.5
(VIII)	34.8 ± 1.4	19.3 ± 0.8	32.6 ± 1.7	24.2 ± 1.3	31.4 ± 1.2	27.2 ± 1.1
(IX)	26.2 ± 1.3	39.3 ± 1.9	25.9 ± 1.4	39.8 ± 2.2	26.3 ± 1.4	38.9 ± 2.1
(X)	31.9 ± 1.9	26.0 ± 1.6	33.7 ± 1.4	21.8 ± 0.9	33.8 ± 1.8	21.5 ± 1.1
(XI)	37.2 ± 1.8	13.7 ± 0.6	37.9 ± 1.7	12.1 ± 0.6	37.5 ± 1.9	12.8 ± 0.6
(XII)	36.8 ± 1.9	14.5 ± 0.7	37.2 ± 1.9	13.7 ± 0.7	38.0 ± 1.9	11.6 ± 0.6
(XIII)	37.5 ± 1.8	13.0 ± 0.6	38.0 ± 1.7	11.6 ± 0.5	37.8 ± 1.9	12.3 ± 0.6
(XIV)	35.7 ± 1.8	17.2 ± 0.9	36.2 ± 1.7	16.0 ± 0.8	36.2 ± 1.6	16.0 ± 0.7
(XV)	29.7 ± 1.8	31.1 ± 1.9	27.8 ± 1.9	35.6 ± 2.5	27.6 ± 1.2	35.8 ± 1.6
Ortophen	36.2 ± 0.1	15.9 ± 0.1	36.2 ± 0.1	15.9 ± 0.1	36.2 ± 0.1	15.9 ± 0.1
Control	43.1 ± 0.2	n.s.	43.1 ± 0.2	n.s.	43.1 ± 0.2	n.s.
Compound	Formalin inflammation, the dose, mg/kg					
	25		50		100	
	A	B	A	B	A	B
(II)	26.1 ± 0.8	27.2 ± 0.9	25.3 ± 1.2	29.5 ± 1.4	23.7 ± 1.2	33.7 ± 1.7
(III)	24.1 ± 1.1	32.5 ± 1.5	23.9 ± 1.0	33.2 ± 1.4	23.6 ± 1.5	33.9 ± 2.2
(V)	26.1 ± 0.9	27.0 ± 1.0	25.3 ± 1.3	29.4 ± 1.6	25.4 ± 0.8	29.0 ± 0.9
(VI)	21.2 ± 1.0	40.7 ± 1.9	22.6 ± 1.3	36.8 ± 2.2	23.1 ± 1.0	35.3 ± 1.6
(VII)	26.1 ± 1.0	27.0 ± 1.1	22.7 ± 1.2	36.5 ± 1.9	22.8 ± 1.2	36.4 ± 1.9
(VIII)	22.0 ± 0.7	38.5 ± 1.2	22.3 ± 1.3	37.5 ± 2.3	23.6 ± 1.0	34.1 ± 1.5
(IX)	23.3 ± 1.2	35.0 ± 1.8	22.2 ± 1.2	38.0 ± 2.0	22.3 ± 0.9	37.6 ± 1.5
(X)	27.8 ± 1.3	22.3 ± 1.1	24.9 ± 1.3	30.6 ± 1.6	23.4 ± 0.9	34.6 ± 1.3
(XI)	25.4 ± 1.1	29.1 ± 1.3	25.4 ± 1.0	28.9 ± 1.2	25.8 ± 0.9	27.9 ± 1.0
(XII)	26.6 ± 1.2	25.6 ± 1.1	27.0 ± 1.1	24.5 ± 1.0	27.0 ± 1.1	24.6 ± 1.0
(XIII)	28.1 ± 1.0	21.6 ± 0.8	28.2 ± 1.5	21.3 ± 1.1	28.1 ± 1.1	21.6 ± 0.9
(XIV)	25.9 ± 1.1	27.6 ± 1.2	26.4 ± 1.5	26.2 ± 1.5	26.1 ± 1.0	27.1 ± 1.0
(XV)	22.9 ± 0.8	37.7 ± 1.4	20.7 ± 0.7	42.2 ± 1.6	23.6 ± 1.5	34.1 ± 2.1
Ortophen	26.1 ± 0.9	27.0 ± 0.9	26.1 ± 0.9	27.0 ± 1.0	26.1 ± 0.9	26.9 ± 1.0
Control	35.8 ± 0.2	n.s.	35.8 ± 0.2	n.s.	35.8 ± 0.2	n.s.

* Was estimated (in per cents) by the increase (A) and depression (B) in the inflammatory edema; (n.s.) not studied.

(**VIII**) can be brought to a level comparable with that of derivative (**VII**) by increasing the dose from 50 to 100 mg/kg.

The amide of maleopimaric acid with β-alanin (**VI**) demonstrates higher anti-inflammatory activity on the model of carrageenin inflammation compared with orthophen. The activity of amide with *L*-alanin (**V**) is comparable with that of the comparison preparation within the range of the effective doses from 25 to 100 mg/kg on all models of inflammation. Compound (**VI**) showed higher activity as compared with that of compound (**V**), but less pronounced as compared with compounds (**VII**) and (**VIII**).

Thus, compounds (**II**), (**III**), and (**XV**) proved to be the most active with steadily high antiphlogistic action, while maleopimaric acid amides with methyl ethers of *L*-methionine (**X**) and *L*-phenyl-β-alanine (**XI**), and heterocyclic residues (**XIII**) and (**XIV**) proved to be the least active relative to the comparison preparation.

The results of the studies on the antiulcer properties of maleopimaric acid (**II**) and its derivatives (**III**) and (**V**)–(**XV**) on two models of experimental ulcers are given in Table 2 and indicate the ability to depress the process of the formation of ulcerations of mucous membranes of the gastrointestinal tract under the influence of unfavorable factors. The highest level of antiulcer activity was noted in compound (**XV**) in a dose of 25 mg/kg. An increase in the dose of compound (**XV**) from 25 to 100 mg/kg on the model of indometacin ulcers did not lead to an improvement of this property, whereas the positive tendency of increasing the activity was noted during the induction of ulcers with acetic acid by increasing the dose to 100 mg/kg. Compounds (**II**), (**III**), (**V**), and (**VII**)–(**IX**) showed activity on the model of indometacin ulcers at a level of ~2.59 at a minimum dose from 50 to 100 mg/kg. At the same time, for acetic ulcers, the activity at level ≥2 was registered only for maleopimaric acid (**II**) and its methyl ether (**III**).

Maleopimaric acid amides (**VI**) and (**X**)–(**XIV**) showed insufficiently pronounced antiulcer activity.

Thus, maleopimaric acid (**II**) and its derivatives (**III**), (**IX**), and (**XV**) show some promise for further study as anti-inflammatory and antiulcer agents. An important advantage of the studied compounds compared with the existing drugs of unidirectional action is the two-way (combined) (anti-inflammatory and antiulcer) activity and the absence of negative influences on the animal's body characteristic of groups of drugs with a similar manifestation of activity.

EXPERIMENTAL

The ^{1}H- and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer (Germany, 300 and 75.5 MHz, respectively, δ, ppm, SSCC, Hz) in $CDCl_3$ using tetramethylsilane as the internal standard. The melting points were determined on a Boetius plate. The optical absorption spectra were measured on a Perkin-Elmer 241 MC polarimeter (Germany) in a tube 1-dm long. An Ozon-2K ozonizer (Russia) was used for ozonation. TLC analysis was conducted on Silufol plates (Chemapol, Czech Republic) using a 20 : 1 chloroform–methanol system of solutions; the compound was detected with a 5% solution of phosphotungstic acid in ethanol (2–3 min at 100–120°C). Compounds (**II**) and (**III**) were obtained according to [2].

(5*R*,9*R*,13*R*,17*R*)-5,9-Dimethyl-19-(1-methylethyl)-15-oxa-14,16-dioxopentacyclo[10.5.2.0^{1,10}.0^{4,9}.0^{13,17}]heptadec-18-ene-5-carbonyl chloride (maleopimaryl chloride) (IV). Oxalyl chloride (0.3 ml, 3.5 mmol) was added dropwise while stirring to compound (**II**) (1 mmol, 0.42 g) in dry chloroform (10 ml). The mixture was kept under nitrogen for 4 h. The solvent was evaporated in the vacuum of a water-jet pump. Yield 0.40 g (95%). Found, %: C 72.09; H 7.92; Cl 8.06. $C_{24}H_{31}ClO_4$ (*M* 418.95). Calculated, %: C 72.45; H 8.18; Cl 8.23.

Synthesis of compounds (V)–(XIV). A solution of one of the following compounds—hydrochloride of the methyl ether of amino acid (*L*-alanine, β-alanine, *L*-valine, *DL*-valine, *L*-leucine, *L*-methionine, and *L*-phenyl-β-alanine, respectively), hexylamine, 1*H*-imidazole, or *N*-methylpiperazine (1.1 mmol)—in dry chloroform (5 ml) was added while stirring to a solution of (**IV**) (1 mmol, 0.43 g) in dry chloroform (15 ml). The solvent was evaporated in the vacuum of a water-jet pump. The reaction product was purified by Al_2O_3 column chromatography (chloroform as the eluent).

***N*-[(5*R*,9*R*,13*R*,17*R*)-5,9-Dimethyl-19-(1-methylethyl)-15-oxa-14,16-dioxopentacyclo[10.5.2.0^{1,10}.0^{4,9}.0^{13,17}]heptadec-18-ene-5-carbonyl]-*L*-alanine methylether (V).** Yield 0.34 g (79%). R_f 0.63. Mp 176–178°C. $[\alpha]_D^{20}$ – 23° (*c* 0.05, $CHCl_3$). Found, %: C 68.97; H 7.86; N 2.65. $C_{28}H_{39}NO_6$ (*M* 485.61). Calculated, %: C 69.25; H 8.09; N 2.88. ^{1}H NMR spectrum: 0.59 (3 H, s, CH_3), 0.99 and 1.00 (6 H, both d, *J* 6.8, $2CH_3$), 1.15 (3 H, s, CH_3), 1.15–1.30 (1 H, m, H4), 1.35–1.80 (15 H, m, CH_2, CH), 2.23 (1 H, m, CH), 2.51 (1 H, dt, *J*3, *J*14, H10), 2.71 (1 H, d, *J*11.0, H12), 3.08 (1 H, dd, *J*3, *J*11, H17), 3.09 (1 H, m, H13), 3.69 (3 H, s, OMe), 4.35 (1 H, m, H3'), 5.53 (1 H, br. s, H18), 6.49 (1 H, dd, *J*5.4, *J*1.2, NH). ^{13}C NMR spectrum: 15.5, 16.6 (C4'), 17.0, 19.9, 20.5, 20.9, 27.1, 32.7, 33.5, 34.6, 35.2, 35.6, 36.7, 37.7, 37.8, 40.3, 45.6, 46.5, 49.6, 51.7 (C1'), 53.0, 53.1 (C3'), 125.1 (C18), 147.9 (C19), 170.9 (C14), 172.7 (C16), 173.3 (C2'), 178.3 (C20).

***N*-[(5*R*,9*R*,13*R*,17*R*)-5,9-Dimethyl-19-(1-methylethyl)-15-oxa-14,16-dioxopentacyclo[10.5.2.0^{1,10}.0^{4,9}.0^{13,17}]heptadec-18-ene-5-carbonyl]-β-alanine methyl ether (VI).** Yield 0.34 g (78%). R_f 0.68. Mp 168–170°C.

Table 2. Antiulcer activity of compounds (**II**), (**III**), and (**V**)–(**XV**)

Compound	Dose, mg/kg	Type of experimental ulcers			
		Indometacin		Acetic acid	
		mean number of destructions	antiulcer activity	mean number of destructions	antiulcer activity
(II)	25	3.9 ± 0.4	3.7 ± 0.1	13.3 ± 0.9	2.1 ± 0.1
	50	3.7 ± 0.3	3.9 ± 0.1	12.9 ± 1.1	2.2 ± 0.1
	100	4.2 ± 0.2	3.4 ± 0.1	13.6 ± 0.8	2.1 ± 0.1
(III)	25	5.6 ± 0.4	2.6 ± 0.1	13.3 ± 0.8	2.1 ± 0.1
	50	4.7 ± 0.4	3.1 ± 0.1	14.1 ± 1.1	2.0 ± 0.1
	100	4.6 ± 0.4	3.2 ± 0.1	14.4 ± 1.2	1.9 ± 0.1
(VI)	25	6.6 ± 0.5	2.2 ± 0.1	15.7 ± 1.1	1.8 ± 0.1
	50	7.6 ± 0.4	1.9 ± 0.1	14.7 ± 1.2	1.9 ± 0.1
	100	7.3 ± 0.5	2.0 ± 0.1	16.1 ± 1.5	1.7 ± 0.1
(X)	25	8.6 ± 0.5	1.7 ± 0.1	18.0 ± 1.1	1.6 ± 0.1
	50	7.7 ± 0.5	1.9 ± 0.1	18.4 ± 1.1	1.5 ± 0.1
	100	7.7 ± 0.5	1.9 ± 0.1	17.9 ± 1.2	1.6 ± 0.1
(V)	25	6.2 ± 0.5	2.5 ± 0.9	16.7 ± 1.1	1.7 ± 0.3
	50	4.9 ± 0.4	3.1 ± 0.9	15.0 ± 1.1	1.9 ± 0.3
	100	6.9 ± 0.5	2.1 ± 0.1	16.3 ± 1.1	1.7 ± 0.1
(IX)	25	5.9 ± 0.4	2.4 ± 0.1	14.6 ± 1.2	1.9 ± 0.1
	50	6.1 ± 0.4	2.4 ± 0.1	13.7 ± 1.0	2.1 ± 0.1
	100	6.1 ± 0.5	2.4 ± 0.1	14.3 ± 0.9	2.0 ± 0.1
(VII)	25	5.2 ± 0.3	2.8 ± 0.1	14.6 ± 1.0	1.9 ± 0.1
	50	5.2 ± 0.4	2.8 ± 0.1	13.8 ± 0.9	2.1 ± 0.1
	100	5.1 ± 0.3	2.8 ± 0.1	14.7 ± 0.9	1.9 ± 0.1
(XI)	25	7.2 ± 0.3	2.0 ± 0.1	17.5 ± 1.3	1.6 ± 0.1
	50	7.4 ± 0.5	1.9 ± 0.1	17.2 ± 0.9	1.6 ± 0.1
	100	7.6 ± 0.3	1.9 ± 0.1	18.6 ± 1.2	1.5 ± 0.1
(VIII)	25	5.6 ± 0.4	2.6 ± 0.1	20.3 ± 0.8	1.4 ± 0.1
	50	6.1 ± 0.4	2.4 ± 0.1	19.8 ± 0.8	1.4 ± 0.1
	100	6.3 ± 0.5	2.3 ± 0.1	20.9 ± 1.0	1.4 ± 0.1
(XIV)	25	7.6 ± 0.3	1.9 ± 0.1	19.7 ± 0.9	1.4 ± 0.1
	50	7.8 ± 0.3	1.9 ± 0.1	19.9 ± 0.9	1.4 ± 0.1
	100	8.0 ± 0.3	1.8 ± 0.1	19.7 ± 0.6	1.4 ± 0.1
(XIII)	25	8.3 ± 0.4	1.7 ± 0.1	20.3 ± 0.7	1.4 ± 0.1
	50	8.3 ± 0.2	1.7 ± 0.1	19.8 ± 0.8	1.4 ± 0.1
	100	8.6 ± 0.4	1.7 ± 0.1	20.1 ± 0.8	1.4 ± 0.1
(XII)	25	9.2 ± 0.3	1.6 ± 0.1	17.3 ± 1.6	1.6 ± 0.1
	50	8.5 ± 0.2	1.7 ± 0.1	14.7 ± 0.9	1.9 ± 0.1
	100	8.8 ± 0.4	1.6 ± 0.1	14.0 ± 0.9	2.0 ± 0.1
(XV)	25	3.2 ± 0.2	4.4 ± 0.1	12.6 ± 1.0	2.2 ± 0.1
	50	3.7 ± 0.2	3.9 ± 0.2	12.3 ± 0.9	2.3 ± 0.1
	100	3.5 ± 0.2	4.1 ± 0.1	11.2 ± 0.7	2.5 ± 0.1
Control	n.s.*	14.4 ± 0.8	n.s.*	28.3 ± 1.3	n.s.*

* (n.s.) not studied.

$[\alpha]_D^{20}$ − 16° (*c* 0.05, $CHCl_3$). Found, %: C 68.93; H 8.01; N 2.70. $C_{28}H_{39}NO_6$ (*M* 485.61). Calculated, %: C 69.25; H 8.09; N 2.88. ^{1}H NMR spectrum: 0.60 (3 H, c, CH_3), 0.99 and 1.01 (6 H, both d, *J* 6.8, $2CH_3$), 1.15 (3 H, s, CH_3), 1 (1 H, m, H4), 1.34–1.80 (15 H, m, CH_2, CH), 2.23 (1 H, m, CH), 2.51 (1 H, dt, *J* 3, *J* 14, H10), 2.70 (1 H, d, *J* 11, H12), 3.05 (1 H, dd, *J* 3, *J* 11, H17), 3.10 (1 H, m, H13), 3.70 (3 H, s, OMe), 4.52 (1 H, m, H3'), 5.54 (1 H, br.s, H18), 6.50 (1 H, dd, *J* 5.4, *J* 1.2, NH). ^{13}C NMR spectrum: 15.5, 16.4, 17.0, 19.9, 20.4, 20.7, 26.9, 32.7, 33.5 (C3'), 34.7, 35.2, 35.6 (C4'), 36.7, 37.5, 37.8, 40.8, 45.2, 45.8, 49.6, 51.9 (C1'), 53.0, 53.2, 125.1 (C18), 148.1 (C19), 170.8 (C14), 172.7 (C16), 172.9 (C2'), 178.2 (C20).

***N*-[(5*R*,9*R*,13*R*,17*R*)-5,9-Dimethyl-19-(1-methylethyl)-15-oxa-14,16-dioxopentacyclo[10.5.2.0^{1,10}.0^{4,9}.0^{13,17}] heptadec-18-ene-5-carbonyl]-*L*-valine methyl ether (VII).** Yield 0.40 g (92%). R_f 0.75. Mp 129–131°C. $[\alpha]_D^{20}$ + 44° (*c* 0.05, $CHCl_3$). Found, %: C 70.26; H 8.47; N 2.77. $C_{30}H_{43}NO_6$ (*M* 513.63). Calculated, %: C 70.15; H 8.44; N 2.73. ^{1}H NMR spectrum: 0.60 (3 H, c, CH_3), 0.97 and 1.00 (6 H, both d, *J* 6.8, $2CH_3$), 1.14 (3 H, s, CH_3), 1.18–1.33 (1 H, m, H4), 1.45–1.85 (19 H, m, CH_2, CH), 2.25 (1 H, m, CH), 2.50 (1 H, dt, *J* 3, *J* 14, H10), 2.70 (1 H, d, *J* 11, H12), 3.08 (1 H, dd, *J* 3, *J* 11, H17), 3.11 (1 H, m, H13), 3.71 (3 H, s, OMe), 4.49 (1 H, m, H3'), 5.52 (1 H, br.s, H18), 6.23 (1 H, dd, *J* 5.4, *J* 1.2, NH). ^{13}C NMR spectrum: 15.2, 16.0, 16.9, 19.7, 20.4, 21.0, 21.5 (C6'), 22.0 (C5'), 22.3, 25.2 (C4'), 27.8, 32.8, 34.6, 35.0, 36.9, 37.1, 37.6, 41.2, 45.1, 47.0, 49.9, 51.8 (C1'), 52.9 (C3'), 53.1, 125.9 (C18), 147.5 (C19), 170.5 (C14), 172.9 (C16), 173.3 (C2'), 178.1 (C20).

***N*-[(5*R*,9*R*,13*R*,17*R*)-5,9-Dimethyl-19-(1-methylethyl)-15-oxa-14,16-dioxopentacyclo[10.5.2.0^{1,10}.0^{4,9}.0^{13,17}]heptadec-18-ene-5-carbonyl]-*DL*-valine methyl ether (VIII).** Yield 0.32 g (74%). R_f 0.75. Mp 106–108°C. $[\alpha]_D^{20}$ + 3° (*c* 0.05, $CHCl_3$). Found, %: C 70.25; H 8.44; N 2.76. $C_{30}H_{43}NO_6$ (*M* 513.67). Calculated, %: C 70.15; H 8.44; N 2.73. ^{1}H NMR spectrum: 0.61 (3 H, s, CH_3), 0.99 and 1.00 (6 H, both d, *J* 6.8, $2CH_3$), 1.15 (3 H, s, CH_3), 1.15–1.29 (1 H, m, H4), 1.45–1.90 (19 H, m, CH_2, CH), 2.25 (1 H, m, CH), 2.50 (1 H, dt, *J* 3, *J* 14, H10), 2.70 (1 H, d, *J* 11, H12), 3.08 (1 H, dd, *J* 3, *J* 11, H17), 3.11 (1 H, m, H13), 3.70 (3 H, s, OMe), 4.47 (1 H, m, H3'), 5.52 (1 H, br.s, H18), 6.23 (1 H, dd, *J* 5.4, *J* 1.2, NH). ^{13}C NMR spectrum: 15.2, 16.0, 16.9, 19.8, 20.4, 21.0, 21.5 (C6'), 22.0 (C5'), 22.3, 25.2 (C4'), 27.8, 32.8, 34.4, 35.0, 36.9, 37.1, 37.6, 41.2, 45.0, 47.0, 49.9, 51.8 (C1'), 52.9 (C3'), 53.2, 125.9 (C18), 147.1 (C19), 170.0 (C14), 172.9 (C16), 173.1 (C2'), 178.0 (C20).

***N*-[(5*R*,9*R*,13*R*,17*R*)-5,9-Dimethyl-19-(1-methylethyl)-15-oxa-14,16-dioxopentacyclo[10.5.2.0^{1,10}.0^{4,9}.0^{13,17}]heptadec-18-ene-5-carbonyl]-*L*-leucine methyl ether (IX).** Yield 0.35 g (81%). R_f 0.72. Mp 117–119°C. $[\alpha]_D^{20}$ + 24° (*c* 0.05, $CHCl_3$). Found, %: C 70.85; H 8.24; N 2.76. $C_{31}H_{45}NO_6$ (*M* 527.69). Calculated, %: C 70.56; H 8.59; N 2.65. ^{1}H NMR spectrum: 0.59 (3 H, s, CH_3), 0.97 and 0.99 (6 H, both d, *J* 6.8, $2CH_3$), 1.15 (3 H, s, CH_3), 1.18–1.30 (1 H, m, H4), 1.37–1.82 (21 H, m, CH_2, CH), 2.23 (1 H, m, CH), 2.51 (1 H, dt, *J* 3, *J* 14, H10), 2.71 (1 H, d, *J* 11, H12), 3.08 (1 H, dd, *J* 3, *J* 11, H17), 3.10 (1 H, m, H13), 3.70 (3 H, s, OMe), 4.51 (1 H, m, H3'), 5.49 (1 H, br.s, H18), 6.19 (1 H, dd, *J* 5.4, *J* 1.2, NH). ^{13}C NMR spectrum: 15.5, 16.6, 16.9, 19.8, 20.4, 20.9, 21.8 (C7'), 22.4 (C6'), 22.6, 24.9 (C5'), 27.1, 32.5, 34.4, 35.5, 36.7, 37.5, 37.6, 40.2, 41.3 (C4'), 45.5, 46.5, 49.2, 50.8 (C1'), 52.1 (C3'), 52.9, 125.1 (C18), 147.8 (C19), 170.9 (C14), 172.7 (C16), 173.6 (C2'), 178.2 (C20).

***N*-[(5*R*,9*R*,13*R*,17*R*)-5,9-Dimethyl-19-(1-methylethyl)-15-oxa-14,16-dioxopentacyclo[10.5.2.0^{1,10}.0^{4,9}.0^{13,17}]heptadec-18-ene-5-carbonyl]-*L*-methionine methyl ether (X).** Yield 0.32 g (74%). R_f 0.68. Mp 79–81°C. $[\alpha]_D^{20}$ − 23° (*c* 0.05, $CHCl_3$). Found, %: C 65.01; H 7.08; N 2.38; S 5.86. $C_{29}H_{41}NSO_6$ (*M* 531.7). Calculated, %: C 65.51; H 7.77; N 2.63. ^{1}H NMR spectrum: 0.61 (3 H, s, CH_3), 0.99 and 1.01 (6 H, both d, *J* 6.8, $2CH_3$), 1.16 (3 H, s, CH_3), 1 (1 H, m, H4), 1.40–1.80 (17 H, m, CH_2, CH), 2.23 (1 H, m, CH), 2.51 (1 H, dt, *J* 3, *J* 14, H10), 2.72 (1 H, d, *J* 11, H12), 3.08 (1 H, dd, *J* 3, *J* 11, H17), 3.09 (1 H, m, H13), 3.71 (3 H, s, OMe), 4.69 (1 H, dt, *J* 5.2, *J* 1.9, *J* 7.1, H3'), 5.53 (1 H, s, H18), 6.56 (1 H, dd, *J* 5.4, *J* 1.2, NH). ^{13}C NMR spectrum: 15.4, 15.5, 16.9, 18.9, 19.3, 19.8, 21.0, 27.0, 30.0 (C5'), 30.8 (C4'), 32.6, 34.5, 35.5, 36.8, 37.6, 37.7, 40.2, 45.5, 46.5, 49.4, 52.3 (C1'), 52.9 (C3'), 53.0, 125.0 (C18), 147.8 (C19), 170.7 (C14), 172.5 (C16), 176.0 (C2'), 178.1 (C20).

***N*-[(5*R*,9*R*,13*R*,17*R*)-5,9-Dimethyl-19-(1-methylethyl)-15-oxa-14,16-dioxopentacyclo[10.5.2.0^{1,10}.0^{4,9}.0^{13,17}]heptadec-18-ene-5-carbonyl]-*L*-phenylalanine methyl ether (XI).** Yield 0.33 g (76%). R_f 0.65. Mp 106–108°C. $[\alpha]_D^{20}$ +10° (*c* 0.05, $CHCl_3$). Found, %: C 72.88; H 7.59; N 2.33. $C_{34}H_{43}NO_6$ (*M* 561.71). Calculated, %: C 72.70; H 7.72; N 2.49. ^{1}H NMR spectrum: 0.59 (3 H, s, CH_3), 0.99 and 1.00 (6 H, both d, *J* 6.8, $2CH_3$), 1.15 (3 H, s, CH_3), 1.17–1.31 (1 H, m, H4), 1.35–1.80 (12 H, m, CH_2, CH), 2.23 (1 H, m, CH), 2.51 (1 H, dt, *J* 3, *J* 14, H10), 2.71 (1 H, d, *J* 11, H12), 3.05 (2 H, dd, *J* 5.6, *J* 6.5, H4'), 3.08 (1 H, dd, *J* 3, *J* 11, H17), 3.12 (1 H, br.s, H13), 3.68 (3H, s, OMe), 4.75 (1 H, dt, *J* 5.8, *J* 5.4, *J* 11.5, H3'), 5.50 (1 H, br.s, H18), 6.15 (1 H, dd, *J* 5.4, *J* 1.2, NH), 6.95–7.12 (2 H, m, H6', H10'), 7.13–7.30 (3 H, m, H7', H8', H9'). ^{13}C NMR spectrum: 15.4, 15.5, 16.4, 16.9, 19.8, 20.5, 27.1, 20.8, 32.6, 34.5, 35.6, 36.8, 37.4 (C4'), 37.5,

37.8, 40.2, 45.6, 46.6, 48.9, 52.6 (C1'), 52.8, 53.1 (C3'), 125.2 (C18), 127.1 (C8'), 128.5 (C10'), 128.6 (C6'), 129.1 (C9'), 129.0 (C7'), 135.8 (C5'), 147.8 (C19), 170.9 (C14), 172.2 (C16), 172.7 (C2'), 178.3 (C20).

***N*-[(5*R*,9*R*,13*R*,17*R*)-5,9-Dimethyl-19-(1-methylethyl)-15-oxa-14,16-dioxopentacyclo[10.5.2.0^{1,10}.0^{4,9}.0^{13,17}]heptadec-18-ene-5-carbonyl]hexylamine (XII).** Yield 0.27 g (64%). R_f 0.72. Mp 100–102°C. $[\alpha]_D^{20}$ – 14° (*c* 0.05, $CHCl_3$). Found, %: C 74.18; H 9.16; N 2.74. $C_{30}H_{45}NO_4$ (*M* 483.68). Calculated, %: C 74.50; H 9.38; N 2.90. ^{1}H NMR spectrum: 0.59 (3 H, s, CH_3), 0.89 (3 H, s, H6'), 0.99 and 1.02 (6 H, both d, *J* 6.8, $2CH_3$), 1.25 (3 H, s, CH_3), 1.26–1.51 (9 H, m, H2', H3', H4', H5', H4), 1.52–1.80 (15 H, m, CH_2, CH), 2.23 (1 H, m, CH), 2.51 (1 H, dt, *J* 3, *J* 14, H10), 2.71 (1 H, d, *J* 11, H12), 3.08 (1 H, dd, *J* 3, *J* 11, H17), 3.11 (1 H, m, H13), 3.46 (2 H, m, H1'), 5.53 (1 H, br.s, H18), 5.70 (1 H, br.s, NH). ^{13}C NMR spectrum: 13.9, 15.5 (C6'), 16.8, 17.0, 19.9, 20.4, 20.9 (C5'), 22.4, 26.5 (C3'), 27.1, 29.5 (C2'), 31.3 (C4'), 32.6, 35.4, 35.6, 36.8, 37.6, 37.8, 39.7 (C1'), 40.2, 45.6, 46.5, 49.7, 54.2, 55.0, 125.2 (C18), 147.8 (C19), 170.9 (C14), 172.7 (C16), 178.0 (C20).

1-[(5*R*,9*R*,13*R*,17*R*)-5,9-Dimethyl-19-(1-methylethyl)-15-oxa-14,16-dioxopentacyclo[10.5.2.0^{1,10}.0^{4,9}.0^{13,17}]heptadec-18-ene-5-carbonyl]-1*H*-imidazole (XIII). Yield 0.30 g (69%). R_f 0.66. Mp 149–151°C. $[\alpha]_D^{20}$ – 5° (*c* 0.05, $CHCl_3$). Found, %: C 71.72; H 7.42; N 6.05. $C_{27}H_{34}N_2O_4$ (*M* 465.58). Calculated, %: C 71.97; H 7.61; N 6.22. ^{1}H NMR spectrum: 0.59 (3 H, s, CH_3), 0.99 and 1.00 (6 H, both d, *J* 6.8, $2CH_3$), 1.15 (3 H, s, CH_3), 1 (1 H, m, H4), 1.80–1.35 (12 H, m, CH_2, CH), 2.23 (1 H, m, CH), 2.51 (1 H, dt, *J* 3, *J* 14, H10), 2.71 (1 H, d, *J* 11, H12), 3.08 (1 H, dd, *J* 3, *J* 11, H17), 3.10 (1 H, m, H13), 5.54 (1 H, s, H18), 7.18 (1 H, s, H2'), 7.42 (1 H, s, H1'), 8.10 (1H, s, H3'). ^{13}C NMR spectrum: 14.1, 15.4, 15.6, 18.7, 19.2, 20.1, 25.7, 31.2, 33.4, 34.2, 35.3, 36.1, 36.6, 38.5, 44.3, 44.9, 47.7, 51.6, 51.8, 119.7 (C2'), 120.0 (C1'), 123.9 (C18), 133.5 (C3'), 146.5 (C19), 170.2 (C14), 171.8 (C16), 179.2 (C20).

1-[(5*R*,9*R*,13*R*,17*R*)-5,9-Dimethyl-19-(1-methylethyl)-15-oxa-14,16-dioxopentacyclo[10.5.2.0^{1,10}.0^{4,9}.0^{13,17}]heptadec-18-ene-5-carbonyl]-4-methylpiperazine (XIV). Yield 0.25 g (58%). R_f 0.78. Mp 161–163°C. $[\alpha]_D^{20}$ –26° (*c* 0.05, $CHCl_3$). Found, %: C 71.98; H 8.62; N 5.64. $C_{29}H_{42}N_2O_4$ (*M* 497.67). Calculated, %: C 72.17; H 8.77; N 5.80. ^{1}H NMR spectrum: 0.59 (3 H, s, CH_3), 0.99 and 1.00 (6 H, both d, *J* 6.8, $2CH_3$), 1.15 (3 H, s, CH_3), 1.15–1.32 (1 H, m, H4), 1.35–1.90 (16 H, m, CH_2, CH), 2.22 (1 H, dt, *J* 3, *J* 14, H10), 2.23 (1 H, m, CH), 2.43 (3 H, s, N-CH_3), 2.68 (1 H, d, *J* 11.0, H12), 3.09 (2 H, m), 3.68–3.89 (4 H, m, H1', H3'), 5.51 (1 H, br.s, H18). ^{13}C NMR spectrum: 15.6, 16.5, 16.7, 18.5 (C5'), 20.0, 20.4, 22.5, 27.0, 32.6, 34.8, 35.5, 36.9, 37.7, 37.8, 40.3, 44.3, 45.6 (C3'), 45.7 (C4'), 47.0, 49.6, 53.0, 53.4, 53.5 (C2'), 54.2 (C1'), 125.3 (C18), 147.9 (C19), 170.9 (C14), 172.7 (C16), 177.4 (C20).

(4*bS*,8*R*)-4*b*,8-Dimethyl-3-isobutyrylperhydrophenanthrene-1,2,8,10*a*-tetracarboxylic acid 8-methyl ether (XV). Ozone was passed through a solution of compound (**III**) (2 mmol, 0.84 g) in a 1 : 1 mixture of CH_2Cl_2 and MeOH at 0°C until the starting compound vanished (TLC). The mixture was kept at room temperature for 3 h. The precipitate was recrystallized from chloroform. Yield 0.75 g (89%). Mp 220–222°C. Found, %: C 62.25; H 7.27. $C_{25}H_{36}O_9$ (*M* 480.55). Calculated, %: C 62.49; H 7.55. ^{1}H NMR spectrum: 0.71 (3 H, s, CH_3), 1.05 and 1.08 (6 H, both d, *J* 6.8, $2CH_3$), 1.09 (3 H, s, CH_3), 1 (3 H, m, H4, H4*a*), 1.48–1.98 (10 H, m, CH_2, CH), 2.00 (1 H, qu, *J* 11.8, H8*a*), 2.27 (1 H, d, *J* 11.8, H3), 2.39 (1 H, d, *J* 11, H2), 2.78 (1 H, m), 2.92 (1 H, dt, *J* 4.5, *J* 11.8, H1), 3.75 (3 H, s, OMe). ^{13}C NMR spectrum: 13.3, 15.2, 16.5, 18.5, 19.6, 21.8, 33.5, 35.6, 36.4, 37.0, 37.5, 42.4, 42.9, 46.3, 47.9, 49.1, 50.7, 55.2, 55.4, 165.8 (COOH), 169.6 (COOH), 173.1 (COOH), 177.5 (COOH), 210.7 (C=O).

(4*bS*,8*R*)-4*b*,8-Dimethyl-3-isobutyrylperhydrophenanthrene-1,2,8,10*a*-tetracarboxylic acid 1,2,8,10*a*-tetramethyl ether (XVI). An ether solution of CH_2N_2 (70 ml) (TLC) was added to compound (**XV**) (1 mmol, 0.48 g). After recrystallization from methanol, the yield was 0.45 g (88%). Mp 104–107°C. Found, %: C 64.49; H 8.27. $C_{28}H_{42}O_9$ (*M* 522.63). Calculated, %: C 64.35; H 8.10. ^{1}H NMR spectrum: 0.73 (3 H s, CH_3), 1.08 and 1.11 (6 H, both d, *J* 6.8, $2CH_3$), 1.13 (3 H, s, CH_3), 1.10–1.40 (3 H, m, H4, H4*a*), 1.50–1.95 (10 H, m, CH_2, CH), 2.05 (1 H, qu, *J* 12 Hz, H8*a*), 2.30 (1 H, d, *J* 12, H3), 2.41 (1 H, d, *J* 12, H2), 2.80 (1 H, m), 2.94 (1 H, dt, *J* 4.5, *J* 12, H1), 3.57, 3.61, 3.63, and 3.75 (12 H, 4 s, 4OMe). ^{13}C NMR spectrum: 13.7, 15.7, 17.4, 17.8, 18.0, 18.7, 21.9, 35.6, 35.9, 36.2, 36.8, 37.9, 43.9, 44.4, 46.9, 49.2, 50.4, 50.8, 50.9, 51.1, 51.2, 56.5, 59.1, 170.0 ($\underline{C}OOCH_3$), 170.5 ($\underline{C}OOCH_3$), 173.8 ($\underline{C}OOCH_3$), 178.3 ($\underline{C}OOCH_3$), 212.8 (C=O).

The acute toxicity of compounds (II), (III), and (V)–(XV) was determined on 686 white non-inbred mice 18–22 g in mass of both sexes by introducing the compounds in the stomach with a probe in doses from 2500 to 16000 mg/kg by the Kerber method [25]. The animals were observed for 30 days. Based on the data on the death of animals from various doses of the stud-

ied compounds, the minimum lethal dose (LD_{100}) and maximum endurable dose (LD_0) were established by the integration method of Berens [26]. The LD_{16} and LD_{84} values were determined by the characteristic curves built based on the integrated data. The variability coefficient of the lethal doses (K) was determined by the equation

$$K = \frac{LD_{84}}{LD_{16}}.$$

The dose that led to the death of half of the animals, LD_{50}, was calculated by the Kerber equation [26]

$$LD_{50} = DM - \frac{\Sigma(Zd)}{n},$$

where DM is the dose that caused the death of all animals (LD_{100}); Z is half the number of animals that died from two subsequent doses; d is the difference between the numerical values of two adjacent doses; $\sum$ is the summation sign; and n is the number of animals in each group.

The mean error of LD_{50} was calculated by the Haddem equation

$$SLD_{50} = \pm\sqrt{\frac{k\,Sd}{n}},$$

where k is the constant coefficient, which was 0.564; d is the mean interval between the doses used; n is the number of animals in each group; and S is the mean-square deviation LD_{50}, which was calculated by the equation

$$S = \frac{LD_{84} - LD_{16}}{2}.$$

The anti-inflammatory activity of the compounds was studied on three models of inflammation caused by carrageenin, silver nitrate, and formalin. The experiments involved 774 white non-inbred mice of both sexes with a living mass of 18–21 g. Phlogogens were introduced subplantarily in one of the hind limbs of the animal. The studied compounds were administered internally (intragastrically) in doses of 25 to 100 mg/kg. The anti-inflammatory activity of the compounds was estimated from the difference in the mass of the paws subjected to the action of phlogogens and controls using the formula [27]

$$\%\text{ of suppression of inflammation} = \frac{V_k - V_0}{V_k},$$

where V_k is the mean increase in the volume of the paw in the controls, and V_0 is the mean increase in the volume of the paw in the experimental group.

The results of the experiments are given in Table1.

The antiulcer activity of the compounds was studied on 480 non-inbred white rats of both sexes (78 experimental groups and 2 control groups; 6 animals in each group) with a living mass of 185–220 g on models of acute stomach ulcers. Indometacin and acetic ulcers were induced by introducing a 3% solution of acetic acid in a dose of 100 mg/kg (based on the active compound) or a solution of indometacin (20 mg/kg) into the rat's stomach using a probe. The animals were kept on a starvation diet. The compounds were introduced as a water solution intragastrially 1 h before the introduction of ulcerogens. The control group received distilled water. After 8 h, the ulcergogens were introduced again. Then, the animals were kept for 24 h on a starvation diet at 4–6°C, after which a laparotomy was conducted with the extraction of the stomachs. The stomachs were opened along the greater curvature and ulcers were counted twice using a magnifying glass. The antiulcer activity (AA) was determined by the equation

$$AA = PI\ (control)/PI\ (experiment)$$

$$\text{Paules Index (PI)} = (A \times B)/100,$$

where A is the mean number of ulcers per animal and B is the number of animals with ulcers in the group, %.

The results are given in Table 2.

ACKNOWLEDGMENTS

This study was supported by the Russian Foundation for Basic Research, project no. 09-03-00831.

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