SYNTHESIS AND STUDY OF ANTIINFLAMMATORY AND ANALGESIC ACTIVITY OF 2-ARYLAMINOCINCHONINIC ACID HYDRAZIDES AND β-(1-CARBOXYETHYLIDENE)HYDRAZIDES

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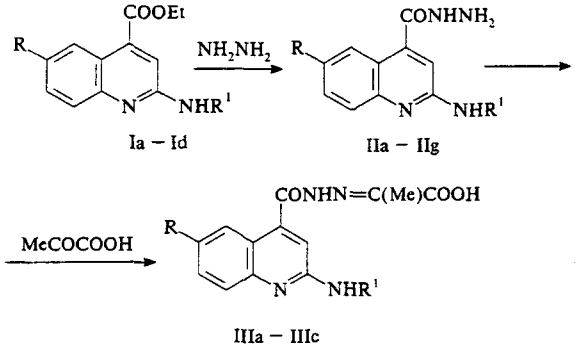
In previous works [1, 2] we have established that the derivatives of – 2-arylaminocinchoninic acid hydrazides exhibit an antiinflammatory action that is most pronounced in the arylidene and 2-oxoindoline-3-ylidene derivatives.

In continuation of that work, we have synthesized and characterized a series of 2-aminocinchoninic acid hydrazides on the basis of esters of 2-arylaminocinchoninic acids (Ia – Id) having various substituents at the amino group and in position 5 of the quinoline cycle (IIa – IIg, Table 1).[3]

In addition, we have synthesized hydrazones of these 2-arylaminocinchoninic acids with pyruvic acid (IIIa – IIIc).



I: R = H (a, b), Br (c) Me (d); R^1 = 4-BrC_6H_4 (a), 2-pyridyl (b), Ph (c, d);
II: R = H (a, b, e – g), Br (c), Me (d); R^1 = 4-BrC_6H_4 (a), 2-pyridyl (b), Ph (c – e), 4-MeC_6H_4 (f), 4-$MeOC_6H_4$ (g);
III: R = H (a – c); R^1 = Ph (a), 4-MeC_6H_4 (b), 4-$MeOC_6H_4$ (c).

The proposed structures of synthesized compounds were confirmed by IR and ^{1}H NMR spectroscopic data.

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[3] Compounds Ic and Id were previously described in [3] and compounds IIe – IIg in [2].)

EXPERIMENTAL CHEMICAL PART

The IR spectra were measured on an UR-20 spectrophotometer using samples prepared as nujol mulls. The ^{1}H NMR spectra were obtained on a RYa-2310 spectrometer using DMSO-d_6 as the solvent and HMDS as the internal standard. The characteristics of the target compounds are given in Table 1. The data of elemental analyses agree with the results of analytical calculations.

TABLE 1. Characteristics and Antiinflammatory Activity of the Synthesized Compounds

Compound	Yield, %	M.p., °C	Empirical formula	Dose, mg/kg (i.p.)	Edema inhibition (% of control) after carrageenan injection	
					3 h	5 h
Ia	73	153 – 155	$C_{18}H_{15}BrN_2O_2$	50	Inactive	
Ib	70	91 – 92	$C_{17}H_{15}N_3O_2$	50	Inactive	
IIa	67	237 – 238	$C_{16}H_{13}BrN_4O$	50	49.9	49.4
IIb	59	205 – 207	$C_{15}H_{13}N_5O$	50	28.0	29.4
IIc	75	242 – 243	$C_{16}H_{13}BrN_4O$	50	Inactive	
IId	78	236 – 238	$C_{17}H_{16}N_4O$	50	31.7	32.0
IIIa	66	207 – 210 (decomp.)	$C_{19}H_{16}N_4O_3$	25	42.3	0
IIIb	95	214 – 216 (decomp.)	$C_{20}H_{18}N_4O_3$	5	37	35
				10	45	33
				50	83	79
				100	82	68
				10*	19	22
				5*	29	41
IIIc	60	210 – 212 (decomp.)	$C_{20}H_{18}N_4O_4$	50	Inactive	
Orthophen				10	55.4	–

* Peroral administration.

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Ethyl esters of 2-(4-bromoanilino)- and 2-(2-pyridylamino)cinchoninic acid (Ia, Ib). A solution of 2.4 g (0.01 mole) of the ethyl ester of 2-chlorocinchoninic acid [4] and 0.012 mole of the corresponding amine in 10 ml of DMF was heated for 4 h at 150°C, poured into 200 ml of water, and neutralized with a 10% sodium carbonate solution. The precipitate was filtered and recrystallized from ethanol.

2-Arylaminocinchoninic acid hydrazides (IIa – IId). A mixture of 0.01 mole of the corresponding ester (Ia – Id), 5 ml hydrazine hydrate, and 5 ml ethanol was boiled for 2 h and cooled. The precipitate was filtered and recrystallized from butanol. IR spectra of compounds IIa – IId (ν_{max}, cm^{-1}): 1625 – 1640 (CO), 3200 – 3330 (NH, NH_2); ^1H NMR spectrum (δ, ppm): 4.42 – 4.50 (d, 2H, NH_2), 7.0 – 7.30 (m, 9 – 10H, Az), 9.0 – 9.30 (d, 1H, NH), 9.40 – 9.60 (s, 1H, NHAr).

β-(1-Carboxyethylidene)hydrazides of 2-arylaminocinchoninic acids (IIIa – IIIc). A mixture of 0.01 mole of the corresponding 2-arylaminocinchoninic acid hydrazide and 1.06 g (0.012 mole) of pyruvic acid in 20 ml of ethanol was heated for 1 h at 60°C and cooled. The precipitate was filtered and recrystallized from dioxane; ^1H NMR spectra of compounds IIIa – IIIc (δ, ppm): 2.1 – 2.35 (s, 3H, CH_3), 9.7 – 9.8 (s, 1H, NH), 11.2 – 11.3 (s, 1H, COOH).

EXPERIMENTAL PHARMACOLOGICAL PART

The antiinflammatory activity was studied on white mongrel rats weighing 170 – 210 g using the model of carrageenan-induced edema. The test substances were introduced either by intraperitoneal injections or perorally at a dose of 5 – 50 mg / kg with an aqueous suspension of Tween-80, 1 h before the carrageenan injection. The inflammation reaction was evaluated oncometrically by determining the change in the volume of foot edema 3 and 5 h after subplantar injection of 0.1 ml of a 0.5% carrageenan solution.

The antiproliferative effect was studied on a model of "paper" granuloma in rats weighing 220 – 250 g, each experiment being performed on a group of 8 – 10 animals. A granuloma, formed as a capsule surrounding a foreign body, was extracted on the 8th day from a narcotized animal, dried to constant weight, and weighed.

The analgesic activity was studied by the method of "vinegar convulsions" [6] on white mongrel mice weighing 20 – 25 g. The test compounds were introduced either perorally or by intraperitoneal and intramuscular injections 1 h before the pain irritant.

The acute toxicity (LD_{50}) upon intraperitoneal injections was determined on a group of white mice weighing 18 – 23 g by monitoring the loss of animals within a time period of 24 h [7].

An analysis of the experimental data showed that the antiinflammatory activity was well pronounced in compounds IIa, IIb, IId, IIIa, and IIIb (Table 1), which produced a 29 – 83% decrease in the exudation at a dose of 50 mg / kg (i.p.). Hydrazide Ia, having a bromine atom in the arylamide fragment, showed the maximum antiinflammatory activity among all the compounds of this series, having no substituents in the hydrazide group, studied both in this work and previously [1, 2]. Note that its isomer IIc, containing a bromine atom in the quinoline cycle, possesses no antiinflammatory properties. Study of the properties of compound IIIb in a wide range of doses showed that the antiinflammatory effect was retained on a sufficiently high level even at a dose of 5 mg / kg.

An analysis of the effect of compound IIIb on the development of paper granuloma showed that peroral administration at a daily dose of 20 mg / kg for 8 days decreases the weight of the fibro-granuloma tissue 34% against the control ($p < 0.5$).

Compound IIIb introduced at a dose of 25 and 50 mg / kg (p.o.) reduced the "vinegar convulsions" by 30 and 42%, respectively. The same pronounced analgesic effect was observed upon the intraperitoneal injection of IIIb at a dose of 10 mg / kg. Compound IIa injected intramuscularly at a dose of 50 mg / kg reduced the pain reaction in 39% of the test animals. The acute toxicity of compound IIIb was LD_{50} = 100 mg / kg, which corresponds to the class of moderate-toxicity compounds.

Thus, the results of our investigation showed that the derivatives of 2-arylaminocinchoninic acid hydrazides constitute a promising group in the search for new antiinflammatory and analgesic drugs.

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