SYNTHESIS AND ANTIINFLAMMATORY ACTIVITY OF ISONICOTINIC AND CINCHONINIC ACID DERIVATIVES

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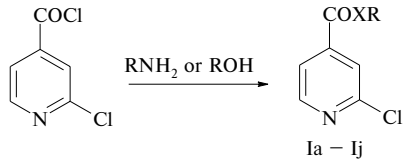
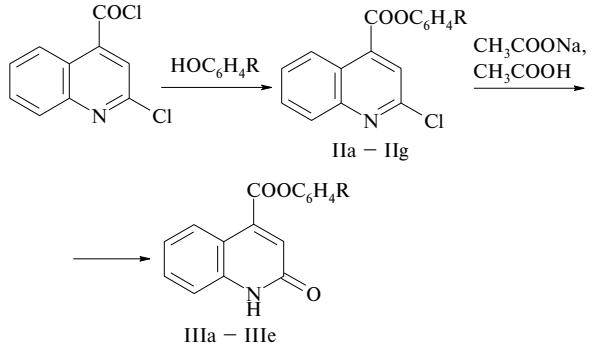
It was reported that amides of isonicotinic [1, 2], 2-chloroisonicotinic [3], 2-chlorocinchoninic [5, 6], and 2-oxocinchoninic [7, 8] acids possess antiinflammatory properties. In continuation of the previous investigations aimed at finding new effective antiinflammatory agents, we have synthesized a series of previously unreported substituted amides and esters of 2-chloroisonicotinic acid (Ia – Ij, Table 1) and aryl esters of 2-chloro-(IIa – IIg) and 2-oxocinchoninic (IIIa – IIIe) acids (Table 2).



Ia – Ij

I: X = NH (a – d), O (e – j); R = *iso*-C_3H_7 (a), *tert*-C_4H_9 (b), 3-ClC_6H_4 (c); 4-ClC_6H_4 (d); 4-BrC_6H_4 (e); 4-$CH_3C_6H_4$ (f); 4-$CH_3OC_6H_4$ (g); 4-$CH_3COC_6H_4$ (h); 2-$CH_3OCOC_6H_4$ (i); 4-$CH_3CONHC_6H_4$ (j)



IIa – IIg

IIIa – IIIe

II: R = 4-Br (a); 4-F (b); 4-CH_3 (c); 4-CH_3O (d); 4-CH_3CO (e); 2-CH_3OCO (f); 4-CH_3CONH (g);
III: R = 4-Br (a); 4-CH_3 (b); 4-CH_3O (c); 4-CH_3CO (d); 2-CH_3OCO (e).

It was established that amides Ia – Id and aryl esters Ie – Ij and IIa – IIg are obtained with a high yield via interaction of chloroanhydrides of the corresponding acids with amines or phenols.

The 2-oxocinchoninic acid esters IIIa – IIIe were obtained on heating aryl esters of 2-chlorocinchoninic acid with concentrated acetic acid in the presence of sodium acetate. The smooth character of this reaction is apparently related to the high nucleophilicity of the acetate ion, the considerable mobility of the chlorine atom, and the solvating action of acetic acid.

Compounds Ia – Ij and IIa – IIg appear as colorless crystalline substances insoluble in water and well soluble in most organic solvents. Esters IIIa – IIIe appear as yellowish crystalline substances insoluble in water and soluble in organic solvents such as dioxane, DMF, and DMSO. The proposed structures were confirmed by the data of ^{1}H NMR spectroscopy.

EXPERIMENTAL CHEMICAL PART

The ^{1}H NMR spectra were measured at 20°C on an RYa-2310 (working frequency, 60 MHz) and Bruker WD-80 (80 MHz) spectrometers using HMDS at the internal standard. The samples were prepared as 5% solutions in DMSO-d_6 (for compounds Ia – Ij and IIa – IIf) and $CDCl_3$ (for IIg and IIIa – IIIe). The yields and some physicochemical characteristics of the synthesized compounds are given in Tables 1 and 2. The data of elemental analyses agree with the results of analytical calculations using empirical formulas.

2-Chloroisonicotinic acid amides (Ia – Id). To 1.57 g (0.01 mole) of 2-chloroisonicotinic acid was added 30 ml of thionyl chloride and the mixture was boiled for 1 h, after which the excess thionyl chloride was distilled off at reduced pressure. The residue was dissolved in 20 ml of benzene. To this solution was added 0.01 mole of the corresponding amine in 50 ml of the same solvent and 0.01 mole of triethylamine and the mixture was heated for 1 h on a water bath. Then benzene was distilled off and the residue was treated with a 10% sodium hydrocarbonate solution. The pre-

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cipitated product was separated by filtration and recrystallized from ethanol; ^{1}H NMR spectrum (δ, ppm): 6.08 – 6.31 (d, 1H, NH-alkylamide) or 10.22 – 10.36 (s, 1H, NH-arylamide), 7.02 – 8.46 (m, ArH).

2-Chloroisonicotinic acid aryl esters (Ie – Ij). To 1.57 g (0.01 mole) of 2-chloroisonicotinic acid was added 30 ml of thionyl chloride and the mixture was boiled for 1 h, after which the excess thionyl chloride was distilled off at reduced pressure. The residue was dissolved in 20 ml of benzene. To this solution was added 0.01 mole of the corresponding phenol in 50 ml of the same solvent and 0.01 mole of triethylamine and the mixture was heated for 1 h on a water bath. Then the benzene was distilled off and the residue was treated with a 10% sodium hydrocarbonate solution. The precipitated product was separated by filtration and recrystallized from ethanol; ^{1}H NMR spectrum (δ, ppm): 6.75 – 8.58 (m, ArH).

2-Chlorocinchoninic acid aryl esters (IIa – IIg). To 2.07 g (0.01 mole) of 2-chlorocinchoninic acid was added 30 ml of thionyl chloride and the mixture was boiled for 1 h, after which the excess thionyl chloride was distilled off at reduced pressure. The residue was dissolved in 20 ml of benzene. To this solution was added 0.01 mole of the corresponding phenol in 50 ml of the same solvent and 0.01 mole of triethylamine and the mixture was heated for 1 h on a water bath. Then benzene was distilled off and the residue was treated with a 10% sodium hydrocarbonate solution. The precipitated product was separated by filtration and recrystallized from isopropyl alcohol; ^{1}H NMR spectrum (δ, ppm): 6.83 – 8.95 (m, ArH).

2-Oxo-1,2-dihydrocinchoninic acid esters (IIIa – IIIe). A mixture of 0.01 mole of 2-chlorocinchoninic acid ester and 1.2 g (0.015 mole) sodium acetate in 10 ml of concentrated acetic acid was boiled for 1 h, cooled, and diluted with water. The precipitated product was separated by filtration and recrystallized from dioxane; ^{1}H NMR spectrum (δ, ppm): 12.21 – 12.42 (bs, 1H, NH rings), 6.95 – 8.48 (m, ArH).

TABLE 1. Yields and Physicochemical Characteristics of Compounds Ia – Ij

Compound	Yield, %	M.p., °C	Empirical formula
Ia	73	104 – 105	$C_9H_{11}ClN_2O$
Ib	76	105 – 106	$C_{10}H_{13}ClN_2O$
Ic	79	131 – 132	$C_{12}H_8Cl_2N_2O$
Id	77	144 – 145	$C_{12}H_8Cl_2N_2O$
Ie	85	80 – 81	$C_{12}H_7BrClNO_2$
If	83	80 – 81	$C_{13}H_{10}ClNO_2$
Ig	79	79 – 80	$C_{13}H_{10}ClNO_3$
Ih	77	63	$C_{14}H_{10}ClNO_3$
Ii	81	80 – 81	$C_{14}H_{10}ClNO_4$
Ij	76	166 – 167	$C_{14}H_{11}ClN_2O_3$

EXPERIMENTAL BIOLOGICAL PART

The antiinflammatory activity of the synthesized compounds (Ia – Ij, IIa – IIg, IIIa – IIIe), 2-chloroisonicotinic acid, and 2-chlorocinchoninic acid was studied on white mongrel rats weighing 150 – 220 g bearing a foot edema model [8] induced by subplantar injections of 0.1 ml of a 1% carrageenan solution into the hind paws of the test animals. The compounds to be tested (in a dose of 50 mg/kg) and the reference drug ortophen (10 or 25 mg/kg) were intraperitoneally injected 1 h prior to carrageenan. The edema growth was evaluated oncometrically, by measuring the inflamed foot volume 3 and 5 h after carrageenan injection [8], and expressed as percentage edema growth inhibition relative to control. The experimental data were statistically processed in terms of the Student *t*-criterion [9].

It was found that 2-chloroisonicotinic acid administered in a dose of 50 mg/kg inhibits the carrageenan edema growth: by 61.2% after 3 h and by 59.4% after 5 h. Among the 2-chloroisonicotinic acid aryl esters and amides (Ia – Ij), a reliable antiinflammatory effect was observed only for compound Ih which, in the same dose of 50 mg/kg, inhibited the edema growth by 57.3 and 52.3% after 3 and 5 h, respectively (thus being inferior to ortophen).

2-Chlorocinchoninic acid in a dose of 50 mg/kg inhibits the carrageenan edema growth by 45.3 and 41.6% after 3 and 5 h, respectively. Among the aryl esters of 2-chloro- and 2-oxocinchoninic acids, a reliable antiinflammatory effect was observed only for compounds IIa, IIb, IIIa, IIIb, and IIIe (Table 2).

TABLE 2. Yields, Physicochemical Characteristics, and Antiinflammatory Activity of Compounds IIa – IIg and IIIa – IIIe

Compound	Yield, %	M.p., °C	Empirical formula	Dose, mg/kg	Edema growth inhibition, % of control	
					3 h	5 h
IIa	83	160 – 161	$C_{16}H_9BrClNO_2$	50	20.3*	26.2*
IIb	81	124 – 125	$C_{16}H_9ClFNO_2$	50	27.6**	34.0***
IIc	79	125 – 126	$C_{17}H_{12}ClNO_2$	50	–	–
IId	81	125 – 127	$C_{17}H_{12}ClNO_3$	…	…	…
IIe	72	120 – 122	$C_{18}H_{12}ClNO_3$	…	…	…
IIf	75	129 – 131	$C_{18}H_{12}ClNO_4$	50	–	–
IIg	64	194 – 196	$C_{18}H_{13}ClN_2O_3$	50	–	–
IIIa	91	260 – 262	$C_{16}H_{10}BrNO_3$	50	43.6**	39.5***
IIIb	83	228 – 229	$C_{17}H_{13}NO_3$	50	22.0*	22.3*
IIIc	78	238 – 240	$C_{17}H_{13}NO_4$	…	…	…
IIId	85	243 – 244	$C_{18}H_{13}NO_4$	…	…	…
IIIe	87	228 – 230	$C_{18}H_{13}NO_5$	50	49.0***	44.4***
Ortophen				25	69.4***	72.2***
				10	55.4**	…

Notes: * $p > 0.05$, ** $p < 0.05$, *** $p < 0.001$ relative to control.

Thus, aryl eaters of 2-chloroisonicotinic acid and 2-chloro- and 2-oxocinchoninic acids are characterized by lower antiinflammatory activity as compared to the acids proper and their amides.

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