SYNTHESIS AND ANTIINFLAMMATORY AND ANALGESIC ACTIVITY OF 2-SUBSTITUTED CINCHONINIC ACID AMIDES

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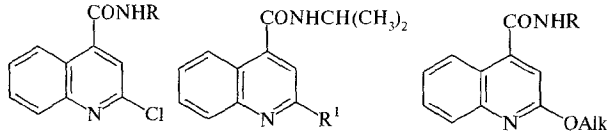
In previous papers we described the synthesis of alkyl(aryl)amides of 2-chloro- [1], 2-hydrazino- [2], 2-oxo- and 2-thio- [3], and 2-arylamino- and 2-aryloxy-substituted [4] cinchoninic acids and the relationship between their structure and the antiinflammatory and analgesic properties.

Below we report on the synthesis and characterization of a series of new amides of 2-chloro- (Ia – Ic), 2-alkylamino- (IIa – IId), and 2-alkoxycinchoninic (IIIa – IIIf) acids (see Table 1).

Compounds IIa – IId were obtained by reactions of amide Ia with morpholine, piperidine, cyclohexylamine, and benzylamine, respectively, in DMF. Amides IIIa – IIIf were synthesized by the interaction of amide Ia or 2-chlorocinchoninic acid arylamides with sodium alcoholates.



Ia - Ic IIa - IId IIIa - IIIf

I: R = *iso*-C_3H_7 (a), 4-ClC_6H_4 (b), 4-$CH_3COC_6H_4$ (c);
II: R^1 = morpholino (a), piperidino (b), NHC_6H_{11} (c), $NHCH_2C_6H_5$ (d);
III: R = *iso*-C_3H_7, Alk = CH_3 (a), R = *iso*-C_3H_7, Alk = C_2H_5 (b), R = 2,4-$Me_2C_6H_3$, Alk = CH_3 (c), R = 2,4-$Me_2C_6H_3$, Alk = C_2H_5 (d), R = 2,6-$Me_2C_6H_3$, Alk = CH_3 (e), R = 2,6-$Me_2C_6H_3$, Alk = C_2H_5 (f).

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TABLE 1. Physicochemical Properties and the Characteristics of Antiinflammatory and Analgesic Activity of the Synthesized Compounds

Compound	Yield, %	M.p., °C	Empirical formula	LD_{50}, mg/kg	Dose, mg/kg	Inhibition of carrageenan edema, % of control		Inhibition of vinegar convulsions, % of control
						3 h	4 h	
Ia	78	161 – 162	$C_{13}H_{13}ClN_2O$	500	25	46.2*	54.3*	65.0**
Ib	85	226 – 228	$C_{16}H_{10}Cl_2N_2O$	> 631	25	48.6**	24.5	27.6
Ic	78	232 – 234	$C_{18}H_{13}ClN_2O_2$	...	25	...	...	...
IIa	81	183 – 185	$C_{17}H_{21}N_3O_2$	> 631	25	49.3*	55.4**	37.3**
IIb	83	174 – 176	$C_{18}H_{23}N_3O$	> 631	25	34.4*	53.7**	26.7
IIc	76	182 – 184	$C_{19}H_{25}N_3O$	280.3 ± 102.0	25	32.3*	36.6**	...
IId	79	148 – 149	$C_{20}H_{21}N_3O$	...	...	...	...	...
IIIa	84	152 – 154	$C_{14}H_{16}N_2O_2$	70.4 ± 25.6	5	36.8*	41.0**	48.0**
IIIb	81	154 – 155	$C_{15}H_{18}N_2O_2$	280.3 ± 102.0	5	46.2*	51.7**	55.3**
IIIc	86	220 – 222	$C_{19}H_{18}N_2O_2$	...	...	...	...	...
IIId	83	188 – 190	$C_{20}H_{20}N_2O_2$	...	...	...	...	...
IIIe	90	201 – 203	$C_{19}H_{18}N_2O_2$	...	...	...	...	...
IIIf	82	195 – 197	$C_{20}H_{20}N_2O_2$	...	...	...	...	...
Orthophen				132 ± 46.8	25	69.4**	72.2**	50.0*
					10	55.4*	...	...

* $p < 0.05$.
** $p < 0.01$.

The proposed structures were confirmed by ^{1}H NMR spectroscopic data.

EXPERIMENTAL CHEMICAL PART

The ^{1}H NMR spectra were measured on an RYa-2310 spectrometer using DMSO-d_6 as the solvent and HMDS as the internal standard. Physicochemical characteristics of the synthesized compounds are given in Table 1. The data of elemental analyses agree with the results of calculations according to the empirical formulas.

2-Chlorocinchoninic acid amides (Ia – Ic). A mixture of 2.07 g (0.01 mole) of 2-chlorocinchoninic acid and 30 ml of thionyl chloride was boiled for 1 h. The excess thionyl chloride was distilled off at a reduced pressure and 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 benzene and 0.01 mole of triethylamine, and the mixture was heated on a water bath for 1 h. Then the solvent (benzene) was distilled off and the residue was treated with a 30% aqueous solution of sodium carbonate, filtered, and recrystallized from ethanol. The ^{1}H NMR spectra of compounds Ia – Ic (δ, ppm): 7.4 – 8.33 (m, H_{arom}), 8.8 – 11.3 (NH).

2-Alkylaminocinchoninic acid isopropylamides (IIa – IId). A solution of 2.49 g (0.01 mole) of 2-chlorocinchoninic acid isopropylamide and 0.01 mole of the corresponding amine in 10 ml DMF was boiled for 4 h, cooled, and neutralized with a 10% sodium carbonate solution. The precipitate was filtered and recrystallized from dioxane. The ^{1}H NMR spectra of compounds IIa – IId (δ, ppm): 6.7 – 8.0 (m, H_{arom}), 8.5 – 9.0 (d, 1H, NH amide).

2-Alkoxycinchoninic acid amides (IIIa – IIIf). To 0.01 mole of the corresponding 2-chlorocinchoninic acid amides was added sodium alcoholate obtained from 0.01 g-atom of metallic sodium and 10 ml of the corresponding alcohol. The mixture was boiled for 6 h, cooled, and diluted with water. The precipitate was filtered and recrystallized from ethanol. The ^{1}H NMR spectra of compounds IIIa – IIf (δ, ppm): 7.0 – 8.26 (m, H_{arom}), 8.67 – 10.3 (NH), 3.97 – 4.06 (s, 3H, OCH_3), 4.4 – 4.5 (q, 2H, CH_2-ethyl), 1.33 – 1.4 (t, CH_3-ethyl).

EXPERIMENTAL PHARMACOLOGICAL PART

The antiinflammatory activity was studied on white mongrel rats weighing 170 – 250 g with an edema model induced by subplantar 0.1 ml injections of a 1% aqueous carrageenan solution into hind paws of the test animals. The test substances and the reference drug orthophen were injected intraperitoneally in the form of aqueous suspensions with Tween-80 1 h before carrageenan injections. The growth of edema volume was determined oncometrically [5] 3 and 5 h after carrageenan injections and expressed as a percentage inhibition of edema growth relative to that in the control.

The analgesic activity was estimated using the test of vinegar-induced convulsions in mice. According to this, 0.25 ml of an 0.75% acetic acid solution was intraperitoneally injected into the test animals and the number of convulsions was counted within a 10 min period of time [6]. The compounds tested and the reference drug orthophen were introduced in the form of aqueous suspensions with Tween-80 1 h before the convulsant injection.

The acute toxicity (LD_{50}) of the test compounds was studied using intraperitoneal injections into white mice weighing 18 – 25 g and determined by a conventional method [7] taking into account the animals lost within 24 h after injection.

The experimental data were statistically processed and the confidence criteria were calculated [8].

It was found that compounds Ia, Ib, IIa – IIc, IIIa, and IIIb possess antiinflammatory activity, although the effect was less pronounced as compared to that of orthophen (Table 1).

Compounds Ia, Ib, IIa, IIb, IIIa, and IIIb also exhibited an analgesic effect, the most active compound (Ia) being superior to orthophen.

On the whole, compounds IIa, IIb and especially IIIa, IIIb have proved to be more active than 2-arylaminocinchoninic acid isopropylamides [4].

Therefore, the introduction of alkoxy groups instead of substituted amino or phenoxy groups into position 2 of isopropylamides leads to an increase in the antiinflammatory and analgesic activity.

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