SYNTHESIS AND BIOLOGICAL ACTIVITY OF AMIDES OF 2-HYDRAZINOCINCHONINIC, 1,2,4-TRIAZOLO[4,3-a]-, AND 1,2,3,4-TETRAZOLO[4,3-a]-QUINOLINE-9-CARBOXYLIC ACIDS

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Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 30, No. 3, pp. 52 – 53, March, 1996.

Original article submitted October 02, 1995.

In continuation of the previous search for new biologically active compounds among the cinchoninic acid substituents [1, 2], we have synthesized derivative amides of 2-hydrazinocinchoninic (Ia – h, IV), 1,2,4-triazolo[4, 3-a]quinoline-9-carboxylic (IIa – c, V), and 1,2,3,4-tetrazolo[4, 3-a]quinoline-9-carboxylic (IIIa – d) acids.

Experiments showed that compounds Ia – h can be obtained with good yield (see Sceme) by boiling 2-chlorocinchoninic acid with hydrazine hydrate in ethanol.

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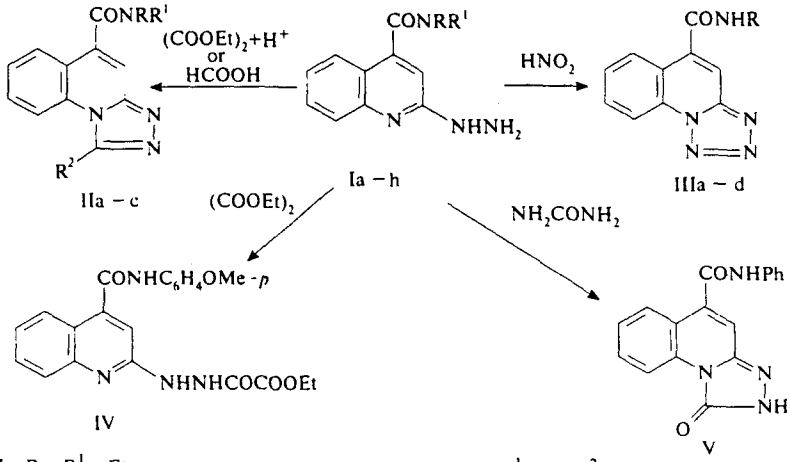
Heating amides If, h with diethyloxalate (in an ethanol medium in the presence of a few drops of concentrated HCl) and amide Ia with formic acid yields 1,2,4-triazolo[4,3-a]quinoline derivatives IIa – c. The reaction between amide Ig and diethyloxalate carried out in the absence of mineral acid leads to an intermediate amide IV, which indicates that cyclization of 2-acylhydrazinoquinolines to compounds IIa – c is catalyzed by acids. Amide V is obtained by heating compound Id with urea in an ethylene glycol medium as described previously [3].

Interaction of amides Ib, c, e, and h with sodium nitrite in an acid medium leads to the formation of amides IIIa – d. Un-

Scheme



Ia: R = R¹ = Et;
Ib: R = *iso*-Am, R¹ = H;
Ic: R = allyl, R¹ = H;
Id: R = Ph, R¹ = H;
Ie: R = *o*, *p*-$Cl_2C_6H_3$, R¹ = H;
If: R = *o*-$MeOC_6H_4$, R¹ = H;
Ig: R = *p*-$MeOC_6H_4$, R¹ = H;
Ih: R = *o*, *p*-$Me_2C_6H_3$, R¹ = H;

IIa: R = R¹ = Et, R² = H;
IIb: R = *o*-$MeOC_6H_4$, R¹ = H, R² = EtOCO;
IIc: R = *o*, *p*-$Me_2C_6H_3$, R¹ = H, R² = EtOCO;
IIIa: R = *iso*-Am;
IIIb: R = allyl;
IIIc: R = *o*, *p*-$Cl_2C_6H_3$;
IIId: R = *o*, *p*-$Me_2C_6H_3$.

0091-150X/96/3003-0197$15.00

TABLE 1. Characteristics and Antiinflammatory Activity of Synthesized Compounds

Compound	Yield, %	M.p., °C	Empirical formula	Antiinflammation activity: edema inhibition as % of control		
				Dose, mg/kg	3 h	5 h
Ib	69	151 – 152	$C_{15}H_{20}N_4O$	...	...	...
Ic	77	168 – 169	$C_{13}H_{14}N_4O$	...	...	...
Ie	75	212 – 213	$C_{16}H_{12}Cl_2N_4O$	...	...	...
If	73	187 – 188	$C_{17}H_{16}N_4O_2$	50	– 26	– 25
Ig	68	229 – 231	$C_{17}H_{16}N_4O_2$	50	10	16
Ih	83	223 – 225	$C_{18}H_{18}N_4O$	50	26	36
IIa	63	165 – 166	$C_{15}H_{16}N_4O$	50	67	50
				25	43	32
IIb	60	178 – 180	$C_{21}H_{18}N_4O_4$	50	10	8
IIc	62	169 – 171	$C_{22}H_{20}N_4O_3$	50	8	0
IIIa	64	188 – 190	$C_{15}H_{17}N_5O$	...	...	...
IIIb	57	226 – 227	$C_{13}H_{11}N_5O$	50	3	...
IIIc	80	258 – 259	$C_{16}H_9Cl_2N_5O$	100	65	66
				50	29	45
IIId	65	261 – 263	$C_{18}H_{15}N_5O$	50	18	35
IV	54	213 – 214	$C_{21}H_{20}N_4O_5$	50	16	21
V	58	232 – 234	$C_{17}H_{12}N_4O_2$	50	45	32
Ortophen				10	55.4	...

Note. Compounds Ia and Id were characterized in [3].

der these conditions, the amide function is not subject to nitrosation.

EXPERIMENTAL CHEMICAL PART

The IR spectra were measured on an UR-20 spectrophotometer (Carl Zeiss, Germany) 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 synthesized compounds are given in Table 1. The data of elemental analyses agree with the results of analytical calculations.

Amides of 2-hydrazinocinchoninic acid (Ia – h). A mixture of 0.01 mole of the corresponding amide of 2-chlorocinchoninic acids [1], 10 ml of 60% aqueous hydrazine hydrate solution, and 5 ml of ethanol is boiled for 2 h and cooled. The precipitate is separated by filtering and crystallized from ethanol. IR spectra, ν_{max}, cm^{-1}: 3180 – 3430 (NH, NH_2), 1624 – 1635 (CO); ^{1}H NMR spectra, δ, ppm: 7.16 – 7.2 (ArH and NH_2), 8.42 – 9.96 (s, 1H, NH).

Diethylamide of 1,2,4-triazolo[4,3-a]quinoline-9-carboxylic acid (IIa). A solution of 2.58 g (0,01 mole) of 2-hydrazinocinchoninic acid diethylamide in 10 ml of formic acid is boiled for 1 h, cooled, poured into 50 ml of water, and neutralized with a 10% solution of sodium carbonate. The precipitate is filtered and crystallized from a DMFA – water (2 : 1) mixture. IR spectrum, ν_{max}, cm^{-1}: 1630 (CO); ^{1}H NMR spectra, δ, ppm: 1.13 (t, 6H, $2CH_3$), 3.30 (q, 4H, $2CH_2$), 7.52 (m, 5H, Ph), 9.92 (s, 1H, =CH).

Substituted amides of 1,2,4-triazolo[4,3-a]quinoline-9-carboxylic acid (IIb, c). A solution of (0,01 mole) of the corresponding amide (If, Ih), 2.2 g (0.015 mole) diethyloxalate, and 3 drops of concentrated HCl in 10 ml of ethanol is boiled for 2 h, cooled, and then treated as in the preceding paragraph. IR spectra, ν_{max}, cm^{-1}: 3240 – 3242 (NH); 1650 – 1654 and 1714 – 1716 (CO); ^{1}H NMR spectra, δ, ppm: 1.38 – 1.40 (s, 3H, CH_3), 4.30 – 4.32 (q, 2H, CH_2), 7.41 – 7.43 (ArH), 10.70 – 10.72 (s, 1H, NH).

Amides of 1,2,3,4-tetrazolo[4,3-a]quinoline-9-carboxylic acid (IIIa – d). To a solution of 0.01 mole of the corresponding amide (Ib, c, e, h) in 10 ml of glacial acetic acid is added dropwise, with stirring and cooling (+5°C), a solution of 1.38 g (0.02 mole) of sodium nitrite in 3 ml of water and the mixture is allowed to stand for 2 h at room temperature. Then the mixture is diluted with water, and the precipitate is filtered and crystallized from water-saturated DMFA. IR spectra, ν_{max}, cm^{-1}: 3300 – 3310 (NH), 1640 – 1654 (CO).

***para*-Anizidide of 2-(β-ethoxalylhydrazino)cinchoninic acid (IV).** A solution of 3.06 g (0,01 mole) of Ig and 2.2 g (0.015 mole) diethyloxalate in 15 ml of ethanol is boiled for 1 h and cooled. The precipitate is separated by filtering and crystallized from ethanol. IR spectrum, ν_{max}, cm^{-1}: 3345, 3442, 3510 (NH); 1625, 1670, 1710 (CO); ^{1}H NMR spectra, δ, ppm: 1.35 (t, 3H, CH_3), 3.80 (s, 3H, CH_3O), 4.28 (q, 2H, CH_2), 7.40 (11H, ArH, NH–NH), 10.74 (s, 1H, CONH).

Anilide of 3-hydroxo-1,2,4-triazolo[4,3-a]quinoline-9-carboxylic acid (V). A mixture of 2.78 g (0.01 mole) of anilide of Id and 0.72 g (0.012 mole) of urea in 30 ml of ethylene glycol is boiled for 6 h and cooled, The precipitate is separated by filtering and crystallized from DMFA.

EXPERIMENTAL PHARMACOLOGICAL PART

The antiinflammatory activity of the synthesized compounds was studied on white mongrel rats weighing 170 – 210 g using a model of an acute carrageenan initiated edema. The test substances were injected intraperitoneally (50 mg/kg i.p.) with an aqueous Tween-80 suspension 1 h before the carrageenan injection. The inflammation reaction was evaluated oncometrically by determining the change in the volume of foot edema in 3 and 5 h after subplantar injection of 0.1 ml of 0.5% carrageenan solution. The degree of edema inhibition was calculated as percentage with respect to control [4].

The analgetic activity was determined on white male and female mongrel mice weighing 20 – 25 g using the method of vinegar writhing [5]. The test compounds were introduced perorally 1 h before injecting the pain stimulant. The acute toxicity (LD_{50}) was studied [6] by intraperitoneal injections to 18 – 23 g white mice [4].

The results of our experiments show that amides of 2-hydrazino- (If – h) and 2-(ethoxalylhydrazino)cinchoninic acid (IV) exhibit no antiinflammatory activity, except for compound Ih weakly inhibiting the carrageenan-induced edema. Compound Ih also suppressed by 59% the vinegar writhing in mice, thus showing a pronounced analgetic effect. In the series of triazolo[4,3-a]quinolines studied, the maximum antiinflammatory activity was observed for compounds IIa and V (reducing the edema by 67 and 45%, respectively). Among the amides (IIIb – e), a noticeable antiinflammatory activity was observed only for compound IIIc.

The LD_{50} values of the most active compounds were greater than 400 mg / kg.

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