HYDRAZIDE AND β-ACYLHYDRAZINE DERIVATIVES OF 2-ARYLAMINOCINCHONINIC ACIDS AND THEIR BIOLOGICAL ACTIVITY

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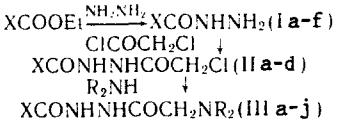
Pharmaceutically effective compounds are known among quinoline derivatives which are used in medicine [2]. Antiviral, antitubercular and antifungal activity has been found in hydrazide, acylhydrazide and urethane derivatives of 2-aryl- and 2-cycloalkylquinoline-4-carbocylic acids [3, 7]. An antiblastic action was found in derivatives of 2-phenylcinchoninic hydrazides [6]. Monooxidase inhibitors were found in the same series of compounds [8]. 2-Aminocinchoninic acid hydrazides have not been studied until now.

In order to find new biologically active compounds and reveal their structure – activity relationship, we synthesized a series of hydrazides (Ia-f), β-(chloroacetyl)-(IIa-d) and β-(dialkylaminoacetyl)hydrazides of 2-arylaminochinchoninic acids (IIIa-j) (Table 1).



R = C_2H_5 (III e, h, j); NR_2 = morpholino (III b, c, f), piperidino (IIIa, d, g, i); R' = C_6H_5 (Ia, IIa, IIIa), p-$CH_3C_6H_4$ (Ib, IIb, IIIc, d, j), m-$CH_3OC_6H_4$ (Ic, IIc, IIIe-g), p-$CH_3O \cdot C_6H_4$ (Id, IId, IIIb, h, i), o-$CH_3C_6H_4$ (Ie), $C_6H_5CH_2$ (If); X = 2-NHR'-quinolyl-4.

The starting 2-arcylaminochinchoninic acid hydrazides (Ia-f) were obtained in good yields by the reaction of the corresponding esters of 2-arylcinchoninic acids with hydrazine hydrate on boiling in ethanol.

The experiments showed that hydrazides Ia-d easily undergo the reaction with chloroacetyl chloride in acetic acid in the presence of sodium acetate with the formation of β-(chloroacetyl) hydrazides (IIa-d). Heating of the latter with amines in dioxane leads to β-(dialkylaminoacetyl)-hydrazides of 2-arylaminoacetylaminocinchoninic acids (IIIa-j).

The structure of the compounds obtained was confirmed by the IR and PMR spectral data (see the Experimental part).

EXPERIMENTAL (CHEMICAL)

The IR spectra were run on a UR-20 spectrophotometer in mineral oil. The PMR spectra were obtained on a RYa-2310 spectrometer (60 MHz), using HMDS as internal standard, and DMSO-d_6 as a solvent. The course of the reactions and the purity of the products were monitored by TLC method on Silufol UV-254 plates in an ethyl acetate–benzene (1:1) system of solvents.

The characteristics of the compounds obtained are given in Table 1. The elemental analysis data correspond to the calculated values.

2-Arylaminocinochoninic Acid Hydrazides (Ia-f). A mixture of 0.01 mole of the corresponding ester of 2-arylaminocinchoninic acid, 5 ml of a 60% of hydrazine hydrate and 5 ml

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TABLE 1 Hydrazides (Ia-f), β-(Chloroacetyl)-(IIa-d) and β-(Dialkylaminoacetyl)-hydrazines (IIIa-j) of 2-Arylaminocinchoninic Acid

Compound	Yield, %	mp, °C	R_f*	Empirical formula
Ia	98	246—248	0,62	$C_{16}H_{14}N_4O$
Ib	90	238—240	0,59	$C_{17}H_{16}N_4O$
Ic	89	181—182	0,68	$C_{17}H_{16}N_4O_2$
Id	94	195—196	0,63	$C_{17}H_{16}N_4O_2$
Ie	78	198—200	0,53	$C_{17}H_{16}N_4O$
If	75	199—201	0,49	$C_{17}H_{16}N_4O$
IIa	80	205—207	0,56	$C_{18}H_{15}ClN_4O_2$
IIb	92	225—226	0,48	$C_{18}H_{17}ClN_4O_2$
IIc	88	202—204	0,51	$C_{19}H_{17}ClN_4O_3$
IId	86	226—228	0,34	$C_{19}H_{17}ClN_4O_3$
IIIa	69	189—191	0,62	$C_{23}H_{25}N_5O_2$
IIIb	58	180—182	0,74	$C_{23}H_{25}N_5O_4$
IIIc	65	195—197	0,59	$C_{23}H_{25}N_5O_3$
IIId	57	185—187	0,67	$C_{24}H_{27}N_5O_2$
IIIe	55	96—98	0,79	$C_{23}H_{27}N_5O_3$
IIIf	61	208—210	0,63	$C_{23}H_{27}N_5O_4$
IIIg	66	117—119	0,75	$C_{24}H_{27}N_5O_3$
IIIh	61	141—143	0,71	$C_{23}H_{27}N_5O_3$
IIIi	62	159—161	0,69	$C_{24}H_{27}N_5O_3$
IIIj	61	163—165	0,68	$C_{23}H_{27}N_5O_2$

*Ethyl acetate—benzene (1:1) system of solvents.

of ethanol was boiled for 2 h, and then cooled. The precipiate was filtered, and crystallized from acetonitrile. IR spectrum, cm^{-1}: 1625-1640 (CO), 3135-3330 (NH, NH_2). PMR spectrum, ppm: 4.45-4.55 (d, 2H, NH_2), 7.05-7.35 (m, 9-10H, Ar), 9.09-9.35 (d, 1H, NH), 8.45-9.62 (s, 1H, NH).

2-Arylaminocinchoninic Acid β-Chloroacetylhydrazides (IIa-d). A 0.8 g portion (0.01 mole) of sodium acetate and was 0.8 ml (0.01 mole) of chloroacetyl chloride was added to a solution of 0.01 mole of hydrazides Ia-d in 10 ml of glacial acetic acid; the mixture was allowed to stand for 24 h at room temperature. It was then poured into 100 ml of water and neutralized with a 40% solution of sodium carbonate. The precipitate was filtered and crystallized from isopropanol. IR spectrum, cm^{-1}: 1655-1690 (CO), 3160-3465 (NH). PMR spectrum, ppm: 4.08-4.25 (s, 2H, CH_2), 6.95-7.32 (m, 9-10H, Ar), 9.02-9.25 (d, 1H, NH), 9.92-10.45 (s, 1H, NH).

2-Arylaminocinchoninic Acid β-Dialkylaminoacetylhydrazides (IIIa-j). A mixture of 0.01 mole of the substituted hydrazide IIa-d and 0.015 mole of the corresponding amine in 10 ml of dioxane was boiled for 1 h. The mixture was poured into 100 ml of water, neutralized with a 40% solution of sodium carbonate, the precipitate was filtered, dried, and crystallized from ethyl acetate. IR spectrum, cm^{-1}: 1650-1695 (CO), 3155-3545 (NH). PMR spectrum, ppm: 2.42-3.02 (s, 2H, CH_2), 7.22-7.35 (m, 9-10H, Ar), 9.22-9.38 (d, 1H, NH), 9.88-10.18 (s, 1H, NH).

EXPERIMENTAL (PHARMACOLOGICAL)

The acute toxicity was studied in tests on white mice of both sexes, each weighing 18-25 g using a single intraperitoneal administration according to G. N. Preshin [4]; the LD_{50} was calculated according to Litchfield and Wilcoxon [1].

The antiinflammatory activity was studied in tests on white rats, each weighing 180-250 g, on a model of an acute inflammatory edema caused by a subplantar administration of 0.1 ml of 1% of carragheenin into a posterior foot of a rat. The increment in the volume of the inflamed paw was evaluated oncometrically 4 h before and 4 h after the introduction of the phlogogenic agent [5]. Orthophen served as reference standard for the antiinflammatroy action. All the synthesized compounds were administered intraperitoneally in a dose of 50 mg/kg, and orthophen — in a dose of 10 mg/kg, 1 h before the introduction of carragheenin.

For the determination of the bacteriostatic activity, the preparations studied were dissolved in DMSO in a ratio of 1:100 and were diluted by a sterile meat-peptone bouillon (MPB) to a ratio of 1:500. The bacteriostatic activity was studied by the method of successive dilutions in MPB with respect to Staphylococcus aureus and Escherichia coli. Thus, the washouts of a day-old culture cultivated on a meat-peptone agar eluted by a sterile

TABLE 2. Antiinflammatory and Bacteriostatic Activity of Hydrazides, β-(Chloroacetyl)- and β-(Dialkylaminoacetyl)-hydrazides of 2-Arylaminocinchoninic Acid

Compound	LD_{50}, mg/kg	Antiinflammatory action, % inhibition of edema	Bacteriostatic activity, μg/ml	
			Escherichia coli	Staphylococcus aureus
Ic	3000	38,8	5000	500
Id	...	10,7	500	500
Ie	3000	30,5	500	5000
If	...	6,28	500	1000
IIa	2000	33,0	1000	125
IIb	...	—39,4*	1000	250
IIc	1500	40,7	1000	31
IId	...	3,76	1000	125
IIIa	...	18,45	-	1000
IIIb	3000	39,0	1000	125
IIIc	2000	38,4	1000	250
IIId	...	18,0	1000	250
IIIe	2000	31,3	1000	500
IIIf	1500	36,4	1000	250
IIIg	2000	42,8	1000	125
IIIj	...	5,76	1000	125
Control — 2% 2% starch mucilage	—	—	—	
Orthophen	74,2	48,0	—	—

*The compound caused an intensification of the edema.

physiological solution of sodium chloride were used, and the starting dilution with a concentration of 500 million microbial bodies in 1 ml of the washes was prepared according to a bacteria standard. The suspension obtained was diluted 100 times by a sterile MPB. This dilution of the bacterial culture with a concentration of 5 million microbial bodies in 1 ml served as the working solution. The latter, in an amount of 0.1 ml was introduced into 2 ml of MPB. Thus, the microbial load comprised 250,000 microbial bodies per 1 ml of the liquid. The experimental results were accounted for after 18-20 h holding of the control and experimental cultures in a thermostat at 36-37°C. The presence or absence of the bacterial growth was recorded through the bacteriostatic action of the preparation. The active dose was considered as the minimal inhibiting concentration of the preparation (in μg/ml) which arrested the growth of the corresponding test-microbe at a standard setting of the experiment. The results of the biological tests are given in Table 2.

Thus, the analysis of the data on the pharmacological activity of the synthesized compounds made it possible to reach the following conclusions.

The β-acyl derivatives of 2-arylaminocinchoninic acid hydrazides are slightly toxic. The maximally tolerated dose for white mice was 1500-3000 μg/kg on intraperitoneal administration. Most of the compounds studied have antiinflammatory activity. This activity is most strongly pronounced in the anisole derivatives IIc and IIIg, which in their action approach orthophen, a preparation whose disadvantage is its high toxicity.

The bacteriostatic activity obtained with respect to Gram-positive and Gram-negative microflora varies from 31 to 1000 μg/ml. The activity of β-(chloroacetyl)hydrazide of 2-m-anisidinocinchoninic acid IIc should be noted. This compound is practically inactive with respect to Escherichia coli, but actively suppresses the growth of Staphylococcus aureus and also has a considerable antiinflammatory activity.

Considering the results obtained, the search for physiologically active compounds, as well as potential drugs in the series of 2-aminocinchoninic acid hydrazide derivatives appears to be promising.

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SYNTHESIS AND TUBERCULOSTATIC ACTIVITY OF DERIVATIVES OF 1,2,4-TRIAZOL-3-THIONE

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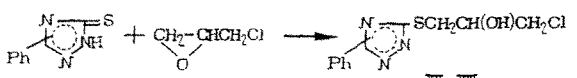
The biological activity of derivatives of 1,2,4-triazol-3-thiones (I) depends on both the nature of the substituent on the 1,2,4-triazole group and the structure of the radical attached to the exocyclic sulfur atom [1]. In an attempt to synthesize an effective tuberculostat, we prepared a series of derivatives of triazolthione I [8, 11]. The hydrazides of 5-(2-furyl)-1,2,4-triazol-3-thiocarboxylic acids are compounds possessing appreciable activity against Mycobacterium tuberculosis [11].

In a continuing systematic study of the synthesis and biological activity of derivatives of triazole I [3, 4] we studied the reaction of triazoles I, 5-methyl (II)- and 5-phenyl (III)-1,2,4-triazol-3-thione with 1-chloro-2,3-epoxypropane (CEP) [6]. It was shown that in the presence of organic bases the reaction proceeds through the cleavage of the epoxide ring and the formation of 3-(1-chloro-2-hydroxypropylthio)-5-R-1,2,4-triazoles [R = H(IV), Me(V), Ph(VI)]. The use of potassium hydroxide as catalyst leads in the resulting reaction to the corresponding 3-hydroxy-7-R-1,2,4-triazolo[2,3-b]tetrahydro-1,3-thiazines [R = Me(VII), and Ph(VIII)].

In the present work we studied the behavior of 1-phenyl(IX)-, 4-phenyl(X)- and 5-(2-furyl) (XI)-1,2,4-triazol-3-thione in this reaction.

We studied the influence of the change of the position of the phenyl substituent on the triazolethione ring. Introduction of a phenyl substituent into position 1 or 4 of the heteroring excludes the possibility of formation of diadducts and the products of heterocyclization. We have isolated the corresponding 1-phenyl(XII)- and 4-phenyl(XIII)-3(1-chloro-2-hydroxypropylthio)-1,2,4-triazole. The reaction is easily accomplished in alcohol solution at room temperature and does not require catalytic initiation.



IX, X XII, XIII

A more complex reaction takes place with the furyl-substituted triazole XI. The furyl substituent apparently activates the reaction centers on the N and S atoms to the same degree.

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