SYNTHESIS, ANTIINFLAMMATORY AND ANALGESIC ACTIVITIES OF 2-ARYLAMINO-5,6,7,8-TETRAHYDROQUINOLINE-3-CARBOXAMIDES

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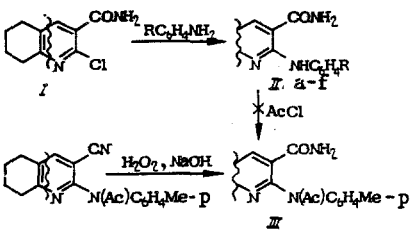
In medical practice the antiinflammatory and analgesic preparation of mefenamic acid is used [2]. The same kind of activities is found in 2-arylaminonicotinic acids [6]. It was of interest to study compounds structurally related to mefenamic acid and its analogs, vis. derivatives of 2-arylamino-5,6,7,8-tetrahydroquinoline-3-carboxylic acids, which have not been studied until recent times, neither chemically nor biologically.

To reach the object in view we have carried out the synthesis of 2-arylamino-5,6,7,8-tetrahydroquinoline-3-carboxamides (IIa-f, Table 1) by reacting 2-chloro-5,6,7,8-tetrahydroquinoline-3-carboxamide with aryl amines.



I III

R = Me-*o* (IIa), Me-*m* (IIb), OMe-*p* (IIc), OMe-*o* (IId), Cl-*p* (IIe), Cl-*o* (IIf).

It was found that the reaction proceeds successfully by refluxing a solution of equimolar amounts of the starting compounds in 50% AcOH. The proton-donor properties of the solvent apparently promote the increase in mobility of the chlorine and facilitates the reaction. Under these conditions, compounds IIa-f are produced in yields of 40-83%. They are white crystalline compounds, which in the IR spectra have bands at 1655-1665 (CO), 3190-3200 and 3470-3490 (NH_2), and 3335 (NH) cm^{-1}.

Attempts to react amide I with an acetylide by refluxing in butanol or by melting (190-230°C) failed. We failed to realize the acylation of amides IIa-f by means of acetyl chloride or chloroacetyl chloride by carrying out the reaction in acetone, benzene, and pyridine, both in the cold and by heating. This is probably connected with the low basicity of the arylamino group, and also with steric hindrance by the voluminous substituents surrounding the reaction center. Refluxing amide IIa in an excess of Ac_2O gives a mixture of starting material and acylation products.

The experiments have shown that N-acetyl-2-(p-toluidino)-5,6,7,8-tetrahydroquinoline-3-carboxamide is formed in a yield of 70% from N-acetyl-2-(p-toluidino)-3-cyano-5,6,7,8-tetrahydroquinoline under the condition of the Radziszewski reaction.

EXPERIMENTAL CHEMICAL

IR spectra were recorded on a UR-20 spectrometer in paraffin oil. TLC was carried out on Silufol UV-254 plates.

2-Arylamino-5,6,7,8,-tetrahydroquinoline-3-carboxamides (IIa, f). A solution of 2.1 g (0.01 mole) of 2-chloro-5,6,7,8-tetrahydroquinoline-3-carboxamide and 0.01 mole of aryl amine in 50 ml of 50% AcOH was refluxed for 6 h, diluted with water, and neutralized with 10% NaOH. The precipitated base, 2-arylamino-5,6,7,8-tetrahydroquinoline-3-carboxamide, was crystallized from ethanol.

N-acetyl-2-(p-toluidino)-5,6,7,8-tetrahydroquinoline-3-carboxamide (III). A solution of 3.05 g (0.01 mole) of N-acetyl-2-(p-toluidino)-5,6,7,8-tetrahydroquinoline-3-carbonitrile

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TABLE 1. 2-Arylamino-5,6,7,8-tetrahydroquinoline-3-carboxamides

Compound	Yield, %	mp, °C	Found, %			Empirical formula	Calculated, %			R_f***
			C	H	N		C	H	N	
IIa	71	192—4	72,56	6,62	14,99	$C_{17}H_{19}N_3O$	72,61	6,76	14,94	0,91
IIb	40	177—8	72,49	6,50	14,71	$C_{17}H_{19}N_3O$	72,61	6,76	14,94	0,42
IIc	81	165—6	68,37	6,18	14,00	$C_{17}H_{19}N_3O_2$	68,70	6,39	14,15	0,82
IId	40	229—30	68,65	6,11	13,95	$C_{17}H_{19}N_3O_2$	68,70	6,39	14,15	0,70
IIe*	83	210—11	—	—	13,61	$C_{16}H_{16}ClN_3O$	—	—	13,93	0,72
IIf**	47	183—5	—	—	14,01	$C_{16}H_{16}ClN_3O$	—	—	13,93	0,53

*For compound IIe found %: Cl 11.75; calculated %: Cl 11.75.

**For compound IIf found %: Cl 11.99; calculated %: Cl 11.75.

***Solvent system butanol—benzene 1:1.

TABLE 2. Toxicity, Antiinflammatory, and Analgesic Activities of Compounds IIa-f

Compound	Acute toxicity, LD_{50}	Experimental dose	Antiinflammatory activity: increase in the volume of the foot of the rat, % of original	Analgesic activity: duration of the conditional-defense reflex at the peak of action, sec
	mg/kg		after 4 h	
IIa	920 793,1—1067,2	50	82,4±3,6 $P_1<0,01$ $P_2<0,001$	14,5±1,9 $P_1<0,1$ $P_2<0,001$
IIb	1250 1126,1—1387,5	50	113,0±2,9 $P_1<0,5$ $P_2<0,001$	15,0±1,5 $P_1<0,1$ $P_2<0,001$
IIc	2000 1680,6—2380,0	50	116,0±4,2 $P_1<0,05$ $P_2<0,001$	24,0±2,0 $P_1<0,001$ $P_2<0,001$
IId	1200 938,6—1464,0	50	103,6±3,9 $P_1<0,5$ $P_2<0,001$	27,0±2,1 $P_1<0,001$ $P_2<0,002$
		120	—	28,8±1,7 $P_1<0,001$ $P_2<0,002$
IIe	4500 3629—5580,0	50	99,2±3,8 $P_1<0,1$ $P_2<0,001$	23,0±2,3 $P_1<0,001$ $P_2<0,001$
IIf	810 736,4—891,0	50	98,2±5,1 $P_1<0,1$ $P_2<0,001$	17,2±2,9 $P_1<0,25$ $P_2<0,001$
Control (2% starch jelly)	—	—	112,7±4,1	12,1±2,1
Amidopyrine	300,0 272—330	50 100	101,0±2,9 42,0±4,9	14,2±2,1 36,4±4,3

Note. P_1 calculated in comparison with control, P_2 calculated in comparison with amidopyrine at a dose of 100 mg/kg.

in 70 ml of methanol containing 3 g (0.01 mole) of NaOH and 2.04 g (0.02 mole) of 30% H_2O_2 is refluxed for 6 h. The mixture is poured out into 200 ml of water, the precipitate is filtered off, dried, and crystallized from ethanol. A white crystalline compound is obtained; yield 2.1 g (70%), mp 219-221°C. Found %: C 70.33, H 6.62, N 13.08. $C_{19}H_{21}N_3O_2$. Calculated %: C 70.59, H 6.50, N 13.00. IR spectrum (paraffin oil), ν_{max}, cm^{-1}: 1660, 1725 (C=O), 3190, 3490, (NH_2).

EXPERIMENTAL (PHARMALOGICAL)

Compounds IIa-f were tested for the presence of antiinflammatory and analgesic activities. First, the acute toxicity (LD_{50}) of the compounds was determined in white mice weighing 18-22 g by single intraperitoneal administration and observing the deaths of the animals for five days. The antiinflammatory activity was studied in white rats weighing 180-200 g accord-

ing to the model of acute inflammation of the paw, evoked by subplantar injection of 0.1 ml of a 1% aqueous carrageenin solution in the hind paw of the rat. The swelling of the inflamed foot was measured oncometrically up to 4 h after injecting the phlogenic agent [3].

The analgesic activity was studied in white mice weighing 18-20 g with the hot-plate test [5]. The effect was judged 30 min and 1, 1.5, 2, and 3 h after administration. Amidopyrine was used as a reference for comparing the antiinflammatory and analgesic activities. All the compounds under investigation were administered intraperitoneally at a dose of 50 mg/kg, and amidopyrine at doses of 50 and 100 mg/kg, 30 min before testing the analgesic activity, but in the inflammation experiments 1 h before administering carrageenin. The control animals were injected with the same volume of a 2% starch jelly. The results were processed statistically with calculation of the reliability criterion [1].

The results of the experiments are listed in Table 2. Study of the antiinflammatory activity of the compounds revealed the presence of a reliable antiinflammatory activity only in compound IIa, which is inferior to that of amidopyrine.

The compounds investigated have distinct analgesic activity. In experiments with a dose of 50 mg/kg, equal to that of amidopyrine, the compounds investigated either surpass amidopyrine in the expression of the analgesic activity or are equal to it. On comparing with amidopyrine at a dose of 100 mg/kg all the compounds are of inferior activity.

The greatest analgesic activity was found in compound IId; at a dose of 50 mg/kg its activity is 27 ± 2.1 sec. Increasing the dose to 120 mg/kg (1/10 of LD_{50}) led to a small increase in activity. However, also at that dose the preparation is inferior to amidopyrine.

All the compounds are considerably less toxic than amidopyrine. It was found that the acute toxicity of the compounds investigated lies in the range of 810-4500 mg/kg. Consequently, according to the classification of K. K. Sidorov [4] they are of low toxicity (IIa, f) or practically nontoxic (IIb-e).

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