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SYNTHESIS OF 2-METHYLQUINOLINE- AND 2-ARYLAMINO-5,6,7,8-TETRAHYDROQUINOLINE-3-CARBOXYLIC ACID β-DIALKALYLAMINOACETYLHYDRAZIDES AND THEIR BIOLOGICAL ACTIVITY

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Nicotinic acid hydrazides are widely used as medicinal preparations [4]. In recent years hydrazides of cinchoninic and 2,3-polymethylenequinoline-4-carboxylic acids have been obtained, which exhibited various types of physiological activity [3, 5]. In the search for biologically active compounds, previously unknown acylhydrazides of 2-methylquinoline- and 2-arylamino-5,6,7,8-tetrahydroquinoline-3-carboxylic acids were synthesized according to the following scheme:

$$\underset{\text{Ia-d}}{\text{XCONHNH}_2} \xrightarrow{\text{ClCH}_2\text{COCl}} \underset{\text{IIa-d}}{\text{XCONHNHCOCH}_2\text{Cl}} \xrightarrow{\text{HNR}'_2} \underset{\text{IIIa-m}}{\text{XCONHNHCOCH}_2\text{NR}'_2}$$

X=2-methylquinol-3-3 (Ia, IIa, IIIa-c), *n*-RC_6H_4NH-5,6,7,8-tetrahydroquinol-3-yl IIb-d, IIId-m);

R=H (IIId-f), CH_3 (IIb, g-j), CH_3O (IIc, IIIk, l), Br (IId, IIIm); R′=CH_3 (IIId, g, m), C_2H_5 (IIIe, h, k), n.-C_4H_9 (IIIc); NR'_2=piperidino (IIIa, f, i), morpholino (III b, j, l).

The synthesis of the starting hydrazides Ia-d was carried out by boiling the esters of the corresponding acids with hydrazine hydrate.

2-Methylquinoline- and 2-arylamino-5,6,7,8-tetrahydroquinoline-3-carboxylic acid β-chloroacetylhydrazides IIa-d (Table 1) were obtained in yields of 89-100% by the reaction of hydrazides Ia-d with chloroacetyl chloride in glacial acetic acid in the presence of anhydrous sodium acetate. Hydrazides IIa-d are yellow crystalline substances which are soluble in toluene, ethanol, and acetic acid. In their IR spectra there are bands at 1660-1700 (CO) and 3190-3400 cm^{-1} (NH). On heating compounds IIa-d with dialkyl amines in a benzene or dioxane medium, 2-methylquinoline- and 2-arylamino-5,6,7,8-tetrahydroquinoline-3-carboxylic acid β-dialkylaminoacetylhydrazides (IIIa-m) are formed. Peaks are observed in the IR spectra of these compounds at 1640-1650 and 1680-1700 (CO) and 3240-3400 cm^{-1} (NH).

EXPERIMENTAL (CHEMICAL)

The IR spectra were run on a UR-20 spectrophotometer in mineral oil. The data of the elemental analysis correspond to the calculated values.

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TABLE 1. Characteristics of Synthesized Compounds

Compound	Yield, %	mp, °C	Empirical formula
Ia	88	207—208	$C_{11}H_{11}N_3O$
IIa	100	223—224	$C_{13}H_{12}ClN_3O_2$
IIb	84	228—230	$C_{19}H_{21}ClN_4O_2$
IIc	86	188—190	$C_{19}H_{21}ClN_4O_3$
IId	89	247—249	$C_{18}H_{18}BrClN_4O_2$
IIIa	57	159—161	$C_{18}H_{22}N_4O_2$
IIIb	56	168—170	$C_{17}H_{20}N_4O_3$
IIIc	40	74—76	$C_{21}H_{30}N_4O_2$
IIId	53	169—171	$C_{20}H_{25}N_5O_2$
IIIe	62	134—136	$C_{22}H_{29}N_5O_2$
IIIf	60	270—272	$C_{23}H_{29}N_5O_2$
IIIg	70	145—147	$C_{21}H_{27}N_5O_2$
IIIh	59	136—138	$C_{23}H_{31}N_5O_2$
IIIi	48	205—207	$C_{24}H_{31}N_5O_2$
IIIj	54	195—197	$C_{24}H_{29}N_5O_3$
IIIk	44	146—148	$C_{23}H_{21}N_5O_3$
IIIl	46	182—184	$C_{23}H_{29}N_5O_4$
IIIm	57	120—122	$C_{20}H_{24}BrN_5O_2$

TABLE 2. Evaluation of Antidepressant Activity of Compounds IIIa-f

Compound	Acute toxicity, LD_{50}	Duration of "Immobilization" (in the first 6 min)	Duration of the hexenal-induced narcosis, min	Orientational reaction	Motive activity
IIIa	815 (567—1110)	212,7	113,5	27,7 (±13,0)	34,9 (±20,9)
IIIb	1780 (1355—2299)	191,6	131,6	22,9 (±8,3)	24,8 (±8,9)
IIIc	1410 (914—2094)	152,5	95,6	20,9 (±8,6)	29,5 (±14,2)
IIIId	—	192,0	—	—	—
IIIe	—	179,1	—	—	—
IIIf	—	205,0	—	—	—
Amitriptiline	76,0	155,5±39,2	213,0	25,1	29,8
Hexenal (control)	—	—	50,2	—	—
2% starch mucilage	—	203,4±17,6	—	34,2 (±6,2)	36,3 (±6,7)

2-Methylquinoline-3-carboxylic Acid Hydrazide (Ia). A mixture of 2.1 g (0.01 mole) of ethyl 2-methylquinoline-3-carboxylate [9] and 5 ml of hydrazine hydrate was heated for 4 h. It was then cooled, and the precipitate that separated out was filtered off and recrystallized from ethanol.

2-Arylamino-5,6,7,8-tetrahydroquinoline-3-carboxylic acid hydrazides Ib-d were described in [2].

2-Methylquinoline- and 2-Arylamino-5,6,7,8-tetrahydroquinoline-3-carboxylic Acid β-Chloroacetylhydrazides (IIa-d). A 1.1 g portion (0.01 mole) of chloroacetyl chloride was added gradually to a solution of 0.01 mole of hydrazides Ia-d and 0.82 g (0.01 mole) of anhydrous sodium acetate in 20 ml of glacial acetic acid, the mixture was heated at 40-50°C for 2 h, and was then allowed to stand overnight. It was then diluted with water and neutralized with a sodium bicarbonate solution. The precipitate that separated out was filtered off and recrystallized from dioxane.

2-Methylquinoline- and 2-Arylamino-5,6,7,8-tetrahydroquinoline-3-carboxylic Acid β-Dialkylaminoacetylhydrazides (IIIa-m). A 0.03 mole portion of a dialkylamine was added to a solution of 0.01 mole of compounds IIa-d in 20 ml of dioxane and the mixture was heated at 100°C for 4 h. It was then cooled and poured into a sodium bicarbonate solution (pH 8.5); the volatile impurities were removed by steam-distillation; the precipitate was filtered off and recrystallized.

EXPERIMENTAL (BIOLOGICAL)

Compounds IIIa-m were tested for evidence of antidepressant, anti-inflammatory, and analgetic activity. First, the acute toxicity (LD_{50}) of the compounds IIIa-c was determined on white mice, each weighing 20-24 g, with a single intraperitoneal adminstration in a 2% starch mucilage. The death of the animals was recorded within 24 h. The data obtained were processed by a rapid method [6], with calculation of the LD_{50} at $p = 0.05$.

TABLE 3. Anti-Inflammatory and Analgetic Activity of Compounds IIId-m

Compound	Anti-inflammatory activity		Analgetic activity, time of defensive reflex, sec
	paw vol. increment., % of init. vol.	edema inhibition %, compared to control	
IIId	78.6	30.3	20.0
IIIe	72.7	35.5	16.1
IIIf	66.5	41.0	19.4
IIIg	123.6	Inactive	19.0
IIIh	111.1	»	15.6
IIIi	115.0	»	18.0
IIIj	98.4	»	20.1
IIIk	148.9	»	14.8
IIIl	108.5	»	13.2
IIIm	116.9	»	16.1
Amidopyrine	42.0	62.7	27.6
2% starch mucilage (control)	112.7		11.2

To evaluate the antidepressant activity of compounds IIIa-f, the swimming test [7] was used. The experiments were carried out on male white mice, each weighing 20-25 g, using the antidepresant amitriptiline as a standard. The compounds studied and amitriptiline were administered intraperitoneally in equal doses – 10 mg/kg [7], in the form of a suspension in 2% starch mucilage, 30 min before testing. The mice swam in a 25 × 25 × 12 cm glass jar with a 15 cm high layer of water, at a water temperature of 22-25°C. An indicator for the presence of an antidepressant action of a compound was the decrease in the "immobilization" time of the swimming mice in the first 6 min of residence in the water.

The influence of compounds IIIa-c on the duration of the hexenal-induced narcosis was studied. The compounds tested were used in a dose of 1/10 of LD_{50}, and were administered to the mice intraperitoneally 30 min before the introduction of hexenal in a dose of 70 mg/kg. The activity was evaluated from the "resting on the side" test [1], compared with animals which received hexenal only. The influence of compounds IIIa-c on the motive activity and the orientational reaction was also studied. The compounds studied were administered to the mice intraperitoneally 60 min before testing in a dose of 1/100 of LD_{50} and amitriptiline – in a dose of 10 mg/kg. A 2% starch mucilage served as the control. In the tests, the number of squares traveled through by the animals in the course of 3 min, characterizing the motive activity and the number of the inspected holes characterizing the orientational reaction were recorded [10]. The experimental results are given in Table 2.

Compounds IIId-m were investigated for evidence of analgetic and anti-inflammatory activity (Table 3). As a standard for comparing the analgetic and anti-inflammatory activity of the compounds amidopyrine was used. All the compounds studied were administered intraperitoneally in a dose of 50 mg/kg, and amidopyrine in a dose of 100 mg/kg 30 min before testing the analgetic action, and in the experiment with inflammation – 1 h before introducing carragheenin. The analgetic activity was studied on white mice of both sexes, each weighing 16-18 g, by the "hot plate" test [11], and the anti-inflammatory action – on nonpedigree white rats of both sexes, each weighing 160-200 g, on a carragheenin model of inflammation [8]. The anti-inflammatory action was indicated from the increment in the volume of the paw in percent compared with the initial volume and from the inhibition of the growth of edema, compared with control.

The evaluation of the antidepressant activity of the compounds showed that compound IIIc has antidepressant activity, which in its degree of intensity is similar to that of amitriptiline, while being considerably less toxic than the latter. Compound IIIc also prolongs hexenal-induced narcosis, inappreciably influences the change in the motive activity, and supresses the orientational reaction.

2-Anilino-5,6,7,8-tetrahydroquinoline-3-carboxylic acid β-dialkylaminoacetylhydrazides IIId-f displayed the strongest anti-inflammatory activity, which increases in the series of compounds IIId > IIIe > IIIf. Introduction of substituents into the para-position of the arylamino fragment leads to a loss of activity. Compounds IIId-f had no analgetic activity.

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IMIDAZOLE DERIVATIVES. XXVI. SYNTHESIS OF IMIDAZOLE-2-CARBOXALDEHYDE DERIVATIVES AND THEIR ANTITUMORIGENIC, MUTAGENIC AND ANTIMUTAGENIC ACTION

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Hydrazine derivatives have drawn the attention of research workers as potential cytostatic agents. The antitumorigenic properties of methyl-, dimethyl, arylsulfonylhydrazones of aromatic and heterocyclic carboxaldehydes [6, 13, 18, 19], of isatine- and 2-formylpyridine hydrazones [8, 15] and of certain azines [9, 16] were investigated. Thiosemicarbazone derivatives were particularly investigated [7, 11, 12]. The search in this direction led to the obtaining of effective antitumorigenic preparations (natulan, bisanthrene, GP-48989, 1-riboxyl) [14].

From imidazole-2-carboxaldehyde (I) containing a methyl, benzyl and 4-methoxy-3-nitrobenzyl substituents at the 1-position, dimethylhydrazones (II), dimethylhydrazones hydrochlorides (III), thiocarbonohydrazones (IV), thiosemicarbazones (V), hydrazones (VI) and azines (VII) were synthesized.

$$H_2NNHC(=S)NHN=CHX\ (IVa\text{-}c)$$

$$H_2NN=CHX \leftarrow O=CHX \rightarrow (CH_3)_2NN=CHX\ (IIa\text{-}c)$$

(VIb,c) (Ia-c)

$$H_2NC(=S)NHN=CHX\ (Va\text{-}c)$$

$$O=C(CH_3)C_6H_3OC_5H_{11}\text{-}4\text{-}NO_2\text{-}3\ (VIII)$$

$$XCH=NN=C(CH_3)C_6H_3OC_5H_{11}\text{-}4\text{-}NO_2\text{-}3\ (VIIb,c)$$

$$+\ (\text{from VIb})\ [3\text{-}NO_2\text{-}4\text{-}C_5H_{11}OC_6H_3C(CH_3)=N-]_2\ (IX)$$

$$[X-CH=N-]_2\ (X)$$

X = 1-R-imidazol-2-yl, where R = CH_3 (a), $CH_2C_6H_5$ (b), $CH_2C_6H_3OCH_3\text{-}4\text{-}NO_2\text{-}3$.

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