SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF 2-ARYLIDENE- AND 2-(5-NITROFURFURYLIDENE)HYDRAZIDES OF 2-CHLORO- AND 2-ARYLAMINO-5,6-TRIMETHYLENE AND 5,6-TETRAMETHYLENEISONICOTINIC ACIDS

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Previously we reported on the synthesis and characterization of a series of isopropylamides of 2-arylamino-5,6,7,8-tetrahydroquinoline-4-carboxylic acids, which showed antiinflammatory and analgesic activity [1]. Another active compound of this class is 5,6,7,8-tetrahydroquinoline-4-carboxylic acid hydrazide, known to possess antitubercu-lous properties [2].

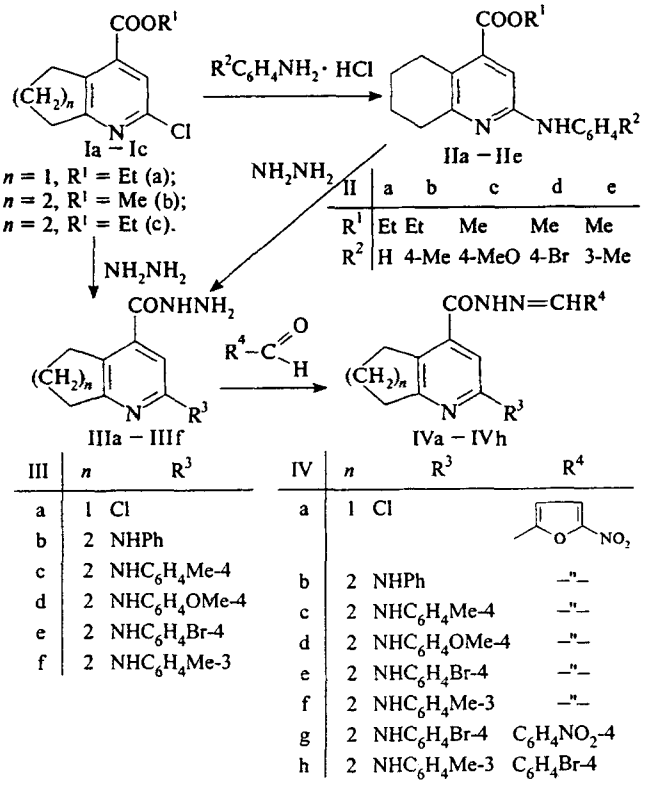
The purpose of this work was to search for compounds possessing antibacterial activity among arylidene- and 5-nitrofurfurylidenehydrazides of 2-chloro- and 2-arylamino-5,6-tri(tetra)methyleneisonicotinic acids

The initial compounds were methyl ester [2] and ethyl esters (Ia – Ic) obtained by successive reactions of 5,6-trimethylene and 5,6-tetramethylene-2-hydroxyisonicotinic acids with phosphorus pentachloride and the corresponding alcohol.

The previous investigation showed that halogen atoms in the esters Ib were not subject to nucleophilic displacement by arylamino groups during 4 – 17 h of boiling in DMF (we reported on a low mobility of 2-chloro-5,6,7,8-tetrahydroquinoline-4-carboxylic acid isopropylamides) [1]. The reaction was conducted only by boiling these esters with arylamine hydrochlorides in anhnydrous butalol for 12 h, leading to a 56 – 95% yield of 2-arylamino-5,6,7,8-tetrahydroquinoline-4-carboxylic acid esters (IIa – IIe).

Interaction of esters Ia and IIa – IIe with hydrazine hydrate led to hydrazides IIIa – IIIf. The latter readily enter into reaction with aromatic aldehydes and 5-nitrofurfurol to yield arylidene- and 5-nitrofurfurylidenehydrazides of 2-chloro- and 2-arylamino-5,6-trimethylene and 5,6-tetramethyleneisonicotinic acids (IVa – IVh). Compounds IIIa – IIIf appear as colorless crystals and compounds IVa – IVh are yellow crystalline substances, both soluble in DMF and acetic acid.

Physicochemical characteristics of the synthesized compounds are presented in Table 1. The proposed structures are confirmed by data of the ^{1}H NMR and IR absorption measurements (see the experimental part).



EXPERIMENTAL CHEMICAL PART

The IR absorption spectra were recorded on an UR-20 spectrophotometer using samples prepared as nujol mulls. The ^{1}H NMR spectra were measured on an RS-60 spectrometer using samples prepared as 5% solutions in DMSO-d_6, with HMDS as the internal standard. TLC was performed on Silufol UV-254 plates eluted in a butanol – benzene (1 : 1) system. The data of elemental analyses correspond to the values calculated by empirical formulas.

5,6-Trimethylene and 5,6-tetramethylene-2-chloroisonicotinic acid esters (Ia – Ic). A mixture of 0.01 mole of 5,6-tri(tetra)methylene-2-chloroisonicotinic acid and 4.17 g

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(0.02 mole) of phosphorus pentachloride was boiled for 2 h, after which phosphorus oxychloride and residual phosphorus pentachloride were distilled off in vacuum. The resulting 5,6-tri(tetra)methylene-2-chloroisonicotinic acid chloroanhydride was dissolved in 20 ml of dry benzene. To this solution was gradually added 20 ml of methyl or ethyl alcohol, and the mixture was heated to 50°C for 1 h. Then the solvent was distilled off, the residue dissolved in benzene, and the solution passed through a column filled with aluminum oxide. Finally, the target compound was crystallized from hexane. IR spectrum (ν, cm^{-1}): 1740–1750 (CO); ^1H NMR spectrum of compound Ic (δ, ppm): 1.36 (t, 3H, CH_3), 1.56–1.90 (m, 4H, 6-CH_2, 7-CH_2), 2.61–2.96 (m, 4H, 5-CH_2, 8-CH_2), 4.0–4.50 (m, 2H, CH_2CH_3), 7.43 (s, 1H, β-pyrid.).

2-Arylamino-5,6,7,8-tetrahydroquinoline-4-carboxylic acid esters (IIa–IIe). To a solution of 0.01 mole of ester Ib in 20 ml of anhydrous butanol was added an equimolar amount of the corresponding arylamine hydrochloride, and the mixture was boiled for 12 h. Then the solvent was distilled off, the residue treated with water, and the aqueous solution was decanted and neutralized with 10% aqueous sodium hydroxide. The resulting precipitate was filtered and crystallized from hexane. IR spectrum (ν, cm^{-1}): 1715–1720 (CO), 3230–3240 (NH); ^1H NMR spectrum of compounds IIa, IIc, and IIe (δ, ppm): 1.46–1.93 (m, 4H, 6-CH_2, 7-CH_2), 2.53–2.93 (m, 4H, 5-CH_2, 8-CH_2), 6.73–6.96 (s, 1H, β-pyrid.), 6.96–7.80 (m, H_{arom}), 8.83–9.10 (s, 1H, NH); in addition, for IIa: 1.19 (s, 3H, CH_3), 4.03–4.46 (m, 2H, OCH_2CH_3); for IIc and IIe: 3.70–3.80 (s, 3H, CH_3).

TABLE 1. Physicochemical Characteristics of Synthesized Compounds

Compound	Yield, %	M.p., °C	R_f	Empirical formula
Ia	54	56–58	...	$C_{12}H_{14}ClNO_2$
Ib	40	57–59	...	$C_{11}H_{12}ClNO_2$
Ic	41	48–51	...	$C_{12}H_{14}ClNO_2$
IIa	56	74–75	0.83	$C_{18}H_{20}N_2O_2$
IIb	95	97–99	0.88	$C_{19}H_{22}N_2O_2$
IIc	60	82–84	0.81	$C_{18}H_{20}N_2O_3$
IId	84	112–114	0.06	$C_{17}H_{17}BrN_2O_2$
IIe	90	89–91	0.92	$C_{18}H_{20}N_2O_2$
IIIa	32	95–97	0.11	$C_9H_{10}ClN_3O$
IIIb	81	161–163	0.47	$C_{16}H_{18}N_4O$
IIIc	64	209–211	0.55	$C_{17}H_{20}N_4O$
IIId	48	162–164	0.59	$C_{17}H_{20}N_4O_2$
IIIe	74	215–217	0.52	$C_{16}H_{17}BrN_4O$
IIIf	67	223–225	0.53	$C_{17}H_{20}N_4O$
IVa	55	219–220	...	$C_{14}H_{11}ClN_4O_4$
IVb	55	236–237	0.88	$C_{21}H_{19}N_5O_4$
IVc	50	204–205	0.84	$C_{21}H_{21}N_5O_4$
IVd	43	241–242	0.78	$C_{22}H_{21}N_5O_5$
IVe	24	256–257	0.89	$C_{21}H_{18}BrN_5O_4$
IVf	23	233–234	0.93	$C_{22}H_{21}N_5O_4$
IVg	78	292–294	...	$C_{23}H_{20}BrN_5O_5$
IVh	91	243–245	...	$C_{24}H_{23}BrN_4O$

2-Chloro- and 2-arylamino-5,6-tri(tetra)methyleneisonicotinic acid hydrazides (IIIa–IIIf). To a solution of 0.01 mole of ester Ia or IIa–IIe in 30 ml of ethyl alcohol was added a 1.5-fold excess of hydrazine hydrate, and the mixture was boiled for 5 h. Then the reaction mixture was cooled and poured into cold water. The precipitate was separated by filtration, washed with hot water to a neutral pH, dried, and crystallized from ethanol. IR spectrum (ν, cm^{-1}): 1660–1665 (CO), 3190–3320 (NH and NH_2); ^1H NMR spectrum of compounds IIIb–IIIf (δ, ppm): 1.36–1.91 (m, 4H, 6-CH_2, 7-CH_2), 2.28–2.96 (m, 4H, 5-CH_2, 8-CH_2), 4.36–4.41 (bs, 2H, NH_2), 8.60–8.86 (s, 1H, NH), 9.30–9.50 (t, 1H, $NH_{hydrazide}$).

2-Chloro- and 2-arylamino-5,6-tri(tetra)methyleneisonicotinic acid 5-nitrofurfurylidenehydrazides (IVa–IVf). To a solution of 0.001 mole of hydrazide IIIa–IIIf in 5 ml of glacial acetic acid was added an equimolar amount of 5-nitrofurfurol and the reaction mixture was allowed to stand at 20°C for 24 h. Then the mixture was cooled and the precipitate was filtered, dried, and crystallized from butanol. IR spectrum (ν, cm^{-1}): 1640–1650 (CO), 3215–3225, 3370–3380 (NH); ^1H NMR spectrum of compounds IVd and IVf (δ, ppm): 1.46–1.83 (m, 4H, 6-CH_2, 7-CH_2), 2.26–2.80 (m, 4H, 5-CH_2, 8-CH_2), 2.16 (3.62 for IVd) (s, 3H, CH_3), 6.33–7.26 (m, 1H, H_{arom}), 7.30–7.37 (s, 1H, =CH), 8.73–8.90 (s, 1H, NH).[2]

2-Arylamino-5,6,7,8-tetrahydroquinoline-4-carboxylic acid arylidenehydrazides (IVg, IVh). To a solution of 0.001 mole of hydrazide IIIe or IIIf in 10 ml of ethanol was added an equimolar amount of the corresponding aromatic aldehyde and 2–3 drops of piperidine. The mixture was boiled for 4 h, cooled, and poured into cold water. The precipitate was separated by filtration, dried, and crystallized from ethanol.

EXPERIMENTAL BIOLOGICAL PART

Compounds IVa–IVh were tested for bacteriostatic activity using the conventional method of serial dilutions [3].

It was established that compounds IVb and IVe–IVh possess weak bacteriostatic properties. The *p*-toluidine derivative IVc and *p*-anisidine derivative IVd showed antibacterial activity with respect to both *E. coli* and *St. aureus* strains (MIC = 250 and 125 μg/ml, respectively). Substitution of chlorine atoms for the arylamino fragments in position 2 noticeably increased the antibacterial activity (for compound IVa, MIC = 7.8 μg/ml).

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[2] A multiplet due to aromatic protons includes the signals from proton of the pyridine cycle, two furan protons, and proton of the amino group.