SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 1-ARYL-2-METHYL- AND 1-ARYL-2-VINYL-4,6,7,8-TETRAHYDRO-1H-PYRIMIDO[4,5-b]PYRINDIN-4-ONES

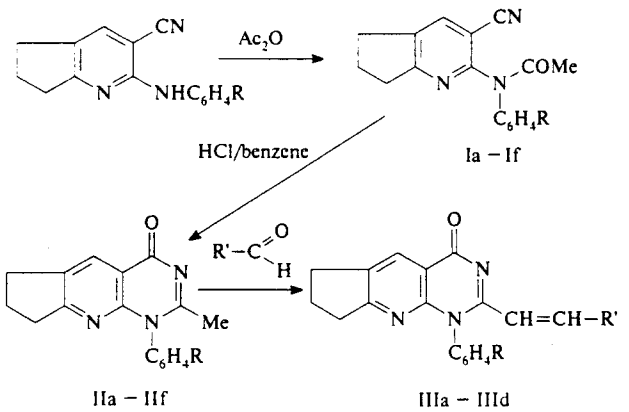
R. N. Galeeva,[1] M. Yu. Gavrilov,[1] É. V. Voronina,[1] and M. E. Konshin[1]

Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 30, No. 11, pp. 37 – 38, November, 1996.

Original article submitted March 26, 1996.

Previously we reported on the synthesis of 1-aryl-1,4-dihydropyrido[2,3-d]pyrimidin-4-ones, their 7-methyl and 5,6-dimethyl derivatives, and 1-aryl-2-methyl-1,4,6,7,8,9-hexahydropyrimido[4,5-b]quinolin-4-ones, which possess analgesic and antiinflammatory activity [1 – 5]. In this work, we have synthesized 1-aryl-2-methyl(vinyl)-4,6,7,8-tetrahydro-1H-pyrimido[4,5-b]pyrindin-4-ones in order to study the antimicrobial properties of pyrido[2,3-d]pyrimidine derivatives.

The initial reagents for the synthesis of these compounds are represented by 2-(N-acetyl-N-aryl)amino-3-cyano-6,7-dihydro-5H-pyrindines (Ia – If) obtained by acylation of 2-arylamino-3-cyano-6,7-dihydro-5H-pyrindines with acetic anhydride (Table 1).



Ia, IIa: R = H;
Ib, IIb: R = 4-Me;
Ic, IIc: R = 4-OMe;
Id, IId: R = 4-Br;
Ie, IIe: R = 3-Me;
If, IIf: R = 3-Cl;
IIIa: R = H, R′ = Ph;
IIIb: R = H, R′ = 4-BrC_6H_4;
IIIc: R = 4-Me, R′ = 5-nitrofuryl-2;
IIId: R = 4-OMe, R′ = 5-nitrofuryl-2.

[1] State Pharmaceutical Academy, Perm, Russia.

On bubbling dry hydrogen chloride through the solutions of Ia – If in anhydrous benzene, these compounds exhibit cyclization with the formation of 1-aryl-2-methyl-4,6,7,8-tetrahydro-1H-pyrimido[4,5-b]pyrindin-4-ones (IIa – IIf).

Compounds IIa – IIf interact with aromatic aldehydes and 5-nitrofurfural. Note that the condensation involves the methyl group in position 2, possessing a considerable CH-acidity, rather than the methylene group in position 8. This reaction leads to the formation of 1-aryl-2-styryl-(4-nitrofurylvinyl)-4,6,7,8-tetrahydro-1H-pyrimido[4,5-b]pyrindin-4-ones (IIIa – IIId). Attempts at benzaldehyde condensation with 2-phenylamino-3-cyano-6,7-dihydro-5H-pyrindine by 4-h heating (130°C) in acetic anhydride only led to N-acetylation with the formation of compound Ia. Interaction of compound IIa with a twofold excess of benzaldehyde under similar rigid conditions (8 h, 130°C) only led to 1-phenyl-2-styryl-4,6,7,8-tetrahydro-1H-pyrimido[4,5-b]pyrindin-4-one (IIIa). The structures of the synthesized compounds were confirmed by IR and ^{1}H NMR spectroscopic data (Table 2).

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 obtained at 20°C with the RS-60 and Tesla BS-587A (80.023 MHz) spectrometers. The measurements were performed using 5% solutions in DMSO-d_6 and $CDCl_3$, 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 corresponded to the calculated values. The yields and melting temperatures of the synthesized compounds are summarized in Table 1.

2-(N-Acetyl-N-arylamino)-3-cyano-6,7-dihydro-5H-pyrindines (Ia – If). A mixture of 0.01 mole of 2-arylamino-3-cyano-6,7-dihydro-5H-pyrindine with 15 ml of acetic anhydride and 15 ml dry pyridine was boiled for 6 h. Then the reaction mass was poured into water, and the residue separated by filtration and crystallized from ethanol. IR spectrum (ν_{max},

TABLE 1. Yields and Characteristics of Synthesized Compounds

Compound	Yield, %	M.p., °C	R_f	Empirical formula
Ia	75	100 – 102	—	$C_{17}H_{15}N_3O$
Ib	69	133 – 135	—	$C_{18}H_{17}N_3O$
Ic	65	58 – 60	—	$C_{18}H_{17}N_3O_2$
Id	72	108 – 110	—	$C_{17}H_{14}BrN_3O$
Ie	77	96 – 98	—	$C_{18}H_{17}N_3O$
If	82	65 – 67	—	$C_{17}H_{14}ClN_3O$
IIa	75	230 – 232	4.8	$C_{17}H_{15}N_3O$
IIb	54	249 – 251	5.9	$C_{18}H_{17}N_3O$
IIc	53	198 – 200	5.3	$C_{18}H_{17}N_3O_2$
IId	40	215 – 21	5.1	$C_{17}H_{14}BrN_3O$
IIe	74	200 – 202	6.0	$C_{18}H_{17}N_3O$
IIf	52	196 – 198	5.5	$C_{17}H_{14}ClN_3O$
IIIa	54	284 – 286	7.9	$C_{24}H_{19}N_3O$
IIIb	58	238 – 240	8.2	$C_{24}H_{18}BrN_3O$
IIIc	73	260 – 262 (p)	5.4	$C_{23}H_{18}N_4O_4$
IIId	91	265 – 266 (p)	4.6	$C_{23}H_{18}N_4O_5$

TABLE 2. Parameters of the ^{1}H NMR Spectra of Compounds II and III

Compound	Chemical shift, δ, ppm					
	m, $HC^{6.8}$	m, HC^7	d, HC=	s, CH_3	m, H_{arom}	s, HC^5
IIa	2.67 – 3.21	1.77 – 2.08	—	2.14	7.53 – 8.01	8.45
IIb	2.74 – 3.19	1.84 – 2.09	—	2.15	7.29 – 7.74	8.43
IIc	2.77 – 3.33	2.11 – 2.36	—	2.50	7.33 – 7.95	8.84
IId	2.84 – 3.36	1.94 – 2.29	—	2.46	7.53 – 8.02	8.50
IIe	2.71 – 3.32	1.95 – 2.33	—	2.43	7.39 – 7.88	8.81
IIf	2.70 – 3.22	1.88 – 2.12	—	2.19	7.63 – 8.05	8.51
IIIa	2.75 – 3.12	1.96 – 2.30	6.37, 8.25	—	7.22 – 7.72	8.42
IIIb	2.62 – 3.07	1.90 – 2.19	6.35, 7.89	—	7.17 – 7.62	8.20
IIIc	2.67 – 3.12	1.92 – 2.15	6.40, 7.89	1.90	7.45 – 7.75	8.21
			7.20, 7.75			
IIId	2.70 – 3.15	1.94 – 2.13	6.42, 7.90	3.60	7.50 – 7.86	8.32
			7.20, 7.65			

cm^{-1}): 1600 – 1610 (CO), 2240 – 2245 (CN); ^{1}H NMR spectrum, $CDCl_3$ (δ, ppm): 1.26 – 1.30 (s, 3H, CH_3CO), 2.12 – 2.16 (m, 2H, C^6H_2), 2.98 – 3.02 (m, 4H, C^5H_2 and C^7H_2), 7.40 – 7.46 (m, arom. H), 7.89 – 8.46 (1H, C^4H).

1-Aryl-2-methyl-4,6,7,8-tetrahydro-1H-pyrimido[4,5-b]-pyrindin-4-ones (IIa – IIf). A solution of 0.01 mole of compound Ia – If in 40 ml of anhydrous benzene was bubbled for 3 h with dry hydrogen chloride. The precipitate was filtered, treated with an aqueous sodium acetate solution, and crystallized from ethanol to obtain the corresponding compound IIa – IIf. IR spectrum (ν_{max}, cm^{-1}): 1645 – 1655 (CO).

1-Phenyl-2-(2-arylvinyl)-4,6,7,8-tetrahydro-1H-pyrimido[4,5-b]-pyrindin-4-ones (IIIa, IIIb). A solution of 0.01 mole of compound IIa and 0.02 mole of an aromatic aldehyde in 40 ml of ethanol with 0.1 ml piperidine was boiled for 12 h. Then the excess aldehyde was distilled off with water vapors, the residue filtered and crystallized from ethyl acetate.

1-Aryl-2-[2-(5-nitrofuryl)-2-vinyl]-4,6,7,8-tetrahydro-1H-pyrimido[4,5-b]pyrindin-4-ones (IIIc, IIId). A solution containing equimolar amounts (0.01 mole) of compound IIb or IIc and 5-nitrofurfural in glacial acetic acid was boiled for 5 min and cooled. The precipitate was filtered and crystallized from acetic acid. IR spectrum (ν, cm^{-1}): 1650 – 1670 (CO).

EXPERIMENTAL BIOLOGICAL PART

Compounds IIIa – IIId were tested for bacteriostatic activity by the method of serial dilutions [6].

TABLE 3. Bacteriostatic Activity of Compounds IIIa – IIId

Compound	*St. aureus*		*E. coli*	
	Dilution	MIC, μg/ml	Dilution	MIC, μg/ml
IIIa	1 : 1000	1000	1 : 1000	1000
IIIb	1 : 1000	1000	1 : 1000	1000
IIIc	1 : 8000	125	1 : 128,000	7.8
IIId	1 : 32,000	31	1 : 8000	125

The experimental results showed that compounds IIIa and IIIb, having styryl and *p*-bromostyryl radicals, possessed weak activity with respect to both *St. aureus* and *E. coli* (Table 3). Replacement of the styryl group in position 2 by the 5-nutrofurylvinyl fragment (compounds IIIc and IIId) leads to a considerable increase in the antimicrobial activity, whereby the MIC value changed from 1000 μg/ml to 7.8 – 125 μg/ml. This result indicates the significant role of the 5-nitrofuryl residue in the antimicrobial activity of the series of compounds studied.

REFERENCES

1. L. M. Demina, M. Yu. Gavrilov, V. É. Kolla, et al., *Khim.-Farm. Zh.*, **26**(3), 45 – 48 (1992).
2. Jpn. Patent No. 7552092; *Chem. Abstr.*, **83**, 206318 (1975).
3. Jpn. Patent No. 7549699; *Chem. Abstr.*, **85**, 21422 (1976).
4. Jpn. Patent No. 7707993; *Chem. Abstr.*, **87**, 68419 (1977).
5. P. I. Shramm and M. E. Konshin, *Khim. Geterotsikl. Soedin.*, No. 1, 114 – 116 (1985).
6. G. N. Pershin, *Methods of Experimental Chemotherapy* [in Russian], Moscow (1959), pp. 109 – 111, 456 – 460.