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4-ARYL-5-(PYRIMIDIN-2′-YL)-1,4-DIHYDROPYRIDINES, -1,4-DI- AND -1,2,3,4-TETRAHYDROPYRIMIDINES

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2-Acetonylpyrimidines readily undergo the Hantzsch–Biginelli cyclocondensation. This method was used to obtain derivatives of 1,4-dihydropyridine and 1,4-di- and 1,2,3,4-tetrahydropyrimidines, containing the pyrimidine fragment in the 5 position of the heterocycle.

The increased interest in hydrogenated derivatives of pyridine and pyrimidine is due to their high biological activity [1, 2]. In particular, derivatives of 4-aryl-1,4-dihydropyridine and -1,4-di- and -1,2,3,4-tetrahydropyrimidines possess the properties of modulators of calcium-ion transport through cell membranes [3-6]. Detailed studies of the methods of synthesis of these compounds have been made, methods that make it possible to introduce substituents of different electronic nature into the 5 position of the heterocyclic fragment [7-9], as this has an appreciable effect on their pharmacological properties [10]. For purposes of possible therapeutic application, 4-aryl-1,4-dihydropyridines were synthesized that at $C_{(5)}$ contain a heterocyclic substituent as a hidden ester group (derivatives of oxazoline, oxa(thia)diazole tetrazole, and oxazine) [11-14]. At the same time, the literature contains no data on 4-aryl-5-hetaryl-1,4-di- and -1,2,3,4-tetrahydropyrimidines.

Earlier, in a study of the reactivity of acetonyl anionic sigma-complexes of 5-nitropyrimidine, we obtained 2-acetonyl-4,6-dimethoxy-5-nitro-(Ia)- and -5-methylpyrimidines (Ib) [15, 16]. In the present work, these compounds were used in different variants by means of the Hantzsch–Biginelli cyclocondensation to obtain derivatives of 4-aryl-1,4-dihydropyridine and -1,4-di- and -1,2,3,4-tetrahydropyrimidines, containing the pyrimidine fragment in the 5 position of the heterocyclic group.

In the reaction of 2-acetonylpyrimidines Ia, b with aromatic aldehydes IIa-d and urea in boiling ethanol in the presence of a catalytic amount of conc. HCl, we obtained 4-aryl-6-methyl-5-(pyrimidin-2′-yl)-2-oxo-1,2,3,4-tetrahydropyrimidines IIIa-h. In the PMR spectra of these compounds (Table 1), the doublet in the 5.55-6.21-ppm range corresponds to the geminal proton at the $C_{(4)}$ tetrahydropyrimidine ring and permits one to assign the signals of NH protons. The bathochromic shift of the long-wavelength absorption band in the UV spectra of compounds IIIa-h (see Table 1), in comparison with 4-aryl-6-methyl-2-oxo-5-alkoxycarbonyl- [17] and -5-nitrotetrahydropyrimidines [18], is explained by an enlargement of the chromophore due to the introduction of the pyrimidine fragment into the 5 position of the heterocycle.

As the starting material for the synthesis of 2-substituted 1,4-dihydropyrimidines we used 1-(3′-nitrobenzylidene)-1-(5′-nitro-4′,6′-dimethoxypyrimidine-2′-yl)-2-propanone (IV), obtained from acetonylpyrimidine Ia and 3-nitrobenzaldehyde (IIa) under Knovenagel-condensation conditions. Boiling of equimolar amounts of IV and O-methylisourea or benzamidine in benzene in the presence of a 10-fold excess of activated alumina gave 2-methoxy- (VIa) and 2-phenyl-1,4-dihydropyrimidines (VIb), respectively. The double set of signals in the PMR spectrum of compounds VIa (Table 1) can be explained by the fact that this compound exists as a mixture of two tautomeric forms. The signal of the geminal proton in the 4 position of the pyrimidine ring is manifested as a singlet at 6.18 ppm and corresponds to the 1,4-dihydropyrimidine form, whereas the doublet at 5.98 ppm with a spin–spin coupling constant of 2.6 Hz belongs to the 3,4-dihydropyrimidine form. The ratio of 1,4 to 3,4 tautomers for this compound is 4:1. At the same time, compound VIb exists exclusively in the 1,4-dihydropyrimidine form, this being due to the steric influence of the phenyl substituents. The position of the long-wavelength absorption band in the electronic spectra of compounds VIa, b (Table 1) corresponds to the previously described dihydropyrimidines [15, 19, 20]. In addition, 1,4-dihydropyrimidines VIa, b are dehydrogenated to the corresponding pyrimidines VIIa, b by the action of 2,3-dichloro-5,6-dicynanobenzoquinone.

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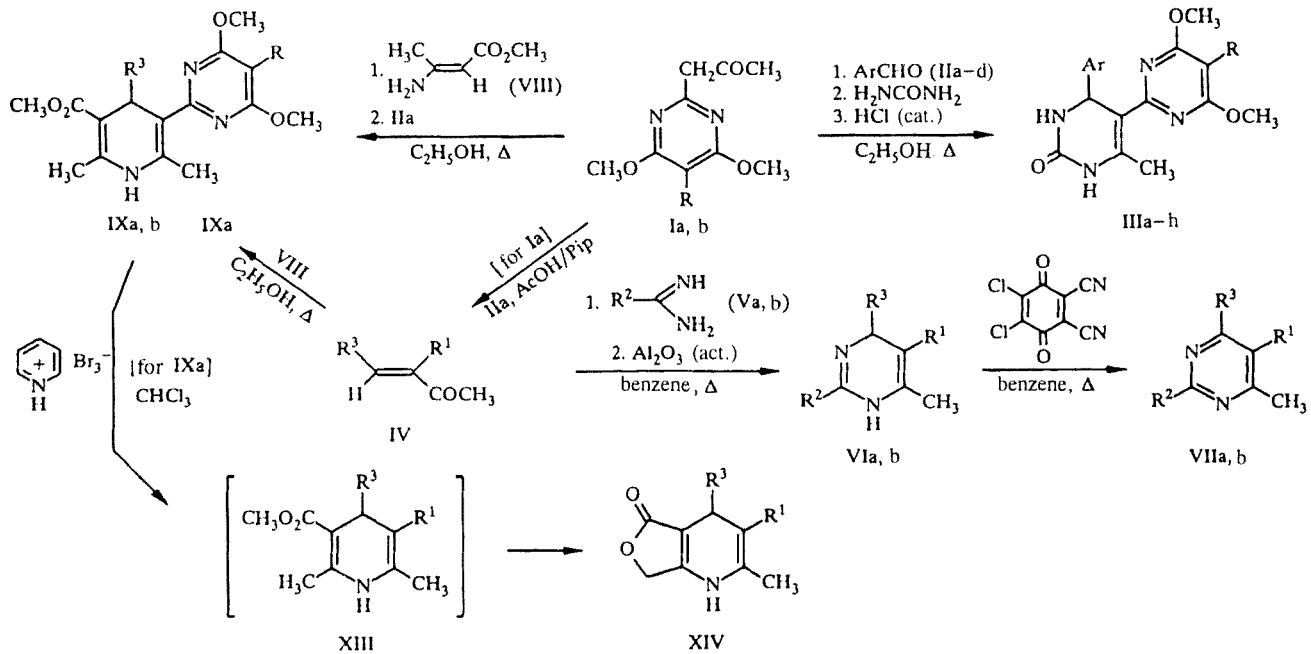

Ia, IIIa,c,e,g, IXa R = NO_2; Ib, IIIb,d,f,h, IXb R = CH_3; IIa, IIIa,b Ar = C_6H_4-3-NO_2; IIb, IIIc,d Ar = C_6H_4-2-NO_2; IIc, IIIe, f Ar = C_6H_3-3,4-$(OCH_3)_2$; IId, IIIg,h Ar = C_6H_3-3,4-methylenedioxy; IV, VI, VII, X–XIV R^1 = 4,6-dimethoxy-5-nitropyrimidin-2-yl; Va-VIIa R^2 = OCH_3; Vb-VIIb R^2 = C_6H_5; IV, VIa,b, VIIa,b, IXa,b, XI-XIV R^3 = C_6H_4-3-NO_2.

TABLE 1. Characteristics of Synthesized Compounds IIIa-j, VIa,b, VIIa,b, IXa,b, XI, XII, XIV

Compound	Empirical formula	R_f*	M.P., °C (ethanol)	λ_{max}, nm (log ε), (methanol)	PMR spectrum, δ,*2 ppm (spin–spin coupling constant J, Hz)						Yield, %
					$NH_{(1)}$, s	$NH_{(3)}$, d	CH, d	$C_{(6)}$–CH_3, s	OCH_3, s	other signals,*3 s	
1	2	3	4	5	6	7	8	9	10	11	12
IIIa	$C_{17}H_{16}N_6O_7$	0,21	> 300	250 (3,4), 327 (3,6), 364 (3,3)	9,56	8,10 (3,4)	5,74 (3,4)	2,58	3,90	–	77
IIIb	$C_{18}H_{19}N_5O_5$	0,26	> 300	231 (3,8), 309 (4,0)	9,02	*4	5,76 (3,4)	2,52	3,77	1,82 (CH_3)	72
IIIв	$C_{17}H_{16}N_6O_7$	0,29	> 300	258 (3,9), 321 (4,1), 357 (3,8)	9,60	8,03 (3,0)	6,21 (3,0)	2,64	3,76	–	51
IIId	$C_{18}H_{19}N_5O_5$	0,36	285...287	263 (3,7), 305 (4,0), 370 (2,8)	9,10	7,98 (3,0)	6,18 (3,0)	2,56	3,64	1,77 (CH_3)	45
IIIд	$C_{19}H_{21}N_5O_7$	0,33	229...231	227 (4,2), 284 (3,9), 331 (4,2), 360 (4,0)	9,34	7,79 (3,3)	5,57 (3,3)	2,55	3,91	3,68 (OCH_3)	54
IIIe	$C_{20}H_{24}N_4O_5$	0,38	265...268	227 (4,1), 290 (4,1), 306 (4,2), 370 (3,9)	8,78	7,51 (3,2)	5,63 (3,2)	2,48	3,80	3,66 (OCH_3), 1,83 (CH_3)	52
IIIж	$C_{18}H_{17}N_5O_7$	0,34	249...252	230 (4,1), 294 (3,9), 328 (4,1), 357 (4,0)	9,33	7,78 (3,0)	5,55 (3,0)	2,55	3,90	5,94 (CH_2)	62
IIIз	$C_{19}H_{20}N_4O_5$	0,36	265...267	231 (4,0), 297 (4,1), 310 (4,1)	8,76	7,90 (2,9)	5,60 (2,9)	2,51	3,80	5,92 (CH_2, d), 1,84 (CH_3)	57
VIa	$C_{18}H_{18}N_6O_7$	0,23	210...212	261 (3,8), 3,45 (3,8), 371 (3,8)	6,22	–	6,16, s	2,64	3,96	3,75 ($C_{(2)}$–OCH_3)	37
VIb	$C_{23}H_{20}N_6O_6$	0,18	171...173	260 (4,5), 4,11 (4,2)	6,87	–	6,39, s	2,75	4,00	–	48

TABLE 1 (continued)

1	2	3	4	5	6	7	8	9	10	11	12
VIIa	$C_{18}H_{16}N_6O_7$	0,42	106...108	271 (4,2)	–	–	–	2,60	3,86	4,14 ($C_{(2)}$–OCH_3)	89
VIIb	$C_{23}H_{18}N_6O_6$	0,58	95...97	222 (4,0), 260 (4,0), 285 (3,95)	–	–	–	2,71	3,89	–	92
IXa	$C_{21}H_{21}N_5O_8$	0,24	187...189	257 (4,3), 4,12 (4,1)	5,93	–	5,57, s	2,65	4,01	3,72 (CO_2CH_3), 2,38 ($C_{(2)}$–CH_3)	83*[5]
IXb	$C_{22}H_{24}N_4O_6$	0,27	200...202	236 (4,6), 268 (4,1), 355 (4,0)	9,00	–	4,98, s	2,27	3,54	1,88 ($C_{(2)}$–CH_3)	39
XI	$C_{25}H_{24}N_8O_{10}$	0,46	285...287	275 (3,8), 446 (3,7)	9,52	–	6,14, s	2,63	4,03	–	46
XII	$C_{19}H_{18}N_6O_8$	0,28	224...226	269 (3,8), 437 (3,6)	6,28	–	6,01, s	2,69	4,07	2,59 ($C_{(2)}$–CH_3)	30
XIV	$C_{20}H_{17}N_5O_8$	0,42	254...255	254 (3,8), 392 (3,7)	10,15	–	5,33, s	2,67	3,87	4,86 (CH_2, d)	41

*For IIIa-h, XIV – in a 15:1 chloroform–methanol system; VIa, b, IXa, b, XI, XII) chloroform; VIIa,b) 1:1 chloroform–hexane.

*[2]Spectra of compounds IIIa-h, IXb, XI, XIV were obtained in DMSO-D_6, VIa,b, VIIa,b, IXa, XII – in $CDCl_3$.

*[3]Aromatic protons resonate in the 5.90-8.30 ppm region.

*[4]The signal is overlapped by the proton multiple of phenyl.

*[5]Method A.

2-Acetonylpyrimidine Ia is a convenient syntone for preparing 5-(pyrimidin-2′-yl)-1,4-dihydropyridines containing substituents of different electronic nature in the 3 position of the pyridine ring. The reaction of Ia, b with 3-nitrobenzaldehyde and methyl 3-aminocrotonate formed 1,4-dihydropyridines IXa, b, respectively (method A). In addition, IXa was also obtained from propanone IV and ester VIII by two-component cyclization (method B).

Amination of Ia forms enamine X, which *in situ* in the presence of aldehyde IIa reacts with pyrimidine Ia or with nitroacetone to form the corresponding 1,4-dihydropyridines XI and XII. The reaction of IXa with pyridinium bromide (by analogy with [21]) formed oxofuropyridine XIV. Obviously, the first stage consists in the formation of the monobromomethyl derivative XIII, which on heating cyclizes to a lactone. The spectroscopic characteristics of the synthesized 1,4-dihydropyridines (Table 1) fully correspond to the data reported in the literature.

It has thus been shown that 2-acetonylpyrimidines are convenient starting compounds for the synthesis of various derivatives of 1,4-dihydropyridine and 1,4-di- and 1,2,3,4-tetrahydropyrimidines containing a pyrimidine fragment in the 5 position of the heterocycle.

EXPERIMENTAL

The PMR spectra were recorded with a WP-200 Bruker spectrometer in DMSO-D_6 and $CDCl_3$, with TMS as the internal standard. The UV spectra were recorded with a Specord M-40 instrument. The course of the reaction and purity of the synthesized compounds were checked by TLC on Silufol UV-254 plates in a 50:1 chloroform–methanol solvent system (development in UV light).

The ultimate-analysis data for C, H and N of the synthesized compounds correspond to the calculated data.

2-Acetonylpyrimidines Ia, b were prepared in accordance with [15] and [16], respectively.

The characteristics of the synthesized compounds are listed in Table 1.

4-Aryl-2-methyl-5-(4′,6′-dimethoxy-5′-nitropyrimidin-2′-yl)-2-oxo-1,2,3,4-tetrahydropyrimidines IIIa,c,e,g. To a mixture of 0.24 g (1 mmole) of pyrimidine Ia, 0.12 g (1 mmole) of urea, and 1 mmole of the corresponding aromatic aldehyde II in 10 ml of absolute ethanol is added with stirring 0.1 ml of conc. HCl. The reaction mixture is boiled for 6 h. The precipitate formed is filtered off and dried.

Similarly, IIIb,d,f,h is obtained from pyrimidine Ib.

1-(4′,6′-Dimethoxy-5′-nitropyrimidin-2′-yl)-1-(3′-, nitrophenyl)-2-propanone (IV, $C_{16}H_{14}N_4O_7$). To a mixture of 1.20 g (5 mmole) of pyrimidine Ia and 0.75 g (5 mmole) IIa in 25 ml of absolute benzene are added with mixing 1.0 ml of acetic acid and 0.1 ml of piperidine. The reaction mass is boiled for 6 h. After cooling to room temperature, the reaction mixture is successively washed with water (100 ml) and a saturated aqueous solution of NaCl (100 ml). The extract is dried over $MgSO_4$, and the solvent is removed. Yield, 1.60 g (86%). mp. 157-158°C (ethanol). UV spectrum (in methanol), λ_{max}, nm (log ε): 217 (4.0), 275 (3.9), 302 (4.0). PMR spectrum ($CDCl_3$): 8.33-7.60 (4H, m, C_6H_4); 7.99 (1H, s, CH); 4.22 (6H, s, $2OCH_3$); 2.48 ppm (3H, s, CH_3).

6-Methyl-2-methoxy-5-(4′,6′-dimethoxy-5′-nitropyrimidin-2′-yl-4-(3′-nitrophenyl)1,4-dihydropyrimidine (VIa). To a suspension of 0.15 g (2.1 mmole) of O-methylisourea (Va) and 7.5 g of activated Al_2O_3 in 20 ml of absolute benzene is added 0.75 g (2.0 mmole) of compound IV. The reaction mixture is boiled for 6 h with stirring, the precipitate is filtered off, and the mother liquor is evaporated to dryness. The residue is purified by chromatography on silica gel (20 g, chloroform eluent).

VIb was similarly obtained from benzamidine and IV.

6-Methyl-2-methoxy-5-(4′,6′-dimethoxy-5′-nitropyrimidin-2′-yl)-4-(3′-nitrophenyl)pyrimidine (VIIa). A mixture of 0.22 g (0.5 mmole) of 1,4-dihydropyrimidine VIa and 0.14 g (0.5 mmole) of dichlorodicyanobenzoquinone in 10 ml of absolute benzene is boiled for 2 h. The hydroquinone precipitate is filtered off, the mother liquor is evaporated to dryness, and the residue is purified by chromatography on silica gel (10 g, chloroform eluent).

2,6-Dimethyl-3-methoxycarbonyl-5-(4′,6′-dimethoxy-5′-nitropyrimidin-2′-yl)-4-(3′-nitrophenyl)-1,4-dihydropyridine (IXa). A. A mixture of 0.24 g (1 mmole) of pyrimidine Ia, 0.15 g (1 mmole) of aldehyde IIa, and 0.12 g (1 mmole) of ester VIII is boiled in 10 ml of ethanol for 6 h with stirring. The precipitate is filtered off, dried, and purified by chromatography on silica gel (20 g, chloroform eluent).

IXb is similarly obtained from pyrimidine Ib.

B. A mixture of 0.37 g (1 mmole) of compound IV and 0.12 g (1 mmole) of ester VIII is boiled in 10 ml of ethanol for 20 h with stirring. Method A is used. Yield, 0.39 g (83%).

2,6-Dimethyl-3,5-bis(4′,6′-dimethoxy-5′-nitropyrimidin-2′-yl)-4-(3′-nitrophenyl)-1,4-dihydropyridine (XI). A mixture of 0.24 g (1 mmole) of pyrimidine Ia and 0.05 mmole of 24% aqueous solution of ammonia in 10 ml of ethanol is stirred for 15 min at room temperature, 0.15 g (1 mmole) of IIa is added, and the mixture is boiled for 6 h. The solvent is then removed by an aspirator, and the residue is purified by chromatography on silica gel (10 g, chloroform eluent).

2,6-Dimethyl-5-(4′,6′-dimethoxy-5′-nitropyrimidin-2′-yl)-3-nitro-4-(3′-nitrophenyl)-1,4-dihydropyridine (XII). A mixture of 0.24 g (1 mmole) of pyrimidine Ia and 0.1 ml of a 24% aqueous solution of ammonia in 10 ml of ethanol is stirred for 15 min at room temperature, then 0.1 g (1 mmole) of nitroacetone and 0.15 g (1 mmole) of IIa are added. The reaction mass is boiled for 8 h, the solvent is removed with an aspirator, and the residue is purified by chromatography on silica gel (10 g, chloroform eluent).

2-Methyl-3-(4′,6′-dimethoxy-5′-nitropyrimidin-2′-yl)-4-(3′-nitrophenyl)-5-oxofuro[3,4-b]-1,4,5,7-tetrahydropyridine (XIV). To a solution of 0.46 g (1 mmole) of 1,4-dihydropyridine IXa in 15 mmole of chloroform, cooled to 0°C, are added with stirring 0.2 ml of pyridine and 0.32 g (1 mmole) of pyridine and 0.32 g (1 mmole) of pyridinium bromide perbromide. The reaction mixture is kept for 30 min at this temperature for 30 min, then boiled for 2 h. After the reaction mass is cooled to room temperature, it is washed with 30 ml of a 2 N solution of HCl and with 30 ml of a saturated aqueous solution of NaCl. The chloroform extract is dried over $CaCl_2$, the solvent is removed at reduced pressure, and the residue is purified by chromatography on silica gel (20 g, chloroform eluent).

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