SYNTHESIS AND PROPERTIES OF 2-AMINO-4,6-DIMETHYLNICOTINIC ACID ARYLAMIDES

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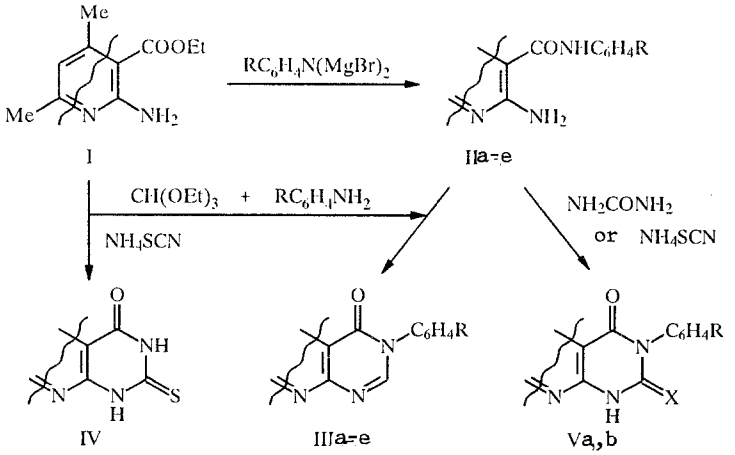
It is shown that on boiling 2-amino-4,6-dimethylnicotinic acid arylamides with triethyl orthoformate in acetic anhydride, derivatives of 3-aryl-5,7-dimethyl-4-oxo-3,4-dihydropyrido[2,3-d]pyrimidine are formed. The same compounds are obtained by ternary condensation of ethyl 2-amino-4,6-dimethylnicotinate with triethyl orthoformate and alrylamines. On reaction with urea or ammonium thiocyanate, the ethyl ester or anilides of 2-amino-4,6-dimethylnicothinic acid are converted to 2,4-dioxo- or 4-oxo-2-thio-pyrido[2,3-d]pyrimidines respectively.

Derivatives of 4-oxo-3,4-dihydropyrido[2,3-d]pyrimidine are of interest as biologically active compounds [1, 2]. These compounds are difficult to obtain because of the complexity of the synthesis of the starting materials – 2-aminonicotinic acid and its derivatives.

The present study has been undertaken in order to extend research on pyrido[2,3-d]pyrimidines and to investigate more convenient methods of synthesizing them. We focused our attention on ethyl 2-amino-4,6-dimethylnicotinate (I), which is obtained with comparative ease from acetylacetone and monoiminomalonic ester hydrochloride [3], as a possible starting material for the synthesis of 5,7-dimethyl-4-oxo-3,4-dihydropyrido[2,3-d]pyrimidines, which had hardly been studied at all previously.



IIa R = H, b R = 4-CH_3, c R = 3-CH_3, d R = 4-CH_3O; e R = 2-CH_3; IIIa R = H, b R = 4-CH_3, c R = 3-CH_3, d R = 4-CH_3O, e R = 2-Cl; Va R = 4-CH_3, X = O; Vb R = 4-CH_3, X = S

It was shown that ester I on reacting with di(bromomagnesium)arylamines is converted to 2-amino-4,6-dimethylnicotinic acid arylamides (IIa-e, Table 1). On heating amides IIa-d with triethyl orthoformate in acetic anhydride, 3-aryl-5,7-dimethyl-4-oxo-3,4-dihydropyrido[2,3-d]pyrimidines (IIIa-d, Table 1) are formed. Compounds IIIa, d, e are also obtained by ternary condensation of ester I with triethyl orthoformate and arylamines. It is likely that the reaction occurs via an intermediate substituted formamidine, which cyclizes to pyridopyrimidines III with elimination of ethanol. The latter reaction has advantages

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Table 1. Properties of Compounds Synthesized

Compound	Empirical formula	mp, °C	TLC, R_f	PMR spectra, δ, ppm*						Yield, %**
				CH_3, s	H_{arom}, m, s	H pyridine, s	2-H pyridine, s	NH, s	NH_2, s	
IIa	$C_{14}H_{15}N_3O$	204...205	0,25	2,18	7,13...7,63	6,26	—	10,06	5,30	45
IIb	$C_{15}H_{17}N_3O$	212...214	0,18	2,10...2,20 (	7,00...7,60	6,37	—	10,13	5,67	56
IIc	$C_{15}H_{17}N_3O$	183...184					—			30
IId	$C_{15}H_{17}N_3O_2$	217...219	0,19				—			27
IIe	$C_{15}H_{17}N_3O$	152...154	0,16	1,83; 2,23; 2,43	7,07...7,38	6,30	—	9,70	5,70	28
IIIa	$C_{15}H_{13}N_3O$	192...194	0,57	2,53; 2,67	7,53	7,23	8,43	—	—	42 (54)
IIIb	$C_{16}H_{15}N_3O$	206...207	0,70	2,35; 2,45; 2,65	7,30	7,20	8,35	—	—	50
IIIc	$C_{16}H_{15}N_3O$	153...154	0,67	2,27; 2,47; 2,63	7,31	7,15	8,40	—	—	67
IIId	$C_{16}H_{15}N_3O_2$	213...215	0,59	2,67; 2,43	7,00...7,40	6,90	8,30	—	—	48 (45)
IIIe	$C_{15}H_{12}ClN_3O$	141...143		2,00; 2,43	6,80...7,43	7,87	9,13	—	—	46
IV	$C_9H_9N_3OS$	>310		2,37; 2,53	—	6,67	—	12,10	—	25
Va	$C_{16}H_{15}N_3O_2$	282...284		2,25; 2,40; 2,50	7,15	6,90	—	11,70	—	50
Vb	$C_{16}H_{15}N_3OS$	>310					—		—	40

*For compound IIId signals also occur at 3.73 ppm (3H, s, CH_3O).

**For compounds IIIe and IIIa, d (in brackets), yields are given from method B.

over the synthesis of compounds IIIa-e from amides IIa-e as it can be used to obtain the final required products from accessible starting materials in one stage.

On heating ester I with ammonium thiocyanate, 5,7-dimethyl-4-oxo-2-thio-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine (IV) is obtained. On fusing arylamide IIb with urea or by heating it with ammonium thiocyanate, 3-(4-tolyl)-5,7-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine (Va) or 3-(4-tolyl)-5,7-dimethyl-4-oxo-2-thio-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine (Vb) respectively are formed.

Compounds IIIa-e and Va were tested for analgesic and antiinflammatory activity.* No distinct antiinflammatory activity was found, while the greatest analgesic activity in the "hot plate" test [4] was detected in compound IIId [by administration ip in a 50 mg/kg dose, its defensive reflex time was 28.3 sec, and it can be classified as compound with low toxicity, LD_{50} = 890 (583-1149) mg/kg].

EXPERIMENTAL

Infrared spectra were recorded on a UR-20 instrument in petrolatum oil, PMR spectra were obtained on an RYa-2310 (60 MHz) spectrometer for 5% solutions of compounds in DMSO-d_6 with HMDS as internal standard. Thin-layer chromatography was conducted on Silufol UV-254 plates in ethylbenzene–benzene (1:1) (IIa-e) or butanol–benzene (1:1) (IIIa-e).

The elemental analysis data corresponded to the calculated values.

2-Amino-4,6-dimethylnicotinic Acid Arylamides (IIa-e). To the dimagnesylamine, obtained from 0.03 mole of

*Studies were carried out at the Department of Pharmacology, Perm' Pharmaceutical Institute by Z. N. Kashina and F. Ya. Nazmetdinov under the supervision of Prof. V. É. Koll.

arylamine and 0.06 mole of ethylmagnesium bromide in anhydrous ether, was added 1.9 g (0.01 mole) of initially ground ester I. The mixture was maintained at 36°C for 2-3 h and decomposed with a saturated solution of ammonium chloride. The ether layer was separated and steam distilled. The product was crystallized from ethanol or a mixture of ethanol and DMF (2:1). IR spectra: 1610-1620 (CO), 3150, 3260-3285 cm^{-1} (NH, NH_2).

3-Aryl-5,7-dimethyl-3,4-dihydropyrido[2,3-d]pyrimidin-4-ones (IIIa-e). A. A mixture of 0.01 mole of arylamide IIa-d and 20 ml of triethyl orthoformate in 20 ml of acetic anhydride was boiled for 6 h. The volatile impurities were then distilled off under vacuum and the residue was crystallized from toluene. Compounds IIIa-d were obtained. IR spectra: 1670 cm^{-1} (CO). **B.** A mixture of 1 g (0.005 mole) of ester I, 1.5 g (0.01 mole) of triethyl orthoformate, and 0.005 mole of arylamine was heated to 145-150°C for 2 h. Crystallization gave compounds IIIa, d, e.

5,7-Dimethyl-4-oxo-2-thio-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine (IV). A mixture of 2 g (0.01 mole) of ester I and 4 g (0.05 mole) of ammonium thiocyanate was heated to 180-190°C for 1.5 h. After treatment with hot water, the product was filtered and crystallized from DMF.

5,7-Dimethyl-3-(4-tolyl)-2,4-dioxo-(4-oxo-2-thio)-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidines (Va, b). Compound IIb (0.01 mole) was heated with a fivefold excess of urea and kept at 210°C for 30 min (Va) or heated with ammonium thiocyanate to 190-210°C for 2 h (Vb). The mixture was cooled, treated with hot water, and the product was crystallized from DMF. IR spectrum (Va): 1660, 1710 cm^{-1} (CO).

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