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Reaction of Ethyl 6-Alkyl(aryl)-4-chloromethyl-2-methylpyridine-3-carboxylates with Ammonia and Primary Amines

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Abstract—Ethyl 6-alkyl(aryl)-4-chloromethyl-2-methylpyridine-3-carboxylates react with ammonia and primary amines to give 6-substituted 3-alkyl(aryl)-1-methyl-1,2-dihydropyrrolo[3,4-*c*]pyridin-7-ones. The reactions with 4-aminopyridine yield ethyl 6-alkyl(aryl)-2-methyl-4-(4-pyridylaminomethyl)pyridine-3-carboxylates.

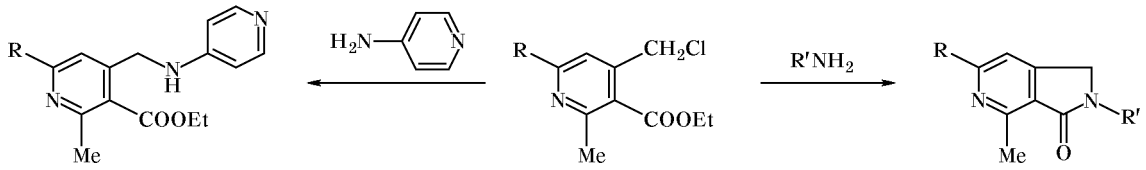
As shown previously, alkyl pyridine-3-carboxylates react with primary amines to give the corresponding nicotinamides [1] some of which exhibit anticonvulsant and antimicrobial activity [2, 3]. The present communication reports on the results of the reaction of ethyl 6-alkyl(aryl)-4-chloromethyl-2-methylpyridine-3-carboxylates **Ia**–**Id** with ammonia and primary amines R′NH_2, which leads to formation of 6-R′-substituted 3-alkyl(aryl)-1-methyl-1,2-dihydropyrrolo[3,4-*c*]pyridin-7-ones **II**–**V**; in the reaction of **I** with 4-aminopyridine the corresponding ethyl 6-alkyl(aryl)-2-methyl-4-(4-pyridylaminomethyl)pyridine-3-carboxylates **VI** are formed (Scheme 1). The reactions were carried out in aqueous–alcoholic or alcoholic medium, and products **II**–**VI** were obtained in 66–83% yield. The initial stage of the reaction of ester **I** with ammonia and primary amines is nucleophilic substitution of chlorine in the chloromethyl group by amino; intermediate 4-aminomethyl derivative of nicotinic acid undergoes cyclization to pyrrolo[3,4-*c*]-pyridines **II**–**V** with liberation of ethanol. The reaction of **I** with 4-aminopyridine stops at the stage of chlorine replacement by 4-pyridylamino group to give compounds **VIa**–**VIc** as final products. No cyclization of **VI** occurred when the reaction was carried out in a higher-boiling solvent, such as 1-propanol or DMF. Presumably, the reason is the lower nucleophilicity of the amino group in 4-aminopyridine, as compared to ammonia and primary aliphatic amines.

The structure of compounds **II**–**VI** was confirmed by the ^{1}H NMR and IR spectra. Pyrrolopyridines **II**–**V** showed in the IR spectra characteristic bands belonging to stretching vibrations of the lactam carbonyl group (1680–1720 cm^{-1}) and pyridine ring (1540–1620 cm^{-1}) [4]. The ^{1}H NMR spectra of **II**–**V** contained singlet signals from protons of the pyrrolopyridine ring system, signals from protons of the alkyl (aryl) substituent in position *3*, and signals from the N-substituent (Table 1).

EXPERIMENTAL

The IR spectra were measured on UR-20 and Specord M-80 spectrometers in mineral oil. The ^{1}H NMR spectra were obtained on a Tesla BS-487B instrument (80 MHz) using hexamethyldisiloxane as

Scheme 1.



VIa–VIc **Ia–Id** **IIa–IId, IIIa–IIId IVa–IVd, Va–Vc**

I–**VI**, R = Me (**a**), Et (**b**), Ph (**c**), 4-ClC_6H_4 (**d**); **II**, R′ = H; **III**, R′ = $CH(CH_3)_2$; **IV**, R′ = CH_2CH_2OH; **V**, R′ = CH_2COOCH_3.

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Table 1. ^{1}H NMR spectra of pyrrolopyridines **IIa**–**IIc**, **IIIa**, **IVa**, and **Va**

Compound no.	Chemical shifts δ, ppm				
	R	CH_3	CH_2	CH	R′
IIa	2.78 s	3.00 s	4.75 s	7.78 s	8.43 s
IIb	1.49 t, 3.58 q	3.08 s	4.78 s	7.86 s	8.42 s
IIc	7.53 m	3.06 s	4.73 s	9.00 s	8.36 s
IIIa	2.96 s	3.20 s	4.86 s	7.93 s	1.45 d, 4.73 q
IVa	3.16 s	2.93 s	4.96 s	7.90 s	4.16 t, 4.76 t
Va	2.98 s	3.25 s	4.91 s	7.86 s	3.60 s, 4.30 s

Table 2. Yields, melting or boiling points, and elemental analyses of compounds **II**–**VI**

Compound no.	Yield, %	mp, °C, or bp, °C (*p*, mm)	Found, %			Formula	Calculated, %		
			C	H	N		C	H	N
IIa	78	196–197	67.03	6.00	17.61	$C_9H_{10}N_2O$	66.66	6.17	17.28
IIb	75	190–192	68.64	6.69	15.67	$C_{10}H_{12}N_2O$	68.18	6.82	15.91
IIc	76	216–217	74.80	5.67	12.24	$C_{14}H_{12}N_2O$	75.00	5.35	12.50
IId	73	174–175	65.69	4.48	10.49	$C_{14}H_{11}ClN_2O$	64.99	4.25	10.83
IIIa	83	131–132	70.06	7.86	14.06	$C_{12}H_{16}N_2O$	70.59	7.64	13.73
IIIb	79	123–124	71.89	8.43	13.07	$C_{13}H_{18}N_2O$	71.56	8.26	12.84
IIIc	70	142–143	76.87	6.68	10.78	$C_{16}H_{16}N_2O$	76.19	6.34	11.11
IIId	71	126–127	67.74	5.41	10.03	$C_{16}H_{15}ClN_2O$	67.01	5.23	9.77
IVa	82	133–134	64.52	7.04	13.89	$C_{11}H_{14}N_2O_2$	64.08	6.80	13.59
IVb	79	126–127	65.83	7.48	12.93	$C_{12}H_{16}N_2O_2$	65.45	7.27	12.72
IVc	75	149–150	71.08	6.10	10.11	$C_{16}H_{16}N_2O_2$	71.64	5.97	10.45
IVd	73	126–127	63.86	5.07	9.48	$C_{16}H_{15}ClN_2O_2$	63.47	4.96	9.26
Va[a]	73	127–129 (2)	60.87	5.73	12.24	$C_{12}H_{14}N_2O_3$	61.54	5.98	11.96
Vb[b]	69	140–141 (3)	63.41	6.61	11.67	$C_{13}H_{16}N_2O_3$	62.90	6.45	11.29
Vc	66	108–110	67.09	5.90	10.13	$C_{16}H_{16}N_2O_3$	67.61	5.63	9.86
VIa	80	213–214	66.94	6.63	14.90	$C_{16}H_{19}N_3O_2$	67.37	6.67	14.73
VIb	74	163–164	67.70	7.11	13.96	$C_{17}H_{21}N_3O_2$	68.23	7.02	14.05
VIc	71	96–97	73.09	6.20	11.87	$C_{21}H_{21}N_3O_2$	72.62	6.05	12.10

[a] d_4^{20} = 1.0966, n_D^{20} = 1.4985. [b] d_4^{20} = 1.0731, n_D^{20} = 1.4951.

reference; samples were examined as 5–10% solutions in CCl_4 or DMSO-d_6. The purity of the products was checked by TLC on Silufol UV-254 plates. Initial ethyl 6-substituted 4-chloromethyl-2-methylpyridine-3-carboxylates **Ia**–**Id** were synthesized by the procedure reported in [5]. The yields, melting or boiling points, and elemental analyses of the products are given in Table 2.

3-Substituted 1-methyl-1,2-dihydropyrrolo-[3,4-*c*]pyridines IIa–IId. A solution of 0.1 mol of ester **Ia**–**Id** in 50 ml of ethanol was added dropwise under vigorous stirring at 20–25°C to a mixture of 30 ml (0.4 mol) of 25% aqueous ammonia and 25 ml of methanol. The mixture was stirred for 5 h at 30–35°C, cooled, and diluted with 100–150 ml of water. The precipitate was filtered off, washed with cold water, and recrystallized from water.

3,6-Disubstituted 1-methyl-1,2-dihydropyrrolo-[3,4-*c*]pyridin-7-ones IIIa–IIId and IVa–IVd. A solution of 0.1 mol of ester **Ia**–**Id** in 25 ml of methanol was added dropwise under vigorous stirring at 25–30°C to a solution of 0.1 mol of isopropylamine or

2-aminoethanol in 25 ml of methanol. Triethylamine, 14 ml (0.1 mol) was then added, and the mixture was refluxed for 4 h and was treated as described above for the synthesis of compounds **IIa**–**IId**.

3-Alkyl-6-(methoxycarbonylmethyl)-1-methyl-1,2-dihydropyrrolo[3,4-*c*]pyridin-7-ones Va–Vc. To a solution of 6.3 g (0.05 mol) of glycine methyl ester hydrochloride in 50 ml of water at 25–30°C we added dropwise 100 ml of a 10% aqueous solution of sodium carbonate and then a solution of 0.05 mol of ester **Ia**–**Ic** in 50 ml of methanol. The mixture was heated for 5 h at 55–60°C, cooled, diluted with water, and extracted with ether. The extract was dried over $MgSO_4$, the solvent was distilled off, and the residue was distilled under reduced pressure.

Ethyl 6-substituted 2-methyl-4-(4-pyridylaminomethyl)pyridine-3-carboxylates VIa–VIc. A solution of 0.1 mol of ester **Ia**–**Ic** in 50 ml of methanol was added dropwise under vigorous stirring at 25–30°C to a solution of 4.7 g (0.05 mol) of 4-aminopyridine in 25 ml of methanol. The mixture was heated for 5 h under reflux, 1/3 of the solvent was distilled off, the mixture was cooled to 15–20°C, and a solution of 3.2 g (0.05 mol) of potassium hydroxide in anhydrous methanol was added dropwise. The precipitate of potassium chloride was filtered off, the filtrate was evaporated under reduced pressure (water-jet pump), and the residue was recrystallized from toluene.

Ethyl 2,6-dimethyl-4-(4-pyridylaminomethyl)-pyridine-3-carboxylate (VIa). IR spectrum, ν, cm^{-1}: 3180 (N–H), 1720 (C=O), 1275 (C–O–C). ^1H NMR spectrum, δ, ppm: 2.23 t (3H, C**H**$_3$CH$_2$O), 4.29 q (2H, OCH$_2$), 2.40 s and 2.46 s (3H each, 2CH$_3$), 4.65 s (2H, CH$_2$), 5.38 s (1H, NH), 6.90–8.03 (two doublets, 5H, pyridine ring protons).

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