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INVESTIGATIONS ON FUROPYRIDINES.

10.* SYNTHESIS OF 4-N-SUBSTITUTED 1H-FURO[3,4]PYRIDIN-3-ONES

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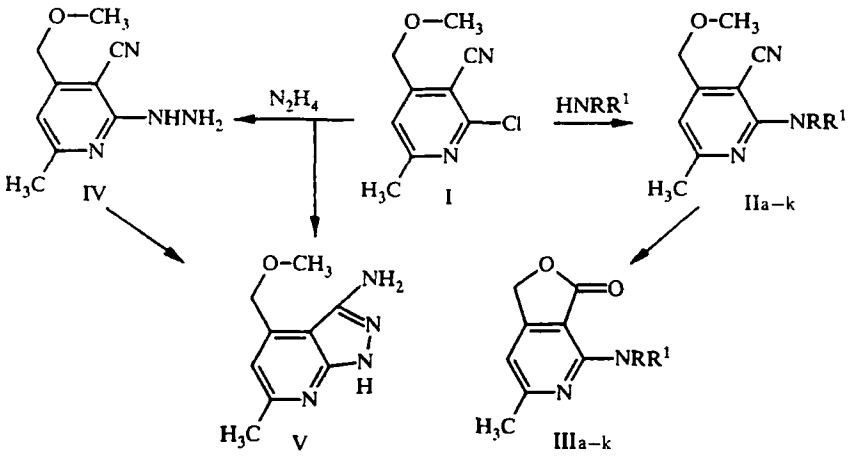
2-Amino or 2-hydrazino derivatives of pyridine or pyridinopyrazole were obtained by amination or hydrazination of 2-chloro-3-cyano-4-methoxy-6-methylpyridine. Acid hydrolysis of these derivatives leads to heterocyclization with formation of 4-amino-1H-furo[3,4-c]pyridines or pyrazolo[3,4-b]pyridine. The possiblility to synthesize 4-arylamino-1H-furo[3,4-c]-pyridines from 4-chloro-6-methyl-1H-furo[3,4-c]-pyridine has been shown.

Derivatives of 1H-furo[3,4-*c*]pyridine have been synthesized previously and the outlook of this class of compounds for practical study has been shown [1-4]. As a continuation of work in this direction it seemed of interest to synthesize 4-amino- or 4-hydrazino- substituted furo[3,4-*c*]pyridin-3-ones.

The polyfunctionality and availability of 2-chloro-3-cyano-4-methoxymethyl-6-methylpyridine (I) [5] enabled its use to obtain the target products. Synthesis of the latter was accomplished in two stages: 1) the corresponding products IIa-k were obtained by the nucleophilic substitution of 2-chlorocyanopyridine (I) with primary and secondary amines, 2) compounds II were converted by lactonization into 4-amino-6-methyl-1H-furo[3,4-*c*]pyridin-3-ones (IIIa-k) (Table 1).

The reaction of chloropyridine (I) with N-containing nucleophiles occurs in the absence of catalyst which is characteristic of *o*-chlorocyanopyridines [6].



II, IIIa R = H, $R^1 = CH_3$; b R = H, $R^1 = C_2H_5$; c R = H, $R^1 = C_4H_9$; d R = $R^1 = CH_3$; e R, $R^1 = -(CH_2)_5-$; f R + $R^1 = -(CH_2)_2-O-(CH_2)_2-$; g R = H, $R^1 = CH_2C_6H_5$; h R = H, $R^1 = C_6H_5$; i R = H, $R^1 = C_6H_4OCH_3$-4; j R = H, $R^1 = C_6H_4Br$-4; k R = H, $R^1 = C_6H_4Cl$-4

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TABLE 1. Characteristics of the Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %				mp,°C	TLC, R_f	Yield, %
		C	H	N	Hal			
IIa	$C_{10}H_{13}N_3O$	63,0 / 62,8	6,4 / 6,8	21,9 / 22,0	—	57...58	0,86	90
IIb	$C_{11}H_{13}N_3O$	64,8 / 64,4	7,5 / 7,3	21,0 / 20,5	—	60...61	0,68	50
IIc	$C_{13}H_{19}N_3O$	66,5 / 66,9	8,4 / 8,2	17,6 / 18,0	—	50...51	0,83	91
IId	$C_{11}H_{15}N_3O$	64,1 / 64,3	7,2 / 7,4	20,8 / 20,5	—	52...54	0,73	80
IIe	$C_{14}H_{19}N_3O$	68,8 / 68,5	7,9 / 7,8	17,5 / 17,1	—	47...48	0,69	83
IIf	$C_{13}H_{17}N_3O_2$	63,5 / 63,1	6,7 / 6,9	17,4 / 17,0	—	83...85	0,80	57
IIg	$C_{16}H_{17}N_3O$	72,2 / 71,9	6,5 / 6,4	15,2 / 15,7	—	95...96	0,98	94
IIh	$C_{15}H_{15}N_3O$	71,5 / 71,1	6,0 / 5,9	15,3 / 15,5	—	90...91	0,87	80
IIi	$C_{16}H_{17}N_3O_2$	67,7 / 67,8	5,9 / 6,0	11,0 / 11,3	—	115...117	0,90	82
IIj	$C_{15}H_{14}BrN_3O$	53,9 / 54,2	4,4 / 4,2	14,2 / 14,5	24,4 / 24,1	110...112	0,81	50
IIk	$C_{15}H_{14}ClN_3O$	62,5 / 62,6	4,7 / 4,9	14,4 / 14,6	12,2 / 12,3	145...147	0,67	66
IIIa	$C_9H_{10}N_2O_2$	60,4 / 60,7	5,3 / 5,6	15,4 / 15,7	—	121...123	0,70	90
IIIb	$C_{10}H_{12}N_2O_2$	62,4 / 62,5	6,5 / 6,3	14,8 / 14,6	—	123...125	0,72	50
IIIc	$C_{12}H_{16}N_2O_2$	65,3 / 65,4	7,6 / 7,3	12,6 / 12,7	—	63...65	0,74	73
IIId	$C_{10}H_{12}N_2O_2$	62,4 / 62,5	6,3 / 6,3	15,0 / 14,6	—	101...103	0,70	80
IIIe	$C_{13}H_{16}N_2O_2$	67,1 / 67,2	6,8 / 6,9	12,2 / 12,1	—	88...89	0,55	73
IIIf	$C_{12}H_{10}N_2O_3$	62,5 / 62,6	4,2 / 4,4	12,3 / 12,2	—	150...152	0,71	90
IIIg	$C_{15}H_{14}N_2O_2$	70,0 / 70,8	5,6 / 5,5	11,2 / 11,0	—	216...218	0,79	75
IIIh	$C_{14}H_{12}N_2O_2$	69,5 / 70,0	4,9 / 5,0	11,1 / 11,7	—	145 with resinification	0,87	80
IIIi	$C_{15}H_{14}N_2O_3$	66,7 / 66,6	5,3 / 5,2	10,5 / 10,4	—	149...150	0,75	50
IIIj	$C_{14}H_{11}BrN_2O_2$	52,7 / 52,7	3,6 / 3,5	9,1 / 8,8	25,6 / 25,0	155 with resinification	0,71	40
IIIk	$C_{14}H_{11}ClN_2O_2$	61,1 / 61,2	5,3 / 5,1	10,5 / 10,2	12,6 / 12,9	175...177	0,67	93

The reaction conditions (solvent, reactant ratio, temperature, duration) varied depending on the N-nucleophile.

In the IR spectra of amines IIa-k the absorption bands for the cyano group in the short frequency region were displaced by 10-20 cm^{-1} in comparison with the analogous bands of initial chloropyridine I and were observed at 2210-2220 cm^{-1}.

The absorption bands of the secondary amino group were observed at 3330-3420 cm^{-1} (Table 2).

In the PMR spectra the signals of protons of all fragments of the molecules resonated in their characteristic regions. The pyridine proton singlet for the aliphatic amines IIa-g was displaced for 0.50-0.62 ppm towards the higher field relative to the analogous signal for the initial chloropyridine due to the shielding action of the amino group (Table 3).

Treatment of aminopyridines IIa-k with 50% H_2SO_4 leads to formation of lactonopyridines IIIa-k with preservation of the amino group on the pyridine ring, unlike the derivatives of 3-cyano-2-methoxypyridine obtained previously [7]. This indicates the stronger conjugation in the 2-aminopyridine structure.

TABLE 2. Characteristics of Compounds II and III

Compound	IR spectrum, ν, cm^{-1}				
	NH	C≡N	C=O	C—O—C	δNH, νC=C, νC≡N
IIa	3420	2220	—	1200, 1180, 1145, 1105	1610, 1575, 1550
IIb	3415	2210	—	1200, 1175, 1145, 1110	1610, 1575, 1550
IIc	3375	2200	—	1180, 1150, 1120, 1080	1600, 1580, 1550
IId	—	2210	—	1200, 1145, 1130, 1100	— 1586, 1575
IIe	—	2200	—	1200, 1160, 1130, 1100	— 1585, 1560
IIf	—	2220	—	1160, 1150, 1135, 1100	— 1580, 1560
IIg	3370	2200	—	1180, 1155, 1135, 1115	1585, 1570, 1550
IIh	3345	2220	—	1190, 1160, 1125, 1100	1610, 1590, 1570
IIi	3330	2220	—	1175, 1170, 1160, 1110	1600, 1590, 1575
IIj	3345	2220	—	1195, 1160, 1155, 1100	1610, 1590, 1560
IIk	3350	2220	—	1190, 1150, 1100, 1075	1610, 1580, 1550
IIIa	3375	—	1725	1180, 1130, 1110, 1065	1610, 1600, 1580
IIIb	3410	—	1710	1195, 1120, 1115, 1020	1610, 1600, 1585
IIIc	3400	—	1710	1185, 1170, 1145, 1095	1635, 1610, 1550
IIId	—	—	1710	1170, 1125, 1115, 1110	— 1580, 1550
IIIe	—	—	1735	1180, 1125, 1115, 1110	— 1580, 1560,
IIIf	—	—	1750	1180, 1160, 1125, 1075	— 1600, 1575
IIIg	3400	—	1730	1190, 1125, 1100, 1030	1610, 1600, 1550
IIIh	3350	—	1720	1200, 1150, 1100, 1050	1640, 1600, 1590
IIIi	3380	—	1725	1180, 1150, 1125, 1115	1630, 1600, 1590
IIIj	3375	—	1730	1200, 1160, 1110, 1050	1620, 1585, 1575
IIIk	3350	—	1710	1200, 1175, 1125, 1100	1600, 1580, 1555

There were no absorption bands for the nitrile group in the IR spectra of compounds IIIa-k but there was a lactone CO band at 1710-1750 cm^{-1}. The signal for the methoxy group OCH_3 was absent in the PMR spectra, which confirms the intramolecular cyclization.

2-Chloro-3-cyanopyridine I was also subjected to the action of hydrazine hydrate analogous to [6]. A mixture was formed in this case consisting of 2-hydrazinopyridine (IV) (10%) and its cyclization product - pyrazolo-[3,4-*b*]pyridine (V) (90%). Conditions were found for preparation of each of these products (see Experimental). The absorption band for the nitrile group was absent in the IR spectrum of pyrazolopyridine V in contrast to that of hydrazinopyridine IV. The band for NH and NH_2 groups was observed at 3180-3430 cm^{-1}.

2-Amino-3-cyanopyridines IIa-k are not only intermediates for synthesis of furopyridines and other organic compounds [8], but are themselves of interest as subjects for biological study [9].

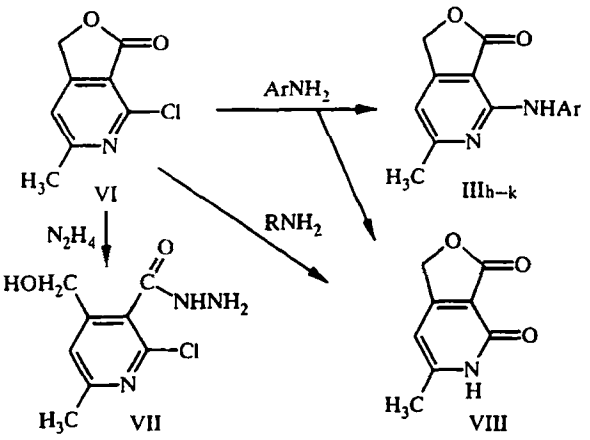
TABLE 3. PMR Spectra of Some Synthesized Compounds

Compound	Chemical shift, δ, ppm
IIa	2,40 (3H, s, 6-CH_3); 3,40 (3H, s, OCH_3); 3,50 (3H, s, NCH_3); 4,40 (2H, s, CH_2O); 5,10 (1H, br s, NH); 6,70 (1H, s, =CH)
IIc	0,80...1,97 (7H, m, $2CH_2$, CH_3); 2,27 (3H, s, 6-CH_3); 3,30 (3H, s, OCH_3); 3,45 (2H, s, NCH_3); 4,28 (2H, s, CH_2O); 5,00 (1H, br s, NH); 6,43 (1H, s, =CH)
IIf	2,40 (3H, s, 6-CH_3); 3,40 (3H, s, OCH_3); 3,63 [4H, s, $N(CH_2)_2$]; 3,70 [4H, s, $(CH_2)_2O$]; 4,47 (2H, s, CH_2O); 6,73 (1H, s, =CH)
IIg	2,42 (3H, s, 6-CH_3); 3,38 (3H, s, OCH_3); 4,43 (2H, s, CH_2O); 6,62 (1H, s, NH); 4,70 (2H, s, NCH_2); 7,03...7,40 (6H, m, C_6H_5, =CH)
IIh	2,40 (3H, s, 6-CH_3); 3,40 (3H, s, OCH_3); 4,45 (2H, s, CH_2O); 6,82 (1H, s, =CH); 6,92...7,42 (6H, m, C_6H_5, NH)
IIi	2,43 (3H, s, 6-CH_3); 3,40 (3H, s, OCH_3); 3,75 (3H, s, OCH_3 arom,); 4,48 (2H, s, CH_2O); 6,63...7,55 (6H, m, C_6H_4, NH, =CH)
IIIa	2,43 (3H, s, 6-CH_3); 3,13 (3H, s, NCH_3); 5,10 (2H, s, CH_2O); 6,10...6,52 (2H, m, NH, =CH)
IIIg	2,43 (3H, s, 6-CH_3); 4,37 (2H, s, CH_2O); 5,17 (2H, s, NCH_2); 6,50 (1H, s, NH); 7,00...7,63 (6H, m, C_6H_5, =CH)

Another route for synthesis of 4-aminofuro[3,4-*c*]pyridines III by the direct amination of the known 4-chloro-6-methyl-3-oxo-1H-furo[3,4-*c*]pyridine VI seemed improbable due to opening of the lactone ring under the action of amines [10,11]. In reality the reaction of chloropyridolactone VI with hydrazine hydrate leads to formation of hydrazide of 2-chloro-4-hydroxymethyl-6-methylnicotinic acid (VII). The absorption band of the lactone C=O group was absent in its IR spectrum and an amide carbonyl band appeared at 1640 cm^{-1}.

Study of conditions for the synthesis of aminopyridines III from chloropyridolactone VI showed the possibility of obtaining arylamines IIIh,i on use of 50% CH_3COOH. A mixture of product III and furopyridine-3,4-dione (VIII) was formed as a result. The former was isolated from the reaction mixture as crystals. According to IR spectral data the residue after evaporation of the chloroform extract of the filtrate contained compounds III and VIII in a ratio of 3:2.

Probably nucleophilic substitution of chlorine by OH group occurs, with subsequent lactim-lactam tautomerization, in parallel with the amination due to the low rate of reaction with weak nucleophiles. Amination of chloropyridolactone VI by aliphatic amines was unsuccessful. Even on extended boiling (up to 20 h) the sole product isolated was furopyridine-3,4-dione (VIII).



EXPERIMENTAL

The IR spectra were taken on a Specord IR 75 spectrometer in nujol, PMR spectra were obtained on a Tesla BS 467 A instrument in CDCl3. The purity of substances as well as the duration of reaction were checked by TLC on Silufol UV 254 plates in the system ethanol-benzene, 20:1 visualizing with iodine vapor.

3-Cyano-4-methoxy-2-methyl-2-methylaminopyridine (IIa). A mixture of chloropyridine I (0.3 g, 0.0015 mole) and 33% aqueous methylamine (0.45 ml) in butanol (3 ml) was stirred at 50°C for 3 h, and then poured into ice water. The separated crystals were filtered off, washed with water, and dried. Product IIa (0.07 g) was obtained. The filtrate was extracted with chloroform and the extract evaporated. The residue was triturated with water, and further 0.18 g of product IIa filtered off. The total yield of compound IIa was 0.25 g (90%); of mp 57-58°C (from chloroform–hexane).

2-Aminopyridines IIb-d were obtained analogously from the appropriate amines.

Compounds IIe,f were synthesized in DMF from chloride I and appropriate amine at a reactant ratio of 1:5.

3-Cyano-4-methoxymethyl-6-methyl-2-phenylamino-pyridine (IIh). A. A mixture of chloride I (0.4 g, 0.001 mole) and aniline (1 ml, 0.01 mol) in butanol (7 ml) was heated at 90°C for 5 h. Further treatment was as described for compound IIa. The yield of product IIh was 0,49 g (97%).

Compounds IIg,i-k were synthesized analogously. An equimolar ratio of starting materials was used in the case of crystalline amines.

B. A mixture of chloropyridine I (0.6 g, 0.003 mole) and aniline (1.5 ml, 0.015 mole) was heated at 120°C for 5 h. The reaction mixture was poured into hot water. The aqueous solution was decanted. The oil was treated

several times with hot water, then crystallized in cold water. The crystals were filtered off and dried. Yield was 0.6 g (80%). IR spectrum: 1575, 2590, 1620 (arom.), 2230 (C≡N), 3325 cm^{-1} (NH). The melting point of a sample mixed with a sample obtained by procedure A showed no depression.

6-Methyl-3-oxo-4-phenylamino-1H-furo[3,4-c]pyridine (IIIh). A. A mixture of aminopyridine IIa (0.25 g, 0.001 mole) with 50% H_2SO_4 was heated at 90-100°C for 5 h. The reaction mixture was poured into ice water, and neutralized to pH 7 with aqueous ammonia solution. The crystals which separated were filtered off and washed with water. Compound IIIh (0.17 g) was obtained. The filtrate was extracted with chloroform, and the extract dried over Na_2SO_4. The solvent was evaporated, the residue triturated with water, and further 0.03 g of product IIIh filtered off. The total yield was 0.20 g (80%). The product was recrystallized from benzene-hexane mixture.

Compounds IIIa-g, i-j were obtained analogously.

B. A mixture of chloropyridolactone VI (0.55 g, 0.003 mole) and aniline (0.45 ml, 0.0045 mole) in 50% CH_3COOH (5 ml) was boiled for 17 h. The mixture was cooled, the solid which separated was filtered off, washed with water, and dried. Product IIIh (0.36 g, 50%); mp 145-147°C was obtained and was identical (mp, R_f, IR spectrum) with a sample synthesized by procedure A. The filtrate was extracted with chloroform and the extract evaporated. The crystals were triturated with benzene, filtered off, and washed with water. Furopyridinedione VIII (0.03 g, 6%) was obtained; mp >320°C (with decomposition). R_f 0.50. IR spectrum: 1640 (C=O amide), 1740 (C=O lactone), 3320 cm^{-1} (NH). Literature mp 340°C (with decomposition) [12]. The benzene filtrate was dried over sodium sulfate, and evaporated. The residue (oil) was triturated with hexane under cooling. Mustard-colored crystals of IIIh (0.06 g, 8%) of mp 145°C were obtained. IR spectrum: 1575, 1630 (arom.), 1720 (C=O lactone), 3320 cm^{-1} (NH).

3-Cyano-2-hydrazino-4-methoxy-6-methylpyridine (IV). A mixture of chloropyridine I (0.4 g, 0.002 mole) and 85% hydrazine hydrate (0.6 ml) in dioxane (5 ml) was heated at 80°C for 3 h. The solution was evaporated to one third volume and the solid which separated on cooling was triturated with petroleum ether. The precipitated solid was filtered off. Fluffy white crystals of product IV (0.34 g, 85%) were obtained; mp 123-125°C. IR spectrum: 1550, 1560, 1660 (C=C, C=N), 2210 (C≡N), 3180, 3285, 3330 cm^{-1} (NH, NH_2). R_f 0.76. Found, %: C 55.9; H 6.2; N 29.2. $C_9H_{12}N_4O$. Calculated, %: C 56.2; H 6.2; N 29.2.

3-Amino-4-methoxymethyl-6-methyl-1H-pyrazolo[3,4-b]pyridine (V). A. A mixture of chloropyridine I (0.3 g, 0.0015 mole) and 85% hydrazine hydrate (0.5 ml) in ethanol (5 ml) was boiled with stirring for 3 h. After cooling, coffee-colored shiny crystals of product V precipitated from the reaction mixture. The crystals were filtered off, washed with alcohol, and with water. Yield was 0.3 g (~100%); mp 226-230°C (with decomposition). IR spectrum: 1565, 1600, 1620 (C=C, C=N), 3180, 3310, 3430 cm^{-1} (NH, NH_2). R_f 0.63. Found, %: C 54.2; H 6.3; N 28.4. $C_9H_{12}N_4O$. Calculated, %: C 54.0; H 6.0; N 28.0.

B. 2-Hydrazinopyridine IV (0.2 g, 0.001 mole) was heated in 50% H_2SO_4 at 90-100°C for 4 h. The reaction mixture was poured onto ice, and the solution neutralized with aqueous ammonia solution. The precipitated crystals were filtered off and washed with water. Product V identical with a sample synthesized by procedure A (mp, R_f, IR spectrum) was obtained (0.12 g, 60%).

2-Chloro-4-hydroxymethyl-6-methylnicotinic Acid Hydrazide (VII). A mixture of chloropyridolactone VI (0.55 g, 0.003 mole) and 85% hydrazine hydrate (1.4 ml) in ethanol (20 ml) was boiled for 12 h. The solvent was evaporated, the product was crystallized from ether, and then from ethanol. Yield was 0.49 g (75.5%); mp 202°C (with decomposition). IR spectrum: 1640 (C=O amide), 3190-3350 cm^{-1} (NH, NH_2, OH). PMR spectrum (CF_3COOH): 2.48 (3H, s, CH_3); 5.03 (2H, s, CH_2O); 6.97 ppm (1H, s, =CH). Found, %: C 44.2; H 4.4; N 19.4; Cl 16.2. $C_8H_{10}N_3O_2Cl$. Calculated, %: C 44.5; H 4.6; N 19.5; Cl 16.5.

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