NUCLEOPHILIC SUBSTITUTION REACTIONS IN 2-CHLOROPYRIDINES AND 2,5-DIOXO-1,2,5,7-TETRAHYDRO-1H-FURO[3,4-b]PYRIDINES

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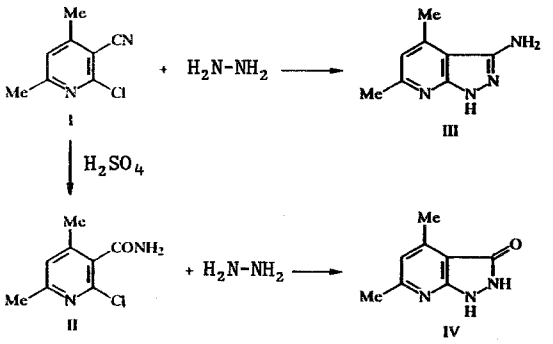
3-Cyano- and 3-carbamoyl-2-chloropyridines react with hydrazine hydrate to form substituted 3-amino-1H-pyrazolo[3,4-b]pyridines and 3-oxo-2,3-dihydro-1H-pyrazolo[3,4-b]pyridines. Hydrazine hydrate reacts with 3-carbamoyl-2-chloro-5-oxo-5,7-dihydrofuro[3,4-b]pyridine to form substituted 3,5-dioxo-2,3,5,7-tetrahydro-1H-pyrazolo[3,4-b]furo[3,4-e]pyridine.

Condensed heterocyclic systems containing a pyridine ring are of interest in connection with their wide spectrum of pharmacological activity [1-4]. The present work is a continuation of studies on the search for new cardiotonic agents among the 2-amino-3-cyanopyridines [5-7].

Unlike the 5-pyridyl substituted 3-cyanopyridines [5-7] the 3-cyano(carbamoyl)-2-chloro-4,6-dimethylpyridines (I) and (II) and the 2-chloro-3-cyano(carbamoyl)-5,7-dihydrofuro[3,4-b]pyridines (VI) and (IX) have been synthesized and investigated in the present study.



3-Carbamoyl-2-chloro-4,6-dimethylpyridine (II) was obtained by the hydrolysis of nitrile (I) is concentrated sulfuric acid. Nitrile (I) was obtained by the action of phosphorus oxychloride on 2-chloro-3-cyano-4,6-dimethylpyridine-2(1H)-one [8]. On reaction of hydrazine hydrate with 2-chloro-3-cyano-4,6-dimethylpyridine (I) replacement of chlorine by a hydrazine group occurs followed by an intramolecular cyclization to 3-amino-4,6-dimethyl-1H-pyrazolo[3,4-b]pyridine (III). Bands for the nitrile group were absent from the IR spectrum of the pyrazolopyridine (III) and absorption of the NH_2 and NH groups was observed in the 3180-3400 cm^{-1} region.

Reaction of the carbamoyl derivative (II) with hydrazine hydrate leads to a bicyclic system containing a carbonyl group, viz. 4,6-dimethyl-2-oxo-2,3-dihydro-1H-pyrazolo[3,4-b]pyridine (IV). The structures of compounds (I)-(IV) were confirmed by data of ^1H NMR spectra (Table 1).

The change in chemical shifts of the 5-H proton in the ^1H NMR spectra of compounds (I) and (III) [and compounds (II) and (IV)] attracts attention. In each pair $\Delta\delta$ = 1.45 ppm and 1.11 ppm respectively. Such a significant difference in shielding may only be explained by a change in the size of the ring currents in the pyridine ring which the formation of the second ring confirms.

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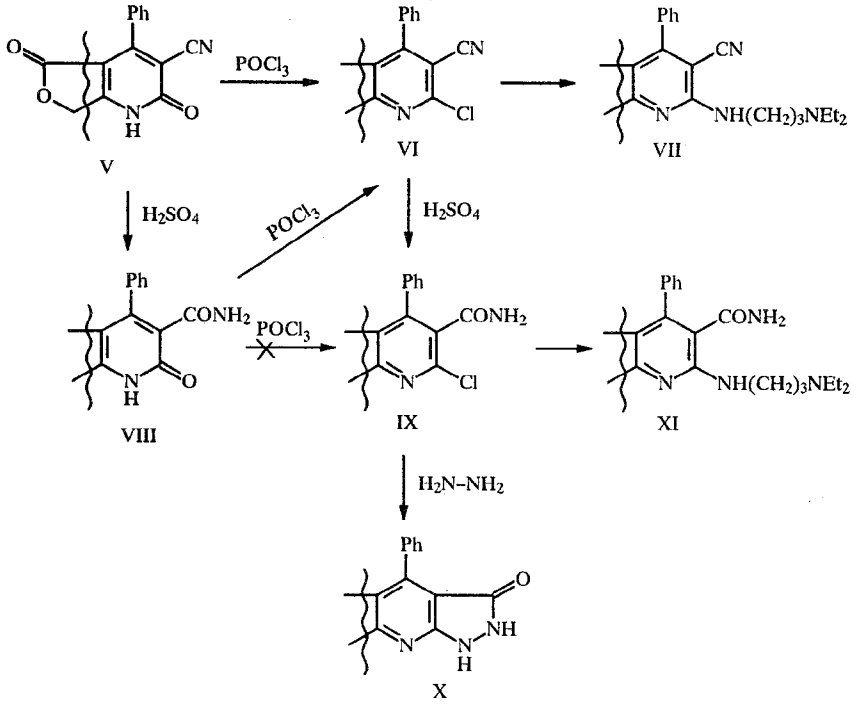
TABLE 1. Characteristics of Compounds (I)-(XI)

Compound	Mp, °C	IR spectrum, ν, cm^{-1}			PMR spectrum, δ, ppm	Yield, %
		C=O	CN	NH, NH_2		
I	99...100		2230		2,40 (6H, s, 4,6-CH_3); 7,33 (1H, s, 5-H)	57,7
II	178...179	1685		3170, 3350	2,17 (3H, s, 4-CH_3); 2,33 (3H, s, 6-CH_3); 7,08 (1H, s, 5-H); 7,64 & 7,86 (2H, s&s, $CONH_2$)	65,0
III	243...244			3170, 3290, 3390	2,13 (3H, s, 4-CH_3); 2,22 (3H, s, 6-CH_3); 4,50 (2H, s, NH_2); 5,88 (1H, s, 5-H); 10,55 (1H, s, NH)	82,5
IV	265...270 (decomp.)	1620		3100, 3170P, 3210P	2,13 (3H, s, 4-CH_3); 2,17 (3H, s, 6-CH_3); 5,97 (1H, s, 5-H); 10,02 (2H, s, NH & NH)	80,6
VI	185...187	1770	2240		5,44 (2H, s, CH_2); 7,55 (5H, s, C_6H_5)	72,4
VII	150...151,5	1770	2220	2980, 3100P	0,91 (6H, t, N–(C–CH_3)$_2$); 1,68 (2H, m, C–CH_2–C); 2,35 (6H, m, –$CH_2N(CH_2C)_2$); 3,45 (2H, m, –NCH_2–C); 5,14 (2H, s, CH_2 lactone); 7,40 (5H, s, C_6H_5); 8,38 (1H, m, NH)	66,9
VIII	260 (decomp.)	1650 1675 1770		3160, 3250, 3390	5,10 (2H, s, CH_2); 7,50 (5H, s, C_6H_5); 7,30 & 7,65 (2H, s&s, $CONH_2$); 11,5...12,0 (1H, br.s, NH)	88,8
IX	223...225	1665 1780		3150, 3260, 3310P	5,37 (2H, s, CH_2); 7,20 (5H, s, C_6H_5); 7,47 & 7,75 (2H, s & s, $CONH_2$)	73,0
X	323...325	1640 1770		3000...3200	5,30 (2H, s, CH_2); 7,24 (5H, m, C_6H_5); 10,4 (1H, br.s, NH); 12,2 (1H, br.s, NH)	54,0
XI	163	1670 1735		3130, 3320	0,90 (6H, t, N–(C–CH_3)$_2$); 1,63 (2H, m, NC–CH_2–CN); 2,45 (6H, m, –$CH_2N(CH_2$–C)$_2$); 3,44 (2H, m, –NCH_2–C); 5,16 (2H, s, CH_2 lactone); 7,31 (5H, s, C_6H_5); 7,43 (2H, s, $CONH_2$)	73,3

In addition to the monocyclic 2-chloropyridines (I) and (II) we have also investigated representatives of a new group of condensed pyridin-2-ones recently synthesized by us, viz. 3-cyano(carbamoyl)-2,5-dioxo-4-phenyl-1,2,5,7-tetrahydrofuro-[3,4-b]pyridines (V) [9] and (VIII).



The nitrile (V) was hydrolyzed in concentrated sulfuric acid to obtain the amido derivative of furo[3,4-b]pyridine (VIII). The absorption of the CN group disappeared from the IR spectrum of (VIII) and an absorption appeared for the exocyclic amide carbonyl at 1650 cm^{-1}. In the ^1H NMR spectrum of compounds (V) and (VIII) (Table 1) signals were observed characteristic of methylene protons of a lactone ring in addition to signals of phenyl and carbamoyl groups.

The 1,2,5,7-tetrahydrofuro[3,4-b]pyridine (V) and the 3-carbamoyl derivative (VIII) react with phosphorus oxychloride with the formation of 2-chloro-3-cyano-4-phenyl-5,7-dihydrofuro[3,4-b]pyridine (VI).

In both cases a transition occurs from the 1,2,5,7-tetrahydrofuro[3,4-b]pyridines (V) and (VIII) to a 5,7-dihydrofuro[3,4-b]pyridine (VI). In addition the amide group of (VIII) is dehydrated to nitrile. In its turn 3-carbamoyl-2-chloro-5-oxo-4-phenyl-5,7-dihydrofuro[3,4-b]pyridine (IX) is formed in good yield by the hydrolysis of nitrile (VI) in concentrated sulfuric acid.

The absorption of the five-membered lactone carbonyl at 1770 cm^{-1} is retained in the IR spectra of both amide derivatives (VIII) and (IX) and of the 3-cyano derivative (VI). This indicates the stability of the 2,5-dioxofuro[3,4-b]pyridine and 2-chloro-5-oxofuro[3,4-b]pyridine systems towards the action of sulfuric acid and phosphorus oxychloride. The structures of (VI) and (IX) were also confirmed by PMR spectra (see Table 1).

Replacement of chlorine by an N,N-diethylaminopropyl group was carried out to obtain amino derivatives of 3-cyano- and 3-carbamoyl derivatives of furano[3,4-b]pyridines [compounds (VI) and (IX)]. The replacement was more difficult in this case than for monocyclic 2-chloropyridines [10]. It was necessary to heat the 2-chloro derivatives for an extended time in isopropanol in the presence of sodium carbonate. 3-Cyano-(or carbamoyl)-2-(3-diethylaminopropyl)-4-phenyl-5,7-dihydrofuro[3,4-b]pyridines (VII) and (XI) were obtained in this way. The proton chemical shifts of compounds (VII) and (XI) and their assignments are given in Table 1.

The 3-carbamoyl derivative of furo[3,4-b]pyridine (IX) reacts with hydrazine hydrate more rapidly than the monocyclic amide (II) (judging by TLC) and forms 3,5-dioxo-4-phenyl-2,3,5,7-tetrahydro-1H-pyrazolo[3,4-b]furo[3,4-e]pyridine (X) in 54% yield. The signal of CH_2 protons (δ = 5.30 ppm) indicates the retention of the lactone ring during the reaction. The formation of the pyrazole ring is confirmed by the disappearance of the signals of the nonequivalent protons of the $CONH_2$ group (δ = 7.47 and 7.75; $\Delta\delta$ = 0.28 ppm) and the appearance at lower field of two new signals (δ = 10.4 and 12.2; $\Delta\delta$ = 1.8 ppm).

The reaction of the 3-cyano-5,7-dihydrofuro[3,4-b]pyridine (VI) with hydrazine hydrate gave a mixture of products which have so far not been successfully separated and identified.

EXPERIMENTAL

IR spectra were recorded on a Specord 72 IR instrument (Carl Zeiss Jena). The PMR spectra were recorded on an 80 MHz Tesla Spectrometer BS 587 (Czechoslovakia).

The principal characteristics of the compounds synthesized are given in Table 1. Data of elemental analysis of the compounds obtained corresponded with calculated values.

2-Chloro-3-cyano-4,6-dimethylpyridine (I, $C_8H_7ClN_2$). A mixture of 3-cyano-4,6-dimethylpyridin-2(1H)-one (1.0 g: 6.75 mmole) [8] and phosphorus oxychloride (3.7 g: 24 mmole) was heated for 4 h with dry DMF (0.1 ml). After cooling, the reaction mixture was poured onto ice (200 g). The solid was filtered off and recrystallized from ethanol (with carbon).

3-Carbamoyl-2-chloro-4,6-dimethylpyridine (II, $C_8H_9ClN_2O$). A mixture of the 2-chloropyridine (I) (1.66 g: 10 mmole) in conc. H_2SO_4 (15 ml) was heated at 70°C for 4 h. After cooling, the reaction mixture was poured into water (50 ml) and the solution neutralized to pH 7 with ammonia. The solid was filtered off and recrystallized from ethanol.

3-Amino-4,6-dimethyl-1H-pyrazolo[3,4-b]pyridine (III, $C_8H_{10}N_4$). Dry DMF (0.5 ml) and hydrazine hydrate (2 ml: 41 mmole) were added to a warm (~50°C) solution of the 2-chloropyridine (I) (1 g: 6 mmole) in absolute ethanol (10 ml) and the reaction mixture boiled for 0.5 h. After cooling the solid was filtered off and recrystallized from ethanol–water (4:1).

4,6-Dimethyl-3-oxo-2,3-dihydro-1H-pyridine (IV, $C_8H_9N_3O$). A mixture of the amide (II) (0.7 g: 3.8 mmole), dry DMF (0.5 ml), and hydrazine hydrate (5 ml: 0.1 mole) in absolute ethanol (10 ml) was boiled for 5 h. After cooling, the mixture was brought to pH 7-8 by adding hydrochloric acid, the precipitated solid was filtered off, and recrystallized from ethanol.

2-Chloro-3-cyano-5-oxo-4-phenyl-5,7-dihydrofuro[3,4-b]pyridine (VI, $C_{14}H_7ClN_2O_2$). Obtained analogously to compound (I) from the furo[3,4-b]pyridine (V) [9].

3-Cyano-2-(3-diethylaminopropyl)-5-oxo-4-phenyl-5,7-dihydrofuro[3,4-b]pyridine (VII, $C_{21}H_{24}N_4O_2$). A mixture of the furo[3,4-b]pyridine (VI) (1.89 g: 7 mmole) and diethylaminopropylamine (2.27 g: 17.5 mmole) in isopropanol (50 ml) was boiled for 6 h. The reaction mixture was filtered and the filtrate evaporated in vacuum. The residue was recrystallized from ethanol by keeping for 2 d in a freezer at −20°C.

3-Carbamoyl-2,5-dioxo-4-phenyl-5,7-dihydrofuro[3,4-b]pyridine (VIII, $C_{14}H_{10}N_2O_4$). Obtained analogously to compound (II) from the furo[3,4-b]pyridine (V) [9]. The product was recrystallized from ethanol by adding acetic acid.

3-Carbamoyl-2-chloro-5-oxo-4-phenyl-5,7-dihydrofuro[3,4-b]pyridine (IX, $C_{14}H_9ClN_2O_3$). Obtained analogously to compound (II) from the furo[3,4-b]pyridine (VI).

3,5-Dioxo-4-phenyl-2,3,5,7-tetrahydro-1H-pyrazolo[3,4-b]furo[3,4-e]pyridine (X, $C_{14}H_9N_3O_3$). A mixture of the furo[3,4-b]pyridine (IX) (0.4 g: 1.38 mmole), hydrazine hydrate (1.6 ml: 30 mmole), and dry DMF (0.1 ml) in absolute ethanol (5 ml) was boiled for 1.5 h. After cooling, the reaction was brought to pH 1-2 by adding hydrochloric acid. The solid was filtered off and recrystallized from ethanol–water, 4:1.

3-Carbamoyl-2-(3-diethylaminopropyl)-5-oxo-4-phenyl-5,7-dihydrofuro[3,4-b]pyridine (XI, $C_{21}H_{26}N_4O_3$). A mixture of the furo[3,4-b]pyridine (IX) (2.88 g: 10 mmole), 3-diethylaminopropylamine (3.25 g: 25 mmole), and Na_2CO_3 (1.59 g: 15 mmole) in isopropanol (50 ml) was boiled for 3 h. After cooling the 2-aminopyridine (XI) precipitated and was filtered off.

REFERENCES

1. G. Carrera, M. T. Mitjavela, and S. Mitjavela, Arzneimittel. Forsch., **11**, 29 (1979).
2. H. Satoh and M. Endoh, Jpn. J. Pharmacol., **52**, 215 (1990).
3. I. P. Skrastyn'sh, V. V. Kastron, R. O. Vitolin', G. Ya. Dubur, and M. I. Stivrinya, and K. A. Kaidaka, Khim.-farm. Zh., No. 11, 1323 (1989).
4. D. Ya. Tirzite, I. E. Kirule, I. M. Biteva, G. D. Tirzit, E. A. Bisenieks, and G. Ya. Dubur, Khim.-farm. Zh., No. 3, 290 (1989).
5. V. Hagen, A. Hagen, S. Heer, R. Mitzner, and H. Niedrich, Pharmazie, **44**, 20 (1989).
6. B. Roloff, J. S. Schafer, A. Rumler, V. Hagen, and A. Hagen, Pharmazie, **44**, 12 (1989).
7. V. Hagen, E. Klauschenz, A. Rumler, A. Hagen, S. Heer, R. Mitzner, H. Niedrich, and D. Lohmann, Pharmazie, **45**, 189 (1990).

8. E. Yu. Gudrinietse and A. V. Nikitenko, Izv. Akad. Nauk Latvian SSR, Ser. Khim., No. 5, 569 (1972).
9. Z. A. Kalme, Yu. E. Pelcher, and G. Ya. Dubur, Khim. Geterotsikl. Soedin., No. 12, 1699 (1991).
10. Z. A. Bomika, M. B. Andaburskaya, Yu. E. Pelcher, and G. Ya. Dubur, Khim. Geterotsikl. Soedin., No. 8, 1085 (1976).